# REVIEW ARTICLE

## SOME RECENT DEVELOPMENTS IN THE PHARMACOLOGY OF THE ANTI-THYROID COMPOUNDS

By W. R. Trotter, D.M., M.R.C.P.

*Medical Unit, University College Hospital, London*

It was established in 1943 that thiouracil and similar drugs inhibit the synthesis of thyroid hormone; that they can control human thyrotoxicosis; and that a necessary corollary of complete inhibition of thyroid hormone synthesis is a compensatory hyperplasia and hypertrophy of the thyroid gland, mediated through the pituitary. It was obvious at that date that these drugs were likely to become both a useful instrument of research into thyroid physiology, and effective therapeutic agents; and such they proved to be. This review will attempt to survey some of the major advances in thyroid physiology, in which the thiouracil derivatives have been implicated, and will also indicate the effect of these advances, coupled with the effect of further clinical experience, upon practical therapeutics.

What has chiefly been gained, so far as thyroid physiology is concerned, is a clearer picture of the course pursued by the iodine atom, from the time when it presents itself as inorganic iodide in the thyroid capillaries, to the time when it is incorporated into the thyroxine molecule. The process occurs in two main stages: entry into the gland, and combination with protein. It is convenient in this review to deal first with the factors governing the entry of iodide into the thyroid, and later with those governing the actual synthesis of thyroxine. There follows a discussion of the relative properties of the anti-thyroid drugs and a consideration of their relative merits in clinical practice. No attempt is made here to assess the value of the long-term treatment of thyrotoxicosis with the thiouracil derivatives, nor to compare it with sub-total thyroidectomy. Finally, recent evidence bearing on the part played by naturally-occurring anti-thyroid substances in the causation of simple goitre is briefly reviewed.

### The Effect of Thiouracil upon the Entry of Iodine into the Thyroid

Astwood and Bissell[1] described the rapid and almost complete disappearance of iodine from the thyroids of rats treated with thiouracil. The iodine content of the gland appeared to be such a sensitive and specific index of thiouracil action that it was adopted as the chief method of assessing the relative potency of the anti-thyroid drugs. This observation suggested that either thiouracil acted by preventing the entry of iodide into the gland; or that entry of iodide was determined by the rate at which it was being converted into thyroxine and that thiouracil

prevented this conversion occurring. The former suggestion appeared to be contradicted by the observations of Chaikoff and his collaborators[2] on the formation of radio-diiodotyrosine and radio-thyroxine in isolated slices of thyroid, for they found that thiouracil, thiourea and the sulphonamides inhibited this formation, while in no way hindering the uptake of iodide by the slices from the fluid medium in which they lay. However, this was not convincing proof of the mode of action of anti-thyroid drugs in the intact animal, for it could be argued that the transference of iodide from an artificial fluid into the thyroid cell was a very different process from the transference of iodide from capillary to cell in the living animal. Thus while it was clear enough from Chaikoff's work that the anti-thyroid drugs could prevent the formation of diiodotyrosine and thyroxine, it remained possible that in the intact animal they also prevented the thyroid from collecting inorganic iodide from the bloodstream.

However, it presently became apparent from the work of McGinty and Sharp[3], Astwood[4] and Vanderlaan and Bissell[5] that the iodine content of the thyroid, under the influence of anti-thyroid drugs, could still vary with the iodine content of the diet. Astwood[4] showed that when rats, who were receiving adequate amounts of thiouracil in the diet, were given a single dose of iodide by injection, the total iodine content of the thyroid rose sharply as soon as 1 hour after the injection. Vanderlaan and Bissell showed that the iodine thus taken up disappears again from the thyroid a short time later. Since it is unlikely that iodide could have become bound to protein and left the gland in so short a time it seemed probable that the temporary increase in thyroid iodine was all in the inorganic form. The three groups of workers also provided direct evidence that the iodine was, in fact, not bound to protein, and was therefore probably inorganic. Further confirmation came from the detailed studies of Vanderlaan and Vanderlaan[6] and of Taurog, Chaikoff and Feller[7], who showed, by a variety of methods, that the iodine which enters the thyroids of rats treated with propylthiouracil is indisputably in the form of inorganic iodide. They showed that under these conditions the non-hyperplastic thyroid (of rats given a single injection of propylthiouracil 1 hour previously) concentrated iodide to about 25 times the concentration present in plasma. The hyperplastic thyroid of rats chronically treated with propylthiouracil concentrated iodide to about 250 times the concentration present in plasma, unless the latter was inordinately high.

This work shows that the thiouracil compounds do not prevent the thyroid from concentrating iodide to a high degree. But though iodide can enter the gland, it cannot become linked to protein. Therefore it cannot be retained in the gland. Thus Vanderlaan and Vanderlaan[6] showed that the normal rat thyroid can retain 20 times as large a proportion of a dose of radioactive iodine as can the thyroid of a rat which has had a single injection of propylthiouracil. The early observation of Astwood and Bissell[1], that treatment with thiouracil lowers the iodine

content of the thyroid, can now be explained. Thiouracil does not stop iodine getting into the thyroid; it prevents it from being retained there.

Vanderlaan and Vanderlaan[6] also showed that thiocyanate prevented the concentration of iodide by the thyroids of rats treated with propyl-thiouracil and, moreover, caused any iodide which was present to be discharged. When thiocyanate is given, the concentration of iodide in the thyroid becomes approximately equal to that in the blood. Thiocyanates can cause goitre, by preventing the thyroid from concentrating iodide. But if there is an excess of iodide in the diet—and hence in the blood—enough iodide can enter the gland even if the concentrating mechanism is out of action. Hence thiocyanates do not cause goitre in the presence of an excess of dietary iodide (Astwood[8]).

The work of Vanderlaan and Vanderlaan[6], and others, has thus shown very clearly the existence of two separate mechanisms in the thyroid: the mechanism which concentrates iodide from the blood, which is inhibited by thiocyanate; and the mechanism which combines iodide with protein, and stores it in the gland, which is inhibited by the thiouracil derivatives. This new conception has been made use of by Stanley and Astwood[9] in a study of the uptake and discharge of radioactive iodide by the thyroid in normal and thyrotoxic human subjects. Under the influence of a thiouracil derivative the proportion of a tracer dose of iodide taken up by the thyroid is reduced, and the peak of the uptake curve is lower and reached much earlier. The work of Vanderlaan and Vanderlaan[6] makes it clear that what is being observed under these conditions is the uptake of inorganic iodide by the thyroid, and its rapid subsequent dilution by non-radioactive iodide, since the thyroid (under the influence of thiouracil) is incapable of binding it to protein. The ability of thiocyanates to discharge iodide from the thyroid made it possible to estimate the proportion of the radioactive atoms which are built up into thyroid hormone under any given conditions. Thus if a thyrotoxic patient, under treatment with a thiouracil derivative, is given a tracer dose of radioactive iodide, and then (after an interval) an adequate dose of thiocyanate, the amount of radioactivity remaining in the thyroid region is an index of the proportion of the administered iodide which has been converted into thyroxine and is bound to protein. In this way an estimate is obtained of the efficacy of the anti-thyroid drug being administered. The practical value of this method is excellent evidence that the conclusions of Vanderlaan and Vanderlaan[6] apply also to the human thyroid, whether normal or thyrotoxic.

### The Effect of Thiouracil upon the Combination of Iodine with Protein

It may be assumed that iodine enters the thyroid in the form of inorganic iodide. But the normal thyroid contains little iodine in this inorganic form. It follows that very soon after its entry into the gland the iodide must enter into combination with protein.

The exact form which this iodine-protein complex takes can at present only be surmised from indirect evidence. Taurog and Chaikoff[10] have

shown that from the blood of normal animals there can be extracted—without the use of any destructive measures—a substance whose properties correspond with those of thyroxine. The same method of extraction failed to remove a similar substance from the thyroid gland. Since this suggests that there is no free thyroxine in the gland, it may be supposed that the tyrosine which becomes iodinated to form thyroxine is already part of a protein molecule when the process takes place. Release of free thyroxine into the circulation would take place when this protein is broken down by enzymic action.

This conception of the form in which the thyroid hormone is stored may be over-simplified. The question of the relative biological potency of thyroglobulin from the thyroid gland, and free thyroxine, is still unsettled. The most recent contribution to this question comes from Frieden and Winzler[11]. They compared the effect of various natural and artificial iodo-proteins in preventing goitrogenesis in rats treated with thiouracil. The biological potency of the natural thyroglobulin preparations was found to be decidedly higher than would be expected from their thyroxine content, as chemically determined. The implications of these findings, if they are to be accepted in spite of other contradictory observations (which the authors review), are far from clear. They are presented here only to remind the reader that the idea that thyroxine (the circulating form of the hormone) is stored in the thyroid by being incorporated into the molecule of a protein (thyroglobin), may not be a wholly adequate account of the situation. It is, however, a highly convenient working hypothesis, and is accepted here for purposes of further discussion.

The analogy of the artificial iodoproteins suggests that iodine in the thyroid combines directly with part of a protein, so that the resulting thyroxine molecule is from its inception built into the structure of the parent protein molecule. The part of the protein with which the iodine combines is presumably the amino-acid tyrosine. Harington[12] pictures the synthesis of thyroxine as occurring in two stages: first the iodination of tyrosine to form diiodotyrosine, then the condensation of two diiodotyrosine molecules to form thyroxine. Oxidation is required for both stages, the first step being the conversion of iodide to iodine. Since, in the presence of thiouracil, iodide can no longer be brought into organic combination in the thyroid, it follows that thiouracil prevents the first step in the process, the iodination of tyrosine. However, Dempsey and Astwood[13] provided evidence that, even if this first step could occur, thiouracil would prevent the second, for diiodotyrosine was extremely ineffective in preventing thyroid enlargement in rats treated with thiouracil. This finding has been confirmed by Frieden and Winzler[11].

It may be assumed that thiouracil prevents the iodination of protein. It could do this by preventing the oxidation of iodide to iodine, or by itself combining with the free iodine after oxidation had occurred. The nature of the enzyme system which effects this oxidation is not known. Schachner, Franklin and Chaikoff[14] showed that the conversion of radio-

active iodine by isolated thyroid slices to diiodotyrosine and thyroxine is prevented by cyanide, azide, sulphide and carbon monoxide. Since all these agents inhibit the cytochrome-oxidase system, they concluded that this system was essential for the production of thyroxine, and suggested that its function was the oxidation of iodide to iodine. However, this enzyme system is of such general importance to the cell that its inhibition might well prevent thyroxine formation indirectly, even if some other enzyme were responsible for the actual oxidation of iodide.

Another system which could oxidise iodide is the hydrogen peroxide—peroxidase system (Westerfield and Lowe[15]). Keston[16] showed that hydrogen peroxide and peroxidase accelerate the iodination of casein *in vitro*. Although there is histochemical evidence for the presence of this enzyme in the rat thyroid[17], Glock[18] and Astwood[4] were quite unable to demonstrate it by chemical means.

Whatever the nature of the enzyme system concerned there are at least three ways in which the anti-thyroid drugs might interfere with its action: they might poison the enzyme itself, they might compete with iodide as substrate or they might themselves combine directly with iodine and thus prevent its combination with protein. If cytochrome-cytochrome oxidase is the effective oxidative system, then the evidence that the anti-thyroid drugs act by enzyme-poisoning is not good. It is true that Paschkis and others[19] claimed that thiouracil inhibits the cytochrome oxidase system of the thyroid, both when added to isolated thyroid slices and when given to the intact animal. However, this enzyme system is responsible for such a large proportion of normal tissue respiration that this finding conflicts with Lerner and Chaikoff's[20] observation that thiourea, thiouracil and sulphonamides have no effect on the oxygen consumption of isolated thyroid slices. Indeed, the thyroids of rats fed on thiouracil have been found to consume more oxygen than normal glands (Jandorff and Williams[21]), presumably as a result of their relatively greater cell mass. It is scarcely likely that this could have occurred if the cytochrome oxidase of the thyroid had been inhibited to any serious extent. McShan and others[22] and Dempsey[17] were unable to confirm the inhibition of cytochrome oxidase by thiouracil.

Dempsey[17] has claimed that peroxidase activity in the follicular cells of the thyroid (as demonstrated by the benzidine reaction) is inhibited by thiouracil. Glock[18] found that thiouracil and thiourea inhibited the actions of peroxidase and hydrogen peroxide on pyrogallol; but, as has been mentioned before, neither she nor Astwood[4] could find any evidence that peroxidase exists in the thyroid gland. Randall[23] examined the behaviour of anti-thyroid compounds *in vitro* in the presence of hydrogen peroxide and peroxidase. He showed that the effect of these compounds on peroxidase cannot be studied by methods involving the oxidation of dyes (*para*-aminobenzoic acid red, 2:6-dichlorophenolindophenol and benzidine blue), because they are such strong reducing agents that they decolourise the dyestuffs. Dempsey's[17] histochemical evidence of

peroxidase inhibition by thiouracil is therefore invalid. Furthermore, if the anti-thyroid compounds are added to hydrogen peroxide and peroxidase it is found that the hydrogen peroxide rapidly disappears. Under these conditions the anti-thyroid compounds do not inhibit the peroxide-peroxidase system; they act as substrate for it. Randall suggests, as a possible mode of action of these compounds *in vivo*, that they may act as reducing agents by competing for hydrogen peroxide as it is formed, and thus prevent it from taking part in the oxidation of iodide. It must, however, be remembered that there is no good evidence that the peroxide-peroxidase system is concerned in thyroxine formation *in vivo*.

Thus the hypothesis that thiouracil and its derivatives act by poisoning oxidative enzymes is unnecessary, and the evidence in its favour can no longer be regarded as substantial. The reducing powers of these substances are such that they could easily act as substrate in competition with iodide. Equally, they could act by combining directly with free iodine as it is formed. The difference between these last two theories is not, from the physiological point of view, very great, for both state that the ability of the thiol compounds to prevent the synthesis of thyroxine is attributable to their reducing properties. However, since it has not been demonstrated that any peroxidase exists in the thyroid, the theory of direct combination with iodine seems the more acceptable.

Direct evidence in favour of this last theory was first presented by Campbell, Landgrebe and Morgan[24], who showed that thiourea reacted with iodine to give formamidine disulphide. If this reaction occurs in the thyroid it would have the effect of keeping the iodine there in the reduced form. Later, Miller, Roblin and Astwood[25] showed that thiouracil was similarly oxidised by iodine to its disulphide. They examined a series of other compounds in a similar way and found that there was a general correlation (with a few exceptions) between the speed of the reaction and the number of molecular equivalents of iodine with which a compound would react, and its goitrogenic power. Some reducing substances, however, such as glutathione, had a marked power of reducing iodine, but no goitrogenic activity. The same authors showed that thiouracil could inhibit the iodination of casein and tyrosine *in vitro*.

More recently, Pitt-Rivers[26] has shown that thiouracil and similar compounds can inhibit the *in vitro* formation of acetylthyroxine from acetyldiiodotyrosine. She demonstrated that when one of these compounds (tetramethylthiourea) is incubated with acetyldiiodotyrosine, iodine is slowly liberated and oxidizes the thiourea compound. The iodine is thus prevented from oxidising the acetyldiiodotyrosine, and no acetylthyroxine is formed. The ability of various compounds to prevent the formation of acetylthyroxine ran roughly parallel to their ability to prevent the synthesis of thyroxine *in vivo*. Thus the iodine-combining power of thiouracil and related compounds provides a satisfactory explanation of their action in preventing the formation of thyroxine in the living animal, even when diiodotyrosine is provided.

## The Relative Effectiveness of the Anti-Thyroid Drugs

Two motives have prompted the various surveys of large numbers of chemical compounds for their ability to inhibit thyroxine synthesis: on the one hand, the desire to define the chemical grouping responsible for the physiological effect; and on the other hand, to find the most suitable substance for the control of thyrotoxicosis. The first of these objectives has not been attained; indeed, it is not likely that it will be attained, at least in terms of conventional organic chemistry. The search for useful therapeutic substances has met with more success.

The methods which have been evolved to compare the various substances belong to three broad types: the purely chemical, the use of slices of thyroid tissue *in vitro,* and tests on intact animals. Miller, Roblin and Astwood[25] showed that thiouracil could inhibit the iodination of casein *in vitro,* by itself reacting with the iodine present, and examined the ability of a number of anti-thyroid compounds to react with iodine. Pitt-Rivers[26] compared the ability of various anti-thyroid compounds to prevent the conversion of acetyldiiodotyrosine to acetylthyroxine. The results of these two methods are in reasonably good agreement with each other and with tests on animals. Thus the thiourea derivatives are a great deal more active in both tests than are the sulphonamide derivatives. Thiouracil is decidedly more active than thiourea. The principal discrepancy is in the case of 6-aminothiouracil. According to Pitt-Rivers, this substance is much less active than thiouracil, but Miller, Roblin and Astwood found it equally reactive with iodine. In the rat[27] and in man[28] it showed no detectable anti-thyroid activity.

The reducing action of a number of substances in the presence of a hydrogen peroxide-peroxidase system was examined by Randall[23]. It was again evident that there was a rough correlation with the results of animal experiments. The sulphonamides were weak reducing agents, and thiouracil was more active than thiourea.

Chaikoff and his collaborators[29,2] have studied the effect of various substances on the conversion of radiodide into radio-diiodotyrosine and radio-thyroxine by isolated slices of thyroid. These studies were very valuable as providing the first evidence that the thiouracil group acted by preventing the synthesis of thyroxine and not the entry of iodide into the thyroid cell. For purposes of comparison of various anti-thyroid substances they are less useful, since for the most part substances were only tested at a single concentration. At the concentration generally used by these workers ($10^{-3}$ M) both thiouracil and thiourea inhibited the formation of radio-thyroxine virtually completely; in the case of the sulphonamides and para-aminobenzoic acid the degree of inhibition was a little less.

For tests on intact animals, rats and chicks have been most commonly used. The results obtained in laboratory animals have been extended by studies of the effects of anti-thyroid compounds on radio-iodine up-

take by the thyroid in the normal human subject, and by clinical trials. Using the rat as test animal, Astwood and his colleagues alone have examined more than 300 substances[8,27]. The method used has been to administer the substance under investigation either in the food or the drinking water for 10 days. The animals are then killed, and the thyroids weighed and either examined histologically or kept for estimation of the iodine content. These methods have fully justified themselves as a means of rapid examination of a large number of possible anti-thyroid substances. The results obtained, however, should not be accepted uncritically as giving a quantitative measure of the ability of a substance to prevent the synthesis of thyroxine. For thyroid weight, histological appearances and iodine content in this test depend not only on the completeness with which thyroxine synthesis is inhibited, but also on the rate at which preformed thyroxine disappears from the gland. This is in turn determined by such factors as temperature and perhaps food intake[13]. The presence of many of the anti-thyroid substances in the diet diminishes food intake and slows growth. Astwood's[27] figures show that even a substance as little toxic as propylthiouracil causes a marked fall in growth-rate at the higher dose levels. This fall in growth-rate is associated with a less marked increase in thyroid weight and a less marked fall in thyroid iodine. Determination of total thyroid iodine is also open to fallacy because it depends on dietary iodide, which may change unexpectedly. When these known sources of error can be excluded there still remains the unexplained phenomenon (discussed by Astwood[4]) of the variations in the shape of the dosage curve from one substance to another. The thiobarbiturates, for instance, give an increased thyroid weight and decreased thyroid iodine at a low dosage; with increasing dosage, however, these effects do not increase proportionately, so that it is never possible to produce a really large goitre with these drugs. This result does not seem to be due to decreased food intake[27].

For the reasons given above, this type of test in rats is not suitable for exact quantitative work. Observation of the effect of anti-thyroid compounds on the uptake of radio-iodine by the thyroid is in some ways more satisfactory. The results of such tests are at present available for the normal human subject. The method employed by Stanley and Astwood[28] was to give tracer doses of $I^{131}$ (without carrier) and then measure the increase in radio-activity over the neck. By plotting the count against the square root of time an approximation to a straight line could be obtained, for a sufficiently long period. The drug to be tested was then administered and the amount of downward deflection of the straight line noted. The responses were graded by degree and duration into 5 classes of increasing inhibition. The method is open to the criticism that the final measurement is not a quantitative one. Nevertheless it has yielded interesting results, and is a much more useful test for clinical purposes in that the experimental animal used is man.

The results obtained in this way show the sulphonamides to be even weaker, relative to the thiourea group, than in other tests; in fact,

sulphadiazine had no detectable anti-thyroid action in a 500 mg. dose. This agrees well with the experience gained in the late war, when large numbers of American troops were given sulphonamides for long periods, as a prophylaxis against streptococcal infections; no goitre was reported. This finding is in contrast with tests in the rat[27], which show sulphonamides to be about as active as thiourea.

Thiourea, on the other hand, showed a much greater activity than would have been expected on the basis of its action *in vitro* and in the rat. In Stanley and Astwood's tests in man thiourea proved as potent as thiouracil. The smaller effect in the rat may perhaps be explained by the great loss of appetite which thiourea causes in this animal. Since thiourea is more soluble than thiouracil, it may be that it penetrates more easily into the thyroid, and thus has a greater potency in Stanley and Astwood's tests than would have been predicted from its behaviour *in vitro.*

The results obtained with 6-substituted thiouracils are also of interest. In the rat, thiouracil, 6-methylthiouracil and 6-*n*-propylthiouracil have relative potencies in the order 1 : 1 : 11. In man, the order is 1 : 2 : 0·75. The reason for the discrepancy is not apparent. Propylthiouracil causes an initial loss of appetite and failure to grow in the rat to about the same extent as the other two compounds. The results of Stanley and Astwood's tests on these three compounds are in fairly good agreement with clinical experience; although the minimal doses necessary to give a full response have never been accurately determined, they are of the order of 200 mg. daily for methylthiouracil, and 300 to 400 mg. daily for the other two compounds.

The most potent substance tested by Stanley and Astwood was 2-mercapto-imidazole. This substance had 1·5 times the potency of thiouracil in the rat, but 10 times the potency in man. There are a number of less striking discrepancies between the values obtained for man and the rat, for which the original paper[28] should be consulted. It is sufficient here to say that the existence of such discrepancies must discourage any attempt to correlate anti-thyroid activity with detailed chemical structure.

The significance of these findings to the clinician is not very apparent. The mere fact that minute doses of a compound, such as 25 mg. of mercapto-imidazole, can cause prolonged inhibition of thyroxine synthesis, does not of itself mean that this is the ideal drug for clinical purposes. It might well be, for instance, that such a drug would produce more toxic reactions than another which had to be used in 10 or 20 times the dose, in order to inhibit thyroxine synthesis. Clinical reports on the practical utility of this drug are not yet available.

In fact, the number of *effective* anti-thyroid drugs available to the clinician is embarassingly large. If a test could be devised which would estimate the proportion of " toxic reactions " to be expected clinically, it would be of great practical value. Unfortunately, no such test exists

at present. All our knowledge of toxic effects comes from clinical experience and is almost useless for purposes of comparison of one drug with another. The only common toxic reactions are drug fever, and rashes; the only dangerous toxic reaction is agranulocytosis. All three of these effects are classed as " idiosyncrasies "; that is to say, they only occur in certain subjects who are said to be " sensitive " to the drug in question. The only way we have of estimating the toxic properties of these drugs is to give them to a large number of subjects, and note the proportion who get these reactions. The accumulated clinical experience up to the present date shows that thiobarbital and aminothiazole are too toxic for routine use, and that thiouracil is more toxic than methylthiouracil or propylthiouracil. These are crude statements of clinical experience, and it is very desirable that they should be amplified by further pharmacological research. In this connection, the observations of Lehr[30] on toxic reactions with sulphonamides are of considerable interest. With these drugs also the common toxic reactions are drug fever and rashes. Lehr presents evidence to show that, although these reactions fall into the category of sensitisation phenomena—i.e., they only occur in susceptible subjects—their incidence still shows a relation to dosage. Since there appears to be a critical dosage, below which no reactions occur, he suggests that combinations of two or three different sulphonamides should be used. Since each sulphonamide would be given in a dose less than the critical one, no toxic reactions should occur. The use of such combinations has, he claims, reduced the incidence of toxic reactions in practice. He suggests that the same line of reasoning might well be tried with the anti-thyroid compounds.

It is always assumed that similar toxic reactions do not occur in laboratory animals. The present writer is not aware, however, that there has been any large-scale attempt to discover whether or not a *small proportion* of animals have, say, a transient bout of fever during the administration of thiouracil. It may be that we are too apt to assume that rats cannot display as much individuality as human beings. However, the stimulus to such investigations has to a large extent passed, since in the doses used at present methylthiouracil and propylthiouracil seldom cause alarming reactions.

## The Significance of Naturally Occurring Anti-Thyroid Substances

It is established beyond all reasonable doubt that an extreme deficiency of iodine in the diet can cause goitre, and that the mechanism by which such goitre is produced is similar to that of the thiouracil goitre; that is to say, in the absence of iodine no thyroxine can be formed, hence a compensatory overactivity of the pituitary occurs, with consequent thyroid enlargement. It is also established that, even where iodine lack is not extreme, there is a general inverse relationship between iodine content of the soil and water, and the incidence of goitre. But this inverse

relationship does not always hold in detail. Hence, if the occurrence of simple goitre is to be fully explained, some other cause must be sought for which is sufficient to produce goitre in areas where the dietary iodine is not low enough to be goitrogenic by itself.

Since Chesney, Clawson and Webster[31] first described, in 1928, the production of goitre in rabbits by feeding cabbage, a number of different foodstuffs have been found to cause goitre in animals. Among such foodstuffs are soya-beans, rape-seeds, turnips and peanuts. Some of the evidence is, however, curiously conflicting. Thus Chesney, Clawson and Webster's results were confirmed by McCarrison[32] in India and Spence, Walker and Scowen[33] in this country, but Hercus and Purves[34] in New Zealand and Zeckwer[35] in U.S.A. found the goitrogenic properties of cabbage to be weak and uncertain. Webster, Marine and Cipra[36] explained these anomalies by showing that there were marked seasonal and year-to-year variations in the potency of cabbage. 1928-9 was a vintage year, for cabbage maturing in that winter produced palpable goitres in 7 to 10 days. Similarly, Hercus and Purves[34] found a great variation in the goitrogenic activity of turnips when tested on rabbits. Turnips from an area where outbreaks of congenital goitre in lambs had occurred caused large goitres in rabbits in 1933, but not in 1934.

Recently Greer and Astwood[38] have tested some 60 different foodstuffs for their ability to check the uptake of radio-iodine by the thyroids of normal human subjects. The technique was the same as that previously used by Stanley and Astwood[28] in their survey of the effect of various anti-thyroid substances in man. The activity of several members of the *Brassica* group of vegetables was confirmed. Cabbage and turnip were both active, but swedes (rutabaga) even more so. However, several members of other vegetable groups were also active, such as peaches, pears, strawberries, spinach, lettuce, peas, walnuts and carrots. In nearly all these cases much larger quantities were consumed in the test than would ever be eaten in normal circumstances. However, peanuts, filberts and swedes showed some effect in relatively small quantities. Of the animal products tested there was some indication of anti-thyroid activity in milk, liver and oysters. As with previous investigations there was a wide variation in the response to the same foodstuffs in different trials. A significant depression of radio-iodine uptake followed a mixed meal, consisting of raw carrots, swedes, lettuce, pears and milk.

The importance of these results is two-fold. In the first place they show that many foodstuffs can have an anti-thyroid effect in man as well as in laboratory animals. The response to anti-thyroid substances varies greatly from one species to another, so that this evidence is indispensable if a case is to be made out for foodstuffs as a cause of human goitre. Secondly, Greer and Astwood have shown that the range of foodstuffs in which anti-thyroid substances may be found is much greater than had previously been suspected.

Greer and Astwood have no further data to present on the nature of the naturally occurring anti-thyroid substance or substances. Such substances could belong either to the thiocyanate group, which prevents the uptake of iodide by the thyroid, or the thiouracil group, which prevent the synthesis of thyroxine. In previous animal experiments it had been found that cabbage leaves and soya-beans resembled the thiocyanates in that their effects were easily preventable by iodide, whereas those of rape-seeds, like thiouracil, were not. The mustard oils are derived from several members of the *Brassica* group, which contain a glycoside (sinigrin) and an enzyme, myrosin; in the presence of water these interact to form allyl isothiocyanate. However, isothiocyanates do not cause goitre in the rat[27].

In the presence of ammonia allyl isothiocyanate is readily converted to allylthiourea. It was for this reason that Kennedy[37] originally suspected that allylthiourea was the active principle in rape-seed. He demonstrated that allylthiourea could cause goitre in the rat. However, neither this nor any other active goitrogenic substance has actually been isolated from any foodstuff. The nature of the substance or substances which cause the effects noted by Greer and Astwood therefore remains unknown; in the absence of direct evidence the balance of probabilities seems to favour a member of the thiourea group, but the thiocyanates may also make a contribution.

It is difficult to assess the practical importance of these findings. In the case of many of the foodstuffs noted as giving a positive result the deflection of the iodine uptake curve was a very minor one, and was, moreover, often inconstant in different trials. It does not necessarily follow that such minor deflections are of any significance to the human organism. In the normal thyroid, with its ample reserves of stored hormone, partial inhibition of thyroxine synthesis would not be reflected by any change in blood thyroxine levels unless such inhibition had persisted continuously for long periods. Clinicians who have tried to produce myxœdema in subjects with normal thyroids for therapeutic reasons are well aware that many months of intensive treatment with anti-thyroid drugs are necessary before goitre results.

If foodstuffs are an important cause of goitre (apart from their iodine content) they are likely to be so when the iodine intake is already low, and when a highly abnormal diet is being consumed. Greer and Astwood[38] have noted the occurrence of goitre in individuals on vegetarian diets, or who developed a craving for certain foods, such as lettuce. Bastenie [39] has brought forward evidence which suggests that there was an increase in simple goitre in occupied Belgium during the last war. The population at that time lived on a largely vegetarian diet, in which *Brassica* roots were prominent. It is conceivable, as Bastenie suggested, that this diet was responsible both for the increase in simple goitre, and also for the apparent decrease in the severity of thyrotoxicosis, which he considered was occurring at the same time.

## REFERENCES


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