Goitrogenic Substances in Food

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ALTHOUGH it had been suggested for centuries that certain articles of diet might play a role in the development of nontoxic goiter, it was not until the work of Chesney, Clawson, and Webster, in 1928, that the first acceptable experimental evidence supporting this hypothesis was presented. These investigators found that a colony of rabbits they were maintaining for studies in experimental syphilis developed truly remarkable thyroid enlargement during their stay in the laboratory.[1-4] After examining other factors which might be involved, Chesney *et al.* came to the conclusion that the daily ration of cabbage was responsible. Although their studies indicated that the available iodine was more than adequate, additional supplementation of the diet with this element effectively prevented the development of goiter in the rabbits.

These studies were soon confirmed by various laboratories in diverse parts of the world. Marine was especially active in this field. Not only did he confirm the goitrogenicity of cabbage in rabbits, but also extended the original observations to include other related foods.[5]

A few investigators could not repeat the original findings of Chesney *et al.* Hercus and Purves,[6] working in New Zealand, were unable to produce any thyroid enlargement. They postulated, however, that the active material might be a glycoside and would therefore be expected to be contained in higher concentration in the seeds of the plants than in the edible parts. Accordingly, the New Zealand group made a study of the goitrogenic properties of various seeds of plants related to cabbage and found that a diet containing a high percentage of such seeds would regularly cause thyroid enlargement in rats.[6] Since these vegetables belong to the genus *Brassica*, the generic term "Brassica-seed goiter" has been subsequently applied in the literature to describe this phenomenon.

Subsequent studies by Purves and his collaborators[7-9] demonstrated that the thyroid enlargement appeared to be a compensatory hypertrophy. The Brassica-seed diet interferred with the normal formation of thyroid hormone, hypothyroidism resulted and secretion of thyrotropin by the pituitary was consequently increased. No goiter could be produced by this diet in hypophysectomized rats nor in intact rats administered thyroxin. One interesting and probably highly significant difference between their findings and the earlier studies of Chesney *et al.* with cabbage was that whereas cabbage-goiter could be prevented by added iodine, Brassica-seed goiter could not. Only a partial inhibition of thyroid hypertrophy would thus be produced.

Much thought and energy was expended on trying to elucidate the nature of the active goitrogen of the *Brassicae*. Marine originally considered that the active principle might be a mustard oil, since such compounds are characteristic for members of the cabbage family; however, none of those tried were found to be goitrogenic. Cyanide is also fairly prevalent among the *Brassicae* and all cyanides tested were found to produce thyroid enlargement. Methyl cyanide, the least toxic of this group, was most active.[10] He thus concluded that this compound was the active agent. Other investigators, however, have been unable to confirm the goitrogenicity of the cyanides.

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The next phase of the story develops from an entirely unexpected quarter. In 1941, Richter and Clisby,[11] testing various materials for their efficacy as rat poisons, noted that phenylthiourea would produce quite striking thyroid enlargement and hyperemia. At about the same time, Mackenzie, Mackenzie and McCollum[12] obtained similar effects in the rat during an investigation of sulfaguanidine. The next year, Kennedy, of the New Zealand group, reported that allylthiourea might be the active antithyroid compound in Brassica seed, since this compound was also goitrogenic.[13] Presumably he suggested allylthiourea because allylisothiocyanate is a common mustard oil among the *Brassicae* and isothiocyanates are known to form thioureas on reaction with ammonia.

These reports culminated in the careful and exhaustive studies of Astwood[14] into the chemical nature of antithyroid compounds. His investigations indicated that two classes of compounds interfered with the synthesis of thyroxin: the aniline derivatives, such as sulfaguanidine, and the thionamide series, such as thiouracil and thiourea. Only the thionamide series was known to be effective in man.

Although the studies of experimental goiter had greatly advanced our knowledge of thyroid physiology and factors which might be responsible for the development of goiter, it was hazardous to extrapolate the results of animal experiments to prove their possible significance in the etiology of human goiter. Isolated cases of the occurrence of thyroid enlargement in man due to the ingestion of goitrogenic foods had been reported from time to time, but the validity of these reports was subject to some question.

About 1946 an extremely important tool became available for the study of human thyroid physiology which had been denied earlier workers. This was the use of radioactive iodine. Utilizing a modification of the Stanley and Astwood rapid screening test[15] for the activity of antithyroid compounds in man by observing the acute change in slope produced by such materials on thyroidal I^{131} accumulation, the antithyroid activity of a series of over 60 foods was studied.[16] (Table I). Several of these foods gave a positive test, but of these rutabaga was consistently most active. Contrary to our expectations, no activity could be detected in several tests of cabbage.

TABLE I

Results of Studies on Antithyroid Potency of Various Foods in Man (Modified from Reference)[16]

Marked effect	Questionable effect	No effect	
Rutabaga	Grape	Beefsteak	Banana squash
Moderate effect	Celery	Bonita	Corn
Turnip	Green pepper	Cheese	Rice
Peach	Orange	Ice cream	Rye
Pear	Apricot	Lobster	Black beans
Strawberry	Peanut	Sardines	Lima beans
Spinach	Pea	Shrimp	Onion
Carrot	String bean	Mushrooms	Olive
	Walnut	Dates	Almond
	Filbert	Pineapple	Apple
	Honeydew	Broccoli	Blackberry
	Cabbage	Cauliflower	Loganberry
	Lettuce	Mustard	Tangerine
	Beet	Radish	Banana
	Oyster	Cucumber	Potato
	Milk		Tomato
	Liver		
	Clam		
	Grapefruit		

One interesting finding was that when the rutabaga had been cooked before eating, no activity could be found. If an aqueous extract of the cooked plant was subsequently treated with a purified enzyme preparation from uncooked rutabaga, it would acquire goitrogenic potency. This indicated that the active ingredient was initially present as inactive precursor and could be liberated only by specific enzymatic hydrolysis and not by the physiologic hydrolysis which would occur in the gut.

An investigation was then made into the nature of the antithyroid principle of rutabaga and related species. Eventually it was possible to isolate a colorless, crystalline material, "goitrin," which had high enough antithyroid activity to account for all the goitrogenic potency of rutabaga. It has been identified as L-5 vinyl, 2-thio-oxazolidone[17] (Table II). This material has been found in rather high concentration in extracts from the seeds of

TABLE II

Thiooxazolidone Content of Seeds of Plants of Mustard Family[11]

Genus	Plant	No. of varieties tested	Content: Range g/kg	Content: Mean g/kg
Brassica	Rutabaga*	7	0.8–8.6	2.5
	Turnip*	9	0.3–2.5	1.0
	Cabbage*	9	0.2–4.7	1.5
	Kale*	3	0.9–6.3	4.4
	Rape*	3	1.8–2.1	1.9
	Chinese cabbage	1		0.7
	Brussels sprouts	2	0.5–0.8	0.7
	Broccoli	1		1.6
	Kohlrabi	2	0.7–1.4	1.1
	Cauliflower	2		0
	Mustard	3		0
Raphanus	Radish	12		0
Lobularia	Sweet alyssum	5		0
Matthiola	Stock			0
Iberis	Candytuft	2		0
Nasturtium	Cress	1		0
Lepidium	Cress	1		0
Arabis	Rock cress	1		0
Cheiranthus	Wallflower	2		0
Lunaria	Honesty	1		0

* Identified by isolation.

most *Brassicae* and in the edible parts of rutabaga and turnip. Goitrin is slightly more active than propylthiouracil in man and about one fifth as active as propylthiouracil in the rat. It is in the thionamide series of antithyroid compounds and is closely related to methimazole.

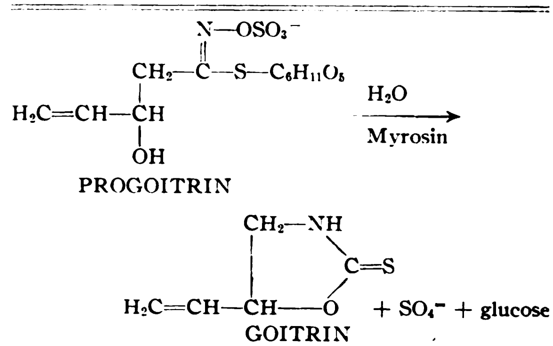
Recently it has been possible to isolate, crystallize, and identify the precursor of goitrin[18] (Table III). This compound has been named "progoitrin." It is a thioglycoside containing sulfate and glucose in addition to the goitrin portion which is present as the aglycone. Actually goitrin is not present in progoitrin as a cyclic structure but as a straight chain. Progoitrin is thus similar to other mustard oil glycosides, such as sinigrin. Because the aglycone contains an unstable hydroxyl group, it apparently cyclizes immediately after hydrolysis. With the elucidation of the correct structure of the mustard oil glycosides by Ettlinger and Lundeen,[19] it is now possible to write the correspondingly correct structure for progoitrin, rather than depending on the original structure for sinigrin proposed by Gadamer in 1897.[20]

Although several foods were found to possess antithyroid activity in our original studies, it has been possible to identify goitrin only in extracts of rutabaga and turnip. Eventually it may be possible to isolate the active compounds which may occur in other goitrogenic foods, but at present there is considerable question as to whether some of the positive effects we originally obtained may not have been artifacts. With rutabaga and turnip, of course, there can be no doubt. The content of progoitrin in the various Brassica seeds and plants varies from season to season and from batch to batch, even within identical varieties. The exact reason for this variation is unknown, but progoitrin has never been found completely absent in those varieties in which it has once been identified.

In view of the widespread occurrence of thioglycosides and the extensive studies being made of them at the present time, it will be quite surprising if other, and possibly more potent, active antithyroid compounds are not isolated from this series. As yet only the previously isolated 5,5-dimethyl, 2-thio-oxazolidone[21] has been found in hare's ear mustard. It is also quite likely that naturally occurring goitrogenic compounds of an entirely different

TABLE III[18]

Progoitrin Undergoes Specific Enzymatic Hydrolysis by the Thioglycosidase, Myrosin, to Form Goitrin by Cyclization of the Aglycone and Concomitantly Liberate Sulfate and Glucose



nature in a different family of foodstuffs will be discovered.

The failure to detect any goitrogenic activity in cabbage while finding it in cabbage seeds and other members of the *Brassicae* was quite surprising. It would indeed be odd if the plant which provided the initial stimulus for the massive accumulation of data on goitrogenic materials should prove to be completely impotent. Such may be the case, however. Complete prevention of cabbage-goiter by added iodine, as reported by Chesney *et al.* is not found either with Brassica-seed goiter or with the thyroid hypertrophy produced by pure antithyroid compounds. Also, the apparent production of hyperthyroidism by administration of iodine to cabbage-treated rabbits which had become goitrous is puzzling. If the goiter were due to the ingestion of compounds which interfere with the formation of thyroxine, it would not be expected that the goitrous thyroid would be capable of synthesizing thyroxine from the additional iodine. It is thus possible that the original cabbage-goiter may have been primarily due to iodine deficiency. It is also conceivable that the thiocyanate content of cabbage may have contributed by interfering with thyroidal iodide concentration without affecting organic binding of iodine by the thyroid.

Although certain cataclysmic events which necessitate a greatly increased consumption of goitrogenic foods by large population groups may contribute to an increased incidence of simple goiter,[22] it is exceedingly difficult to incriminate the ingestion of such foods as a factor in the etiology of the goiter in any individual patient. For the present, the best course would appear to be to make enquiries into the possible ingestion of such materials in each goitrous patient, but to concentrate our energies on other factors which may be involved. In any event, present evidence leads us to believe that goitrin cannot be formed from progoitrin if turnips and rutabagas are cooked before they are eaten. Only the consumption of raw vegetables of this class should therefore be looked upon with suspicion.

SUMMARY

The more recent literature on the production of goiter by various foodstuffs is briefly reviewed. Rutabaga and turnip are the only edible plants from which an active goitrogen has so far been isolated. The active antithyroid agent in these vegetables has been identified as goitrin. It is present in the plant, and in the seeds of most *Brassicae*, as progoitrin, an inactive compound. Goitrin is apparently liberated from progoitrin only through specific enzymatic hydrolysis by a thioglycosidase contained in the plant or seed itself. Cooking destroys this enzyme and thus negates its goitrogenic potency by preventing the liberation of goitrin from progoitrin. Although the ingestion of considerable quantities of goitrogenic foods may contribute to the development of goiter under certain circumstances, it is very difficult to incriminate them as an etiologic factor in the vast majority of goitrous patients.

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