

PROPYL THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM

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The medical treatment of hyperthyroidism is much more satisfactory today than it was even such a short time ago as the early part of this year. A year ago thiouracil had already been proved capable of controlling all types of hyperthyroidism, whether associated with Graves' disease or with adenomatous goiter, except when crisis was present or impending. It was used with outstanding success in the preoperative preparation of severely ill patients and those in whom complete control of hyperthyroidism before operation was an especial advantage. It was used successfully in many cases as the sole method of treatment.

There were two great obstacles to the general use of thiouracil. The first was the risk of severe agranulocytosis, known to occur in as many as 3 per cent of the patients and fatal in perhaps half of these. This was comparable to the surgical mortality in good hands and might have been an acceptable risk except for the second obstacle. This was our lack of knowledge as to the rate of recurrence of the disease after the withdrawal of treatment. It is this fact which still tips the balance slightly in favor of surgery in many patients, since the rate of recurrence of hyperthyroidism following subtotal thyroidectomy competently done is probably not more than 5 per cent in Graves' disease and much lower in adenomatous goiter.

For reasons such as these it has been our policy to recommend thiouracil only for those patients in whom the risk of surgery or complications was high, and for those patients whose safety was definitely increased by its use. Iodine preparation and thyroidectomy was considered the treatment of choice in all patients in whom the surgical risk was obviously very slight. By these means the surgical mortality of the disease was reduced almost to the vanishing point.

The problems peculiar to adenomatous goiter are clearly problems for the surgeon, whenever the issue is one of cosmetics, pressure, or the possibility of malignant change. The advisability of the use of the thiourea compounds is therefore more distinct in the diffuse gland than in adenomatous goiter, the diffuse goiter having no potential risk of enlarging greatly or becoming malignant.

The slowness of the action of the thioureas obviously renders them entirely unsuitable for the management of crises. Here iodine, sedation,

refrigeration, oxygen, blood, and all the adjuvant measures so well established must be employed.

In some of the seriously ill patients who were denied surgery and treated with thiouracil, operation was later considered advisable. Reasons for this included the following: (1) tendency to recurrence of the disease, (2) presence of pressure symptoms, and (3) the possibility of malignancy. In some severely ill patients when the hyperthyroidism had been completely controlled, clinical improvement was so great as to make surgery appear unnecessary. Some of these individuals were continued on thiouracil for many months and now have remained in remission following cessation of treatment for periods extending to a year and a half or more.

The use of propyl thiouracil has almost completely removed the objection raised against thiouracil because of toxic reactions. Astwood,¹ who proposed the use of this drug, recently reported its use in 100 cases of hyperthyroidism without a single toxic reaction of note. Among more than 500 patients who have been treated with propyl thiouracil in various parts of the country we are aware of only 1 instance of agranulocytosis.² This person may have had agranulocytosis on previous occasions. Recovery followed the generous use of penicillin.

We have now used propyl thiouracil in the management of 110 patients with hyperthyroidism. Among these are 4 who had had toxic reactions to thiouracil sufficiently severe to prevent its use. One woman could not take thiouracil or thiobarbital because of fever, nausea, and a fall in neutrophil count, but propyl thiouracil produced no untoward effects and controlled her hyperthyroidism completely. In only 1 of our patients has propyl thiouracil been discontinued. In this instance mild sore throat and a fall in leukocyte count followed repeated trials. Finally, the neutrophils fell to 22 per cent, and this, plus the anxiety incident to it, was considered sufficient reason to abandon the treatment in favor of iodine and surgery.

It is much too early to know what the rate of recurrence will be after the drug has been stopped. In our patients the duration of treatment varies from one week to eight months. Our present plan is to continue the drug for six to nine months after the metabolic rate has become normal. It is not too early, however, to state that the drug is an effective means of controlling the hyperthyroidism of Graves' disease as well as that associated with adenomatous goiter.

Symptoms and complications both disappear under its effect, just as with any other method which controls the hyperthyroidism completely. The response closely parallels the drop in basal metabolic rate, although in severely ill patients, old people, or any who have been severely ill for a long time, many months may be necessary for complete recovery.

In most instances a great advantage to treatment with propyl thiouracil is that almost all patients can remain ambulatory throughout their entire treatment, and most of them can continue with their usual employment. Even those with metabolic rates 50 per cent above normal may be able to maintain their weight while working when a high caloric intake is properly arranged. In some, sedation or extra rest is useful, and in those with cardiac decompensation, digitalis alone or coupled with sufficient rest and other means to relieve cardiac strain and edema may be necessary.

Propyl thiouracil, therefore, is a safe and effective method of treatment. It obviates in almost all patients the expenses incident to work loss, hospital, and surgical expenses. In addition, such complications as recurrent nerve injury or parathyroid tetany need not be considered. Up to the present there appears to be no tendency to hypothyroidism, and in no instance observed has exophthalmos become worse or the goiter increased materially in size. In some patients a striking thrill and bruit appear in the gland during therapy, but these disappear promptly on 10 mg. of iodine per day with no loss of effectiveness in control of the hyperthyroidism.

The rate of response to propyl thiouracil at proper dose levels apparently differs little from that seen with thiouracil. In this respect it should be recalled that there was an extremely wide variation in the rate of response to thiouracil. In some patients treated with this drug the

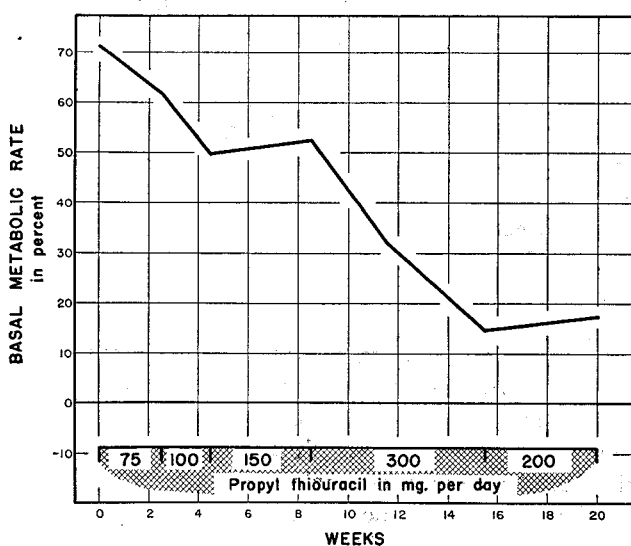


CHART 1.

PROPYL THIOURACIL IN HYPERTHYROIDISM

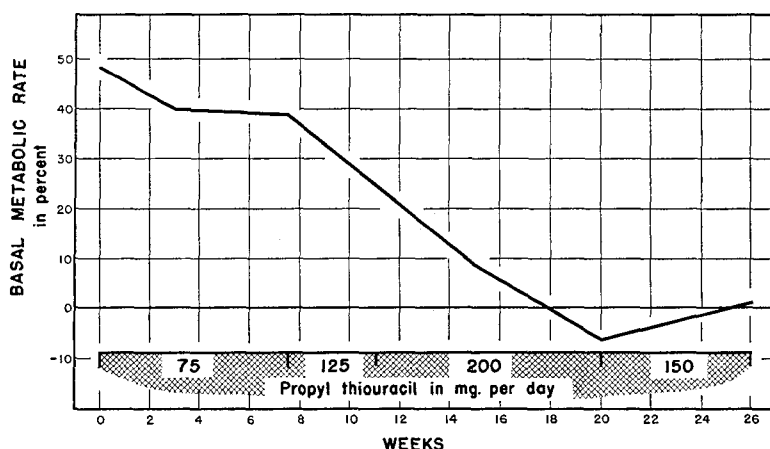


CHART 2.

metabolic rate fell more than 1 per cent per day, while in others no response was evident for many months. As with thiouracil, the response to propyl thiouracil is most dramatic in Graves' disease which is of short duration, when the thyroid gland is small, and in which no previous iodine therapy has been applied. Whether or not the combined use of iodine and propyl thiouracil may combine speed of response (iodine) with safety of prolonged control (propyl thiouracil) is a problem now being explored.

The size of the dose is a large factor in the rate of response to the drug. Until a few months ago the dose was raised above 100 mg. per day only with caution. It was soon learned that unless the symptoms and metabolic rate responded promptly, doses of 200 mg. or 300 mg. per day might bring about much more rapid recovery (chart 1). In many of our patients who were started on doses of 75 mg. per day and increased gradually, a fall of 50 per cent in metabolic rate in about three months was common (chart 2). In others, even in the presence of extremely active Graves' disease, the response may be more rapid (chart 3). At present the usual dose in starting treatment is 200 mg. per day given in divided doses.

Summary

Experience with the use of propyl thiouracil in the treatment of 110 patients with hyperthyroidism during the past eight months has led us to consider it a safe and effective means of treatment except in crisis.

If future experience establishes the fact that the rate of recurrence of hyperthyroidism is low following such therapy, or if the prolonged

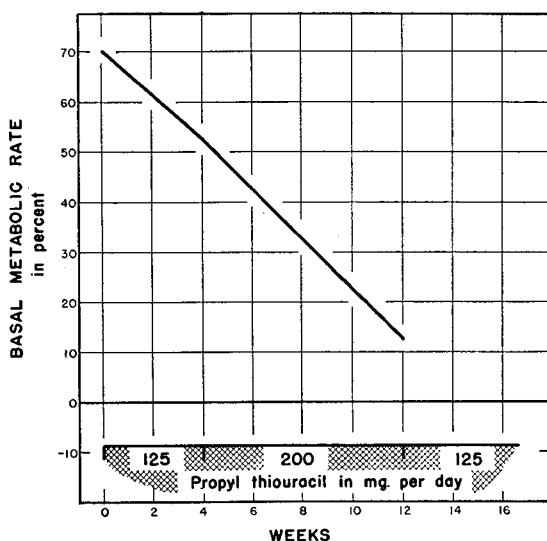


CHART 3.

use of the drug is practicable, propyl thiouracil bids well to become the treatment of choice, particularly in the hyperthyroidism of Graves' disease.

Hyperthyroidism associated with adenomatous goiter can be controlled by propyl thiouracil. The cosmetic aspects of the problem as well as pressure symptoms and possibility of malignancy remain. These require careful evaluation and should influence the decision as to the type of treatment prescribed for these patients.

References

1. Astwood, E. B.: Use of Thiouracil in Hyperthyroidism. Paper read at twenty-seventh annual session of American College of Physicians, May 13-17, 1946.
2. Bartels, E.: Personal communication.