A SURVEY OF THE FACTORS CONTROLLING THYROID FUNCTION, WITH ESPECIAL REFERENCE TO NEWER VIEWS ON ANTITHYROID SUBSTANCES[1]

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Common usage has restricted "antithyroid drugs" to mean those substances which specifically inhibit the organic binding of iodine in the process of formation of thyroid hormone but do not directly alter other known functions of the thyroid gland; this review will be concerned with these substances. In addition, the effects of thyroid hormone, of iodine, and of thiocyanate and similar agents will be considered.

In order to provide a frame of reference for a discussion of agents altering thyroid function, thyroid-pituitary relationships and the metabolism of iodine will be touched upon; however, for an exhaustive analysis the several recent, and excellent reviews of these subjects should be consulted (1, 5, 7, 80, 98, 157, 171, 178).

The main purposes will be to review newer evidence on the nature and mode of action of the antithyroid substances, to assess the effects of those which have been put to clinical trial, and to weigh the evidence of the influence exerted by these substances on the natural history of hyperthyroidism. Because of the vastness of the available material, selectivity will be employed in developing a point of view.

I. THYROID-PITUITARY RELATIONSHIPS

The functions of the thyroid gland are to form, to store, and to release its hormone. Consideration of these functions involves the relationship of the thyroid gland to the pituitary gland and the general topic of iodine metabolism.

The relationship of the thyroid gland to the pituitary gland is such that hypophysectomy causes atrophy of the thyroid gland, whereas thyroidectomy is followed by characteristic histological changes in the pituitary gland (85, 92). The administration of pituitary extracts rich in thyrotropin results in growth of the thyroid gland, loss of colloid, abundant mitoses, and increased vascularity and cell height. On the other hand, feeding thyroid powder to intact animals results in changes in the thyroid gland suggesting hypophysectomy and, in the thyroidectomized animal, leads to disappearance of the cellular changes in the pituitary characteristic of the post-thyroidectomy state.

The administration of thyroid hormone lowers the thyrotropin content of the pituitary, and it causes the thyroidal metabolism of iodine to resemble that which follows hypophysectomy. Administration of thyrotropin increases the

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rate of removal of iodine from the circulation by the thyroid gland, the rate of thyroid hormone formation, and the rate of its discharge. A reasonable and generally accepted interpretation of these observations is that thyrotropin stimulates the thyroid anatomically and functionally, with a resulting increased rate of secretion of thyroid hormone. A rising level of circulating thyroid hormone finally satisfies the pituitary and equilibrium is restored. Depression of thyroid function with decline of the concentration of circulating thyroid hormone acts as a stimulus to the output of thyrotropin by the pituitary. Thus, a servo relationship exists between thyroid and pituitary glands. Some observers have felt that this mechanism provides an adequate explanation for all aspects of the regulation of thyroid function, but recent observations make this view untenable.

II. SUBSTANCES INFLUENCING THE REGULATION OF THYROID FUNCTION

A. Iodide ion

Abundant evidence indicates that iodide ion accumulation by the thyroid gland is a distinct phase of iodine metabolism. This was first established in tissue slices by Schachner *et al.* (179), and it has been shown that in the intact animal treated chronically with an antithyroid drug the injection of potassium iodide was followed promptly by the appearance of iodine in the thyroid gland (5). Further, the iodine accumulated under these circumstances was retained by the thyroid gland for only a few hours (208). McGinty and Sharp (136) found iodine thus concentrated was not precipitated with proteins, and when thyroid tissue, ground in water but not chemically treated, was ultrafiltered through cellophane, the ultrafiltrate contained iodine which behaved as iodide ion in potentiometric studies (206). Chromatographic studies by Taurog *et al.* (201) indicated the presence of iodide ion in the thyroid gland of the rat, rabbit, dog, and sheep in an amount about 1 per cent of the total iodine even in the absence of an antithyroid drug.

In the rat fed a diet ample in iodine iodide ion is distributed between thyroid gland and plasma in the ratio of 25:1 (94, 206), and this ratio is maintained over a wide range of iodine dosage. Because serum rather than plasma is usually studied this is commonly referred to as the thyroid: serum (T/S) ratio; these studies are ordinarily carried out one hour after propylthiouracil has been administered. Under conditions of hyperplasia induced by chronically feeding propylthiouracil this ratio of iodide ion in the thyroid to that in the serum rises to 300:1, and a gradient for iodide has been demonstrated even after 10,000 μg. of potassium iodide have been given to a 50–75 g. rat. A discrepancy exists between the figures for iodide ion content of the thyroid by the method of comparing T/S ratios and those chromatographically determined. The effectiveness of thiocyanate in discharging iodide as determined chromatographically has not been studied.

The general assumption which formerly prevailed was that the enhanced

capacity of the hyperplastic thyroid to accumulate iodide ion was due to increased activity of the pituitary gland in the elaboration of thyrotropin. Thyrotropin has been shown to result in a sharp rise in T/S ratios 24 hours after injection in hypophysectomized rats; this was maximal after 48 hours and was declining after 72 hours (211). However, Halmi *et al.* (94) have demonstrated that the effect of thyrotropin on the T/S ratio was markedly increased by the concomitant administration of propylthiouracil, and Halmi (93b) has subsequently found that when constant doses of thyrotropin were administered to hypophysectomized rats, decreasing the quantity of iodine in the diet was followed by a rise in the T/S ratio. Substantially the same effects were observed by VanderLaan and Caplan (210), who noted an inverse relationship between iodine stores in the thyroid gland and the capacity of the gland to pump iodide ion. In the intact rat this observation was made after the administration of propylthiouracil, and in hypophysectomized rats many-fold differences in T/S ratios were noted despite the use of unvarying doses of thyrotropin. The T/S ratios in these circumstances were related inversely to the stores of iodine in the thyroid gland. For a rise in T/S ratio to occur the extent of lowering of the total stores of iodine appeared more significant than the agent through which the depletion of iodine was effected.

VanderLaan and Caplan (210) postulated that in some measure the thyroid gland regulates the metabolism of iodine autonomously and that this autonomous regulatory mechanism of the thyroid gland suffices as an explanation for the constancy of the levels of iodine stored in the thyroid, a widely observed phenomenon not readily explicable on the basis of pituitary regulation. The hypothesis was based on the observations of Morton *et al.* (146), of Raben (165), of Stanley (191), and of Childs *et al.* (40), who demonstrated that increasing the amount of iodide ion made available to the thyroid gland resulted in an increase in the amount of iodine that was bound by it, provided only that relatively small doses were used, higher doses blocking binding. These observations combined with those just cited appeared to warrant the conclusion that the thyroid gland was in part self-regulatory.

Anatomical evidence that the thyroid gland is not wholly dependent on pituitary regulation has been presented by Wolf and Greep (227), who found that hypophysectomized rats responded to lowered environmental temperatures with hyperplasia of the thyroid, and by Chapman (38), who found the hypophysectomized rat responded to lowering of the dietary intake of iodine with increased thyroid weight, cell height, and vascularity. Goldberg *et al.* (72) partially confirmed Chapman's findings but did not observe increased thyroid weight in hypophysectomized rats fed a diet low in iodine. They observed an increased thyroid avidity for iodine not associated with any decrease in iodine content.

Although these observations have been made in experimental animals rather than in man, they provide a basis for speculation on the nature of Graves' disease, particularly in regard to the continuing high rate of turnover of iodine. Not only the direct evidence of Gutman *et al.* (88) but also indirect evidence

supports the general opinion that the iodine content of the thyroid gland is low in Graves' disease. Gutman's analyses of iodine content of thyroid glands removed from thyrotoxic patients pretreated with iodine, when compared with the previously recorded figures, indicated that iodine treatment in this disorder resulted in a several-fold rise in the content of iodine of the thyroid gland. Less direct evidence includes the observation that pretreatment of patients with Graves' disease with iodine not only increases the amount of colloid in the gland but also delays the beneficial effect of antithyroid drug administration, a delay attributable to the increase in thyroid stores of hormone during the period of therapy with iodine. The slower response to antithyroid drugs under these circumstances begins to approach that observed in normal individuals (5). Thus, in Graves' disease the iodine content of the thyroid gland is low, there is a great capacity for iodide ion accumulation, and there is an increased capacity for thyroid hormone formation. The experimental evidence would make explicable the continuing overactivity of the thyroid gland in Graves' disease on the basis that there is an inability to store hormone, a resultant lowering of hormonal stores, and a rise in the capacity to accumulate iodide from the plasma which in turn provides for a continuing rapid rate of hormone formation. This resembles the sequence which follows thyrotropin administration to experimental animals where the increased rate of discharge is noted before there is an increase in the rate of accumulation of iodine. In Graves' disease the capacity to accumulate iodide ion, the rate of binding of iodine, and the shortened biological half-life of radioiodine are consistent with such an hypothesis. The hypothesis is strengthened by observations of Werner *et al.* (216, 217, 218), who have deduced that thyrotropin production is not excessive in Graves' disease because the injection of thyrotropin in hyperthyroid subjects results in a significant rise in serum organic iodine; this would not be expected if the thyrotropin were added to an already large amount of circulating hormone. In 20 patients the daily administration of 11.2 mg. sodium iodide decreased the concentration of organic iodine from 11.3 to 8.5 μg./100 ml., and the radioiodine-uptake from 61 per cent in 24 hours to 16 per cent. At this point the administration of thyrotropin for three days had little effect on radioiodine uptake but raised the organic iodine to 13.0 μg./100 ml., or above the original concentration. Thus improvement with iodide despite a continuing sensitivity to thyrotropin was held inconsistent with thyrotropic excess as a cause of Graves' disease. It also was held to indicate that iodides act on the thyroid cell directly rather than modify the effect of thyrotropin. These studies lend support to the earlier contention of Purves and Griesbach (164) that thyrotropic excess is not a defensible explanation for thyrotoxicosis since they could not detect thyrotropin in the sera of patients with thyrotoxicosis except after treatment. D'Angelo (45), using a less direct method of assay, found thyrotropin concentrations normal in Graves' disease. Moreover, the data of VanderLaan *et al.* (207) and of Berson and Yalow (31) support the concept that in Graves' disease, as well as in normal subjects, the capacity of the thyroid gland to accumulate iodide ion is the rate-limiting factor in the binding process. Using in part the same

techniques they investigated the state of I^{131} in the thyroid shortly after its intravenous injection into thyrotoxic patients. Even when 50 per cent of the carrier-free tracer was present in the thyroid within an hour of its injection, detectable amounts of iodide could not be demonstrated by the administration of thiocyanate or of large doses of stable sodium iodide. In hyperthyroidism, the gland that is prevented from synthesizing hormone accumulates a large amount of iodide (193); this appears to be in sharp contrast to the situation in untreated hyperthyroidism where the iodide compartment is only a potential one. The observations support the contention that the rate of accumulation of iodide limits the binding-rate under ordinary circumstances. Ingbar (104) has claimed to demonstrate simultaneously the iodide-concentrating and protein-binding capacities of the human thyroid gland, but the method involved assumptions which the later studies render invalid, as Berson and Yalow (31) clearly state. Exceptions exist to the rule that the capacity to concentrate iodide limits the rate of hormone synthesis. In human beings following radioiodine treatment for hyperthyroidism, Kirkland (115) found an impairment of organic binding of radioiodine, 55 per cent of the tracer accumulated after three hours being discharged by the administration of thiocyanate. Additional exceptions have been provided by Stanbury and Hedge (190) and by Stanbury (189). They described cretins with thyroid enlargement, and found from five to twenty-four hours after the administration of a tracer dose of I^{131} that thiocyanate would effect almost total discharge. Stanbury and Hedge studied a family of goitrous cretins and a euthyroid sibling as well, and they found that thiocyanate discharged from the thyroid 10 per cent of the accumulated tracer in the euthyroid, non-goitrous sibling. Some defect in capacity to bind iodine was probably present in this subject. Wollman and Zwilling (235) have shown that the thyroid gland of the chick embryo at seven days has the capacity to concentrate iodide; ability to bind iodine is acquired later.

If the iodide-concentrating mechanism is rate-limiting in thyroid hormone synthesis, it follows that an increase in blood iodide concentrations would increase the rate of hormone formation. It is remarkable that high concentrations of iodide in the fluid bathing thyroid slices (146) and in the serum of rats (229–232) inhibit thyroid function. In their experiments in intact rats Wolff and coworkers found that concentrations of iodide ranging from 20 μg. to 35 μg. of iodide per 100 ml. serum inhibited organic binding of radioiodine as indicated by the amount of radioactivity precipitated by trichloracetic acid added to the thyroid glands. This inhibitory effect was found to be of short duration, 10 to 17 hours. Nephrectomy, however, prolonged the inhibition of binding for the longest period tested, 40 hours, when the inhibiting dose of iodide injected was 500 μg. (230). This led them to believe that, nephrectomy having prevented the normal decline in plasma iodine following a single injection, "inhibition of organic binding by the thyroid gland can be extended at will by maintenance of a high plasma-iodine level". Subsequently (232) a temporary inhibitory effect of iodide in high concentration in the serum of normal rats was again found; 500 μg. of iodide injected every eight hours for periods as long as four weeks failed to

induce the degranulation of pituitary acidophilic cells and hyalinization of basophils characteristic of thyroxine deficiency. In this study the maximum duration of inhibition was 26 hours. The concentration of iodide in serum has been proposed as a regulator of thyroid function, but Raben (165) has shown conclusively that the intrathyroidal concentration of iodide is the governing factor. It is possible that any free iodide in the thyroid gland may exert some blocking effect on hormone synthesis. Thus, thiocyanate, by preventing the thyroid gland from maintaining a significant gradient between cells and serum, acted in the presence of high concentrations of iodide in the serum to release the thyroid gland from inhibition by iodide ion by reducing the rate of iodide uptake. Conversely, thyrotropin injections, by increasing the capacity of the thyroid gland to concentrate iodide ion, promoted inhibition of hormone formation when iodide was present in concentrations ordinarily permissive of normal thyroid function.

The evidence reviewed indicates that the effect of iodide ion on thyroid function is complex. It could well have been anticipated that antithyroid drugs of the thiourea and of the sulfonamide series administered concurrently with excess iodine in the diet would not lead with monotonous regularity to results immediately illuminating. Early observations indicated that iodine administration did not alter the goitrogenic properties of sulfaguanidine but did lessen those of thiourea or thiouracil. MacKenzie (124) reinvestigated this subject. In his studies in rats the dietary concentration of thiourea was 0.1 per cent; of thiouracil, 0.005 to 0.05 per cent; of sulfaguanidine, 0.5 to 2.0 per cent; and of sodium iodide, 0.05 per cent. He observed that thiourea and thiouracil produced less thyroid enlargement when given with iodine, and it was noteworthy that histologically the thyroid gland resembled colloid goiter. When sulfaguanidine was administered in 2 per cent concentration iodide did not alter the hypertrophy of the thyroid gland, but with concentrations of 0.5 per cent and 0.75 per cent iodine augmented the goiter. The difficulties of interpretation are enhanced by the finding that paraaminobenzoic acid (2 per cent in the diet) was less goitrogenic in the presence of added iodine. Further experiments are required before these interesting observations are altogether explicable; however, Thompson *et al.* recently reported increase in the goitrogenic properties of the metabolites of chloramphenicol when the dietary iodide level was raised 100-fold (203a). The studies of Purves and Griesbach (163) on rats given drinking water containing thiourea (0.25 per cent) and injected with 1 mg. of iodide per day provide further information about the inhibitory effect of excessive iodine on thyroid function. They found that administration of thiourea alone caused enlargement of the pituitary and changes in the basophils, but only minor degranulation of acidophils —an incomplete picture of thyroxine deficiency. However, thiourea plus iodine in four weeks produced degranulation of the acidophilic cells characteristic of complete thyroidectomy. This was reversed by the administration of thyroxine.

It would appear therefore that in the normal rat treated with large amounts of iodine there is temporary inhibition of thyroxine synthesis due to a high concentration of iodide ion in the thyroid gland. The work of Purves and

Griesbach indicates that the inhibitory effect of iodine can be made permanent if a partially effective antithyroid substance is given concurrently. This may relate to the effect of antithyroid agents on the iodide-concentrating mechanism (94). The diminution of goitrogenicity of thiourea by addition of iodine would be explained best by the direct effect of iodine on the thyroid gland as postulated by Werner (216).

Feeding iodinated protein to laying hens causes the thyroxine-like effect of thyroid involution in the dams but in their eggs are found such evidences of hypothyroidism as delayed hatching, late closure of the umbilicus, and goiter of the colloid type. Conversely, feeding increasing amounts of iodine in the diet causes goiter in the hen and in her chicks as well (219). Further, goiter in the chick results from injecting potassium iodide into the white of the fertile egg. Three-fold enlargement of the thyroid results from the injection of 40,000 μg. of iodide (220). The evidence indicates that iodide released during the metabolism of iodinated protein by the hen results in goiter in her chicks (221). Iodinated protein when injected into the white of the fertile egg causes no goiter, and it seems clear from these studies that both young and adult chickens respond to excessive iodine administration with manifestations of hypothyroidism, including goiter. It would be of interest to know if this response is general in birds.

Iodine metabolism in man has been discussed in detail by Riggs (171). He has reviewed the evidence of an antithyroid effect of iodine in Graves' disease, pointing to the critical value of 6 mg. of iodine per day as the smallest amount likely to produce amelioration of symptoms, and to the observation that doses of iodine smaller than this occasionally lead to exacerbation of the disorder. These observations would be consistent with the view that in Graves' disease iodine is relatively deficient, and that restoration of strongly positive iodine balance is associated with clinical improvement. An explanation of the mode of action of iodine in Graves' disease must account for the fact that the administration of large amounts of iodine raises the concentration of organic and inorganic iodine in the thyroid gland and lowers the concentration of organic iodine in the plasma. From these facts it is obvious that there is a decline in the rate of delivery of thyroid hormone to the plasma. It is of interest that Wolff (228) has shown that large amounts of stable iodine do not prolong the biological half-life of I^{131} in the normal or propylthiouracil-treated rat nor alter the ability of large doses of thyrotropin to shorten the biological half-life of I^{131}. One conclusion which could be drawn is that the human being with Graves' disease is fundamentally different from the rat in this regard; a more likely deduction, in keeping with other observations in Graves' disease, is that this aspect of Wolff's experiments does not apply on the ground that in Graves' disease the excessive delivery of thyroid hormone is not due to an abnormally high level of thyrotropin. This point of view is supported by the findings of Goldsmith (75) and of Solomon (186) that iodine administered in large quantity in Graves' disease does decrease the rate of discharge of labelled hormone, a view previously advanced by Ansell and Miller (2).

It is also tempting to speculate that the arresting effect of iodine on thyroid hormone synthesis as described by Wolff and Chaikoff is important in the therapeutic effect of iodine in Graves' disease, and the reviewers succumb to this temptation despite the objection that rate of synthesis of hormone exceeds rate of secretion during iodide administration. The "Wolff-Chaikoff phenomenon" has been found to be temporary in normal rats despite continuing high plasma levels of iodide. However, the experiments of Purves and Griesbach (163) indicate a permanent inhibitory influence of iodine in large amounts in the presence of thiourea, and may provide a thyroid gland in the rat more suitable than the normal for comparison with the thyroid gland in Graves' disease, for thiourea is an incompletely effective antithyroid substance in the rat but provokes some degree of hyperplasia and depletion of organic iodine. Further experiments in the rat should be designed to test the validity of these observations of Purves and Griesbach.

The observation that hormonal stores in the histologically involuted thyroid gland are increased during therapy with iodine in Graves' disease does not invalidate the hypothesis that the inhibitory action of iodine on hormone synthesis as described by Wolff and Chaikoff is operative, although it does indicate that the effect of iodine in slowing release of hormone must exceed that on the rate of hormone synthesis. This is quite possible since their data do not indicate a total suppression of organic binding of iodine.

Interest in iodine as a factor in the production of goiter in man has been stimulated by the recent observations of myxedema and goiter developing in the course of treatment of non-thyroid diseases with iodides in large doses (29, 144, 166). Some observers have noted goiter in the newly-born infants of mothers taking large doses of iodine (200a).

The fact that myxedema and goiter can develop in the course of administration of iodine to euthyroid individuals indicates that in man iodide may exert an antithyroid action which can be maintained over a long period. A few instances of myxedema developing in the course of iodine therapy of hyperthyroidism have been noted (89, 162, 204).

The chemical mechanism by which iodide ion may inhibit iodination of protein has been reviewed by Pitt-Rivers (157), and a modification of the original hypothesis has been recently advanced by Fawcett and Kirkwood (57). It is clear, however, that iodine, probably as iodide ion, acts to modify the thyroid gland directly, and that it exerts an influence on the thyroid even when iodination of tyrosyl residues is prevented by thiouracil. Iodine in minute amounts also influences the thyroid gland morphologically as well as functionally in the absence of the pituitary. It is therefore likely that a chemical formulation of the effect of excess iodide ion on the oxidative process is not a sufficient explanation for the complexities of the relationship of the metabolism of iodine to thyroid function. It seems at present that the inhibitory effect of iodide ion on hormone synthesis is most likely to be observed on a permanent basis in association with either hyperplasia of the thyroid or some other means by which the iodide-concentrating mechanism is made highly active; in respect to this it is enigmatic

that iodide ion in blocked glands appears to be concentrated in the lumina of the follicles rather than in the cells in the radioautographs of Pitt-Rivers and Trotter (158).

B. Thiocyanate

Early evidence did not clearly differentiate the mode of antithyroid action of thiocyanate ion from that of thiourea derivatives. Although it was noted that thiocyanate was a weak goitrogen and that it was probably unique in exerting no goitrogenic effect when iodide was added to the diet, Astwood (5) considered this inconclusive evidence on the ground that the goitrogenicity of small dietary concentrations of thiouracil was greatly enhanced by reduction of the iodine content of the diet. A logical extension of this observation would be that minute quantities of thiouracil would exert a detectable effect only in the absence of appreciable dietary iodine. This is known to be true for thiocyanate. The first step in resolving this difficulty was taken by Franklin *et al.* (61), who showed that the accumulation of iodine by slices of thyroid tissue was depressed by thiocyanate but not by thiouracil, suggesting that thiocyanate acted upon an initial phase of iodine metabolism, iodide ion uptake, whereas thiouracil altered iodine metabolism at a later phase. Subsequent investigations in intact animals confirmed these conclusions (208, 233). The practice of studying iodide accumulation and inhibitors of this process in the presence of thiouracil or its derivatives has often proved advantageous. Wolff *et al.* (233) demonstrated a relationship between the concentration of thiocyanate in plasma and the inhibition of iodine-uptake, establishing the effectiveness of thiocyanate administered either acutely or chronically. VanderLaan and Bissell (208) fed young rats propylthiouracil for many days until the thyroid glands were hyperplastic and depleted of iodine. They then injected potassium iodide in 50 μg. and in 500 μg. doses and followed the curve of uptake and release of iodine over the ensuing 24 hours. Maximal uptake of iodine occurred in an hour or less, and a continuous decrease in iodine concentration occurred over the succeeding 24 hours, suggesting a relation to renal excretion of iodine. It was noted that uptake was considerably depressed by concurrent thiocyanate feeding or by injection of thiocyanate two hours before the administration of iodide. Subsequently VanderLaan and VanderLaan (206) adduced additional evidence that the initial phase of iodine metabolism involved iodide accumulation, and that a concentrating-mechanism or "pump" for iodide ion existed, ensuring a many-fold concentration of iodide ion from plasma to cells, and they demonstrated that it was this mechanism which was disrupted by thiocyanate. It appeared most significant that thiocyanate was able to discharge iodide from the thyroid gland as well as to prevent its concentration initially. Until recently it appeared that thiocyanate could not depress the ratio of thyroid iodide to plasma iodide to unity, but Halmi (93a) using enormous doses of thiocyanate has depressed the ratio to 0.66.

The mechanism by which thiocyanate inhibits the iodide ion-concentrating device of the thyroid gland remains obscure. Although it behaves chemically in a manner similar to halides, in the experiments of Wood and Williams (236,

237) it was only slightly concentrated in the thyroid gland of the rat even when the gland was made avid for iodide by chronic propylthiouracil administration or by a diet deficient in iodine. Using thiocyanate labelled with radioactive sulfur, they demonstrated oxidation to sulfate, a process inhibited by propylthiouracil. It is of interest that thiocyanate was fixed to thyroid proteins to a greater extent than to adrenal or liver proteins and that this was inhibited by propylthiouracil. The significance of this finding is in doubt since thiocyanate is effective in inhibiting the iodide-concentrating mechanism in the presence of propylthiouracil, as well as in its absence.

A most interesting discovery is that other ions of the Hofmeister series share with thiocyanate the capacity to depress the iodide-concentrating mechanism. Wyngaarden *et al.* (238) have shown in rats that perchlorate ion is 10-fold more active than thiocyanate. Periodate, iodate, biiodate, and nitrate possess activity, but not bromate. In the reviewers' opinion the weight of evidence is also against the view that bromide is a significant competitor with iodide for uptake in the thyroid gland because it is not capable of displacing iodide, although bromide has been shown to be concentrated by the thyroid gland. Astatine is concentrated by the thyroid gland and exerts a radiation effect on it (95). The data of Shellabarger and Godwin (184) suggest that astatine behaves like iodide in that the prior administration of thiouracil enhances rather than diminishes its uptake by the thyroid gland of the rat.

C. Antithyroid substances

Since the reviews of Astwood (5, 7) and Pitt-Rivers (157) concerning the mechanisms of action of antithyroid agents, a new group of substances inhibiting organic binding of iodine by thyroid tissue has been discovered. Bull and Fraser (35) reported myxedema and goiter occurring in a 60-year-old woman who had been under treatment for a leg ulcer to which resorcinol ointment was applied. The evidence of myxedema was unequivocal, and at autopsy the thyroid gland was four-fold enlarged and showed parenchymatous hyperplasia. The likelihood that resorcinol was the antithyroid agent was reinforced by two additional cases of myxedema and thyroid hyperplasia in which percutaneous absorption of resorcinol was suspected following prolonged treatment of leg ulcers with an ointment. The removal of the drug was followed by relief from myxedema, and its readministration in one patient was followed by return of myxedema. Thus resorcinol, a dihydroxyphenol, was recognized as an antithyroid agent in man. Doniach and Fraser (52) concurrently reported the antithyroid effect of resorcinol in rats. In this species 5 mg. of resorcinol per kg. of body weight given by injection reduced the thyroid capacity to accumulate I^{131} to a level 50 per cent to 11 per cent that of control animals. Oral administration was not effective. The depression of thyroid function was shown to be due to inhibition of organic binding rather than of iodide accumulation.

In the next year paraaminosalicylic acid was shown to produce myxedema and goiter (116). Hanngren (97) found in three patients that I^{131} accumulation by the thyroid gland was suppressed in the presence of concentrations of paraaminosalicylic acid in the blood in the range of 25 mg. per 100 ml. Clausen and

Kjerulf-Jensen (43) found that paraaminosalicylic acid was antithyroid judged histologically and by changes in gross weight in rats, mice, and rabbits but not in guinea-pigs. The activity of the drug was not reversed with additional iodine in the diet but was not evident when thyroid was fed. Meta-aminophenol was a more effective drug in rats but neither exceeded one per cent of the activity of methylthiouracil.

Arnott and Doniach (3) and Rosenberg (177) extended the investigation of compounds allied to resorcinol and inhibiting thyroid function. The former compiled a considerable number of compounds suppressing accumulation of I^{131} by the thyroid gland of the rat and noted this activity when two hydroxyl groups were substituted in meta position in the benzene ring. One substance, 2,7-dihydroxynaphthalene, was an exception to this generalization. Close correlation with earlier work on peroxidase activity was noted, resorcinol being an inhibitor of peroxidase. Rosenberg found a striking correlation between the capacity of aniline derivatives and polyphenols to suppress radioactive iodine accumulation by the thyroid gland of the rat and the capacity to inhibit peroxidase of milk. He observed that substances having antithyroid activity either compete as substrates for peroxidase, *e.g.*, the thiocarbonamides, or inhibit peroxidase, *e.g.*, aniline, resorcinol, and sulfaguanidine.

Phenothiazine (thiodiphenylamine), an anthelminthic in veterinary and human therapy, has been found by Talmage *et al.* (200) to suppress significantly radioiodine uptake in rats. A recent paper (147a) indicates this effect of phenothiazine is largely if not entirely due to its high iodine content. Phenylbutazone (3,5-dioxo-1,2-diphenyl-4-n-butylpyrazolidin) suppressed radioiodine uptake in rats (181) and in man (78). In both species parenteral injection was used.

Fawcett and Kirkwood (57) have suggested a quite different interpretation of the observations of Arnott and Doniach and of Rosenberg. They stressed the importance of studying the problem by *in vitro* methods, using tissue slices in their own experiments. It may be stressed that the biological significance of substances affecting thyroid function can only be assessed in the intact animal. Fawcett and Kirkwood (57) have grouped the sulfonamides, phloroglucinol, resorcinol, etc., and the "aromatic" antithyroid drugs and postulate that the group acts by forming molecular compounds with elemental iodine. Although resorcinol inhibits peroxidase, they have questioned this as an explanation for its antithyroid activity when iodination of the substance itself by thyroid tissue can occur. This was demonstrated by paper-chromatographic identification using carrier-free I^{131}. They also claimed to have seen iodomorpholine crystals which had been formed in the presence of thyroid tissue and have submitted these observations as proof that elemental iodine occurs in thyroid tissue. Their contentions appear incompatible with the observation of Wollman and Scow (234) that T/S ratios are high after administration of phloroglucinol to mice. Paper-chromatographic studies indicated that the I^{131} in the thyroid was in the form of iodide. The evidence that peroxidase activity is essential to thyroid tissue function deserves consideration until Fawcett and Kirkwood's observations are confirmed by others.

The extraction and identification of *l*-5-vinyl-2-thiooxazolidone from yellow

turnip and Brassica seeds (12), a compound equalling thiouracil in its antithyroid potency, represented a most significant advance in the understanding of the problem of goiter in man. In regard to positive factors in the causation of goiter as contrasted to dietary deficiency of iodine, it should be recalled that the goiter induced experimentally by thiouracil is appreciably diminished by excess dietary iodine. Hence the prevention of goiter by iodine does not necessarily indicate that lack of iodine caused the goiter.

For consideration of the status of the mechanism of action of antithyroid drugs as indicated by studies *in vitro*, including those on homogenates of thyroid tissue and the significance of cupric ions and allied topics, the reader is referred to the recent review by Astwood (10).

D. Thyroid hormone

Thyroid hormone stimulates tissues generally. Claims have been advanced that thyroid hormone inhibits the respiration of thyroid tissue, measured *in vitro* (67), and that thyroxine inhibits the response of the thyroid gland to thyrotropin in regard to cell height (44) and in regard to iodide-ion accumulation (94).

Goiter results from feeding thiouracil to rats, and it is prevented by the concurrent administration of thyroid hormone (13). This has served as a method for estimating the thyroxine output of the thyroid gland (49) at various temperatures. By this method 3 μg. per day appears to be the thyroxine output of the normal rat. It has also been used in comparing the relative potency of thyroxine and triiodothyronine (87). Astwood and Bissel (11) and McGinty (135) noted that thyroxine administered to rats prevents the discharge of hormonal stores, as indicated by total content of iodine, resulting from the administration of thiouracil. It is interesting that a daily dose of 20 to 30 μg. of thyroxine by injection was required to suppress loss of iodine, an amount 4 to 10 times that required to prevent goiter. Since Astwood and Bissell (11) and later VanderLaan and Greer (211) showed that the pituitary must be present for thiouracil to reduce the iodine content of the thyroid and that thyrotropin injection promotes this loss in the hypophysectomized rat receiving thiouracil, it follows that the dose of thyroxine necessary to suppress production of thyrotropin is approximately seven times that necessary to preserve normal thyroid-pituitary relations, that is, seven times the dose required for goiter prevention. According to McGinty (135), even larger daily doses of thyroxine, 40 μg. to 80 μg., are required to allow involution of the thyroid gland of the rat to occur when thiouracil administration both precedes and accompanies the administration of thyroxine. This experiment, however, is complicated by the fact that the tissues have been depleted of thyroid hormone and hence quantitative interpretation is difficult.

Although hypertrophy of the pituitary gland in myxedema has long been known, there appears to be variation amongst species in this regard. Gorbman (76) noted striking enlargement of the pituitary glands of mice eight months after I^{131} administration. Goldberg and Chaikoff (70) confirmed its occurrence in the mouse after obliteration of the thyroid by radioiodine but not in the rat

or in the dog. In the mouse 3 to 6-fold enlargement of the pituitary gland was observed 6 to 10 months after the thyroid was destroyed. The hypertrophy was limited to the anterior lobe and was due to hyperplasia of basophils with degranulation of acidophils. Since it was abolished by feeding desiccated thyroid, it is a consequence of hypothyroidism rather than a direct effect of I^{131} on the pituitary gland. The situation in the rat is obscure in that Higgins (99) found appreciable enlargement of the pituitary gland after the administration of promizole, a goitrogen. The enlargement was prevented by thyroid hormone but not by iodide. For a discussion of histological changes in the pituitary produced by alterations of thyroid function the reader is referred to the recent article of Halmi (93).

Griesbach *et al.* (84) have investigated the physiological activity of the stereo-isomers of thyroxine by finding the dose needed to prevent the pituitary basophilia that follows antithyroid drug administration in rats. By this technique 2.3 μg. of *d-l*-thyroxine per 100 g. rat per day is the smallest dose maintaining normal conditions, and the racemic mixture is two-thirds as active as *l*-thyroxine, which is three times more active than *d*-thyroxine.

Evidence of an alteration of function of the thyroid gland of man following the administration of thyroid hormone was noted by Riggs *et al.* (172), who found in psychotic patients receiving daily doses of 3 to 5 grains of desiccated thyroid there occurred no rise in the concentration of organic iodine. The organic iodine did rise as this dose was exceeded and a decline of organic iodine and of the metabolic rate to subnormal levels followed the abrupt withdrawal of desiccated thyroid. Danowski *et al.* (46) noted that 0.2 g. desiccated thyroid was the smallest daily dose that raised the concentration of organic iodine in normal human subjects and that 0.4 g. per day was effective in all three subjects tested. Suppression of the thyroid gland in normal human subjects by desiccated thyroid was shown by Stanley and Astwood (194), by Skanse (185), and by Greer (181). The administration of thyroid hormone for one week depressed I^{131} uptake in normal subjects and doses as low as 0.065 g. daily were often effective. This dose after three weeks depressed the accumulation of I^{131} by the thyroid gland to 10 per cent or less per 24 hours, in one-third of the patients tested, and 0.26 g. was effective in all patients tested. In studying the recovery rate Greer noted a return to normal I^{131} accumulation in two weeks in most patients, but the maximum period of recovery exceeded 11 weeks. This suppression was not due to the iodine administered, since an amount of iodine equivalent to that in the desiccated thyroid had no effect. It was notable that prompt recovery of the ability to accumulate iodine occurred even after years of suppression from thyroid hormone. Greer (82) found the thyroid glands of thyrotoxic subjects more resistant to suppression by thyroid hormone as measured by I^{131} accumulation. It is probable that the small suppression Greer observed was due to the large amount of iodine in the doses of thyroid used, 0.7 g., for Werner *et al.* (218) have shown that *l*-triiodothyronine, 2 mg. daily for one week, equivalent to 3 g. thyroid, fails to suppress iodine uptake in thyrotoxic patients despite a marked worsening of symptoms.

Drummy (54) found that failure of thyroid feeding to suppress I^{131} accumulation was an indication of hyperthyroidism in 24 of 28 subjects in whom the diagnosis was confirmed by their subsequent course. Greer and Astwood (83) recorded their five-year experience with desiccated thyroid in the treatment of simple goiter and of nodular goiter. Complete or partial regression occurred in diffuse goiter and multinodular goiter, as well as in single nodules. They reviewed the German literature of the latter part of the 19th century and indicated the essential agreement of their therapeutic results with those of sixty years ago. Papper *et al.* (152), using *l*-thyroxine in 0.1 mg. to 0.5 mg. oral doses for two to eight weeks, recorded effects on I^{131} uptake and on thyroid size in non-toxic goiter which were in substantial agreement with those of Greer and Astwood. From these studies it is apparent that administration of thyroid hormone causes inhibition of thyroid function in euthyroid but not in hyperthyroid human beings.

Goldberg and Chaikoff (71) showed that the fall in plasma protein-bound iodine occurring in rats fed 2,4-dinitrophenol fails to induce a change in the basophils of the pituitary, although methylthiouracil in combination with dinitrophenol increases both the basophilic cell count of the pituitary and thyroid size. They concluded, therefore, that the concentration of circulating thyroxine is not the only factor regulating thyrotropic hormone production.

III. ANTITHYROID SUBSTANCES IN MAN

Antithyroid drugs have figured importantly in the treatment of Graves' disease. Their introduction to therapeutics rests on a basis that deserves statement. The original observations on goitrogenic substances did not declare their antithyroid activity, and it was a keen perception which led to the conclusion that the development of more potent goitrogenic substances should *pari passu* provide agents effective in the control of hyperthyroidism. The subsequent investigations bore out this point of view by establishing that the goitrogenic effect was a result of thyroid inhibition by these drugs and was dependent upon an intact pituitary gland. The development and application of methods for inquiring into the chemical nature of substances inhibiting thyroid function were deftly executed, but, in the reviewers' opinion, it was in the conceptual sphere that brilliance was attained.

The question of what has been learned of the nature of Graves' disease from the use of antithyroid drugs can be put fairly. Early evidence (167) indicated that antithyroid drugs increased thyroid hyperplasia in Graves' disease, favoring the view that thyrotropic activity became increased. The small number of cases studied and the difficulties inherent in the method of biopsy and estimation of cell-height make this evidence inconclusive. On the other hand, the general experience that thyroid size frequently diminishes during prolonged treatment with antithyroid drugs favors the opinion that there is either no change in thyrotropic activity or actually a decrease as the change from hyperthyroidism to a euthyroid state is induced. This stands in sharp contrast to the enlargement of the thyroid gland which accompanies induction of hypothyroidism and indicates that the progression from the hyperthyroid state to euthyroidism does not promote physiological responses comparable to those which follow change

from the euthyroid state to hypothyroidism. These observations are consistent with Werner's deductions that thyrotropic activity is not increased in Graves' disease (216).

The use of antithyroid drugs in the treatment of hyperthyroidism has become standard medical practice. The decision to use this method of treatment in preference to others is often intuitive or arbitrary.

Among the advantages accruing to treatment of Graves' disease with antithyroid drugs in contrast to the use of measures which destroy thyroid tissue are its widespread availability, the simplicity of treatment, the great uniformity of success in the control of the disease, and the low cost to the patient. Among the disadvantages of treatment with antithyroid drugs are the prolonged period of treatment and the tendency for relapses to occur when the drug is discontinued. Some of these points deserve elaboration.

Antithyroid therapy is the only treatment for Graves' disease which can be considered physiological. Antithyroid drugs administered over a period of months, by partially suppressing thyroid function, provide a period of good health in which Graves' disease tends to disappear, leaving an intact individual often with a normal-appearing thyroid gland. The treatment need not entail hospitalization in the vast majority of patients, and, if the diagnosis is reasonably well defined, expensive diagnostic tests can be avoided both initially and in the period of treatment, the control of signs and symptoms being adequate for judging the efficacy of treatment. Expensive instruments and testing are required for treatment with radioiodine, which is not widely available. The expense and risk of operation exceed those of therapy with drugs.

On the other side of the coin there are the prolonged period during which the patient is under supervision and the tendency for relapse to occur when treatment has been discontinued. A year or more of treatment clearly offers disadvantages. Among these are the discouragement of the patient and the possibility that he will become too dependent on the physician. The discouragement undoubtedly is real, but it is sometimes obviated by frank explanation to the patient in advance. Too great a dependence on the physician because of the long period of treatment of Graves' disease is a problem with which the physician should be prepared to cope. Graves' disease is characterized by nervousness but is not proved to be caused by emotional factors. However, it may be benefited by the psychological support of a physician. Cognizant of the problem, a physician may employ his position to foster the independence of the patient, or, if this is not possible, to support the patient in terms of his dependent needs without threatening or dominating him.

The basis for advocating antithyroid drugs as the primary agents for the definitive treatment of hyperthyroidism is that they provide inhibition of function without destruction of tissue. The rates of remission following the three methods are sufficiently of an order to make this consideration compelling.

A. Substances available for the treatment of hyperthyroidism

In 1948 the Council on Pharmacy and Chemistry of the American Medical Association announced it would not sanction thiouracil for therapeutic purposes

TABLE 1

Incidence of toxic effects during the clinical use of thiouracil

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Astwood (4)	62	7	1	1	4							1			
Beardwood and Levinson (25)	20	3		2						1					
Beierwaltes and Sturgis (27)	80	8	3	3	1	1									
Boyd and Connell (32)	9	6			2	2								2	
Bram (33)	50	2	1				1								
Brull and Lefebvre (34)	23	5				1								4	
Cannon (36)	10	2				1						1			
Donald and Dunlop (50)	31	1		1											
Eaton (55)	36	0													
Evans and Flink (56)	18	4		1		1								2	
Fishberg and Vorzimer (58)	96	19	1	18											
Fowler (60)	61	14*		3		2				1	1	1		8	
Gabrilove and Kert (65)	9	3*		1	2	2			1						
Gargill and Lesses (68)	43	7	1		2			2						2	1
Grauer *et al.* (77)	63	11*	1	3	4					1	1			2	
Greenberg and Bruger (79)	37	7		3		1		1			2				
Grollman and Gryte (86)	18	4					4								
Himsworth and Joll (101)	33	4	1	2		1									
Himsworth *et al.* (102)	91	13*	2	8	3	1			1		1			1	2
Jackson (108)	30	2				1						1			
Kennie *et al.* (112)	42	8		1		5								3	
Lahey (117)	196	23	2	7	7	4				2				1	1
Lesses and Gargill (120)	62	4	3	1											1
Maxwell (126)	10	0													
McArthur *et al.* (127)	104	15			5									10	
McGavack *et al.* (133)	78	15*	2		2	3	2			3		1		5	

McGregor (137)	20	0													
Montague and Wilson (139)	43	1*				1	1								
Moore (140)	53	10		2	2				1					5	
Morgans (142)	49	8	2	3	2									1	
Morton (145)	80	2	2												1
Muether (147)	38	6		3			1	1				1			
Newman (148)	34	0													
Nussey (149)	27	0													
Palmer (151)	100	0													
Paschkis *et al.* (153)	30	4		1	4		3	1			2				
Payne (154)	45	5		5											
Rawson (167)	25	0													
Reveno (168)	32	8*			1	3						5			
Robertson (174)	111	0													
Rose and McConnell (175)	37	5*		5	1				1					2	
Seligman (182)	26	6	1	2	1	1		1							
Sharpey-Shafer (183)	30	0													
Sprunt (188)	36	14		9						5					
Stuart (199)	42	20*	1	6	6	5					9	5			
Thomson (205)	13	5		1	1	1								2	
Vorhaus and Rothendler (213)	25	3			1					1				1	
Watson (215)	35	1*		1	1										
Williams *et al.* (223)	247	36	3	13	7	6	5			6	2		5	1	
Total	2490	321 (12.9%)	27	106	59	43	17	6	4	20	18	16	5	52	6

* Multiple reactions in these patients.

in the United States (41). Previously (212) the Council had reported on 5,745 cases treated with thiouracil by 328 investigators. Although this substance is no longer in use many of the statements presented about it are valid for all antithyroid drugs and deserve recapitulation. Thiouracil was found effective whether the thyroid gland was smooth or nodular. The importance of administering three or four doses per day was emphasized. The delayed response to thiouracil which is observed when iodine has been administered in the previous four to eight weeks was noted to account for many "failures of response". The toxicity of thiouracil in this study and in Moore's (141) was quite comparable to that shown in table 1 summarizing 2,490 cases. In this and in the subsequent tables an attempt was made to choose representative papers which had been written to present experience in treating hyperthyroidism rather than to report an untoward reaction to a drug, as in most case reports.

6-Methylthiouracil (table 2) in the British Commonwealth and on the European Continent and 6-n-propylthiouracil (table 3) in America have been widely used. The tables indicate that propylthiouracil is considerably less toxic than either thiouracil or methylthiouracil. Other derivatives of thiouracil, 6-ethylthiouracil, 6-cyclopropylthiouracil, 6-butylthiouracil, and 6-isobutylthiouracil have had insufficient clinical trial (14, 222) to allow comparison of toxicity.

As previously mentioned, the compounds used early in the treatment of hyperthyroidism were selected because of potent antithyroid activity in the rat. Subsequent experience has indicated that little correlation exists between the potencies in rats and those found by clinical trial. Stanley and Astwood (192, 194) studied the effects of antithyroid drugs on radioiodine accumulation by the thyroid glands of normal subjects, and they selected 2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole (methimazole) as agents 10 and 100 times as active as thiouracil. Mercaptoimidazole has not found widespread use, but methylmercaptoimidazole has been put to extensive clinical trial. The estimations of proper dosage range from 5 to 10 mg. every eight hours; occasionally doubling the larger dose is required. Thus it is from 10 to 30 times as active as propylthiouracil. However, table 4 indicates its toxicity to be little different from that of propylthiouracil. Irwin *et al.* (105) estimated the therapeutic response to be more rapid with methylmercaptoimidazole than with propylthiouracil, but Bartels and Sjogren (24a) found no difference in rate of response.

In 1951 a derivative of methylmercaptoimidazole (mercazole, in Great Britain) in which the thiol is "blocked" by a carbethoxy group was synthesized by Lawson and Barry (118) and introduced for clinical use (119). Neomercazole (2-carbethoxythio-1-methylglyoxaline) was thought to have an advantage over the parent substance in that the latter may be released by hydrolysis and therefore a more steady supply of the inhibiting configuration be received by the thyroid gland. Proof of these assumptions has not been provided. Although the initial dosage followed was too low, the subsequent experience of Doniach (51) has indicated this to be an effective drug in the amount of 45 mg. per day or less. Although the series of patients treated with neomercazole is too small to

TABLE 2

Incidence of toxic effects during the clinical use of methylthiouracil

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Barfred (16)	61	34*	1	3	16	13						14	2	7	
Bartels (22)	40	5		1		4									
Brull and Lefebvre (34)	5	1				1									
Frisk (63)	115	13*		7	9						1				
Hallahan and Perloff (90)	27	3		2		1									
Iversen (107)	244	29*		4	26	15					3	4	6	5	
Leys (121)	16	0													
Lou and Wulff (122)	76	13*	2	2	15	7									
Lundbaek (123)	35	4	1		1	1								1	
McCullagh and Sirridge (132)	100	5		1		2								2	
Meulengracht (138)	80	3*			3	1									
Morgans (142)	23	10		1	2				3		1			3	
Poate (159)	200	16	1	1	6	4								4	
Stirrett *et al.* (197)	70	7						3			1	1		2	
Wahlberg (214)	24	11	1	2						3		1		2	
Total	1116	154 (13.8%)	6	24	78	49		3	3	3	6	20	8	26	

* Multiple reactions in these patients.

TABLE 3

Incidence of toxic effects during the clinical use of propylthiouracil

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Astwood and VanderLaan (14a)	100	2					2								
Aspenstrom (15)	120	5	1	1		1					2				
Barr (17)	81	0													
Bartels (22)	820	15	3	7	3	1				1					
Bell and Mishtowt (30)	56	6	1	1	1	2								1	
Brull and Lefebvre (34)	25	2									1	1			
Crile *et al.* (42)	218	8		1		1	1				2	1	2		
Donoso *et al.* (53)	15	1		1											
Futcher *et al.* (64)	27	1	1												
Grauer *et al.* (77)	37	3					3								
Greenberg and Bruger (79)	46	2		1							1				
Hallman and Bondy (91)	50	2	2												
Hamilton and Werner (96)	15	0													
Irwin *et al.* (105)	54	5	1	3		1									
Kent *et al.* (113)	51	3		1	1							1			
Maddox (125)	34	0													
McCullagh *et al.* (131)	190	2		1		1									
McGavack *et al.* (134)	75	1			1										
Rose and Shorey (176)	25	4		2		1								1	
Reveno (169)	95	2		1	1										
Starr *et al.* (196)	40	6		6											
Taylor *et al.* (202)	52	2	1	1											
Wahlberg (214)	46	4				1								3	
Wilson and Goodwin (225)	16	1				1									
Wing and Asper (226)	203	4	1				2							1	
Total	2491	81 (3.25%)	11	27	7	10	8			1	6	3	2	6	

TABLE 4

Incidence of toxic effects during the clinical use of methimazole

Author and Reference No.	No of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Astwood (9)	2	0													
Bartels (23)	214	16		1		14					1				
Beierwaltes (26)	20	0													
Chevalley *et al.* (39)	184	8		3		4	1								
Davidson (48)	44	2				1								1	
Foss (59)	15	4				1								3	
Fraser, Garrod *et al.* (62)	56	6*			4	5					5			3	
Hallman and Bondy (91)	35	0													
Hamilton and Werner (96)	18	0													
Irwin *et al.* (105)	45	3	1	1		1									
Isbister and Rundle (106)	36	5					1					3		1	
Kendrick *et al.* (111)	32	3				2	1								
Kilpinen (114)	50	4		1		3									
Reveno and Rosenbaum (170)	18	0													
Schermann and Eseostegeny (180)	10	0													
Stone *et al.* (198)	29	8		1		4						2		1	
Taylor *et al.* (203)	23	0													
Total	831	59 (7.1%)	1	7	4	35	3				6	5		9	

* Multiple reactions in these patients.

allow assessment of the place it will hold in therapeutics there have been two cases of agranulocytosis.

Of the other drugs which have been put to clinical trial, there remains to comment on the iodinated substances, of which 5-iodo-2-thiouracil is the antetype. Barrett and Gassner (18) found 5-iodothiouracil to equal thiouracil in its capacity to lower oxygen consumption in rats. This was accomplished without measurable hyperplasia of the thyroid gland and led to the noteworthy suggestion "that the unique effect of the iodo derivative is due to the entire molecule rather than to any particular moiety". Barrett *et al.* (19) found iodothiouracil to be less goitrogenic in rats than equimolar amounts of KI and thiouracil. The notion that iodination of thiouracil would increase the intrathyroidal concentration of the agent found more credence than its slender foundation warranted, and a fairly extensive clinical trial resulted. Iodothiouracil appeared satisfactory in many studies in which it was used preoperatively, the consistence of the thyroid being sufficiently altered to permit surgical manipulations. It also has been noted to be less effective than nonhalogenated thiouracils, to allow escape from control and even thyroid "storm" to occur (74) and in general behaves much like a combination of iodine and a weakly antithyroid drug. Galbraith *et al.* (66) on clinical grounds have written, "It is not so certain, however, that iodothiouracil possesses any new or distinctive features as a drug for the specific treatment of hyperthyroidism", and two groups on the basis of animal experiments have differed with the view that iodothiouracil is in any way unique (73, 209).

Godley and Stanbury (69) have reported a preliminary study of perchlorate in the treatment of hyperthyroidism, and it will be necessary to await further clinical evaluations, including attempts at definitive treatment, to evaluate the place of this substance.

Tables 1 to 9 represent a compilation of data in an attempt to depict the toxic effects of the antithyroid substances which have been given significant clinical trial. Case reports are not included. Table 10 has been derived from the preceding tables and records the relative frequency with which fever and agranulocytosis, the most frequent serious complications, and death have occurred.

Individual case reports indicate that the toxic reactions to thiouracil include pericarditis with effusion and complete heart block, pancreatitis, fatal periarteritis, fatal jaundice, and nystagmus. Holliday (103) reviewed 66 published cases of agranulocytosis and concluded that in 27 the data established it as the correct diagnosis. Fifteen actually were considered examples of neutropenia and 24 could not be classified. Of interest in his analysis is the statement that 11 cases of agranulocytosis were diagnosed on the basis of leukocyte counts one to three days before symptoms began; two died. Of the 16 who presented with symptoms, 7 died. His compilation indicated that two-thirds of all cases of agranulocytosis had developed in the first two months of treatment.

Thiourea has been found to cause thrombopenia and granulopenia, and fatal agranulocytosis. Methylthiouracil and propylthiouracil have been reported to

TABLE 5

Incidence of toxic effects during the clinical use of thiourea

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Brull and Lefebvre (34)	6	0													
Danowski *et al.* (47)	118	0													
Himsworth (100)	6	0													
Johnston, C. R. St. (109)	7	3*			3	1			1			1		3	
Johnston, W. W. S. (110)	10	10			6	1					3				
Kent *et al.* (113)	49	8			4	2						3			
Maxwell (126)	6	3		1		1					1	2			
Morgans (142)	7	7*			6	1						7		11	
Paschkis *et al.* (153)	6	4		1	1	2						2			
Peters (156)	300	6			3		1					2			
Ritchie and Geddes (173)	10	8	1	2	1	1				1				6	
Total	525	49 (9.3%)	1	4	24	9	1		1	1	4	17		20	

* Multiple reactions in these patients.

TABLE 6

Incidence of toxic effects during the clinical use of thiobarbital

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Astwood (6).....	30	10*	1		6			1						2	2
Bartels (20).....	28	8	2	2	4										
Total.....	58	18 (31%)	3	2	10			1						2	2

* Multiple reactions in these patients.

TABLE 7

Incidence of toxic effects during the clinical use of aminothiazole

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Brull and Lefebvre (34).....	12	7					2							5	
McConnell *et al.* (128).....	23	12*			2	1	3	2	2		3	2		1	
Morgans (142).....	13	13*			6	5		2	1		3	3		4	
Perrault and Bovet (155)....	129	15			7		1					2		5	
Rose and Shorey (176).....	2	1					1								
Total.....	179	48 (26.8%)			15	6	7	4	3		6	7		15	

* Multiple reactions in these patients.

TABLE 8

Incidence of toxic effects during the clinical use of iodothiouracil

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Bartels (23).....	34	0													
Catz *et al.* (37).....	26	1		1											
Galbraith *et al.* (66).....	29	1				1									
Goldner and Kirschenfeld (74).....	10	1*			1				1						
McClintock and Lyons (129)..	107	5			2							3			
Williams *et al.* (224).....	46	0													
Total.....	252	8 (3.18%)		1	3	1			1			3			

* Multiple reactions in these patients.

TABLE 9

Incidence of toxic effects during the clinical use of 2-carbethoxythio-1-methylglyoxaline (carbimazole) (neo-mercazole)

Author and Reference No.	No. of Cases	No. of Reactions	Agranulocytosis	Leukopenia	Fever	Rash	Urticaria	Jaundice	Lymph Node Enlargement	Edema	Arthralgia and Myalgia	Gastrointestinal Disturbance	Neurological Disturbance	Miscellaneous	Deaths
Bartels (24)	52	3*	1			1	1				1				
Doniach (51)	120	0													
Fraser, Garrod *et al.* (62)	57	2	1			1									
Isbister and Rundle (106)	11	0													
Lawson and Barry (118)	14	0													
Poate (161)	9	0													
Total	263	5 (1.9%)	2			2	1				1				

* Multiple reactions in these patients.

TABLE 10

Incidence of serious toxic effects and death during the clinical use of antithyroid agents

Drug	Total Cases	% of Total Cases		
		Agranulocytosis	Fever	Death
Thiouracil	2490	1.07	2.37	0.24
Methylthiouracil	1116	0.54	7.0	0.00
Propylthiouracil	2491	0.44	0.28	0.00
Methylmercaptoimidazole	831	0.12	0.48	0.00
Thiourea	525	0.19	4.57	0.00
Thiobarbital	58	5.17	17.2	3.45
Aminothiazole	179	0.0	8.4	0.00
Iodothiouracil	252	0.0	1.19	0.00
Carbethoxymethylglyoxaline	263	0.76	0.0	0.00

cause hair loss and pigmentation, vertigo, paresthesiae and dysesthesiae, and other neurotoxic manifestations. Fatal periarteritis, hypoprothrombinemia, and thrombopenic purpura have been subjects of case reports on propylthiouracil. Methimazole has caused loss of taste, as well as agranulocytosis with recovery and with death. Neomercazole has caused agranulocytosis with recovery, and fatal bone marrow aplasia has been attributed to it.

B. Clinical use of antithyroid substances

Astwood summarized his views on this topic in 1950 (8), and few additional points can be made at this time. As indicated by him, propylthiouracil, 100 mg. every eight hours, methylthiouracil in the same or lower dosage, and methylmercaptoimidazole in the range of 5, 10, or even 20 mg. every eight hours are the preferred drugs; the carbethoxy derivative of the last is still being assessed. In regard to the importance of proper timing in the administration of drugs,

Berson and Yalow (31) have shown an appreciable increase in suppression of radioiodine uptake when 200 mg. of propylthiouracil was administered every three hours, instead of 400 mg. every six hours. In one subject 400 mg. every six hours allowed 50 per cent uptake of a tracer in 24 hours. Similarly methylmercaptoimidazole, as previously shown by Stanley and Astwood (195), was not fully effective in suppressing radioiodine uptake in doses of 10 to 40 mg. per day, and Berson and Yalow described one instance in which 25 mg. of methylmercaptoimidazole every six hours failed to suppress uptake completely. Clinical experience indicates that suppression of thyroid function which is quite incomplete is consistent with good therapeutic results.

Once control of hyperthyroidism has been gained, the initial dose of the antithyroid substance may be continued until early signs of myxedema appear, or dosage may be reduced as recommended by Doniach (51) in an attempt to avoid the thyroidal enlargement which occurs as an early sign of oversuppression. Opinions differ about the advantage of maintaining full control of the disease at all times, compared with the possible disadvantage of inducing thyroid growth temporarily. A third maneuver is to maintain full dosage of antithyroid substance throughout treatment and to supply exogenous thyroid, 0.1 to 0.2 g. daily, to avoid hypothyroidism. Conclusive evidence does not exist to allow a firm choice among these methods, although the desirability of fully controlling the hyperthyroidism at all times seems well established. The means of assessing the degree of control vary; determinations of cholesterol and of organic iodine concentrations in the serum, basal metabolism, and clinical signs all have advocates. In the use of antithyroid drugs there exists general agreement that therapy provide a period of at least six months of complete freedom from symptoms, signs, and laboratory evidence of hyperthyroidism. Medication may then be withdrawn. In the event of persistence of the disease, which will usually be apparent within two months, the maintenance treatment may be resumed for another four- to six-month period.

C. Antithyroid substances and the prognosis of hyperthyroidism

There exists a wide diversity of opinion concerning the influence of antithyroid drugs on the natural history of hyperthyroidism (107, 130, 150, 197). In this situation the prudent course is to give greater weight to the reports which have been submitted in support of this method of treatment, assuming with Poate (160) that the technique is grossly at fault with those who have been entirely unable to achieve results.

Solomon *et al.* (187) presented observations on 101 patients treated with antithyroid drugs evaluated four or more years after the completion of treatment and attempted to discover factors influencing the incidence of remission. A decrease in the size of the thyroid gland during treatment was the only factor which indicated a favorable prognosis. Williams *et al.* (222, 223) had previously noted the importance of regression in thyroid size. In Solomon's study, age, sex, size of the thyroid at the outset, nodularity, duration of illness, severity of illness, previous iodine therapy, cardiac involvement, severity of ocular involve-

ment, and treatment being prolonged for more than a year, all were without significant influence on the likelihood of sustained remission after treatment with antithyroid drugs. Recurrence of hyperthyroidism was unfavorable. Although not apparent in their study, other data suggested that primary hyperthyroidism and a small diffuse goiter were favorable indications. Although Iversen (107) did not comment on the significance of a regression in thyroid size, he noted that it occurred in 53 per cent of the patients with diffuse goiter and that in more than 80 per cent thyroid size was normal at the end of treatment. Poate (160) found the thyroid regressed to normal size in 64 per cent of 128 patients. Meulengracht and Kjerulf-Jensen (137a) held that in their experience the thyroid tended to regress in size after cessation of treatment, not during it.

Divergence of opinion has existed about many of the factors held to influence prognosis favorably. Williams *et al.* (223) held that female sex, small goiter, mild hyperthyroidism, more than one year of treatment, and a decrease in thyroid size were favorable prognostically. In regard to the favorable influence of female sex, Williams was supported by Bartels (21), Rose and McConnell (175a), and Rose and Shorey (176). Barfred (16), on the contrary, found male sex more favorable and in addition found youth a favorable influence, agreeing with Beierwaltes and Sturgis (28), and Maddox (125). Rose *et al.* (175a, 176), on the other hand, found youth an unfavorable influence for sustained remission. Most workers have found a small goiter favorable, Frisk (63) finding it unfavorable, and several studies indicating initial thyroid size to have no effect. No study encountered indicated diffuseness of the enlargement to be unfavorable, and a fairly even division has been found between its being favorable or of no significance. Recurrent hyperthyroidism has been held to militate against lasting remission by Bartels (21), Frisk (63), McCullagh (131), and Rose *et al.* (175a, 176). Williams *et al.* (223) received support from Bartels (21), Maddox (125), Rose *et al.* (175a, 176), and Wing and Asper (226) in his finding that mild hyperthyroidism was likely to undergo lasting remission, but several studies have indicated the severity of the disease to be without significance. There is general agreement that the likelihood of remission cannot be correlated with the severity of the ocular findings nor is it prejudiced by the previous administration of iodine. In general the duration of the illness has been found not to alter the likelihood of remission.

McCullagh and Cassidy (130) have reported a four- to six-year follow-up study of 60 patients with Graves' disease treated with propylthiouracil, 66.7 per cent remaining in remission. This was a series in which patients were selected for this form of treatment because of the diffuseness and moderateness of thyroid enlargement. It is not apparent upon comparison with Solomon's study of unselected patients, of whom 55 per cent had a remission after one course of treatment and 70 per cent after more than one course, that selection on the basis mentioned is necessarily valid.

The features of hyperthyroidism which are not clearly the result of the excessive production of thyroid hormone are the ocular manifestations and the

hyperplastic goiter, with its disturbed metabolism. Although the milder ocular manifestations customarily run a favorable course with antithyroid therapy as with other effective forms of treatment, little evidence or opinion relates the prognosis of hyperthyroidism to the course or severity of the ocular signs. On the other hand, Frisk (63), Iversen (107), Poate (160), Rose and Shorey (176), Williams *et al.* (222, 223), and Solomon *et al.* (187) have found that the thyroid gland regresses in size during prolonged antithyroid drug therapy. Solomon presented evidence that hyperplasia disappeared in those who remained euthyroid after cessation of treatment, radioactive iodine accumulation being normal in 32 of 34 patients tested. In one patient who died of myocardial infarction no residual hyperplasia was found histologically 8.5 years after treatment. Morgans *et al.* (143) found the avidity of the thyroid for iodine suppressed after thyroxine administration in patients who had recovered from Graves' disease. It seems highly significant that the prognosis of hyperthyroidism during antithyroid drug therapy is best indicated by the state of the thyroid gland. The correlation between regression in thyroid size and favorable prognosis supports the point of view that the thyroid gland is the site of the basic disturbance in Graves' disease.

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