Ann. Rev. Nutr. 1983. 3:341–412

ENDEMIC GOITER AND CRETINISM AT THE DAWN OF THE THIRD MILLENNIUM

Josip Matovinovic

Department of Internal Medicine, University of Michigan Hospitals, Ann Arbor, Michigan 48109

CONTENTS

INTRODUCTION

In Jivananda, an allegorical Sanskrit drama of the 17th century, a war takes place between Life and the Diseases. The king of diseases is Consumption, the

0199–9885/83/0715–0341$02.00

Commander-in-Chief of the army is Jaundice, and Goiter, as the Master of Ceremonies, opens the debate of the council of war (186).

Tragically, even at present, endemic goiter continues with enduring authority to enact that very same role in the reality of a large part of the world. During the last 50 years, the prevalence of endemic goiter and its horrible complication, cretinism, remained unchanged or even worsened in most of the "less developed" regions, and especially in remote areas of countries with recent statehood and/or harsh environmental conditions of life.

In contrast, in the same period of time, endemic goiter and its adverse effects have been virtually eliminated by iodine prophylaxis in "more developed" industrialized states.

Unfortunately, there is a possibility that in many of these countries, endemic goiter may soon reappear in a new and more complex manner. This prospect may become reality if the increasing utilization of and pollution with various iodinated compounds and goitrogens are not rationally contained. For despite present preventive measures, sporadic and even endemic goiter, like the many heads of the mythological Hydra of Learnean marshes, may start growing again in fish, birds, mammals, and ultimately in man.

During the 5th century, before our era, Gautama Buddha defined the philosophy of inquiry into the human condition in terms of "the four noble truths" (23):

1. there is disease and suffering in the world;
2. there is a cause;
3. there are means of eliminating the cause;
4. there is a path toward that goal.

"Greek culture has always been the culture of the body as well as of the soul" (79), and human life and fate were the preoccupation of many of Buddha's contemporaries in Greece—Herodotus, Sophocles, Democritus, Socrates, Plato, Phidias, Hippocrates, and Pericles. We shall consider our subject in keeping with these four viable concepts.

ENDEMIC GOITER IS A WORLDWIDE DISEASE: ITS CLINICAL AND PUBLIC HEALTH ASPECTS ARE OF CONCERN TO ALL MANKIND

According to William James, "Truth happens to an idea. It becomes true, is made true by events. Its validity is the process of its validation." (80)

In 1915, H. Hunziker-Schild, a Swiss physician, wrote a booklet entitled *Goiter, An Adaptation to Iodine-Poor Nutrition: Aprioristic Thoughts About the Nature and Prevention of Goiter* (71), and in 1954, J. B. Stanbury with his colleagues of Boston, Mass., USA, and Cuyo, Mendoza, Argentina, published

an experimental study under a similar title, *Endemic Goiter. The Adaptation of Man to Iodine Deficiency* (161).

Both treatises correctly viewed goiter as an adaptative phenomenon caused by difficulties in the secretion of thyroid hormone. However, the enlarged thyroid may cause ill health. Goiter differs from the normal thyroid in size, structure, and an increased tendency to abnormal function and malignant growth. Many excellent observations of morbid manifestations of endemic goiter have been made on patients at clinics or hospitals. However, the study of public health aspects of endemic goiter in settlements with high goiter prevalence—by examination of either the whole population or well-defined groups like school children—is more impressive. Therefore, a description of endemic goiter in Yugoslavia before and after 25 years of general prophylaxis with iodized salt may be of interest.

Endemic Goiter in Yugoslavia

ENDEMIC GOITER IN THE RURAL POPULATION

Socioeconomic and cultural observations In 1952, two villages, Rude and Brasovlje, situated about 25 km southwest of Zagreb, the capital of Croatia, had a total population of 1594 individuals, living in 347 households with an average of five family members per household (48). Housing was poor and crowded—86% of the homes had earth floors, 476 individuals had no more than 6–7 cubic meters of living space, and only 25.6% slept one to a bed.

About 65% were employed in small industries, and the rest worked on about 650 acres of land (250 acres of vineyards and fields, 150 acres of orchards and vegetable gardens, and 250 acres of grassland). The livestock consisted of 151 head of cattle, 18 pigs, a few horses, and approximately 1056 head of poultry.

The staple food was corn bread, potatoes, and beans, with little meat or milk. The food supplied an average of 40.4 g protein, 45.5 g fat, with a total of 1327 calories. Wine was an important source of calories—7.4% drank more than one liter per day, and 83% of children consumed alcohol; breakfast for some consisted of corn bread and wine. Drinking water, from wells and a small brook, contained an average of 1.3 and 0.43 μg iodine/liter respectively.

Most of the population had gone to school, but many had dropped out and illiteracy was common.

Medical care was available to persons working in factories, but otherwise the population had access to a physician who visited the village once a week.

Medical observations Of the 1594 individuals, 865 volunteered for a complete medical history, physical and laboratory examination, including examination of the thyroid by three observers. The classification of thyroid enlargement of the Swiss Goiter Commission, identical with that recommended by the WHO Study Group in 1953, was used (191). The normal thyroid is

barely visible and/or palpable in any position of the neck. In Goiter Grade I (GG I), the thyroid is visibly and palpably enlarged, causing a slight bulging of the sternocleidomastoid muscles and the suprasternal area. Goiter Grade II (GG II) produces a "thick neck". In Goiter Grade III (GG III), the goiter is large, often asymmetrical or nodular, and visible at a distance.

Eighty-three percent of 865 individuals had goiter. Prevalence of GG I and GG II was similar in both sexes, 53.5% and 19.1%, respectively. GG III occurred in 10.1%, and was slightly more prevalent in females (Figure 1). Among the 145 infants and preschoolchildren, the goiter prevalence was 60.7%. In the school age and adolescent group of 209 (101 boys and 108 girls), 85.2% had goiter. GG II was more common in girls than in boys (23.8%:16.8%), and GG III was found in females only. In adults over age 21, goiter occurred in 88.7%, being more prevalent and severe in women.

The most common disease of this population was endemic goiter, its prevalence being 76.0% in males, 88.5% in females; it increased with age, 60.7% in infants and preschooolchildren, 85% in schoolchildren and adolescents, and 88.7% in adults.

For some young villagers, goiter was not considered of consequence and a young girl "without a neck" was not considered beautiful. In the local church, the angels were represented as goitrous. But the older people saw the other side of the coin.

The discerned consequences of goiter in the older population are summarized as follows:

1. Compression of vital structures of the neck. In 84 adults, compression of the trachea produced dyspnea during physical work. Dysphagia was the chief complaint of 24 adult individuals, and for these two reasons 16 adults had had thyroidectomy. In addition, compression symptoms of the trachea, esophagus, blood vessels, and brachial plexus were found during examination in 120 or 14% of 865 individuals (Table 1).

Table 1 Endemic goiter in two villages of Croatia, Yugoslavia, 1952 (clinical aspects I); compression of vital organ of the neck*

Number of cases (%)**	Effect
a. 84 (9.7)	Trachea-dyspnea
b. 24 (2.8)	Esophagus-Dysphagia
c. 16 (1.8)	Strumectomy for a and/or b***
d. 120 (13.9)	Observed compression of trachea, esophagus, blood vessels, nerves

*From (48).

**Out of total of 865 individuals examined.

***Complications of strumectomy: about 1% of hypothyroidism; 0.5% tetany, vocal cord paralysis; and 0.1% mortality (average in Europe).

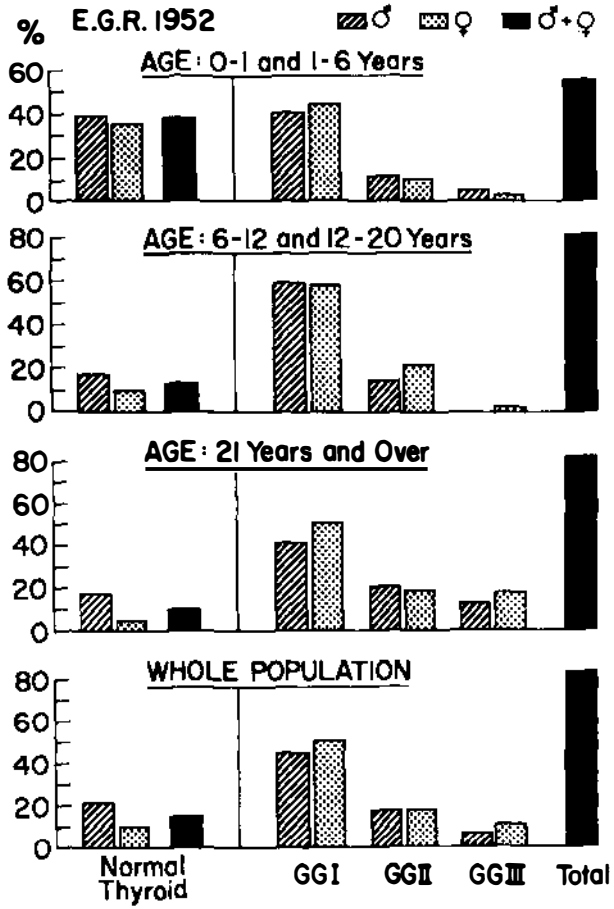


Figure 1 Endemic goiter in the whole population, Rude Croatia, Yugoslavia. In 1949, 856 of 1594 individuals were examined. Goiter was observed in 713 (83.3%); 76.9% were males and 88.5% females. Goiter Grade I (GG I) was found in 51.0% males and 56.1% females; GG II in 18.7% males and 19.4% females; GG III in 7.2% males and 13.9% females. With age, the prevalence and size of the goiter increased in both sexes, but significantly more in females.

Goiter in adults over age 21. The total prevalence was 88.7%; 80.4% were males and 94.7% females. GG I was found in 45.0% males and 54.5% females; GG II in 22.8% males and 20.5% females; GG III (large, mostly nodular) in 12.6% males and 19.7% females [From (48)]

2. Endemic goiter and hyperthyroidism. Five adult patients had obvious symptoms and signs of toxic adenoma. This complication was probably more common, but was diagnostically missed.

3. Endemic goiter and effect of large amounts of iodine. Iodine-hyperthyroidism (Jod-Basedow) was not observed because the population did not have access to large amounts of iodine.

4. Endemic goiter and hypothyroidism. A few elderly women who had breast-fed many children probably were hypothyroid because of chronic exhaustion of a large, degenerated thyroid.

5. Endemic goiter and thyroid carcinoma. No case of anaplastic thyroid carcinoma was observed during the twelve months of regular weekly visits. Slow growing solitary nodules observed in several children or young adults might have been unrecognized differentiated thyroid carcinoma.

6. Endemic goiter and cretinism. The most tragic complication encountered was endemic cretinism. In twenty persons (14 males and 6 females), or 2.3% of the 865 people examined, cretinous retardation was obvious (Table 2). Their face was expressionless, empty, and homely with low, prominent, wrinkled forehead and a deep saddled root of the nose creating widely set and often crossed eyes. An open drooling mouth---often with a large tongue and irregular carious teeth—was common.

Most cretins were short, and of poor posture. They were seen sitting or lying on the ground disinterested in their environment. Their clothes were worn and dirty. Most had a relatively small nodular goiter and were euthyroid. A few had a barely palpable thyroid and appeared hypothyroid. Cretins with goiter were taller than those without it. The majority were severely mentally retarded, recognizing only closest relatives or a fellow cretin. Their speech was inarticulate and limited to but a few words related to food, cigarettes, fear, anger, or gratitude for some kindness. Their mimic and gesticulation was commensurate to their speech; their smile distorted, often inappropriate. Some were deaf-mute, and often handicapped by spastic paralysis. They were accepted as "good, poor fellows" who may have been innocent victims of their parent's sins. Cretinism was also considered an inheritable, familial defect, adversely

Table 2 Endemic goiter in two villages of Croatia, Yugoslavia, 1952 (clinical aspects II)*

Aspect
1. Hyperthyroidism: 5/865 (0.6%)
2. Iodine hyperthyroidism (Jod-Basedow) Θ
3. Hypothyroidism: ?**
4. Thyroid carcinoma
a. Anaplastic Θ
b. Differentiated ?***
5. Endemic cretinism: 20/865 (2.3%) (small number examined)
6. Scholastic accomplishments in the elementary school
a. 139/187 (74.3%) Average
b. 48/187 (25.7%) failure

*From (48).

**Relatively common in old mothers with large goiters.

***Incidence in goitrous areas is about $60/10^6$/year; 865 persons examined.

affecting the marriage prospects and social standing of close relatives. The life of the cretin was affected by the number of cretin siblings; his destiny tied inseparably to the life of his mother. Her care for her unfortunate child reflected boundless love, terror of his disease, the height of ignorance and superstition, torment of guilt, and desolation of hopelessness. She was aware that after her death her beloved cretin would most likely suffer from neglect, malnutrition, or die in confinement.

7. Endemic goiter and educability. An inquiry among 187 elementary school students showed that 139 had obtained an average education, but 48 were classified as failing in school.

ENDEMIC GOITER IN SCHOOLCHILDREN IN ZAGREB, CROATIA

Socioeconomic observations Zagreb is located between a medium-sized mountain range and a plain along the Sava River. It is the cultural, political, and economic center of the Republic of Croatia. Ethnically, its population of 200,000 represents all parts of Croatia. The iodine content of the central water supply was 2–3 μg/liter. The food supply was mostly from iodine deficient areas, and the consumption of seafood was low. No iodized salt was available. A goiter survey was made in 1953–54 of 19,437 children from 66 four- and eight-year schools in Zagreb (144). There were 9,932 boys and 9,502 girls, 6–16 years of age.

Medical observations and methods of analysis The thyroid classification of the WHO Study Group in 1953 was again used (191). The thyroid examinations were made by trained and supervised physicians. The data were then statistically evaluated at the Central Institute of Hygiene in Zagreb (78, 193).

The overall goiter prevalence was 46.5%, again more common in girls (49.1%) than in boys (42.2%) (Table 3).

With comparably increasing age, both the prevalence and size of goiter were significantly greater in girls than in boys (Table 4). Taller and heavier girls had a significantly greater goiter prevalence (Table 5). Boys with goiter, age

Table 3 Endemic goiter in schoolchildren of elementary schools in Zagreb, Croatia, Yugoslavia, 1953–1954[a]

	Schoolchildren examined[b]		Goiter prevalence	
Gender	Number	Percentage of study population	Number	Percentage
Boys	9,932	51.1	4,191	42.2
Girls	9,507	48.9	4,665	49.1
Total	19,439	100	9,033	46.5

[a]From (144).

[b]Out of all of the schoolchildren examined, 311 (1.6%) were 6 years old; 18,525 (95.3%) were 7–11 years old; and 603 (3.1%) were 12–16 years old.

Table 4 Endemic goiter in schoolchildren in Zagreb, Croatia, Yugoslavia, 1953–1954; prevalence and size of the goiter according to age and sex[a]

Age	Prevalence (%)		Size of goiter (%)			
	Boys	Girls	Boys		Girls	
			I	II & III	I	II & III
6–7	34.8	48.3[b]	97.7	2.3	94.4	5.6[c]
8–9	42.9	50.2[b]	95.3	4.7	91.5	8.5[b]
10–11	46.9	56.7[b]	94.8	5.2	88.2	11.8[b]
12–16	50.2	63.7[d]	75.0	5.0	77.3	32.7[b]

[a]From (144).
[b]$P < 0.001$.
[c]P 0.02.
[d]P 0.002.

7–10, were noticeably taller and heavier than their peers with a normal thyroid (Table 6). Goitrous girls age 7–10 were also significantly taller and heavier than their peers with a normal thyroid (Table 7). A significantly higher percentage of boys with goiter had poor and fair grades in school (46.1% and 46.2%, respectively), a phenomenon even more pronounced in girls with goiter (56.0% and 53.1%) (Table 8). Obviously, learning ability is affected by many factors. Both hearing and speech defects were more common among goitrous children.

The predisposition for developement of goiter is greater in girls than boys, even before puberty. The higher goiter prevalence with age in children from 7–11 was related to an increase in body height and weight, and while dependent on various factors, one factor logically is a higher requirement of thyroid

Table 5 Endemic goiter in schoolchildren in Zagreb, Croatia, Yugoslavia, 1953–1954; prevalence of goiter in girls age 10 years according to body height and weight[a]

Height(cm)	Goiter(%)	Weight(kg)	Goiter(%)[b]
115–119	35.6	20–24	38.3
120–124		25–29	50.9
125–129	42.9	30–34	58.3
130–134	53.6	35–39	58.7
135–139	56.6	40–44	54.4
140–144	58.9	45–49	68.1
145–149	66.8	50–54	
150–154		55–59	
155–159	63.6	60–64	64.3
160–164		65–69	

[a]From (144).
[b]$P < 0.001$.

Table 6 Endemic goiter in schoolchildren in Zagreb, Croatia, Yugoslavia, 1953–1954; average height and weight of boys according to age and thyroid size[a]

Age	Average height(cm)		Average weight(kg)	
	Goiter	Normal thyroid	Goiter	Normal thyroid
6	123.0	120.0[b]	25.4	24.8[b]
7	123.8	122.6[c]	25.3	24.6[c]
8	128.4	127.1[c]	27.8	27.0[c]
9	133.6	132.3[c]	30.4	29.8[d]
10	137.5	136.3[e]	32.7	32.1[c]
11	139.6	138.6[c]	33.6	33.7[b]
12	142.9	142.6[b]	36.3	36.3[b]

[a]From (144).
[b]P NS.
[c]$P < 0.001$.
[d]$P < 0.01$.
[e]$P < 0.05$.

hormone by a faster growing organism. The relationship of body growth to size of goiter is not a simple one. In the sample, some children with normal thyroids were large, and some goitrous children were small.

By inference to endemic goitrous cretinism, the difficulty in thyroid hormone supply in utero and during early infancy may be one of the factors related to lower scholastic achievements of some of the children. Therefore, under conditions of an adequate iodine supply, some of the tall and goitrous children perhaps might have had a normal thyroid and might have grown taller and possibly brighter.

Table 7 Endemic goiter in schoolchildren in Zagreb, Croatia, Yugoslavia 1953–1954; average height and weight of girls according to age and thyroid size[a]

Age	Average height(cm)		Average weight(kg)	
	Goiter	Normal thyroid	Goiter	Normal thyroid
6	123.1	122.1[b]	25.3	25.2[b]
7	123.0	122.0[c]	24.7	24.2[e]
8	127.6	126.6[c]	27.3	26.5[c]
9	133.1	131.8[c]	30.0	28.4[d]
10	137.8	136.1[c]	33.1	32.1[c]
11	139.9	138.2[d]	34.1	33.3[b]
12	143.4	142.4[b]	37.6	36.6[b]

[a]From (144).
[b]P NS.
[c]$P < 0.001$.
[d]$P < 0.01$.
[e]$P = 0.002$.

Table 8 Endemic goiter in schoolchildren in Zagreb, Croatia, Yugoslavia, 1953–1954; scholastic achievements and prevalence of goiter[a]

Marks	Boys[b]		Girls[c]	
	Examined	Goiter(%)	Examined	Goiter(%)
a. Poor	836	46.1	637	56.0
b. Fair	1,040	46.2	725	53.1
c. Good	2,873	41.8	2,500	53.8
d. Very good	2,345	41.9	2,558	51.2
e. Excellent	1,944	42.6	2,263	48.5
Total	9,033	42.2	9,507	49.1

[a]From (144).
[b]$P = 0.01$; $P = 0.002(a + b > c + d + e)$.
[c]$P < 0.001$; $P = 0.03(a + b > c + d + e)$.

PUBLIC HEALTH SIGNIFICANCE OF ENDEMIC GOITER IN YUGOSLAVIA Numerous surveys indicated widespread prevalence of goiter in Yugoslavia. Only the Dalmatian coast and the northeastern plains were goiter free. It was estimated that about 2 million persons had endemic goiter, with prevalence varying from 10 –90% in different areas. Resulting adverse effects on the general health and working capacity were enormous.

Endemic cretinism and deaf-mutism There were about 20,000 endemic cretins and two to four thousand deaf-mutes. The social, economic and cultural impact of endemic cretinism on the families in those areas is impossible to express. The large number of individuals of small stature and/or poor intelligence in epicenters of endemic goiter was another tragic dimension of that disease.

Morbidity Large goiter per se, or compression of the organs of the neck required medical therapy in about 200,000 persons (or about 10%), while an estimated 20,000 (or 1%) needed surgery. A conservative estimate of surgical complications would be 1% hypothyroidism, 0.5% hypoparathyroidism and vocal chord paralysis, with surgical mortality of 0.1%. Additionally, a second thyroidectomy, often at the age of 40 –50 years, could be predicted in about 10% of all strumectomies.

Toxic nodular goiter Toxic nodular goiter was relatively common in middle-aged or older goitrous individuals, especially women, but accurate estimates are not available.

Thyroid carcinoma in goitrous areas The clinical incidence of differentiated thyroid carcinoma in severely goitrous areas is approximately 60 per 1,000,000

per year (183), or an estimated 120 new patients per 2,000,000 goitrous individuals per year in need of lifelong care.

Existing medical facilities in goitrous areas of the country could not begin to meet the health care needs created by the disease. The destiny of the endemic cretins was tragic indeed. Chronic mental institutions were overcrowded and unable to admit the good-natured cretins, whose families usually were opposed to institutionalization anyway. The education of endemic deaf-mutes, with or without significant mental retardation, represented another serious unmet burden.

Endemic goiter was also common in domestic animals (horses, cattle, sheep, and swine), a fact that had obvious detrimental effects on animal husbandry and the economy, as well as human nutrition.

EFFECT OF GOITER PROPHYLAXIS IN YUGOSLAVIA A law requiring the compulsory iodization of all salt for human and animal consumption, with 10 mg KI/kg of salt, was enacted in Yugoslavia in 1953, and by 1956 all salt, including sea salt, was iodized (27). Ten years later a highly significant threefold reduction of goiter prevalence in schoolchildren in Croatia was recorded. However, in several places, 20–30% of children still had goiter, and about 3–6% of children had developed goiter de novo (27). After 20 years of iodization, the average prevalence of goiter in schoolchildren in Bosnia, the central part of the severely goitrous area, was reduced from 60% –20% (49). In Serbia, in the southeast, goiter prophylaxis showed better results after 20 years. No cretin was born during that period of time, and goiter prevalence in schoolchildren decreased in several areas from between 70 and 90% to between 10 and 15%. A temporary increase in hyperthyroidism was observed only at the beginning of goiter prophylaxis. The failure completely to eradicate goiter was ascribed to defects in the iodization techniques and/or loss of iodine from the salt (85, 86).

Public Health Aspects of Endemic Goiter in the World

The worldwide overview of endemic goiter is pictorially segregated within political boundaries, but in reality its spread depends on the presence of similar environmental and socioeconomic conditions of life. In compiling the map of geographic prevalence of endemic goiter in the world (Figures 2, 3, 5, 6), the states are grouped by continents and labeled numerically in alphabetical order. The keys to these maps indicate approximate goiter prevalence in percentage of the population of a country. Symbols: A = endemic goiter present but prevalence not known; B = goiter prevalence probably 5–10% or reduced to 5–10% by prophylaxis; C = goiter prevalence established mostly or only by surveys of children; * = endemic cretinism present.

Goiter in "More Developed" Countries

With few exceptions, elimination of endemic goiter (to 0–5%) has been achieved in practically all the economically more developed countries of North America, Europe, Asia (Israel and Japan), and Oceania (New Zealand and Australia). The less affluent countries in the Balkans and in Eastern Europe, as well as the Soviet Union and the People's Republic of China, have also been successful in this endeavor (Figures 2, 3, and 5).

However, as is evident from the map, goiter prevalence could be further reduced in Switzerland, the Federal Republic of Germany, Austria, Italy,

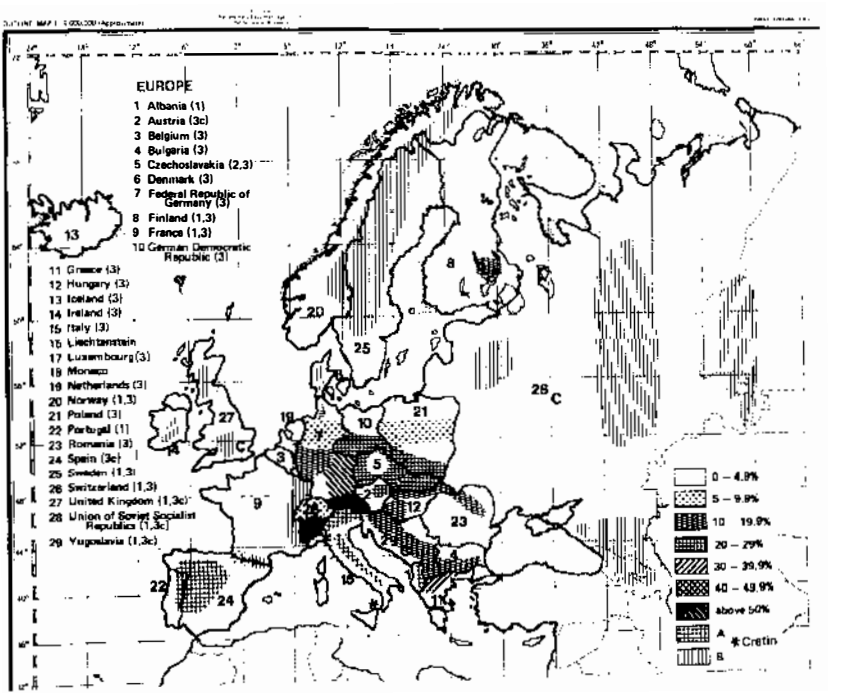


Figure 2 Europe. The prevalence of endemic goiter has been reduced to 5–10% in most European countries. Further decrease in goiter prevalence by 10–20% should occur with an increased iodine supplement in mountainous areas of some countries of Central and Southern Europe

The keys on these maps refer to the following: A = endemic goiter present but prevalence unknown; B = goiter prevalence probably 5–10% or reduced to 5–10% by prophylaxis; * = endemic cretinism present. Sources for the maps are identified by one of three numbers in parentheses after each country: 1. (Ref. 83); 2. (Ref. 40); and 3. (Ref. 14,65,88,90,93,113,118). By kind permissions of authors, editors, and the WHO, Geneva (1 and 2) and John Wiley and Sons, Inc., New York (3).

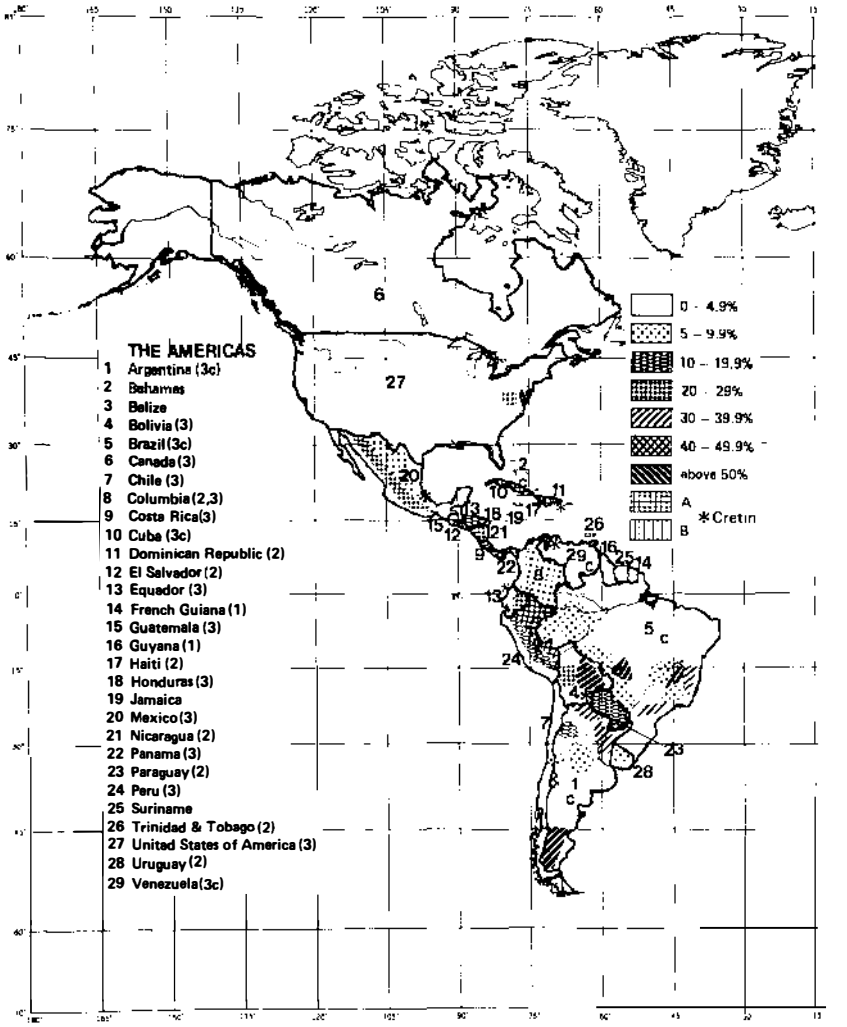
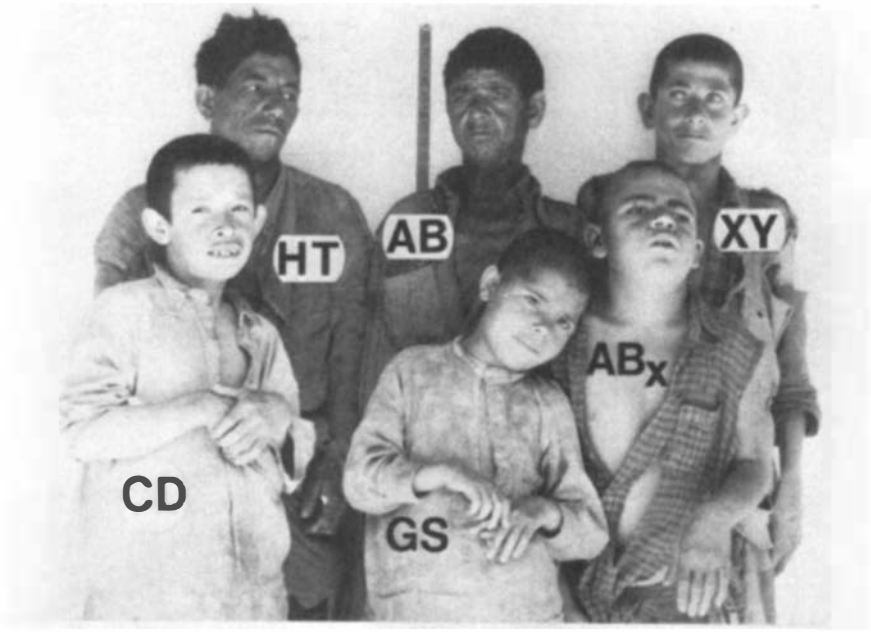


Figure 3 The Americas. Sporadic goiter (about 5%) exists in Canada, the USA, and Guatemala. In Mexico, goiter prevalence has been greatly reduced. All countries of Central and South America have started goiter prevention programs. In high elevations of the Andes and in tropical areas of several countries preventive measures are difficult to implement and endemic goiter and cretinism are therefore still prevalent.

See also second paragraph of legend to Figure 2.

Czechoslovakia, and Yugoslavia. In 1924, an optional goiter prevention program was pioneered in Europe by the Swiss Goiter Commission. Because of concern with the possibility of Jod-Basedow, the dose of iodine was very gradually raised from 5–10 mg KI/kg of salt, and finally in 1980 to the level of 20 mg KI/kg of salt [Burgi, H., private communication, 1981]. The latter dose



IN	M	S	H	I	PBI	BEI µg/100 ml	II Serum
HT	E?	+	+	–	2.8	1.5	0.5
AB	E	+	+	–	2.3	1.2	–
XY	E	–	–	–	1.7	0.5	–
CD	H	–	–	–	1.1	0.3	–
GS	H	–	–	–	2.4	1.0	0.5
ABx	H	–	–	–	2.4	1.2	0.5
Chitral	E	Goiter		+	3.3 - 3.8	1.2 - 2.6	0.5
Gujrat	E	⊖ Goiter		+	4.7 - 6.8	2.9 - 5.1	0.5 - 1.0
U.S.A.	E	⊖ Goiter		+	4.0 - 8.0	3.2 - 6.4	1.0 - 1.5

M = Metabolism, E = Euthyroid, H = Hypothyroid, S = Speech, H = Hearing, I = Intelligence, PBI = Protein Bound Iodine, BEI = Butanol Extractable Iodine, I I = Inorganic Iodine.

Figure 4 Endemic cretinism observed in 1960 in Chitral, Pakistan. First row: one of the three persons with myxedematous cretinism had a small fibrotic remnant of the thyroid. Second row: all three goitrous persons with "nervous cretinism" were euthyroid. In all six the serum PBI and BEI were significantly lower than in goitrous but otherwise normal individuals from the same area. (Reproduced by the kind permission of authorities of the WHO Office of Publications) [From (108)]

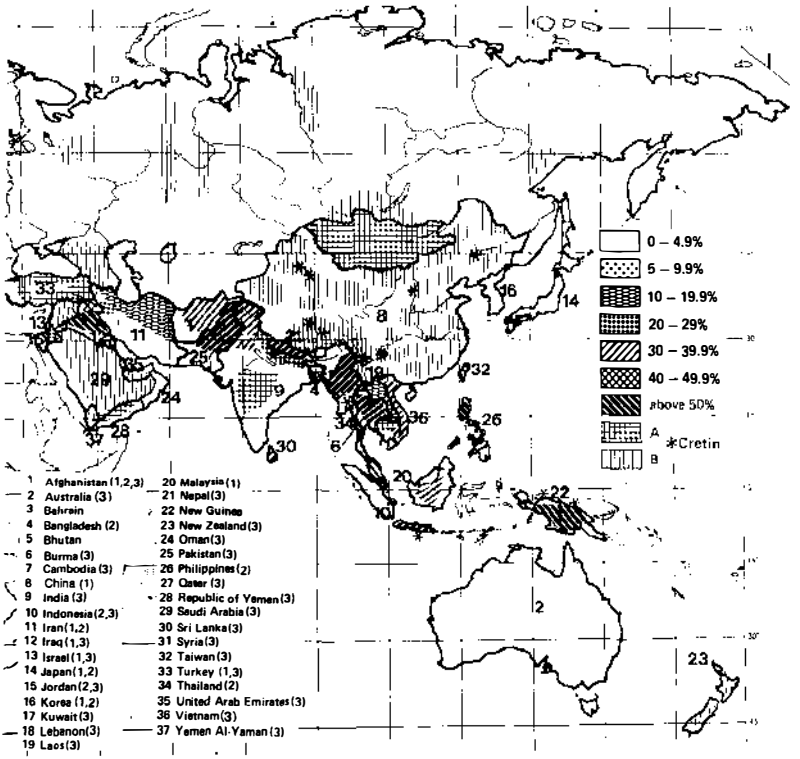


Figure 5 Asia, Australia, New Zealand. *The WHO Eastern Mediterranean.* This region includes states in the eastern Mediterranean, the Middle East, the Persian Gulf states, and Pakistan. In some of these countries goiter surveys are needed. Except for some littoral states or their coastal areas and countries of the Arabian Peninsula, endemic goiter and cretinism are prevalent in most of this region. In several states serious economic and technological difficulties impede the introduction of a general goiter prophylaxis with iodized salt. Therefore, a temporary iodized oil program is urgently needed to prevent severe goiter and cretinism in high mountainous and remote continental areas of several countries.

The WHO Southeast Asia Region. Much more information is needed on endemic goiter and cretinism from many countries of the vast territories and enormous populations of this region. There is no endemic goiter in Japan.

From the limited data available it appears that in the Republic of China the prophylaxis of previously widespread and severe endemic goiter and cretinism has been successful. The map roughly and uniformly indicates the present topography of endemic goiter and cretinism.

The mountainous areas of the states on both subcontinents and those of the archipelagos in the Indian and Pacific Oceans represent the greatest region with one of the most severe endemias of goiter and cretinism. The overall 20–50% prevalence of goiter in this region has its epicenters in the Himalayan range, the mountainous islands of Java, New Guinea, and the Phillipines. The intensive iodized oil programs in New Guinea should be extended to other parts of this region.

Goiter prophylaxis is successful in both Australia and New Zealand, which are free of endemic goiter.

See also second paragraph of legend of Figure 2.

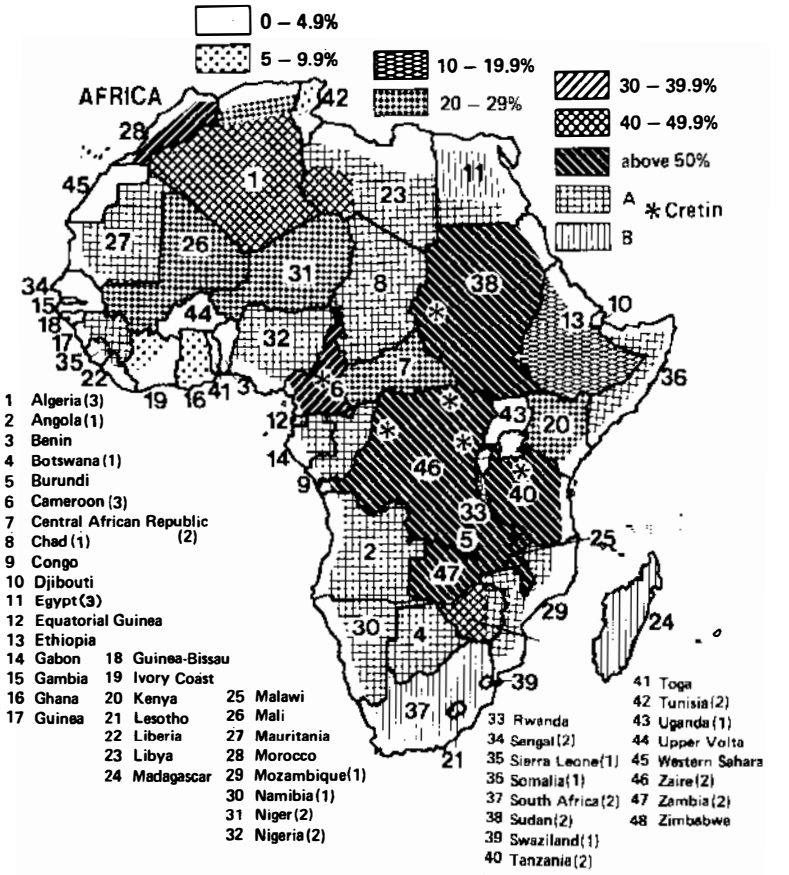


Figure 6 Africa. With few exceptions the data on the prevalence of endemic goiter and cretinism in most African countries are limited and outdated. Therefore, it is probable that goiter prevalence in many states is more severe than tentatively indicated on this map. The epicenter of endemic goiter and cretinism is in Central Africa, but severe goiter is prevalent in many countries, except for the littoral states or their coastal areas.

Intensive surveys and studies in the Republic of Zaire indicate that goiter and the predominantly myxedematous cretinism are due to severe iodine deficiency combined with the goitrogenic effects of thiocyanate from linamarin of cassava, a staple food in the tropical areas.

The average goiter prevalence in the Union of South Africa is below 10%.

See also second paragraph of legend to Figure 2.

was adopted in Czechoslovakia only a few years earlier. In these countries, a short, temporary episode of slight increase in incidence of Jod-Basedow was unavoidable in adults and old people with nodular goiter ("hot autonomous nodules"), the "risks" for the benefit of healthier young and yet-to-be-born generations.

Comments on the role of natural goitrogens in some areas in this group of countries (e.g. Virginia in the USA, Sicily in Italy, the island Krk in Yugosla-

via, as well as areas in Czechoslovakia and Finland), and the problem of persistent low goiter prevalence (5%) in the USA and in Canada, are deferred until later.

Endemic Goiter in "Less Developed" Countries

These are predominantly agricultural countries with small to moderate industries. The tragic reality of goiter and cretinism in Yugoslavia some three decades ago was described as a relevant example of clinical and public health aspects of endemic goiter in many areas around the world in our time. The experience there also exemplifies safe, simple, and cheap general prophylaxis with iodized salt. The less developed world has enormous goitrous areas. In the Americas, it encompasses all the countries except Canada, the USA and Guatemala. Similar goiter prevalence exists in some of the Mediterranean countries of Europe, Africa, Asia Minor, and, with some exceptions, in the mostly goiter-free Arabian peninsula. But endemic goiter is most serious throughout the enormous expanses of the Southeast Asian countries, including the archipelago states of the Indian and Pacific Oceans.

THE AMERICAS A promising program is also under way in Mexico, where severe endemic goiter has been considerably reduced by the introduction of iodized salt in 1967, and by the fact that at present 70% of all salt consumed is iodized (113) (Figure 3).

Goiter prevalence is high in most South American countries, especially the mountainous ranges of the Andes (Ecuador, Peru, Bolivia, and Argentina) as well as in the enormous tropical rainy and hot territories of Argentina and Brazil. In schoolchildren, it is in the range of 30 to over 50% and severe endemic cretinism accompanies it.

The remarkable exception is Guatemala, where goiter prophylaxis with iodized salt, introduced by the Institute of Nutrition of Central America and Panama (INCAP) in cooperation with the government, has reduced goiter in schoolchildren from 38% in 1956 to 5% in 1972 (39).

Other countries of the Americas have been less successful, despite efforts. A penetrating analysis of the complex and interrelated administrative, technical, economic, and political difficulties involved has been made by two advisors on nutrition to the Pan American Health Organization by Kevany (84) in 1968 and by Schaefer (156) in 1973. These difficulties were compounded by poverty of the population and lack of experience in the improvement of public health by means of a political process. Other reasons for slow progress have been the pressing need for combating serious infectious diseases, wide-spread parasitic infestations and malnutrition in general. However, during the last 5–10 years some improvement in goiter prevention has been achieved in some of these countries, and important studies on goiter and especially on endemic cretinism are being carried out (118).

Endemic goiter and cretinism in Ecuador and Peru, as well as scientific studies and efforts towards their prevention, may serve also as the prototypes of the disease and the programs of its eradication in parts of South America (50, 66).

The history of the pioneer investigations and eventual prevention of endemic goiter in Mendoza, Argentina are too well known to repeat them here (118, 161).

ECUADOR Investigations of endemic goiter and cretinism in Ecuador conducted by Fierro-Benitez and his colleagues (50) established the prevalence of endemic goiter and cretinism in the villages Tocachi and La Esperanza, located in the high Andes near the capital city of Quito, as 50–70% and 6–7% respectively. They developed a comprehensive classification of speech disorders of the mentally retarded. The urinary iodine excretion of that population was below 20 μg/g creatinine, but two years after administration of iodized oil, it was increased to 87 μg/g creatinine and the goiter prevalence was reduced by 36%. The serum protein bound iodine (PBI) rose from 2.8–7.1 μg/100 ml, and the thyroidal uptake fell from 75%–38% per 24 hours. When iodized oil was administered, not a single cretin was born in these villages and the children's IQ improved considerably.

PERU Endemic goiter and cretinism in Peru have been studied intensively by Pretel and his colleagues (66, 145). Since 1960, specific regulations for the supply of iodized salt in iodine deficient areas have been in effect in Peru. In 1967, some 181,000 schoolchildren were surveyed. Goiter prevalence of more than 20% was recorded in 12% of coastal villages, 48% of mountain villages, and 80% of jungle villages. In 1975, the same type of survey, but on a smaller scale, was carried out in the same areas. A community was defined as goitrous if 10% of the population had goiter. There was no endemic goiter in coastal communities, but 21% of villages in the Sierra Mountains and 50% of the jungle villages were still goitrous, and the risk of endemic cretinism remained at 5%. The mean daily urinary iodine excretion of the same population was 236 μg in the coastal areas, 91 μg in the mountain villages, and 66 μg (with a majority in the range of 50–25 μg) in the jungle areas. The iodized salt program did not meet expectations; it was expensive and iodine content of the salt was not reliable.

THE WHO EASTERN MEDITERRANEAN REGION This region includes the Mediterranean and the Middle East, the Persian Gulf States, and Pakistan (Figure 5). Various factors, such as fossil iodine-rich soil, the vicinity of the sea, weather, deforested mountains, deserts, and other factors have by their presence (and absence) influenced the goiter prevalence in this area. It can be

low (less than 10%) as in the Arabian Peninsula states, or 20–30% in the Persian Gulf States and in some areas of Pakistan. The large lands, depressed agricultural settlements, poverty, and diseases in general were important obstacles to the prevention of endemic goiter. In addition, the delay in eliminating goiter along the Mediterranean, and especially in the Middle East, must be ascribed to political difficulties, civil unrest, and war, which are serious impediments to any attempt of improving health standards. An example of such conditions is illustrated in a short review of endemic goiter in Lebanon.

LEBANON The health authorities in Lebanon have for years been concerned with the prevention of endemic goiter in their country. Therefore, in 1960 a WHO consultant made the first goiter survey in Lebanon (107), which was similar to the study of schoolchildren in Zagreb, Yugoslavia (144). The goiter was defined according to the WHO Study Group Classification of 1953 (191). Within one month, 3427 schoolchildren (1902 males and 1525 females) were examined in 20 urban and rural areas. The age of the children was between 5 and 16 years. The communities studied were located in the northern, central, and southern part of the country—eight were in the hills (Liban and Antiliban), three were in mountain valleys, five were in the plains between Liban and Antiliban, and four were in the littoral area (Tables 9 and 10). The goiter prevalence in children of all ages was 50.0%. The regional average goiter prevalence in decreasing order was 72.5% in mountain valleys, 53.3% in the hills, 45.7% in the plains, and 45.5% along the coast. However, goiter prevalence varied within the same zone. In seaports like Tripoli and Tyr, it was 37.4% and 11.5% respectively because most fish from Tripoli were shipped to Beirut; whereas the fish from Tyr were consumed locally. High goiter prevalence (51.7%) was found in well-nourished children in two orphanages in Beirut; their main source of protein was the cheaper but iodine-poor beef and lamb.

Table 9 Endemic goiter in schoolchildren in 20 villages and small and large towns in Lebanon, 1960[a]

	Schoolchildren examined[b]		Goiter prevalence	
Gender	Number	Percentage of study population	Number	Percentage
Boys	1,902	55.5	889	46.7
Girls	1,525	44.5	823	54.0
Total	3,427	100	1,712	50.0

[a]From (107); reproduced by the kind permission of the World Health Organization.
[b]Out of all of the schoolchildren examined, 231 (6.7%) were 6 years old; 2,193 (64.0%) were 7–11 years old; and 1,003 (29.3%) were 12–16 years old.

Table 10 Endemic goiter in schoolchildren Lebanon, 1960; prevalence and size of the goiter according to age and sex[a]

Age	Prevalence(%)		Size of goiter(%)			
	Boys	Girls	Boys		Girls	
			I	II & III	I	II & III
6–7	39.7	38.1[b]	99.1	0.9	94.1	5.9[b]
8–9	45.4	41.8[b]	97.4	2.6	94.7	5.3[b]
10–11	50.8	60.3[c]	97.4	2.6	90.9	9.1[b]
13–15	59.4	73.2[c]	92.8	7.2	85.2	14.8[d]

[a]From (107); reproduced by the kind permission of the World Health Organization.
[b]P NS.
[c]$P < 0.05$.
[d]$P < 0.01$.

The prevalence and size of goiter in girls was significantly higher than in boys in the age groups 10–12 and 13–15, but otherwise no effect of age, body height, or weight on goiter was observed. No statistical correlation between goiter and scholastic achievement was found. Also, the impression was gained that goiter was less common in adults than in children. One cretin was seen, but there probably were more in the mountainous areas. In addition to documented iodine deficiency, goitrogenic disulfides of the onion, a common condiment in Lebanon, were suggested as influencing the high prevalence of endemic goiter (172, 173).

Most salt (about 10,000 tons) was produced by numerous small private sea-salt works, and distributed locally. It was coarse, wet, iodine-poor sea salt and an equivalent 2,500 tons was imported from Egypt and Holland. Technical difficulties with iodization of salt due to multiple production and import sites, lack of quality control, and very difficult political conditions obstructed the introduction of a goiter prophylaxis program in Lebanon. No recent publications on goiter in Lebanon were available.

PAKISTAN Observations made from 1902–1972 in the sub-Himalayan area of Pakistan indicate the nature of endemic goiter in the cold mountain ranges. The brilliant field and laboratory studies by Sir Robert McCarrison in Chitral (in 1902) and in Gilgit (in 1904) were expanded during the subsequent 30 years all over the Subcontinent. Data obtained include the following: the prevalence of endemic goiter, deaf-mutism and, cretinism in Chitral and Gilgit, and classification of "nervous", myxedematous, and combined nervous-myxedematous forms of endemic cretinism (114, 115); the geographic distribution of endemic goiter in the Subcontinent; the correlation between iodine content of the soil, water, and salt, and goiter prevalence; and experimental goiter in

animals and man and the significance of poor sanitary conditions, faulty nutrition, and iodine deficiency in goiter development.

From the time the state of Pakistan was established, its health authorities were concerned with prevention of endemic goiter. Eventually, in 1960, a WHO consultant carried out *(a)* a goiter survey in schoolchildren in urban communities, starting in Gujrat at the periphery of the goiter area and proceeding to McCarrison's epicenters of goiter in Chitral; *(b)* the collection of blood samples for protein bound iodine, butanol extractable iodine, and inorganic iodine in Chitral; *(c)* an inspection of the largest Pakistani salt mines in Khewra, as well as of the sea salt works at Maripur, near Karachi, in order to examine the possibility for iodization of salt (108).

The school children from eight district centers and two smaller communities in the plains and high mountain valleys were surveyed. Of the 5196 children examined, 3696 were boys and 1500 were girls, aged 6–16 years.

The overall prevalence of goiter was 39.7%, with 41% in boys and 36.3% in girls. One district was goiter free (0.3%) and goiter was more common in districts closer to the Himalayan range. There was no significant sex-related difference in goiter prevalence and size in children of the same age groups. The body weight was significantly greater ($P<0.001$) in goitrous boys than in their peers with a normal thyroid (Table 11). Poor scholastic marks were more frequent in goitrous boys ($P<0.001$) than in boys with a normal thyroid. No correlation was found between goiter and scholastic marks in girls. (Table 12). The impression was gained that goiter prevalence in adults was similar or even higher than that in children (108).

Endemic cretinism was common. One cretin each was found in Murree and Balakot, but searches were not possible for cretins in other communities with high prevalence of goiter. In Chitral, with a population of about 4000, there was a high prevalence of severe goiter in elementary school boys (girls did not attend school) of 72.2%, 5.5% of whom had GG II and III, and 18.7% had a nodular goiter. The six cretins, 5 males and one female examined, were small

Table 11 Endemic goiter in schoolchildren in 10 small and medium size towns in Pakistan, 1960[a]

	Schoolchildren examined		Goiter prevalence	
Gender	Number	Percentage of study population	Number	Percentage
Boys	3,696	71.1	1,517	41.0
Girls	1,500	28.9	544	36.3
Total	5,196	100	2,061	39.7

[a]From (108); reproduced by the kind permission of the World Health Organization.
[b]Out of all of the schoolchildren examined, 543 (10.4%) were 6 years old; 3,777 (72.7%) were 7–11 years old; and 876 (16.7%) were 12–16 years old.

Table 12 Endemic goiter in schoolchildren in Pakistan, 1960; scholastic achievements and prevalence of goiter[a]

Marks	Boys[b]		Girls[c]	
	Examined	Goiter(%)	Examined	Goiter(%)
Poor	294	44.2	140	36.4
Fair	906	53.6	292	37.3
Good	1,276	39.6	574	36.4
Very good	782	33.2	208	38.0
Excellent	330	31.2	267	33.3
Total	3,696	41.0	1,500	36.3

[a]From (108); reproduced by the kind permission of the World Health Organization.
[b]$P < 0.001$.
[c]P NS.

in stature, their faces having a characteristic, unforgettable expression. All were underdeveloped and undernourished; some had spastic hands and feet. Four cretins had large goiters, and in two the thyroid was not palpable. Three were myxedematous. Two cretins were completely deaf-mute, two others had poor speech and hearing, and the remaining two could both hear and speak. Intelligence was low in all (108).

Serum protein bound iodine (PBI) and butanol extractable iodine (BEI) (thyroxine and triiodothyronine) were very low in all cretins, and considerably lower than in goitrous but otherwise normal individuals from Chitral. They were much lower than in individuals with a normal thyroid in Gujrat (with a goiter prevalence of 10.1%), or than in normal individuals in the USA (Figure 4).

Most of Pakistan's salt requirements were met by the crystalline, reddish rock salt, in lumps of 25–50 kg mined in Khewra and distributed throughout the country. No facilities for crushing and iodization of that salt were available. The coarse, wet, crystalline sea salt inspected at Maripur was distributed more locally and was not iodized either. The iodine content of a dozen samples of both types of salt was very low (108).

In 1972, in Gilgit, east of Chitral, another goiter survey was carried out by Chapman and colleagues (29) in 589 of about 1000 individuals from 140 households of the village Dainyor, located on the bank of the Gilgit River. The town of Gilgit developed through consolidation of several villages where, in 1904, McCarrison had found an increase in goiter prevalence in the downstream hamlets. He ascribed this to a more severe bacterial pollution of the water and reproduced similar goiter in volunteers, including himself, by taking orally the sediment of the water. In 1972, Chapman et al reported a similar increase in frequency of goiter in downstream areas of the village Dainyor (29). He ascribed the higher prevalence to a more severe iodine deficiency due to the

binding of halogens to the silt of the river water. The overall goiter prevalence for all ages was 74%, 17.5% of all goiters being nodular. Ten cretins were studied, two of whom were females. This number was misleadingly low, for female cretins did not come to be examined. In four cretins, the total serum iodine (TI) was low, 1.4 μg/100 ml. Six deaf-mutes without mental retardation had a relatively normal TI of 3.2 μg/100 ml (29).

There were 24 hypothyroid individuals. Their total serum iodine was low, 1.0 μg/100 ml, compared to 2.7 μg/100 ml in 57 euthyroid subjects. Urinary iodine excretion was also low (50.0 μg/day). A very high thyroidal ^{131}I uptake confirmed severe iodine deficiency as the cause of goiter.

The authors found no difference in the prevalence of endemic goiter and cretinism in 1972 from that observed by McCarrison in 1902. Since the "traditional rock salt was a luxury and the population had not been prepared for iodized salt", the authors administered iodized oil to 447 goitrous persons. The people readily permitted the intramuscular injections. No more recent publications on goiter in Pakistan were available.

THE WHO SOUTHEAST ASIA REGION The Himalayas of India, Nepal, Butan, and southern China—and the mountains extending into northern Burma, Thailand, Laos, and Vietnam, with their widely dispersed settlements that are inaccessible in winter—have long been known as seriously goitrous areas. However, the many tropical countries throughout the two subcontinents, as well as the Phillipines and Indonesia with their thousands of islands in the Pacific and Indian Oceans, are also severely iodine deficient. There, goiter prevalence (of 20% to over 50%) and frequent endemic cretinism are even more critical. The problem is compounded by an explosive over-population and lack of financial means and/or technical facilities for goiter prophylaxis in the widely dispersed regions of the large subcontinents and archipelagos populated by 800 million to one billion people (Figure 5).

India Further to the east, goiter endemia in India was the subject of intensive studies. According to Kochupillai, Ramalingaswami, & Stanbury (88), about 300 million people living along the southern slopes and foothills extending 1500 miles from Kashmir to Naga, and in the plains of the Himalayas as well as in several states in Northern India, are "at risk" of endemic goiter. And since about 60 million people actually have goiter, this represents the largest goiter endemia in the world. Other parts of India are not spared from goiter, and it exists even on the island of Bombay. All strata of the population are affected, but children and women of reproductive age are the ones most often goitrous. Severe iodine deficiency is the dominant cause of goiter. In areas where the urinary excretion is below 25 μg/g creatinine, goiter prevalence is about 50%, and about 4.0% suffer from various forms of mental deficiency. Karmarkar &

Ramalingaswami (82) have documented the regulatory and metabolic mechanisms of the pituitary and the thyroid of iodine-deficient individuals in India, and established the effectiveness of iodized salt prophylaxis.

Nepal From 1966 to 1972, Ibbertson (73) reported several studies of endemic goiter in the Everest region of the Nepalese Himalayas. Goiter prevalence was 70–90%. Clinical hypothyroidism and cretinism were unusually high (50% and 8%, respectively). Iodized oil injected in 1966 had by 1972 reduced the prevalence of goiter and cretinism, and the iodine from injected individuals had found its way into the metabolism of untreated ones.

AFRICA AND NEW GUINEA Evidence reviewed in this section is from remote areas in countries with harsh environmental conditions and recent statehood.

Even worse conditions than already described persist in the remote regions of countries with recent statehood, often with a harsh climate in the continental parts of Africa. The most tragic form of endemic goiter probably exists in the Republic of Zaire, Africa. Similar conditions probably pertain in mountainous or respectively tropical parts of Algeria, Morocco, Mali, Sierra Leone, Cameroon, the Sudan, the Central African Empire, Kenya, Tanzania, and Zambia, but observations of endemic cretinism were reported only from Cameroon (Figure 6). There is goiter in Mauritania, Chad, Niger, Nigeria, Angola, Nambia, Botswana, and other countries too, but data on its prevalence and severity are not available.

Republic of Zaire Pioneering surveys, combined with experimental investigation of endemic goiter and cretinism in humans and animals, have been carried out by investigators from Belgium (Bastenie, Ermans, Thilly, Delange, Beckers, Dumont, and many others) and were reported in numerous publications and monographs (11, 14, 37, 38, 45). The population of several regions of this large country is probably afflicted with the most severe endemic goiter and cretinism in the world. In the Uele region of 25,000 square km in the north-central part of the country with a population of 600,000, goiter prevalence ranged from 25%–100%. The frequency of myxedematous endemic cretinism was 0.3%, and the frequency of deaf-mutism 0.1%. In the Bambesi district with about 7,000 people, 64.5% had goiter, 2.3% had myxedematous cretinism, and 0.1% had nervous cretinism (Figure 7).

Idjwi Island in Lake Kiwu, with a population of about 9,000 (on 300 square km), is divided into two parts by a mountain. In the northern part, 54% of the people were goitrous and 1.1% or 99 individuals were cretins, of whom only 11 were deaf-mute but euthyroid. The southern part of Idjwi Island had a goiter prevalence of 5%, and it was free from endemic cretinism. In Ubanga, the

Figure 7 Myxedematous cretinism. Individuals aged 16–30 years (characteristic dwarfism, defects in maturation of the face and puffy skin), and euthyroid adults. Northern part of the Republic of Zaire, Africa. [Reproduced by the kind permission of the authors, editors, and publisher of (38).]

northwestern province of Zaire, with a population of more than 2 million, 26–60% of males and 48–78% of females were goitrous. The frequency of myxedematous cretinism is a frightening 0.7%–7.6%. The cause of goiter in these provinces of the Republic of Zaire are severe iodine deficiency and the goitrogenic effect of the cyanogenic glucoside linamarin in the tubera and leaves of cassava, the staple source of carbohydrate.

New Guinea Several islands of Indonesia, such as central Java (58), Sumatra, Kalamathan, and Sulivavesi, are known for their severe goiter and cretinism. However, in New Guinea, there is goiter and cretinism of severity similar to that of some provinces of the Republic of Zaire. Covering an area of 805,800 square km^2, New Guinea is the second largest island in the world, with a population of about 2,620,000. The northwestern part, West Irian, belongs to Indonesia, while the southeastern part, the Territory of Papua, is a United Nations Trust territory under Australian control. With a 2500 km long mountain range (elevations up to 5030 m), and an enormous rainfall of 2.5–3.0 m/year over eons of time, the soil of the island is most severely iodine-depleted, except in some small oases and in the coastal areas (65) (Figure 5).

Most goitrous are the numerous small tribes in the central highlands of the west, with the epicenter of this endemia in the Mulia Valley, having an estimated population of about 100,000 (55) (Figure 8). Similar conditions exist in the Huon Peninsula of Papua. The goitrous regions in the central highlands, especially Mulia and the surrounding areas, were studied most intensively by Gajdusek (54) and Garruto (55), Choufoer, Van Rhyin, Kassenaar, and Querido (30, 31). The goiter endemia of Papua, especially the Huon Peninsula, was first investigated by McCullagh (116, 117), followed by intensive studies by Buttfield (24, 25, 26) and Hetzel et al (65, 66), while Pharaoh studied cretinism in the Jimi Valley (140).

In the Mulia Valley, Gajdusek & Garruto (55), as well as expeditions led by Querido (30, 31), observed a goiter prevalence of over 50%. Moreover, out of the 1426 individuals examined, 80 exhibited various states of endemic goitrous cretinism and deaf-mutism (31). The serum PBI was in the hypothyroid range, but no overt hypothyroidism was observed in either goitrous or cretinous individuals. Mental retardation, spasticity, and deaf-mutism were common. Urinary iodine excretion was below 20 μg/day. It is of interest that Choufoer et al (30, 31) found practically no goiter and definitely no cretinism in Tiom, a

Figure 8 Five women and three men with endemic goiter at Mulia, West Irian (New Guinea), Indonesia, 1959. Reproduced by the kind permission of the authors, editors, and publisher of *Biosocial Interrelations in Population Adaptation*. [From (55)]

community close to Mulia, although the living conditions and urinary iodine excretion were the same in both villages. Gajdusek entertained the possibility that consumption of the green leaves of sweet potatoes could cause intestinal loss of iodine. Although the population was inbred, there was no evidence of genetic determinants in goiter development. Gajdusek (54) was impressed with the fact that practically the whole goitrous population of the Mulia Valley had suffered some neuromuscular retardation in infancy, and was actually considered intellectually inferior by their goiter-free western Dani neighbors. This opinion was not shared by Querido and his colleagues. In an additional study in central Java, they found no mental retardation in goiter-free individuals in an area of severe endemic goiter and cretinism (148).

The goiter prevalence in the Huon peninsula increased with the altitude of the land from 5% at 600 m to 40–50% at 1800 m. Except in the coastal areas, the salt supply was low. Reportedly, 120,000 people in the Papua region were given iodized oil in 1971–72 (65).

Present Prevalence of Endemic Goiter and its Prospects for the Year 2000

In 1960, Kelly & Snedden (83) in a monumental study (232 pages with 1369 references) concluded, "The number of goitrous people in the world is not known, but if the statistics available for some countries may be taken as a guide, the total is probably not far from 200 million." Their data suggested that goiter was prevalent throughout the world, with the exception of the United States, Canada, Japan, some western European countries, the Soviet Union, Australia, and New Zealand. Twenty years later, in 1980, we are still unable precisely to define the goiter prevalence in the world. A significant numerical decrease of goiter has occurred in Mexico, Guatemala, Colombia, most Western European and all Eastern European countries, Israel, the Republic of China, and the Union of South Africa. Some reduction in goiter prevalence has been accomplished in several states of South America. This progress was achieved partly by independent national goiter prevention efforts, but in many countries these programs were carried out under the guidance and/or scientific, financial, and technical assistance of the World Health Organization, UNICEF, Food and Agricultural Organizations of the United Nations, and many international agencies, medical schools, and health institutions. But, despite good will and persistent efforts, endemic goiter, with or without endemic cretinism, continues prevalent in numerous countries of South America, Europe, Africa, South Asia, and the Indian and Pacific Archipelagos.

To assess the goiter prevalence in 1980 and to try to appraise the prospects for the end of this century, it is necessary to correlate present information on the frequency of goiter in the world with the population data of "World Population and Prospects" as assessed in 1980 (171) (Table 13). According to this docu-

Table 13 World population and prospects[a]

Years	"Less Developed" Regions[b]	"More Developed" Regions[b]	Total World[b]
1960	2092	945	3037
1980	3301	1131	4432
2000	4847	1272	6119

[a]From (171); reproduced by the kind permission of the UN Dept. Intl. Econ. & Soc. Aff.
[b]Population in millions.

ment, "more developed" regions include North America, Japan, Europe, Australia-New Zealand, and Eastern Europe-USSR. "Less developed" regions include all others.

This classification defines the overall socioeconomic conditions of regions and countries, but with some exceptions it also grossly correlates with the prevalence of endemic goiter. However, with respect to goiter prevalence in 1960, Eastern Europe (without the USSR) had about 97 million people with rather a high goiter prevalence who therefore belonged in the group of "less developed" regions. Thus by assuming that, in 1960, the risk of goiter in approximately 2189 million inhabitants (2092 + 97 East Europeans = 2189 million) of the "less developed" regions, as newly defined, was 10%, the endemic goiter prevalence of these peoples ($2189 \times 0.1 = 218.9$ million) could have been approximately 219 million.

At the same time the goiter prevalence of 848 million people (945–97 million in Eastern Europe) in "more developed" regions, as newly defined, could at best correspond to that of Canada and the United States, i.e. 5.0% (113). By this assumption, in 1960 about 42 million (848×0.05) of the population in "more developed" countries had goiter. This goiter is mostly sporadic, and it develops and persists despite adequate iodine nutriture or iodine prophylaxis. Multiple factors (genetic, acquired thyroid diseases, and various goitrogens), often in combination, are responsible for sporadic goiter.

Unfortunately, the world goiter prevalence in 1980 is probably higher than in 1960. The risk of goiter in most of the "more developed" regions, with few exceptions, remains 5.0%. It is true that goiter prevalence in Eastern Europe [population 110 million in 1980, (171)] and the Republic of China [population 995 million in 1980, (171)] has declined close to that of the "more developed" regions. That is also the case in Mexico, Guatemala and, to a certain extent, in some other states of South America, but there are no data to account for that change in goiter prevalence. In addition, in contrast to data on goiter prevalence until 1960, during the last twenty years, goiter prevalence was usually found to be much higher in many countries with recent statehood, especially in large areas with difficult living conditions.

By 1980, the population of the "less developed" regions increased to 3301 million and their goiter risk, according to recent surveys, is probably higher, about 15.0%. For reasons noted, the population of 995 million in the Republic of China and 110 million in Eastern Europe (995 + 110 = 1105) can be removed from this group (3301 − 1105 = 2196), and in 1980 the goiter prevalence in the "less developed" regions could be (2196 × 0.15) about 329 million. According to Hetzel (64), however, in 1981, "it is estimated that there are 1–2 million cretins in China, and 30 million with goiter." That would suggest that the prevalence of goiter and cretinism in the Republic of China is 3.0% and 0.1–0.2%, respectively.

During the same period of time, the population of the "more developed" regions increased to 1131 million, but its risk of goiter possibly remained the same at 5.0%. By adding 110 million people in Eastern Europe and Republic of China (population 995 million) in 1980 (171) (110 + 995 + 1131 = 2236 million) to this group, the prevalence of mostly sporadic goiter in the "more developed" regions could be 112 million. Thus by such rough extrapolation one may estimate that in 1980 about 329 million people in the "less developed" regions had endemic goiter and about 112 million in "more developed" areas had mostly sporadic goiter. Although the morbidity of sporadic goiter is vastly different from that of endemic goiter, its adverse effect on health and well-being is enormous. Therefore, sporadic goiter is now an important problem of public health in "more developed" areas, while in the "less developed" regions it is, for the time being, hidden under the cloak of endemic goiter.

Finally, it is stated in the same documents of the United Nations that during the next 20 years the world population will increase by more than 1.687 billion. Therefore, tragically endemic goiter may become worse and spread further. The prospect of frightening stagnation of human society at the epicenters of endemic goiter, with countless victims of cretinism and deaf-mutism, leaves but two alternatives. One is to erect signs with "Lasciate ogni speranza voi ch'entrate" (Abandon all hope ye who enter here) on the roads leading to these areas, as was considered by a colleague of ours more than 100 years ago, or to attempt to find a final program of world public health and welfare for elimination of endemic goiter and cretinism.

THE CAUSATION OF ENDEMIC GOITER IS COMPLEX AND PARTLY KNOWN

In support of this postulate, it seems appropriate to quote from J. Huxley's *Essays of a Humanist* (1964): "The old ideas of simple causation are no more valid. In the first place, in actual existence, causation is always multiple. Still more basically, evolutionary and human processes are not based on cause and

effect relations. They are all cybernetic, involving feedback, and their products are always simultaneously results and causes" (72).

Before examining the etiology of goiter, brief comments concerning the normal thyroid and iodine requirement are in order.

The Normal Thyroid

The normal human thyroid weighs 20–25 g in adults. It contains 8–10 mg of iodine, 95% of it bound to thyroglobulin. Some 45% and 3% of iodine is in the form of the hormones, thyroxine (T_4) and triiodothyronine (T_3) respectively, and 42% in their precursors, mono-, and diiodotyrosine (MIT and DIT).

Thyroid structure and function are regulated by two interrelated systems. The phylogenetically older regulator is iodine itself, and it controls both the thyroid hormone secretion and the reserves of iodine in the form of iodotyrosines in thyroglobulin. When the iodine supply is low, all functions of the thyroid gland are accelerated; at a short or prolonged excessive iodine intake, all processes in the thyroid are slowed or modified. The younger regulatory system, the pituitary thyroid stimulator (TSH) and the thyrotropin-releasing hormone (TRH) of the hypothalamus, controls the thyroid function, serving to maintain the normal concentration of free thyroid hormone in the blood. Both control systems, the iodine and the TRH-TSH, regulate the intermediary metabolism of the thyroid cell, largely via the adenyl-cyclase-cyclic adenosine monophosphate. Under physiological conditions, their effects are complementary (36).

The production of thyroid hormone involves the following processes:

1. Iodide transport. The transport of iodide from the plasma across the cell membrane is an active process against electrical and mass gradients. The normal concentration of iodide in thyroid cells is 30–40 times higher than in the serum.
2. Synthesis of thyroid hormones. At the interface of the cell and the colloid, a peroxidase is instrumental in oxidizing iodide (^{-}I) into an "iodine-intermediate". It facilitates the formation of MIT and DIT by incorporating iodine into the tyrosyl residues of thyroglobulin. The subsequent oxidative coupling of iodotyrosines into T_4 and T_3 is also carried out by the same peroxidase, possibly in cooperation with another enzyme.
3. Secretion of thyroid hormones. Thyroglobulin is engulfed by the cytoplasm of the thyroid cells and it undergoes proteolysis. The secretory phase ends by diffusion of the hormones into the capillaries via extracellular space (36).

Iodine Requirement

The nutritional need of iodine is influenced by growth, body weight, sex, age, nutrition, reproductive functions, climate, and disease. The definitions of

iodine requirement vary with the methods of estimation. In a large number of individuals living in a goiter-free area, the average urinary excretion of iodine was 150 μg per day (151). The mean thyroidal uptake of stable iodine was 72 ± 48 μg per 24 hr as determined by neutron activation analysis (182). The daily requirement in adults is placed at about 1–2 μg/kg of body weight. An iodine intake between "a minimum of 50 μg and a maximum of 1000 μg" is considered safe (126). The 1980 US Recommended Daily Allowance (USRDA) of iodine is in the range of 40–120 μg for children up to age 10, and 150 μg for older children and adults. An additional 25 μg and 50 μg are recommended during pregnancy and lactation, respectively (127).

Classification of Thyroid Enlargement

According to Perez et al (138), "A thyroid gland whose lateral lobes have a volume greater than the terminal phalanges of the thumb of the person examined, will be considered goitrous."

The PAHO classification of 1974 (149) is a slight modification of the system of Perez et al (138). It includes these categories:

Stage O: Normal thyroid.
Stage Ia: Goiter detectable only by palpation and not visible, even when the neck is fully extended.
Stage Ib: Goiter palpable, but visible only when the neck is fully extended. This stage also includes nodular glands, even if not enlarged.
Stage II: Goiter visible with neck in normal position; palpation is not needed for diagnosis.
Stage III: Very large goiter which can be recognized at a considerable distance.

Definition of Endemic and Sporadic Goiter

Earlier, the prevalence of sporadic and endemic goiter in the general population was arbitrarily defined as below 5% and above 5–10%, respectively (112). According to a more recent criterion, endemic goiter exists if more than 5% of schoolchildren have goiter grade Ib, and if goiter grade Ia is present in 30% of the adult population (44).

Etiology of Endemic Goiter

In decreasing order, the most common causes of goiter are absolute iodine deficiency, manifestational factors in goiter development, natural and synthetic goitrogens, iodine excess, and the combination of various goitrogenic agents.

ABSOLUTE IODINE DEFICIENCY The second law of thermodynamics, the weathering of the soil over eons of time, and the last glaciation 11,000–8,000

years ago, are all responsible for the transfer of iodine into the sea and consequently for an uneven and deficient distribution of this halogen in the soil and water in large regions of the world. Therefore, absolute iodine deficiency is the *dominant* cause of endemic goiter in the world.

Classification of endemic iodine deficiency It is difficult to measure iodine in food, and the 24 hr collection of urine is often unreliable. Therefore, the severity of iodine deficiency is evaluated according to the excretion of iodine in μg per g creatinine in a casual urine specimen of a representative sample of the population in an area (149). Accordingly, the severity of iodine deficiency is classified as follows:

1. Grade I iodine deficiency. There is an average of more than 50 μg iodine/g creatinine in the urine. The thyroid hormone supply is adequate for normal physical and mental development.
2. Grade II iodine deficiency. The average urinary excretion of iodine is 25–50 μg/g creatinine. The secretion of thyroid hormone may not be adequate, and these individuals are at risk of developing hypothyroidism, but not overt cretinism.
3. Grade III iodine deficiency. The average urinary excretion of iodine is below 25 μg/g creatinine. The population is at serious risk of cretinism (149).

Goiter: An adaptation of the thyroid to iodine deficiency Starting in 1905, Marine has shown that, after prolonged periods of iodine deficiency, the thyroid gland of dogs and many other species responds simultaneously by depletion of the follicular colloid and by hypertrophy and hyperplasia of the thyroid cells. Relief of iodine deficiency is regularly followed by colloid involution and a decrease in size of the goiter. Frequent or continuous staging of the hyperplasia-colloid involution repertory is an inevitable cause of exhaustion and necrosis of some thyroid cells, leading to cystic degeneration, fibrosis, and calcifications of thyroid tissues. The irregularity of the inner structure of the thyroid is expressed in the nodularity of the goiter. Prolonged repetitions of hyperplasia may lead to hyperthyroidism (toxic nodular goiter) or end in either benign or malignant neoplasia. This phenomenon became known as "Marine's cycle". Thus Marine formulated the laws of goiter development and in the irregular, disfiguring goiter discovered an orderly cycle (109).

Later studies by Stanbury et al (161), Ermans (44), and many others, using more precise measurements with ^{131}I, achieved a deeper insight into the nature of goitrogenesis. They all agreed that the reaction to a negative iodine balance was at first corrected by an increased response of the thyroid to normal amounts of TSH. If that mechanism fails to preserve the normal serum level of T_4 and T_3, an increase in secretion of TSH further augments the above compensatory

mechanism. Thereafter, chronic high stimulation by TSH produces a relative increase in secretion of T_3 over T_4, accompanied by continuous, at first patchy and later nodular, thyroidal hyperplasia as well as degenerative exhaustion and atrophy of thyroid tissues in other areas. The advantages of relatively higher secretion of T_3 over T_4 are that T_3 contains 25% less iodine than T_4; T_3 is 3–4 times more potent than T_4; and the half-life of T_3 and T_4 are 1 and 7 days respectively. Therefore, the relative increase in secretion of T_3 represents a further modality of adaptation to severe iodine deficiency.

Experimental Goiter and Thyroid Carcinoma

At the beginning of this century goiter in animals was both produced and intensively studied by David Marine and Sir Robert McCarrison. Both accepted the theory of multifactorial etiology of the goiter, but Marine considered iodine deficiency as the dominant goitrogen by its absence. McCarrison, in addition, stressed the importance of bacterial toxins and various food goitrogens. Both were right.

Historically, it is of interest that J. Saint-Lager (153), in his book *Études sur les Causes du Crétinisme et du Goître Endémique,* [1867] mentioned that sulfur and iron sulfate mixed with food produced goiter in 3 of 12 mice in three months. He did this experiment because he found much pyrite (iron disulfide) in the soil of many goitrous areas. After these geological observations, he was encouraged to carry out his experiments because he found that Paracelsus had written, "Goiter development is caused by minerals like immoderate amount of marchasita (pyrite) and other crude minerals, like other things which are produced by the same." Saint-Lager's account of nonscientific difficulties and failure to continue the same experiments in the dog have a tragic background, when he wrote, "I have finally decided to publish my present study in order to invite more lucky and capable investigators to continue my unfinished work."

The classical purely iodine-deficient goiter with development of functioning and nonfunctioning benign nodules as well as malignant primary and metastatic carcinomas was elegantly produced and lucidly studied by Leblond and his colleagues (7, 76, 77) from 1950–1970 in Montreal, Canada.

As mentioned, the incidence of thyroid carcinoma is about 5–6 times higher in areas with than without severe endemic goiter. In addition, the follicular and anaplastic thyroid carcinoma are twice more common in iodine-deficient goiter than in normal thyroid (33, 183). Excellent investigations of transplantable thyroid tumors produced by feeding animals the goitrogen thiouracil were reported from 1949–1965 by Bielschowsky et al (15), Money & Rawson (123), Morris & Green (124), Purves, Griesbach & Kennedy (147); with a combination of iodine-deficient diet and thiouracil by Wollman (190) and by implanting thyrotropin secreting tumors by Sinha, Pascal & Furth (157). From 1959–1978, the studies of Leblond and colleagues on the development of strictly iodine-

deficient goiter have been repeated and extended by producing transplantable thyroid tumors with implants of iodine-deficient thyroid tissue into usually ^{131}I thyroidectomized iodine-deficient isologous, inbred rats. After several generations, these tumors grew in isologus normal (nonthyroidectomized) rats fed a regular iodine-rich diet. These tumors were then transplanted for 20–50 generations and some have been kept in cell cultures for about 10 years.

GROWTH AND FUNCTION OF EXPERIMENTAL TRANSPLANTABLE THYROID TUMORS IN THE RAT The thyroid gland is an endodermal organ and does not have a stem cell and a special growth compartment. It was established that during severe iodine deficiency every cell can divide (139). During that process the thyroid can undergo epigenetic and/or gene mutational carcinogenesis. Like goiter, transplantable tumors may grow faster and function more actively in iodine deficient hosts than when implanted in normal rats fed an iodine-rich diet. Their structure may differ also. Phenotypically, most tumors are stabile for unpredictable periods of time. Only 2 tumors out of more than 25 lines became early and suddenly very malignant and anaplastic, killing the host within 1–3 weeks. Despite enormous evolutionary differences, tumors in chronically iodine-deficient man and rat are similar, except that the clock of the rat is about 30 times faster.

EFFECT OF THYROTROPIN ON GROWTH, STRUCTURE AND FUNCTION OF THE TRANSPLANTABLE THYROID TUMOR OF THE RAT Implants of iodine-deficient goiters, containing either pure papillary or pure follicular tumor, grew large papillary-follicular tumors (weighing several g) in ^{131}I-thyroidectomized iodine-deficient host with enlarged pituitaries, suggesting high serum TSH and low thyroid hormones. Then the same iodine-deficient thyroid tissue was injected into normal isologous rats fed an iodine-rich diet (with presumably normal serum TSH and thyroid hormones). The tumors slowly grew to 3–4 times larger than the host's thyroid and formed large islets of normal-appearing and functioning thyroid follicles clearly separated from areas of malignant papillary or follicular structures. By analogy with humans, these observations suggest that normal appearing follicles around the overt thyroid carcinoma may also be malignant (111) (Figure 9).

EFFECT OF NUTRITIONAL IODINE ON ONE AUTONOMOUS LINE OF TRANSPLANTABLE THYROID TUMOR OF THE RAT Variation of the iodine consumption and the level of endogenous TSH influenced the function of an autonomous transplantable follicular tumor in the rat. Only in the completely ^{131}I-thyroidectomized host (with presumably high endogenous TSH) fed regular iodine-rich chow did the tumor produce enough ^{131}I-diiodotyrosine and more ^{131}I-T_4 and ^{131}I-T_3 than either tumors grown in normal

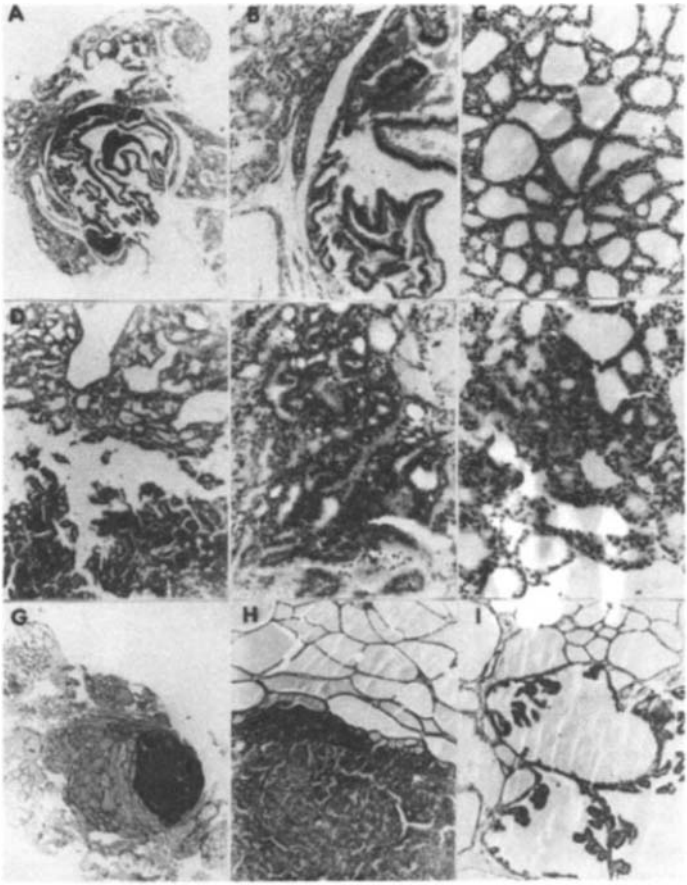


Figure 9 **Iodine-deficient thyroid tissue containing a pure papillary tumor was implanted from the** same syringe into: 1. ^{131}I-thyroidectomized iodine-deficient rats (high serum thyrotropin TSH), and 2. normal rats on a regular diet (normal serum TSH). The first group of rats grew large papillary-follicular tumors, and the second developed small papillary-follicular tumors surrounded by normal-appearing follicles.

A. Iodine-deficient goiter containing papillary tumor (ID-G + Tu) in the rat, × 25. B. ID-G + Tu detail from A, × 125. C. Thyroid gland of the normal rat fed regular diet N-RD, which was host of the tumor in G, × 150. D. Transplantable papillary-follicular tumor developed from ID-G + Tu in the ^{131}I-thyroidectomized iodine-deficient (Tx-ID) rat, × 125. E. Papillary-follicular tumor; detail from D, × 175. F. Hyperplastic thyroid tissue; detail from D, × 200. G. Autonomous papillary and follicular tumor developed from ID-G + Tu seen at A in normal rat on regular iodine-rich diet (N-RD) rat, × 50. H. Autonomous follicular tumor with normal-appearing thyroid follicles; detail from G, × 130. I. Thyroid follicles with and without papillation; detail from G, × 130.

Thus iodine deficiency contributes to the growth and morphology of thyroid tumors in the rat. This phenomenon occurs also in humans and domestic animals in areas of severe endemic goiter. (Reproduced by the kind permission of the editor of *Cancer Research*) [From (111)]

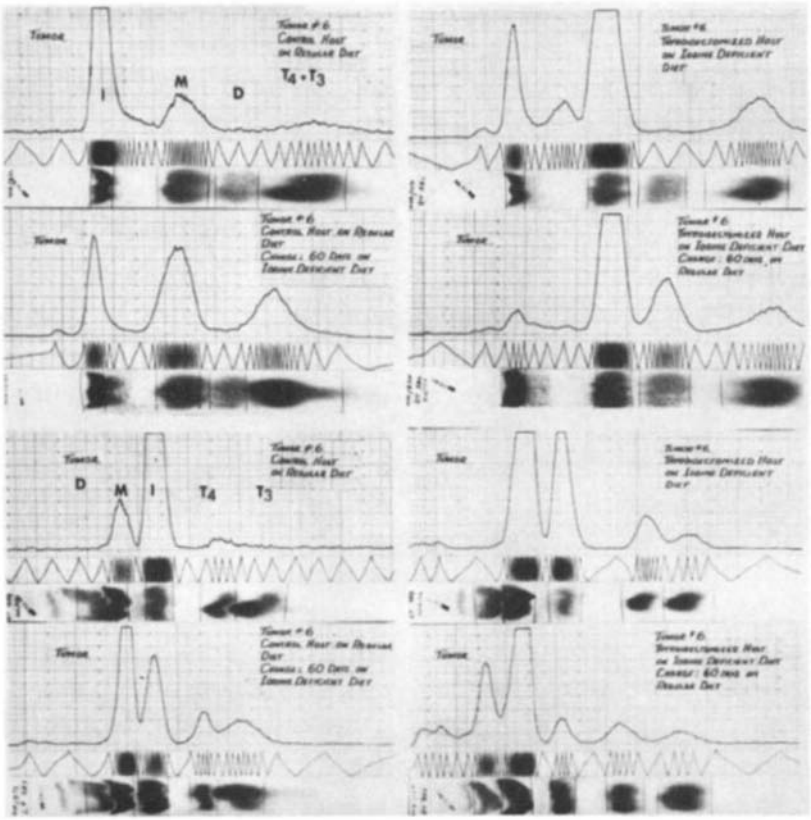


Figure 10 **The endocrine function of the well-differentiated follicular tumor in the ^{131}I-**thyroidectomized rat (high serum thyrotropin TSH) is improved when the host is fed an optimal amount of iodine. Effect of iodine and thyrotropin (TSH) on the synthesis of iodotyrosines and iodothyronines by a transplanted thyroid tumor grown in *(a)* normal rat fed a regular diet; *(b)* normal rat switched from a regular diet to an iodine-deficient diet; *(c)* thyroidectomized, iodine-deficient rat; and *(d)* thyroidectomized iodine-deficient rat switched to a regular diet.

The upper four chromatograms were made in a butanol-acetic acid system. The four stained areas, from left to right, are iodide, MIT, DIT, and iodothyronines (T_4 and T_3). The lower four chromatograms were made in a butanol-dioxane-ammonia system. The five major stained areas are, from left to right, DIT, MIT, iodide, T_4, and T_3. As seen in both systems, DIT is abundantly produced in the thyroidectomized rat with presumably high TSH and on an iodine-rich diet. T_3 is produced in all tumors grown in animals with presumably high TSH secretion but not in tumors grown in normal rats. Thus TSH and iodine regulate the endocrine function of the normal thyroid and its differentiated tumors. (Reproduced by the kind permission of the editors and authorities of the Publication Office of the Pan American Health Organization) [From (110)]

rats fed a regular diet (normal TSH) or tumors in ^{131}I-thyroidectomized rats on an iodine-deficient diet (high TSH levels) (110). This observation indicates that iodine, in addition to being a nutrient and constituent of thyroid hormone, also has per se some regulatory effect on the function of even neoplastic thyroid tissue (Figure 10).

EFFECT OF THYROXINE AND NORMAL DIET ON LONGSTANDING IODINE-DEFICIENT GOITER OF THE RAT Rats fed an iodine-deficient diet for 18 months were then given a regular diet and daily injection of 5 μg sodium-l-thyroxine for two months. The goiters involuted considerably. The implants of these iodine-deficient thyroxine-involuted goiters in ^{131}I-thyroidectomized rats grew either large papillar-follicular tumors or small benign nodules of hyperplastic tissues. Reimplants of segments of these small benign-appearing nodules into the ^{131}I-thyroidectomized iodine-deficient hosts became large papillary-follicular carcinomas (111) (Figure 11).

Therefore, it is possible, even in man, that a long-standing goiter completely involuted by therapy with thyroxine may retain the potential for malignant growth after thyroxine therapy is omitted or even continued (111).

Complications of goiter

ADVERSE EFFECTS OF GOITER ON HEALTH IN GENERAL The most common are: 1. Mechanical complications, i.e. compression of vital organs of the neck. 2. Endocrine disorders: *(a)* hyperthyroidism, an escape to TSH-independent hyperfunction which can cause hyperthyroidism spontaneously, and especially in the presence of a large supply of iodine (Jod-Basedow), and *(b)* hypothyroidism, usually in older women, due to exhaustion of thyroid tissue after many pregnancies and prolonged breast feeding. 3. Neoplastic alterations in endemic goiter after a life-long increased growth and hyperfunction of thyroid tissue.

ENDEMIC CRETINISM Endemic cretinism occurs only in areas of severe endemic goiter, and its pathogenesis is not well understood. Transplacental transfer of maternal thyroid hormones to the human embryo and fetus is minimal. Maternal hypothyroidism can cause abortion, stillbirth, and some congenital anomalies (phenocopies) that have nothing in common with endemic cretinism. Hypothyroid mothers have delivered perfectly normal children. The fetal thyroid begins the secretion of thyroid hormone after the twelfth week of pregnancy and thereafter the fetus depends on its own thyroid hormone. The athyroidal sporadic cretin is hypothyroid during fetal life and at birth, but is free of deaf-mutism and neurospasticity of the extremities characteristic of endemic cretinism. Early thyroid hormone therapy ensures a normal mental and physical development of the sporadic athyroidal but not of the endemic cretin. Some

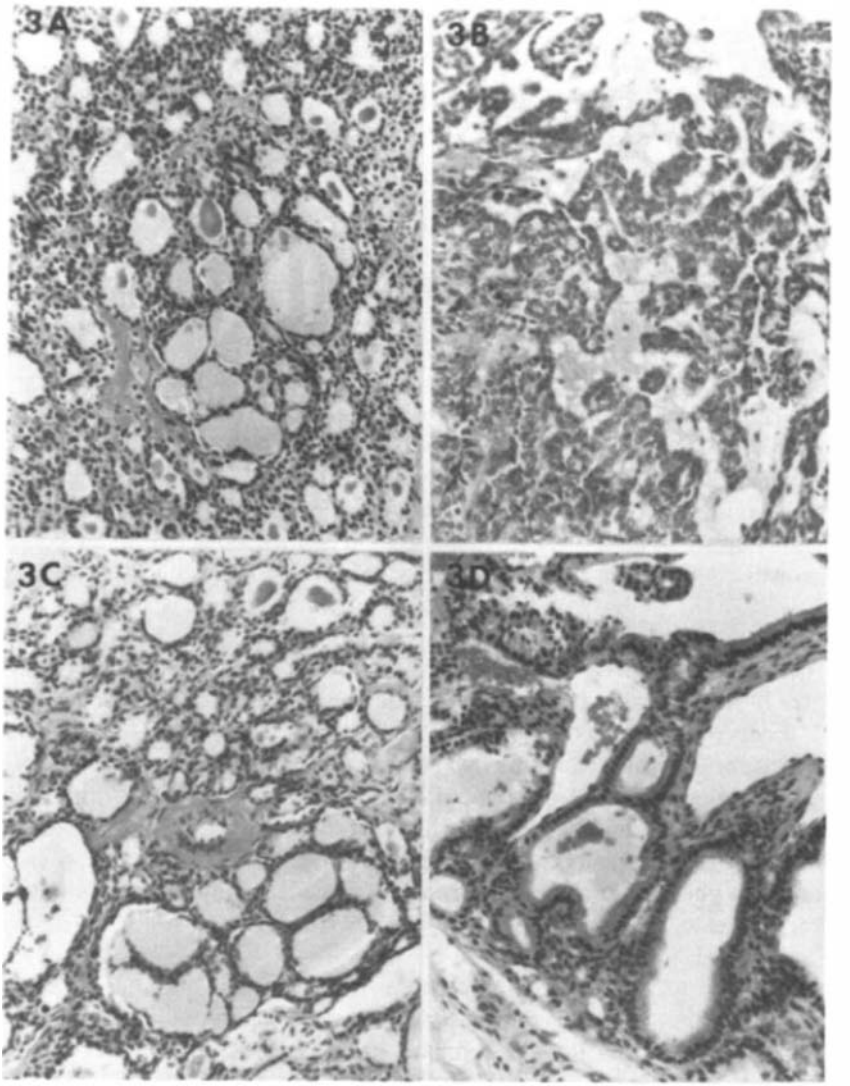


Figure 11 **Rats fed a severely iodine-deficient diet developed large goiters. Thereafter the size of** the goiters was greatly reduced by an iodine-rich diet and daily injections of thyroxine. No malignant tumors were found in the thyroids. However, implants of sections of these thyroid glands in the thyroidectomized (Tx-ID) iodine-deficient rat grew both benign nodules and malignant thyroid tumors. 3A. Iodine-deficient, thyroxine-involuted goiter (ID-T_4G) of a rat, × 200. 3B. Transplantable thyroid tumor developed from the implant of ID-T_4G of another rat, × 200. 3C. Transplantable nodule of hyperplastic tissue developed from the implant of ID-T_4G in Tx-ID rat, × 250.

Therefore, humans with a longstanding iodine-deficient goiter can also develop thyroid carcinoma even after therapy of the goiter with thyroid hormone. (Reproduced by the kind permission of the editor of *Cancer Research*) [From (111)]

have considered endemic cretinism to be a consequence of simultaneous hypothyroidism of the mother and the fetus caused by severe iodine deficiency. However, there is no good evidence for this mechanism. Therefore, it seems that severe deficiency of iodine per se, as an essential micronutrient, could cause endemic cretinism by disturbing the genesis of the nervous system during the first 12 weeks of embryonal life, i.e. before development of the fetal thyroid.

The embryo can be severely iodine-deficient because the overactive iodine-deficient goiter of the mother concentrates all iodine, before the fetal thyroid develops and begins its own accumulation and storage of iodine in the form of iodotyrosines, and eventually starts secreting thyroid hormones. There is some circumstantial support for the role of iodine deficiency per se in the development of endemic cretinism. It seems that in severely iodine-deficient areas the iodine stores of the mother's thyroid become more depleted with each successive pregnancy and lactation, and her thyroid accumulates iodine more avidly. It is an old experience that the successive children are usually more retarded and finally only cretins are born. Such children belong to the group of "nervous cretins", because the fetal thyroid, after the twelfth week of pregnancy, succeeds more or less in producing minimal amounts of hormone for euthyroid development. Obviously, under conditions of extreme iodine deficiency, sometimes intrauterine or neonatal exhaustion of the thyroid can cause mixed forms of "nervous" and "myxedematous" cretinism, as seen in Rude, Yugoslavia, and in Chitral, Pakistan.

In addition, it is possible that some goitrogens, such as thiocyanate (a metabolite of hydrocyanic acid in cassava) or thiocyanate and vinyl-thio-oxazolidone (from cabbage, etc.), could make cretinism worse by disturbing the utilization of the scarce supplies of iodine by the brain tissue, in the same way as they prevent uptake of ^{131}I by the egg yolk in poultry (152). After the twelfth week of pregnancy, through infancy and early childhood, the effect of such goitrogens also could contribute to the development of hypothyroidism with some brain damage or, if very severe, to exhaustion atrophy of the iodine-deficient thyroid of the fetus—leading to "myxedematous" cretinism in Ubangi, Republic of Zaire, as described by Ermans et al (45).

Thus it appears that the three forms of endemic cretinism, "nervous", mixed "nervous-myxedematous", and myxedematous represent three stages of the same disease due to possible variations in intensity of action and/or number of pathogenic agents.

Etkin's hypothesis of iodine as a separate essential micronutrient per se deserves more attention. He reminds us that marine fish do not undergo metamorphosis and are poikilotherm, but have retained the thyroid gland. The same is true of poikilotherm frogs and lizards. They need the thyroid hormone for larval metamorphosis only, while in the adult organism there is no evidence of endocrine function of the thyroid.

These observations, and especially the exceptional persistence of the thyroid without apparent endocrine values to some organisms, prompted Etkin to suggest that iodine is a micronutrient per se; and the thyroid gland is also the storage organ for iodine (in the form of iodotyrosines) needed to meet the special metabolic and/or structural functions of this halogen in various tissues of the body (46).

Manifestational Factors in Goiter Development

Under conditions of equal iodine supply, certain factors can contribute to a higher prevalence and larger goiter in some individuals. The most important are the following:

1. Increased requirement of thyroid hormone. Some fast-growing children, as well as some pregnant and lactating women develop goiter due to a relative iodine deficiency produced by an increased requirement of thyroid hormone.

2. Genetic disorders of the thyroid. Statistical studies of the prevalence of and freedom from goiter in homozygous and heterozygous twins suggest that genetic factors do indeed affect goiter development. It seems that the higher prevalence of goiter in some families is partly due to a "lower biological efficiency" of the thyroid. About 30% of humans and chimpanzees have a lower than normal taste for the bitter phenylthiocarbamates. In the white race, this taste deficiency can also extend to some antithyroid compounds such as methylthiouracil. This anomaly occurs more frequently in some individuals with either sporadic nodular nontoxic goiter or with endemic goiter of any type. Heterozygous inborn errors of iodine metabolism are relatively rare disorders that can also contribute to goiter development.

3. Hashimoto's thyroiditis. Individuals with latent Hashimoto's thyroiditis can develop goiter when exposed to either deficiency or excess of iodine (113).

Natural Goitrogens

Recently, Gaitan (52) reported a great disparity in goiter prevalence in several adjacent communities in various countries around the world, in spite of the same severe iodine deficiency—i.e., urinary iodine excretion of less than 25 μg/g creatinine. He cited several examples, including Alto Ventuary and Bailadores, Venezuela, 5% and 55.8%; Tion and Mulia, Western New Guinea, 5% and 58.0%; Southern and Northern Idjwi Island in Lake Kivu, Zaire, 5.3% and 54.0%; Guangaje, Cumbaya, and Pisiculla, 12.4%, 16.3% and 26.1%; versus Penipe, La Esperanza, and Tocachi, in Ecuador, 49.0%, 51.0% and 54.4%. Therefore, it seems that iodine deficiency in some areas is only the permissive factor, while the natural goitrogens are the significant determinants in the prevalence of endemic goiter.

Furthermore, natural goitrogens are probably the dominant cause of goiter in some localities where iodine intake is abundant. In 1963–64, the population of

Indian Creek, Kentucky, USA, had optimal iodine nutriture but the goiter prevalence was 33.1% (96). Similarly, in Richmond County, Virginia, USA, goiter prevalence in schoolchildren was 29.0%, while the average daily iodine intake was 165–384 μg/day. Goiter prevalence in children drinking artesian waters was 9.8 + 2%, while 28.4 + 2.8% of children drinking water from surface springs and shallow dug wells were goitrous (181). The endemic goiter in schoolchildren in 37 communities in the Cauca Valley, Colombia, South America, was also caused by goitrogens. After 10–20 years of goiter prophylaxis with iodized salt, the average daily urinary iodine excretion was in the range of 65–295 μg, but the goiter prevalence in schoolchildren in several towns was 1–42%. In a prospective study, started in 1959, it was observed that goiter prevalence in schoolchildren had decreased from 82% to 30% in Candellaria, and had remained at that level for 15 years. In Zarza, only 80 km away, goiter prevalence had decreased from 16% to less than 9% (52).

Natural goitrogens vary by origin and by their adverse mechanism of action. The most important goitrogenic substances of natural origin will be briefly mentioned (Figure 12).

CASSAVA Cassava *(Manihot edulis, genus Manihot)* was allegedly brought by slave traders from South America to tropical Africa. The tubers and leaves of cassava are the staple source of carbohydrates for about 250 million people in tropical countries. During processing of the plants, the enzyme linamarase liberates hydrocyanic acid (HCN) from linamarin in amounts of 9–162 mg/kg of fresh roots. The consumers apply relatively effective procedures to eliminate HCN from cassava dishes. The body also has an impressive number of detoxifying mechanisms that change HCN into thiocyanate (SCN^-). Only under conditions of moderate to severe iodine deficiency is SCN^- a strong goitrogen. It is not concentrated by the thyroid, but it competitively inhibits trapping, and promotes efflux of already intrathyroidal iodine. In large doses, it inhibits iodination of tyrosil residues and the coupling of iodotyrosines. SCN^- affects the fetus/infant indirectly by impairing the transplacental and mammary transport of iodine, and directly by disturbing the utilization of iodide by the fetal thyroid gland. It reaches the milk only by diffusion. Because of large renal clearance, the serum level of SCN^- is not a useful indicator for this goitrogen. Instead, the urinary SCN^- mg/μg/^{127}I ratio correlates very well with the goiter prevalence (45).

The goitrogenic effect of cassava was first observed by Ekpechi in Nigeria (43). Severe iodine deficiency combined with high HCN in cassava is responsible for widespread endemic goiter (+50%) and myxedematous endemic cretinism (1–7%) in a population of 1.5–2 million people in the northern part of Idjwi Island and Ubanga, Zaire. Congenital hypothyroidism occurs in 20% of the newborn in Ubanga compared to 1:5000 births in the Western World (45). The

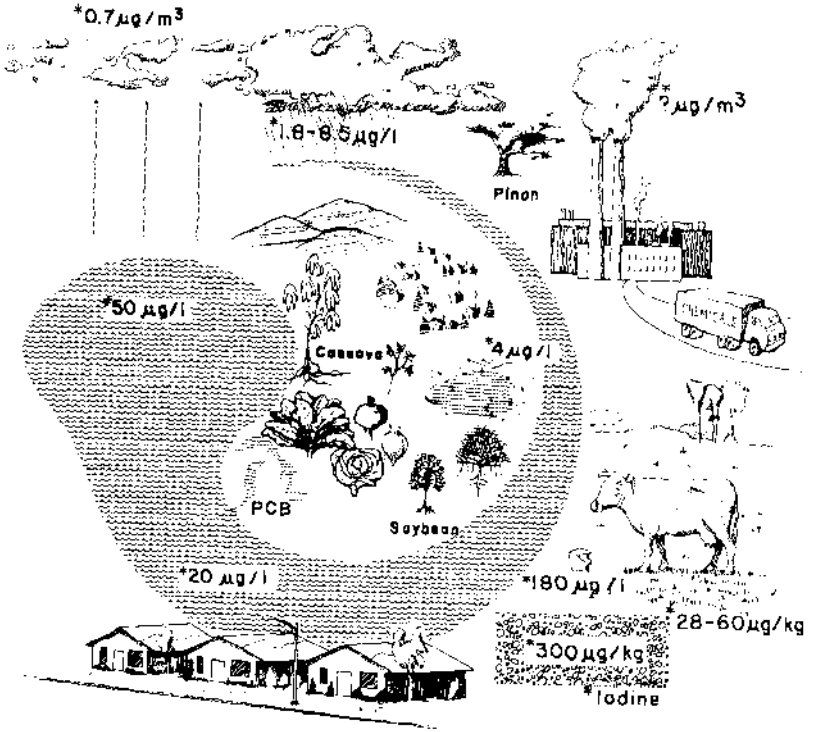


Figure 12 A simple scheme of the turnover of iodine in nature. Iodine in the air and soil, to the river, sea, and back to air. Iodine in salt, feed, food, and chemical products.

Natural goitrogens: cassava, cabbage, and rape seed meal, soybean, peanut, walnut, pinon, bacterial products in table waters, and disulfides of aliphatic hydrocarbons from sedimentary rocks in deep well waters.

Synthetic goitrogens: some polychlorinated biphenyls and polybrominated biphenyls; organochlorine insecticides—DDT, etc; fungicides—ethylenbisdithiocarbamates; bacteriostatic sulfonamides; antibiotics—tetracyclines; excessive amounts of iodine in kelp and from adventitious sources in industrially processed food. (Original illustration modified.) (Reproduced by the kind permission of the editor of the University of Missouri Press) [From (179)]

West African cassava-yam crop belt extends from the eastern half of the Guinea Coast through the Congo River system to the Bandama River at the Ivory Coast. Recently, cultivation of cassava has been replacing sorgham and millet in some other regions of Africa. There is no information on the extent of combined iodine-deficient and SCN^- endemic goiter elsewhere in the world. Recent methods of application of a specific ion electrode permit accurate, simple, fast and cheap measurement of both ^{127}I and SCN^- in the urine. This type of goiter is completely preventable by a generous supplement of iodine (45).

CABBAGE, RAPE AND MUSTARD These vegetables belong to the genus Brassica and the family of Cruciferae. The leaves of cabbages *(Brassica oleracea),* the roots and seeds of Argentine rape *(B. napa),* and Polish rape *(B. campestris),* as well as the seeds of mustard *(B. Nigra),* and many varieties of these three groups are important foods, feed, and condiments. The ancient Greeks used rapeseed oil for lighting and cooking too. The renewed impetus for increased rapeseed oil production occurred after the development of the steam engine, because it clung better than any other lubricant to its water-steam–washed surfaces. The same was true during World War II of the huge Canadian production for the needs of Allied navy and merchant ships. Today these plants are enormously important sources of rapeseed meal for animal feed as well as purified proteins, and especially as rapeseed oil in the food industry. In 1979–80 the world production of rapeseed was about 11.5 million metric tons, with the Canadian Canola share of about 4.5 million metric tons. In the United States the cultivation of Abyssinian Kale *(Crambe Abyssinica),* is the favored crop for industrial oil purposes (35).

The major technical and nutritional difficulties with roots, leaves, and especially seeds of domestic and wild Cruciferae is their high content of glucosinolates (172), which during processing of the plant are hydrolyzed by their enzyme myrosinase [thioglucohydrolase EC 3.2.3.1]. It releases glucose, sulfate, and an aglucon molecule that is further converted into thiocyanate, nitriles, sulfur, and isothiocyanates. The allyl-, 3-butenyl-, 4-pentenyl-, benzyl-, phenyl-, ethyl, and 4-methyl-3-butenyl glucosinolates are converted into isothiocyanates—i.e., steam volatile mustard oils. Some isothiocyanates degrade further to a thiocyanate ion. More importantly, one isothiocyanate-intermediate, also called progoitrin, is transformed by spontaneous cyclation into 1-5-vinyl-2-thiooxazolidone (VTO), also known as "goitrin" (172, 173).

The pioneering studies of VTO, from isolation to synthesis, and elucidation of its function were done by Astwood (4, 5), Greer (59, 60, 61), followed by Virtannen (178), Michajlowski et al (120), and Bowland et al (19, 20, 21, 22), Paik, Robbles & Clanidinin (136). The VTO compounds are by action and potency similar to synthetic thionamide antithyroid drugs. They inhibit both the iodination of tyrosine and the coupling processes in the synthesis of thyroid hormone. It is especially important that their goitrogenic effect is not relieved by the addition of iodine to food. They cross the placenta and are strong fetal goitrogens. By diffusion, they accumulate in the milk. They enter into eggs and inhibit the thyroid function of the avian fetus (57).

The Canadian "Canola", variety "Tower", of Argentine rape was developed by selection from *B. napus Bronowski*. It contains less than 5% erucic acid and 3 mg or less glucosinolate per g of rapeseed. This represents about 10% of the amount of glucosinolates in standard varieties of rapeseed in other countries

(18). In order to eliminate the goitrogenic effect, the mirosinase is destroyed by prepress heating of the seeds, but intestinal *Escherichia coli* and similar organisms can change the inactive progoitrin into active goitrin (61, 178). Therefore, further genetic/technological improvement of this crop is desirable in order to prevent goiter in domestic animals.

It was reported that the VTO from wild Cruciferae, consumed by dairy cattle, can contaminate the milk—which, taken over a long period of time, can cause goiter in man. In rats the thyroidal ^{131}I uptake is too insensitive to detect the antithyroid effect of such small, but goitrogenic, amounts of VTO (91).

In addition, in some areas of Czechoslovakia and in one part of the island Krk in Yugoslavia, certain varieties of cabbage contain enough SCN^- and VTO to significantly increase the prevalence of iodine-deficient goiter (119, 143). Of three goitrous communities in Sicily, Italy, iodine deficiency was the main cause of goiter in only one. In the other two a combined effect of thiocyanate and lower than normal iodine levels had a similar effect as severe iodine deficiency. In these two communities, several endemic cretins were found. The source of goitrogen was not definitely determined, but it is probably a glucosinolate-rich cabbage. It is consumed in large quantities and its glucosinolates are converted to thiocyanate (45, 159).

SOYBEAN Originally grown in China, soybean *(Glycine Soja,* family *Fabaceae)* has for thousands of years been a principal crop of the warm and tropical areas of the Orient. During World War II, cultivation of soybean has increased considerably, and today approximately 30–40 million metric tons, or about 33% of the total world production, is grown in the USA.

As quoted by Van Middlesworth (174), McCarrison in 1933 reported soybean was a goitrogen in the rat. By adding more iodine to the diet, its goitrogenic effect was eliminated, and Astwood also noted that ^{131}I uptake was increased in the soybean goiter of the rat. Van Middlesworth injected ^{131}I-thyroxine intraperitoneally in the rat and observed that soybean-fed animals wasted large amounts of ^{131}I-thyroxine in the stool. The goiter development in soybean-fed rats is secondary to a relative iodine deficiency (1 mg T_4 contains 0.68 mg iodine). The great loss of thyroxine in the stool occurs because *(a)* the rat normally excretes 100% of thyroxine from the blood via bile into the gut within one hour, and normally 97% of it is reabsorbed into the blood; *(b)* thyroxine bound to soybean flour is not reabsorbed by the intestine; *(c)* the fecal loss of ^{131}I-thyroxine in soybean-fed rats was partly due to large fecal bulk, as adding 30% of pure cellulose to the control diet also resulted in an increased fecal loss of thyroxine; *(d)* addition of iodine to a soybean diet prevents the development of goiter, because soybean does not disturb the absorption of iodine from the intestine (174). This type of goitrogenesis is characteristic of the rat. The blood-biliary turnover of thyroxine in man is too small for such a

pathogenic mechanism. An exception to this postulate is an observation of persistent congenital athyroidal hypothyroidism treated orally with thyroxine, until the soybean milk formula was replaced by whole milk (141).

In 1971, it was reported that dairy cows, given soybean meal without an addition of iodine, "bore goitrous calves, consumed less feed, and produced less milk, with a lower than normal fat content." Although these studies were not pursued further, the daily supplement of iodine in dairy cattle was increased by an average of 10 mg (63).

Finally, it was observed that soybean milk can lower the thyroidal ^{131}I uptake and the synthesis of thyroid hormone in susceptible adults, as well as produce goiter with hypothyroidism in a susceptible infant (176).

In search of the goitrogenic agent, an oligo- or glucopeptide with 2–3 amino-acids and sugar was isolated. It inhibits thyroidal ^{131}I uptake and organification of iodine, characterized by a high ^{131}I-MIT/^{131}I-DIT ratio (89). However, in 1979, the largest goiter was observed in rats fed soybean curd, but the goitrogenic substance in the curd was not a protein nor a peptide-like compound, because proteolytic digestion of the curd did not eliminate its goitrogenic properties (163). Obviously, more work is needed to settle this important question.

THE WALNUT In 1970, it was established that an unknown compound in the Persian walnut *(Juglans Regia,* genus *Juglans),* produced—similarly to soybean—a waste of thyroxine in the feces of the rat. Increased fecal excretion of orally given ^{131}I-thyroxine persists in the walnut-fed rat even after ligation of the ductus choledochus. The relative iodine deficiency is evident from the increased thyroidal uptake of ^{131}I in the experimental animals. The walnut diet has no direct effect on the thyroid, for the thyroidal concentrations of ^{131}I T_4, and ^{131}I T_3, and their precursors are similar in both the experimental and control groups of animals. Again, the goitrogenic effect of the walnut is predicated on a normally large hepato-enteral thyroxine cycle in the rat (95). No experimental evidence on this subject is available in humans and the walnut is not an important goitrogen in man.

THE PEANUT The peanut or ground nut *(Arachis hypogaea,* family *Fabaceae)* was originally cultivated by the South American Indians. At present, the largest producers are India, China, the USA, and Brazil, while the world crop is approximately 15–20 million metric tons per year. In 1935, McCarrison reported that rats fed peanuts developed goiter. This observation was later confirmed and expanded (160). It was noted that phenolic derivates in the skin of the peanut and in several similar nuts are active goitrogens. They are polyphenolic metabolites of anthocyanin pigments, constituents of the glucoside arachidosine in the peanut skin. By forming stabile iodophenols, the

compounds are goitrogens because they compete for iodine with tyrosyl residues. In 1953, this effect of the phenols was observed in experiments in vitro by Fawced & Kirkwood (47). Experimental animals developed goiter due to a reduced thyroidal uptake and organic binding of ^{131}I. The goitrogenic effect can be lessened by adding more iodine to the diet.

THE PINON The pinon *(Auraea Auracana,* genus *Pinus)* grows mostly as a coniferous shrub in arid areas of the southwestern United States and throughout similar regions of South America. The female cones contain small pine nuts, important in the Indian diet. At the Pedregoso Indian reservation in Chile, goiter is more prevalent among individuals who consume more than 100 g of pinon per day. An unknown goitrogenic substance inhibits thyroidal uptake and organification of ^{131}I in the rat, and its effect is not reversed by administration of iodine (166).

BACTERIAL PRODUCTS AS GOITROGENS High goiter prevalence, despite abundant iodine intake, was observed in Eastern Kentucky (96) and Northern Virginia (181), where the drinking water came from shallow dug wells and was bacteriologically polluted. The cell-free filtrates of cultures of *E. coli* from these waters contained a substance with mol wt 1×10^5, which had an inhibitory effect on the thyroidal uptake of ^{131}I in the rat (53, 180).

GOITROGENS IN GEOLOGICAL SEDIMENTS Disulfides of saturated and unsaturated aliphatic hydrocarbons from sedimentary rock drained by waters into deep wells were identified as the cause for an unsatisfactory reduction of endemic goiter with iodized salt in Candellaria, in the Cauca Valley, Colombia, South America (see above). Experimentally, the ether-methanol extracts from the charcoal filters kept at the outlets of those wells caused inhibition of ^{131}I uptake, synthesis of thyroid hormone, and produced enlargement of the thyroid in the rat. Further studies indicated that a number of bacteria *(E. coli, Baccillus sp., Proteus sp.,* and *Neisseria sp.)* in the water also contributed to the prevalence of goiter, while the *K. pneumoniae* organisms in the water lowered the goiter prevalence, possibly by natural biodegradation of organic goitrogenic contaminants (52, 53).

Synthetic Goitrogens

Some members of the following classes of compounds are goitrogenic: *(a)* plasticizers, polychlorinated biophenyls, PCBs; *(b)* fire retardants, polybrominated biphenyls, PBBs; *(c)* organochlorine insecticides, DDT, DDD, and Dieldrin; *(d)* fungicides, ethylenbidithiocarbamates (EBDC); *(e)* bacteriostatic agents, sulfonamides; and *(f)* antibiotics, tetracyclines.

POLYCHLORINATED BIPHENYLS (PCBs) PCBs are not soluble in water but adhere to floating and sedimented organic particles. Along the chain of food, their bioconcentration increases steeply (thousandfold) from bacteria, algae to various fish, birds, and mammals. In the Great Lakes, the most contaminated fish in increasing order are herring, small mouth bass, lake trout, and especially Coho salmon. In 1966, the Coho salmon was introduced into the Lake Michigan tributaries, by 1972 thyroid nodules or multinodular goiter were found in 44% of fall-spawning Coho salmon in the Pennsylvania tributaries of Lake Erie (16). In 1976, 5–24% of Coho salmon in some tributaries of Lake Ontario had thyroid nodules (158). From 1972–1976, the iodine content of Lakes Michigan, Erie, and Ontario was stabile (0.9 μg/liter, 1.7 μg/liter, and 2.9 μg/liter respectively), but during that period the goiter prevalence of Coho salmon increased in the same order from 1.0 to 6.3%, 44.0 to 79.5% and 24.0 to 47.6% (122). The most goitrogenic PCB is Aroclor 1254 (184). In a series of experiments, Bastomsky et al clarified the goitrogenic actions of PCB (13) and proved that these compounds act mostly by inducing the thyroxine uridine diphosphate (UPD) glucuronyl-transferase activity of the liver. This leads to an excessive biliary excretion of T_4-glucuronate in the bowel, which is beyond the capacity of intestinal reabsorption of thyroxine. The high fecal loss of thyroxine results in the lowering of its serum level. In a servo-mechanism type of reaction, the pituitary, sustained by the hypothalamic TRH, augments the secretion of TSH. This, in turn, stimulates simultaneously an increased function and enlargement of the thyroid gland. Finally, in a study with rats given 0.25% Aroclor 1254 in food for 14 days, even animals on an iodine-rich diet, but especially those on an iodine-deficient diet, became goitrous and hypothyroid (12).

These observations were complemented by Collins et al (32). Rats fed for 2–12 weeks with 50–500 mg of Aroclor 1254/kg in an iodine-abundant chow diet, developed a dose-dependent thyroid enlargement with ultrastructural lesions of thyroid cells. The damaged cell could not compensate for the fecal loss of thyroxine. Because of a large release of Aroclor 1254 from fat, the damaging effect on thyroid cells lasted for several weeks after discontinuing administration of this PCB compound.

It is not known what implications these observations in fish and rat have for man. Kimbrough (87) and the "Panel on Hazardous Trace Substances" (128) postulate that the PCBs are enzyme inducers in humans. In the tragic Yusho disease, when 1241 Japanese in 1968 consumed rice oil contaminated with PCBs and polychlorinated benzofurans, no abnormalities of the thyroid gland or the thyroid hormone metabolism were reported. The poisoning was severe, 22 of the 1241 individuals died by 1972, and at autopsy malignant tumors were found in nine patients (92). Not all the literature on this subject was available,

but it is possible that the high iodine content of the Japanese diet could have prevented the goitrogenic effect of PCB.

Finally, even if PCBs are not goitrogenic in man, the PCB-induced goiter, hypothyroidism, and other toxic effects on fish in general could have a serious indirect effect on human nutrition. The US marine fisheries are producing about 10 million tons of fish with a PCB level of 200 μg/kg of fish, while the Great Lakes fisheries supply about 100,000 tons of fish with approximately 5 mg of PCB/kg fish (130). The Michigan sport fishermen have been advised by the Michigan Department of Natural Resources to limit consumption of Great Lakes fish to once a week and "catch and release" warnings are posted at many waterways. Because the Coho salmon meat had an adverse effect on the reproduction of mink, its use was discontinued on mink farms in the USA. During the last 50 years, about 690,000 tons of PCBs were used in the USA alone; about 69,000 tons are in the air, water, and water sediment, while about 340,000 tons are still in service. Since 1978, the production of these compounds has been banned, but those still in use will eventually end up in the rivers, lakes, and seas (186). It is of public health importance that in 1972 the estimated PCB content in 45% of the population of the US was about 1 μg/g of body fat (158).

FIRE RETARDANTS (PBBs) In Michigan, during 1973–74, about 500–2000 lbs. of PBB, instead of calcium oxyde, was accidentally added to the mineral mixture feed of cattle and poultry. This compound was detected in blood of the population throughout the state as well as in milk of lactating women. No definite adverse effects on general health or thyroid function in humans were observed (162).

Using the same methods as in his studies of goitrogenic action of PCB, Bastomsky examined the effect of PBB-hexabromobiphenyl (BB-6) in the rat. He observed that the mechanism of action and the final effect of both groups of compounds are the same (Bastomsky, personal communication, 1978). By force-feeding rats with PBB (1 mg/kg, 3 mg/kg, and 6 mg/kg per day for 10 and 20 days), a nondose response in the enlargement of the thyroid gland was observed, but the large reduction of serum T_4 was time- and dose-dependent (2).

In a study of thyroid function of 35 individuals employed in direct production of PBB and PPBO and/or working in PBB storage areas, four persons were found to have persistent hypothyroidism. They had an elevated TSH and titer of antimicrosomal antibodies, without enlargement of the thyroid. No individual in the control group of 89 persons was hypothyroid (8). This evidence for adverse effect of PBB on the thyroid is impressive, but one student of PBB toxicity questioned the validity of the conclusions because no analysis of PBB in the fat of both groups was carried out.

ORGANOCHLORINE INSECTICIDES (DDT, DDE, AND DIELDRIN) Homing pigeons *(Columbia livia)* force-fed DDT 3–54 mg/kg body wt/day for eight weeks developed hyperplastic goiters depleted of colloid. Similar results were produced with the other two compounds, and their mechanisms of action were the same as those of the PCBs (81).

FUNGICIDES: ETHYLEN BISDITHIOCARBAMATES These compounds, especially Nabam, Maneb, and Zinab are used widely in agriculture as fungicides for protection of tomatoes. During canning, tomatoes and tomato juice are exposed to heat and, according to Marshall, these compounds decompose into ethylenthiourea (106). Bastomsky (unpublished data, 1978) fed rats for 12 days with Purina Chow and Maneb in concentrations of 0.34% and 0.034%. He observed that 0.34% Maneb produced an increase in thyroid weight ($P < 0.002$) combined with a lowering of the 24 hr ^{131}I uptake and of serum T_4 ($P < 0.001$).

Bacteriostatics: sulfonamides About 21 sulfonamide compounds are used in animal husbandry as feed additives and medications. They are weak goitrogens and act by inhibiting organification of iodine and coupling of iodotyrosines. The discovery of the goitrogenic effect of this group of compounds was made in 1941 by Mackenzie, Mackenzie & McCollum (102). During studies of the antibacterial effect of sulfaguanidine on the synthesis of Vitamin E by the intestinal flora, they observed for the first time that enlargement of the thyroid was produced by a chemical compound. They immediately established that the goitrogenic effect was neither in the sulfanilic acid nor in the guanidine part of the molecule. Therefore, they tested the compounds related to those two parts of sulfaguanidine and found that both sulfanilamide and thiourea were potent goitrogens. In searching for the mechanism of action they reported that the action of sulfanilamide and thiourea could not be prevented by massive doses of iodine. In addition, these compounds produced a severe lowering of the metabolic rate. By simultaneously injecting thyroxine and giving antithyroid drugs to thyroidectomized rats, they observed no inhibition of the metabolic response to thyroxine. They concluded that these drugs acted by suppressing the synthesis of thyroid hormone. Mackenzie & Mackenzie also first observed that the goitrogenic effect of the sulfonamides is enhanced by iodine. Given for a prolonged time in large doses, they can cause hypothyroidism (98, 99, 100, 101).

ANTIBIOTICS: TETRACYCLINES Various antibiotics are used as additives to feed or as medication. In 1978 in the USA alone, pigs were given approximately 1,400,000 kg or 40% of all types of marketed antibiotics (129). The tetracycline derivates (tetracycline phosphate, metacycline, and doxycycline) are goitrogenic in the rat, and act similarly to minocycline (7 dimethyl amino-6-

methyl-6-deoxytetracycline), which specifically disturbs the coupling of iodotyrosines into T_4 and T_3 (154).

Excess Iodine in Food and Feed as Goitrogen

MECHANISM OF IODINE EFFECT ON THE THYROID In contrast to all other goitrogens, iodine in large amounts disturbs all thyroid functions—from the transport of iodine through synthesis and secretion of the thyroid hormone. Iodide in large doses (i.e., usually more than 50 mg per day) or at serum iodide concentration of 20 μg/100 ml inhibits the thyroidal transport of ^{131}I-iodide. All steps in the biosynthesis of thyroid hormone, starting with iodination of tyrosyl residues up to the formation of T_4 and T_3, are progressively inhibited by acute and chronic intake of large amounts of iodine. This phenomenon, known as the Wolff-Chaikoff effect, is persistent in only 3–4% of otherwise healthy individuals for whom iodine in large doses (more than 100 mg) is a goitrogen, and some of them may become hypothyroid (189). In a great majority of individuals, an escape from or adaptation to this mechanism occurs after 48 hr because of a more efficient hormone synthesis enhanced by a drop in intrathyroidal iodine concentration, which in turn is due to a persistent reduction of iodide transport into the thyroid cell.

Iodine in large doses is the only constituent of food that can disturb the secretion of thyroid hormone. It acts by inhibiting proteolysis of thyroglobulin directly in the thyroid cell, or indirectly, via inhibition of the TSH stimulating effect on this mechanism.

The thyroid in normal persons responds temporarily to chronic consumption of increasing amounts of iodine by augmenting the synthesis and storage of thyroid hormone without increasing the hormone's release into the blood stream. Thereafter, the thyroid responds with a steady state of high uptake and excretion of iodine. This phenomenon is balanced by an increased thyroidal synthesis and simultaneous deiodination of iodotyrosines with a subsequently increased "leak of iodine" from the thyroid. The total thyroidal iodine is increased, but there is no disturbance of normal production and secretion of thyroid hormone (75).

EFFECT OF HIGH IODINE INTAKE AS A NATURAL CONSTITUENT OF FOOD There are instances when large consumption of iodine-rich kelp has caused sporadic and even endemic goiter in man, as well as sporadic goiter in animals.

Endemic iodide goiter: coastal goiter in Japan In 1965, Suzuki et al (164) reported that goiter prevalence in 8077 schoolchildren in the coastal districts of Hidaka (Hokkaido) and on the island Rishiri was 9.0% and 2.6%, respectively.

In 3400 schoolchildren in Sapporo, an inland town, it was only 1.3%. The population of seaweed fishermen of Hidaka and Rishiri consumed 10–50 g of dry seaweed (kelp-korubo), mostly in soup, while kelp was not included in the diet of the people of Sapporo, a town far from the coast. The iodine content of several varieties of kelp was between 0.8 and 4.5 g/kg of the dried plant, about 80% of which was in the form of iodide. A bowl of seaweed soup contained 80–200 mg iodide, but the consumption was on an intermittent basis, depending on the surplus of kelp unsold at the market place. Goiter was more frequent in girls at puberty, and it was also more common in some families, suggesting a possible goitrogenic influence of additional factors.

Some characteristics of iodide goiter may be of interest: *(a)* the thyroid was diffusely enlarged in all patients, but they were euthyroid and otherwise healthy; *(b)* the thyroidal ^{131}I uptake was within normal range; *(c)* the organification of ^{131}I and the synthesis of T_4 and T_3 were lower than normal—there was a large "leak" of iodine from the thyroid; *(d)* the serum level of thyroid hormone was within normal range; *(e)* the urinary iodine excretion was high (in five individuals it was 23.3 ± 1.0 mg/24 h); *(f)* after thyroidectomy, a colloid, iodine-rich goiter was observed in all patients. With improvement in the seaweed trade and restriction in its consumption, at the advice of medical authorities, there was a significant reduction in the prevalence and size of goiter in this population (164).

In other countries, iodide goiter due to consumption of kelp is very rare because it is consumed irregularly and by only a small number of people.

Sporadic iodide goiter in animals An iodide type of goiter was observed in foals when horses (mares) were fed kelp on a farm in Florida (9).

Iodine consumption and goiter prevalence in the USA and Canada, 1960–1980 There are indications of an upward trend in iodine consumption above the USRDA of 100–200 μg in the USA and possibly in Canada. An early indication of an increased iodine intake was a 1969 report by Pittman et al (142) that the normal thyroidal 24 hr ^{131}I uptake had decreased during the preceding ten years from 28.6 ± 6.8% to 15.4 ± 6.8%. Similarly, by using thyroidal ^{131}I uptake, a reassessment of iodine consumption in 30,000 individuals from all parts of the country indicated that the average iodine intake was in the range of 270–740 μg/day, but that it varied with different areas (131).

The Ten State Nutrition Survey of 1968–1970 in the USA showed that in six of the ten states, the urinary excretion of iodine was >799 μg/g of creatinine in 14% of the persons examined (169). There was no iodine deficiency in the USA. The overall goiter prevalence in 39,555 examinees was less than 5% (Table 14).

Table 14 Ten-state nutrition survey USA, 1968–1970: goiter prevalence and urinary iodine excretion[a]

Survey area	Goiter		Urinary iodine excretion, μg/g creatinine			
	No. examined[b]	With goiter(%)	No. examined[c]	Percentage with < 25 μg	Percentage with 25–49 μg	Percentage with > 799 μg
California	4,971	7.2	833	0.2	0.8	14.6
Texas	3,632	5.3	3,426	0.1	0.3	21.9
Kentucky	1,362	4.9	1,185	2.4	3.0	13.8
Louisiana	3,932	3.9	207	0.0	0.0	10.6
South Carolina	3,739	3.6	2,210	0.2	2.6	9.5
New York state	2,709	2.7	1,130	0.4	1.4	4.7
New York City	1,625	2.4	1,160	0.2	2.8	3.0
West Virginia	1,310	1.9	725	0.7	1.9	13.8
Washington	4,379	1.2	1,990	0.0	0.4	14.2
Michigan	1,947	1.1	1,383	0.2	0.7	5.6
Massachusetts	3,619	0.4	2,550	.06	2.1	2.2

[a]From (169); reproduced by the kind permission of the authors and editor of the American Journal of Nutrition.
[b]Computed for persons 6 years of age and over.
[c]Computed for all ages.

Nutrition Canada, a nutrition survey carried out in 1972 in all enumeration units of Canada, established that the urinary excretion of iodine was 1.0–10.0 mg/g creatinine in about 2% of all age groups (74). The urinary excretion of creatinine in small children is considerably less than 1.0 g/24 hr. Therefore, the daily urinary iodine excretion is also proportionally smaller, yet it might still be several times above the optimal nutritional requirement. It is important, however, that most of the population consume an optimal amount of iodine, and no evidence of iodine deficiency occurred in Canada. Goiter prevalence in general is below 5% (Table 15).

The 1971 survey of 7785 schoolchildren age 10–15, from four states (Michigan, Kentucky, Texas, and Georgia) found the average iodine intake to be per day 100–200 μg higher than the USRDA, and the average goiter prevalence was 6.8%. In addition, there was no difference in iodine consumption between children with or without goiter. Both the iodine intake and goiter prevalence were higher in Michigan than in Georgia. It seems worth noting that the range of iodine supply was 98–2293 μg/day, according to three urine samples taken at weekly intervals. In 101, or 20% of the 530 goitrous children, the thyroid changes found by physical examination were suggestive of Hashimoto's thyroiditis (170) (Table 16).

Similarly, Rallison et al reported in 1975 that of the 5179 schoolchildren examined between 1965 and 1968 in Utah, Arizona, and Nevada, 179 (or 2%)

Table 15 Canadian national survey: percentage distribution of urinary iodine (1970–1972)[a]

Creatinine (μg/g)	Age(yrs)/Gender 0–4 MF	5–9 MF	10–19 M	20–39 M	40–64 M	65+ M	10–19 F	20–39 F	40–64 F	65+ F	Pregnant Women
0–50	0.0%	0.0%	0.3%	0.3%	0.1%	0.8%	0.2%	0.0%	0.2%	0.0%	0.0%
50–100	1.4	1.4	8.9	12.7	6.8	5.4	7.0	8.4	4.9	5.3	2.8
100–150	2.7	5.3	15.4	26.0	15.0	24.0	13.0	15.9	15.4	12.1	11.7
150–200	2.8	10.3	12.1	18.8	21.0	17.9	17.4	18.6	17.3	16.6	17.0
200–250	9.6	10.7	16.6	13.5	17.9	12.0	15.7	14.6	19.8	20.0	17.5
250–300	9.3	12.4	10.0	9.9	9.7	12.7	11.7	15.0	10.7	9.9	15.1
300–350	6.8	9.5	8.5	4.8	6.5	6.1	9.3	7.2	8.0	8.5	8.8
350–400	8.7	9.6	7.4	2.6	7.0	7.1	6.8	7.5	4.9	5.7	6.7
400–450	9.0	6.9	3.7	1.4	4.1	2.9	3.9	4.3	4.0	5.7	6.7
450–500	5.3	5.8	3.1	3.1	2.1	2.8	2.4	2.1	3.9	2.3	3.0
500–550	4.4	3.3	2.7	1.8	2.8	2.6	2.3	1.2	1.3	2.3	2.5
550–600	4.2	4.5	2.0	0.6	0.7	0.9	1.3	1.0	2.7	1.6	1.6
600–650	2.5	2.0	0.6	0.5	1.9	0.2	2.8	0.9	0.9	2.2	1.7
650–700	3.0	3.9	0.8	0.9	0.4	0.9	0.6	0.4	1.7	3.3	0.6
700–750	2.9	2.3	0.4	0.5	0.8	0.2	2.7	0.5	0.1	0.2	0.8
750–800	3.8	1.8	0.6	0.2	0.0	0.1	0.2	0.1	0.2	0.1	0.4
800–850	2.4	1.2	1.8	0.0	0.0	0.1	0.0	0.2	0.6	0.6	0.5
850–900	3.8	1.6	1.4	0.6	0.7	0.1	0.4	0.0	0.1	0.5	0.4
900–950	1.2	0.2	0.3	0.6	0.0	0.2	0.1	0.0	0.1	0.0	0.1
950–1,000	1.3	1.5	1.3	0.0	0.0	0.2	0.0	0.0	1.1	0.3	0.2
1,000+	13.9	4.9	1.1	0.3	1.7	1.8	1.2	1.2	1.0	2.0	1.2
Sample Size	742	1,282	1,416	995	1,218	884	1,388	1,295	1,460	795	746
Percentiles											
5	157.00	130.00	83.00	78.00	88.00	95.00	89.00	91.00	96.00	93.00	111.00
25	294.00	241.00	151.00	123.00	157.00	146.00	168.00	151.00	161.00	176.00	181.00
50	440.00	356.00	235.00	181.00	223.00	207.00	236.00	223.00	232.00	234.00	250.00
75	770.00	536.00	359.00	266.00	328.00	317.00	353.00	310.00	347.00	363.00	362.00
95	1585.00	998.00	805.00	526.00	616.00	556.00	694.00	538.00	660.00	682.00	626.00

[a]From (74); reproduced by the kind permission of the Dept. Natl. Health & Welfare, Canada.

had a goiter—which in 31% of the cases was, according to laboratory studies and/or histological examination, due to Hashimoto's thyroiditis. The mean iodine intake of these children was 214–523 μg/day (150).

Iodine content of the human thyroid gland The increased iodine consumption is evident from the total thyroidal iodine content in man. Recently Thrall et al (168) have, by fluorescent scanner measurements, obtained the following values of iodine in mg for 30 normal thyroids (10.1 ± 3.9, range 2.4 – 18.0), 12 diffuse goiters (16.1 ± 7.42, range 4.7 – 28.0), 28 nontoxic nodular goiters (7.3 ± 4.1, range 1.6 – 13.2), Graves' disease (24.4 ± 9.9, range 5.3 – 45.3), and 5 primary hypothyroidisms (trace).

Table 16 Goiter prevalence and iodine excretion in schoolchildren in the USA[a,b]

Study area	No. examined	Percentage with goiter	No. tested	Urinary iodine excretion[c] μg/g creatinine	Urinary iodine excretion[c] μg/day[d]
Tecumseh, Michigan	1,147	9.8	212	535 ± 193	567 ± 210
Brethitt County, Kentucky	1,267	8.4	164	497 ± 231	472 ± 208
Newton County, Texas	809	8.3	58	392 ± 203	381 ± 191
Guadalupe County, Texas	1,967	6.6	150	433 ± 185	436 ± 224
Savannah, Georgia	2,595	4.4	170	344 ± 213	358 ± 350
All areas	7,785	6.8	754	452 ± 219	459 ± 249

[a]From (170); reproduced by the kind permission of the authors and the editor of *Pediatrics*.
[b]Age 9–16 years. Individual iodine excretion in 3 urine samples varied from 98–2,293 μg/g creatinine.
[c]Mean ± SD.
[d]Calculated value. Differences between means were significant ($P < 0.005$).

Sources of iodine in food The FDA "Total Diet Study" is also known as "Market Basket" study based on four-week supplies of food adequate for 15–20 year old males and consisting of 117 food items (allowing a high calorie diet of 3900 kcal/day, and permitting extrapolation for lower calorie intakes). The toddler's diet contains 100 different foods for the two-week supply of a two-year-old child, while the infant diet contains 50 foods for a normal two week intake of a six month old baby (137). The 1980 USRDA of iodine for adults, toddlers and infants was 150, 70, and 40 μg, respectively (Tables 17, 18).

All other nutrients contain manyfold smaller, practically insignificant amounts of iodine. Iodized salt is rarely added to industrially processed food. Although in 1978–79 about 62.8% of all table salt was iodized. The average per capita consumption of iodized salt has been 2.4 g, 1.7 g, and 1.5 g in 1959, 1969–70, and 1978–79, respectively (69). Thus a consumer of iodized salt received in 1978–79 on the average 115 μg of iodine per day from table salt.

Table 17 Daily iodine intake as a percent of iodine μg of the 1980 USRDA

Age Group	Year 1975	1976	1978	1979
Adults[b]	428	—	487	294
Toddlers	589	769	1040	464
Infants	840	953	1280	398

[a]From FDA "Total Diet Study"–"Market Basket Study" (137); reproduced by permission of the author and the editor of *FDA Bylines*.
[b]Based on 2800–3000 kcal/day.

Table 18 Percent contribution of total iodine by commodity groups[a,b]

Age and commodity groups	Year 1975	1976	1978
Adults			
Dairy products	50.4	—	56.1
Meat, fish, poultry	10.7	—	10.8
Grain and cereals	16.0	—	16.1
Sugar and adjuncts	12.7	—	10.7
Toddlers			
Whole milk	45.7	44.2	47.0
Dairy products and substitutes	11.8	17.5	8.6
Meat, fish, poultry	8.6	7.3	6.7
Grain and cereals	12.5	20.8	27.7
Infants			
Whole milk	63.8	68.8	74.4
Dairy products and substitutes	21.3	16.1	6.1
Meat, fish, poultry	5.4	5.0	4.9
Grain and cereals	2.6	6.1	7.0

[a]From FDA "Total Diet Study"–"Market Basket Study" (137); reproduced by the kind permission of the author and the editor of *FDA Bylines*.
[b]The commodity groups represent the four largest sources of iodine.

These studies indicate a continuous increase in total iodine intake by infants and toddlers between 1975 and 1978, reaching a level several times that of the USRDA, but a significant decrease in iodine intake in all three groups was observed in 1979 studies. In addition, one must add that the total amount of bioavailable iodine is not known because, e.g., red dye #3, erythrocine, (2,4,5,7 tetraiodofluorescein), much used in coloring medicines, ice cream, cereals, etc. contains 58% of iodine that is not bioavailable in man (56).

The main adventitious sources of iodine in food are milk and dairy products, bread and bakery products, canned fruit, iodine in drinking water, and possibly iodine as an environmental pollutant.

The iodine content of milk in 1952 was about 210 μg/liter (103). In 1973, Van Patten (175) of the Dairy Division of the Michigan Department of Agriculture reported that the average mean iodine content of raw milk from 25 individual producers was 565 μg/liter (range 111–2320 μg). Raw milk from 14 dairy companies was 729 μg/liter (range 500–1100 μg), and vitamin D milk from 25 dairy companies was 823 μg/liter (range 400–1230 μg). The raw milk of one producer contained over 4000 μg iodine/liter on two occasions. The reported iodine content of milk varies widely from area to area, and interstate variations are substantial.

The iodine content of bread and bakery products increased due to the use of iodates as dough conditioners in the conventional, and especially in the con-

tinuous-mix, vacuum process (51). Also, iodine containing sanitizing agents has been used for bakery equipment. The average iodine content of bread by continuous-mix process is about 5–8 mg/kg. More recently, companies are using azodicarbonamide in combination with bromates, or encapsulated ascorbic acid, as dough conditioners (51). Many cereals, fruits, beverages, and ice cream, etc. are colored with red dye #3(erythrocine). Its iodine is not bioavailable (56).

About 98 μg of potassium iodide is added to some canned fruit or cereal for taste improvement (28).

Drinking water in some National Parks and small communities may contain 1 mg iodine/liter water. Adding such amounts of free iodine to drinking water represents a cheaper and technically more simple method of disinfection of smaller quantities of water than the usual chlorination of water used in larger cities.

In 1965, industry in the United States used about 1,500,000 kg of iodine (121). The destiny of that huge amount of this hallogen is not known. However, it is likely that a considerable fraction is disposed of in sewage. If so, the use of processed sewage as fertilizer may increase the iodine content of water, plants, and air.

The main sources of iodine in milk and dairy products are the following: *(a)* idophors, which liberate volatile iodine in an aqueous solution and have a biocidal effect. It serves as a cleansing agent for teats and udders as well as for sanitation of milking machines and industrial dairy equipment; *(b)* ethylenediamine dihydroiodide, which is used for the prevention and therapy of lumpy jaw (actinomycosis) and foot-rot (necrobacilosis) (51). It contains 5% bioavailable iodine and its daily doses are 50–200 mg. A recent study by Hillman and Curtis illustrates the metabolism of ethylenediamine dihydroiodide (67) (see Table 19).

Table 19 Excretion of iodine in milk and urine in groups of cows from herds in Michigan, fed normal requirement and high prophylactic amounts of iodine[ab]

	Normal		High		
	Mean±	Range	Mean±	Range	P
Iodine intake (mg/day)	16.01±1.04	11.0–25.0	164.34±18.60	74–402	0.001
Milk iodine (mg/kg)	0.37±0.03	0.1–1.0	2.16± 0.25	0.3–6.4	0.001
Urinary iodine (mg/kg)	1.87±0.19	—	6.81± 0.9	—	0.001
Average milk/cow/day	19.6 kg	—	18.9 kg	—	NS
Average milk fat (%)	3.6		3.6	—	NS

[a]From (67); reproduced by the kind permission of the author and the editor of the *Journal of Dairy Science*.

[b]Groups of 45 animals each, studied 21 days. Normal iodine requirement: iodine in protein concentrate, salt, and mineral supplements. High prophylactic amounts of iodine: ethylenediamine dihydroiodine plus normal iodine requirement.

Recently, several experimental reports indicate that high iodine content in cattle feed (164–1250 mg/day) is responsible for the following disorders of cattle:

1. Iodism with severe lacrimation, salivation, and increased bronchial secretion complicated by pulmonary infections (68).
2. Iodide goiter with or without hypothyroidism (characterized by involuted colloid goiter with large follicles, sometimes dry, scaly skin, hair loss, and swelling around the eyes) (94, 105).
3. Iodine-hyperthyroidism accompanied by marked exophthalmus, (owing to accumulation of fat behind the eyeballs), tachycardia, tachypnea, increased temperature, and loss of weight. A temporary increase in milk production is followed by eventual considerable decline (68).
4. Disturbance of the autoimmune system. This was studied by Haggard et al (62) in groups of calves fed 0, 50, 250 and 1250 mg of iodine per day for six months. Experimental animals receiving 1250 mg of iodine developed a decrease in cell-mediated and humoral responses as determined by *(a)* antibody titers to brucella and leptospira organisms; *(b)* stimulation of lymphocytic mitoses with pokeweed, phytohemaglutinin (PHA), convacalin mitogens, and intradermal PHA responses; *(c)* in vitro phagocytosis of candida albicans by white blood cells; and *(d)* total white blood count.

Obviously, these observations are of great concern to veterinary medicine and the economy in general. According to Huxley's dictum, one should not humanize the rat nor animalize man, but iodine nutriture of man and animal are two closely interrelated subjects. Proper iodine nutrition of both man and animal should be based on a rational national and international policy as an integral part of a world-wide renaissance of nutrition.

It is important to note that, at present, in spite of high intake of iodine in human nutrition, there is no evidence of its contributing to iodism, goiter and/or other thyroid diseases. Children, given 2.0 mg of iodine per day exhibited a reduced thyroidal ^{131}I uptake for several weeks (155). This phenomenon is not pathological per se, yet nutritional data indicate that the child's thyroid might be exposed to similar amounts of iodine in food for a long time and perhaps respond with a Wolff-Chaikoff mechanism (189).

The increased sensitivity of the fetal thyroid to large amounts of iodine was observed at the turn of the century, when newborns had large goiters because pregnant women were given hundreds of mg of iodine for prevention of congenital goitrous cretinism (6). This phenomenon had a delaying effect on the introduction of iodized salt prophylaxis. Such goiter was reproduced experimentally by injecting iodine into hatching eggs. With a constant high concentration of iodine in the egg, all chickens were hatched goitrous and hypothyroid (187). At present, nutritional iodide goiter in the newborn is rare.

Vitamin supplements given to pregnant women do not contain large amounts of iodine.

Development of endemic goiter due to large amounts of iodine from adventitious sources in human food has not been reported. Iodine intake from conventional food sources is much smaller than that from kelp. One case of sporadic goiter was reported after an intake of only 500 μg of iodine per day for three months (189). It is not known whether prolonged consumption of 1–10 mg of iodine could cause goiter development in individuals with some familial or acquired thyroid disorders.

In a significant number of individuals with Hashimoto's thyroiditis, a relatively small dose of 500 μg of iodine can aggravate a latent or overt disturbance in organification of ^{131}I for several hr (165). It is not known whether a chronic intake of 1.0–2.0 mg iodine per day in food can contribute to a further enlargement of Hashimoto's goiter. This subject deserves more attention because of the general impression that 20–30% of all thyroid enlargements in the USA are due to Hashimoto's thyroiditis.

It is possible, but not proven, that high iodine content of the thyroid in Graves' disease may prolong the therapy with antithyroid drugs. It is also known that hyperthyroid patients, treated surgically or with radioactive iodine may develop hypothyroidism when exposed to large pharmaceutical doses of iodine over a prolonged period of time. It has not been established whether present amounts of iodine in food can cause that effect.

Differentiated thyroid carcinoma is about twice more common in Iceland than in northwestern Scotland (188); and in Hawaii than in the continental United States (110). The iodine intake in these two islands is considerably higher than in their counterpart countries. This is important circumstantial evidence, but the cause and effect relationship requires experimental confirmation.

Very large doses of iodine (1 g) can aggravate hypocomplementic vasculitis (34). The amounts required sets this phenomenon apart from effects of high nutritional iodine intake.

One is reminded of the wise definition of multiple causation by J. Huxley. The questions of the effect of many goitrogenic agents in minute amounts has not been scientifically documented in endemic goiter development.

METHODS FOR PREVENTION OF ENDEMIC GOITER

According to Aristotle in *Nicomachean Ethics,* "A man is the origin of his action" (3). Our philosophy of life must be brought face-to-face with our science. Effective and practical measures for control of endemic goiter were known long before their rationale was understood. Today, advances in our

understanding of the causation of goiter have far outstripped our progress made in its control.

Prevention of Iodine-Deficient Goiter

Iodine deficiency is the *dominant* cause of endemic goiter. David Marine was absolutely right in his contention that simple replenishment of this halogen is in most cases sufficient to eliminate endemic goiter. There are numerous practical methods for supplementing the intake of iodine.

IODIZED SALT The most widely used natural, safe, cheap, practical, and technically simple supplementation of iodine is via salt. In areas of endemic goiter, all salt for human and animal consumption should be enriched with iodine. "*Vollsalz*" or complete salt is the Swiss name for such salt. The compounds of choice are iodides and iodates of potassium, sodium, and calcium. They can be added by spray-mixing, drip-feeding, and dry-blending methods. In areas with an average temperature and humidity, iodization of pure, dry, and fine powdered rock or sea salt is most simply done by spray-mixing with potassium iodide, which is preferable to the more hygroscopic sodium iodide. By adding various stabilizing agents and/or with special packaging, moist acid salt containing iodide oxidating impurities can be iodized with potassium iodide, but this procedure costs more than the salt itself.

If any or several of the above specifications are not met, the iodation is best carried out with potassium iodate. The cheapest method for iodation of coarse sea salt is by the drip-feed method which, however, cannot uniformly iodate the fine powdered table salt. Dry-blending with iodate is also practical, but must be done in two steps or else the mixing time will be prolonged.

The dose of iodine in salt should meet the daily nutritional requirement and the empirically established losses due to the quality of the iodine compound and of the salt, storage time, processing, and cooking of food. The concentration of iodine in salt depends on daily and seasonal consumption of salt and whether iodine is added to all salt or only to table salt. This method of supplementation of iodine is obviously not possible in remote areas where nonsalt cultures still exist. Further detailed and especially technical and cost aspects of supplementation of iodine in salt are available in excellent recent publications (40, 70).

IODINATION OF BREAD In societies where home-made bread has been completely replaced by bakery bread, the addition of iodate to bread can ensure reliable supplementation of iodine. However, infants may not eat bread in sufficient quantity to depend on this as the source of iodine. Other age groups may differ in its consumption.

IODINE IN CANDIES In the past, iodinated sweets were given once a week to schoolchildren. The method suffered from two deficiencies: it was limited to one part of population, although the one at great risk of goiter; and it was too dependent on teacher-pupil cooperation.

IODINATION OF THE LARGE COMMUNITY WATER SUPPLY This has been tried, but was found technically complex and wasteful because drinking water represented a small fraction of total water supply.

IMPORT OF FOOD FROM IODINE RICH AREAS AND PROMOTION OF CONSUMPTION OF SEA FOOD Intrinsic food sources of iodine, e.g., fish, crab, and kelp have played an important role in the reduction of goiter prevalence ("the automobile chased the goiter"), but were the result of increased trade and improved food marketing without a specific aim of prevention of the disease.

IMPORT OF KELP Around many countries, about 50–75 feet below the surface of the sea grow enormous quantities of seaweed (brown kelp). Kelp is nutritious, and contains enough usable proteins, carbohydrates, minerals, and vitamins. It has a pleasant oyster-like taste. Harvesting it for use in less developed countries is beneficial. All its iodine is in an inorganic form. Wide use requires understanding of its iodine content and use level, however.

IODINATED OIL The iodized ethyl esters of fatty acids of poppyseed oil have been used as an X-ray contrast medium. In 1963, McCullagh in Papua, New Guinea started to inject this oil (475 mg iodine per ml, i.e., 37% iodine by weight) in 5 ml intramuscular injections for therapy and prevention of endemic goiter and cretinism (116, 117). This mode of administration of iodine has been extended to remote areas with severe endemic goiter and cretinism in Peru, Ecuador, Bolivia, Brazil, Argentina, Zaire, Nepal, and Gilgit, in Pakistan; the doses used have varied from 0.2–0.5 ml for infants to 1.0–5.0 ml for adults. The iodized oil is injected in the buttocks in small children and the deltoid muscle of the adults. Oil should not get into the blood vessels, but large needles must be used. The oil is stored in the muscle and intermuscular fibrous tissue. During the first few months, there is a large breakdown of the iodinated compounds and urine may contain 1–5 mg of iodine per day. Thereafter the excretion of iodine decreases, and depending on the initial dose, the urine may contain some 50 μg iodine per day for 2–5 years. After injection of iodized oil, the serum protein bound iodine becomes elevated, and the serum T_4 and T_3 increase to normal levels. In a few Nepalese Himalayan patients, Ibbertson (73) observed a lowering of serum T_3 and an increase of TSH (without change in serum T_4) about 4–10 days after injection of iodized oil. That phenomenon

suggested an acute Wolff-Chaikoff effect with inhibition in synthesis and release of T_3 with consecutive rise in serum TSH. The raise of TSH persisted in 25% of individuals (mostly children) for several months. Soon after injection of iodized oil, levels of both serum T_3 and T_4 were above normal in a few patients, none of whom developed hyperthyroidism.

This administration of iodine is also used in areas of nonsalt cultures, no-money economy, or where salt is too expensive. Iodized oil prevents endemic cretinism if administered before conception. An improvement of IQ of children was observed (66). Goiter in treated children and adolescents involutes completely and considerable reduction in prevalence and size of goiter follows in the adult population. In Argentina, 220 children were given 0.7 ml iodized oil per os, and decrease of goiter was observed. The ratio of effectiveness of the injected and oral doses was 1:1.4.

Adverse effects have been relatively rarely observed. During the last seven years, several hundred thousands of individuals were injected and reinjected with iodized oil. Only 30–40 cases of iodine-hyperthyroidism (Jod-Basedow) were reported, surprisingly without mortality even in hot and humid climates. Improvement occurred spontaneously or with regular therapy. To avoid this complication, individuals over age 45 most likely to have "hot" autonomous nodules were not treated. Neither iodism and iodide-thyroiditis nor iodide goiter were observed. When pregnant women were injected with iodized oil, their serum inorganic iodine as well as milk inorganic iodine were high, but no harmful effect was observed in the newborn and infants. Some mental and neural abnormalities in small children of Ecuador could not be eliminated (66), but their cause(s) may be some other nutritional deficiencies.

Sterile inflammation at the site of oil injections have rarely occurred. Most investigators were impressed with the cooperative, trusting attitude of the population reflected in a participation rate up to 80%. The medication is cheap, costing only a 7–9 US cents per dose. Special teams visit the villages and can administer up to 500 injections per day. Recurrence of iodine deficiency begins if the injection is not repeated within five years, but the serum thyroxine level remains normal for a longer time, suggesting that the thyroid has large stores of iodine in the form of hormones and their precursors.

These data are truly remarkable because, in the past after introduction of iodine prophylaxis, most areas with severe to moderately severe iodine-deficient goiter have had a period of several years of increased incidence of hyperthyroidism. In Tasmania, introduction of iodized bread was followed by a two- to threefold increase in incidence of iodine hyperthyroidism (Jod-Basedow) from 1967–1971 in the elderly (3.8 times), and Graves' disease in younger individuals (1.6 times) (177). In a study of 30 patients from November 1970 to December 1971 by Adams et al (1), using ^{131}I thyroid scan and measuring LATS (serum globulin capable of TSH-like delayed stimulation of

the thyroid in mice) and LATSP (immunoglobulin that competes with LATS for receptor), the authors concluded that 16 patients had or were developing Jod-Basedow and 14 probably had Graves' disease. The average intake of iodine in bread was 139 μg (range 32–544 μg), but it is possible that the use of iodophors contributed to slightly higher total iodine intake.

From these still incomplete data, one may tentatively assume that the following factors could be responsible for lack of complications due to large doses of iodized oil: *(a)* Graves' disease is still rare in the non-industrialized societies; *(b)* severe iodine deficient goiter contains less autonomous areas ("hot nodules") to develop iodine hyperthyroidism; *(c)* large doses of iodine may inhibit directly the secretion of hormone from autonomous or TSH-dependent hot nodule; *(d)* some patients, due to malnutrition, do not respond with hyperthyroidism; *(e)* some patients are lost to follow-up; and *(f)* finally, some combinations of nutritional, biological, and evolutionary factors may be responsible for this unusual phenomenon.

The first goiter prophylaxis, in the 1850s, with 10 gm KI/kg salt and open bottles with elemental iodine in bedrooms and schools in two counties in France ended disastrously because of many severe cases of iodism and hyperthyroidism (41). Oil, as a carrier of pharmacological doses, offers markedly contrasting toxicity. It has become a necessary method in numerous areas of central, northeast, and southern Africa, where the precolonial scarcity of salt persists (17). It is estimated that at present, the total salt production in Africa is 100,000 tons lower than the calculated alimentary requirement. Actually, the nutritional deficit of salt is probably even greater, as much salt is used in nonfood industries. In some "more developed" regions, the alimentary/industrial ratio of salt utilization is 1:3 to 1:25 (40).

Nonsalt cultures exist in some ethnic groups of the Szechwan province of West China (125), of Africa (134), and in some tribes of Melanesia (104), Polynesia (146), the Solomon Islands (135), and especially in New Guinea (116, 117). Also, salt is a precious commodity for poorer families in remote communities in the foothills of the Himalayas (29, 108). According to Oliver et al (132, 133), the Yanomama Indians, in 150 villages in the northern Brazilian and Venezuelan jungle area of about 100,000 square miles, represent a society without salt as a food additive except for limited use in the border area inhabited by Caucasians since 1950. The stress induced on sodium balance during pregnancy and lactation causes pronounced hormonal adaptation in the Yanomama Indians, when compared to pregnant Guaymi Indians of Panama, who for generations have been consuming unlimited amounts of salt. The average 24 hr urinary excretion of sodium in Yanomama males and females, as well as in pregnant females, was 1 meq. The urinary excretion of aldosterone was extremely elevated, coupled with higher serum renin and aldosterone concentrations when compared with nonpregnant Yanomama and pregnant Guaymis.

The serum sodium and potassium in female and male members of the Yanomama and in members of the research team were not significantly different (141.1 ± 4.1 and 5.3 ± 0.5 meq/liter versus 143.0 ± 2.5 and 5.7 ± 0.5 meq/liter, respectively).

In the Guaymi Indians of Panama and members of the research team who consumed an average amount of salt, the average urinary sodium excretion was 60–140 times higher than in the Yanomama. Urinary potassium excretion, although normal in the control groups, was 4–6 times higher in the Yanomama. Correspondingly, the concentration of aldosterone of the control groups was 10 times lower in the serum and about 12 and 5 times lower in the urine than in the Yanomama population. There was no significant difference in blood pressure in the Guaymi and the researchers (116.0 ± 4.3, 117 ± 1.4) versus the Yanomama (110.3 ± 11.8). The blood pressure was not significantly different in pregnant Yanomama and Guaymi Indians, but the homeostatic hormonal responses and consequent changes in mineral concentrations were more pronounced in the Yanomama during pregnancy and lactation. Importantly, the mothers and their infants were healthy, without evidence of any adverse effect from salt deficiency. This is true of other societies with salt-free cultures, and exemplify successful adaptation to a vegetarian diet (133).

The experimental observations comparing blood pressure and homeostatic mechanisms in a salt-free society with a control population that had freely consumed salt for many generations is relevant to prophylaxis of iodine-deficient goiter with iodized salt. No data are available, however, on size of the adrenal gland and its structure in populations living practically on a vegetarian salt-free diet. It is of interest that Prior et al (146) observed two ethnically similar populations in the Polynesian Islands, Rarotonga and Pukapuka, that differ socially, economically, and in their dietary habits. An increase in systolic and diastolic pressure with age was significantly higher in the Rarotonga women than in those on Pukapuka, corresponding with their higher sodium intake (120–140 meq versus 50–70 meq). No correlation between sodium excretion and blood pressure was observed within the same population. Although the Raratonga live in towns and have a cash economy and the Pukapuka live at a subsistence level, there is no marked difference in their body build. Therefore, the authors consider that the difference in blood pressure in these two populations is compatible with Dahl's hypothesis that higher blood pressure is related to greater salt consumption.

Warren & O'Connor recently postulated, from clinical and epidemiogical data, that higher incidence and severity of essential hypertension in the black population of the United States is due to genetic factors. The patients show a striking prevalence of low renin, combined with volume expanded hypertension, and an increased tendency for sodium retention. The authors suggest a deficiency in the natriuretic and renal kalikreinkinin vasodilatory system as the

cause of this phenomenon. This constellation of factors could have a survival value in a sodium-poor and potassium-rich subtropical environment, but may represent a serious disadvantage when black people live on the high-sodium, low-potassium diet of the Western world (185).

More study is needed in this field. Prophylaxis of endemic goiter with iodized salt may in some areas depend on the realities of salt metabolism in certain groups of populations.

Elimination of Natural Goitrogens

This enormously important subject was touched upon in the description of natural food goitrogens. Solution of this problem must become of primary concern to experts and authorities responsible for feed and food production. The solution rests with developing simple and effective detoxifying procedures for goitrogenic nutrients processed at home and industrially, and selective breeding of plants free from goitrogens. Prevention of goiter caused by bacterial goitrogenic compounds can be achieved by digging deep artesian wells and by a bacteria-free water supply.

The prevention of goiter from organic disulfides of saturated and unsaturated hydrocarbons from sedimentary rocks drained by deep well waters requires biological study of such waters. The Romans, before founding a community, autopsied and examined the livers of rabbits and pheasants from the local area to ascertain whether the air and water were conducive to good health (97).

Prevention of Feed and Food Pollution with Synthetic Goitrogens

The correction of this serious damage to fish and bird predators by a variety of compounds and possibly by chemicals in the future is a difficult problem of environmental pollution in general. Nutritionists, veterinarians, and physicians should carefully monitor the content of these compounds in feed and food, as well as in the blood and fat of fish, animals, and man, and they should develop continuous consultation—promoting decontamination and prevention policies. Excessive administration of these compounds to domestic animals should be prohibited.

SIMPLE GOITER: THE EASIEST OF ALL KNOWN DISEASES TO PREVENT

In the above statement, David Marine (109) postulated that the policy on prevention of endemic goiter should combine scientific concepts and technological methods with social and philosophical awareness of human values. An elaborate policy of prevention of endemic and sporadic goiter should supersede the elementary goiter prevention program of iodization of salt or any other

vehicle for this micronutrient. The policy on goiter should prevent deficiency of and flooding with iodine, as well as include the elimination of antithyroid effects of goitrogens, ionizing irradiation, and all other factors adverse to the thyroid presently known or yet to appear in the future.

GOITER PREVENTION POLICY IN "LESS DEVELOPED" COUNTRIES The work enthusiastically initiated and supported by the WHO, UNICEF, FAO, and other agencies should obviously be intensified and expanded across all political borders and natural, physical, and psychological barriers. Good will, knowledge, experience, financial, and technical help should be offered and accepted on humanistic principles.

These countries need help, starting at the epicenters of endemic goiter and their most affected environs. This help should also include the metropolitan areas. Except for the absolutely and completely isolated communities, prevention of iodine-deficient goiter should be a nutritional program. The "Home of Health" should become the first, no matter how simple, public health institution, devoted for the time being to all preventive medicine measures and education. Its leaders and workers should be members of the community, helped by centrally trained laymen and, whenever possible, professionals.

Iodization of coarse salt, if needed, can be undertaken safely even at a community level. It should be carried out under supervision. Participation of villagers should be encouraged, and they should at the same time be instructed in the prevention of infectious diseases from water and food as well as improvement of agriculture and animal husbandry (167).

The iodinated oil program is only temporarily indispensable in some areas. The population receives this valuable help passively, and at intervals of several years, as well as by changing personnel and with the least possible expenditure of time. It offers little opportunity for education. The history of the vaccination programs in the Western world is an example of the decreasing interest of the public as soon as the imminent danger is over.

GOITER PREVENTION POLICY IN MORE DEVELOPED COUNTRIES Prevention of endemic goiter caused by natural, and especially synthetic goitrogens, and by ionizing irradiation remains a challenge that the more developed countries should meet with common sense.

Finally, all countries of the world should embrace the "Global Strategy for Health for All by the Year 2000," launched in 1979 by the World Health Organization and adopted by the United Nations General Assembly (192). The fundamental right to health for every human being as a worldwide social goal should also include freedom from endemic goiter, cretinism, and deaf-mutism. Thus in a higher sense, Health should become the ideal of the culture of all mankind at the dawn of the third millennium.

Literature Cited

1. Adams, D. D., Kennedy, T. H., Stewart, J. C., Utiger, R. D., Vidor, G. I. 1975. Hyperthyroidism in Tasmania following iodine supplementation. Measurements of thyroid-stimulating antibodies and thyrotropin. *J. Clin. Endocrinol. Metab.* 41:221–28
2. Allen-Rowland, C. D., Castracane, V. D., Seifter, J. 1979. In *Programs and Abstracts,* p. 301. Anaheim: Endocrine Soc.
3. Aristotle. 1962. *Nicomachean Ethics,* ed. M. Otswald. Indianapolis, Ind:Bobbs Merrill
4. Astwood, E. B. 1943. The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharmacol. Exp. Ther.* 78:79–89
5. Astwood, E. B., Greer, M. A., Ettlinger, M. G. 1949. 1-5-vinyl-2-thiooxazolidone, an antithyroid compound from yellow turnip and Brassica seeds. *J. Biol. Chem.* 181:121–30
6. Astwood, E. F., Raben, M. S. J. 1953. Teaching clinic. *J. Clin. Endocrinol. Metab.* 13:469–77
7. Axelrad, A. A., Leblond, C. P. 1955. Induction of thyroid tumors in rats by a low iodine diet. *Cancer* 8:339–67
8. Bahn, A., Mills, J. L., Snyder, P. J., Gann, P. H., Houten, L., Bialik, O., Hollman, L., Utiger, R. 1980. Hypothyroidism in workers exposed to polybrominated biphenyls. *New Engl. J. Med.* 302:31–33
9. Baker, H. J., Lindesy, J. R. 1968. Equine goiter due to excess of dietary iodine. *J. Am. Vet. Med. Assoc.* 153:1618–30
10. Barnhard, C. L., ed. 1964. *The American Dictionary.* NY: Random House
11. Bastenie, P. A., Ermans, A. M., Thys, O., Beckers, C., Van de Schriek, H. G., de Visscher, M. 1962. Endemic goiter in the Uele region. III. Endemic cretinism. *J. Clin. Endocrinol. Metab.* 22:187–94
12. Bastomsky, C. H. 1977. Goitres in rats fed polychlorinated biphenyls. *Can. J. Physiol. Pharmacol.* 55:288–95
13. Bastomsky, C. H., Murthy, P. V. N., Banoval, K., 1976. Alterations in thyroxine metabolism produced by cutaneous administration of microscope immersion oil: effects due to polychlorinated biphenyls. *Endocrinology* 98:1309–14
14. Beckers, C., Benmiloud, M. 1980. The present status of endemic goiter as a problem of public health: Africa. In *Endemic Goiter and Endemic Cretinism,* ed. J. B. Stanbury, B. S. Hetzel, pp. 69–78. NY: Wiley
15. Bielschowsky, F., Griesbach, W. E., Hall, W. H., Kennedy, T. H., Purves, H. D. 1949. Studies on experimental goitre. The transplantability of experimental thyroid tumours of the rat. *Br. J. Cancer* 3:541–46
16. Black, J. J., Simpson, C. L. 1974. Thyroid enlargement in Lake Erie Coho salmon. *J. Nat. Cancer Inst.* 53:725–32
17. Bloch, M. R. 1963. The social influence of salt. *Sci. Am.* 200:88–99
18. Bowland, J. P. 1975. Evaluation of glucosinolate-low erucic acid rapeseed-meal as protein supplements for young growing pigs, including effects on blood serum constituents. *Can. J. Anim. Sci.* 55:409–19
19. Bowland, J. P. 1971. Rapeseed as an energy and protein source in diets for growing pigs. *Can. J. Anim. Sci.* 51:503–10
20. Bowland, J. P. 1974. Comparisons of several wheat cultivars and a barley cultivar in diets for young pigs. *Can. J. Anim. Sci.* 54:629–38
21. Bowland, J. P. 1974. Comparisons of low glucosinolate rapeseed meal, commercial rapeseed meal and soybean meal as protein supplement for growing pigs. *Can. J. Anim. Sci.* 54:679–85
22. Bowland, J. P., Hardin, R. T. 1973. Rapeseed meal as partial replacement for soybean meal in the diets of growing gilts and sows for up to three reproductive cycles. *Can. J. Anim. Sci.* 53:356–63
23. Bridgwater, W., Kurtz, S., eds. 1963. Buddhism, The sermon of the turning wheel of the law. In *The Columbia Encyclopedia,* p. 290. NY: Columbia Univ. Press
24. Buttfield, I. H., Black, M. L., Hoffmann, M. L., Mason, E. K., Hetzel, B. S. 1965. Correction of iodine deficiency in New Guinea natives by iodized oil injection. *Lancet* 2:767–69
25. Buttfield, I. H., Hetzel, B. S. 1967. Endemic goitre in Eastern New Guinea with special reference to the use of iodized oil in prophylaxis and treatment. *WHO Bull.* 36:243–62
26. Buttfield, I. H., Hetzel, B. S. 1971. Endemic cretinism in Eastern New Guinea. Its relation to goitre and iodine deficiency. In *Endemic Cretinism,* ed. B. S. Hetzel, P. O. D. Pharoah, pp. 55–69. Papua, New Guinea Inst. Human Biol.
27. Buzina, R. 1970. Ten years of goiter prophylaxis in Croatia, Yugoslavia. *Am. J. Clin. Nutr.* 23:1085–89

28. Chao, H. M. 1979. Other food colorings, food additives and incidental sources of iodine. Paper presented at the Iodine in American Foods Workshop, Dept. of Foods, Nutr., AMA, Nov. 13–14, Scottsdale, Arizona
29. Chapman, J. A., Grant, I. S., Taylor, G., Khalida, M., Sardar-Ul-Mulk. 1971–72. Endemic goiter in the Gilgit Agency, West Pakistan, with an appendix on dermatoglyphics and taste testing. *Philos. Trans. R. Soc. London, Ser. B* 263:460–91
30. Choufoer, J. C., Van Rhijn, M., Kassenaar, A. A. H., Querido, A. 1963. Endemic goiter in Western New Guinea: iodine metabolism in goitrous and nongoitrous subjects. *J. Clin. Endocrinol. Metab.* 23:1203–17
31. Choufoer, J. C., Van Rhijn, M., Querido, A. 1965. Endemic goitre in Western New Guinea. II. Clinical picture, incidence and pathogenesis of endemic cretinism. *J. Clin. Endocrinol.* 25:385–402
32. Collins, W. C., Capen, C. C., Kasza, L., Carter, C., Dailey, R. E. 1977. Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats. Ultrastructural and biochemical investigations. *Am. J. Pathol.* 89:119–26
33. Correa, P., Llanos, G. 1966. Morbidity and mortality from cancer in Cali. *J. Natl. Cancer Inst.* 36:717
34. Curd, J. G., Milgrom, H., Stevenson, D. D., Mathison, D. A., Vaughan, J. H. 1979. Potassium iodide sensitivity in four patients with hypocomplementemic vasculitis. *Ann. Intern. Med.* 91:853–57
35. Dale, A. 1979. Canola, Canada's rapeseed crop. In *Canola*. Winnipeg: Rapeseed Assoc. Canada, Publ. No. 56:2–39
36. DeGroot, L. J., Stanbury, J. B. 1975. *The Thyroid and Its Diseases*, pp. 37–109. NY: Wiley. 4th ed.
37. Delange, F. 1974. *Endemic Goitre and Thyroid Function in Central Africa*. Basel: Karger
38. Delange, F., Valeix, P., Bourdoux, P., Lagasse, R., Ermans, J. P., Thilly, C., Ermans, A. M. 1981. Comparison of the epidemiological and clinical aspects of endemic cretinism in Central Africa and in the Himalayas. In *Fetal Brain Disorders. Recent Approaches to the Problem of Mental Deficiency*, ed. B. S. Hetzel, R. M. Smith. NY: Elsevier/North-Holland
39. De Leon, R., Retana, O. G. 1974. Eradication of endemic goiter as a public health problem in Guatemala. *PAHO Sci. Publ.* 192:227
40. De Maeyer, E. M., Lowenstein, F. W., Thilly, C. H. 1979. *The Control of Endemic Goiter*. Geneva: WHO
41. De Quervain, F. 1922. Schilddruse und Jod mit Rucksicht auf die Kropfprophylaxe. *Schweiz. Med. Wschr.* 52:857–77
42. Djokomoeljanto, R. 1974. *The effect of severe iodine deficiency; a study on a population in Central Java, Indonesia*. PhD thesis. Univ. Diponegoro di Semarang
43. Ekpechi, O. L. 1967. Pathogenesis of endemic goitre in Eastern Nigeria. *Br. J. Nutr.* 21:537–45
44. Ermans, A. M. 1980. Etiopathogenesis of endemic goiter. See Ref. 14, pp. 287–301
45. Ermans, A. M. 1980. General Conclusions. In *Role of Cassava in the Etiology of Endemic Goitre and Cretinism*, ed. A. M. Ermans, N. M. Mbulamoko, F. Delange, R. Ahluwalia. pp. 1–182. Ottawa, Ontario: Int. Dev. Res. Cent.
46. Etkin, W. 1978. The thyroid—a gland in search of a function. *Perspect. Biol. Med.* 22:19–30
47. Fawcett, D. M., Kirkwood, S. 1953. The mechanism of the antithyroid action of iodide and the "aromatic" thyroid inhibitors. *J. Biol. Chem.* 204:787–96
48. Ferber, E., Matovinovic, J., Kovacic, N., Buzina, R. 1956. Ispitivanje gusavosti u selu Rude kod Zagreba. *Higijena* 7:295–304
49. Filipovic, A., Siljak, D. 1974. Stanje gusavosti u pet hyperendemskih zarista Bosne i Hercegovine na uzorku skolske djece nakon 20 godina jodne profilakse. *Med. Arh.* 28:471–74
50. Fierro-Benitez, R., Ramirez, I., Estrella, E., Jaramilla, C., Diaz, C., Urresta, J. 1969. Iodized oil in prevention of endemic goiter and associated defects with Andean Region of Ecuador. In *Endemic Goiter*, ed. J. Stanbury, pp. 306–40. NY: Wiley
51. Fisher, K. D., Carr, J. C. 1974. Iodine in foods; chemical methodology and sources of iodine in the human diet. Bethesda, MD: Life Sci. Res. Off. Fed. Am. Soc. Exp. Biol.
52. Gaitan, E. 1980. Goitrogens in the etiology of endemic goiter. See Ref. 14, pp. 219–36
53. Gaitan, E., Medina, P., De Rouen, T. A., Zia, M. S. 1980. Goiter prevalence and bacterial contamination of water. *J. Clin. Endocrinol. Metab.* 51:957–61
54. Gajdusek, D. C. 1962. Congenital defects of the central nervous system associated with hyperendemic goiter in a neolithic highland society of the Nether-

lands New Guinea. *Pediatrics* 29:345–63
55. Gajdusek, D. C., Garruto, R. M. 1975. The focus of hyperendemic goiter, cretinism, and associated deafmutism in Western New Guinea. In *Biosocial Interrelations in Population Adaptations*, ed. F. Watts, F. E. Johnston, G. W. Laker, pp. 267–85. The Hague: Mouton
56. Garber, J., Ruiz, M., Iflah, S., Gluckin, D., Ingbar, S. 1981. Effects of erythrosine (2',4',5',7' tetraiodofluorescein; red dye 3) on aspect of thyroid hormone economy in rats and humans. In *Program and Abstracts,* Ann. Meet. Endocrine Society, June 17–19. N. 439, p. 192
57. Goh, Y. K., Clandinin, D. R. 1977. Transfer of ^{125}I to eggs in hens fed on diets containing high- and low-glucosinolate rapeseed meals. *Br. Poult. Sci.* 18:705–19
58. Goslings, B. M., Djokomoeljanto, R., Docter, R., van Hardeveld, C., Hennemann, G., Smeenk, D., Querido, A. 1977. Hypothyroidism in an area of endemic goiter and cretinism in Central Java, Indonesia. *J. Clin. Endocrinol. Metab.* 44:481–90
59. Greer, M. A., Astwood, E. B. 1948. The antithyroid effect of certain foods in man as determined with radioactive iodine. *Endocrinology* 43:105–19
60. Greer, M. A. 1960. The significance of naturally occurring antithyroid compounds in the production of goiter in man. *Rev. Nutr. Res.* 21:61–73
61. Greer, M. A. 1965. Isolation from rutabaga seed of progoitrin, the precursor of the naturally occurring antithyroid compound, goitrin (1-5-vinyl-thiooxazolidone). *Biochemistry* 4:1260–61
62. Haggard, D. L., Stowe, H. D., Conner, G. H., Johnson, D. W. 1980. Immunologic effects of experimental iodine toxicosis in young cattle. *Am. J. Vet. Res.* 41:539–43
63. Hemken, R. W., Vandersall, J. H., Sass, B. A., Hibbs, J. W. 1971. Goitrogenic effects of a corn silage-soybean meal supplemented ration. *J. Diary Sci.* 54: 85–88
64. Hetzel, B. S. 1981. Nutritional problems in China. Unpublished
65. Hetzel, B. S., Hales, I. B. 1980. The present status of endemic goiter as a problem of public health: New Zealand, Australia, Papua, New Guinea. See Ref. 14, pp. 123–53
66. Hetzel, B. S., Thilly, C. H., Fierro-Benitez, R., Pretell, E. A., Buttfield, I. H., Stanbury, J. B. 1980. Prevention of endemic goiter and endemic cretinism. Iodized oil in the prevention of endemic goiter and cretinism. See Ref. 14, pp. 513–32
67. Hillman, D., Curtis, A. R. 1979. Chronic iodine toxicity in dairy cattle: blood chemistry, leukocytes and milk iodide. *J. Dairy Sci.* 63:55–63
68. Hillman, D., Sleight, S. D., Whitehair, C. K. 1979. Iodine nutrition and toxicity in cattle. Cooperative Extensive Service, Michigan State University, E–1335
69. Hoogendoorn, A. L. 1979. Iodized salt. Paper presented at The Iodine in American Foods Workshop, Dept. Foods, Nutrition, AMA, Nov. 13–14, Scottsdale, Arizona
70. Hunnikin, C., Wood, F. O. 1980. Iodization of salt. See Ref. 14, pp. 497–512
71. Hunziker-Schild, H. 1915. Der Kropf, eine Anpassung an jodarme Nahrung. Aprioristische Gedanken über Wesen und Verhütung des Kropfes. Bern: A. Francke
72. Huxley, J. 1964. *Essays of a Humanist,* p. 6. NY: Harper & Row
73. Ibbertson, H. K. 1979. Endemic goiter and cretinism. *Clin. Endocrinol. Metab.* 8:97–127
74. Information Canada. 1975. *Nutrition Canada, Saskatchewan Survey,* Ottawa: Dept. Natl. Health & Welfare
75. Ingbar, S. H. 1972. Autoregulation of the thyroid: the response to thyroid excess and depletion. *Mayo Clin. Proc.* 47:814–23
76. Isler, H. 1959. Effect of iodine in thyroid tumors induced in the rat by a low-iodine diet. *J. Natl. Cancer Inst.* 23:675–93
77. Isler, H., Leblond, C. P., Axelrad, A. A. 1958. Influence of age and of iodine intake on the production of thyroid tumors in the rat. *J. Natl. Cancer Inst.* 21:1065–81
78. Irving, J. O. 1935. Tests of significance for differences between percentages based on small numbers. *Metron* 12:1–94
79. Jaeger, W. 1944. *Paideia: The Ideals of Greek Culture. Vol. 3, Book 4. Greek Medicine as Paideia,* p. 4. (Transl. by G. Highet) NY:Oxford Univ. Press
80. James, W. 1907. *Pragmatism. Lecture 6.* London: Longmans, Green
81. Jefferies, D. J., French, M. C. 1969. Avian thyroid: Effect of pp'DDT on size and activity. *Science* 166:1278–80
82. Karmarkar, M. G., Ramalingaswami, V. 1973. Pathophysiology of Himalayan endemic goitre. *Acta Endocrinol.* 179(Suppl.): 38–39
83. Kelly, F. C., Snedden, W. W. 1960. Prevalence and geographical distribution of endemic goitre. In *Endemic Goitre.*

WHO Monograph Series No. 44, pp. 27–33. Geneva: WHO
84. Kevany, J. P. 1969. Prevention of endemic goiter in Latin America. In *Endemic Goiter*, ed. J. B. Stanbury. Washington DC: PAHO Sci. Publ. 193:78–84
85. Kicic, M. 1977. Problemi hipertireoze u toku uvodenja jodne profilakse endemske tireopatske distrofije. *Vojnosanitetski Pregled* 34:409–13
86. Kicic, M., Ramzin, S., Dordevic, S., Janjic, M., Milutinovic, P., Lazic, R., Holcer, K., Todorovic, M. 1977. Dvadeset godina opste jodne profilakse endemske gusavosti i endemskog kretinizma u Jugoslaviji. *Vojnosanitetski Pregled* 3:401–8
87. Kimbrough, R. D. 1974. The toxicity of polychlorinated polycyclic compounds and related chemicals. *Crit. Rev. Toxicol.* 2:445–60
88. Kochupillai, N., Ramalingaswami, V., Stanbury, J. B. 1980. The present status of endemic goiter as a problem of public health: Southeast Asia. See Ref. 14, pp. 101–21
89. Konijn, A. M., Gershon, B., Guggenheim, K. 1973. Further purification and mode of action of goitrogenic material from soybean flour. *J. Nutr.* 103:378–83
90. Koutras, D. A. 1980. Europe and Middle East. See Ref. 14, pp. 79–100
91. Krusius, F. E., Peltola, P. 1966. The goitrogenic effect of naturally occurring 1-5-vinyl and 1-5-phenyl-2 thiooxazolidone in rats. *Acta Endocrinol.* 53:342–52
92. Kuratsume, M., Masuda, Y., Nagayama, J. 1976. Some of the recent finding concerning Yusho, *Natl. Conf. on Polychlorinated Biphenyls, Chicago, 1975, Proc. sponsored by the Environmental Protection Agency, EPS 560: 6–75*, comp. F. Ayer, pp. 14–29
93. Langer, P. 1980. Eastern and Southeastern Europe. See Ref. 14, pp. 141–53
94. Leung, K., Convey, E. M., Conner, G. H. 1980. Effect of dietary iodine on hypophyseal and thyroid hormone secretions in Holstein-Friesian heifers. *Am. J. Vet. Res.* 41:1402–7
95. Linazasoro, J. M., Sanchez-Martin, J. A., Jimenez-Diaz, C. 1970. Goitrogenic effect of walnut and its action on thyroxine excretion. *Endocrinology* 86:696–700
96. London, W. T., Koutras, D. A., Pressman, A., Vought, R. L. 1965. Epidemiologic and metabolic studies of a goiter endemic in Eastern Kentucky. *J. Clin. Endocrinol. Metab.* 25:1091–97
97. Macaulay, D. 1974. *A Story of Roman Planning and Construction*, p. 8. Boston: Houghton Mifflin
98. Mackenzie, C. G. 1947. Differentiation of the antithyroid action of thiouracil, thiourea and PABA from sulfonamides by iodide administration. *Endocrinology* 40:137–53
99. Mackenzie, C. G., Mackenzie, J. B. 1943. Effects of sulfonamides and thiourea on thyroid gland and basal metabolism. *Endocrinology* 32:185–209
100. Mackenzie, J. B., Mackenzie, C. G. 1944. Effect of prolonged and intermittent sulfonamide feeding on the basal metabolic rate, thyroid and pituitary. *Bull. Johns Hopkins Hosp.* 74:85–97
101. Mackenzie, J. B., Mackenzie, C. G. 1942. The effect of "Sulfa" drugs on the thyroid gland in rats and mice. *Fed. Proc.* 1:121–22
102. Mackenzie, J. B., Mackenzie, C., G., McCollum, E. V. 1941. The effect of sulfanilylguanidine in the thyroid of the rat. *Science* 94:518–19
103. Macy, I. G., Kelley, H., Sloan, R. (quoted by McLester, J. A., Darby, W. J.). 1952. *Nutrition and Diet in Health and Disease*. Philadelphia: Saunders. 6th ed. p. 154
104. Maddocks, I. 1967. Blood pressure in Melanesians. *Med. J. Aust.* 1:1123–26
105. Mangkoewidjojo, S., Sleight, S. D., Convey, E. M. 1980. Pathologic features of iodide toxicosis in calves. *Am. J. Vet. Res.* 41:1057–61
106. Marshall, W. D. 1977. Thermo decomposition of ethylenbisdithiocarbamate to ethylenethiourea in aqueous media. *J. Agric. Food Chem.* 25:357–61
107. Matovinovic, J. 1960. Final Report. Goitre Survey in Lebanon, June 1960. WHO Regional Office for the Eastern Mediterranean. EM/NUT/13, Lebanon 40/R, April 1961
108. Matovinovic, J. 1960. Final Report. Goitre Survey in West Pakistan, May–June 1960. WHO Regional Office for the Eastern Mediterranean. EM/NUT/12, Pakistan 46/R-UNICEF, April 1961
109. Matovinovic, J. 1978. David Marine (1880–1976): Nestor of Thyroidology. *Perspect. Biol. Med.* 21:565–89
110. Matovinovic, J., Child, M. A., Nichaman, M. Z., Trowbridge, F. L. 1974. Iodine and endemic goiter. In *Endemic Goiter and Cretinism: Continuing Threats to World Health*, ed. J. T. Dunn, G. A. Medeiros-Neto, Washington DC: PAHO Sci. Publ. 292:67–84

111. Matovinovic, J., Nishiyama, R. H., Poissant, G. 1970. Transplantable thyroid tumors in the rat: Development of normal-appearing thyroid follicles in the differentiated tumors, and development of differentiated tumors from iodine-deficient, thyroxine-involuted goiters. *Cancer Res.* 30:504–14
112. Matovinovic, J., Ramalingaswami, V. 1960. Therapy and prophylaxis of endemic goitre. In *Endemic Goitre,* pp. 385–410. Geneva: WHO Monogr. Ser. No. 44
113. Matovinovic, J., Trowbridge F. 1980. Present status of endemic goiter as a problem of public health: North America. See Ref. 14, pp. 31–67
114. McCarrison, R. 1906. Observations on endemic goitre in the Chitral and Gilgit Valleys. *Med. Chir. Trans. London* 2:437–70
115. McCarrison, R. 1908. Observations on endemic cretinism in the Chitral and Gilgit Valleys. *Lancet* 2:1275–80
116. McCullagh, S. F. 1963. The Huon Peninsula endemic. I. The effectiveness of an intramuscular depot of iodized oil in the control of endemic goitre. *Med. J. Aust.* 1:769–77
117. McCullagh, S. F. 1963. The Huon Peninsula endemic. IV. Endemic goitre and congenital defects. *Med. J. Aust.* 1:884–90
118. Medeiros-Neto, G. A., Dunn, J. T. 1980. Present status of endemic goitre as a problem of public health: Central and South America. See Ref. 14, pp. 3–29
119. Michajlovskij, N., Sedlak, J., Jusic, M., Buzina, R. 1969. Goitrogenic substances of kale and their possible relations to the endemic goiter on the island of Krk (Yugoslavia). *Endocrinol. Exp.* 3:65–72
120. Michajlovskij, N., Sedlak, J., Kostekova, O. 1969. Effect of thermal treatment on the goitrogenic substances in plant foods. *Rev. Czech. Med.* 15:132–44
121. Miller, W. C. 1965. Iodine. *Min. Yrk.* 1:471–74
122. Moccia, R. D., Leatherland, J. F., Sonstegard, R. A. 1977. Increasing frequency of thyroid goiters in Coho salmon (Oncorhynchus kisutch I) in the Great Lakes. *Science* 198:425–31
123. Money, W. L., Fitzgerald, P. J., Godwin, J. T., Rawson, R. W. 1953. The effect of thiouracil on the collection of radioactive iodine in experimentally induced thyroid tumors. *Cancer* 6:111–20
124. Morris, H. P., Green, C. D. 1951. The role of thiouracil in the induction, growth and transplantability of mouse thyroid tumors. *Science* 114:44–46
125. Morse, W. R., Beh, Y. T. 1937. Blood pressure among aboriginal ethnic groups of Szechwan Province, West China. *Lancet* 1:966–67
126. National Academy of Sciences, Food Nutrition Board. 1971. Iodine nutriture in the United States. Summary of a Conference, Oct. 21, 1970, p. 51. Washington DC: Natl. Acad. Sci.
127. National Academy of Sciences. 1980. *Recommended Dietary Allowances.* Washington DC: Food and Nutrition Bd. Natl. Res. Counc., pp. 147–51. 9th ed.
128. Nelson, N., Hammond, P. B., Nisbet, I. C. T., Sorafim, A. F. 1972. Polychlorinated biphenyls—environmental impact. A review of the panel on hazardous trace substances. *Environ. Res.* 5:249–362
129. News. Antibiotics in the Barnyard. 1980. *Science* 208:376
130. Nisbet, I. C. T., Serafim, A. F. 1972. Rates and routes of transport of PCB in the environment. *Environ. Health Perspect.* No. 21, (Exp. Iss. 1):21–38
131. Oddie, T. H., Fisher, D. A., McConahey, W. M., Thompson, C. S. 1970. Iodine intake in the United States: a reassessment. *J. Clin. Endocrinol. Metab.* 30:659–65
132. Oliver, W. J., Cohen, E. L., Neel, J. V. 1975. Blood pressure, sodium intake and sodium related hormones in the Yanomama Indians, a "no-salt" culture. *Circulation* 52:146–51
133. Oliver, W. J., Neel, J. V., Grekin, R. J., Cohen, E. L. 1981. Hormonal adaptation to the stresses imposed upon sodium balance by pregnancy and lactation in the Yanomama Indians, a culture without salt. *Circulation* 63:110–16
134. Orr, J. B., Gilks, J. L. 1931. Studies of nutrition: The physique and health of two African tribes. *Med. Res. Counc. Spec. Rep.* 155:1–82
135. Page, L. B., Damon, A., Moellering, R. C. 1974. Antecedents of cardiovascular disease in six Solomon Island societies. *Circulation* 48:1132–46
136. Paik, I. K., Robble, A. R., Clandinin, D. R. 1980. Products of the hydrolysis of rapeseed glucosinolates. *Can. J. Anim. Sci.* 60:481–93
137. Penington, J. A. T. 1980. Total diet study. Results and plans for selected minerals in food. *FDA Bylines* 10:179–88
138. Perez, C., Scrimshaw, N. J., Munoz, J. A. 1960. See Ref. 112, pp. 369–78
139. Peter, H. J., Studer, H., Forster, R., Gerber, H. 1982. The pathogenesis of "hot" and "cold" follicles in multinodular

goiters. *J. Clin. Endocrinol. Metab.* 55:941–46
140. Pharoah, P. O. D. 1971. Epidemiological studies of endemic cretinism in the Jimi River Valley in New Guinea. See Ref. 26, pp. 109–16
141. Pinchera, A., MacGillivray, M. H., Crawford, J. D., Freeman, A. G. 1965. Thyroid refractoriness in an athyreotic cretin fed soybean formula. *New Engl. J. Med.* 273:83–87
142. Pittman, J. A., Daily, G. E., Beschi, R. J. 1969. Changing normal values for thyroidal radioiodine uptake. *New Engl. J. Med.* 280:1431–34
143. Podoba, J. 1973. Iodine deficiency, environmental goitrogens and genetic factors in the etiology of endemic goiter. *Acta Endocrinol.* 179(Suppl.): 36–37
144. Prebeg, Z., Bajzer, M., Matovinovic, J., Kovacic, N. 1955. Rasirenost gusavosti medu skolskom djecom u Zagrebu. *Higijena* 7:307–21
145. Pretell, E. A., Moncloa, F., Salinas, R., Guerra-Garcia, R., Kawano, A., Gutierrez, L., Pretell, J., Wan, M. 1969. Endemic goiter in rural Peru: Effect of iodized oil on prevalence and size of goiter and on thyroid iodine metabolism in known endemic goitrous populations. See Ref. 84, pp. 419–36
146. Prior, I. A., Evans, J. G., Harvey, H. P. B., Davidson, F., Lindsey, M. 1968. Sodium intake and blood pressure in two Polynesian populations. *New Engl. J. Med.* 279:515–20
147. Purves, H. D., Griesbach, W. E., Kennedy, T. H. 1951. Studies in experimental goitre: Malignant change in a transplantable rat thyroid tumour. *Br. J. Cancer* 5:301–10
148. Querido, A., Bleichrodt, N., Djokomeljanto, R. 1978. Thyroid hormones and human mental development. Prog. Brain Res. 48:337–44
149. Querido, A., Delange, F., Dunn, J., Fierro-Benitez, R., Ibbertson, H. K., Koutras, D. A., Perinetti, H. 1974. Definition of endemic goiter and cretinism, classifications of goiter size and severity of endemias and survey techniques. See Ref. 105, pp. 267–72
150. Rallison, M., Dobyns, B. M., Keating, F. R., Rall, J. E., Tyler, F. H. 1975. Occurrence and natural history of chronic lymphocytic thyroiditis in childhood. *J. Pediatr.* 86:675–82
151. Riggs, D. S. 1952. Quantitative aspects of iodine metabolism in man. *Pharmacol. Rev.* 4:284–370
152. Roos, A. J., Clandinin, D. R. 1975. Transfer of ^{125}I to eggs in hens fed on diets containing rapeseed meal. *Br. Poult. Sci.* 16:413–15
153. Saint-Lager, J. 1867. *Étude sur les Causes du Crétinisme et du Goître Endémique*, p. 280. Paris:Balliere
154. Saito, K., Jujio, T., Hashizume, I., Yamada, T., Onaya, T., Uehara, T., Kajihara, A., Kojima, A., Takemura, Y. 1972. Studies on goitrogenic action of minocycline and related compounds. *Endocrinology* 90:1192–1201
155. Saxena, K. M., Chapman, E. M., Pryles, C. V. 1962. Minimal dosage of iodide required to suppress uptake of iodine 131 by normal thyroid. *Science* 138:430–31
156. Schaefer, A. E. 1974. The status of salt iodization of PAHO member countries. See Ref. 105, pp. 242–50
157. Sinha, D., Pascal, R., Furth, J. 1965. Transplantable thyroid carcinoma induced by thyrotropin: Its similarity to human Hurthle cell tumors. *Arch. Pathol.* 79:192–98
158. Sonstegard, R. A., Leatherland, J. F. 1976. The epizootiology and pathogenesis of thyroid hyperplasia in Coho salmon *(Oncorhynchus kisutch)* in Lake Ontario. *Cancer Res.* 36:4467–73
159. Squatrito, S., Delange, F., Trimacihi, F., Liss, E., Vigneri, R. 1981. Endemic cretinism in Sicily. *J. Endocrinol. Inves.* 4:295–302
160. Srinivasan, V., Moudgal, N. R., Sarma, P. A. 1957. Studies on goitrogenic agents in food. *J. Nutr.* 61:87–95
161. Stanbury, J. B., Brownell, G. L., Riggs, D. S., Perinetti, H., Itoiz, J., Del Castillo, E. B. 1954. *Endemic Goiter. The Adaptation of Man to Iodine Deficiency*. Cambridge, MA: Harvard Univ. Press
162. Stross, J., Smokler, I. A., Isbister, J., Wilcox, K. R. 1981. The human health effects of exposure to polybrominated biphenyls. *Toxicol. Appl. Pharmacol.* 58:145–50
163. Suwa, J., Koyanagi, T., Kimura, S. 1979. Studies on soybean factors which produce goiter in rats. *J. Nutr. Sci. Vitaminol. (Tokyo)* 25:309–15
164. Suzuki, H., Higuchi, T., Sawa, K., Ohtaki, S., Horiuchi, Y. 1965. "Endemic Coast Goiter" in Hokkaido, Japan. *Acta Endocrinol.* 50:161–76
165. Takeuchi, K., Suzuki, H., Horiuchi, Y., Machimo, K. 1970. Significance of iodide-perchlorate discharge test for detection of iodine organification defect of the thyroid. *J. Clin. Endocrinol. Metab.* 31:144–46
166. Tellez, M., Gianetti, A., Covarrubias, E., Barzelatto, J. 1969. See Ref. 49, pp. 245–51

167. Thilly, C. H., Delange, F., Ramioull, F., Lagasse, R., Luivilla, K., Ermans, A. M. 1977. Strategy of goiter and cretinism control in Central Africa. *Int. J. Epidemiol.* 6:43–53
168. Thrall, J. H., Gillen, M. T., Johnson, M. C., Corcoran, R. J., Wartofsky, L. 1978. Quantitative fluorescent thyroid scanning technique and clinical experience. *Am. J. Roentgenol.* 130:517–22
169. Trowbridge, F. L., Hand, K. A., Nichaman, M. Z. 1975. Findings relating to goiter and iodine in the Ten States Nutrition Survey. *Am. J. Clin. Nutr.* 28:712–16
170. Trowbridge, F. L., Matovinovic, J., McLaren, G. D., Nichaman, M. Z. 1975. Iodine and goiter in children. *Pediatrics* 56:82–90
171. United Nations. 1981. *World Population Trends and Prospects Assessed in 1980. Summary Population Studies No. 78.* NY:U.N. Dept. Int. Econ. Soc. Affairs, ST/ESA/78
172. Van Etten, C. H. 1969. Goitrogens. In *Toxic Constituents of Plant Foodstuffs,* ed. I. E. Liener, pp. 103–34. NY: Academic
173. Van Etten, C. H., Wolff, I. A. 1973. Natural sulfur compounds. In *Toxicants Occurring Naturally in Foods.* Committee on Food Protection, Food and Nutrition Board, National Research Council. Washington DC: *NAS-NRC Publ.* 72:210–34
174. Van Middlesworth, L. 1960. Re-evaluation of certain aspects of iodine metabolism. *Rec. Prog. Hormone Res.* 16:405–31
175. Van Patten, V. K. 1973. *Iodine Survey—Milk Memorandum.* Lansing, MI: Michigan Dept. Health
176. Van Wyk, J. J., Arnold, M. B., Wynn, J., Pepper, F. 1959. The effects of a soybean product on thyroid function in humans. *Pediatrics* 24:752–60
177. Vidor, G. I., Stewart, J. C., Wall, J. R., Wangel, A., Hetzel, B. S. 1973. Pathogenesis of iodine induced thyrotoxicosis. Studies in Northern Tasmania. *J. Clin. Endocrinol. Metab.* 37:901–9
178. Virtanen, A. I. 1961. Über die Chemie der Brassica-Faktoren, ihre Wirkung auf die Funktion der Schilddruse und ihr Übergehen in die Milch. *Experientia* 17:241–51
179. Vought, R. L. 1972. Upward trend in iodide consumption in the United States. In *Trace Substances in Environmental Health,* ed. D. D. Hemphil, 5:303. Columbia: Univ. Mo. Press
180. Vought, R. L., Brown, F. A., Sibinovic, K. H. 1974. Antithyroid compound(s) produced by *Escherichia coli:* Preliminary Report. *J. Clin. Endocrinol. Metab.* 38:861–65
181. Vought, R. L., London, W. T., Stebbing, G. E. T. 1967. Endemic goiter in Northern Virginia. *J. Clin. Endocrinol. Metab.* 27:1381–89
182. Wagner, H. N., Nelp, W. B., Dowling, J. H. 1961. Use of neutron activation analysis for studying stable iodine metabolism in man. *J. Clin. Invest.* 40:1984–92
183. Wahner, H. W., Cuello, C., Correa, P., Wribe, L. F., Gaitan, E. 1966. Thyroid carcinoma in an endemic goiter area. Cali, Columbia. *Am. J. Med.* 40:58–66
184. Walker, C. R. 1976. Pre–1972 knowledge of nonhuman effects of polychlorinated biphenyls. *Proc. Natl. Conf. on Polychlorinated Biphenyls,* EP, (USA) Publ. 560/6–75–004:268–81
185. Warren, S. E., O'Connor, D. T. 1980. Does a renal vasodilator system mediate racial differences in essential hypertension? *Am. J. Med.* 69:425–29
186. Weber, W. J. 1978. Troubled fish in troubled waters: PCBs in the Great Lakes and the control of toxic substances. In *Towards Cleaner Water. Studies in Toxic Substances and Other Contaminants,* ed. J. Wei, 3:26–33. Ann Arbor: Univ. Mich. Res. News
187. Wheeler, F. H., Hoffmann, E. 1949. Goitrous chicken from iodine-injected eggs. *Endocrinology* 45:208–9
188. Williams, E. D., Doniach, I., Bjarnason, O., Michie, W. 1977. Thyroid cancer in an iodide rich area. *Cancer* 39:215–22
189. Wolff, J. 1969. Iodine-goiter and the pharmacological effects of excess iodine. *Am. J. Med.* 47:101–24
190. Wollman, S. H. 1963. Production and properties of transplantable tumors of the thyroid gland in the Fischer rat. *Rec. Prog. Hormone Res.* 19:579–618
191. World Health Organization. 1953. Study Group on Endemic Goiter. Final Report. *WHO Bull.* 9:293–309
192. World Health Organization. 1981. Global strategy for health for all by the year 2000. Geneva: WHO, Health For All Series No. 3
193. Yates, F. 1934. Contingency tables involving small numbers and the x_2 test. *R. Stat. Soc.* 1:217–35
194. Zimmer, H. R. 1948. *Hindu Medicine.* Baltimore:Johns Hopkins Inst. Hist. Med., Johns Hopkins Press. pp. 60–75