GOITROGENS IN FOOD AND WATER

Eduardo Gaitan

Department of Medicine, University of Mississippi School of Medicine and Endocrinology Section, Veterans Administration Medical Center, Jackson, Mississippi 39216

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INTRODUCTION

No less than 5% of the world's population have goiters. Many of these are associated with other disorders and constitute a major public health problem. Although 300 million people with goiter live in less highly developed countries where iodine deficiency is prevalent, 100 million individuals with goiter live in more highly developed countries where goiter continues to occur in certain areas, despite iodine prophylaxis (68). Although endemic goiter and iodine deficiency are commonly associated with cretinism, congenital hypothyroidism, and various degrees of impairment of growth and mental

development (conditions grouped under the name of iodine deficiency disorders), iodine-sufficient goiters are associated with autoimmune thyroiditis, hypothyroidism, hyperthyroidism, and probably thyroid carcinoma.

For centuries, countless theories have attempted to explain the etiology of endemic goiter. However, only three are supported by experimental evidence. These are the theories that nutritional iodine deficiency, goitrogens in foodstuffs, and the quality of drinking water are causative factors in goiter endemias (31, 92a, 106).

The role of iodine deficiency as an environmental determinant in the development of endemic goiter is firmly established. However, three observations indicate the existence of factors other than iodine deficiency in the etiopathogenesis of endemic goiter. First, iodine deficiency does not always result in endemic goiter. Second, there is epidemiological and experimental evidence that concomitant exposure to other naturally occurring antithyroid agents magnifies the severity of the goiter endemia. Third, iodine supplementation does not always result in complete eradication and prevention of goiter. This article reviews those environmental agents that, acting through the food and/or water exposure pathways, may be responsible for the exaggeration, persistence, or development of goiter.

GENERAL CONSIDERATIONS

Many agents in the environment interfere with thyroid gland morphology and function (30, 31). Agents that cause thyroid enlargement are known as environmental goitrogens; they may cause the goitrous condition by acting directly on the thryoid gland, but they can also act indirectly by altering the regulatory mechanisms of the thyroid gland and the pheripheral metabolism and excretion of thyroid hormones. However, the mechanism that induces the trophic changes leading to goiter formation is not well understood, because besides thyrotropin, or thyroid-stimulating hormone (TSH), other humoral, paracrine, and autocrine growth factors may be involved in the process.

Figure 1 illustrates the three main steps in thyroid gland function, showing the environmental agents that act directly in the gland by interfering with the process of hormone synthesis.

GOITROGENS IN FOODSTUFF

Human Goiter Endemias from Naturally Occurring Goitrogens in Food

Several goiter endemias have been attributed to environmental goitrogens in foodstuff (25, 31) (Table 1). Two goiter endemias were ascribed to the presence of goitrogenic substances in milk (25). One was in Tasmania, where a seasonal variation in goiter prevalence in schoolchildren was noted despite
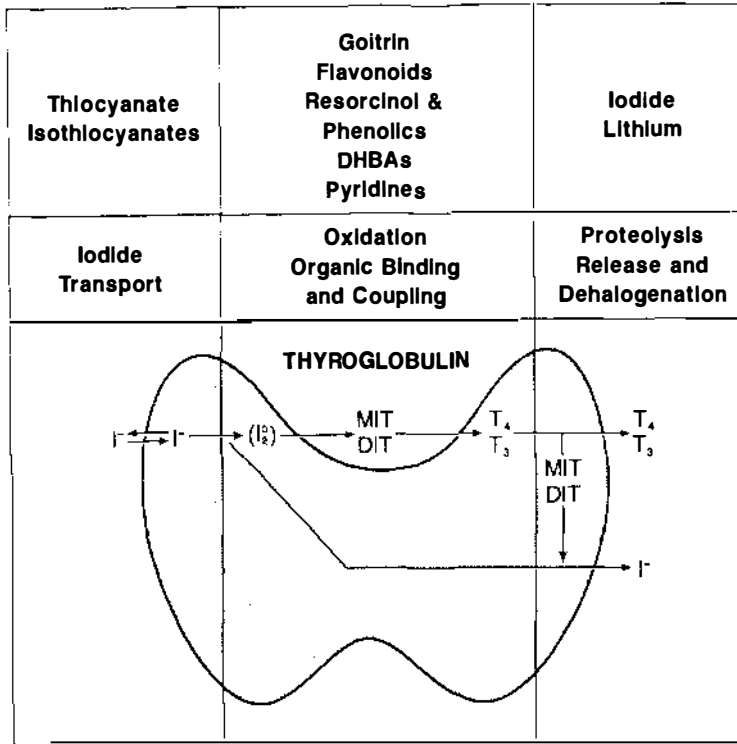
Thiocyanate Isothiocyanates	Goitrin Flavonoids Resorcinol & Phenolics DHBAs Pyridines	Iodide Lithium
Iodide Transport	Oxidation Organic Binding and Coupling	Proteolysis Release and Dehalogenation

Figure 1 Environmental goitrogens and their site of action in the thyroid gland. Abbreviations: goitrin, = L,5-vinyl-2-thiooxazolidone; DHBAs, dihydroxibenzoic acids; I. iodide; MIT, monoiodotyrosine; DIT, diiodotyrosine: T_4, thyroxine; T_3, triiodothyronine.

adequate iodine intake; in this endemia, cheilorine, an isothiocyanate, was suspected as the principal goitrogen. The other occurred in Finland; in this endemia, goitrin, a thiooxazolidone present in cows' milk from the goitrous region, was considered the causative factor. Rats fed for 1–2 years on milk produced in endemic goiter districts developed thyroid glands almost twice as large as those in control rats given milk from nongoitrous districts. The concentration of L-5-vinyl-2-thiooxazolidone (goitrin), in the range of 35–100 μg/l in milk specimens from goitrous districts, exceeded the level necesssary to explain the goitrogenic effect of this milk when fed to rats in long-term experiments. Thus, the study concluded that goitrin might well be responsible, at least in part, for the goiter endemia in those areas of Finland. On the other hand, available data from the Tasmanian endemia failed to establish the goitrogenic properties of milk.

Goitrogenic substances in cassava have been implicated in the etiology of two other endemias. In eastern Nigeria, goitrogenic and thionamidelike anti-

Table 1 Goiter endemias attributed to goitrogens in food

Locality	Source	Vehicle	Active principle	References
Tasmania	Grass and weeds	Milk	Isothiocyanate (cheilorine)	25
Finland	Grass and weeds	Milk	L-5-vinyl-2-thiooxazolidone (goitrin)	25
Nigeria	Cassava		Thionamidelike goitrogen	25
Central Africa	Cassava		Thiocyanate from linamarin (cyanogenic glucoside)	14, 15, 22
Sudan	Millet		C-glycosylflavones and thiocyanate	18, 19, 39, 41, 43, 55, 79, 80, 85
Chile	Piñon nut		—	25
Brazil	Babassu		—	42, 71
Japan	Seaweeds		Iodide and polyhydroxyphenols (?)	17, 24, 48, 95

thyroid activity was found in cassava from endemic areas (25). Another endemia, the best documented (14, 15, 22), is the one in the Idjwi Island, Kivu, and Ubangi areas of Zaire, where as many as 60% of the population are affected by goiter. Studies have shown that cassava, a staple food in these areas, has definite antithyroid effects in humans and experimental animals. Thus, daily consumption of cassava, in the presence of severe iodine deficiency, is thought to be the cause of endemic goiter and cretinism in these areas of Zaire. The goitrogenic action of cassava is due to endogenous release of thiocyanate from linamarin, a cyanogenic glucoside present in cassava, particularly in the tuberous roots.

Pearl millet [*Pennisetum americanum* (L.) Leeke] is one of the most important food crops of the semiarid tropics, an ecologic zone that includes portions of Africa and Asia and almost encircles the Earth (55, 85). Because of its perennial growth, millet constitutes the main source of food energy for many very poor people in these areas. Epidemiologic evidence suggests that ingestion of millet plays a role in the genesis of endemic goiter in these areas. For instance, goiter is more prevalent in rural villages of the Darfur Province in Sudan, where as much as 74% of dietary energy is derived from millet, than in an urban area, where millet provides only 37% of calories, even though the degree of iodine deficiency is similar in the two areas (18, 19, 79, 80).

Studies demonstrate that a diet composed largely of millet is goitrogenic in the rat, and that this effect is not overcome by a high iodine intake (39, 41, 43). Heating or boiling and storage of millet, similar to the procedures used

to prepare millet for consumption in the natural setting (millet in the rural villages is characteristically eaten twice daily, after being cooked in a porridge), increase its antithyroid activity. *Pennisetum* millet is very rich in C-glycosylflavones (C-GFs) (85). The C-GFs glucosylvitexin, glucosylorientin, and vitexin, which constitute the largest proportion of the phenolic compounds in millet, all possess antithyroid activity and appear to be the goitrogens in millet. Thiocyanate is also present in millet, and its antithyroid effects are additive to those of the C-GF (41, 66). Thus, in areas of iodine deficiency where millet is a major component of the diet, ingestion of millet may contribute to the genesis of endemic goiter.

The nut of piñon *(Araucaria araucana)* may have a role in the pathogenesis of endemic goiter in an Indian reservation in Chile (25). A piñon diet fed to rats showed goitrogenic activity that was not due to iodine deficiency.

Babassu *(Orbignya phalerata),* a palm tree fruit, mixed with mandioca *(Manioca utilessima),* a cassavalike root, is the staple food of people in the endemic goiter area of Maranhao in Brazil (42, 71). In vitro studies demonstrate that the mesocarp flour and the pressed paste of kernel with skin, which are the edible parts of babassu, are potent inhibitors of thyroid peroxidase (TPO) and of iodide organification and coupling to form the active thyroid hormones. Thus, daily consumption of babassu may explain the persistence of goiter in the absence of iodine deficiency in some endemic areas of Brazil.

An excess intake of iodine, arbitrarily defined as at least 2 mg per day, inhibits thyroglobulin proteolysis and the release of thyroid hormones (Figure 1) and eventually produces "iodide goiter" and hypothyroidism (17, 24). Sustained ingestion of seaweeds (kelp) rich in iodine causes "endemic coast goiter," as described among natives in Hokkaido, Japan (24, 95). Seaweeds of the genera *Laminaria* have a high content of phloroglucinol and polyhydroxyphenols, some in the form of phloroglucinol polymers (fucophloroethols) (48). Phloroglucinol and other polyhydroxyphenols, which are potent antithyroid compounds (Figure 1), may play an additional role to that of iodine excess in the development of these goiters.

Chemical Categories, Metabolism, and Mechanism of Action

SULFURATED ORGANICS

Thiocyanate, isothiocyanates, and thiooxazolidone Extensive reviews describe sources (cyanogenic glycosides and thioglycosides or glycosinolates), metabolic pathways, and action of thiocyanate, isothiocyanates, and goitrin (21, 63, 98).

Although the presence of goitrogenic substances in foodstuff had been suspected for many years, it was not until 1929, when Chesney et al (6) demonstrated the development of goiter in rabbits fed on cabbage, that the existence of these substances was firmly established. Since then, other vegetables of the Cruciferae family have been found to possess goitrogenic proper-

ties. Thiocyanate and isothiocyanates have been demonstrated as goitrogenic principles in members of the Cruciferae family. The potent antithyroid compound goitrin was isolated from yellow turnips and from *Brassica* seeds. Cyanogenic glycosides (thiocyanate precursors) have also been found in several staple foods (cassava, maize, bamboo shoots, sweet potatoes, and lima beans) from the Third World. After ingestion, these glycosides can be readily converted to thiocyanate by widespread glycosidases and the sulfur transferase enzyme. Isothiocyanates not only use the thiocyanate metabolic pathway but also form derivatives with thiourealike antithyroid effects. Thus, the actual concentration of thiocyanates or isothiocyanates in a given foodstuff may not represent its true goitrogenic potential, nor does the absence of these compounds negate a possible antithyroid effect, because inactive precursors can be converted into goitrogenic agents both in the plant itself or in the animal after ingestion. Thioglycosides undergo a rearrangement to form isothiocyanate derivatives and, in some instances, thiocyanate. Therefore, the amount of thiocyanate in the urine is a good indicator of the presence of thioglycosides in food. Also, a mustard oil glucoside yields thiocyanate under the action of myrosinase, an enzyme present in plants. However, ingestion of pure progoitrin, a naturally occurring thioglycoside, elicits antithyroid activity in rats and humans in the absence of that enzyme, because progoitrin is partially converted by intestinal microorganisms into the more potent antithyroid compound goitrin. This ability of plants and animals to readily convert inactive precursors into goitrogenic agents must be considered when the possible etiologic role of dietary elements in endemic goiter is being investigated.

Thiocyanate or thiocyanatelike compounds primarily inhibit the iodine-concentrating mechanism of the thyroid, and their goitrogenic activity can be overcome by iodine administration (Figure 1). The isothiocyanates and cyanogenic glycosides act on the thyroid mainly by their rapid conversion to thiocyanate. However, isothiocyanates, as previously mentioned, not only use the thiocyanate metabolic pathway but also react spontaneously with amino groups to form thiourea derivatives, which produce a thiourealike antithyroid effect. The thionamide or thiourealike goitrogens interfere in the thyroid gland with the organification of iodine and formation of the active thyroid hormones, and their action usually cannot be antagonized by iodine. Naturally occurring goitrin is representative of this category (Figure 1). Goitrin is unique in that it is not degraded like thioglycosides. Additive antithyroidal effects of thiocyanate, isothiocyanate, and goitrin occur with combinations of these naturally occurring goitrogens.

Disulfides   Small aliphatic disulfides, the major components of onion and garlic, exert marked thiourealike antithyroid activity in the rat (21, 25, 30, 35).

FLAVONOIDS   Flavonoids are important stable organic constituents of a wide variety of plants. They are present in high concentrations in polymeric (tannins) and oligomeric (pigments) forms in various staple foods of the Third World (e.g. millet, sorghum, beans, groundnut) (54, 55). Flavonoids, which exert a thiourealike antithyroid effect (Figure 1), are polyhydroxyphenolic compounds with a C_6-C_3-C_6 structure. Flavonoids usually exist in plants as complex glycoside polymers.

After ingestion by mammals, flavonoid glycosides are hydrolyzed by intestinal microbial glycosidases to flavonoid aglycones. These may be absorbed and undergo metabolism by mammalian tissues or be further metabolized by intestinal microorganisms to undergo B-ring hydroxylation and middle-ring fission, with production of various metabolic compounds, including phenolic acids, phloroglucinol, and gallic acid (11, 66). Each metabolic step is characterized by marked increases in antithyroid effects (28, 66). For instance, flavonoid glycosides, which include the C-glycosylflavones in millet, are 0.2–2 times as potent inhibitors of TPO as propylthiouracil (PTU) is, whereas their corresponding aglycones are 0.5–14 times as potent and the middle-ring fission metabolite phloroglucinol is 38 times as potent.

Flavonoids not only inhibit the thyroid peroxidase but, acting on iodothyronine deiodinase enzymes, also inhibit the peripheral metabolism of thyroid hormones (10, 11). Furthermore, polymers of the flavonoid phloretin interact with thyroid-stimulating hormone (TSH), preventing its action at the thyroid cell (72, 97). Thus, this class of compounds alters thyroid hormone economy in a complex manner.

PYRIDINES   Dihydroxypyridines and 3-hydroxypyridine are potent inhibitors of TPO, producing effects comparable to or greater than those of PTU (8, 64, 94) (Figure 1). After ingestion, mimosine, a naturally occurring amino acid in the seeds and foliage of the tropical legume *Leucaena leucocephala,* is metabolized to 3,4-dihydroxypyridine, a potent antithyroid agent that produces goiter in mice, rats, sheep, and cattle (8).

GOITROGENS IN WATER

Historical Background

The concept that certain water may cause goiter is an ancient one. Innumerable descriptions attribute goiter to the poor quality of drinking water (40, 62). Such descriptions appeared as early as 770 B.C. in China. Caldas in 1808 and Camacho in 1810 were the first to attribute the Colombian endemia to the quality of local drinking water (58, 91). Stott suggested in 1931 that goiter in India was directly related to the high calcium content of drinking water (93). Murray et al (77), studying goiter, or Derby neck, as it is sometimes called in

England, concluded that even where iodine levels were similar, there was a greater incidence of visible thyroid glands in people in areas with hard water, as in England, than in areas with soft water, as in Scotland. However, they also mentioned that goiter could occur in places with soft water, such as Devon in England. In the Tjibodas district of Indonesia there is a well called the well of Gondok (well of goiter). By superstition, drinking from this well leads to the development of goiter (75). It is appropriate to recall the following paragraph, written by Hirsch in 1883 (53): "In the doctrine of the causes of disease, there is hardly any idea that has taken so deep a root, both in the popular belief and in the convictions of medical observers, as that goiter is caused by the use of drinking water from particular sources." Nevertheless, scientific evidence is scanty, consisting of a few experiments from the early 1900s, in which goitrogenic water produced goiter in humans, trout, and rats (69, 86). Three of these investigators, working independently, all concluded that prolonged boiling inactivates goitrogenic waters. High mineral content, particularly of magnesium and calcium salts (61, 62, 96), and bacterial contamination (40, 45, 61, 62, 67, 69, 96, 101) have also been implicated as goitrogenic factors in water. Goitrogens that contaminate water are likely to be widely consumed, because water is such a ubiquitous component of the diet.

Human Goiter Endemias from Goitrogens and Bacteria in Water Supplies

Table 2 lists the goiter endemias that have been attributed to water-borne goitrogens and bacterial contamination of drinking water.

Studies in Trujillo State, Venezuela, documented higher (Li^+) concentrations in the water supply of a high-incidence endemic goiter locality

Table 2   Goiter endemias attributed to chemical and bacterial pollution of the water-exposure p.

Locality	Source	Active principle	References
Venezuela	Various rocks and soils	Lithium	35, 92
Virginia	E. coli	High-molecular-weight fraction from cell-free E. coli incubate	100, 101
Greece	E. coli	—	67
Western Colombia	Shales and coals, HS,[a] and gram-negative bacteria	Resorcinol, phthalate ester derivatives (DHBA), disulfides	23, 26–29, 34, 40, 45, 47,
Eastern Kentucky	Coals and gram-negative bacteria	Phenolics, phthalate ester derivatives (DHBA), methylanthracene (PAH)	27–29, 33, 34

[a] Abbreviations: HS, humic substances; DHBA, dihydroxybenzoic acids; PAH, polycyclic aromatic hydroca.

than in that of nearby nonendemic communities. Experimental observations indicated the Li^+ at those concentrations can be goitrogenic, but this effect is conditioned by dietary protein and iodine intake (35, 92).

Microorganisms that contaminate water supplies have been implicated as causative factors in at least two instances of endemic goiter (40, 61, 67, 100, 101). In bacteriologic studies of some Greek villages, the drinking water in villages with a high prevalence of goiter was significantly more likely to be polluted with *Escherichia coli* and colilike organisms than was water from nongoitrous localities (61, 67). Vought et al (100, 101) demonstrated a similar relationship in Richmond County, Virginia (USA), where goiter existed despite adequate iodine supplementation. These observations support the hypothesis that microorganisms such as *E. coli* are involved in the pathogenesis of endemic goiter.

Demonstration of thyroid growth–stimulating immunoglobulins in some goitrous individuals (16) and evidence of immunologic cross-reactivity between the human thyroid plasma membrane and antigenic determinants in *E. coli* and *Yersinia enterocolitica* (104, 105) raise the interesting possibility that bacterial antibodies exert a growth-promoting effect on the thyroid, thus playing a role in the pathogenesis of goiter in endemic areas.

Epidemiologic evidence from western Colombia and eastern Kentucky indicates that environmental factors other than nutritional iodine deficiency are responsible for the persistence of goiter in those areas (26, 27, 34, 40). Studies in Colombia demonstrate a positive relationship of goiter prevalence with goitrogenic and antithyroid activities in drinking water, a relationship that cannot be explained by total hardness or concentrations of individual inorganic compounds (23, 26, 36, 37, 38, 40). Furthermore, epidemiologic observations in 41 localities of western Colombia, all of which had been on iodine supplementation for 10–20 years, demonstrate that the geologic composition of aquifers and watersheds is significantly associated with goiter prevalence rates (26, 47, 74). Towns located downstream from organic-rich rocks, i.e. coal and shales, have the highest goiter prevalence. In contrast, populations taking their drinking water from streams flowing across igneous rocks, devoid of organic matter, show a low goiter prevalence. Mixed lithologies are associated with intermediate levels of goiter. These results support the hypothesis that sedimentary rocks rich in organic matter, such as coals and shales, as also occur in eastern Kentucky, are the main source of water-borne goitrogens. Actually, coal water extracts and drinking water from the goitrous coal-rich Appalachian area in Kentucky produce goiter in the Buffalo rat strain (13, 33).

Bacteriologic studies in 34 of the 41 localities surveyed in western Colombia (26, 40, 45) showed significantly higher goiter prevalence associated with the overall concentration of bacteria in the pipeline system and lower

prevalence associated with *Klebsiella pneumoniae* in the water source. These results may represent natural examples of bacterial intermediation in the process of biomagnification and biodegradation of the organic pollutants that produce goiter.

Sources, Chemical Categories, Biogeochemical Cycle, and Mechanism of Action

Coal is a source of a large variety of antithyroid and goitrogenic compounds, e.g. phenol, dihydroxyphenols (resorcinol), substituted dihydroxybenzenes, thiocyanate, disulfides, phthalic acids, pyridines, and halogenated and polycyclic aromatic hydrocarbons (PAH) (28, 29, 31, 56, 60, 73, 76, 82) (Table 3). Most of these compounds have been identified in drinking water from the iodine-sufficient goitrous areas of Kentucky and Colombia (23, 26, 28, 29, 37, 38, 40).

POLYHYDROXYPHENOLS AND PHENOL DERIVATIVES   Phenolics are the major organic pollutants in wastewater effluents from various types of coal treatment processes (28, 56, 60, 65, 73, 76, 82). Resorcinol, substituted resorcinols, and other antithyroid phenolic pollutants are present at as much as 5 g/liter in coal-derived effluents. Up to 8% of shale bitumen is also composed of phenols (99). Resorcinol and a substituted resorcinol, *m*-dihydroxyacetophenone, have also been isolated from water supplies of endemic goiter districts in western Colombia and the coal-rich Appalachian area of eastern Kentucky (26, 28, 29, 38, 40).

Resorcinol, the prototype of this group of compounds, is antithyroid and goitrogenic in both humans and experimental animals (12, 29, 38, 40, 63, 98). In the early 1950s the goitrogenic effect of resorcinol was demonstrated when patients applying resorcinol ointments for the treatment of varicose ulcers developed goiter and hypothyroidism (4, 84). Several observations also

Table 3   List of coal-derived organic pollutants

Category	Description
Phenolics	Phenol, cresol, catechol, resorcinol, hydroquinone, methylresorc orcinol, methylcatechol, other substituted dihydroxybenzenes
Sulfurated organics	Thiocyanate, disulfides, thiophenes, thiophenols
Phthalates	Esters, phthalic acids
Pyridines	Methylpyridines, hydroxypyridines
PAH[a]	Anthracene, benzanthracene, BaP
Other hydrocarbons	Aliphatics, aromatics (naphthalenes)
Organochlorines	Dichloromethane, chloroform, carbon tetrachloride

[a] Abbreviations: PAH, polycyclic aromatic hydrocarbons; BaP, benzpyrene.

suggest that resorcinol crosses the human placenta and may cause both neonatal goiter and hypothyroidism (102).

Resorcinol and the substituted resorcinols 2-methylresorcinol, 3',5'-dihydroxyacetophenone, and 5-methylresorcinol (orcinol) are 27, 23, 19 and 7 times more potent, respectively, than PTU in the TPO assay (12, 29, 65) (Figure 1). Other dihydroxyphenols are less potent than but comparable in activity to PTU. A comparison of the antiperoxidase activity of resorcinol (1,3-dihydroxybenzene), catechol (1,2-dihydroxybenzene), and hydroquinone (1,4-dihydroxybenzene) indicates the importance of hydroxyl groups in the *meta* position for maximal activity. In the in vitro assay in which thyroid slices were used, resorcinol, orcinol, 2-methylresorcinol, and *m*-dihydroxyacetophenones inhibit both the thyroidal uptake of ^{125}I and its organification (12, 29, 30, 31, 65). Resorcinol in this assay is 20 times as potent as PTU. Furthermore, the net antiperoxidase effects of mixtures of dihydroxyphenols, as well as dihydroxyphenols and thiocyanate [also a coal-derived pollutant (Table 3)], are equivalent to or greater than the sum of the effects produced by individual compounds; this indicates that the true goitrogenic potential of the major water-soluble compounds present in coal and shales appears to be due to the combined effects of the individual constituents rather than to any single compound (65).

Studies of the physical state of organic goitrogens in water indicate that the active compounds form dissociable complexes and that they are part of larger organic molecules, possibly humic substances (HS) (12, 26, 38, 40). Furthermore, resorcinol and other parent antithyroid phenolic and phenolic-carboxylic compounds are degradation monomeric byproducts of reduction, oxidation, and microbial degradation of HS (3, 5, 7, 9, 12, 50, 87, 89). HS, high-molecular-weight complex polymeric compounds, are the principal organic components of soils and waters. More than 90% of total organic matter in water consists of HS, which are also present in coals and shales (1, 7, 12, 90). Concordant with these results, fulvic and humic acids, two major fractions of HS, inhibit TPO, displaying 15% of the activity of PTU on a dry-weight basis (38, 40). In contrast to lignin-derived HS, up to 70% of flavonoid HS may be made up of phenolic and carboxylic benzene rings (7, 51, 90). The suggestion that coals and shales may be major sources of contamination of water supplies with this type of HS is supported by the observation that phenols are the major organic pollutants in aqueous effluents from coal conversion processes (56, 60, 76, 82).

Decaying organic matter (plants and animals) becomes the substrate of lignin and flavonoid types of HS during fossilization (or coalification). Actually, cyanidin, a naturally occurring flavonol used as the model subunit of flavonoid-type HS, yields, by reductive degradation, resorcinol, phloroglucinol, orcinol, and 3,4-dihydroxybenzoic acid (5). Thus, flavonoid structures

might be the link between phenolic goitrogens in foodstuffs (e.g. millet) and those in coals, shales, soils, and water (31). The biogeochemical cycle of phenolic goitrogens and interrelationships among plant flavonoids, polyhydroxyphenols, HS, coals, and shales are illustrated in Figure 2.

PHTHALATE ESTERS AND METABOLITES   Phthalic acid esters or phthalates are ubiquitous in their distribution and have been frequently identified as water pollutants (32, 81, 83). Dibutyl and dioctyl phthalates have been repeatedly isolated from the goitrogenic well water supplying the high-endemic-goiter district of Candelaria Town in western Colombia (26, 28, 35, 37, 38). Phthalate esters were also found in water supplies from the goitrous coal-rich Appalachian district of eastern Kentucky and from other goiter localities in western Colombia (28, 29, 40). Although phthalate esters are most commonly the result of industrial pollution, e.g. as emission pollutants from coal-liquefaction plants, they also appear naturally in shale, crude oil, petroleum, plants, and fungal metabolites (28, 32, 76, 81).

Although phthalate esters and phthalic acids do not possess intrinsic antithyroid activity (30, 32), they undergo degradation by gram-negative bacteria to form dihydroxybenzoic acid (DHBA) (20, 59). DHBA possess antithyroid properties (12, 29, 32, 65). 3,4-DHBA, an obligate metabolite in the catabolic pathway of phthalate esters, is a potent inhibitor of TPO, being as effective as PTU. In the in vitro assay with thyroid slices, 3,4- and 3,5-DHBA also inhibit the incorporation of iodide into thyroid hormones. The proven effective role of gram-negative bacteria in phthalate biodegradation may explain in part the relationship established between the frequency of goiter and bacterial contamination of water supplies. Furthermore, marked ultrastructural changes of the thyroid gland, similar to those seen after administration of TSH, and decreased serum thyroxine (T_4) concentration, have been observed in rats treated with phtalic acid esters (52). Thus, phthalates may become goitrogenic under appropriate conditions.

DISULFIDES   Disulfides are present in high concentration (0.3–0.5 g/liter) in aqueous effluents from coal conversion processes (Table 3) (28, 56, 60,
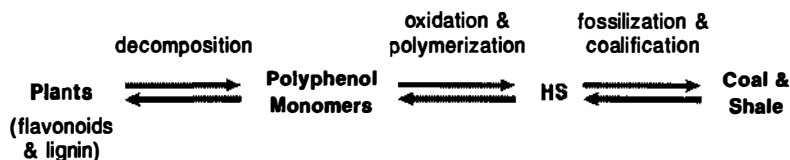

Figure 2 Simplified scheme of the biogeochemical cycle of phenolic goitrogens and interrelationships among plant flavonoids (e.g. millet), polyhydroxyphenols, humic substances (HS), coals, and shales.

76). Disulfides have also been identified as water contaminants in the United States and in a water supply to a Colombian district with a high incidence of endemic goiter (23, 28, 29, 37, 40). The most frequently isolated compounds in the United States are dimethyl, diethyl, and diphenyl disulfides. Although none of these disulfides inhibits TPO in vitro, small aliphatic disulfides exert marked antithyroid activity in the rat (21, 25, 30, 35), and fractions with sulfur-bearing organic compounds, possibly aliphatic disulfides from the goitrogenic well supplying the above-mentioned Colombian district, inhibited in vitro iodine organification in experiments with thyroid slices (23, 37).

POLYCYCLIC AROMATIC HYDROCARBONS   PAH have been found repeatedly in food, domestic water supplies, and industrial and municipal waste effluents (57, 88). They also occur naturally in coal, soils, groundwater, and surface water and in their sediments and biota. One of the most potent of the carcinogenic PAH, 3,4-benzpyrene (BaP), is widely distributed and, similar to other PAH, is not efficiently removed by conventional water-treatment processes.

The PAH carcinogens BaP and 3-methylcolanthrene (MCA) accelerate T_4 metabolism and excretion of T_4-glucuronide, resulting in decreased serum T_4 concentrations, activation of the pituitary-thyrotropin-thyroid axis, and, eventually, goiter formation (2, 49, 78). There is also evidence that MCA interfers directly with hormonal synthesis in the thyroid gland (30, 31). Furthermore, MCA, as well as 7,12-dimethylbenzanthracene, also induces goitrous thyroiditis in the BUF rat (103). Thus, MCA exerts its deleterious effects on the thyroid gland by at least three different mechanisms. Recently, the coal-derived PAH methylanthracene (Table 3), which has been identified in drinking water from the goitrous coal-rich district of eastern Kentucky (28, 29, 40), was found to produce goiter in the BUF rat without alterations of hormone synthesis or lymphocytic infiltration of the thyroid gland (13, 33).

In conclusion, many major coal-derived and water-borne organic pollutants from iodine-sufficient goiter areas display potent antithyroid and goitrogenic activities, and the effects produced by these compounds are additive. Soluble and colloidal organic substances leached from coal or shale contaminate watersheds and aquifers and are the source, probably with microbial intermediation, of goitrogenic pollutants and precursors of antithyroid compounds in water supplies. These pollutants may also enter the air and food exposure pathways, becoming important goitrogenic environmental factors in humans and other animals. Thus, shale- and coal-derived organic pollutants may be a major factor contributing to the goiter endemia and associated disorders that are observed in certain areas with aquifers and watersheds rich in these organic rocks.

NUTRITIONAL STATUS AND GOITER

Besides iodine deficiency and environmental goitrogens, protein-calorie malnutrition (PCM) also results in various alterations of thyroid gland morphology and function (35, 70). PCM and endemic goiter frequently coexist, and poor nutrition appears to increase the risk of goiter development in susceptible groups of the population (infants, children, and pregnant women). Studies demonstrate that malnourished individuals have the same thyroid gland abnormalities (44) that have been shown in experimental animals to favor enlargement of the thyroid gland (46). A low-protein diet in rats impairs the thyroidal transport of iodine, decreases iodine concentration in the thyroid, and is accompanied by an enlargement of the thyroid. Under these circumstances, the goitrogenic effect of antithyroid agents is enhanced. The administration of protein reverses these alterations and decreases the action of such goitrogenic agents.

CLOSING REMARKS

The multifactorial nature and complex interactions of host factors with region-specific environmental conditions in the pathogenesis of endemic goiter constitute a major challenge to the understanding and control of the problem of goitrogenic substances in endemic areas. However, to control and prevent this important public health problem, the most obvious but difficult initial step requires substantial socioeconomic improvements in the affected areas of the Third World, including provision of efficient iodine supplementation programs, diversification of dietary constituents with adequate daily protein-calorie intake, and institution of proper sanitary conditions with effective water treatment to eliminate organic and bacterial pollutants. This last intervention is also a requirement to control and prevent goiter in the iodine-sufficient more highly developed countries. In this regard, more research is needed to provide effective ways of water treatment that can be applied in individual households or at the community level. At present, medical or surgical treatments for the individual, but not measures for prevention and control, are being applied, when available, in iodine-sufficient goiter areas. Until preventive measures are available, the physician will be restricted to observation, administration of thyroid hormones, or surgery.

SUMMARY

Epidemiologic and experimental evidence reviewed in this article emphasizes the complex and multifactorial etiology of endemic goiter. The important role of iodine deficiency as an etiologic factor in endemic goiter is firmly es-

tablished, but there is evidence that other environmental factors can play an equally important role in the pathogenesis of this condition.

Chemical categories, sources, and sites of action of the various classes of naturally occurring goitrogens and antithyroid agents are reviewed in this article. Evidence of the presence of these compounds in foodstuffs and drinking water is discussed. Bacterial contamination of water supplies also appears to be important in the development of goiter. Microorganisms appear to intervene in the biosynthesis and degradation of organic goitrogenic pollutants or may induce thyroid growth–promoting activity in the host, or both. Malnutrition and poor socioeconomic conditions, as for iodine deficiency, enhance the action of environmental goitrogens. Thus, a coordinated multidisciplinary approach is essential to solving this public health problem.

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