1945

Thiouracil

100 45

Excellent survey of an important subject — thorough, thoughtful, well conceived, & clearly composed.

THIOURACIL

Sidney Kibrick
B. U. S. M. III
April 1, 1945

TABLE OF CONTENTS

THIOURACIL

INTRODUCTORY AND HISTORICAL

In 1941 MacKenzie, MacKenzie and McCollum (1) during the course of some experiments to determine whether sulfaguanidine, when fed to rats on a purified diet containing synthetic B vitamins, might prevent the synthesis of additional essential nutrients by the intestinal flora, noted that the thyroid glands became hyperemic and enlarged to several times the size of the controls. Histologically, the epithelium of the hypertrophied thyroids was columnar in type with papillary overgrowth, and there was an associated quantitative depletion of the intrafollicular colloid. The widespread and increasing use of sulfonamides at that time prompted them to further investigation.

Further studies by these same workers (2) showed that an enlargement of the thyroid could be produced by other compounds of the sulfonamide series and by thiourea. This thyroid hypertrophy was accompanied by a marked drop in the basal metabolic rate. Both of these changes were prevented or counteracted by the administration of thyroxin but not by iodine.

At about the same time, Kennedy, Purves and Griesbach (3) (4) (5) reported the occurrence of thyroid hyperplasia in rats which had been fed the seeds of various species of Brassicae, a genus of plants which includes cabbage, cauliflower, turnip and rape. The presence of associated histological changes in the pituitary glands of their animals suggested that the goitrogenic effect was produced through the mediation of the thyro-

tropic hormone of the anterior pituitary. In an attempt to isolate the goitrogenic substance present in rape-seed, Kennedy (6) was prompted to test the effect of a derivative of thiourea, allylthiourea. This substance, on oral administration, was found to produce changes in both the thyroid and pituitary of rats similar to those caused by a diet containing rape-seed.

From a third laboratory, also at this time, came the work of Richter and Clisby (7) describing the development of thyroid hyperplasia in rats, following the addition of phenyl thiourea to their drinking water. The MacKenzies (8) in an elaboration of their previous work, now stated that in addition to the anatomical changes in the thyroid and the drop in basal metabolism previously noted with the administration of sulfonamides and thiourea, thyroidectomy cells were observed in the pituitary. Hypophysectomy prevented the characteristic changes in the thyroid.

A number of other investigators have been able to show that changes in the cellular pattern of the anterior pituitary are associated with dysfunction of the thyroid (9) (10) (11) (12). Marine et al (9) reported not only cellular changes in the anterior pituitary of rabbits with parenchymatous goiter but also an increase in weight of the gland. Administration of iodine or dessicated thyroid was found to restore the cells to normal. MacKenzie et al (8) using differential stains on the pituitaries of rats fed sulfonamides and thiourea was able to show a degranulation and decrease in the number of the acidophils, vacuolation and increase in number and size of the basophils. These changes corresponded closely to those reported following thyroidectomy (12), and were confirmed by Astwood

and his co-workers, (13).

The above and similar studies on the mechanism whereby sulfonamides and thiourea induce thyroid enlargement led to the concept that the goiter is compensatory in nature and that the primary action of such compounds is the inhibition of thyroid hormone synthesis (8) (13). This suggested to Astwood (14) that compounds related to the sulfonamides or thiourea might be useful therapeutic agents, and consequently the activity of a large number of such compounds was explored. The relative effectiveness of 106 chemical compounds in inhibiting the function of the thyroid gland was tested in young rats. These substances were administered in the food or drinking water for a period of ten days, the degree of gross and microscopic thyroid hyperplasia providing an estimate of their activity.

It was found that the compounds tested could be divided into three classes: thiourea derivatives, those containing an aminobenzene grouping, and the thiocyanates. The thioureas on the whole were the most active and among these, thiouracil had the highest activity. The aminobenzene derivatives included the common sulfonamides of which sulfadiazene was the most active. The thiocyanates were distinct from the other two classes in requiring a diet low in iodine, and their goitrogenic action was completely inhibited by added iodide. With regard to this point, Rawson et al (15) have shown that the thiocyanate goiter readily takes up radioactive iodine while the enlarged glands resulting from thiouracil administration do not.

With reference to the compounds tested, it was found that

all of the compounds having within their structure the grouping -NH·CS·NH- (thiourea and its derivatives) were active, with the exception of those of very low solubility in water or of high toxicity. The inclusion of thiourea in a five or six membered heterocyclic structure resulted in a pronounced enhancement of activity (e.g. thiouracil). The six membered heterocycles containing 3N atoms, however, although non-toxic in large doses, were of very low potency.

Most of the heterocycles were of low toxicity, and thiouracil and thiobarbituric acid, in addition to exhibiting an unusually high activity were particularly non toxic and therefore of greatest interest clinically. Thiouracil ranked highest in both respects.

From a structural point of view it was apparent that the entire grouping -NH·CS·NH- is essential to the thyroid effect. Activity is lost if the S is replaced by another element or group as in urea, guanidine and their derivatives. Apparently both amino N atoms are essential, for activity is lost when one of these groups is absent. The S itself is obviously not the active agent as a number of compounds containing S in different forms were inactive. Therefore, it appears that the entire thiourea grouping is essential to the type of biological response under investigation.

The biologically active grouping in the second series of compounds tested was not entirely clear, the only structure common to all being the aniline group $NH_2C_6H_4$-. It is apparently necessary that the amino group be free, for activity was lost when this group was substituted.

As a working hypothesis, Astwood (14) suggested that the aniline derivatives act through a competitive mechanism in the enzyme system responsible for the conversion of diiodotyrosine to thyroxin, the thioureas being possibly specific inhibitors of the same system.

MECHANISM OF THIOURACIL ACTION

Stimulated by the early reports, interest in the action of thiourea and its derivatives began to increase and further evidence was accumulated supporting the view that these compounds inhibit the formation of thyroid hormone or depress the activity of the thyroid gland. The findings previously reported that the administration of thiourea to normal rats resulted in an enlarged, hyperemic and hyperplastic thyroid gland, coincident with a state of hypothyroidism as indicated by decreased food intake, decreased growth and development and by lowered basal oxygen consumption, were confirmed (13) (16). The thyroid hyperplasia was not influenced by large supplements of iodine but was abolished by the administration of thyroid powder and by hypophysectomy. The calorigenic action of thyroid powder was found to be uninhibited by these compounds in both normal and hypophysectomized rats. These facts were interpreted as evidence that the thyroid hyperplasia which occurs under the influence of these drugs was compensatory to the failure of thyroid hormone synthesis (13) (16).

A number of further observations were made. The administration of thiouracil to young rats was followed by a nearly complete disappearance of iodine from the thyroid along with the hypertrophy of the gland. Withdrawal of the drug was followed by a prompt decrease in the size of the glands and a rapid reaccumulation of iodine (16). Hughes (17) was able to show that the continued administration of thiouracil to rats from the time of birth resulted in a marked retardation of growth, arrested development, and changes similar to those seen in cretinism.

These effects were not observed if thyroxin was given concurrently, offering further evidence that the observed results were brought about by an inhibition of thyroid activity. Similar results were obtained with tadpoles, where it was found that thiouracil in a concentration of 1:2000 inhibited the metamorphosis of Rana clamitans, ordinarily induced by injections of thyrotropin. Since the action of thyroxin in inducing metamorphosis was not inhibited, it was postulated that the drug prevents the production of thyroid hormone. Experiments on the chick (19) (20) gave essentially the same results, the thyroid becoming markedly enlarged, their endocrine function inhibited, and a state analogous to cretinism being produced.

The exact mechanism of thiouracil action has not as yet been definitely ascertained. The present hypothesis is based on the following experimental findings:

1. Drugs of the thiourea series produce marked hyperplasia and enlargement of the thyroid, associated with evidences of diminished thyroid function such as a decrease in basal metabolic rate (2) (8) (13) (16)-(20).

2. When thiouracil is given to very young animals growth is checked and cretinism may be produced, indicating that thyroid hormone production is inhibited (22).

3. Coincident with the thyroid hyperplasia and hypertrophy there is a definite decrease in thyroid iodine concentration (16) (21).

4. The thyroids of animals being treated with thiouracil remain low in iodine as compared to controls, regardless of the iodine intake (15) (23) (25).

The greater portion of this iodine is inorganic. In untreated controls, however, the organically bound iodine comprises almost all of the demonstrable iodine. The concentration of inorganic iodine in the thyroids of controls is of the same order of magnitude as in animals treated with thiouracil. This indicates that this drug affects the synthesis of organic iodine compounds by the thyroid (16) (25).

5. The feeding of thiouracil to experimental animals has been shown to interfere with the incorporation of injected iodine into thyroxin and diiodotyrosine by the thyroid. (The thyroxin and diiodotyrosine were determined as total organic thyroid iodine.) This has also been demonstrated in vitro (26).

6. On cessation of thiouracil administration, the iodine concentration in the thyroid increases to its normal level (16) (24) (25). This increase is due to an increase in thyroid organic iodine (26).

7. The concurrent administration of thyroxin to thiouracil treated animals completely prevents the hyperplasia and other changes that normally follow thiouracil administration (13) (15) (16). It is not prevented by iodine or by diiodotyrosine.(13) (15) (21) (22). It is, however, abolished by hypophysectomy, indicating that the pituitary mediates this effect (13).

8. Thiouracil does not block the liberation of previously formed thyroxin from the thyroids. Any preformed and stored hormone continues to be secreted, although further synthesis of the hormone is inhibited (16) (24) (27).

9. Thiouracil has no action on thyroxin itself. It interferes with the production of this hormone but not with its activity.(13) (15) (16).

As a result of this work the following sequence of events has been postulated (13) (14) (16). Shortly after thiouracil is administered the organism becomes unable to synthesize thyroid hormone at a normal rate. As stored hormone is used up the quantity of circulating hormone tends to fall as shown by protein-bound iodine determinations. In response to this deficit an excess of thyrotropin is produced by the pituitary and this stimulates the thyroid to hyperplasia. So long as thyroid hormone is available in sufficient amounts the metabolic rate is maintained at a normal level. Eventually, however, the stores of hormone are exhausted as evidenced by a complete loss of demonstrable colloid, and the metabolic rate begins to fall even though the thyroid hyperplasia is still advancing. The actual level of hypometabolism reached depends partly upon the degree to which the process of thyroid hormone synthesis is hindered, partly on environmental and other factors which alter the thyroid hormone requirement.

The discovery that thyroid hormone formation is prevented by sulfonamides and thiourea led Dempsey (28) to investigate the possibility that these drugs, which are well known anti-enzymes, might act by poisoning an enzyme system necessary for the synthesis of the thyroid hormone. Since it had previously been established that the hyperplasia induced by the administration of thiourea and its derivatives was prevented or repaired by thyroxin (8) (13) but not by diiodotyrosine (22), it appeared that these antithyroid drugs might act by preventing the condensation of this compound into ~~thiouracil~~ thyroxin. Since peroxidase is present in many animal tissues, since it is

known to be poisoned by thiourea, and since it can catalyze reactions similar to the diiodotyrosine condensation, it appeared possible that this enzyme might also catalyze the formation of thyroxin. By means of the benzidine test on frozen thyroid sections Dempsey was able to demonstrate not only the presence of a true peroxidase in the follicular cells, but also the fact that its action was inhibited by thiouracil.

The hypothesis that thiouracil acts by preventing the condensation of diiodotyrosine into thyroxin does not exclude the participation of thiouracil in preventing the synthesis of thyroid hormone in other ways. The natural synthesis of thyroxin appears to involve two main steps: first, the iodization of tyrosine and second, the coupling of two molecules of diiodotyrosine to form thyroxin. The first of these requires the presence of free iodine and, since exogenous iodine is known to reach the thyroid as iodide, a strong oxidizing system is required to convert the iodide to iodine before diiodotyrosine can be formed. Peroxidase is known to be able to set free iodine from iodides. The failure of such a reaction in the thyroid gland could conceivably prevent the iodization of tyrosine and thus interfere with the thyroxin synthesis. While such a mechanism does not account for the failure of thyroxin synthesis on administration of diiodotyrosine to thiouracil treated animals, the postulation that thiouracil acts solely by preventing the etheric condensation of diiodotyrosine is in turn open to the objection that the thyroids of animals treated with this drug show an almost complete disappearance of organic iodine which is presumably at least in large part diiodotyrosine and thyroxin. Thus, all that can be said at present is that

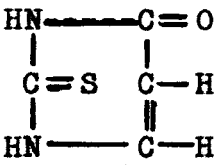
thiouracil blocks thyroid hormone synthesis, the mode of action being either prevention of tyrosine iodization or of diiodotyrosine condensation or of both.

THYROID HORMONE ASSAY WITH THIOURACIL

The findings that thyroid hormone synthesis is inhibited in animals by thiouracil but that this drug has no effect on thyroxin itself has suggested a method of thyroid hormone assay to several workers. (20) (22) Both chicks (20) and rats (22) have been used. The assay in general consists of determining quantitatively the effect of various thyroid preparation in maintaining or restoring normal thyroid weight in thiouracilized animals.

PHYSICAL AND CHEMICAL PROPERTIES OF THIOURACIL

Little or no data on the properties of thiouracil seem to have been published since Wheeler and Liddle (29) reported the synthesis of this compound in 1908. Thiouracil is a heterocyclic derivative of thiourea, and has the following formula



It is a white, odorless, bitter powder, insoluble in alcohol, CCl_4, acetone and mineral acids, and somewhat soluble in ether. A saturated aqueous solution contains about 50mg. of thiouracil per 100cc. at 25° C. Due to its acid properties it forms very soluble salts on addition of Na or KOH to an aqueous solution. It is relatively stable in solution, more so in dry form, and is not affected by sunlight. (30)

Several methods all employing Grotes' reagent have been published for the determination of thiourea and thiouracil in serum, urine, tissue extracts and body fluids. (30) (31) This reaction depends on the fact that the $>N-\overset{S}{\overset{\|}{C}}-N<$ linkage of thiouracil reacts with sodium nitroferricyanide in alkaline solution (Grotes' reagent) giving a greenish color which can be quantitated in a colorimeter.

ABSORPTION, TISSUE DISTRIBUTION AND EXCRETION OF THIOURACIL

Experimental studies on both animals and man have shown that thiouracil is rapidly absorbed from the gastro-intestinal tract (80% in two hours). Following the administration of 0.2 gm. of thiouracil to a normal individual, Williams and Bissell (35) found a high blood level (2.3 mg. 100cc) was attained after 15 minutes. This fell rapidly until at eight hours only 0.3 mg 100cc. was present; the drug, however, did not entirely disappear until the third day. The most rapid rate of excretion of the drug occurred during the second hour.

When thiouracil was given in doses of 0.2 gm. at four hour intervals, it required about 24 hours to reach a more or less constant blood level (about 3mg. 100cc) and rate of urinary excretion (300mg. daily). When the dosage was 0.2gm. three or four times daily, about 48 hours were required. (35)

Frequent small doses were found to maintain a greater constancy in the blood and urine levels than did equivalent daily amounts administered less frequently. (34) In a series of patients given dosages varying from 0.2 to 1.2gm. daily, the blood levels were found to remain relatively constant, regardless of what dose in this range was given. (33).

On ingestion of thiouracil, all of the drug was found to be either absorbed or broken down in the gastro-intestinal tract. In patients receiving from 0.4 to 1.0gm. daily, approximately one-third is excreted unchanged in the urine. On the average, 15% of the quantity ingested is destroyed in the gastro-intestinal tract, 33% excreted in the urine and the remainder is broken down in the body tissues and fluids.(32)(34)

In an effort to determine the end products of thiouracil metabolism sulfur balance studies were undertaken. (32) (34) These revealed an increased excretion of urinary neutral sulfur. The other end products of thiouracil metabolism have not yet been determined.

After absorption, the drug is distributed throughout all of the body tissues and fluids, the thyroid, pituitary, adrenals and bone marrow storing the largest amounts. Skin, muscles and liver contained the least. Thiouracil in the blood is largely bound to protein, the cells possessing several times as much as the plasma. Cerebrospinal fluid, edema and pericardial fluids were found to contain distinctly less than did whole blood, the concentration in pleural and ascitic ~~and ascitic~~ fluid was about equal to that of blood, and milk was found to contain about three times as much. (33)

There is also evidence that thiouracil can pass through the placenta. (17) (34)

EXPERIMENTAL DATA ON THIOURACIL TOXICITY

Published studies on the toxicity of thiouracil for experimental animals are meager but indicate that the drug has a relatively large margin of safety. Astwood (14) found that toxic manifestations do not occur in rats until a daily dose of 100 mg. per 100 gm. of body weight is exceeded. When thiouracil was fed at a level of 1% of the diet, concretions in the urinary tract were observed in about one third of the animals. Animals surviving this complication have been maintained on this dosage for five months without showing signs other than those attributable to a state of hypothyroidism. This dosage amounts to more than 100 times the minimal effective dose for thyroid hyperplasia and about 20 times the amount required for a full thyroid effect.

Williams and his co-workers (36) have reported the results of an investigation of structural alterations produced in rats fed thiouracil in relatively large doses (0.25% solution as Na salt, in the drinking water) for intervals of from five to ninety days. In more than 700 microscopic sections made from essentially all of the tissues of the body of many series of rats, no notable alterations were found which were attributable to thiouracil with the exception of those in the thyroid gland. The blood levels of these animals were distinctly higher than those encountered in man. Six patients who were given thiouracil for from 6 to 28 days preceeding death, were not found on post-mortem examination to show any gross or microscopic effects of this drug. With a dosage of one gram or less daily, the drug has not been found to accumulate appreciably in the blood, in spite of the presence of severe disease of the kidneys or liver (37).

Studies made on the effect of thiouracil therapy on various metabolic processes have demonstrated that blood Na, K and Cl levels are unaffected by this drug. No appreciable change was found in the glucose tolerance, and no evidence of liver damage could be found. The figures for blood proteins and blood phosphatase were found to remain within normal limits (38).

The toxic effects reported in the clinical use of this drug will be considered separately in another section.

HYPERTHYROIDISM - ETIOLOGY, CLINICAL PICTURE, AND PATHOLOGY (39) (40) (41)

Hyperthyroidism is a disease in which the thyroid gland produces and releases its hormone in amounts exceeding the physiological needs of the organism. There are two main types: exophthalmic goiter (Graves' disease, thyrotoxicosis, Basedow's disease) and toxic adenoma.

A. Exophthalmic goiter

This is apparently a disease of civilization, occurring most frequently among young adults in cities where life is strenuous, and especially in people of narrow frame, light skeletal structure and nervous temperament. Women are much more often afflicted than men. It bears no apparent relationship to iodine deficiency. In a large percentage of cases, nervous shock or strains play an important role and cures are difficult until this strain has been relieved.

The thyroid gland in this condition shows a diffuse enlargement, and becomes soft and very vascular. Microscopically,

the acini show hypertrophy, hyperplasia and infolding of cells. The amount of colloid is diminished and there is lymphoid hyperplasia. The gland iodine content is low, but the blood organic iodine is elevated. After iodine administration the gland tends to assume the histological appearance of colloid goiter and a temporary remission of symptoms may occur.

The patient with exophthalmic goiter may show a number of characteristic features.

1. the blood supply of the gland is greatly increased, the rush of blood through the superior thyroid arteries often producing a loud bruit or a distinct thrill.

2. the thyroid is enlarged.

3. the patient may complain of easy fatiguability, nervousness, irritability.

4. loss of weight despite an increased appetite.

5. tachycardia is present. This may progress to auricular fibrillation. The patient may also complain of palpitation.

6. fine tremor of the hands.

7. the skin is warm and moist. There is usually a sensitivity to heat.

8. vomiting and diarrhea may develop.

9. the basal metabolic rate may reach as high as +125 or even higher.

10. exophthalmos - the eyes develop a staring expression with the whites very prominent.

11. winking is infrequent and other eye signs such as lid lag may occur.

Most of these symptoms are directly referable to the increased thyroid secretion.

The course of the disease varies. It may be acute and fulminating, the patient dying with all the classical symptoms

of exophthalmic goiter. Sometimes there is an acute exacerbation of symptoms after thyroidectomy or during the course of the disease, the patient dying in a so-called thyroid storm usually from exhaustion or cardiac failure. In other cases the course is less violent and is marked by a series of remissions and exacerbations. In all patients who have suffered from exophthalmic goiter there is danger of recurrence even after operation.

B. Toxic Adenoma

A thyroid gland which has gone through any degree of hyperplasia and involution has a marked tendency to develop nodular formations which are commonly known as adenomas. Most adenomas produce no symptoms except mild disfigurement and pressure. A small number become toxic, a very small percentage malignant.

A simple adenomatous goiter may undergo an increased functional activity and produce the features associated with hyperthyroidism. This toxic change most usually occurs between the ages of 35 and 40. The onset of the constitutional symptoms is often without apparent cause but it may be initiated by the administration of iodine and, once started, continues even after the iodine has been withdrawn. The patient usually gives a history of having had a swelling of the neck for many years. There is a gradual onset of symptoms with a rising BMR which reaches an average of about +30 but may be higher. Exophthalmos seldom occurs, ~~A suggested explanation is the fact that toxic adenoma appears later in life than exophthalmic goiter, i.e. at a period when there is less thyroid epithelium which is capable~~

~~of reacting violently to the stimulus, so that exophthalmos is absent~~ and the nervous symptoms are less marked. On the other hand, the myocardium is more easily exhausted and fibrillation more readily produced.

At one time it was thought that exophthalmic goiter and toxic adenoma showed distinct differences in etiology, symptomology, course, and response to treatment. Most observers now feel that there is no essential difference between the two but that they are clinical variations of a single disease.

TREATMENT OF HYPERTHROIDISM WITH THIOURACIL

In view of the finding in animals that the formation of thyroid hormone is inhibited by relatively non-toxic compounds it seemed of interest and importance to determine whether the excessive production of hormone in human thyrotoxicosis could be checked by the administration of one of these agents.

The first compound to be tested clinically was thiourea, which appeared to be particularly non-toxic in animals. During the early part of 1942 several normal and hyperthyroid individuals were given from one to two gram doses of this drug for several days. No toxic effects were noted and there was no immediate change in the metabolic rate. When treatment was continued for several weeks improvement of thyrotoxic symptoms and a satisfactory response of the BMR were observed (42).

This effect of thiourea was confirmed and extended by Himsworth (43), who treated six patients with hyperthyroidism with good results. Thiourea was found to be unpleasant to some persons because of the aftertaste and because of the unpleasant odor imparted to the breath. Some of the patients experienced nausea and vomiting and the development of a skin rash when treated with adequate doses of this drug. Other unfavorable side effects with this drug have been reported (44) (45). In general it appeared that the activity of thiourea was too low and the incidence of a toxic reaction too high for it to be recommended as a useful drug.

Shortly after the first successful trials with thiourea had been initiated, a study of the activity of a number of related compounds revealed that thiouracil was a more highly active drug (14). As a result most of the studies on the

chemotherapy of thyrotoxicosis have been confined to this drug.

When thiouracil was tested in clinical hyperthyroidism its high activity was soon apparent. A total daily dose of from 0.2 to 0.6 gm. was found to be effective in controlling the symptoms of hyperthyroidism and in reducing the BMR to normal (42). In one case a dose of 2 gm. daily resulted in a severe but temporary agranulocytosis serving to show that caution and close observation are essential when this drug is being given.

The first published confirmation of the clinical effectiveness of thiouracil was that of Williams and Bissell (35) who treated nine patients with doses of about one gram daily. Hyperthyroidism was adequately controlled and no serious toxic manifestations were noted. It has recently been indicated by Gabrilove and Kert (46) that doses of this order of magnitude are not safe since three out of their nine patients so treated showed toxic manifestations, 2 consisting of fever and one of leucopenia.

To date a sufficient series of cases have been treated with thiouracil to form the basis for at least a preliminary estimation of its value in hyperthyroidism. The following reports have been consulted in arriving at the conclusions presented below.

(Table on next page)

Reference	No.of Cases Reported	No.treated Medically	Continued Remissions on Cessation of Thiouracil	No.treated with Thiouracil Preoperatively
Rawson et al (27)	19	0	-	19
Astwood (42)	1	1	-	--
Williams et al (35)	9	9	-	--
Palmer (47)	12	12	-	--
Gabrilove et al (46)	9	9	-	--
Paschkis et al (45)	15	12	1	3
Grollman et al (48)	18	0	-	16
Rose et al (49)	37	37	8	4
Watson et al (50)	11	11	-	--
McGregor (51)	20	20	-	--
Reveno (52)	9	9	-	--
McGavack et al (38)	26	26	-	--
Moore et al (53)	53	19	-	34
Clute et al (37)(54)	115	81	-	34
Astwood (55)	62	62	9	--
Bartels (56)	11	0	-	11
	427	308	18	121

The low number of complete remissions on cessation of therapy is due primarily to the fact that few investigators have as yet published reports on the results of discontinuance of the drug after adequate therapy. The Lahey Clinic has used thiouracil preoperatively on some hundreds of patients with excellent results although statistical data have not as yet been published. (57)

Dosage

The first clinical dosages were determined on the basis of the minimum amount of the drug required to produce a complete or nearly complete inhibition of thyroid hormone synthesis in the rat, the results being transposed to man on the basis of body weight. (55) As more and more data became available it became obvious that the amount of drug necessary

to obtain an adequate response in thyrotoxicity was distinctly less than the amounts first used (1 to 1.2gm. or more per day) and the dosages were accordingly lowered. A scheme of medication found satisfactory by Williams and Clute (37) in a series of 72 cases treated medically with this drug consisted of

> 0.2gm. t.i.d. for the first 2 weeks, followed by
> 0.2gm. b.i.d. until the BMR is normal
> 0.1gm. b.i.d. is then instituted and this dosage continued until the BMR has been maintained well within normal limits for several weeks. At this point, the dosage can be reduced to o.1gm. daily as a maintenance dose. Only rarely were larger doses found necessary.

Astwood, who has done considerable of the early work with this drug, in his report on treatment of 62 patients (55) used total daily dosages of 0.3 to 0.6gms. initially, reducing this to 0.2 to 0.4gm. within five weeks. In his more recent work this has been reduced even further with satisfactory results. The dosage now employed is 0.4gm. daily in two doses of 0.2gm. each at twelve-hour intervals. Larger doses and a further subdivision of the daily dose do not appear to be more effective. (33) (58) As little as 0.2gm. daily in two doses has been effective and in only a few cases did 0.3gm. daily appear inadequate. Currently, a dose of 0.6gm. daily is given only to large individuals and to those in whom a slow response is anticipated. Since instituting this reduction in dosage, Astwood has noted no toxic reactions of any consequence.

Whatever schedule of dosage is used, it should be borne in mind that thiouracil is rapidly absorbed and excreted. Thus it is better to give 2 or 3 decreased doses per day than one large dose.

Response to Thiouracil Therapy

The patient may remain ambulatory during thiouracil treatment although a short period of hospitalization at the onset of this therapy for purposes of study has been advocated. The patient may then be released and followed by hospital visits at intervals. The more severely thyrotoxic patients are best kept in bed. Sedatives are given at the beginning of treatment if necessary, phenobarbital giving good results. As improvement progresses under continued therapy, sedatives can usually be dispensed with. A high caloric diet, rich in carbohydrates and protein, supplemented by Vitamin B complex is prescribed routinely. (54) (57)

The usual pattern of response in previously untreated cases of Graves' disease was as follows. When an adequate control period of rest in bed and sedation is allowed before thiouracil is begun, an estimation of the rate of response to this therapy can be obtained by frequent determinations of the basal metabolic rate. Usually, about a week of treatment was required before a distinct effect was obtained. Once the metabolic rate had begun to fall it continued to decline in a fairly regular manner for the next seven to ten days, then exhibiting considerable individual variation. In some cases the response continued rapidly and the metabolic rate reached normal levels within two weeks although on the average, three weeks were required.

Clinical improvement seemed to parallel quite closely the fall in metabolic rate. Subjective improvement was usually claimed almost immediately after therapy was instituted and before there were any objective signs of a therapeutic effect

but an evaluation of this phenomenon is not at present possible. Other indices of improvement which paralleled closely the metabolic response were weight gain, slowing of the basal pulse rate, return of protein-bound blood iodine to normal, and a decrease in tremor. After the metabolic rate had reached normal, most of the signs and symptoms of hyperthyroidism had disappeared. In most instances muscular weakness was the last symptom to clear and usually it continued until after the normal body weight had been regained.

The daily dosage of drug is gradually reduced and a maintenance dose is established (i.e. the lowest dose compatible with continued regression of signs and symptoms). Adequate treatment continued for longer than six months was attended by a high incidense of lasting remissions on cessation of therapy. (49) (55)

Exophthalmos was not obviously influenced during the first few weeks of treatment. There is some doubt in the literature as to whether regression of the eye changes does occur under this therapy. (37) (49) (55) Williams and Clute (37) have reported five cases in which the ocular manifestations became worse during the first few weeks of thiouracil treatment. Presumably, when the production of thyroid hormone is markedly inhibited, there results an excessive production of thyrotropic hormone which in turn causes hyperplasia of the acinar cells of the thyroid and certain manifestations of malignant exophthalmos. Thus with the use of thiouracil, especially in excessive quantities, in thyrotoxic patients, a still greater enlargement of the thyroid may result and the manifestations of malignant exophthalmos be accentuated. Under such conditions, it is ad-

visable to reduce the dosage of thiouracil. In some cases the use of dessicated thyroid also seems indicated since it not only inhibits the production of thyrotropic hormone but also exerts a diuretic effect that is of advantage in the control of severe cases of malignant exophthalmos. On an empirical basis, best results were obtained by decreasing thiouracil to a sufficiently small dosage to maintain a normal BMR and then giving 1 to 1.5 grains of dessicated thyroid daily. In general, in individuals showing manifestations of malignant exophthalmos, the minimal effective dose of thiouracil should be used to bring the metabolism to normal since overtreatment may lead to an increase in the exophthalmos.

The size of the thyroid gland does not exhibit constant changes during therapy. The gland was noted to become softer, however. In patients with large diffuse goiter, there was usually an increase in size during the first few weeks and an increase in the signs of hyperemia, followed by a slow regression.

Patients previously treated with iodine were found to exhibit a greatly delayed response to thiouracil. Presumably iodine therapy tends to cause the deposition of large stores of thyroid hormone within the gland. These must be exhausted before an effect upon the metabolic rate can be achieved. The action of the drug is to block the formation of new hormone and it is without effect on the release or the activity of hormone already stored within the gland. It has consequently been the recent practice to discontinue iodine, if being given, for some weeks prior to starting thiouracil therapy, if possible.

Long latent periods have also been noted in several instances of toxic nodular goiter and in these as in the iodine-treated cases of Graves' disease, there is presumably a large amount of hormone-containing colloid within the gland, and presumably the same mechanism is operative in causing a delayed response. This factor is apparently also responsible for the fact that in persons with normal glands a prolonged period of treatment is required before a fall in the metabolic rate occurs. In the normal individual, there is a large store of hormone and the time required for the gland to become depleted is further extended by the fact that the rate of release of hormone is much slower than in the case of the overactive glands of hyperthyroid individuals.

The effects of adequate thiouracil therapy in hyperthyroidism may be summarized as follows:

1. The BMR and protein-bound iodine are reduced to normal limits.

2. Symptoms of hyperthyroidism are in general relieved.

3. Thyroid hyperplasia and vascularity is increased, and there is loss of colloid from the gland.

4. The avidity of the thyroid for iodine is decreased.

5. Complications, either toxic or allergic may sometimes occur. These may require either permanent or temporary cessation of treatment. (This is more fully discussed in a separate section below).

6. Exophthalmos tends either to remain stationary or to increase, although some apparent remissions have been reported.

In addition it should be pointed out that overdosage may result in a myxedematous state but that this is easily controllable by temporary cessation of therapy or readjustment of the dosage.

A few studies have been reported on the effect of thiouracil on the disturbances in Ca, P, N, creative - creatinine, cholesterol and 17 - ketosteroid metabolism in hyperthyroidism. (60) (38) The results, demonstrating that all these various metabolic derangements were corrected by the administration of thiouracil just as occurs after subtotal thyroidectomy, may be considered as further evidence that the remissions produced during use of this drug are physiologic.

Remission and Thiouracil Therapy

After the full effect of thiouracil therapy is achieved as gauged by clinical improvement and return of pulse rate and BMR to normal, two courses are open for permanent maintenance of those patients scheduled for medical treatment. Inasmuch as experimental and clinical observations have shown that the effect of the drug is reversible, treatment may be either a) discontinued until signs and symptoms of hyperthyroidism recur and then reinstituted (intermittent treatment) or b) maintained and an attempt made to establish a small permanent maintenance dose. In the first few treated patients therapy was withdrawn shortly after the metabolic rate had reached normal in order further to establish that the observed effect was attributable to the drug. The results showed that all the manifestations of the disease returned promptly when treatment was discontinued and that no lasting improvement could be obtained from short periods of medication. In subsequent cases (55) the treatment was continued for an arbitrary period of from six to eight months in dosages that maintained a normal or somewhat subnormal metabolic rate. During this period the patients remained free of symptoms and appeared normal in every way with the exceptions usually of continued eye signs where originally present, and thyroid enlargement in some cases. At some time during this period of treatment a spontaneous remission presumably occurs. Of twelve patients who have thus far completed such a course of therapy (55) and from whom the drug has been withdrawn, nine have remained symptom free for periods ranging from two to six months. As the effect of the drug subsides in

a few days after the last dose (35), it must be presumed that remissions occur. Since there is no experimental basis at present for assuming that thiouracil was responsible for the remissions it is more reasonable to suppose that the drug merely controlled the disease and maintained a state of health which permitted a spontaneous and apparently complete recovery to occur.

PSYCHOGENIC ASPECTS OF HYPERTHYROIDISM

The importance of psychic factors in the etiology of hyperthyroidism has already been mentioned. There is, moreover, evidence to indicate that thyrotoxicosis is essentially a biphasic disorder - one phase the result of cellular metabolic changes produced by thyroid hormone in excessive amounts; and the other a more fundamental etiologic process related perhaps either to the pituitary or autonomic nervous system or both.

It is well established, for example, that thyrotoxicosis may recur in the same individual even after several partial thyroidectomies each of which may give some degree of temporary relief. It is also known that symptoms of this condition may be retained even after subtotal thyroidectomy or thiouracil has reduced the BMR to within normal limits. Moss (59) has cited similar cases in which amelioration of symptoms did not occur with reduction of the BMR until psychotherapy had been instituted. From examples such as these it would seem that control of the cellular metabolic abnormality alone does not always suffice to produce a cure so long as the fundamental underlying etiological

factors remain unchanged and the body is unable to cope with them.

An attempt to present an outline of the role of psychic factors in hyperthyroidism has been made by Moschowitz. (60) He conceives of a constitutional type in whom there develops an exaggeration of normal body function (elevated BMR) with subsequent morbid anatomic changes which become fixed as hyperthyroidism. His picture of the hyperthyroid diathesis is that of a shy introverted person, very sensitive and responsive to his environment, tending to be of the manic-depressive type. The person is physically and mentally quick but also tires quickly. Most of the patients studied had a childhood history of unsuccessful family adjustment, and an inability to adjust to an adult environment due to overprotection in early life. There was frequent escape from realities. All the patients showed sexual difficulties of one sort or another. The onset of the disease in this constitutional type is ushered in by a severe psychic insult for which the patient is unprepared. Fear is an essential ingredient to this insult. Exophthalmic goiter, from this viewpoint, may then be considered as an incident in the life history of a personality disorder associated with emotion and due to an acute panic state. (59) Thus, the physician must consider the ability of the patient to meet the stresses of his daily life in the environment to which he returns after the thyroid aspects of the disease are controlled. Psychotherapy may be of importance in these cases if a lasting cure is to result.

It has already been noted that in those cases in which remissions have continued after cessation of thiouracil therapy, the patients had been maintained at a normal metabolic rate for long periods of time (6-8 mos.) before the drug was withdrawn. In the absence of any evidence of a return of the disease when the drug is discontinued it must be concluded that some change in the endocrine system has taken place which has permitted the patient to return to a normal physiological state. It is not known with certainty what pathologic changes cause hyperthyroidism and it is impossible to say whether thiouracil treatment modifies the cause of the disease. It is possible, however, that the disturbing effects of hyperthyroidism contribute to the maintenance of the disease, and that only if thiouracil is continued long enough will it provide a sufficient interval during which recovery can take place. If the etiological factor is indeed psychic trauma as suggested above, a combination of thiouracil for immediate control and psychotherapy for etiological control may prove to be the ideal method of treatment in terms of permanent results.

A number of important questions still remain to be answered regarding the effect and clinical usefulness of thiouracil, especially with respect to its prolonged use for the medical treatment of hyperthyroidism. For example

1. The possibility of late toxic effects following prolonged use of this drug cannot at present be eliminated. It is possible for example that depression or exhaustion of the bone marrow may follow prolonged ingestion of this drug in some cases.

2. What undesirable dislocations of endocrine relationship may be induced by prolonged inhibition of thyroid hormone production and the consequent disturbance of the thyroid-pituitary balance? Is there a possibility that hyperfunction of the pituitary might eventually be produced, or that pituitary exhaustion might ensue? With regard to this point it may be recalled (32) (34) that the drug, after absorption, is found in largest amounts in the thyroid, pituitary, adrenals and bone marrow.

3. Is it possible that the maintenance of a chronically hyperplastic state of the thyroid might be followed by fibrosis, or atrophy, or neoplastic change?

4. How long must cases remain under treatment before a permanent cure is effected?

5. Could the therapeutic response in thyrotoxicosis be enhanced by the coincidental use of anti pituitary agents such as estrogens, etc?

The observation of many more cases over a much longer period of time is necessary before these questions can be answered and before the usefulness of thiouracil in the medical treatment of hyperthyroidism can be ultimately evaluated.

TOXIC REACTIONS RESULTING FROM THE CLINICAL USE OF THIOURACIL

Since the extended use of thiouracil will depend chiefly on whether its beneficial effects can be obtained without incurring undue risk as a result of its toxic action, a careful evaluation of this point is primary to any consideration of the problem as a whole. McGavack and his co-workers (38) have collected one hundred thirty-five cases treated with thiouracil by various investigators (all cases reported up to that time) and reviewed them in relation to toxic symptoms. The results of their findings are given below:

Sixteen of the one hundred thirty-five patients developed toxic reactions. The majority of these have involved the hematopoietic system.

1. Agranulocytic angina was reported in two patients.

2. Leukopenia and relative lymphocytosis - six patients.

It was felt that this complication does not warrant complete cessation of therapy but that such responses may perhaps be considered an indication for temporary or permanent decrease in the size of the dose used, since in three cases the reaction subsided without interrupting the treatment.

3. Fever - This was the chief toxic manifestation in four of the cases. The common association of urticarial skin rashes, the fluctuant nature of the fever, and the smallness of the total dose received (less than 5gm.) led to the conclusion that such reactions are probably more in the nature of a true sensitivity than the end result of a cumulative toxic reaction.

4. Diarrhea - reported as the only toxic manifestation in one patient.

5. Slight pitting edema with elevation of the serum Cl and decrease in CO_2 combining power - two cases. This disappeared without discontinuing therapy.

6. Swelling and tenderness of the submaxillary gland - one case. Therapy was not discontinued.

7. Urticarial rashes, usually associated with fever and a leukopenia appeared in five cases. In only two cases was the drug stopped, however.

8. Mild jaundice. This was described in one case following twenty days of therapy, 0.8gm. thiouracil being taken daily. The reaction subsided completely within ten days after the drug was stopped and no interference with liver function could be detected.

9. Hematuria - (microscopic) - one patient.

From these results it appears that some form of toxic reaction has been observed in 16 or 11.8% of 135 patients who have received thiouracil for the treatment of thyrotoxicosis. No fatal complications were found but two of the patients were severely ill. Eight of the reactions reported were very mild and seven were not considered sufficiently severe to justify the interruption of therapy.

Astwood (55) in an analysis of sixty-two cases not included by McGavack et al, reported about 10% showing major toxic effects. Each of these reactions came early in the course of therapy. He reported no evidence of chronic toxicity to date. The complications seen included

1. Agranulocytosis - one case. This patient had a history of previous sensitivity to other drugs.

2. Marked leukopenia - one case.

3. Febrile reactions - four cases, two of which were severe.

Astwood suggests on the basis of his observations that the best indication of impending danger of toxic reactions are the subjective sensations of the patient and the body temperature although routine white counts are also important.

Of fifty-two patients treated by Moore and his co-workers (53) and not included in McGavack's series, two cases of leukopenia, four oral infections possibly related to the drug and one case of generalized lymphadenopathy were reported. In two patients the development of a fever was associated with sensitivity to the drug.

Rose and McConnell (49) reporting on thirty-seven cases noted untoward reactions attributed to thiouracil in eight patients, the most important complication being severe leukopenia associated with pharyngitis and fever, which was observed in two cases. ← Therapy was eventually successfully resumed with small doses. In addition fourteen other patients, whose white blood counts were within normal limits prior to therapy, showed a fall to below 5000 within 4 to 55 days after the drug was begun. In six of these patients the white count returned to normal levels despite continuation of therapy. Other toxic manifestations noted were:

1. mild maculopapular facial eruptions - two patients.

2. urticaria - two patients.

3. myalgia and anorexia - one patient.

4. pruritis - one patient.

The authors advise that patients who develop urticaria or any other allergic manifestation be carefully observed when therapy is resumed since other sensitivity phenomena may result.

Of the various complications encountered with thiouracil the only one to cause appreciable concern is agranulocytosis. Not only has this been reported by a number of investigators (37) (38) (55) (61) (62) (63) but it has also been implicated in three deaths.

Himsworth (64) has reported one fatal case of agranulocytosis occurring during thiouracil therapy but details as to total dosage and duration of treatment were not given.

A second case was reported by Kahn and Stock (65). Their patient, a diabetic, received a total dosage of 30.8gm. in 54 days. In this case, the white blood count dropped to 1100 accompanied by the appearance of a rash and pharyngitis. Despite intensive treatment, the patient died in a diebetic coma five days after the onset of the symptoms. In this case there seems to be little doubt that the diabetes was contributory.

The third case, reported recently by Ferrer, Spain and Cathcart (66), was that of a seventy year old male who had received 113.6gm. of the drug in 128 days, an excessive dosage by present standards.

Rubinstein (63) following a case of thiouracil agranulocytosis by serial bone marrow studies, was able to show that the cause of the agranulocytosis was arrest of maturation associated with hypoplasia of the myeloid elements of the bone marrow. On discontinuing the drug, complete hematological recovery followed, the bone marrow recovery preceding that of the peripheral blood.

Since the marrow has been demonstrated to contain a relatively high thiouracil concentration, and since the white cells contain a much higher concentration than the red cells (35) this predilection of thiouracil for the white cells and the bone marrow may well be the reason why the myeloid elements of the marrow are affected. Since agranulocytosis is only an infrequent complication, it is not at all unlikely that a certain specific sensitivity to the drug must probably also be present for this complication to occur.

Summary

There remains little doubt that thiouracil can effectively block the synthesis of thyroid hormone. Administered to hyperthyroid patients the value of such therapy is obvious. Advantages over other forms of therapy include the avoidance of surgical operation, the reproducible nature of the response, the lack of any evidence of the development of tolerance or refractiveness, and the ease with which the metabolic rate can be controlled at any desired level.

The main disadvantage of thiouracil therapy is the occurrence of toxic reactions in a small percentage of cases. The use of small doses as now practiced may help to reduce the incidence or severity of such reactions. As thiouracil is only one of a number of active compounds it is quite likely that equally effective though less toxic substances will eventually be discovered.

Dangerous toxic reactions are apparently quite rare; the more common reactions may be such that treatment has to be discontinued but in such instances nothing has been lost. The subsequent response to iodine remains unaffected and surgery can be

performed when necessary without added danger. In many cases, it has been possible to continue therapy despite reactions, by decreasing the dosage, the blood picture and the patient being carefully followed. In others, cessation of the drug at the first signs of a reaction, followed by continuation of therapy a few days later has been successful. It is probably wise to give thiouracil with great care to any patient known to have any allergic symptoms. It is not unlikely that the more serious side - effects resulting from the drug could probably be avoided if the patients were instructed to seek medical advice as soon as abnormal symptoms are experienced.

THIOURACIL AS AN AID IN THE PREOPERATIVE PREPARATION FOR THYROIDECTOMY

The preparation of the thyrotoxic patient for thyroidectomy has undergone a gradual evolution in the attempt to bring the patient to surgery in as nearly a normal state as possible. The ideal preoperative preparation would be a regimen of therapy which would so modify the underlying metabolic abnormality as to bring the patient to the surgeon with no evidence of thyrotoxicosis, allowing removal of the gland and permanent relief without subjecting the patient to the hazards of surgery while thyrotoxic. Bed rest alone, with adequate sedation, accomplished a minimal but significant change in this direction. The introduction of the use of iodine for this purpose by Plummer in 1923 (67) marked an important advance and was followed by a marked decrease in operative morbidity and mortality. The next period of thyroid surgery

was chiefly devoted to improvement in surgical technic. However, the fundamental problem still remained of a patient undergoing operation suffering from a metabolic abnormality greatly aggravated by the physiologic stress and local manipulation incident to thyroidectomy.

The complications of thyroidectomy are divisible into three main groups: those related to surgery in general, such as hemorrhage and sepsis; those related to the peculiar anatomical relationships of the thyroid gland, such as nerve or parathyroid injury; and lastly, those which stem from the pathologic physiology of thyrotoxicosis, chiefly storm and postoperative thermal reactions. With competent surgery and asepsis, dangers from the first two of these groups can be minimized. The discovery of the anti-thyroid action of thiouracil and of its effect in reducing the metabolic rate led at once to the hope that this drug would be useful in the preparation of the thyrotoxic patient for surgery and in the control of complications incident to this condition (i.e. storm and post operative thermal reactions)

A survey of the literature has revealed some 121 cases where thiouracil has been used preparatory to thyroidectomy.(see table above P. 22) From these data the following conclusions can be drawn:

1. Thiouracil is superior to iodine as a preparation for thyroidectomy because, regardless of the degree of elevation of the metabolic rate prior to therapy, it will bring the patient to operation with a normal metabolic rate. In a series by Moore et al (53) the preoperative metabolic response to thiouracil was found to differ strikingly from iodine in that iodine treated cases showed a downward shift in metabolic rate averaging about

twenty-five points, whereas adequate thiouracil preparation reduced the rate to normal. With iodine, there was no regularity of response.

2. The histologic change accompanying the decrease in metabolic rate is an intensification of the hyperplasia seen in thyrotoxicosis. Thiouracil produces an hyperplastic but non functioning goiter.

3. Preliminary, or concomitant, iodine administration delays the thiouracil response.

4. Toxic reactions occasionally occur.

5. The operative course in thyrotoxic patients treated preoperatively for five or six weeks with thiouracil was remarkable only for its smoothness. They reacted as would patients with a normal metabolism to a moderate surgical procedure, with no marked changes in pulse or blood pressure. The postoperative course was equally smooth and uneventful. (54)

6. From the viewpoint of anesthesia, the induction and maintenance of these patients is like that of any patient with a normal metabolism. Only average amounts of preoperative sedation are necessary. Cyclopropane and oxygen anesthesia has given excellent results. (54)

7. Those thyrocardiac patients which have come to operation after preoperative preparation with thiouracil have done very well. The absence of severe postoperative reactions has helped materially in making their final recovery smooth and rapid. (53)(54)

8. The preoperative use of thiouracil in severe hyperthyroidism shortens the time of treatment, reduces the hospital stay, and limits the procedure to a subtotal thyroidectomy. (56)

The one disadvantage of thiouracil in the preparation of

patients for surgery lies in the fact that the hyperplasia resulting with this drug is usually accompanied by an increased vascularity and friability which makes the gland more difficult to handle and renders hemostasis arduous. (53) (68) This difficulty has been solved, however, by the use of a short period of iodine therapy to involute the gland following reduction of the metabolic rate with thiouracil. The Lahey Clinic has now operated successfully on several hundred cases following this routine. (57) (68) (69)

Thiouracil Dosage in Preoperative Preparation

The preoperative preparation of thyrotoxic patients with thiouracil is considerably more simple than with iodine. Clute and Williams (54) have suggested the following routine. The patient is started on thiouracil in doses of 0.2gm. three times a day at about eight hour intervals. Within a day or two the patient is usually sent home to take 0.4 or 0.6gm. thiouracil a day. The patients are permitted to carry on their usual work but requested to return at two week intervals for a check-up metabolism and blood test. Patients are treated for about five weeks preceding thyroidectomy and for about four to six days postoperatively. During the preoperative period, the patient is given thiamin chloride, 5mg. daily, and urged to eat food containing much carbohydrate and protein.

Future Indications for Surgery

Until more adequate information on long term thiouracil therapy is available, the following future indications for thyroidectomy have been suggested. (54) These are based on the assumption that hyperthyroidism can be fully controlled by the use

of this drug.

1. Patients with a very large goiter.

2. Patients who live in isolated areas and cannot readily have the frequent check up examinations required during thiouracil treatment.

3. Patients who through ignorance or temperamental difficulties cannot be depended upon to carefully follow medical treatment.

4. The small number of cases who have undesirable reactions to this drug.

A SUMMARY OF THE POTENTIALITIES OF THIOURACIL IN MEDICINE

1. Thiouracil vs operation in hyperthyroidism

Whether thiouracil will prove to be a satisfactory substitute for the surgical treatment of diffuse toxic goiter cannot at present be stated due to limited experience with this form of therapy. The chief advantages of treatment with this agent would seem to lie in the possibility of controlled suppression of thyroid hyperactivity and in the ready reversibility of the effect of this drug. This would seem preferable to subtotal thyroidectomy with its inherent dangers of post-operative myxedema and residual or recurrent thyrotoxicosis, entirely apart from the ordinary surgical risk involved.

2. Thiouracil promises to be of great value in cases in which operation is inadvisable or contraindicated. These include:

a. Cases in which exophthalmos is prominent and there is danger of malignant exophthalmos following surgical removal. (37)

b. Cases with severe hypertension.

c. Cases who have psychotic tendencies. (55)

d. Cases in thyrocardiacs. (54)

3. Cases of persistent or recurrent toxicity after thyroidectomy may be controlled with this drug. One such case with complete remission after cessation of therapy has now been followed for seven months. (45) Clute & Williams (54) have reported fifteen such cases, some having been subjected to two or three operations without results, all of whom have responded satisfactorily to thiouracil.

4. Thiouracil combined with X-ray therapy.

The effectiveness of thiouracil in causing a remission of the acute symptoms of thyrotoxicosis has suggested a combination of this therapy with irradiation of the gland as a substitute for the usual procedure of administration of iodine followed by thyroidectomy. Two cases so treated gave good results. (48)

5. Thiouracil as a therapeutic test

This drug has proven valuable as a means of determining the presence of thyrotoxicosis in the so-called cases of "apathetic" or "marked" hyperthyroidism in which the evidence for the existence of a thyrotoxic state although suspected, is insufficient to warrant surgical interference. The difficulty of proving the existence of thyrotoxicosis in such patients is well known for they often present an atypical clinical picture of some other type of disease such as organic heart failure, gastro-intestinal disorders, psychoneurosis, (NCA especially) etc. Remission of symptoms or lack of response to thiouracil may aid the diagnosis. (48)

6. Preoperative treatment with thiouracil is becoming a recognized therapeutic procedure. It is of especial value in:

a. Cases where iodine therapy has had little or no effect on the basal metabolic rate.

b. Cases who because of the severity of their hyperthyroidism are unusually poor surgical risks.

c. Cases of similarly high surgical risk because of complicating conditions added to severe hyperthyroidism.

So-called adenomas of the thyroid as a rule war-

rant surgery whether they are toxic or not. Formerly, their toxicity was feared as it did not respond satisfactorily to iodine. Thiouracil acts as readily in adenomas as it does in the diffusely hyperplastic gland although the former are not as quickly controlled. (55) Despite this fact, these tumefactions still remain as a possible mechanical problem, and as the precursor of a cancerous lesion which develops in about 3.7% of all nodular goiters. Therefore, it seems wise to reserve thiouracil only for preoperative preparation in such cases rather than to undertake medical treatment alone.

7. Thiouracil has advantages over iodine in the preoperative management of thyrotoxic patients.

a. It can be used in patients who either do not tolerate iodine or do not respond.

b. Patients who are mishandled by too prolonged administration of iodine can be adequately prepared for surgery with thiouracil.

c. In the average case, neither intolerant nor irresponsive to iodine, an important advantage is seen in the fact that with the use of adequate thiouracil therapy the thyroid function can be decreased to the desired normal or even hypothyroid level. In contradistinction, the BMR in moderately severe or severe cases of thyrotoxicosis cannot as a rule be reduced to entirely normal levels with iodine and patients have to be operated upon in a more or less mild thyrotoxic condition. The operative and postoperative course is smoother and less dangerous if thyroid function has previously been depressed to normal. (53)

8. The drug promises to be of special value in the thyrocardiacs. This group represents the patient carrying the worst surgical risk. These are usually patients in the older age-group, in whom the limited cardiac reserve of age has been completely absorbed by the excessive cardiac load of thyrotoxicosis and in whom therefore the added burden of operation is prone to initiate serious decompensation. In such cases much is to be gained by reducing the BMR to normal before operation.

9. The possibility of thyroid enlargement under thiouracil therapy has already been mentioned. Whether individuals with very large goiters may experience a further growth of the gland with resulting pressure symptoms is still controversial. Sufficient data is not yet available to indicate whether this is a real danger.

10. At present the chief objection to the use of this drug is the possibility of toxic and allergic manifestations. There is good indication that the present use of decreased dosage combined with careful observation of the patient will limit the severity of these reactions to a minimum.

BIBLIOGRAPHY

1. MacKenzie, J. B., MacKenzie, C. G., and McCollum, E.V., Effect of Sulfanilylguanidine on the Thyroid of the Rat, Science, 94: 518, 1941.

2. MacKenzie, J. B., and MacKenzie, C. G., The Effect of "Sulfa" Drugs on the Thyroid Gland in Rats and Mice, Federation Proc., 1: 122, 1942.

3. Kennedy, T. H., and Purves, H. D., Studies on Experimental Goitre. I. The Effect of Brassica Seed Diet on Rats, Brit. J. Exper. Path., 22: 241, 1941.

4. Griesbach, W. E., II. Changes in the Ant. Pituitary of the Rat, Produced by Brassica Seed Diet, Brit. J. Exper. Path., 22: 245, 1941.

5. Griesbach, W. E., II. Kennedy, T. H., and Purves, H. D., III. The Effect of Goitrogenic Diet on Hypophysectomized Rats, Brit. J. Exper. Path., 22: 249, 1941.

6. Kennedy, T. H., Thio-ureas as Goitrogenic Substances, Nature, London 150: 233, 1942.

7. Richter, C. P., and Clisby, K. H., Toxic Effects of Bitter Tasting Phenylthiocarbamide, Arch. Path., 33: 46, 1942.

8. MacKenzie, C. G., and MacKenzie, J. B., Effect of Sulfonamides and Thoureas on the Thyroid Glandand Basal Metabolism Endocrinology, 32: 185, 1943.

9. Marine, D., Rosen, S. H., and Spark, C., Effect of Iodine and Desiccated Thyroid on the Ant. Pituitary of Goitrous and Thyroidectomized Rabbits. Proc., Soc. Exper. Biol. and Med., 32: 803, 1935.

10. Sharpless, G. R., and Hopson, E. M., Cellular Changes in the Ant. Pituitary Gland of Rats and Experimental Goiter. Endocrinology, 27: 129, 1940.

11. Nelson, R. C., and Warkany, J., Changes in the Ant. Pituitary Gland of Rats and Experimatal Goiter. Proc., Soc. Exper. Biol. and Med., 39: 66, 1938.

12. Zeckwer, I. T., Davison, L. W., Keller, T. B., and Livingood, C. S., The Pituitary in Experimental Cretinism. I. Structural Changes in the Pituitaries of Thyroidectomized Rats. Am. J. M. S., 190: 145, 1935.

13. Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R., Action ofCertain Sulfonamides and of Thiourea on the Functi on of the Thyroid Gland, Endocrinology, 32: 210, 1943.

14. Astwood, E. B., The Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland. J. Pharmacol. and Exper. Therap., 78: 79, 1942.

15. Rawson, R. W., Tannheimer, J. F. and Peacock, W., The Uptake of Radioactive Iodine by the Thyroids of Rats Made Goitrous by Potassium Thiocyanate and by Thiouracil. Endocrinology, 34: 245, 1944.

16. Astwood, E. B., and Bissell, A., Effect of Thiouracil on the Iodine Content of the Thyroid Gland, Endocrinology, 34: 282, 1944.

17. Hughes, A. M., Cretinism in Rats Induced by Thiouracil, Endocrinology, 34: 138, 1944.

18. Hughes, A. M., and Astwood, E. B., Inhibition of Metamorphoses in Tadpoles by Thiouracil. Endocrinology, 34: 138, 1944.

19. Astwood, E. B., Bissell, A., and Hughes, A. M., Inhibition of the Endocrine Function of the Chick Thyroid, Federation Proceedings, 3: No. 1, March, 1944.

20. Mixner, J. P., Reineke, E. P., and Turner, C. W., Effect of Thiouracil and Thiourea on the Thyroid Gland of the Chick. Endocrinology, 36: 168, 1944.

21. Baumann, E. J., Metzger, N., and Marine, D., Mode of Action of Thiourea on the Thyroid Glandof Rabbits, Endocrinology, 34: 44, 1944.

22. Dempsey, E. W., and Astwood, E. B., Determination of the Rate ofThy roid Hormone Secretion at Various Environmental Temperatures. Endocrinology, 32: 509, 1943.

23. Rawson, R. W., Cortell, R. E., Peacock, W., and Means, J.H., The Effect ofThiouracil and Potassium Thyocyanate on the Thyroids of Animals and Man, Endocrinology, 35: 201, 1944.

24. Larson, R. A., Keating, F. R. Jr., Peacock, W., and Rawson, R. W., A Comparison of the Effect of Thiouracil and of Injected Thyrotropic Hormone on the Collection of Radioactive Iodine and the Anatomic Changes Induced in the Thyroid of the Chick, Endocrinology, 36: 149, 1945.

25. Larson, R. A., Keating, R. F. Jr., Peacock, W., and Rawson, R. W., The Effect of Thiouracil on the Collection of Radioactive, Iodine by the Thyroid of the Chick, Endocrinology, 36: 160, 1945.

26. Franklin, A. L., Lerner, S. R., and Chaikoff, I. L., The Effect of Thiouracil on the Formation of Thyroxine and Diiodotyrosine by the Thyroid Gland of the Rat with Radioactive Iodine as Indicator, Endocrinology, 34: 265, 1944.

27. Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Lerman, J., and Cortell, R. E., The Action of Thiouracil upon the Thyroid Gland in Grave's Disease, J. Clin. Endocrin. 4: 1, 1944.

28. Dempsey, E. W., Flourescent and Histochemical Reactions in the Rat Thyroid Gland at Different States of Physiological Activity, Endocrinology, 34: 27, 1944.

29. Wheeler, H. L., and Liddle, L. M., CLXIV. Researches on Pyrimidines: The Thio Derivatives of Uracil and the Preparation of Uracil in Quantity, Am. Chem. J. 40: 547, 1908.

30. Williams, R. H., Jandorf, B. J., and Kay, G. A., Methods for the Determin. of Thiouracil in Tissues and Body Fluids, J. Lab. and Clin. Med. 29: 329, 1944.

31. Paschkis, K. E., Treatment of Thyrotoxicosis with Thiouracil. M. Clin. North America, Nov. 1944, Phila. p.1362.

32. Williams, R. H., and Clute, H., The Absorption, Distribution and Excretion of Thiouracil andthe Importance of These Factors in the Treatment of Thyrotoxicosis, Endocrinology, 35: 200, 1944.

33. Williams, R. H., Kay, G. A., and Jandorf, B. J., Thiouracil. Its Absorption, Distribution and Excretion, J. Clin. Invest., 23; 613, 1944.

34. Williams, R. H., Further Studies of the Absorption, Distribution and Elimination ofThiouracil, J. Clin. Endocrin., 4; 385, 1944.

35. Williams, R. H., and Bissell, G. W., Thiouracil in the Treatment of Thyrotoxicosis. New England J. Med. 229: 97, 1943.

36. Williams, R. H., Weinglass, A. R., Bissell, G. W., and Peters, J. B. Anatomical Effects of Thiouracil. Endocrinology, 34: 317, 1944.

37. Williams, R. H., and Clute, H. M., Thiouracil in Thyrotoxicosis; Treatment of 72 Cases, N. E. Jour. of Med., 230: 657, 1944.

38. McGavack, T. H., Gerl, A. J., Vogel, M., and Schwimmer, D., The Treatment of 26 Thyrotoxic Patients with Thiouracil and a Review of Toxic Reactions in All (135) Reported Cases, J. Clin. Endocrinology, 4: 249, 1944.

39. Boyd, W., A Text Book of Pathology, Lea and Febiger, Phila., 4th Edition, pp. 735-742.

40. Best, C. H., and Taylor, N. B., The Physiological Basis of of Medical Practice, 1943, 3rd Ed., The Williams and Wilkins Co., Baltimore. pp. 1125-1148.

41. Textbook of Medicine, Cecil R. L., Editor, W. B. Saunders Co., Phila. and London, 6th Edition, 1944, pp. 1208-1214.

42. Astwood, E. B., Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. 122: 78, 1943.

43. Himsworth, H. P., Thyrotoxicosis Treated with Thiourea, Laucet, 2: 465, 1943.

44. Newcomb, P. B., and Deane, E. W., Thiourea Causing Granulopenia and Thrombopenia, Laucet, 246: 179, 1944.

45. Paschkis, K. E., Canterow, A., Rakoff, A. E., Walkling, A. A., and Taurish, W. J., Thiourea and Thiouracil in Treatment of Thyrotoxicosis, J Clin. Endocrinology, 4: 179, 1944.

46. Gabrilove, J. L. and Kert M. J., Sensitivity of Thiouracil, J. A. M. A., 124: 504, 1944.

47. Palmer, V., Hyperthyroidism and Thiouracil, Bull. School Med. Univ. Maryland 28: 125, 1944.

48. Grollman, A., and Gryte, C. F., The Use of Thiouracil in Thyrotoxicosis, J of Clin. Endocrinology, 4: 444, 1944.

49. Rose, E. and McConnell, J., Thiouracil in The Treatment of Thyrotoxicosis. Clinical Experience with 37 Cases, Am. J. Med. Sc., 208: 561, 1944.

50. Watson, C. M., and Wilcox, L. D., Thiouracil in the Treatment of Thyrotoxicosis, Canadian Med. Assoc. J., 51: 37, 1944.

51. McGregor, J. K., Thiouracil And Its Effects upon Hyperthyroidism, Canadian Med. Assoc. J., 51: 37, 1944.

52. Reveno, W. S., Thyrotoxicosis Treated with Thiouracil, J. A. M. A., 126: 153, 1944.

53. Moore, F. D., Sweeny, D. W. Jr., Cope, O., Rawson, R. W., and Means, J. H., The Use of Thiouracil in The Preparation of Patients with Hyperthyroidism for Thyroidectomy, Annals of Surgery, 120: 152, 1944.

54. Clute, H. M., and Williams, R. H., Thiouracil in The Preparation of Thyrotoxic Patients for Surgery, Annals of Surgery, 120: 505, 1944.

55. Astwood, E. B., Thiouracil Treatment in Hyperthyroidism, J. of Clin. Endocrinology, 4: 229, 1944.

56. Bartels, E. C., Thiouracil, Its Use in the Preoperative Management of Severe Hyperthyroidism. Preliminary Report, J. A. M. A., 125: 24, 1944.

57. Walker, H. V., Fellow in Surgery, Lahey Clinic, Boston, Mass. Personal Communication.

58. Astwood, E. B., Chemotherapy in Hyperthyroidism, Surgery 16: 679, 1944.

59. Moss, R. E., Department of Medicine, Mass. Memorial Hospital, Personal Communication.

60. Moschowitz, E., The Hyperkinetic Diseases, Am. J. Med. Sci., 206: 576, 1943.

61. Linsell, D., Agranulocytosis after Use of Thiouracil, Brit. M. J., 2: 597, 1944.

62. Cantor, M. M., and Scott, J. W., Effect of Vitamin B6 (Pyridoxine) in the Treatment of Leucopenia. Science, 100, 545, '44

63. Rubinstein, M. A., Agranulocytosis Following Thiouracil Administration, Am. J. Clin, Path., 14: 540, 1944.

64. Himsworth, H. P., Thiouracil in the Treatment of Thyrotoxicosis, J. A. M. A., 125: 1053, 1944.

65. Kahn, J. & Stock, R. P., Fatal Agranulocytosis Resulting from Thiouracil, J. A. M. A., 126: 358, 1944.

66. Ferrer, M. I., Spain, D. M., and Cathcart, R. T., Fatal Agranulocytosis Resulting from Thiouracil, J. A. M. A., 127: 646, 1945.

67. Plummer, H. S., Results of Administrating Iodine to Patients with Exophthalmic Goiter, J. A. M. A., 80: 1955, 1923.

68. Lahey, F. H., The Combination of Lugol's Solution with Thiouracil in the Preoperative Preparation of Patients with Toxic Goiter, The Lahey Clinic Bulletin, 4, 2, July, 1944.