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Status of thiouracil in treatment of hyperthyroidism

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THE STATUS OF THIOURACIL
IN TREATMENT OF HYPERTHYROIDISM

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INTRODUCTION

The state of hyperthyroidism has been recognized as a clinical entity for many years and with investigation into the possible causes of this condition the theory of thyroid hypersecretion opened an era of the first successful treatment of the condition which consisted of sub-total extirpation of the thyroid gland.

The theory of the cause of hyperthyroidism has become markedly more complex, the disease now being considered as a vastly more complicated hormonal imbalance than can be explained on a thyroid basis which has important neurologic and multiglandular associations. Basically, however, all successful forms of treatment have been aimed at, or have coincidentally produced the same effect in one way or another, namely, supression of the secretion of the thyroid gland.

The present-day management of hyperthyroidism centers about these two forms of treatment:

1. Sub-total ablation of the thyroid gland.
2. Anti-thyroid drugs.

The first group mentioned above is usually preceded by treatment with anti-thyroid drugs. Within the anti-thyroid drug group is a comparitively recent addition, thiouracil. It is the purpose of this thesis to draw tentative conclusions on the basis of reports in the literature concerning the question: "WHAT, TO DATE, IS CONSIDERED THE PLACE OF THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM, EITHER WITH OR WITHOUT THYROIDECTOMY?"

There are different schools of thought on the status of thiouracil because hyperthyroidism is not necessarily fatal. Occasional spontaneous remissions occur even in the absence of any treatment. This is also true because methods of treatment of hyperthyroidism, which are fairly successful, were already present before thiouracil was introduced. Consequently, the problem is to determine what the thiouracil-treated patient's chances are for a complete and lasting relief, what risk, inconvenience, and expense thiouracil-treatment subjects the patient to, and whether thiouracil is better for one type of case or another.

HISTORICAL REVIEW

In 1928 Chesney and co-workers (8) observed the development of goiter in rabbits which they had kept on a cabbage diet. They found on microscopic study of excised glands of these animals that they were histologically hyperplastic with decreased size of acini and with a complete lack of colloid. Associated with this histological picture was a decreased heat production and a decreased basal metabolical rate. Iodine was then administered to the cabbage fed rabbits causing a stepping-up of the metabolism and involution of the hyperplastic gland.

In 1930, Webster and Chesney (52) noted that administration of iodine to rabbits would prevent the goitrogenic effect of cabbage. Other members of the Brassica group, which cabbage belongs to, were also found to be goitrogenic by Marine (38) and he further noted that the goitrogenic powers were inversely proportional to its iodine content. The conclusion drawn, therefore, was that cabbage contained a substance that decreased the effective thyroxin and iodine in the thyroid gland, causing hyperplasia of the gland.

The most important constituent of the Brassica group were mustard oils which are isothiocyanates. Consequently the effects of isothiocyanates and their cyanide precursors were investigated. With acetonitrile, and chemically related compounds, Marine (38) produced hyperplasia of the thyroid gland and in some animals exophthalmus. Cyanogens were also assumed to be goitrogenic since goiters were developed in rats by feeding soy bean flour, a substance rich in cyanogens.

Further evidence that cyanide derivatives are goitrogenic is manifest by the frequency of goiter in hypertensive patients given thiocyanate treatment. Associated with marked hyperplasia and decreased colloid of the thyroid gland is an exophthalmus, lid lag, decreased blood iodine level and decreased basal metabolic rate, all of which return to normal when medication is stopped (6).

In 1941, Richter and Clisby (47)(48) found that when phenylthiocarbamide was administered to rats they developed marked hyperplasia of the thyroid gland and an exophthalmus.

Considering the relationship of the pituitary gland to thyroid secretion, Griesbach (21) studied the pituitary of rats that had been fed soy bean flour and found histological changes in the basophile cells similar to that seen after thyroidectomy. The pituitary was also seen to reflect the changes in the thyroid when rats were fed rape seed. The basophiles increased in number when thyroid hyperplasia occurred and the acidophilic elements accumulated when colloid storage occurred. From this he concluded that the thyrotropic hormone increase in the blood coincided with changes in the basophile cells.

Kennedy (28) and co-workers were able to show that in order for thyroid hyperplasia to take place the hypophysis must be intact. When hypophysectomy was performed the hyperplasia of the thyroid produced by a goitrogenic diet disappeared and colloid formation was not prevented by the diet.

About the same time MacKenzie and McCollum (36) noted that sulfaquanadine produced thyroid hyperplasia and hypertrophy in rats.

Sulfanilamide and thiourea produced similar changes. These effects were discovered coincidentally as the above investigators were studying the effect of these drugs on the coliform bacteria in rats.

Kennedy (28) then attempted to show a reaction of the goitrogenic agent in rape seed and thiourea. He suggested that this agent might be a derivative of thiourea. Allylthiourea was tested and found to produce goiter in rats, with changes in the thyroid gland and pituitary similar to those seen after the injection of rape seed.

It was in 1943 when the MacKenzies (35) and Astwood (1) simultaneously published their results on the mechanism of the production of goiter by sulfonamide and thiourea derivatives. They pointed out that these substances produced thyroid hyperplasia, a decreased metabolical rate and thyroidectomy changes in the anterior lobe of the pituitary. They further showed that iodine could not counteract these changes but that the changes could be prevented by thyroid administration or by hypophysectomy.

Astwood (2) then attempted to determine the chemical grouping responsible for the action of sulfonamide and thiourea derivatives. He also attempted to ascertain which substances were most effective with the least toxicity. He found two classes which were effective and these included one hundred six compounds. These were:

1. Derivatives of thiourea —

   thiouracil was the most effective.

2. Derivatives of aniline dies —

   these included the sulfonamides.

He noted that thiocyanates were active only in the absence of iodine and that organic cyanides were without effect.

To Astwood goes credit for first applying the newly discovered anti-thyroid drugs to the treatment of human hyperthyroidism.

THE EFFECT OF THIOURACIL ON THE ANATOMY OF THE THYROID GLAND

Gross Changes.

It is now generally conceded that thiouracil produces gross enlargement of the thyroid gland in some cases and a decrease in size of the gland in others. Gabrilove (16) reports that he has noticed a primary increase in the size of the thyroid in the early stages of treatment with later regression in size. In other patients he has noticed an immediate decrease in size. Astwood (3), on the other hand, states that there is less frequently a dimunition in size than is thought because the increased softening of the gland is frequently mistaken for decrease in size. There were, however, instances of actual decrease in size noted by Astwood. He further reports unquestionable enlargement in some cases. Riker and Wescoe (49) report that there are instances in which relatively large doses early in the course of treatment caused increase in size of the gland with symptoms of pressure and pain. In other cases the gland is decreased in size, especially after prolonged treatment.

Palmer (43) in her review of cases treated with thiouracil mentioned a group in which surgery was done because, if patients had previous colloid goiter which had become toxic, thiouracil caused no decrease in size after the thyroid had returned to its pre-toxic state. Also, it was found that the size of thyroid adenomata was not affected by thiouracil.

There is usually a softening of the gland after treatment is begun which is assumed to result from increased vascularity produced by the drug.

Changes in Histology.

The general picture of a microscopic section of the thyroid after administration of thiouracil is one of marked hyperplasia. The cells are taller than usual, frequently twenty microns high. They show a pale, granular cytoplasm with large vesicular nuclei occupying the center of the cell.

The acini have small lumina and occasionally papillary infoldings though they may have obliterated lumina. The colloid content of most acini is scarce. Some contain thin, stringy colloid.

Thin walled blood sinuses traverse the gland and when compared with normal gland, blood vessels are far more abundant in the thiouracil-treated gland.

There are occasional areas where cell outline is distorted and where there is extensive desquamation of cells especially at points of papillary infoldings.

In some instances the acini disappear entirely and extensive growth of follicle epitheluim form a contiguous cellular mass. This might suggest a danger of neoplastic changes though incidence of neoplasm resulting from the administration of thiouracil has not been reported.

There are occasionally small islands of lymphocytes present. Rarely one sees an accumulation of lymphocytes into lymph follicles though Means (41) describes an example of this after seventeen days of treatment with thiouracil.

Some maintain (20) that the thiouracil-prepared gland appears histologically like the gland of hyperthyroidism before the use of iodine, and also that it is similar to that of endemic goiter. Others (50) do not agree with this but notice that if the thiouracil-treated and the hyperthyroid or endemic goiter gland are compared the cells of the acini will not be as tall and their cytoplasm not as granular in the latter.

The length of time of treatment seems to effect the histology of the gland. Shirer and Cohen (50), for example, report the case of a sixty-seven year old white male patient who received .2 gram thiouracil three times daily over a period of seven months. This patient had a diffuse toxic goiter which developed after a left lobectomy had been done without relief of symptoms. The total dosage of thiouracil administered was 135 grams. The clinical results were relief of symptoms and a drop of the basal metabolic rate to minus three percent. Thyroidectomy was then done and microscopic findings revealed small and large acini, none of them definitely hyperplastic. Most of them were distended with colloid. The general appearance was that of involution. There were, however, yet small patches of hyperplasia representing the typical picture of a thiouracil-treated gland.

On the other extreme, a case is reported (50) where thiouracil was administered in dosage of .2 gram three times daily for only ten days before thyroidectomy was done and the histology of the gland studied. The patient was a thirty-one year old colored female with a diffuse toxic goiter. The total dosage of 6.6 grams produced a drop in basal metabolic rate from plus fifty-three to plus sixteen percent. The gland

showed a picture of marked hyperplasia with acini which frequently had no lumina. The cells were tall with pale cytoplasm and vesicular, centrally-located nuclei. The picture was that of a typical thiouracil-treated gland.

In the case (50) where iodine treatment followed treatment with thiouracil the result was a gland that resembled that of iodine effect alone. The patient was a thirty-nine year old white female who had a diffuse toxic thyroid. The basal metabolic rate at the onset of treatment was plus forty-nine percent. Iodine had been administered one and one-half years before. Thiouracil in dosage of .2 gram three times daily was given but resulted in development of a macular rash, fever and nausea within a short time. The drug was stopped but started again in five days with return of toxic symptoms. The patient was then put on Lugol's solution. In four days the basal metabolical rate was down to plus twenty-five percent and operation was performed. Histologically, the gland differed only slightly from that of the iodine-prepared gland being somewhat more vascular and friable. It is questionable whether thiouracil was administered long enough to produce the thiouracil effect on its histology. A latent period has been described by several investigators which will be discussed later.

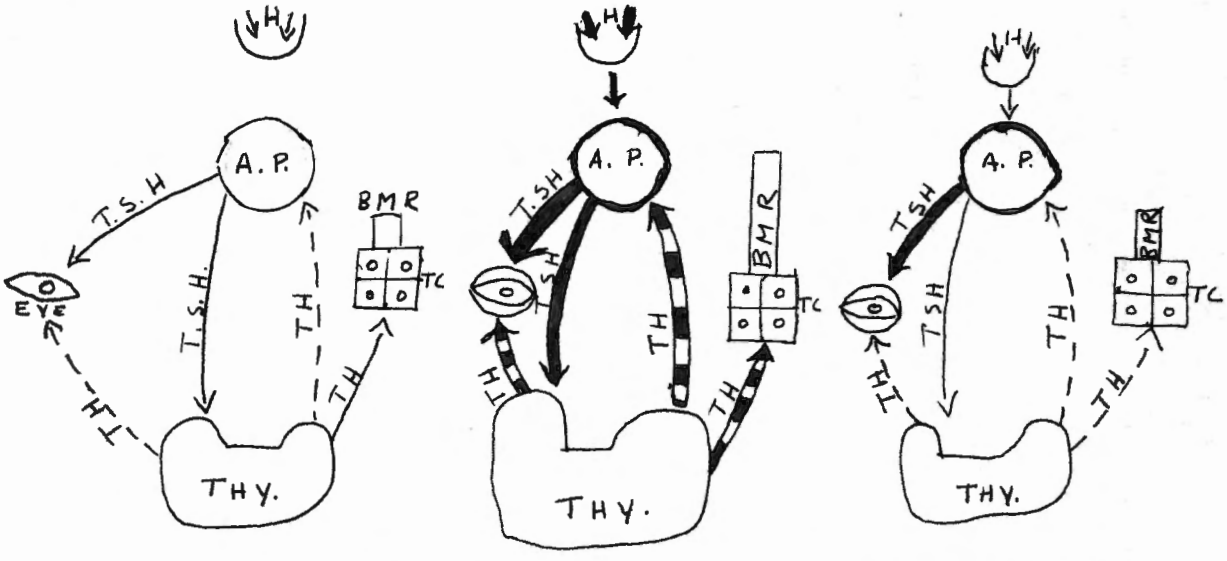
Just what the relations are between the histological features of the gland and clinical condition of the patient is yet a matter of much debate. Graham (20) maintains that occasionally the clinical condition and histology of gland are hard to correlate. One must take into consideration the duration of the disease, previous iodine treatment,

the natural history of remissions and relapses and varying degrees of severity of the hyperthyroidism. Even the untreated gland may show various of the changes described above. The knowledge that the human thyroid may undergo a cycle of hyperplasia and involution (the Marine cycle) must be kept in mind. Also in man, the thyroid gland having passed through a varying number of cycles, depending on the stage of the disease, may be resistant to induced changes. There may also be several adenomata and foci of non-responsive thyroid tissue present.

MECHANISM OF ACTION OF THIOURACIL

It has previously been inferred that the state of hyperthyroidism is not simply one of hyper-secretion of the thyroid gland but that there are multiglandular associations. Certainly the pituitary gland must be intimately related to this dyscrinism.

Means (40) in his study of the physiology of the thyroid gland has gone to great effort to describe a so-called "pituitary-thyroid axis" and has explained the equilibrium that exists between the two glands both normally and in hyperthyroidism. The diagrams below adequately illustrate his theory.



Normal Relations | Graves' Disease | Exophthalmus with Minor or no Hyperthyroidism

Although thyroxin is increased in Graves' Disease, it exerts its main effect on the tissue cells and less effect on the anterior pituitary and the eye. (AP - anterior pituitary; TC - tissue cells; H- hypothalamus; TSH - thyrotropic hormone; THY - thyroid gland; TH - thyroxin).

Hertz and Roberts (23) concluded after giving thyrotropic hormone to rabbits that it causes initial stimulation of the thyroid cells to collect iodine and if iodine is not sufficient there is exhaustion of the thyroid with resulting loss of its capacity to collect iodine. Contrary to this finding Astwood and Bissell (5) report that the only noticeable effect which appeared when rats were fed the thyrotropic hormone was hyperplasia of the thyroid gland. The gland contained an almost normal amount of iodine. Extirpation of the pituitary was found to hinder the ability of the thyroid to re-accumulate iodine after its store had been depleted. They also showed that thyroxin injection caused an appearance of the histology of the thyroid similar to that seen in hypophysectomy. It was concluded that under certain conditions the administration of thyrotropic hormone promotes iodine uptake and storage by the thyroid gland. Absence of the thyrotropic hormone, however, hinders the ability of the gland to re-accumulate iodine after its depletion.

After administration of thiouracil to rats it was observed (45) that the thyroid took up about ten percent of radio-active iodine on the average as compared with an average of fifty-six percent uptake in the normal gland. However, if the animals were treated with both thiouracil and thyroxin, the gland would lose about fifty percent of their iodine content but still more than those treated with thiouracil alone.

It was on the basis of the above mentioned observations that the theory (43) that thiouracil exerts its action by causing a block to the uptake of iodine was devised. The theory suggests that the thyroid is made refractory to iodine. It further assumes that thiouracil does

not act locally on the thyroid gland. If this were true one would expect the thiouracil-treated gland to appear histologically like one of simple iodine deficiency which is not the case. Furthermore, if thiouracil causes a local block to synthesis and delivery of the thyroid hormone, the line of reason continues, clinical feeling of improvement in patients would follow a decrease in the circulating thyroxin. Though the level of the circulating thyroxin when this feeling of improvement occurs has not been ascertained, the basal metabolic rate is yet up when this begins. Instead of a local block then, following this reasoning, thiouracil acts as a tissue cell depressant which exerts its effects first on the most delicate structures, that is, tissues in which there is a constantly shifting dynamic equilibrium as in the pituitary and the adrenals.

In considering the thyroid effect of thiouracil the MacKenzies (35) in 1943 proposed the following mechanisms as possibilities:

1. Retention of thyroxin by the thyroid gland;
2. Elevation of tissue requirements for thyroxin, (eg) through the inhibition of some enzyme system;
3. Destruction or inactivation of the circulating hormone;
4. Depression of the rate of thyroxin formation.

They suggested that results of animal experimentations favored the latter possibility. Astwood (2) was convinced that there must be such an interference with the production of thyroid hormone. This was based on the fact that presence of pituitary was found to be essential for the production of thyroid hyperplasia with thiouracil and the other goitrogenic drug administration. In hypophysectomized animals, administration

of anti-thyroid drugs produced no change in histology. Furthermore, concurrent feeding of whole pituitary powder and anti-thyroid drug in the hypophysectomized rats caused a maintenance of a normal histologic picture with little evidence of thyroid stimulation.

Subsequently, it was (19) hoped to show that there was increased blood and pituitary content of thyrotropic hormone in anti-thyroid drug administration but it was found to be actually somewhat decreased. It was maintained, however, that this does not necessarily contradict the concept of an increased thyrotropic activity in drug-treated rats but may rather indicate an increased utilization and a resultant inactivation of thyrotropic hormone by an enlarging thyroid gland.

Proof (26) that stimulation of the thiouracilized thyroid is caused by thyrotropic hormone is shown by the fact that the thyroid of animals treated with thiouracil showed an increased oxygen utilization in vitro. This increased oxygen utilization could be increased further by previous treatment of the animals with both thiouracil and thyrotropic hormone.

This is consistent with anatomical findings of more severe hyperplasia of the thyroid in animals given both thiouracil and thyrotropic hormone rather than one alone (48).

On the basis of the foregoing (48) it is concluded that in anti-thyroid drug administration there is an increased thyrotropic hormone activity not due to direct action of the pituitary but it may be looked upon as a "reflex effect".

That the hypothyroid state resulting from the administration of anti-thyroid agents is not produced by inhibition of the action of the thyroid hormone is suggested by the fact that the goitrogenic property of any of the anti-thyroid drugs could be abolished by exogenous thyroxin (1)(2). The metamorphosis of tadpoles (25) produced by injection of the thyrotropic hormone could be inhibited by thiouracil while that produced by thyroxin could not.

This would suggest that the synthesis of the thyroid hormone is actually inhibited. Malkiel (37) attempted to prove this beyond a doubt by taking a number of mice and dividing them into four groups into which he injected: Group I - thiouracil and thyroxin; Group II - thiouracil; Group III - thyroxin. Then he injected twice the M.L.D. of acetonitrile in those that had received thiouracil alone. All mice died in Group II. There was no mortality in the remaining groups.

The interference of the synthesis of thyroxin in the thyroid gland subsequently activates the pituitary which elaborates an increased amount of thyrotropic hormone. This results in ineffectual hyperplasia of the thyroid.

In an attempt to explain the mechanism by which synthesis of thyroxin is prevented by administration of goitrogenic drugs, Franklin and Chaikoff (12) first demonstrated that sulfanilamide inhibited the conversion of iodine to di-iodo-tyrosine and thyroxin. Bauman and Metzger (7) showed a rapid loss of both thyroxin and non-thyroxin iodine from the thyroid in animals treated with thiourea. Even if iodine and di-iodo-tyrosine were administered, they had no effect and excess iodine was

promptly excreted in the urine. Glands made hyperplastic by administration of the thyrotropic hormone showed no loss of iodine while those treated with thiouracil did (5).

Confirmation of these findings was accomplished by injection of radio-active iodine into rats as has been mentioned previously (45). It was shown that rats fed the goitrogenic drugs showed a decreased concentration of radio-active iodine of any form in the thyroid (29) and that thiouracilized rats showed decreased incorporation of the injected radio-active iodine into di-iodo-tyrosine and thyroxin (13). When thiouracil was withdrawn the amount of radio-active iodine converted to thyroxin increased with time.

That the hyperplasia of thyroid tissue produced by administration of the thiouracil and by the thyrotropic hormone was quite similar was also noted by radio-active iodine studies. The gland, after withdrawal of thiouracil showed ability to concentrate iodine in amounts comparable to that of thyrotropic hormone-stimulated hyperplasia (30).

ABSORPTION, DISTRIBUTION AND ELIMINATION

Thiouracil is rapidly absorbed from the gastro-intestional tract. In rats, more than eighty percent of a single dose disappeared from the gastro-intestinal tract within two hours after administration. In man the drug was present in the blood fifteen to thirty minutes after oral doses of .1 to 2 grams were given (56)(57). It is assumed that essentially all of the drug not appearing in the urine was broken down in the body or in the gastro-intestinal tract. The amount destroyed varies with the size and frequency of dosage, the amount of intake of fluids, the rate of absorption from the gastro-intestional tract, the kidney function and perhaps unknown factors. The amount destroyed in the gastro-intestional tract, when it is injected, is roughly equal to the amounts excreted in the urine within thirty minutes after its injection intravenously. Destruction is apparently very rapid when the concentration of thiouracil in the body is high but much less rapid when the content is low.

After a single dose, peak concentrations of the blood are reached within fifteen to thirty minutes. Following about thirty minutes there is a gradual decline in the blood level until a complete disappearance occurs within forty-eight to seventy-two hours (56). A single dose ordinarily is .1 gram although frequently it is .2 gram. When .1 gram of the drug is given twice daily its concentration in the blood tends to be maintained at a higher level than when the same quantity is given in one dose and likewise the concentration is greater

when .1 gram is given four times daily than when .2 gram is given twice. Generally, the individual receiving small doses frequently maintains a higher concentration than those given large doses less frequently.

The concentration of the drug is seven to ten times greater in the blood cells than in plasma. The red cells collectively contain the greater amount of the drug though per cell, the leukocytes contain more than the red cells. Lymphocytes and granulocytes actively absorb the drug from the plasma solution.

Concentrations of thiouracil were found in all body fluids, including cerebrospinal, edema fluid, pericardial, chest, ascitic fluid, urine and milk. In breast milk the concentration was found to be three times that of whole blood which will later be considered when discussing thiouracil in pregnancy (56).

In the various tissue of the body thiouracil was found in large quantities in bone marrow, in the thyroid, in the ovaries and in the pituitary. The greatest concentration of the drug was in the bone marrow. Smaller amounts were found in the tissue of the adrenals, pancreas, kidneys, spleen, liver, testis, striated muscles, brain, heart, lung and prostate (56).

The fetuses of rats given .1 percent thiouracil in drinking water during pregnancy were found to contain significant quantities of thiouracil, usually about one-half the concentration of that in the mother. The placentae contained slightly greater concentration of thiouracil than the serum concentration of the mother. The small size of the

fetuses as well as the goiters attested to the physiological activity of the drug *in utero*.

The amount of thiouracil present in adenomatous portions of thyroid tissue was much greater than that in normal sections of the same gland.

Thyrotropic hormone administration was shown to decrease the amount of thiouracil stored in the thyroid but potassuim iodide given with thiouracil increased the drug storage.

Thiouracil is excreted chiefly in the urine. None has been found in stools. It appears in the urine of fasting man in small amounts thirty minutes after injection.. The normal amounts of urinary excretion occurs during the second hour and excretion declines to very small amounts in twelve to twenty-four hours. The amount excreted varies with daily dose though the precentage of total dose excreted is lower with large doses (56).

SIDE ACTIONS OF THIOURACIL

Hughes (25) reports that in over 700 microscopic sections made from essentially all the body tissues, there were no notable alterations except in the thyroid gland. Others fail to agree with him and have noted several side effects of the drug.

Griesbach (21) in experiments with the goitrogens previous to the discovery of thiouracil noted an increase in basophiles in the pituitarity of rats when thyroid occurred as a result of feeding rape seed. The acidophilic elements, on the contrary accumulated when colloid storage took place. The MacKensies (34) likewise reported the same change of structure of the pituitary following thiouracil and thiourea feeding to rats and noted that withdrawal of the drug from these animals resulted in a return of the basal metabolical rate and pituitary histology to normal.

Apparently the activity of the anterior pituitary is not limited entirely to thyrotropic hormone. Leathem (31) reports that the adrenal gland of rats treated with sulfonamides, thiourea and thiouracil were smaller than those from animals that received no treatment. This is presumedly due to increased activity of the adrenotropic hormone. No dysfunction of the adrenal has been reported.

Gonadotrope was similarly found to be increased in amount in the glands of thiouracil-treated rats (49).

The heart (32) of experimental animals showed atrophy of the myocardium following administration of thiourea. This is likewise seen

following thyroidectomy. Slowing of the heart with an increased tolerance to epinephrine by the myocardium has also been observed as a result of thiouracil administration (44). Thyroxin, on the other hand, caused decreased tolerance to epinephrine.

Riker and Wescoe (49) report hematuria and crystalline deposits of the drug in the kidney, ureters, and bladder after large doses of thiouracil in rats. Palmer (17) reports three cases of crystalluria produced by the drug but after subsequent simultaneous administration of sodium bicarbonate has noticed none.

Atrophic changes within the glomeruli and tubules of the kidney have been reported by Lebland and Hoff (32).

DOSAGE

Thiouracil has been administered in various dosages, ranging from 2 to 0.1 grams daily. It was soon decided that large doses are no more effective than small ones beyond a certain limit and the trend has been toward lower dosage. .6 grams seems to be about the optimum maximal dose though good results have been obtained with less. Astwood (4), on first using the drug, gave it in doses of .2 to 1 gram daily and found these amounts to be adequate in all cases. Gabrilove (16) gave 0.4 to 1.0 gram daily in divided doses for the first four weeks in the hospital. After discharge the patients received .1 to .2 grams daily.

At present two methods (49)(46) of effective dosage are most generally used:

1. a. 0.6 gram per day initially.
   b. Reduce to 0.1 to 0.2 gram daily after the basal metabolical rate is normal.
2. a. Initial dosage of 0.6 gram per day in three doses of 0.2 gram each.
   b. Reduce to 0.4 gram daily when the basal rate has dropped one-half the distance to normal.
   c. 0.1 to 0.3 gram daily when the basal rate is stabilized between plus five percent and minus ten percent.

To counteract the depressent effect on bone marrow, cevitamic

acid in dosage of one hundred milligrams per day and liver extract have been given concomittantly (43).

Multivitamim capsules have similarly been given with the rationale that the blood levels of thiamin and diphosphothiamin were below normal in thyrotoxic patients and that pyruvic acid level was elevated (54). Previously it had been noted that administration of vitamin B complex resulted in greater reduction of pulse rate, more rapid weight gain and a shorter pre-operative period (14).

As previously stated, sodium bicarbonate has been given with thiouracil in an effort to prevent the infrequent cases of crystalluria that occur when the drug is administered. This was given in dosage of 10 grams with each dose (43). There is some debate regarding the effectiveness in abolishing this complication in this manner (49).

THERAPEUTIC APPLICATION

Since the evaluation of the therapeutic effects of thiouracil depends on the response in symptoms and signs of hyperthyroidism, the recognition of these factors is important.

The classic symptoms which the patient with hyperthyroidism presents are goiter, tachycardia, exophthalmus and tremor. This quadrad is incomplete and inconstant and there are a vast number of other important symptoms and signs. It is not proposed to give a discussion of the diagnostic significance of these various complaints but rather it is to be pointed out that many characteristic symptoms may be absent in some patients with thyrotoxicocis although others may be present. Also, the incidence of symptoms is not always proportional to their diagnostic significance.

Williams (53) in his study of two hundred forty-seven cases determined the percentage incidence of the various symptoms that appear in hyperthyroidism. Nervousness was the most common complaint and occurred in ninety-nine percent of the cases. Hyperhidrosis occurred in ninety-one percent; hypersensitivity to heat in eighty-nine percent; palpitation in ninety-eight percent; fatigue in eighty-eight percent; weight loss in eighty-five percent; tachycardia in eighty-two percent; dyspnea in seventy-five percent; weakness in seventy percent; hyperorexia in sixty-five percent; eye complaints in fifty-four percent; swelling of legs in thirty-five percent; diarrhea in twenty-three percent; nine percent had anorexia; thirteen percent showed no loss in weight and two percent showed actual gain.

Likewise, on determining the incidence of physical signs in these hyperthyroid patients he discovered that all patients were found to have a degree of enlargement of the thyroid gland. The degree of enlargement varied from one-fifth to twenty-five times normal size. Tachycardia was likewise found in one hundred percent of the patients. The pulse rate was faster than eighty beats per minute in all cases. Skin changes characteristic of the disease were seen in ninety-seven percent of the patients; tremor in ninety-seven percent; bruit over thyroid in seventy-seven percent; eye signs of Graves' Disease in seventy-one percent; thyroid heart disease in fifteen percent; auricular fibrillation in ten percent; splenomegaly, gynecomastia and liver palms each in about ten percent of the subjects.

The ages of all cases reported treated with thiouracil ranged between the first and eighth decades. The majority of the cases was in the fourth decade. Females were by far more commonly effected with hyperthyroidism, the sex ratio being estimated usually about four to one or five to one.

The basal metabolical rate was elevated to a variable degree previous to treatment. The lowest rates preceding therapy reported were about plus fifteen percent and diagnosis on these cases was chiefly on the basis of physical signs and symptoms. Average basal rate in cases reported ranged from about plus twenty-five percent to plus fifty percent.

SYSTEM OF TREATMENT

In most patients treated with thiouracil hospitalization is apparently not necessary. However, this has seemed to depend largely upon the clinician who administers the drug and whether or not the drug is yet in an experimental stage with him.

Gabrilove (16) hospitalized his patients treated with thiouracil for a period of four to six weeks. Meanwhile he determined basal metabolical rate before treatment and at various stages during treatment. He further made renal and hepatic function tests before and after thiouracil; complete blood count two times weekly continued as long as patient received the drug; sternal marrow punctures at intervals during drug administration; determination of blood cholesterol levels before and after; determination of circulation time; electrocardiograph studies and measurements of neck size and degree exopthalmus once weekly.

Palmer (43) maintained hospitalization until the basal rate had undergone a sustained fall and then allowed the patient to return home if he were willing to come back for weekly check-ups. It was also insisted upon that the patient be on a "small" maintenance dose and that there was no trend toward toxic reactions before release. During hospitalization, uninalysis and white cell count were performed every other day and weekly blood chemistry tests were done.

Many of Williams' (47) series of two hundred forty-seven patients were ambulatory throughout the time of treatment with thiouracil. Those that were hospitalized were in the hospital no more than two days.

Patients were re-examined at first every two weeks for eight weeks, then at monthly intervals for four months, and then every six to eight weeks.

Pre-operative treatment with thiouracil by the Lahey Clinic (5) did not require hospitalization of the patients. The patients came in every two to three weeks for differential blood count, except those with complications, as cardiac conditions, who returned oftener.

CLINICAL RESULTS

Most investigations report that all cases of hyperthyroidism responded to thiouracil. The estimates of incidence of failure of response to the drug vary from two percent (46) to less than five percent (49). Many of these reported failures of response are thought to be due to too short periods of administration (16)(4).

Rate of Clinical Response.

Subjective improvement in symptoms usually occurred first in the thiouracil-treated patients (16). This was described as a "feeling of well being" or "improved physical condition" (43). However, there was a marked individual variation between the beginning of treatment and clinical response. This was readily noticeable by some patients in a "few days" (53); by others by the end of the first or early in the second week (16); and by a few up to six months before there was any decrease in the basal rate. This is used as an argument by some that thiouracil acts generally as a cell depressant. Of the subjective symptoms to disappear first were irritability, apprehension and tension. Following this there was relief from palpitation thermophobia and perspiration which came at about the time the basal rate began to drop. The last of the subjective symptoms to disappear was muscular weakness (3).

Improvement in objective symptoms usually did not occur until there was a fall in the basal rate and usually accompanied this fall. Astwood (3) states that decrease in the pulse rate is a good index of the onset of objective improvement. Following this decrease in pulse

rate and initial fall of basal rate there is an increase in body weight which continues for months. Williams (53) reports that weight gain usually does not occur until about two weeks after the beginning of treatment. Following gain of weight there is a disappearance of tremor, sweating, vasodilation and overactivity (3).

Rate of Metabolical Response.

Often the basal metabolical rate drops immediately after thiouracil is started though there are many exceptions in which there is no apparent change in basal rate for two to three weeks (43). At any rate, the metabolical response is usually most marked in the first two weeks following which initial drop there is a plateau either due to decreased dosage or unknown factors (3). Generally, the higher the initial basal rate the more sharp was the fall after the administration of thiouracil (49)(43).

The length required for the basal rate to reach normal also varied considerably with the individual case. Reveno (46) states that the average time requirement is six weeks. Riker and Wescoe (49) report that in eighty percent of the one thousand cases studied normal basal rates were attained within ten to forty days after onset of treatment. Bartels (6) asserts that about one day of treatment has been found to be required for each percent elevation in basal rate.

Clinical and metabolical response to thiouracil are usually delayed in three main conditions:

1. If iodine has been previously administered.
2. In cases of toxic adenoma of the thyroid.

3. If the drug is administered to a patient with a normal thyroid.

Iodine used prior to thiouracil occasionally caused delayed therapeutic results. Occasionally there was actually an initial increase in basal metabolical rate in these instances which was assumed to be due to storage of colloids by the thyroid gland while iodine is used, thus causing a longer period of time to be required before the colloid can be utilized and the effect of thiouracil can be noted (16)(49). The exacerbation of the disease following thiouracil administration is also explained by the fact that increase in colloid and decrease in size of the acinar cells of the thyroid caused by administration of iodine antagonizes the thyrotropic hormone which in turn causes hyperplasia of the acinar cells and promotes transfer of the thyroid hormone from the thyroid gland into the blood stream. Thiouracil, on the other hand, decreases the synthesis of thyroxin but does not antagonize the action of the thyrotropic hormone. Therefore, on discontinuing iodine therapy, the thyrotropic hormone is permitted to promote rapid transfer of thyroxin into the blood stream (53).

The response of thiouracil in toxic nodular goiter was similar to that seen in patients pre-treated with iodine. The slow response in these cases is assumed to be due to patches in the gland which are filled with colloid and probably store a good deal of thyroid hormone.

Hypothyroidism develops only after a prolonged latent period when the normal individual is given thiouracil. Likewise, here it is

thought to be due to the fact that thiouracil acts specifically on inhibiting thyroid hormone secretion and since the normal gland can store more thyroid-laden colloid than the hypertrophied one, this will be responsible for a latent period (53).

SPECIFIC EFFECTS OF THIOURACIL

On Blood Chemistry.

The blood cholesterol level has never been a good index of the degree of hyperthyroidism. Astwood (3) reported a rise in blood cholesterol as a result of treatment with thiouracil already in the first patients treated with the drug. This rise in cholesterol usually is concomitant with clinical improvement though it is reported (51) that the level is often increased beyond myxedema level before the basal rate gives evidence of myxedema. Occasionally there have been cases reported where there is no change (16).

It is reported (51) that nitrogen, calcium and phosphorus balances tended to become more positive during the administration of thiouracil.

On Renal Function.

Kidney damage has been produced (4) experimentally by thiouracil. There have also been reports of a few instances of crystalluria (43) as a result clinical use of the drug though the number is not significant.

On Liver Function.

Evidence of impairment of liver function has been sought for by clinical jaundice, blood icterus index, cephalin flocculation tests, urinary bile and urobilinogen estimations and galactose tolerance tests. The onset of jaundice has been noted (51) in one case.

On Exophthalmus.

Some investigators have been hesitant about committing their

opinions on what effect thiouracil has on exophthalmus. There have been some cases of definite increase in exophthalmus reported (43)(49) even to the extent of "malignant exophthalmus" (53). In the majority of cases, however, exophthalmus appeared to decrease during the early months of treatment. There was usually a decreased stare and less marked widening of the palpebral fissue in a few weeks. This decrease was in most cases apparently due to actual decrease in proptosis (3). In other cases the decrease in exopthalmus was merely a manifestation of increased weight with increased subcutaneous fat and a decrease in lid retraction (3)(49). Some administered thyroid extract simultaneously and found it to produce some "beneficial effect" in relieving exophthalmus (49)(43)(53).

Hyperthyroidism with complications.

Thyrocardiacs are assumed to be tolerant to thiouracil and the drug is in no way counter-indicated in this condition. In cases of cardiac decompensation due to latent hyperthyroidism or in mild toxic states more thiouracil seemed to be required to affect the pulse pressure and to control the thyrotoxic symptoms (43). Instances of auricular fibillation and flutter have on the contrary been treated without effect on the rhythm (16). In several cases reported, concomittant administration of quinidine caused fibrillation to revert to normal rhythm. However, if the disturbance in heart rhythm is caused only by thyrotoxicosis, it is now generally assumed that thiouracil alone will cause a return to normal rhythm.

Thiouracil has been administered in diabetes with fairly gratifying results. Astwood (4) had a case of hyperthyroidism complicated

by diabetes among the first group of patients to which thiouracil was administered. He described clinical improvement of the hyperthyroidism as well as a decreased glycosuria which followed the establishment of a normal basal metabolical rate. His findings have been confirmed by others (49)(53). Other instances of complete disappearance of glycosuria in hyperthyroid diabetes have been cited (49). On the contrary, there have been reports of failure of thiouracil in hyperthyroid diabetics. Gabrilove (16) noticed no improvement of either of the conditions with thiouracil treatment. McGavack (33) also failed to notice response in these patients.

Much divergence of opinions yet exists concerning the advisability of feeding thiouracil to patients during pregnancy. This lack of agreement has arisen from investigation of thiouracil concentration and distribution within the body elements as well as some reports as to results obtained clinically and on experimental animals.

It has already been mentioned that in experimental animals the fetuses contained a drug concentration of one-half that of the mother. The concentration in the placenta was somewhat greater than that in the mother. It was further mentioned that the concentration of thiouracil in breast milk is three times that of whole blood.

There are several reports of fetal injury as a result of thiouracil treatment during pregnancy. Hughes (25) reports that the young of thiouracil-treated rats appeared normal at birth but had hyperplastic thyroids and showed retardation in growth after about the tenth day.

Eaton (9) also reports a baby born with goiter as a result of the drug. However, he blames it onto a greater dosage than others were getting in this instance.

There have, however, been reports favorable to thiouracil administration during pregnancy which outnumber the unfavorable ones. Eaton (9) mentions one case where the drug was given all during pregnancy until one month prior to delivery when iodine was substituted. Both fetus and mother were in good condition at birth. Five months after birth the child's thyroid, which was palpable at delivery, had receded to normal size. Riker and Wescoe (49) cite three instances where no ill effects followed thiouracil administration. Three patients were treated before and during entire pregnancy by Williams (53). One patient was treated during the last six weeks of pregnancy and one during the last month. All babies were in excellent condition at birth and none showed a goiter at birth.

None of the investigators reporting results of thiouracil in pregnancy mentioned whether or not the children were breast fed. This should be important.

Astwood (3) reports treatment of two patients with hyperthyroidism superimposed on acromegaly with thiouracil. In one the basal rate fell but not to normal. The patient subsequently died and examination of the thyroid after death showed that it contained a high iodine content. In the other, thiouracil caused no improvement of clinical symptoms or basal rate.

The patients with toxic nodular goiter, as has already been mentioned, showed a longer latent period before clinical response than those with a diffuse goiter. In some instances early in the use of the drug, this was interpreted as a refractoriness to the drug but response in these patients after prolonged treatment disproved such assumptions.

Remission.

All literature concludes that there is eventual remission of hyperthyroidism in practically all patients treated with thiouracil as long as the drug is continued. Less of the drug is needed to maintain remission as the disease subsides, probably due to the larger amounts of thiouracil stored in the thyroid when the activity of the thyroid hormone is normal than when it is increased. However, we are more interested in what the patient's chances are for a full and permanent cure after the drug has been withdrawn.

Of all cases reported, it is estimated that about ten percent continued satisfactorily after thiouracil had been withdrawn (53)(46). The length of time the patients have gone without the drug varies considerably and in some instances it is yet hard to determine whether or not there will eventually be a return of symptoms. There have been attempts to set up a group of criteria, on the basis of clinical experience, useful in predicting relapse on remission after the drug has been withdrawn. These we shall mention.

There is a definite relationship between the duration of treatment and tendency to maintain remission after discontinuance. Astwood (3) advises at least six months treatment before attempt of withdrawal

is made. Williams (53) asserts that the longer the patient is treated, the longer the interval of non-treatment preceding relapse. There are, however, exceptions to this. He favors treatment of nine months or longer if permanent cure with the drug alone is the objective. How can one decide when it is time for discontinuance of drug? There is as yet no definite criterion for this. Astwood (3) suggests that it is possible that the size and vascularity of the gland are important factors. The bruit must be absent.

The age of the patient or duration of the disease (53) are in no way related to incidence of relapse and cannot be used as a criterion for prognosis. The sex of patient may have some prognostic significance. It is reported that males experienced relapse more frequently than females. Nodulor goiters responded as well as diffuse in Williams' (53) series of patients. Palmer (43), however, observed no nodular thyroid to have remission longer than four months.

Patients (53)(3) with only slight enlargement of the thyroid gland demonstrated a higher incidence of remission than those with larger goiters. However, some very large glands sustained remission. Patients who have remission show a "distinctly greater tendency" for a decrease in size of the gland than patients who experienced relapses.

Patients with a moderately increased basal rate showed remission more often than those with markedly increased rate.

The exophthalmus also appeared to be more malignant in those patients who did not show remission.

There appears to be no relation of the dosage of thiouracil or the rate of drop of basal rate and remission. X-ray and thyroxin administration also did not appear to influence the rate of remission.

Thiouracil Used Pre-operatively.

There is at present little disagreement concerning the statement that thiouracil has a place in pre-operative preparation of the hyperthyroid patient but also that if used alone it produces certain undersirable surgical complications.

The reasons for thyroidectomy varied. Some (6) considered thiouracil not as a substitute for thyroidectomy in any case but did thyroidectomies routinely on all hyperthyroid patients of significant severity. Others (43) resorted to surgery because of conditions, where previous large colloid goiters, which had become toxic, were not decreased in size after the thyroid gland had returned to its pretoxic state under thiouracil administration; also where large adenomata which were not effected by thiouracil were present. In these instances surgery was chiefly for cosmetic purposes. Occasionally it was necessary to do surgery because of refractoriness to thiouracil and in some instances because of toxic reactions in the drug. Finally surgery was done because certain patients found it difficult or impossible to return regularly for check-ups under thiouracil management.

The Lahey Clinic (6) found that the maximum amount of improvement must be obtained by thiouracil before operation is attempted. The basal rate must be as nearly normal as possible and the symptoms must be absent. Others (43) suggest that the basal rate must be down

one-third or one-half but not necessarily as low as plus ten percent because the physiologic equalibruim is reached some time before it is reflected in the basal rate. Bartels (6) reports two patients where maximum improvement was not obtained pre-operatively. The operative course was so unsatisfactory that only hemi-thyroidectomy was possible and the post-operative course was stormy.

Thiouracil delivers the patient to surgery more dependably in a euthyroid state than was ever possible with iodine. Thyroxtic reactions (53) are less during and immediately following operation than in comparable patients treated with iodine. It is now thought (53)(6) that hemi-thyroidectomies, which iodine pre-operative medication made necessary in many patients, are now unnecessary because of smooth anesthesia and the smooth post-operative course that "always" follows thiouracil-treated thyroidectomies.

There are, however, as mentioned, undesirable surgical complications in all patients receiving thiouracil alone. The gland is found to be soft and firable and bleeding is extensive. To overcome this the Lahey Clinic advocates thiouracil until the basal rate is at least down to plus twenty, by beginning iodine three weeks pre-operatively and discontinuing thiouracil one week pre-operatively. This produces satisfactory involution in most cases. Williams (53) suggests use of iodine both before and during thiouracil treatment for best results.

There are reports (16)(43) of excellent results with thiouracil used preoperatively without added iodine administration. This was probably due to the fact that these were cases of primary hyperthyroidism

of long standing where spontaneous involution over the years is sufficient to prevent the gland from bleeding excessively or adenomatous goiters where the gland remained firm in spite of thiouracil treatment.

TOXICOLOGY

The fact that long periods of treatment with thiouracil are necessary to produce remission of hyperthyroidism and that in many instances permanent remission after withdrawal can obviously not be obtained with the drug would alone not make us hesitate to use the drug exclusively for treatment of hyperthyroidism. However, there is a "fly in the ointment" and this consists of the toxicity of thiouracil.

The toxic reactions resulting from thiouracil administration have been estimated to occur in not over 14.5 percent of patients treated and fatalities due to the drug in not over .5 per cent (39). This compares favorably with incidence of tetanies and vocal cord paralysis occurring in about one percent of thyroidectomies and likewise a fatality rate of .5 percent in surgery (39). However, one must not fail to consider that the risk extends over a much longer period of time in the administration of the drug than with surgery. If the peace of mind of the physician and of the patient is a factor, this is significant.

Types of Reactions.

Throughout the literature that was reviewed, the following enumeration includes most of the toxic reactions that have been reported: agranulocytosis, arthritis, diarrhea, enlargement of salivary glands, edema of the legs, fever, generalized enlargement of lymph nodes, headache, hematuria, icterus, leukopenia, nausea and vomiting, rash and urticaria and purpura.

The terms agranulocytosis and leukopenia must first be differentiated and defined. Williams (53) has arbitrarily described agranulocytosis as applying only to patients experiencing a decrease in the total white blood cell count to about two thousand or below, and/or a decrease in the granulocytes to about two percent or lower. The presence of infection is not regarded as a requirement for this designation. To have a small percentage of granulocytes seems to offer a far better prognosis than to have none.

The term leucopenia is generally applied by hematologists when the leucocyte count is less than five thousand. However, in dealing with thyrotoxic patients one must bear in mind that leucopenia and neutropenia may occur in untreated cases. It is therefore often difficult to differentiate between the leucopenia of thyroxicosis and that due to thiouracil. Williams (53) here also has designated an arbitrary figure, namely, leucocyte counts below three thousand five hundred as being due to the toxic action of the drug, and most of those below four thousand as probably being due to the drug.

The incidence of agranulocytosis has been estimated as occuring in not over 2.5 percent of all cases treated with thiouracil (39) though individual reports usually describe a lower incidence. Williams (53) reports an incidence of .6 percent in series of seven hundred ninety-three reported cases. Leukopenia occurred in about 4.8 percent of these cases.

Although generalized aching and malaise were associated with several of the toxic reactions, significant joint changes occurred in

less than .1 percent of the cases. Williams (53) describes one case in which an acute inflammation of many joints occurred, along with fever and urticaria appearing after two weeks of thiouracil treatment but on cessation of the drug therapy, the reactions rapidly disappeared.

Diarrhea has been reported by some clinicians, as a toxic manifestation of thiouracil. Usually it is severe and occasionally intractible (4). It occurred shortly after therapy was introduced and believed by some to be a manifestation of too large dosage and not a toxic reaction (53).

Enlargement of the submaxillary salivary glands has been reported in one case (54). Experimentally it was found that thiouracil decreases the peroxidase content of submaxillary glands (53). Whether this has anything to do with enlargement is not known.

Edema of the legs developed in some patients without any evidence of renal or cardiac damage. Generalized edema has also been described (16). The total serum protein concentration was normal, but in some instances there was evidence of retention of sodium chloride in the body. It seemed to occur in patients receiving larger doses of the drug (daily doses of one gram)(53).

Fever has been given as an indication of impending danger of toxic reactions by some (4). It has been estimated to occur in about three percent of the patients treated with thiouracil (53).

Generalized enlargement of lymph nodes has been observed and reported (15)(42)(16) in a few instances. Some suspect that this was not a manifestation of drug toxicity.

Headache developed in occasional patients but quite infrequently when the dosage remained small. Daily dosage of one gram seemed to cause headache in a significant number of patients to make one suspect that dosage was the factor responsible (53).

In a very few cases hematuria has been attributed to thiouracil (43). Very large dosage of thiouracil in rats produced no kidney changes (58).

Icterus has been reported (17)(27)(51) in a few cases and parenchymatous liver changes (51) have also been seen.

Nausea and vomiting seemed to occur mainly in those cases where large dosage were administered and shortly after beginning treatment. Incidence of such reaction has not been significant where dosage was small (53).

Most investigators who have treated many patients have observed development of a maculo-papular rash. It usually showed a generalized distribution. Urticaria was usually associated with the rash and occasionally there was also fever in these cases (16).

A thrombocytoperic purpura has been described as it occurred in one patient (10). Others have noted a few cases of spontaneous ecchymoses without a thrombocytopenia and without apparent vitamin C deficiency (53).

Factors Related to Toxic Reactions.

Among all reports concerning toxic reactions, it appears that the age of the patient, the sex of the patient, the type and rate of

response of the hyperthyroidism, the concentration of thiouracil in the blood and the total dosage of the drug seemed to be unrelated to toxic reactions.

The general condition of the patient did seem to be related to toxic reactions according to some reports. Two patients who died of agraulocytosis seemed to be in very poor general condition (11)(27); one patient (27) had diabetes, weighed only seventy-seven pounds and was sixty-two years old. Others report that the condition of the patient did not seem to play a significant part (53).

Manifestations of sensitivity of patients to other substances has been reported. Some patients developed a rash when put on iodine after thiouracil was withdrawn (53). Some patients who developed leucopenia to thiouracil had previously developed skin rashes to phenobarbital. Astwood (3)(4) reports a patient who developed and recovered from agranulocytosis due to thiouracil and later developed a febrile reaction to sulfathiazole and a scarlatiniform eruption to phenobarbital. Conversely, there were other patients who had shown previous sensivivity to iodine, sulfadiazine and phenobarbital but did not react to thiouracil. As has been mentioned, the total dosage of thiouracil apparently is not significant in determining reactions. The total daily dose, however, seems to be important. Slightly over one-half the cases of leukopenia noticed by Williams (53) had what is not considered too large daily doses. Seven-eighth of the cases of agranulocytosis were likewise seen in patients getting one gram daily. Other reactions already mentioned

seemed to depend directly on dosage. On the contrary, fever and urticaria did not seem to be lated to dosage.

The duration of treatment with thiouracil prior to onset of reactions varied considerably for different reactions and for the same reactions. Agramulocytosis occurred most frequently five to eight weeks after the onset of therapy. There were, however, instances where it occurred after four to eleven months of treatment and in one instance after the third course of therapy was begun (53).

Leucopenias appeared most often during the first four months of treatment. A slight decrease in white blood cells has been described to occur when treatment is started and a mean drop of seven hundred during the first month of treatment has been observed (9). Leucopenia has also been reported as suddenly developing after twelve to fourteen months of treatment.

The question arises whether thiouracil should be continued in spite of appearance of leucopenia. Continuation of thiouracil therapy may change some benign leucopenias into agranulocytosis though some leucopenias disappear in spite of continued therapy. Just how long it takes for the leukocyte count to change from a normal level to agranulocytosis is not known. Sometimes the white cell level returns to normal even thiouracil is continued but later a decrease is noted (53). In most of these where thiouracil was withdrawn and resumed after the reaction disappeared leucopenia developed within forty-eight hours to five weeks after thiouracil was started for the second time (53). However, there

are also reports (43) of cases in which resumption of treatment, after reactions disappeared, produced no recurrence of reactions.

Many of the febrile reactions reported developed between the seventh and eleventh day (3)(6)(15). In other instances fever did not develop until up to eighteen months after onset of treatment. In practically all cases resumption of treatment after fever was down produced recurrences.

The rash appeared in the first few weeks but tended to disappear in spite of continuance of thiouracil within a few days. Edema appeared in the first month, Urticaria, headache, nausea, vomiting and diarrhea in the first few weeks.

CONCLUSIONS

Thiouracil is of great aid in the treatment of hyperthyroidism, whether used in conjunction with thyroidectomy or not. It is not necessary to use thiouracil in all cases of toxic goiter because in certain patients iodide is just as effective as thiouracil in controlling the disease, and in patients treated with iodide the technical difficulties of thyroidectomy do not tend to be as great as in ones treated with thiouracil. Moreover, the incidence of toxic reactions is less with iodide than with thiouracil. Although the effectiveness with which iodide can control a given case of thyrotoxicosis is often unpredictable, this is no serious drawback to a trial with it, because if the iodide is found to be unsuccessful thiouracil treatment can then be used in conjunction with the iodide. There are some patients with thyrotoxicosis to whom it seems imperative that thiouracil be given, as for example, individuals with severe disease which is refractory to iodide therapy and associated with heart failure. Indeed, the drug is quite desirable in many less severe cases. However, it is welcomed for that group of patients who seemingly would prefer to die of thyrotoxicosis than be subjected to thyroidectomy.

Whether it is wise to plan to treat most instances of toxic goiter with thiouracil and without thyroidectomy is still in the realm of investigation. The most significant handicap to such a plan is the nature and relative frequency of the toxic reactions to thiouracil. This, however, has by no means settled the question; the chief point awaiting

elucidation is a determination of the proportion of patients who will attain sustained or permanent remissions of the thyrotoxicosis on cessation of all antithyroid treatment. To be sure, the latter point would be less significant if the toxic reactions were less prominent since the drug could be used more or less indefinitely.

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