THIOUREA AND RELATED COMPOUNDS IN THE TREATMENT OF HYPERTHYROIDISM*

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The use of thyroid-depressant agents in the control of hyperthyroidism has raised questions concerning their relationship to other goitrogens and their mode of action. Other problems have been encountered as well, particularly with respect to toxic reactions, the effect of preliminary iodine administraton, and the control of the hypothyroid state which may result. The information available on these subjects has, therefore, been analyzed critically, and the relative merits of thyroidectomy and of medical treatment of hyperthyroidism are discussed.

Types of goiter. More than a quarter of a century ago Marine and Kimball[49] demonstrated that endemic goiter could be prevented by the administration of iodine. In the two decades prior to 1941 it was possible to assert that all nontoxic goiter was due to an insufficient supply of iodine. This statement was based on the observation that iodine counteracted the effects of all known goitrogenic diets. Thus, simultaneous administration of iodine prevented the development of goiters in animals fed winter cabbage[16, 74, 75, 76, 77] and in those fed soy-bean flour.[70, 71, 78] Further investigation had proven that a number of pure organic cyanides and thiocyanates were goitrogenic,[9, 50, 61] and that their action was also preventable by iodine.[48] Since organic cyanides and cyanogens[48] are regular constituents of winter cabbage and of soy-beans, it was concluded that these compounds were responsible for the goitrogenic action. Means,[51] writing in 1936, asserted: "Thus cabbage goiter is cyanide goiter, and cyanide goiter is iodine-want goiter conditioned by an increased secretory demand placed upon the thyroid gland by a retarded tissue oxidation resulting from the action of hydrogen cyanide."

In 1941 a type of goiter was discovered whose production could not be prevented by large doses of iodine. The goiter was produced by feeding Brassica seeds and rape seeds.[32, 33, 39] These plants belong to the cabbage family, but the effects were not due to any cyanides which they might contain. The active agent was thought by Ken-

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nedy to be a thiourea derivative.[38] Allyl-thiourea was found, in fact, to produce a goiter entirely similar in character to that seen after the ingestion of rape seed. Independently in the same year Richter and Clisby,[67] studying the general toxicity of phenylthiourea (phenylthiocarbamide), reported a goitrogenic action.

Mackenzie, Mackenzie, and McCollum[47] found, in 1941, another class of compounds, the sulfonamides, to be goitrogenic despite a high intake of iodine. Sulfaguanidine was the most effective member of this group. Astwood[3, 7] then reported that thiourea derivatives, aminobenzenes, and sulfonamides (which are chemically related both to the aminobenzenes and to the thioureas) possessed similar goitrogenic properties (Fig. 1). Treatment of animals with these substances produced a fall in the basal metabolic rate[3, 45, 46, 47] and histological changes in the pituitary closely resembling those which follow thyroidectomy.[46] Using the rat as a test animal, thiouracil appeared to be the most potent thyroid-depressant in all 3 series of compounds.[3]

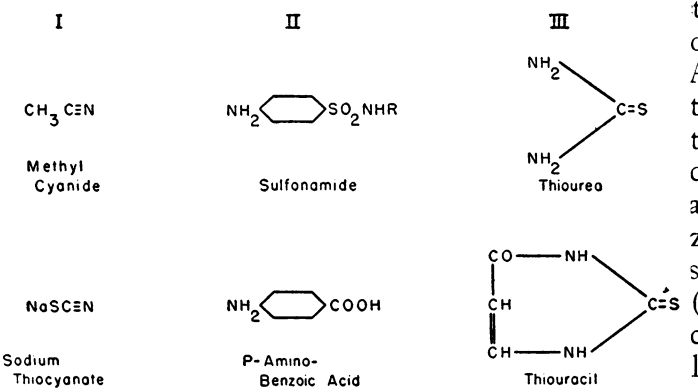

Fig. 1. Three groups of thyroid depressant drugs.

The ability of substances of this new type to induce hypothyroidism with great regularity clearly separates their action from that of the various cyanides and other goitrogenic diets. The demarcation is, however, by no means absolute. Although diets deficient in iodine, or containing cyanide, do not commonly cause hypothyroidism, there are certain exceptions. Deficiency of iodine in the maternal diet may produce endemic cretinism.[51] Furthermore, hypothyroidism in thiocyanate goiter of man has been reported.[61] Functional depression occurs, however, only sporadically and is easily prevented by iodine administration. Moreover, within a certain range of dosage, intermediate between ineffective and fully effective

amounts, simultaneous administration of iodine has an action markedly antagonistic to that of thiouracil *in normal rats.* Conversely, iodine deficiency favors the action of thiouracil in small doses.[4]

Mechanism of action. Under thiourea, thiouracil, or sulfonamide treatment the iodine content of the thyroid gland decreases rapidly.[5, 12] Studies with radio-active iodine have demonstrated conclusively that inorganic iodine can enter the thyroid gland in the presence of these compounds, but is not synthesized into diiodotyrosine or thyroxine.[4, 25, 26, 27, 28, 37, 40, 63] These substances produce hypothyroidism, therefore, by blocking the formation of thyroid hormone. They do not interfere with the release of hormone already present in the gland.

Peripheral utilization of thyroid hormone is not affected significantly, if at all, since desiccated thyroid or thyroxine prevents both the hypometabolism and the glandular hyperplasia.[22, 53] No direct effect on tissue metabolism has been reported as yet, other than that which results from depression of the thyroid gland. On the other hand, the onset of the hypometabolic state in rats can be accelerated by lowering the temperature of the environment.[22] The animals are then far more susceptible to the action of thiouracil as a result of the greater demand for thyroid hormone in a cold environment.

The goiter which develops is mediated through the pituitary gland, since hypophysectomy prevents the thyroid hyperplasia even though the metabolism is profoundly depressed by thiourea or thiouracil.[7, 46] An intact pituitary gland is necessary, since injection of pituitary extract into hypophysectomized-thiouracilized rats is not followed by goiter formation. It has been shown by Gordon and his co-workers that the thyroid becomes hyperplastic as a result of increased pituitary secretion of thyrotropic hormone.[31] This can be demonstrated only under specific experimental conditions, since the thyroid gland possesses an extraordinary avidity for thyrotropic hormone. This prevents an increase in the amount present in the circulation. Thiouracil does not enhance the activity of thyrotropic hormone.[40] These interrelationships are shown in Fig. 2. Clinical studies support this interpretation. Hyperthyroid patients under thiourea treatment develop low concentrations of serum iodine, indicating that the output of thyroid hormone is reduced.[20, 42]

Conclusive experiments are lacking as to the exact mechanism whereby the synthesis of thyroid hormone is abolished. Hundreds

of compounds have now been tested for thyroid-depressant activity not preventable by iodine.[6] All of the effective drugs possess either a thiocarbamide or an aminobenzene group. Astwood has suggested that the reducing powers of the =C=S portion of the thiocarbamide molecule are important. This theory fails to explain, however, the activity of the aminobenzenes which lack this group. Lerner and

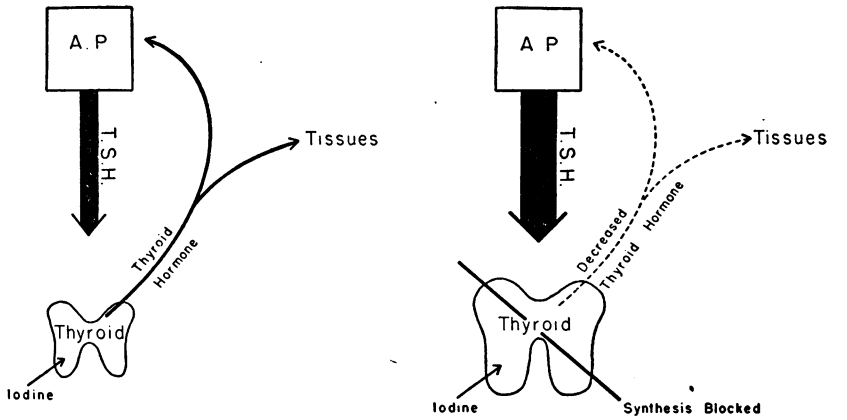

Fig. 2. Mechanism of goiter production during thiourea and thiouracil treatment.

Chaikoff have shown that thiourea is without effect on the cytochrome-cytochrome oxidase system.[41]

It has been found in dog experiments that thiourea exerts its thyroid-depressant effect without undergoing destruction in measurable amounts in the gland. The thiourea which is not recovered in urine is apparently destroyed in the kidney, and in no other tissue.[18] This suggests that thiourea stops the elaboration of thyroid hormone either by its simple presence in the gland, or by entering into a reversible combination with some component of the thyroid tissue. It is also pertinent that it has not been possible to demonstrate any particular avidity of the thyroid gland for thiourea. The drug is not concentrated in the gland in amounts greater than those which would be expected from its concentration in body water as a whole.[18] The metabolism of thiouracil, however, differs from that of thiourea, since it is destroyed in practically all body tissues.[81] The highest concentrations of this drug have been found in the bone-marrow. This may well be responsible for the marked tendency of this drug

to produce depression of the bone-marrow. Thiourea may ultimately, therefore, prove to be a safer agent in this respect.

Any theory of the action of these substances must account for their effectiveness in very small amounts when given once daily in the treatment of hyperthyroidism.[20] It should be remembered, however, that the demonstration that thiourea and thiouracil depress the thyroid gland does not preclude some peripheral action as well. If, as has been suggested, there is extrathyroidal production of thyroid hormone, thiourea and thiouracil may prevent the formation of this moiety as well.

Clinical experience with thiouracil and thiourea. The first account of clinical success was that of Astwood[2] in 1943, using both thiourea and thiouracil. Since then the effectiveness of these and similar drugs in hyperthyroidism has been abundantly confirmed.[1, 8, 10, 11, 13, 15, 17, 20, 23, 24, 29, 35, 43, 44, 55, 57, 58, 59, 60, 66, 68, 73, 79, 80] Certain facts are now established. These may be briefly summarized:

(1) The great majority of cases of hyperthyroidism will respond with a drop in basal metabolism and in serum precipitable iodine with concomitant clinical improvement. Partially refractory cases are occasionally encountered. Patients with toxic adenomata as well as those with diffuse goiter improve under treatment.

(2) The time required for the return to a normal metabolic status is variable. Four to six weeks is the most common interval.

(3) The dose necessary to bring about and maintain a remission varies somewhat from one case to another. The customary dose of thiouracil has been 0.6 gm. daily, and of thiourea from 0.3 to 0.1 gm. Smaller amounts of each drug have, however, been effective. Irrespective of the dose a certain time interval is necessary before the drug is fully effective.

(4) Continued administration of the drug frequently produces hypothyroidism, with subnormal levels of the metabolic rate and of the serum iodine. Desiccated thyroid will prevent or correct the hypothyroidism.

(5) Discontinuance of the drug within the first year may result in an exacerbation of the hyperthyroidism, but in some cases the remission persists after medication is interrupted. The longer the drug is continued the larger the proportion of persistent remissions.

(6) Thiouracil, the substance used by most observers, produces a toxic reaction in about 13 per cent of the cases.[54, 72]. Leukopenia develops in over 4 per cent of the cases and granulocytopenia in 2.5

per cent. The granulocytopenia leads to a fatal agranulocytosis in about one case in 200. Discontinuance of the thiouracil followed by penicillin treatment will save some patients.[69] The agranulocytosis usually occurs during the first 3 months but may appear after as much as 8 months of treatment; no reliable warning sign has been noted.

Thiourea used in large amounts, 1 to 3 gm. daily, produced halitosis, nausea, vomiting, skin eruptions, fever, and rarely leukopenia.[35, 56] Smaller amounts, 75 to 300 mg. daily, have eliminated most of these reactions. Drug fever, however, has been encountered in 2 of 54 cases.[20] Agranulocytosis has not been reported with this drug nor with propylthiouracil.[8] The experience with these compounds, however, is limited.

(7) Pregnancy does not appear to be a contraindication to treatment of hyperthyroidism with thiouracil or thiourea, despite the findings of Hughes,[36] and of Goldsmith, Gordon, and Charipper[30] in rat experiments. The fetus developed a hyperplastic thyroid gland and the growth of the offspring was retarded. These effects probably resulted from the transmission of the drug through the placenta and, later, through the maternal milk.

Hyperthyroidism has been successfully treated, however, during human pregnancy without any evident ill effect upon the child.[79] Cretinism will probably not develop if hypothroidism is avoided. It must be pointed out that during pregnancy an increase in the serum precipitable iodine may be observed.[34] Since this is not associated with stigmata of hyperthyroidism it is thought to be physiological. This development must be differentiated from true hyperthyroidism, lest the patient be given thyroid-depressant drugs unnecessarily.

Rôle of iodine in the response to thyroid-depressant agents. Astwood's demonstration *in rats* that within a certain range of thiouracil dosage iodine may delay the response has deeply influenced clinical thinking concerning the simultaneous use of these two drugs in the treatment of *patients with hyperthyroidism.* This is not wholly logical, since the effects of iodine therapy in hyperthyroidism are quite different from those in normal subjects. There is a widespread belief that preliminary medication with iodine delays the action of thiouracil in hyperthyroidism. This has been ascribed to the interval needed for degradation of extra hormone stored during the period of iodine medication. On the other hand, it has been rec-

ognized that iodine may reduce the hyperplasia induced by thiouracil. Thus thiouracil alone is an unsatisfactory pre-operative agent because of the intense hyperplasia and vascularity of the gland, but treatment first with thiouracil and then with iodine will produce a surgically much more manageable gland.[17, 62] The independence of the effects of iodine and of thiouracil has recently been clearly demonstrated by Rawson and his associates.[62] They treated hyperthyroid subjects with thiouracil alone for a time, then supplemented this with a course of iodine medication. Biopsies of the gland were obtained at intervals. They found that the initial hyperplasia of the thyroid gland in Graves' disease was greatly intensified by thiouracil alone, although metabolism fell and the gland lost much of its iodine. The administration of iodine in addition to thiouracil was followed by marked resolution of the hyperplasia, although no iodine was stored in the gland. This evidence clearly separates the action of iodine in the reduction of glandular hyperplasia from its action in increasing the storage of iodine by the gland, and thus disposes of any unitary theory of the action of iodine in Graves' disease. It also indicates differing actions by thiouracil and by iodine in Graves' disease, although both actions are inhibitory in character. Rawson believes that the iodine in some way blocks the action of thyrotropic hormone on the gland, while thiouracil simply bars iodine from elaboration into complex organic form. This explanation presupposes a blockage by iodine of an excess of thyrotropic hormone without interference with the action of normal amounts of thyrotropic hormone, since in normal subjects iodine is without demonstrable effect on the output of thyroid hormone. This hypothesis is as yet unproven.

Practically every clinical report has noted that cases which had been previously receiving iodine took from 60 to 100 days for the basal to return to normal, whereas a period of 30 or 40 days was the usual time in other cases. Danowski, Man, and Winkler, on the basis of clinical observations,[19] have recently questioned the existence of an antagonistic effect of iodine on thiourea activity.* They found that if iodine was given prior to thiourea in unselected cases and then was continued during the period of thiourea medication, the

* Thiourea, rather than thiouracil, was used throughout, because it is at least as effective as thiouracil or any of its known derivatives[5, 20] and is probably less toxic. Astwood originally selected thiouracil rather than thiourea for extensive clinical trial because of its greater goitrogenic potency in the normal rat. The human patient with hyperthyroidism reacts differently, however.

rate of fall was on the average no different from that of unselected cases treated with thiourea alone. If thiourea and iodine were given simultaneously, the rate of fall of serum precipitable iodine and basal metabolism was somewhat more rapid than that following thiourea alone. Three possible explanations of this apparent discrepancy exist. First, it may be a difference between thiourea and thiouracil. Since their action on the thyroid gland is the same, this appears unlikely. Second, these workers continued the iodine medication after thiourea was started whereas most previous workers had discontinued the iodine when thiouracil was started because of a supposed antagonism as reported experimentally in rats.[4] Third, patients in this series were treated at random, some with and some without iodine, before the thiourea was commenced. The majority of the cases reported in the literature and cited as showing delay were those who had received iodine medication for a long time and in whom hyperthyroidism still remained very active; they were thus a peculiarly selected group of cases. Danowski and co-workers showed that in certain cases in whom a remission had been obtained while the patient was on both iodine and thiourea, omission of the iodine produced an exacerbation of the hyperthyroidism before the thiourea had taken full effect. In other words, the result actually noted is a combination of escape from iodine inhibition superimposed upon a direct thiouracil effect. The conclusion seems reasonably justified that iodine and thiourea medication supplement one another, and that, in general, both should be used together.

Control of hypothyroidism produced by thiouracil or thiourea. The hypothyroidism which develops during the course of prolonged thiourea therapy can be prevented by thyroid or thyroxine medication or by reduction in the dosage of thiourea.[19, 20, 58] There is no apparent advantage of thyroxine over thyroid and its intravenous administration obviously makes it much less practical. Whichever method is used there is a tendency to alternate between hypothyroidism due to excessive dosage and relapse of the hyperthyroidism. The matter is further complicated by the fact that, as time goes on in the course of thiourea medication, progressively smaller doses will serve to maintain the patient in remission, and continuance of the same dose which was at first necessary to control the hyperthyroidism may, after some weeks, regularly produce hypothyroidism. Avoidance of these complications by either method requires continuous observation. The basal metabolism may be somewhat

misleading since the metabolism may remain within normal range for a considerable period after the serum precipitable iodine has fallen to subnormal values and symptoms of hypothyroidism develop.[19, 20] It is particularly unfortunate if, as seems likely, hypothyroidism favors progression of exophthalmos.[52]

The dose of thyroid necessary to prevent hypothyroidism is quite variable both among patients and at different times in the same patient.[19] This may be due to a number of factors but one of them may well be the variable degree of inactivation of the hormone. Dempsey and Astwood have assumed that the minimum amount of thyroid necessary to prevent the goitrogenic activity of thiouracil in the normal animal is equal to the daily maintenance requirement of hormone.[22, 64, 65] This assumption implies that none of the administered hormone is inactivated and so is probably not wholly justified. The inconsistency of the results obtained by different workers using this method of assay and the evidence from other sources that inactivation of administered hormone may take place is strong evidence against the validity of the basic assumption.[21]

Treatment of hyperthyroidism by thyroidectomy and by thyroid-depressant drugs. During the years preceding the introduction of thyroid-depressant drugs thyroid surgery had progressed to a high state of technical perfection. The operative mortality with subtotal thyroidectomy following preliminary treatment with iodine has been reduced to less than one per cent under favorable circumstances. The operative mortality is higher than this, however, if the series includes a high proportion of elderly patients with cardiovascular and other complications. Several disadvantages are inherent, however, in the surgical treatment of hyperthyroidism apart from the immediate operative risk. Accidental injury to the laryngeal nerve and to the parathyroid glands is occasionally inescapable. More common is the failure of the operation to achieve a permanent cure of the hyperthyroidism. For example, in one recent series 7 per cent had recurred within 18 months.[79] Experience indicates that the percentage of recurrences will increase with the passage of time. The incidence of recurrences may be reduced by a more radical removal of the gland, but with this type of operation the percentage of cases of persistent hypothroidism is increased.[82]

Treatment with thiouracil, thiourea, and their derivatives eliminates all the surgical risks of thyroidectomy, but substitutes the risks of toxic reactions to the drugs themselves. Some type of toxic reac-

tions occurs in 13 per cent of all patients treated with thiouracil, including leukopenia in 5 per cent and agranulocytosis in about 1 per cent of the patients treated. The incidence may be somewhat less with other thyroid-depressant drugs.[8, 19] These unfavorable reactions are most frequent during the first few weeks of treatment, but may occur at any time thereafter. In any one patient, therefore, the risk of a toxic reaction increases the longer the drug is continued. Interruption of medication favors toxic reactions when the drug is again taken.

Discontinuance of treatment with thiouracil after the first few months results in an early relapse of the hyperthyroidism in about half of the cases.[79] The longer the drug is continued, the lower the percentage of relapses. Apart from the liability to toxic reactions, this tendency to relapse with interruption of treatment is the most serious limitation to the practical employment of the antithyroid drugs. The tendency to develop hypothyroidism if the dosage is not wisely adjusted constitutes another complication of this form of prolonged medical therapy. Whether the prolonged use of these substances may lead to the development of carcinoma remains unsettled.[14]

The high proportion of permanent cures which follow skillful thyroid surgery makes this procedure still a suitable form of treatment in hyperthyroidism. Prolonged medical treatment with certain of the thyroid-depressant drugs has also proven satisfactory. The discovery in the near future of safer drugs than thiouracil may confidently be predicted. With this development the rôle of medical therapy can be greatly expanded.

References

1 Astwood, E. B.: Chemotherapy in hyperthyroidism. Surgery, 1944, *16*, 679.
2 Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. J. Am. Med. Asso., 1943, *122*, 78.
3 Astwood, E. B.: The chemical nature of the compounds which inhibit the function of the thyroid gland. J. Pharm. & Exper. Therap., 1943, *78*, 79.
4 Astwood, E. B.: Chemotherapy of hyperthyroidism. Harvey Lectures, 1944-45.
5 Astwood, E. B., and A. Bissell: Effect of thiouracil on the iodine content of the thyroid gland. Endocrinol., 1944, *34*, 282.
6 Astwood, E. B., A. Bissell, and A. M. Hughes: Further studies on the chemical nature of compounds which inhibit the function of the thyroid gland. Endocrinol., 1945, *37*, 456.
7 Astwood, E. B., J. Sullivan, A. Bissell, and R. Tyslowitz: Action of certain

sulfonamides and of thiourea upon the function of the thyroid of the rat. Endocrinol., 1943, *32*, 210.

8 Astwood, E. B., and W. P. VanderLaan: Thiouracil derivatives of greater activity for the treatment of hyperthyroidism. J. Clin. Endocrinol., 1945, *5*, 424.

9 Barker, M. H., H. A. Lindberg, and M. H. Wald: Further experiences with thiocyanates. J. Am. Med. Asso., 1941, *117*, 1591.

10 Barr, D. P., and E. Shorr: Observations on the treatment of Graves' disease with thiouracil. Ann. Int. Med., 1945, *23*, 754.

11 Bartels, E. L.: Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism. Ann. Int. Med., 1945, *22*, 365.

12 Baumann, E. J., N. Metzger, and D. Marine: Mode of action of thiourea on the thyroid gland of rabbits. Endocrinol., 1944, *34*, 44.

13 Berman, L.: Human thyrotoxicosis: Response to para-aminobenzoic acid. Proc. Soc. Exper. Biol. & Med., 1945, *59*, 70.

14 Bielschowsky, F.: Tumors of the thyroid produced by 2-acetyl-amino-fluorene and allyl-thiourea. Brit. J. Exper. Path., 1944, *25*, 90.

15 Boyd, E. M., and W. F. Connell: Thiouracil. Canad. Med. Asso. J., 1945, *52*, 362.

16 Chesney, A. M., T. A. Clawson, and A. Webster: Endemic goiter in rabbits. I. Incidence and characteristics. Bull. Johns Hopkins Hosp., 1928, *43*, 261.

17 Clute, H. M., and R. H. Williams: Thiouracil in the preparation of thyrotoxic patients for surgery. Ann. Surg., 1944, *120*, 504.

18 Danowski, T. S.: Unpublished data.

19 Danowski, T. S., E. B. Man, and A. W. Winkler: Additive effects of iodine and thiourea in the treatment of hyperthyroidism. J. Clin. Invest., 1946, (In press).

20 Danowski, T. S., E. B. Man, and A. W. Winkler: Treatment of hyperthyroidism with a combination of iodine, thiourea in small doses, and desiccated thyroid. Am. J. Med. Sci., 1945, *210*, 777.

21 Danowski, T. S., E. B. Man, and A. W. Winkler: Tolerance of normal, of thyroidectomized, and of thiourea or thiouracil treated dogs to oral desiccated thyroid and to intravenous thyroxine. Endocrinol., 1946, *38*, 230.

22 Dempsey, E. W., and E. B. Astwood: Determination of the rate of thyroid hormone secretion at various environmental temperatures. Endocrinol., 1943, *32*, 509.

23 Eaton, J. C.: Treatment of thyrotoxicosis with thiouracil. Lancet, 1945, *i*, 171.

24 Evans, G. T., and E. B. Flink: Thiouracil therapy in hyperthyroidism. Minnesota Med., 1944, *27*, 1002.

25 Franklin, A. L., and I. L. Chaikoff: The effect of sulfanilamide on the conversion in vitro of inorganic iodine to thyroxine and diiodotyrosine by thyroid slices. J. Biol. Chem., 1943, *148*, 719.,

26 Franklin, A. L., and I. L. Chaikoff: The effect of sulfonamides on the conversion in vitro of inorganic iodide to thyroxine and diiodotyrosine by thyroid tissues with radioactive iodine as indicator. J. Biol. Chem., 1944, *152*, 295.

27 Franklin, A. L., I. L. Chaikoff, and S. R. Lerner: The influence of goitrogenic substances on the conversion in vitro of inorganic iodide to thyroxine and diiodotyrosine by thyroid tissue with radioactive iodine as indicator. J. Biol. Chem., 1944, *153*, 151.

28 Franklin, A. L., S. R. Lerner, and I. L. Chaikoff: The effect of thiouracil on the formation of thyroxine and diiodotyrosine by the thyroid gland of the rat with radioactive iodine as indicator. Endocrinol., 1944, *34*, 265.

29 Gabrilove, J. L., M. J. Kert, and L. J. Soffer: The use of thiouracil in the treatment of patients with hyperthyroidism. Ann. Int. Med., 1945, *23*, 537.

30 Goldsmith, E. D., A. S. Gordon, and H. A. Charipper: An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat. Am. J. Obst. & Gynecol., 1945, *49*, 197.

31 Gordon, A. S., E. D. Goldsmith, and H. A. Charipper: Effects of thiourea and sulfadiazine on the thyrotropic hormone content of the pituitary gland and blood serum of rats. Anat. Record, 1943, *87*, 445.

32 Griesbach, W. E.: Studies on experimental goitre. II. Changes in the anterior pituitary of the rat, produced by Brassica seed diet. Brit. J. Exper. Path., 1941, *22*, 245.

33 Griesbach, W. E., T. H. Kennedy, and H. D. Purves: Studies on experimental goitre. III. The effect of goitrogenic diet on hypophysectomized rats. Brit. J. Exper. Path., 1941, *22*, 249.

34 Heinemann, M., C. Johnson, and E. B. Man: Elevation of serum precipitable iodine during pregnancy. J. Clin. Invest., 1946 (In press).

35 Himsworth, H. P.: Thyrotoxicosis treated with thiourea. Lancet, 1943, *ii*, 465.

36 Hughes, A. M.: Cretinism in rats induced by thiouracil. Endocrinol., 1944, *34*, 69.

37 Keating, F. R., Jr., R. W. Rawson, W. Peacock, and R. D. Evans: The collection and loss of radioactive iodine compared with the anatomic changes induced in the thyroid of the chick by the injection of thyrotropic hormone. Endocrinol., 1945, *36*, 137.

38 Kennedy, T. H.: Thiourea as goitrogenic substances. Nature, 1942, *150*, 233.

39 Kennedy, T. H., and H. D. Purves: Studies on experimental goitre. I. The effect of Brassica seed diets on rats. Brit. J. Exper. Path., 1941, *22*, 241.

40 Larson, R., F. R. Keating, Jr., W. Peacock, and R. Rawson: A comparison of the effect of thiouracil and of injected thyrotropic hormone on the collection of radioactive iodine and the anatomic changes induced in the thyroid of the chick. Endocrinol., 1945, *36*, 149.

41 Lerner, S. R. and I. L. Chaikoff: The influence of goitrogenic compounds (sulfonamides and their derivatives, thiourea and its derivatives) on respiration of thyroid tissue. Endocrinol., 1945, *37*, 362.

42 Lowenstein, B. E., M. Bruger, W. J. Hinton, and W. G. Lough: The protein-bound plasma iodine in patients with thyroid disease. II. The effect of thiouracil. J. Clin. Endocrinol., 1945, *5*, 181.

43 Lozinski, E., and J. Siminovitch: Thiouracil in the treatment of thyrotoxicosis. Canad. Med. Asso. J., 1944, *51*, 422.

44 McGavack, T. H., A. J. Gerl, J. N. Morton, M. Vogel, and D. Schwimmer: Observations on 78 thyrotoxic patients treated with thiouracil. J. Clin. Endocrinol., 1945, *5*, 259.

45 Mackenzie, C. G., and J. B. Mackenzie: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. Endocrinol., 1943, *32*, 185.

46 Mackenzie, J. B., and C. G. Mackenzie: Effect of prolonged and intermittent sulfonamide feeding on the basal metabolic rate, thyroid, and pituitary. Bull. Johns Hopkins Hosp., 1944, *74*, 85.

47 Mackenzie, J. B., C. G. Mackenzie, and E. V. McCollum: The effect of sulfanilylguanidine on the thyroid of the rat. Science, 1941, *94*, 518.

48 Marine, D., E. J. Baumann, B. Webster, and A. Cipra: The occurrence of antigoitrous substances in plants. J. Exper. Med., 1933, *57*, 121.

49 Marine, D., and O. P. Kimball: Prevention of simple goiter in man. Arch. Int. Med., 1920, *25*, 661.

50 Marine, D., A. W. Spence, and A. Cipra: Production of goiter and exophthalmos in rabbits by administration of cyanide. Proc. Soc. Exper. Biol. & Med., 1932, *29*, 822.

51 Means, J. H.: *The Thyroid and its Diseases.* J. B. Lippincott, Philadelphia, 1937.

52 Means, J. H.: Hyperophthalmopathic Graves' disease. Ann. Int. Med., 1945, *23*, 779.

53 Meyer, A. E., and G. V. Ransom: The metabolism of rats after thyroidectomy or during thiouracil treatment, and the effect of thyroid feeding. Endocrinol., 1945, *36*, 259.

54 Moore, F. D.: Toxic manifestations of thiouracil therapy. J. Am. Med. Asso., 1946, *130*, 315.

55 Moore, F. D., D. N. Sweeny, Jr., O. Cope, R. W. Rawson, and J. Means: The use of thiouracil in the preparation of patients with hyperthyroidism for thyroidectomy. Ann. Surg., 1944, *120*, 152.

56 Newcomb, P. B., and E. W. Deane: Thiourea causing granulopenia and thrombopenia. Lancet, 1944, *i*, 179.

57 Nussey, A. M.: Treatment of hyperthyroidism with thiouracil. Brit. Med. J., 1944, *ii*, 745.

58 Palmer, M. V.: Hyperthyroidism and thiouracil. Ann. Int. Med., 1945, *22*, 335.

59 Paschkis, K. E., A. Cantarow, A. E. Rakoff, A. A. Walkling, and W. J. Tourish: Thiourea and thiouracil in treatment of thyrotoxicosis. J. Clin. Endocrinol., 1944, *4*, 179.

60 Rawson, R. W., R. D. Evans, J. H. Means, W. C. Peacock, J. Lerman, and R. E. Cortell: The action of thiouracil upon the thyroid gland in Graves' disease. J. Clin. Endocrinol., 1944, *4*, 1.

61 Rawson, R. W., S. Hertz, and J. H. Means: Cyanate goiter in man. Report of a case with histological and metabolic studies. J. Clin. Invest., 1942, *21*, 624.

62 Rawson, R. W., F. D. Moore, W. Peacock, J. H. Means, O. Cope, and C. Riddell: Effect of iodine on the thyroid gland in Graves' disease when given in conjunction with thiouracil—a two action theory of iodine. J. Clin. Invest., 1945, *24*, 869.

63 Rawson, R. W., J. T. Tannheimer, and W. C. Peacock: The uptake of radioactive iodine by the thyroids of rats made goiterous by potassium thiocyanate and by thiouracil. Endocrinol., 1944, *34*, 245.

64 Reineke, E. P., J. P. Mixner, and C. W. Turner: Effect of graded doses of thyroxine on metabolism and thyroid weight of rats treated with thiouracil. Endocrinol., 1945, *36*, 64.

65 Reineke, E. P., and C. W. Turner: The relative thyroidal potency of *l*- and of *d*, *l*-thyroxine. Endocrinol., 1945, *36*, 200.

66 Reveno, W. S.: Thyrotoxicosis treated with thiouracil. J. Am. Med. Asso., 1944, *126*, 153.

67 Richter, C. P., and K. H. Clisby: Graying of hair produced by ingestion of phenylthiocarbamide. Proc. Soc. Exper. Biol. & Med., 1941, *48*, 684.

68 Rose, E., and J. McConnell: Thiouracil in the treatment of thyrotoxicosis. Am. J. Med. Sci., 1944, *208*, 561.

69 Rothendler, H. H., and M. G. Vorhaus: Penicillin in thiouracil-induced agranulocytosis. J. Am. Med. Asso., 1945, *129*, 739.

70 Sharpless, G.: A new goiter-production diet for the rat. Proc. Soc. Exper. Biol. & Med., 1938, *38*, 166.

71 Sharpless, G., J. Pearson, and G. S. Prato: Production of goiter in rats with raw and with treated soybean flour. J. Nutrition, 1939, *17*, 545.

72 Van Winkle, W., Jr., S. M. Hardy, G. R. Hazel, D. C. Hines, H. S. Newcomer, E. A. Sharp, and W. N. Sisk: The clinical toxicity of thiouracil. A survey of 5,745 cases. J. Am. Med. Asso., 1946, *130*, 343.

73 Watson, E. M.: Thiouracil in the control of thyrotoxicosis. J. Clin. Endocrinol., 1945, *5*, 273.

74 Webster, B.: Studies in the reactions of simple goiter to iodine. Bull. Johns Hopkins Hosp., 1929, *45*, 215.

75 Webster, B.: Studies in the experimental production of simple goiter. Endocrinol., 1932, *16*, 617.

76 Webster, B., and A. M. Chesney: Endemic goiter in rabbits. III. Effect of administration of iodine. Bull. Johns Hopkins Hosp., 1928, *43*, 291.

77 Webster, B., T. A. Clawson, and A. M. Chesney: Endemic goiter in rabbits. II. Heat production in goitrous and non-goitrous animals. Bull. Johns Hopkins Hosp., 1928, *43*, 278.

78 Wilgus, H. S., F. X. Gassner, A. R. Patton, and R. G. Gustavson: The goitrogenicity of soybeans. J. Nutrition, 1941, *22*, 43.

79 Williams, R. H.: Thiouracil treatment of thyrotoxicosis. I. The results of prolonged treatment. J. Clin. Endocrinol., 1946, *6*, 1.

80 Williams, R. H., and G. W. Bissell: Thiouracil in the treatment of thyrotoxicosis. New England J. Med., 1943, *229*, 97.

81 Williams, R. H., B. J. Jandorf, and G. A. Kay: Methods for the determination of thiouracil in tissues and body fluids. J. Lab. & Clin. Med., 1944, *29*, 329.

82 Winkler, A. W., D. S. Riggs, K. W. Thompson, and E. B. Man: Serum iodine in hyperthyroidism, with particular reference to the effects of subtotal thyroidectomy. J. Clin. Invest., 1946, *25*, 404.