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Iodine deficiency and excess, endemic cretinism

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INTRODUCTION

Bernard Courtois, a French chemist, accidentally discovered iodine (atomic weight 126.9) in 1811 while producing gunpowder for Napoleon's army. He was extracting sodium carbonate from seaweed ash to use for manufacture of saltpeter (nitrate). Applying sulfuric acid to clean out the metal vats used to burn the seaweed, he produced an intense violet-colored vapor that cooled into dark violet crystals. He gave the crystalline material to Gay-Lussac who identified it as a new element and named it "iode," from the Greek ιώδης (i.e., *violet*) (1). In 1819, Jean-François Coindet, in Geneva, successfully treated goiter with tincture of iodine. In 1883, Semon suggested that myxedema was due to thyroid insufficiency and the link between goiter, myxedema, and iodine was established in 1896, when Baumann and Roos discovered iodine in the thyroid (1). In the first two decades of the 20th century, pioneering studies by Swiss and American physicians demonstrated the efficacy of iodine prophylaxis in the prevention of goiter and cretinism in populations. The first use of salt iodization as a general public health measure was by the surgeon H. Eggenberger in northern Switzerland in the early 1920s (Fig. 15-1) (1).

THE ECOLOGY OF IODINE

Iodine (as iodide) is widely but unevenly distributed in the earth's environment (2). In many regions, leaching from glaciations, flooding, and erosion have depleted surface soils of iodide, and most iodide is found in the oceans; the concentration of iodide in seawater is ≈50 μg/L. Iodide ions in seawater and coastal seaweed beds are oxidized to elemental iodine, which volatilizes into the atmosphere and is returned to the soil by rain. However, this iodine cycle is slow and incomplete in many regions, leaving soils and drinking water depleted of iodine. Crops grown in these soils will be low in iodine, and humans and animals consuming food grown in these soils become iodine deficient. In plant foods grown in deficient soils, iodine concentration may be as low as 10 μg/kg dry weight, compared to ≈1 mg/kg in plants from iodine-sufficient soils. Iodine deficiency in humans and animals in these areas will persist until iodine enters the food chain through dietary diversification using foods produced outside the iodine-deficient area or addition of iodine to foods (e.g., iodization of salt). Today, iodine is mainly produced from brines in natural gas fields (mainly in Japan) and from Chilean caliche deposits (2).

FIGURE 15-1. The birthplace of iodized salt as a public health intervention: H. Eggenberger and his family iodizing salt for distribution in the Canton of Appenzell, Switzerland, in 1922. (Reproduced with permission from

Zimmermann MB. Research on iodine deficiency and goiter in the 19th and early 20th centuries. *J Nutr* 2008;138[11]:2060–2063.)

DIETARY SOURCES, ABSORPTION, AND METABOLISM OF IODINE

The native iodine content of most foods and beverages is low; commonly consumed foods provide 3 to 80 μg per serving (3). Foods of marine origin have higher iodine content because marine plants and animals concentrate iodine from seawater. However, so-called "sea salt," harvested during evaporation of salt water in coastal areas, typically contains negligible iodine; nearly all the native iodine is lost by sublimation due to prolonged sunlight exposure during production. Major dietary sources of iodine in industrialized countries like the United States and Switzerland are milk and bread (containing iodized salt) (3–5). Most of the iodine in dairy products is adventitious; milk has low native iodine content but this is usually increased by iodine supplements given to livestock as well as by residues of iodine disinfectants used in dairying (5). In many low-income countries, iodized salt used for cooking and seasoning of foods is the main dietary source. Infants during the weaning period may be at risk of iodine deficiency (6), because iodized salt (and, in industrialized countries, iodine in milk) contribute little dietary iodine during this period. To fill this gap, iodine in infant formula milk and complementary foods is likely important (6). Dietary supplements often contain potassium iodide at doses in the range of 100 to 200 μg (7).

In healthy adults, iodide is rapidly and nearly completely absorbed (>90%) in the stomach and duodenum (7). Iodide absorption in the gut is thought to be mainly passive, but active absorption may also occur through the sodium/iodide symporter (NIS) (8) and the sodium/multivitamin transporter (SMVT) (9); both are present in intestinal mucosa. Iodate, widely used in salt iodization because of its high stability during storage in humid conditions, is rapidly reduced in the stomach and absorbed as iodide (10). Organically bound iodine is typically digested and the released iodide absorbed, but some forms may be absorbed intact; for example, ≈70% of an oral dose of thyroxine (T4), is absorbed intact (11). Iodine is cleared from the circulation mainly by the thyroid and kidney, and while renal iodine clearance (RIC) is

fairly constant, thyroid clearance varies markedly depending on iodine intake. In conditions of adequate dietary iodine supply, the healthy thyroid usually takes up <20% of absorbed iodine. In chronic iodine deficiency, this fraction can exceed 80% (12). During lactation, the mammary gland concentrates iodine and secretes it into breast milk to provide for the newborn. The salivary glands, gastric mucosa, and choroid plexus also take up small amounts of iodine.

Iodine in the blood is turned over rapidly; under normal circumstances, plasma iodide has a half-life of ≈10 hours, but this is shortened in iodine deficiency or hyperthyroidism (12). The body of a healthy adult contains up to 20 mg of iodine, of which 70% to 80% is in the thyroid (12). In chronic iodine deficiency, the iodine content of the thyroid may fall to <20 μg. In iodine-sufficient areas, the adult thyroid traps ≈60 μg of iodine/day to balance losses and maintain thyroid hormone synthesis. The NIS, a transmembrane protein in the basolateral membrane of the thyrocyte, transfers iodide into the thyroid at a concentration gradient 20 to 50 times that of plasma (13). It concentrates iodine by an active transport process that couples the energy released by the inward translocation of sodium down its electrochemical gradient to the simultaneous inward translocation of iodine against its electrochemical gradient (13). Metabolism of circulating thyroid hormone in peripheral tissues releases iodine that enters the plasma iodine pool and can be taken up by the thyroid or excreted by the kidney. More than 90% of ingested iodine is ultimately excreted in the urine, with only a small amount appearing in the feces and sweat.

GOITROGENS

Although iodine deficiency is usually the cause of endemic goiter, a variety of naturally occurring compounds and environmental pollutants may disrupt thyroid function and be goitrogenic (see Chapter 13) (14). Cigarette smoking is associated with higher serum levels of thiocyanate that may compete with iodine for uptake via the NIS into both the thyroid and the secretory epithelium of the lactating breast; smoking during the period of breastfeeding is associated with reduced iodine levels in breast milk (15). Various dietary components have been implicated as goitrogens (14). Cruciferous vegetables,

including cabbage, kale, cauliflower, broccoli, turnips, and rapeseed, contain glucosinolates; their metabolites compete with iodine for thyroidal uptake. Similarly, cassava, lima beans, linseed, sorghum, and sweet potato contain cyanogenic glucosides; these may be metabolized to thiocyanates that compete with iodine for thyroidal uptake. For example, linamarin is a thioglycoside found in cassava, a staple food in many developing counties. If cassava is not adequately soaked or cooked to remove the linamarin, it is hydrolyzed in the gut to release cyanide, which is metabolized to thiocyanate. Soy and millet contain flavonoids that may impair thyroid peroxidase activity. Use of soy-based formula without added iodine may produce goiter and hypothyroidism in infants, but in healthy adults, soy-based products appear to have negligible effects on thyroid function (16). Most goitrogens are likely to be clinically relevant only if dietary iodine supply is limited and/or goitrogen intake is high and prolonged.

Deficiencies of selenium, iron, and vitamin A exacerbate the effects of iodine deficiency. Glutathione peroxidase and the deiodinases are selenium-dependent enzymes. In selenium deficiency, accumulated peroxides may damage the thyroid and deiodinase deficiency impairs thyroid hormone synthesis; these effects have been implicated in the etiology of myxedematous cretinism (17). Iron deficiency reduces heme-dependent thyroperoxidase activity in the thyroid and impairs production of thyroid hormone. In areas of endemic goiter, iron deficiency anemia blunts the efficacy of iodine prophylaxis while iron supplementation improves the efficacy of iodized oil and iodized salt (18). Pregnant women are highly vulnerable to iron deficiency anemia, and poor maternal iron status predicts both higher thyroid-stimulating hormone (TSH) and lower T4 concentrations during pregnancy in areas of borderline iodine deficiency (19,20). Vitamin A deficiency in iodine-deficient children increases TSH stimulation and risk for goiter through decreased vitamin A–mediated suppression of the pituitary TSHβ gene (21).

IODINE REQUIREMENTS

There are several approaches for describing human iodine requirements (Table 15-1). The World Health Organization (WHO) (22) uses the

recommended nutrient intake (RNI) to define iodine requirements; the RNI is the intake estimated to cover the needs of “nearly all” healthy individuals in the specified life stage. The U.S. Institute of Medicine (IOM) (7) uses the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the adequate intake (AI). The EAR is the daily iodine intake that meets the requirement of half of the healthy individuals in a particular life stage. The RDA is the average daily intake sufficient to meet the iodine requirement of 97% to 98% of healthy individuals in a life stage (7). The AI is used if there is insufficient scientific evidence to calculate an EAR. The AI is expected to meet or exceed the amount of iodine needed in “essentially all” individuals in the specified population group (7).

ADULTHOOD

Iodine turnover, thyroidal radioiodine uptake, and balance studies in euthyroid adults have suggested the average daily requirement for iodine is 91 to 96 µg/day (12). There is no evidence to suggest that the average iodine requirement in adults varies with age. Thus, the EAR for iodine for men and nonpregnant, nonlactating women ≥14 years from the IOM has been set at 95 µg/day (7). The corresponding RDA is 150 µg/day (7). This agrees with the WHO recommendation for adequate daily iodine intake of 150 µg/day for men and nonpregnant, nonlactating women (22).

TABLE 15-1. Recommendations for Iodine Intake (µg/day) by Age or Population Group

Population Group	U.S. Institute of Medicine (7)		Population Group	World Health Organization (22)
	EAR	AI* or RDA		RNI
Infants 0–12 mo	—	110–130*	Children 0–5 y	90
Children 1–8 y	65	90	Children 6–12 y	120

Children 9–13 y	73	120		
Adults ≥14 y	95	150	Adults >12 y	150
Pregnancy	160	220	Pregnancy	250
Lactation	200	290	Lactation	250

EAR, estimated average requirement; AI, adequate intake; RDA, recommended daily allowance; RNI, recommended nutrient intake.

PREGNANCY AND LACTATION

The iodine requirement during pregnancy is increased due to: (1) an increase in maternal T4 production to maintain maternal euthyroidism and transfer thyroid hormone to the fetus early in the first trimester, before the fetal thyroid is functioning, (2) iodine transfer to the fetus, particularly in later gestation, and (3) an increase in RIC (23). The IOM set the EAR at 160 μg/day for pregnancy in women ≥14 years, and the RDA at 220 μg/day (7). WHO recommends a daily iodine intake of 250 μg/day for pregnant women (22). On the basis of mean breast milk excretion of 0.78 and 0.6 L/day in the first and second 6 months of infancy, respectively (7), and a mean BMIC of 146 μg/L in iodine-sufficient women from the United States, the average daily loss of iodine in breast milk has been estimated to be ≈115 μg/day (7). Added to the EAR for nonpregnant women of 95 μg/day, the EAR for lactating women ≥14 years is set at 209 μg/day by the IOM (7), and the RDA is 290 μg/day. WHO recommends a daily iodine intake of 250 μg/day for lactating women (22).

INFANCY AND CHILDHOOD

A recent dose–response crossover study in healthy infants reported that the iodine requirement in 2- to 5-month-old infants is 70 μg/day. Adding an allowance for accumulation of thyroidal iodine stores would produce an EAR of 72 μg and an RDA of 80 μg (24). Thus, it is likely that the current AI of 110 to 130 μg/day for infants (7) exceeds actual infant requirements. Children 8 years of age who consumed ≈40 μg/day of iodine were in negative iodine

balance (−23 to −26 µg/day), suggesting that the average minimum requirement is approximately 65 µg/day (25). Therefore, an EAR of 65 µg/day was set for ages 1 to 8 years (8). For the remainder of childhood and adolescence, the EAR was set by extrapolating down from adult data (8). WHO recommends a daily intake of iodine of 90 µg for preschool children (0 to 59 months) and 120 µg for schoolchildren (6 to 12 years) (22).

ASSESSMENT OF IODINE DEFICIENCY

Four methods are generally recommended for assessment of iodine nutrition in populations: urinary iodine concentration (UIC), the goiter rate, TSH, and thyroglobulin (Tg). These indicators are complementary, in that UIC is a sensitive indicator of recent iodine intake (days) and Tg shows an intermediate response (weeks to months), whereas changes in the goiter rate reflect long-term iodine nutrition (months to years) (12).

URINARY IODINE CONCENTRATION

Because >90% of dietary iodine eventually appears in the urine (12), UIC is an excellent indicator of recent iodine intake. UIC can be expressed as a concentration (µg/L), in relation to creatinine excretion (µg iodine/g creatinine), or as 24-hour excretion (µg/day). For population surveys, UIC can be measured in spot urine specimens from a representative sample of the target group, and expressed as the median, in µg/L (22). Variations in hydration among individuals generally even out in a large number of samples, so that the median UIC in spot samples correlates well with that from 24-hour collections. For national, school-based surveys of iodine nutrition, the median UIC from a representative sample of spot urine collections from ≈1,200 children (30 sampling clusters × 40 children per cluster) can be used to classify a population's iodine status (Table 15-2) (22). Recent data in schoolchildren and adults suggest the WHO UIC categories (Table 15-2) of "adequate" and "more than adequate" iodine intake can be combined into a single category (100 to 299 µg/L) to denote adequate iodine nutrition (26,27). Although the median UIC does not provide direct

information on thyroid function, a low value suggests that a population is at higher risk of developing thyroid disorders.

Although the median UIC is a good indicator of iodine status in populations, its value for assessing individual status is limited by high day-to-day variability in iodine intakes (28). In European adults, intraindividual variation in UIC is ca. 35% for both 24-hour collections and spot samples, so that urine samples from ≈10 different days are needed to assess individual iodine status with 20% precision (28). In population studies, the median UIC is often misinterpreted: A common mistake is to assume that all subjects with a spot UIC <100 μg/L are iodine deficient. But because individual iodine intakes are highly variable from day to day, on any given day, it is inevitable that some individuals will have a low UIC, despite average daily intakes that are adequate to maintain thyroidal iodine stores (28).

TABLE 15-2. Epidemiologic Criteria for Assessment of Iodine Nutrition in a Population Based on Median or Range of Urinary Iodine Concentrations

	Iodine Intake	Iodine Nutrition
School-age Children		
<20 μg/L	Insufficient	Severe iodine deficiency
20–49 μg/L	Insufficient	Moderate iodine deficiency
50–99 μg/L	Insufficient	Mild iodine deficiency
100–299 μg/L	Adequate	Optimum
>300 μg/L	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant Women		
<150 μg/L	Insufficient	
150–249 μg/L	Adequate	
250–499 μg/L	More than adequate	
≥500 μg/L[a]	Excessive	

Lactating Women[b]	
<100 μg/L	Insufficient
≥100 μg/L	Adequate
Children Less Than 2 Years of Age	
<100 μg/L	Insufficient
≥100 μg/L	Adequate

[a]The term excessive means in excess of the amount needed to prevent and control iodine deficiency.

[b]In lactating women, the numbers for median urinary iodine are lower than the iodine requirements, because of the iodine excreted in breast milk.

From World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination. A Guide for Programme Managers*. 3rd ed. Geneva: World Health Organization; 2007; Zimmermann MB, Aeberli I, Andersson M, et al. Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 μg/L: a UNICEF/ICCIDD study group report. *J Clin Endocrinol Metab* 2013;98(3):1271–1280; and WHO Secretariat; Andersson M, de Benoist B, Delange F, et al. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* 2007;10(12A):1606–1611.

BREAST MILK IODINE CONCENTRATION

For the breastfeeding mother, although the iodine requirement is high (250 to 290 μg/day), after accounting for iodine losses into breast milk, the median UIC in lactating women that indicates adequate iodine nutrition is the same as that of nonpregnant, nonlactating women, that is, 100 to 199 μg/L (22). Because the mammary gland is able to concentrate iodine, iodine supply to the newborn via the breast milk may be maintained even in the face of maternal iodine deficiency (29). This may help explain why, in areas of iodine deficiency, BMICs are often greater than expected based on the UIC of the lactating mother (29). For this reason, maternal UIC alone may not accurately reflect iodine status, and BMIC should also be measured to assess iodine status in lactating women (29).

THYROID SIZE

Two methods are available for measuring goiter: neck inspection and palpation, and thyroid ultrasonography. By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined. In the classification system of WHO (22), grade 0 is defined as a thyroid that is not palpable or visible, grade 1 is a goiter that is palpable but not visible when the neck is in the normal position (i.e., the thyroid is not visibly enlarged), and grade 2 goiter is a thyroid that is clearly visible when the neck is in a normal position. Goiter surveys are usually done in school-age children. However, palpation of goiter in areas of mild iodine deficiency has poor sensitivity and specificity; in such areas, measurement of thyroid volume by ultrasound is preferable. Thyroid ultrasound is quickly done (2 to 3 minutes per subject), feasible even in remote areas using portable equipment, and references for thyroid volume are available from iodine-sufficient children (22). In areas of endemic goiter, although thyroid size predictably decreases in response to increases in iodine intake, thyroid size may not return to normal for months or years after correction of iodine deficiency (30). During this transition period, the goiter rate is difficult to interpret, because it reflects both a population's history of iodine nutrition and its present status. A sustained salt iodization program will decrease the goiter rate to <5% in school-age children and this indicates disappearance of iodine deficiency as a significant public health problem (22). WHO recommends the total goiter rate be used to define severity of iodine deficiency in populations using the following criteria: <5%, iodine sufficiency; 5.0% to 19.9%, mild deficiency; 20.0% to 29.9%, moderate deficiency; and >30%, severe deficiency (22).

THYROID-STIMULATING HORMONE AND THYROID HORMONES

Circulating TSH is an indirect indicator of iodine nutrition because its level in blood is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake. However, in older children and adults,

although serum TSH may be variably increased by iodine deficiency, values often remain within the normal range. An elevated TSH is therefore an insensitive indicator of iodine nutrition in adults. It may, however, be a sensitive indicator of iodine status in the newborn period (22,31). TSH is used in many countries for routine newborn screening to detect congenital hypothyroidism. If already in place, such screening offers a sensitive indicator of iodine nutrition (22). Newborn TSH is an important measure because it reflects iodine status during a period when the developing brain is particularly sensitive to iodine deficiency. Compared to the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Serum TSH concentrations are therefore increased in iodine-deficient infants for the first few weeks of life. As demonstrated in national data from Switzerland (31), if <3% of newborn TSH values are above 5 mU/L in whole blood collected 3 to 4 days after birth, this suggests iodine sufficiency in the population (22). Thyroid hormone concentrations are generally poor indicators of iodine status in children and adults, except in severe deficiency, when hypothyroidism develops. In mild to moderately deficient populations, serum T3 increases or remains unchanged, and serum T4 may decrease, but these changes are often within the normal range, and the overlap with iodine-sufficient populations is large (32). Thus, thyroid hormone concentrations are an insensitive measure of iodine nutrition (22).

THYROGLOBULIN

Tg is synthesized only in the thyroid, and is the most abundant intrathyroidal protein. In iodine sufficiency, small amounts of Tg are secreted into the circulation, and serum Tg is normally <10 μg/L (33). In areas of endemic goiter, serum Tg increases due to greater thyroid cell mass and TSH stimulation. Serum Tg is well correlated with the severity of iodine deficiency as measured by UIC (34). Intervention studies examining the potential of Tg as an indicator of response to iodized oil and potassium iodide have shown that Tg concentrations fall rapidly with iodine repletion, and that Tg is a more sensitive indicator of iodine repletion than TSH or T4 (35).

Commercial Tg assays measure serum concentrations, but iodine surveys are often done in remote areas where venipuncture, centrifugation, and frozen sample transport are difficult. Thus, a new assay for Tg has been developed for dried blood spots taken by a finger prick (36), simplifying collection and transport. In prospective studies, dried blood spot Tg has been shown to be a sensitive measure of iodine status and reflects improved thyroid function within several months after iodine repletion (Fig. 15-2) (35); international reference ranges in iodine-sufficient schoolchildren (36) and pregnant women (37) are available. A reference range for serum Tg has also been proposed for Chinese adults (38). The use of Tg to assess population response to introduction of iodized salt has been demonstrated in a national study in Denmark, where correction of mild to moderate iodine deficiency decreased the prevalence of elevated Tg (>40 μg/L) from 11.3% to 3.7% (39).

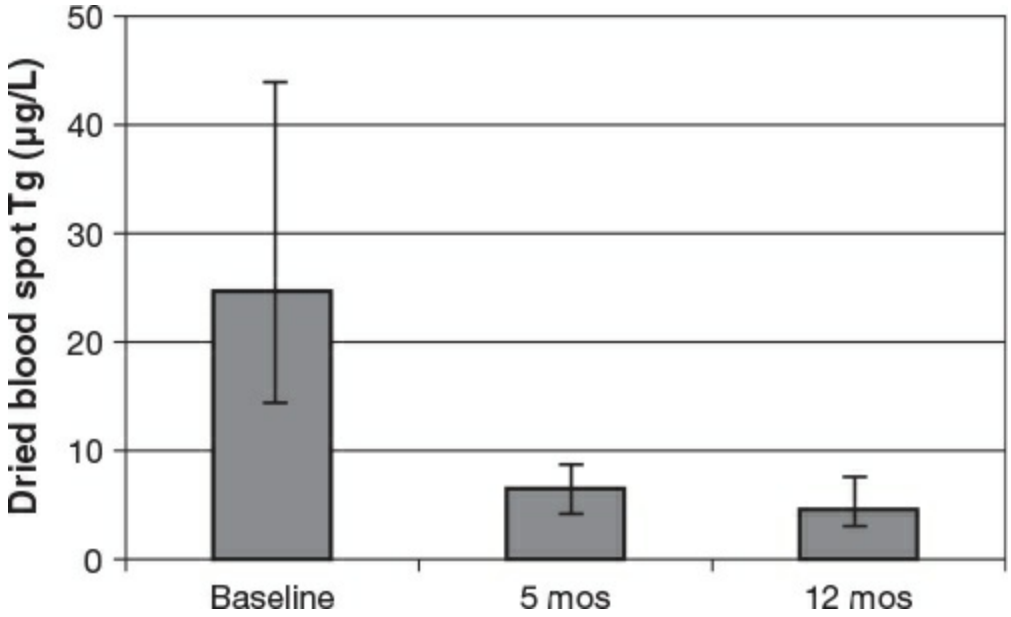

FIGURE 15-2. Thyroglobulin concentrations in dried whole blood spots in Moroccan schoolchildren (*n* = 377) with severe iodine deficiency (median UIC of 17 μg/L and a goiter rate of 72%), at baseline and 5 and 12 months after the introduction of iodized salt. The boxes show the median and the whiskers the 25th and 75th percentiles. (Adapted from Zimmermann MB, Moretti D, Chaouki N, et al. Development of a dried whole-blood spot thyroglobulin assay and its evaluation as an indicator of thyroid status in goitrous children receiving iodized salt. *Am J Clin Nutr* 2003;77[6]:1453–1458.)

EFFECTS OF IODINE DEFICIENCY

Iodine deficiency has multiple adverse effects on growth and development in humans. These are collectively termed the iodine deficiency disorders (IDDs) (Table 15-3), and are one of the most important and common human diseases (22,40). They result from inadequate thyroid hormone production due to lack of sufficient iodine.

THYROIDAL ADAPTATION TO IODINE DEFICIENCY

The thyroid adapts to low intakes of dietary iodine by marked modification of its activity. In most adults, if iodine intake falls below ≈100 μg/day, TSH secretion is augmented. This increases plasma iodide clearance by the thyroid through stimulation of NIS expression. TSH exerts its action at the transcription level of the NIS gene through a thyroid-specific enhancer that contains binding sites for the transcription factor Pax8 and a cAMP response element–like sequence (41). There is a clear inverse relation between dietary iodine supply and thyroidal uptake of radioiodide. However, in areas of endemic goiter, a generalized increase in TSH is seen in populations only when iodine deficiency is severe (12). In areas of milder iodine deficiency, TSH is usually only increased in a minority of subjects, often the youngest. Thus, it is possible that thyroid sensitivity to TSH (rather than the TSH level itself) varies with iodide supply. As the thyroid clears a greater fraction of circulating iodide, there is a progressive reduction in renal iodide excretion, and the UIC falls. Nevertheless, in most healthy adults, as long as daily iodine intake is at least ≈60 μg, despite a decrease in circulating plasma inorganic iodine and UIC, absolute uptake of iodine by the thyroid and thyroidal iodine stores remain adequate. Below this threshold, despite maximal fractional clearance of circulating iodine by the thyroid, absolute uptake falls, the iodine content of the thyroid is depleted, and many individuals develop goiter (Fig. 15-3) (12).

TABLE 15-3. The Iodine Deficiency Disorders, by Age Group

Age Groups	Health Consequences of Iodine Deficiency

All ages	Goiter Increased susceptibility of the thyroid gland to nuclear radiation
Fetus	Abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Infant mortality Endemic cretinism
Child and adolescent	Impaired mental function Goiter Delayed physical development
Adults	Impaired mental function Reduced work productivity Goiter Increased occurrence of hypothyroidism in moderate to severe iodine deficiency; increased occurrence of thyroid nodules and hyperthyroidism in mild to moderate iodine deficiency

From Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet* 2008;372(9645):1251–1262; Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol* 2015;3(4):286–295.

In iodine deficiency, goiters are initially characterized by diffuse, homogeneous enlargement, but over time, nodules often develop (Fig. 15-4). While iodine deficiency produces diffuse goiter in all age groups, it also increases risk for multinodular toxic goiter, mainly in women older than 50 years (42). Many thyroid nodules derive from a somatic mutation and are of monoclonal origin (43); the mutations appear to be more likely in nodules under the influence of a growth promoter, such as iodine deficiency. There are no gross or microscopic features that distinguish the thyroid of endemic goiter from changes that appear in simple and sporadic goiter. In mild iodine deficiency, there is usually only a slight enlargement of the thyroid and the characteristic microscopic findings are hyperplasia with abundant parenchyma, high follicular epithelium, and rare colloid. In chronic severe deficiency, repeated episodes of hyperplasia followed by involution and atrophy result in a thyroid with a mixture of nodules, zones of hyperplasia, and involuting, degenerative, and repair elements. Scanning with radioiodide or pertechnetate shows a mottled distribution of the isotope. In areas known

to be iodine deficient, goiter is usually assumed to be due to iodine deficiency, but individual patients may have goiter due to other causes, such as thyroiditis, thyrotoxicosis, or thyroid carcinoma.

Thyroid hyperplasia induced by iodine deficiency is associated with an altered pattern of thyroid hormonogenesis. Poorly iodinated Tg in the colloid leads to an increase in monoiodotyrosine and T3, and a decrease in diiodotyrosine and T4. The increase of the ratios of monoiodotyrosine/diiodotyrosine and T3/T4 directly correlates with the degree of thyroidal iodine depletion. The characteristic pattern of circulating thyroid hormones in children in areas of moderate to severe iodine deficiency is a variably elevated TSH, a normal or high-normal serum T3, and a low serum T4; this pattern is also seen in adults, but less predictably and it may not be present (33,44). The serum Tg concentration is typically elevated (45). The increased serum T3/T4 ratio plays an important role in the adaptation to iodine deficiency because T3 possesses ≈4 times the metabolic potency of T4 but requires only 75% as much iodine for synthesis. Laboratory findings in iodine deficiency include elevated radioiodine thyroidal uptake (RAIU) (Fig. 15-3) and diminished urinary ^{127}I excretion. RAIU is typically suppressible when thyroid hormone is given, but not always. Anti-Tg or antithyroperoxidase antibodies are usually absent. Thyroid failure and cretinism usually develop only in regions of chronic, severe iodine deficiency where most individuals have low circulating T4 and T3 and dramatically elevated TSH (33,44). It should be emphasized that the effects of iodine deficiency on the development of goiter and thyroid hypofunction are extremely variable among populations and individuals, even in endemic areas. The dietary, environmental, and/or genetic factors that account for this variability in the expression of iodine deficiency from one locality to the next remain largely undefined.

EFFECTS OF HYPOTHYROIDISM DUE TO IODINE DEFICIENCY ON THE DEVELOPING BRAIN

In areas of sufficient dietary iodine, women maintain thyroidal iodine stores of up to 20 mg that can be drawn upon during pregnancy to help cover their increased iodine requirement (46). But in areas of chronic iodine deficiency,

women enter pregnancy with already depleted iodine stores which, combined with low dietary iodine supply, may limit maternal and fetal thyroid hormone production (47). The adverse effects of hypothyroidism in utero depend upon its timing and severity. T3 is the active form of thyroid hormone in the brain and ≈80% of brain T3 is generated locally from T4 (48). T3 plays a central role in brain myelination and cell migration, differentiation, and maturation (49,50). In animal models, hypothyroidism in utero and in the early postnatal period due to iodine deficiency causes a downregulation of hippocampal synaptophysin, a vesicle protein involved in the release of neurotransmitters, and irreversibly alters synaptic development and reduces hippocampal cell numbers (51). Fetal brain development may be sensitive to maternal hypothyroidism as early as the first trimester; nuclear thyroid hormone receptors are present in the fetal brain by 9 weeks, before full development of the fetal thyroid (52). Fetal thyroid function only becomes important later in pregnancy; onset of fetal thyroid hormone secretion occurs late in the second trimester, at 18 to 22 weeks of gestation (52). Thus, adequate maternal thyroid status is essential for normal fetal brain development during the first half of pregnancy and severe maternal hypothyroxinemia is thought to be the cause of cretinism (53).

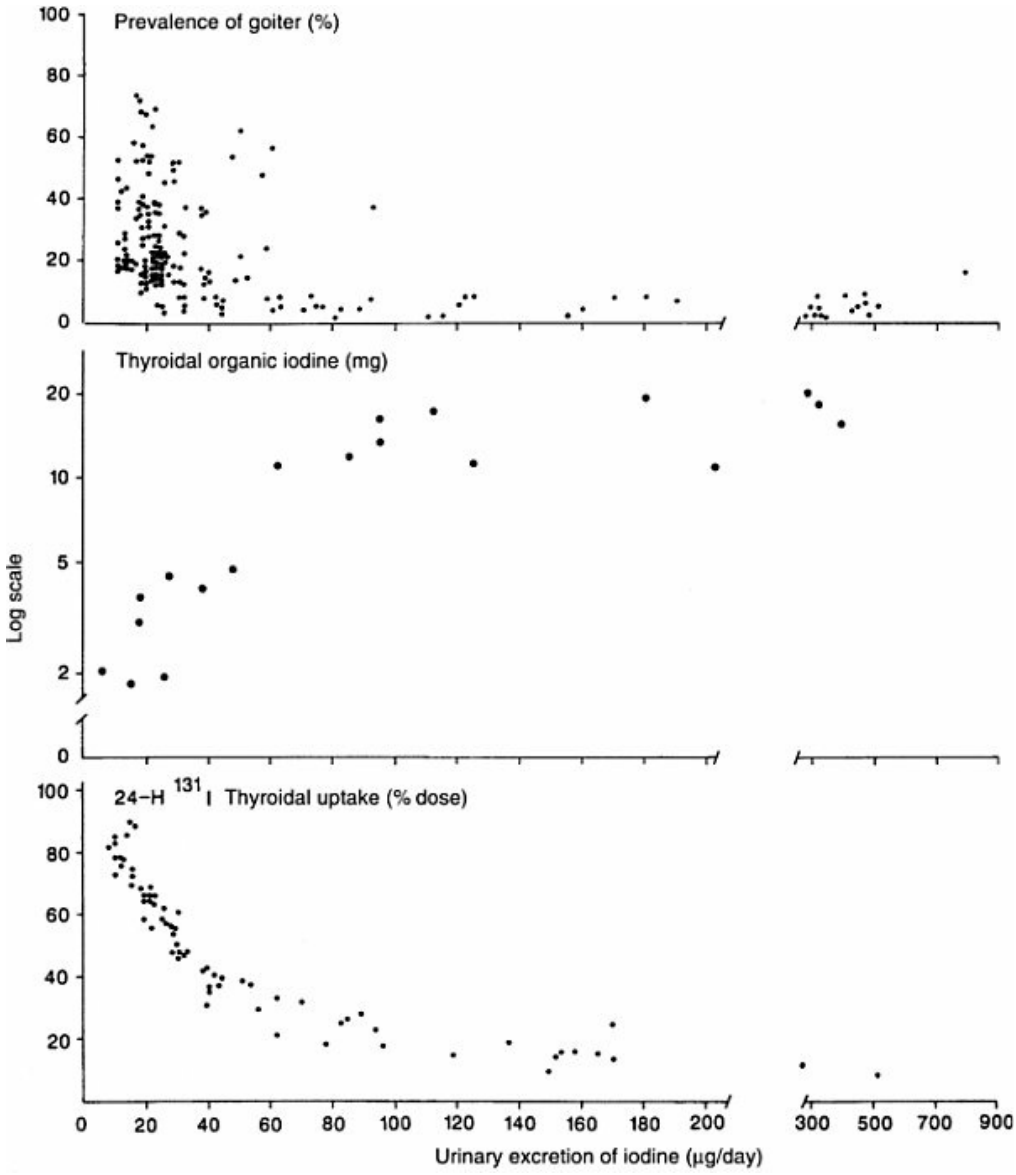

FIGURE 15-3. Relationship between the daily urinary excretion of iodine and the prevalence of goiter, the hormonal iodine content of the thyroid (exchangeable organic iodine pool determined by kinetic studies), and thyroidal uptake of radioiodine. (From Schaefer AE. Status of salt iodization in PAHO member countries. In: Dunn JT, Medeiros-Neto GA, eds. *Endemic Goiter and Cretinism: Continuing Threats to World Health*. Washington, DC: Pan American Health Organization [PAHO]; 1974. Scientific No. 292:242; Delange F, Bourdoux P, Chanoine JP, et al. Physiopathology of iodine nutrition during pregnancy, lactation and early postnatal life. In: Berger H, ed. *Vitamins and Minerals in Pregnancy and Lactation*. New York: Raven Press; 1988:205; and Tovar E, Maisterrena JA, Chavez A. Iodine nutrition levels of schoolchildren in rural Mexico. In: Stanbury JB, ed. *Endemic Goiter*. Washington, DC: Pan American Health Organization [PAHO]; 1969. Scientific No. 193:411, with permission.)

CRETINISM

The most severe manifestation of iodine deficiency during pregnancy is cretinism. The term “cretin” was first used in Diderot’s Encyclopedia in 1754 to refer to “an imbecile who is deaf and dumb, with a goiter hanging down to the waist”; at that time, the condition was common in the Alpine regions of Switzerland, Southern France, and Northern Italy. In McCarrison’s original description of cretinism in northern India in 1908 (54), he delineated a neurologic form, with predominantly neuromotor defects, and a myxedematous form, marked by severe hypothyroidism and short stature. The different features of the two types are summarized in Table 15-4. Endemic cretinism is defined by three major features:

1. It occurs in areas of endemic goiter and severe iodine deficiency.
2. Its clinical manifestations comprise mental deficiency, together with either:
   i. A predominant neurologic syndrome including defects of hearing and speech and characteristic disorders of stance and gait of varying degree (termed neurologic cretinism); or
   ii. Predominant hypothyroidism and stunted growth (termed myxedematous cretinism).
3. It is prevented by the correction of iodine deficiency.

Neurologic Cretinism

The three characteristic features of neurologic cretinism in its fully developed form are severe mental retardation with squint, deaf–mutism, and motor spasticity (Figs. 15-5 and 15-6) (12). The mental deficiency is characterized by a marked impairment of abstract thought, while autonomic and vegetative functions and memory are relatively well preserved, except in the most severe cases. Vision is unaffected while deafness is the striking feature. This may be complete in as many as 50% cretins as confirmed by studies of auditory evoked potentials which show no cochlear or brain stem responses even at the highest sound amplitudes. In subjects with reduced hearing, a high tone defect is apparent. Nearly all totally deaf cretins are mute and many with some hearing have no intelligible speech.

The motor disorder shows proximal rigidity of both upper and lower extremities and the trunk, and corresponding proximal spasticity with exaggerated deep tendon reflexes at the knees, adductors, and biceps. Spastic involvement of the feet and hands is unusual, and their function is characteristically preserved so that most cretins can walk. This may be useful in differentiating cretinism from other common forms of cerebral palsy. In addition to frank cretinism, a larger proportion of an affected population suffers from some degree of mental retardation, elevated hearing thresholds (the sound level below which a person's ear is unable to detect any sound), and coordination defects. DeLong (55) proposed that the neuropathologic basis of the clinical picture of neurologic cretinism includes underdevelopment of the cochlea for deafness; maldevelopment of the cerebral neocortex for mental retardation; and maldevelopment of the corpus striatum (especially the putamen and globus pallidus) for the motor disorder. The cerebellum, hypothalamus, visual system, and hippocampus are usually relatively spared. Developmental neuropathology suggests that the period from about 12 to 14 weeks until 20 to 30 weeks of gestation may be the critical period during which damage occurs. This time frame is supported by intervention trials that indicate iodine repletion must occur in the first half of pregnancy to entirely prevent cretinism (see below).

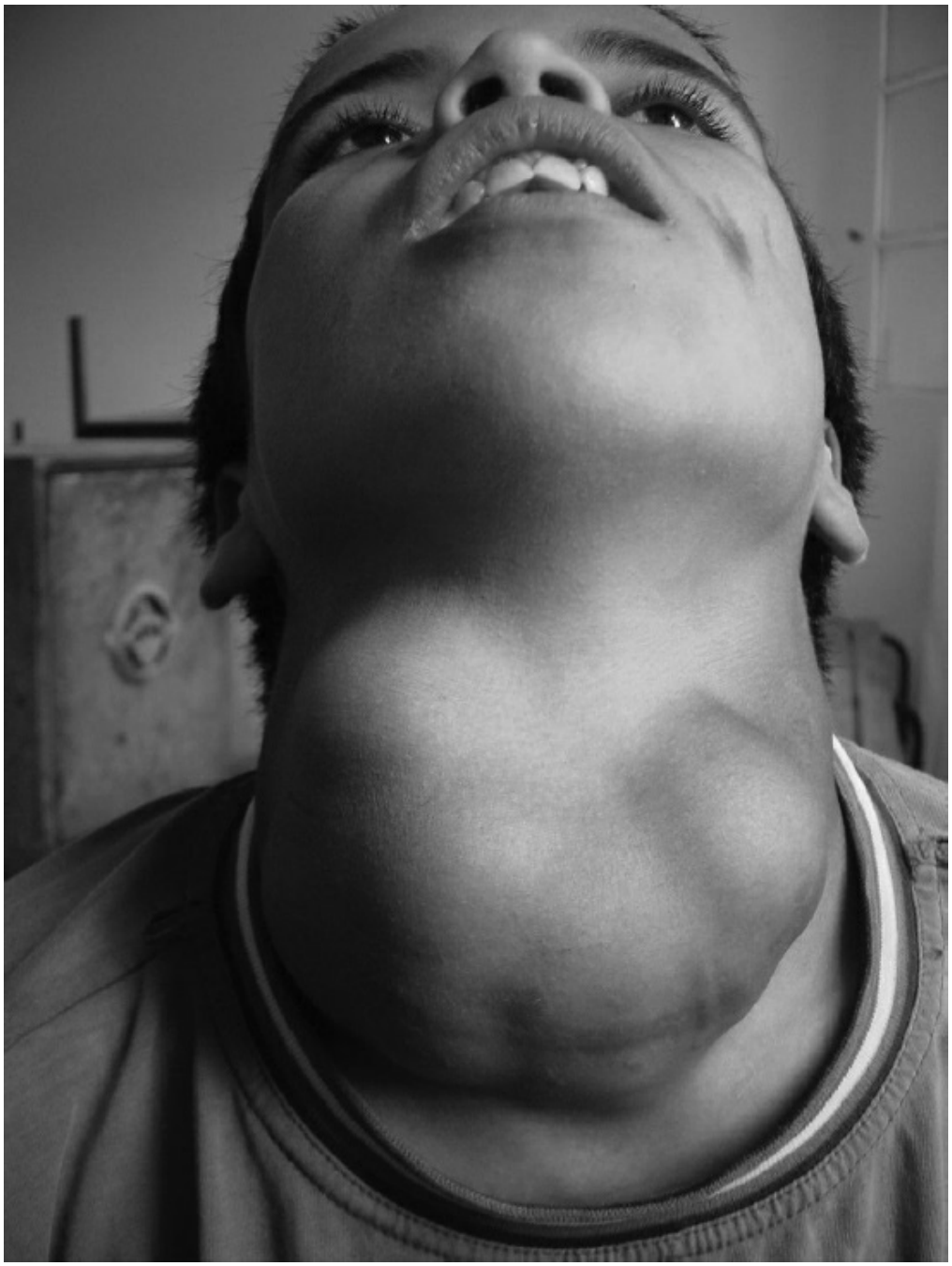

FIGURE 15-4. Large nodular goiter in a 14-year-old boy photographed in an area of severe IDD in northern Morocco, with tracheal and esophageal compression and hoarseness, likely due to damage to the recurrent laryngeal nerves. (Photograph courtesy of M.B. Zimmermann.)

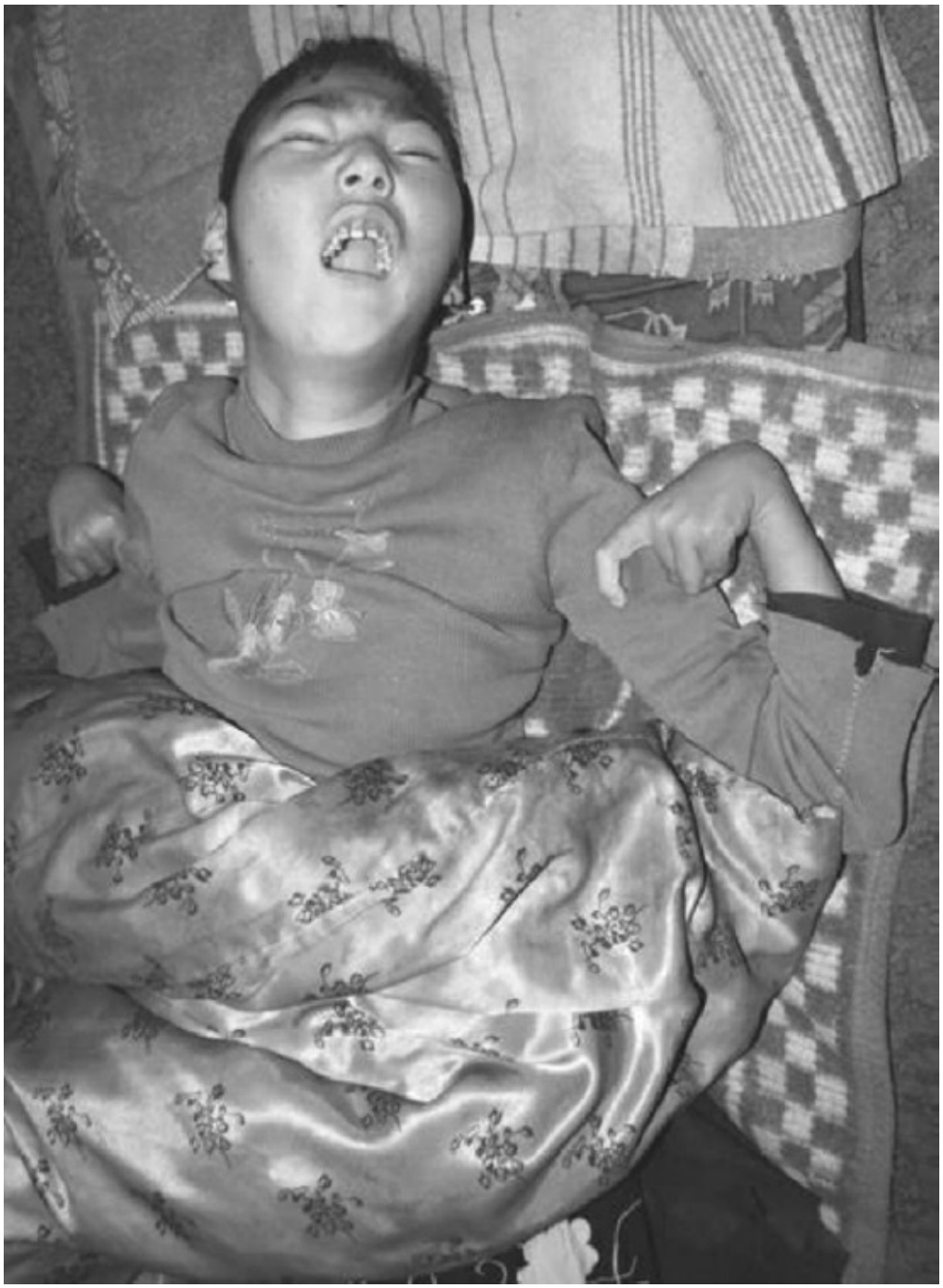

FIGURE 15-5. Neurologic cretinism in a 9-year-old girl from Western China with the characteristic features: severe mental deficiency together with squint, deaf–mutism, and motor spasticity of the arms and legs. (Photograph courtesy of M.B. Zimmermann.)

TABLE 15-4. The Comparative Clinical Features in Neurologic and Myxedematous Cretinism

Features	Neurologic Cretin	Myxedematous Cretin
Mental retardation	Present, often severe	Present, less severe
Deaf–mutism	Usually present	Absent
Cerebral diplegia	Often present	Absent
Squint	Often present	Absent
Stature	Usually normal	Severe growth retardation usual
General features	No physical signs of hypothyroidism	Coarse dry skin, husky voice
Reflexes	Excessively brisk	Delayed relaxation
ECG	Normal	Low voltage QRS complexes and other abnormalities of hypothyroidism
X-ray limbs	Normal	Epiphyseal dysgenesis
Effect of thyroid hormones	No effect	Improvement in signs of hypothyroidism

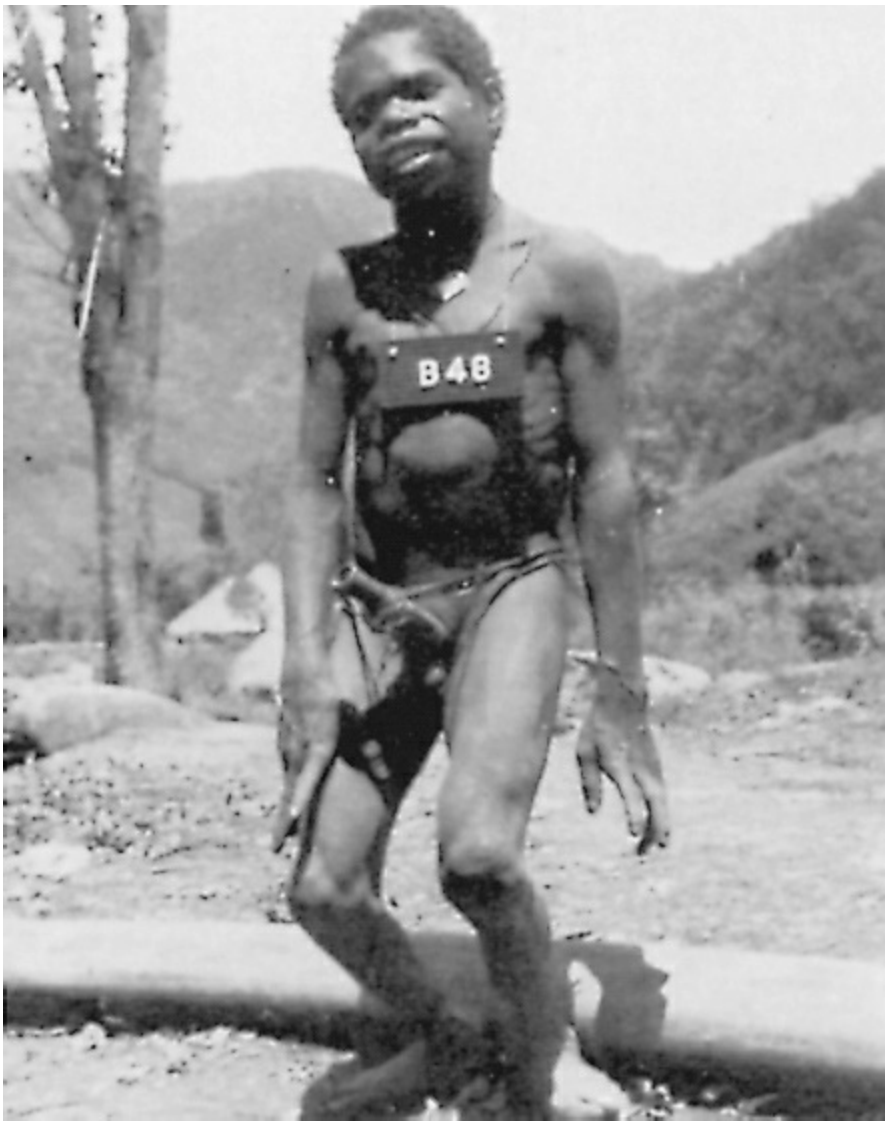

FIGURE 15-6. Neurologic cretinism in a 14-year-old boy in Western New Guinea. He has severe mental retardation, deaf–mutism, spastic diplegia, and strabismus. There are no clinical signs of hypothyroidism. (Photograph courtesy of Professor A. Querido, Leiden, The Netherlands.)

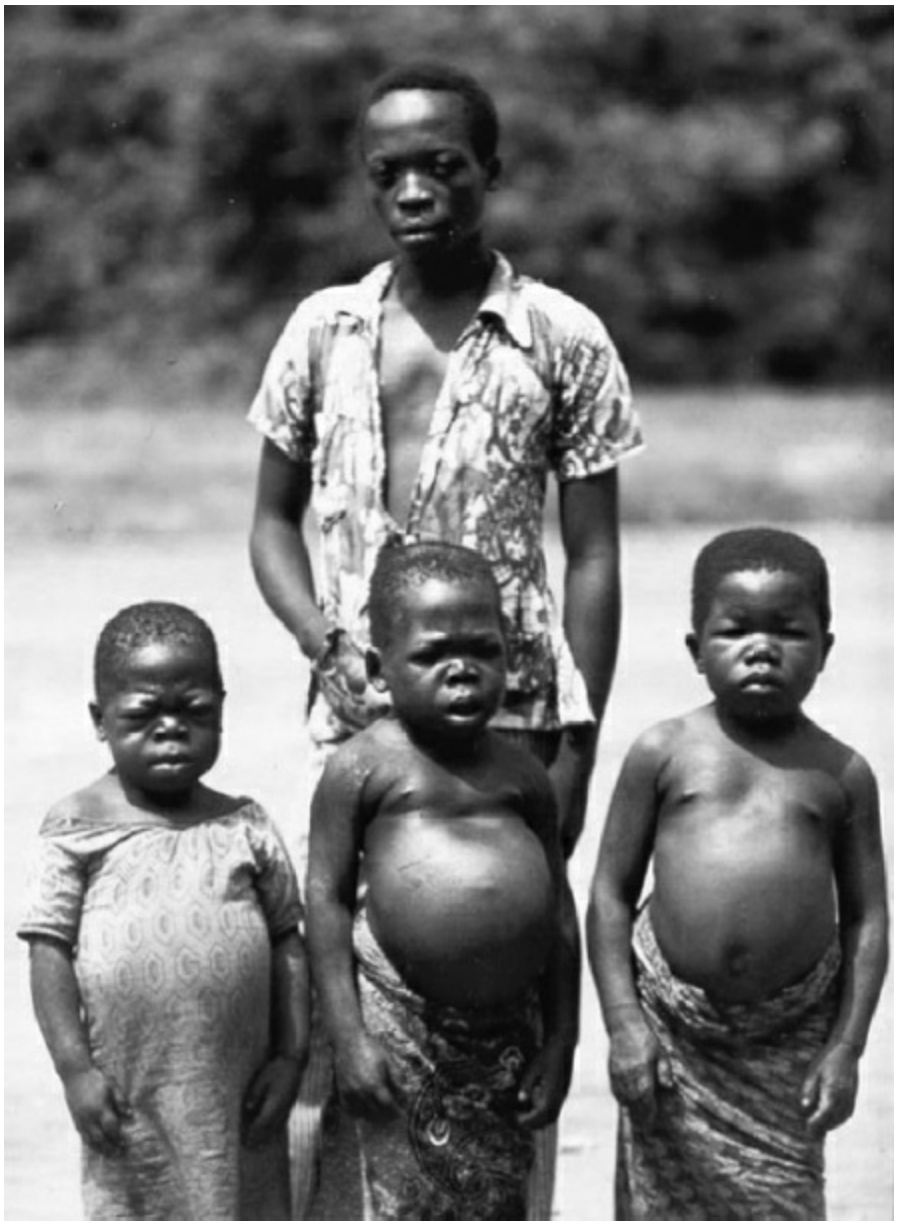

FIGURE 15-7. Myxedematous cretinism in the Democratic Republic of Congo. Four inhabitants aged 15 to 20 years: A normal male and three cretinous females with severe hypothyroidism with dwarfism, retarded sexual development, puffy features, dry skin and hair, and severe mental retardation. (Photograph courtesy of Professor F. Delange, Brussels, Belgium.)

Myxedematous Cretinism

The typical myxedematous cretin (Figs. 15-7 to 15-9) has a less severe degree of mental retardation than the neurologic cretin. But myxedematous cretins have all the features of severe hypothyroidism present since early life, as in

untreated sporadic congenital hypothyroidism. These include severe growth retardation; incomplete maturation of the face and the naso-orbital configuration; atrophy of the mandible; puffy features; myxedematous, thickened, and dry skin; dry and rare hair; and delayed sexual maturation. The movements are torpid and the reflex relaxation is usually prolonged. Genu valgum (knock knees) and pes planus (flat feet) are common. In contrast to the general population in endemic areas and to neurologic cretins, goiter is usually absent and the thyroid is usually atrophic. Circulating T4 and T3 are extremely low, often undetectable, and TSH is dramatically high. Thyroid scans typically demonstrate a thyroid in the normal location but of small volume with heterogeneous and patchy distribution of the tracer; uptake of radioiodine is much lower than in the general population. It may be difficult to differentiate between neurologic and myxedematous cretinism; cretinism may present as a mixed form with features of both.

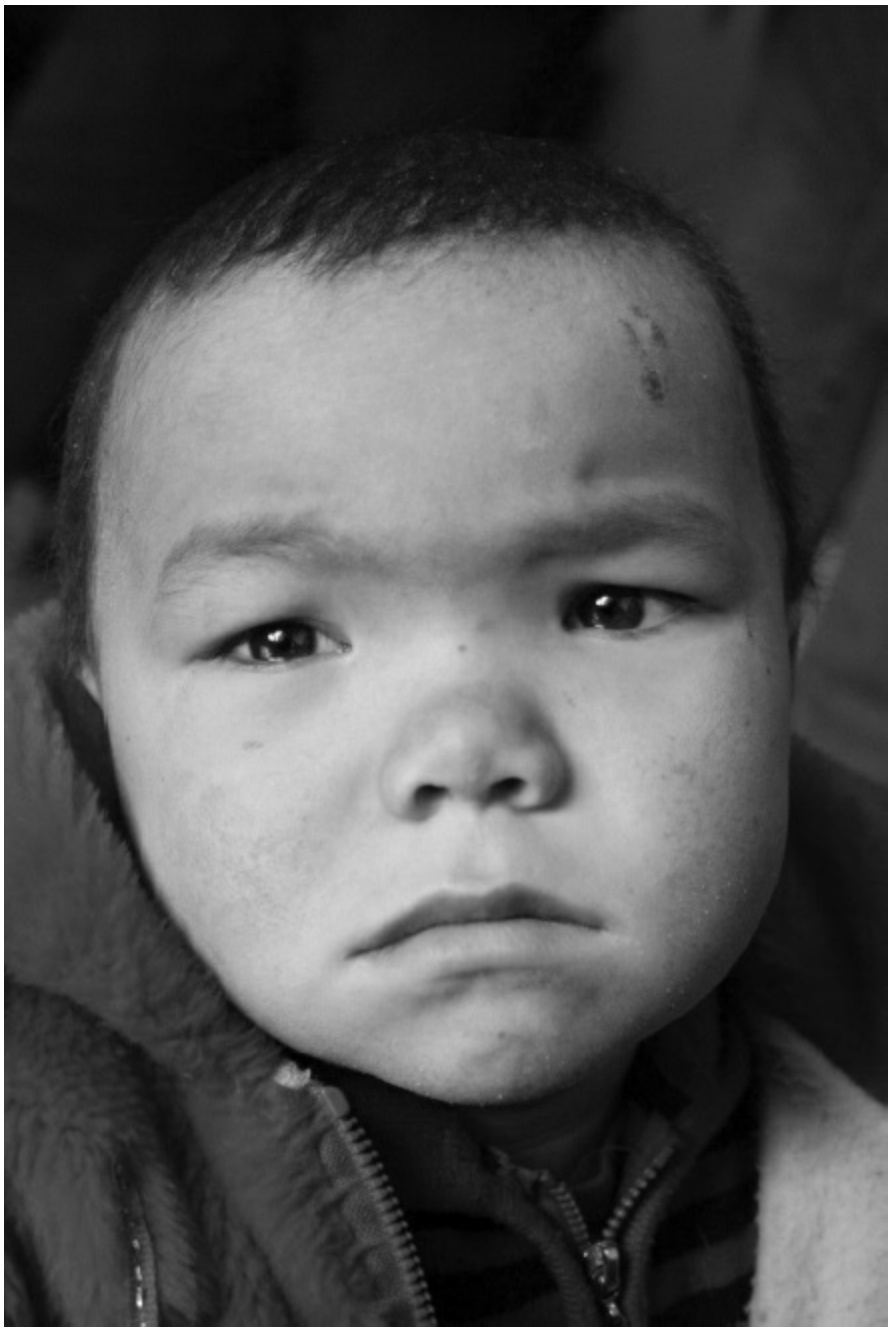

FIGURE 15-8. Myxedematous cretinism in a 7-year-old girl from Western China (height 106 cm) demonstrates the characteristic facial features: incomplete maturation of the naso-orbital configuration, wide-set eyes, atrophy of the mandible, myxedematous, thickened, dry skin and dry hair, eyelashes, and eyebrows. (Photograph courtesy of M.B. Zimmermann.)

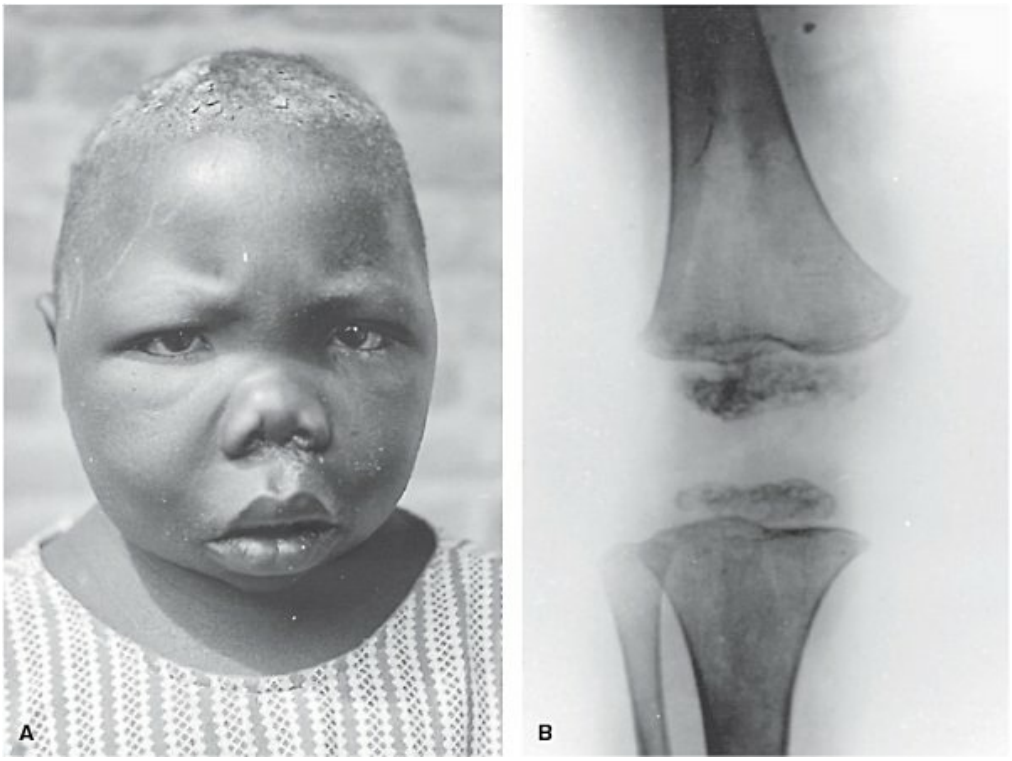

FIGURE 15-9. Clinical appearance (**A**) and knee x-ray (**B**) of a 17-year-old myxedematous cretin with a height of 88 cm (56% of normal for the local population) and a serum protein–bound iodine of 1.0 μg/dL. Bone maturation is estimated at 2 to 5 years. The x-ray film shows failure of modeling, and tibial and femoral epiphyseal dysgenesis. (Photograph courtesy of Professor F. Delange, Brussels, Belgium.)

THE BENEFITS OF CORRECTION OF IODINE DEFICIENCY

IODINE INTERVENTIONS IN SEVERELY DEFICIENT PREGNANT WOMEN

In a landmark trial in an area of severe iodine deficiency in Papua New Guinea (56,57), alternate families received saline (control) or iodized oil injection. The primary outcome was the prevalence of cretinism at 4- and 10-year follow-up, with more sensitive diagnostic tests applied at the 10-year follow-up. Iodine supplementation was associated with a significant reduction in the prevalence of endemic cretinism: At 4 years of age, the

relative risk (95% CI) was 0.27 (0.12, 0.60) and at 10 years of age, the relative risk (95% CI) was 0.17 (0.05, 0.58). In studies in Zaire (58–60), participants were pregnant women attending antenatal clinics in an area of severe iodine deficiency with a 4% cretinism rate. Pregnant women were randomly allocated to two groups: one received iodized oil injection, the other an injection of vitamins. Women were on average 28 weeks pregnant when they were treated. Psychomotor development scores were measured in the offspring at ≈72 months of age, but there was a loss to follow-up of ≈50% in both groups. The psychomotor development scores were significantly higher in the iodine group (mean psychomotor development score, 91±13 vs. 82±14 in the controls); the prevalence of psychomotor scores ≤60 were 0.5% in the iodine group versus 9.7% in the controls.

In a study in western China, an area of severe iodine deficiency and endemic cretinism, participants were groups of children from birth to 3 years and women at each trimester of pregnancy (53). Untreated children 1 to 3 years of age, studied when first seen, served as controls. The intervention was oral iodized oil and treated children and the babies born to the treated women were followed for 2 years. The main outcomes were neurologic examination, head circumference, and indexes of cognitive and motor development. A small subsample was followed to ≈7 years of age (61). The prevalence of moderate or severe neurologic abnormalities among the infants whose mothers received iodine in the first or second trimester was 2%, as compared with 9% among the infants who received iodine during the third trimester (through the treatment of their mothers) or after birth. Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but head growth and developmental quotients improved slightly. Treatment at the end of the first trimester did improve neurologic outcome. The prevalence of microcephaly was 27% in the untreated children compared to 11% in the treated children. The mean (±SD) developmental quotient at 2 years of age was higher in the treated than in the untreated children (90 ± 14 vs. 75 ± 18) (61). Several prospective studies in pregnant women in Latin America have shown comparable results (62,63). In general, these trials suggest that the full picture of neurologic cretinism can only be prevented when iodine is given before or early in pregnancy.

IODINE INTERVENTIONS IN MILD TO MODERATELY DEFICIENT PREGNANT WOMEN

The cognitive deficits associated with iodine deficiency may not be limited to remote, severely iodine-deficient areas. Case control studies in iodine-sufficient women with only mild thyroid hypofunction have reported developmental impairment in their offspring (64,65). These studies suggest cognitive deficits may occur in the offspring even if maternal hypothyroidism is mild and asymptomatic. However, two recent randomized controlled trials (66,67) failed to show cognitive deficits in the offspring of mothers with untreated maternal hypothyroxinemia or subclinical hypothyroidism; one was done in mildly iodine-deficient women (66). Two observational studies reported lower IQ and poorer school performance in children born to mildly iodine-deficient mothers (68,69); others comparing different doses of iodine supplements have not (70). In Europe, several randomized controlled trials of iodine supplementation in mild to moderately iodine-deficient pregnant women have been done (46). In these trials, iodine treatment reduced maternal and newborn thyroid size, and, in some, decreased maternal TSH. However, none of the trials showed an effect on maternal and newborn total or free thyroid hormone concentrations, which may be the best surrogate markers of future infant development (46). For example, in a double-blind, placebo-controlled trial, pregnant Belgian women (n = 120; median UIC 36 μg/L) were supplemented with 100-μg iodine/day from ~14 weeks to term; treatment had no significant effect on maternal or cord thyroid hormones (71). A recent multicenter trial randomized pregnant women in India and Thailand (n = 832; median UIC 131 μg/L) to receive daily 200-μg oral iodine or placebo until term (72). Primary outcomes were child development assessed at 1, 2, and 5 to 6 years; supplementation had no effect on child neurodevelopment (72). These studies are reassuring in that they suggest that in areas of mild to moderate iodine deficiency, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy (72). The American (73) and European Thyroid Associations (74) recommend women take a supplement containing 150-μg iodine daily during pregnancy. In contrast, WHO does not recommend maternal iodine supplements in countries with iodized salt programs (75) concluding that if women are iodine

replete before they enter pregnancy, they can cover their requirements by increasing fractional clearance of plasma iodide and drawing from thyroidal iodine stores. Of concern, observational studies have linked maternal UIC greater than 250 μg/L with subclinical hypothyroidism and hypothyroxinemia (76) and maternal iodine supplementation with impaired infant development (70). In areas of mild to moderate iodine deficiency, pregnancy has been suggested as an environmental factor contributing to a higher prevalence of goiter and thyroid disorders in women, compared with men. In European studies, an uncontrolled prospective study in 10 women (77), a retrospective study (78), and a cross-sectional study in smoking women (79) suggest that goiters formed during pregnancy may only partially regress after parturition.

INFANCY

In areas of severe iodine deficiency, lower maternal T4 concentrations predict higher infant mortality (80), and the infant mortality rate (IMR) will decrease if iodine deficiency is corrected before or during pregnancy. Delong et al. (81) added potassium iodate to irrigation water over a 2- to 4-week period in three areas of severe iodine deficiency in China and found a large reduction in both neonatal and infant mortality in the following 2 to 3 years compared with areas that did not receive iodine. Iodine treatment increased the median UIC in women of childbearing age from <10 μg/L to 55 μg/L and in the three treated areas, the IMR fell from 58.2 to 28.7/1,000 births, from 47.4 to 19.1/1,000 births, and from 106.2 to 57.3/1,000 births. Iodized oil given intramuscularly to severely iodine-deficient pregnant women in Zaire at ≈28 weeks of gestation decreased infant mortality; the IMR in treated and untreated mothers was 113 versus 243/1,000 births, respectively (59). Similarly, in Algeria, compared to untreated women, rates of abortion, stillbirth, and prematurity were significantly lower in women treated with oral iodized oil in the periconceptional period or during pregnancy (82). Infant survival may also be improved by iodine supplementation in the newborn period. A randomized, placebo-controlled trial of oral iodized oil (100-mg iodine) was conducted in Indonesia to evaluate the effect on mortality (83). The iodine or placebo was given in conjunction with oral poliovirus vaccine; infants (n = 617) were treated at ≈6 weeks of age and

were followed up for 6 months. There was a 72% decrease in risk of infant death during the first 2 months of follow-up (83). Taken together, these results suggest iodine prophylaxis in severely iodine-deficient populations, or iodine supplementation of severely deficient pregnant women or infants, may sharply reduce perinatal and infant mortality. However, the mechanism for this beneficial effect remains uncertain.

CHILDHOOD

Two recent systematic reviews (84,85) have confirmed the benefits of correcting iodine deficiency. The first systematic review looked at 89 studies that provided iodized salt to pediatric and adult populations and reported a significant 72% to 76% reduction in risk for low intelligence (defined as IQ <70) and an 8.2 to 10.5 point overall increase in IQ (84). The second systematic review similarly concluded that iodine-sufficient children have a 6.9 to 10.2 point higher IQ than iodine-deficient children (85). Although the overall quality of the studies included in these analyses is low, their conclusions are similar. They suggest that populations, and particularly children, with chronic, severe iodine deficiency experience a mean reduction in IQ of 7 to 11 points. Two high-quality randomized, controlled trials in school-age children have measured the effect of iodine treatment on cognition (86,87). A placebo-controlled, double-blind 6-month intervention trial in moderately iodine-deficient 10- to 12-year-old children (n = 310) in Albania randomized subjects to receive either 400 mg of iodine as oral iodized oil or placebo (86). Treatment with iodine markedly improved iodine and thyroid status: At 24 weeks, median UIC in the treated group was 172 μg/L and mean circulating TT4 increased ≈40%. Compared to placebo, iodine treatment significantly improved performance on several cognitive and motor tests (86). A randomized controlled trial in mildly iodine-deficient 10- to 13-year-old children (n = 184) in New Zealand (87) gave a daily tablet containing 150-μg iodine as KI or placebo for 28 weeks. Overall cognitive score of the iodine group was 0.19 SDs higher than that of the placebo group (Fig. 15-8) (87). Thus, limited available data suggest that in children born and raised in areas of mild to moderate iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion.

Severe iodine deficiency in utero causes cretinism and dwarfism (Fig. 15-6), and iodized oil given during pregnancy in areas of moderate iodine deficiency can increase birth weight (82). Less clear is the relationship between iodine deficiency and postnatal growth. In five Asian countries, household access to iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy (88). If iodine status influences growth, it is likely through its effects on the thyroid axis and growth hormone secretion and action (89). In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-1 and IGFBP-3 concentrations (90). In a prospective, double-blind intervention study in moderate to severely iodine-deficient children, iodine repletion significantly increased T4, IGF-1, IGFBP-3, weight-for-age z scores, and height-for-age z scores (91). A recent systematic review of 18 studies assessed the effects of iodine fortification or supplementation on pre- and postnatal growth outcomes (92). Iodine supplementation of severely iodine-deficient pregnant women increased mean birth weight, but iodine repletion across the other groups showed no effects on primary growth outcomes (92).

ADULTHOOD

Iodine status of a population is an important determinant of thyroid diseases in adults (26,93,94). In adults, iodine deficiency increases risk for diffuse goiter and thyroid nodules (26,95). As an adult population moves from severe iodine deficiency to mild iodine deficiency and then to iodine sufficiency, there is a shift from excess hypothyroidism to excess hyperthyroidism, which is transient, and then a small shift back toward excess mild subclinical hypothyroidism (26). Severe iodine deficiency causes hypothyroidism because, despite an increase in thyroid activity to maximize iodine uptake and recycling, iodine concentrations are simply not high enough to maintain thyroid hormone production. In mild to moderate iodine deficiency, the thyroid gland is able to compensate for deficient dietary intake by increasing thyroid activity, which maintains thyroid hormone production, but at a price: in some individuals, chronic stimulation of the thyroid leads to thyroid nodularity and autonomy (26,95). This increase in nodularity subsequently increases risk of hyperthyroidism if iodine intakes are raised by

supplementation or fortification (26). However, this increased risk of hyperthyroidism in the population is transient, as iodine sufficiency normalizes thyroid activity resulting, in the long term, in reduced nodularity and autonomy (96). The small increase in mild subclinical hypothyroidism that occurs with a shift from deficient to optimum or excessive iodine intakes might be linked to an increased risk of thyroid autoimmunity and might also be transient, but more long-term studies are needed (26). In a large epidemiologic survey on iodine status and prevalence of thyroid diseases in all provinces of China 20 years after the implementation of salt iodization, iodine deficiency was significantly associated with most thyroid disorders, while excessive iodine intake was only associated with an increased prevalence of subclinical hypothyroidism and clinical hyperthyroidism (27).

THYROID CANCER

The available evidence suggests iodine deficiency is a risk factor for thyroid cancer, particularly for follicular thyroid cancer and possibly, for anaplastic thyroid cancer (97). This conclusion is based on: (a) consistent data showing an increase in thyroid cancer (mainly follicular thyroid cancer) in iodine-deficient animals; (b) a plausible mechanism (chronic TSH stimulation induced by iodine deficiency); (c) consistent data from before and after studies of iodine prophylaxis showing a decrease in follicular and anaplastic thyroid cancer; (d) the indirect association between changes in iodine intake and thyroid cancer mortality in the decade from 2000 to 2010; (e) the autopsy studies of occult thyroid cancer showing higher microcarcinoma rates with lower iodine intakes; and (f) the case control studies suggesting lower risk of overall thyroid cancer with higher total iodine intakes (97).

An early systematic review reported no association of thyroid cancer risk with dietary iodine intake, but it was based on 2 case control studies done in populations with sufficient iodine intake and three ecologic studies; the risk estimate range was 0.49 to 1.6 (98). In addition, there was no association of thyroid cancer risk with fish consumption as a surrogate for dietary iodine intake: the risk estimate range was 0.6 to 2.2 (16 case control studies). In contrast, a pooled analysis of 13 case control studies reported a significant decrease in thyroid cancer risk with high fish consumption in regions with

endemic goiter (odds ratio 0.65, 95% CI 0.48 to 0.88) but not in iodine-sufficient regions (1.1, 0.85 to 1.5) (99). Although several ecologic studies have suggested an increase in papillary thyroid cancer after the introduction of iodized salt to populations (100), many confounding factors could account for this association, including other environmental factors and, more likely, increasing diagnostic intensity. Finally, a recently published meta-analysis that included 8 case control studies, including data from China (n = 4,974; 2,213 cases; 2,761 controls), concluded that high iodine intake decreased the risk of overall thyroid cancer (OR 0.74, 95% CI 0.60, 0.92) (101). During the past several decades in the United States, the prevalence of thyroid cancer has been steadily increasing (102), but iodine intakes during the same period have decreased by about 50%. Although more high-quality case control studies are needed, the available data suggest iodine deficiency increases risk for follicular thyroid cancer (97), and a higher intake of dietary iodine is a protective factor against overall thyroid cancer (101).

In conclusion, increasing iodine intake in adult populations decreases the prevalence of goiter, thyroid nodules, thyrotoxicosis, and possibly, thyroid cancer. Observational studies suggest subtle but widespread adverse effects of iodine deficiency in adults secondary to hypothyroidism, including impaired mental function with decreased educability, apathy, and reduced work productivity (12). These benefits occur at the expense of a small increase in the prevalence of mild subclinical hypothyroidism, but this increase is easily correctable (103) and can be minimized by avoiding excessive intakes.

EPIDEMIOLOGY

In 1980, WHO's first global estimate of the prevalence of goiter suggested that 20% to 60% of the world's population was affected, with most of the burden in developing countries. But little attention was paid to iodine deficiency in public health programs in most countries—goiter was considered a lump in the neck, primarily of cosmetic concern. This changed during the period of 1970 to 1990. The term "iodine deficiency disorders (IDDs)" was coined, and the IDDs gained recognition as a spectrum of related disorders affecting billions of people (40). Programs against IDD had

clear political appeal because its human, economic, and social consequences could be averted by a low-cost intervention, universal salt iodization (USI). Since 1990, elimination of the IDDs has been an integral part of many national nutrition strategies (22) and the number of global households with access to iodized salt has risen from <20% to >86% (104), dramatically reducing iodine deficiency.

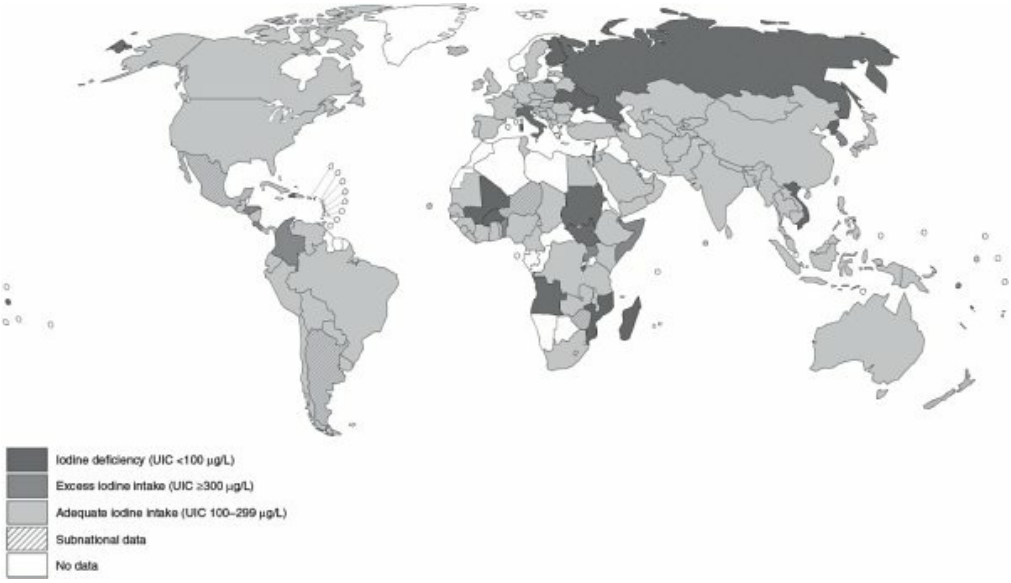

FIGURE 15-10. World map showing national iodine status based on the median UIC in school-age children in 2018. (From Global Iodine Scorecard, Iodine Global Network. Available at http://www.ign.org.)

The median UIC is used to classify national iodine status (Table 15-2) (22). UIC surveys are usually done in children, because they are a convenient population, easy to reach through school-based surveys and usually representative of the general population. National (n = 136) or large subnational (n = 23) UIC surveys have been done in 159 countries, representing 98% of the world's population (Fig. 15-10) (98). In 2018, iodine intake was adequate in 125 countries, deficient in 21 countries, and excessive in 13 countries. Over the past 15 years, the number of iodine-sufficient countries has increased from 67 to 125, showing major progress (105). Large populous countries that are still iodine deficient include low-income countries (e.g., Mozambique) and countries in transition (e.g., Ukraine), but also several high-income countries (e.g., Finland) (105). A limitation of these data is that only a few countries have done national UIC surveys in pregnant

women, a key target group. However, the limited survey data suggest that many pregnant women in both low- and high-income countries, including the United States (106) and several European countries (107), have deficient iodine intakes.

The International Child Development Steering Group identified iodine deficiency as one of the four key global risk factors for impaired child development where the need for intervention is urgent (108). But reaching economically disadvantaged groups living in remote areas and convincing small-scale salt producers to iodize their salt are major challenges. An important strategy will be to strengthen national coalitions that include government partners, national and international agencies, the healthcare sector, and salt producers. In the countries that have begun iodized salt programs, sustainability will become a major focus. These programs are fragile (109) and require a long-term commitment from governments (110).

TREATMENT AND PREVENTION

SALT FORTIFICATION WITH IODINE

In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodization (22). Salt iodization is the recommended strategy for control of IDD because:

- Salt is one of few foodstuffs consumed by virtually everyone.
- Salt intake is fairly consistent through the year.
- In many countries, salt production/importation is limited to a few sources.
- Iodization technology is simple and relatively inexpensive to implement.
- The addition of iodine to salt does not affect its color or taste.
- The quantity of iodine in salt can be simply and inexpensively monitored at the production, retail, and household levels.

WHO/UNICEF/ICCIDD recommends that iodine is added at a level of 14- to 65-mg iodine/kg salt, depending on local estimated salt consumption (111). Iodine can be added to salt in the form of potassium iodide (KI) or potassium iodate (KIO_3). Because KIO_3 has higher stability than KI in the

presence of salt impurities, humidity, and porous packaging (112,113), it is the recommended form in tropical countries and those with low-grade salt. Potassium iodate has been conferred generally recognized as safe (GRAS) status by the U.S. Food and Drug Administration and it has been used for decades as an additive to salt and bread (10). Salt iodization is highly cost effective (114,115). Worldwide, the annual costs of salt iodization are estimated at US $0.02 to 0.05 per child covered, and the costs per child death averted are US $1,000 and per disability-adjusted life years (DALYs) gained are US $34 to 36 (116).

In industrialized countries, because greater than 80% of salt consumption is from purchased processed foods, if only household salt is iodized, it will not supply adequate iodine. Thus, to successfully control iodine deficiency in industrialized countries, it is critical to convince the food industry to use iodized salt in their products (117). Fortunately, iodine at parts per million (ppm) levels in foods does not cause any sensory changes, and, in most countries, the price difference between iodized and noniodized salt is negligible, so there are no major barriers to its use in foods. In Denmark and the Netherlands, nearly all salt used by the baking industry is iodized, and this controls iodine deficiency. Switzerland's long-running iodized salt program has been successful because ca. 60% of salt used by the food industry is iodized on a voluntary basis. The current global push to reduce salt consumption to prevent chronic diseases and the policy of salt iodization to control iodine deficiency do not conflict: iodization methods can fortify salt to provide adequate iodine even if per capita salt intakes are reduced to <5 g/day, as long as all salt consumed is iodized (118).

IODINE SUPPLEMENTATION

In some regions, iodization of salt may not be practical for control of iodine deficiency. In these areas, iodine supplements can be given (22). Iodized oil supplements are prepared by esterification of the unsaturated fatty acids in seed or vegetable oils, and addition of iodine to the double bonds (119). It can be given orally or by intramuscular injection, and can be given safely to pregnant women (22,120). The intramuscular route has a longer duration of action, but oral administration is more common because it is simpler. Usual

doses are 200- to 400-mg iodine/y (Table 15-5) (22). Iodine can also be given as KI or KIO_3 as drops or tablets. Single oral doses of potassium iodide monthly (30 mg) or biweekly (8 mg) can provide adequate iodine for school-age children (121). Lugol iodine, containing ≈6-mg iodine per drop, and similar preparations are often available as antiseptics in rural dispensaries in developing countries and offer another simple way to deliver iodine locally.

In iodine-deficient countries or regions that have weak iodized salt distribution, that is, in countries or areas where <90% of households are using iodized salt and the median UIC is <100 µg/L in schoolchildren, supplements should be given to pregnant women, lactating women, and infants, according to the strategy shown in Table 15-5 (75). Lactating women who receive one dose of 400-mg iodine as oral iodized oil soon after delivery can provide adequate iodine to their infants through breastmilk for at least 6 months, enabling the infants to achieve euthyroidism (122). In the United States, the American Thyroid Association recommends that women receive 150-µg iodine supplements daily, starting 3 months before conception, and during pregnancy and lactation, and that all prenatal vitamin/mineral preparations contain 150 µg of iodine (123).

Iodine Supplementation in Preterm Infants

Balance studies in healthy preterm infants have suggested iodine intakes of at least 30 µg/kg body weight/day are required to maintain positive balance, and experts generally recommend iodine intakes of 30 to 60 µg/kg/day for this group (124–126). Formula milks for preterm infants contain 20- to 170-µg iodine/L. Preterm infants may not achieve AI of iodine particularly during the first postnatal weeks if feed volumes are low (127). Because oral iodine bioavailability is typically 90% to 95% (12), iodine dosages via the enteral or parenteral route should be nearly equivalent. However, commercial parenteral nutrition (PN) solutions contain much less iodine than breast milk or preterm formula milks because expert panels recommend parenteral iodine intakes of only 1 µg/kg body weight/day (128,129). This conservative recommendation assumes parenterally fed preterm infants will absorb iodine through the skin from topical iodinated disinfectants, and also receive small amounts of adventitious iodine in other infusions. For example, in 18 infants receiving

long-term total parenteral nutrition (TPN) without iodine supplementation, thyroid function and serum iodide concentrations were normal (130). Iodine deficiency should be avoided during the neonatal period because it may transiently lower thyroid hormone levels in the first weeks of life and transient hypothyroxinemia in preterm infants has been linked to impaired neurodevelopment (131). The potential contribution of iodine deficiency to transient hypothyroxinemia was investigated in a controlled trial (132) where infants born before 33 weeks of gestation (n = 121) were randomized to receive either iodine-supplemented formula milk or the same formula without iodine supplementation until 40 weeks of postconceptional age. There was no statistically significant effect on thyroid function or several functional outcomes (132). The overall data are insufficient to recommend supplementation of preterm infants with prophylactic iodine (133).

TABLE 15-5. Recommendations for Iodine Supplementation in Pregnancy and Infancy in Areas Where <90% of Households are Using Iodized Salt and the Median UIC is <100 µg/L in Schoolchildren

Women of childbearing age	A single annual oral dose of 400 mg of iodine as iodized oil OR A daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the RNI of 150 µg/day of iodine.
Women who are pregnant or lactating	A single annual oral dose of 400 mg of iodine as iodized oil OR A daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the RNI of 250 µg/day iodine. Iodized oil should not be given to a woman who has already been given iodized oil during her current pregnancy or up to 3 mo before her current pregnancy started.
Children aged 0–6 mo	A single oral dose of 100 mg of iodine as iodized oil OR A daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the RNI of 90 µg/day of iodine. Should be given iodized oil only if the mother was not supplemented during pregnancy or if the child is not being breastfed.
Children aged 7–24 mo	A single annual oral dose of 200 mg of iodine as iodized oil as soon as possible after reaching 7 mo of age

OR

A daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the RNI of 90 µg/day of iodine.

From WHO Secretariat; Andersson M, de Benoist B, Delange F, et al. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* 2007;10(12A):1606–1611.

EFFECTS OF EXCESS IODIDE

PHYSIOLOGIC RESPONSE TO EXCESS IODIDE

In animals and humans, the thyroid gland has intrinsic autoregulatory mechanisms to effectively handle excess iodine intake, involving the NIS (13). The acute, transient inhibitory effect of iodine excess on thyroid iodine organification is termed as the acute Wolff–Chaikoff effect, and appears that adaptation to or escape from the acute Wolff–Chaikoff effect is due to a decrease in NIS messenger RNA (mRNA) and protein (134) and to increased NIS protein turnover (135), thereby lowering intrathyroidal iodine and permitting normal hormone synthesis to resume. When normal subjects were given up to 150-mg iodine for 1 to 3 weeks, a small but significant decrease in the serum T4 and T3 occurred, with a small but significant compensatory increase in serum TSH and an increased TSH response to thyrotropin-releasing hormone (TRH) (136,137). These alterations were all within the normal range. Smaller quantities of iodine (1,500 and 4,500 µg/day) administered to normal subjects who resided in iodide-replete areas resulted in significant decreases in serum T4 and free T4 but not in serum T3 (138). Serum TSH increased, as did the serum TSH response to TRH. The smallest quantity of iodine that did not affect thyroid function was 500 µg/day (138). In another study, however, this small quantity of iodine enhanced the TSH response to TRH and also increased basal serum TSH above the normal range in a few patients (139). Thus, iodine supplements of about 500 µg/day above the normal diet in iodide-sufficient areas may cause subtle changes in thyroid function (140). These subtle changes in thyroid function during iodine administration are accompanied by a small increase in thyroid volume determined by echography (141). In animals, prolonged high intake of iodine

causes inhibition of the type 2 deiodinase in the hypothalamus and pituitary and increases serum TSH (142). This mechanism may explain the higher reference intervals TSH proposed for healthy Chinese (27) and South Korean (143) adults with high iodine intakes.

TOLERABLE UPPER LIMITS FOR IODINE INTAKE

Based on the above studies, the lowest observed adverse effect level (LOAEL) proposed for iodine intakes is 1,700 to 1,800 µg/day. To obtain a tolerable upper intake level (UL) from a LOAEL, an uncertainty factor (UF) is applied to adjust for precision and accuracy across study results, the severity of the adverse effects, and account for differences between populations or varying environmental conditions (7). The UL is the highest average daily intake that is likely to pose no risk of adverse health effects in the general population (Table 15-6) (7). The IOM used a UF of 1.5, bringing the UL to 1,100 µg/day (7), whereas the European Union Scientific Committee on Foods used a UF of 3 to reach a UL of 600 µg/day (144) due to differences in interpretation of the LOAEL effect. In 1988, the joint Food and Agriculture Organization of the United Nations (FAO) and WHO Expert Committee on Food Additives suggested the UL from all iodine sources of 1 mg/day would be safe for most of the population except those with iodine sensitivity or underlying thyroid disorders (145,146).

TABLE 15-6. Recommended Safe Upper Intake Levels for Iodine

Age Group	IOM (µg/day) (7)	SCF (µg/day) (135)	WHO (µg/kg/day) (136,137)
Premature infants	ND	ND	100
0–6 mo	ND	ND	150
7–12 mo	ND	ND	140
1–3 y	200	200	50
4–6 y	300 (4–8 y)	250	

7–10 y	600 (9–13 y)	300	50 (7–12 y)
11–14 y		450	30 (>13 y)
15–17 y	900 (14–18 y)	500	
Adults	1,100	600	
Pregnant and lactating women	1,100	600	40

IOM, United States Institute of Medicine; SCF, European Union Scientific Committee on Foods; WHO, World Health Organization; ND, not determined.

MONITORING OF IODINE EXCESS IN POPULATIONS

For population monitoring of iodine excess, WHO recommends using the median UIC; the upper threshold for iodine excess is a median UIC ≥300 μg /L in 6- to 12-year-old children, or ≥500 μg/L in pregnant women (22). Serum or dried blood spot Tg appears to be a sensitive population indicator of both low and excess iodine intake: the relationship between Tg and UIC in populations is U shaped, as shown in schoolchildren (147), pregnant women (37), and infants (148). Similarly, both deficient and excess iodine intakes may increase thyroid volume in children (149). Thus, in population monitoring for potential iodine excess, a high median UIC indicates that total iodine intake is excessive, and in conjunction with an increased serum or dried blood spot Tg and/or thyroid volume, indicates an increased risk for thyroid disorders.

SOURCES OF EXCESS IODIDE

Various drugs and foods contain a large quantity of iodine that is either absorbed directly or released after metabolism of the drug. Though most foods are poor in native iodine, certain seaweeds, including kelp and kombu are iodine rich (150). Seaweed ingestion is common in Japan (151), Korea (152), and elsewhere in East Asia. Daily consumption of iodine in milligram doses in these regions (153) is well tolerated by most of the population, but not all (154). Unprocessed meat is generally low in iodine, but accidental

thyroid tissue found in ground beef has caused thyrotoxicosis (hamburger thyrotoxicosis) (155). Drinking water typically has an iodine content of approximately 1 to 10 μg/L. Groundwater high in iodine is widely reported in literature (156–158). Drinking water is a source of excess iodine intake in regions of China, where the drinking water has an iodine concentration in the range of 300 to 500 μg/L (159–163). Also, iodine-based water purification systems may cause chronic excess iodine intake (164). In dietary supplements containing iodine, the labeled iodine content may be incorrect and may exceed the UL (165), particularly supplements containing kelp (166).

The use of contrast media in radiologic studies is another potential source of excess iodine. These preparations are cleared from the plasma relatively quickly, but the iodine released may affect thyroid function. In 22 euthyroid patients without thyroid antibodies the administration of iodine-containing contrast media, 300- to 1,100-mg iodine/kg body weight, induced an increase of serum TSH within the normal range in the large majority of subjects, but 18% had a transient TSH rise above 4 mU/L (167). Coronary angiography performed in 788 euthyroid patients induced thyrotoxicosis in only two patients within 12 weeks; baseline serum TSH was normal, and ultrasonography of the thyroid showed no abnormalities (168). Drugs used in the past for imaging studies were lipid soluble and cleared slowly, maintaining high plasma inorganic iodide concentrations for years. The newer water-soluble iodine-containing preparations have markedly reduced this problem. A partial list of medications and other preparations containing large quantities of iodine is given in Table 15-7.

IODINE-INDUCED HYPOTHYROIDISM OR GOITER IN THE ABSENCE OF APPARENT UNDERLYING THYROID DISEASE

In susceptible people, such as those with autoimmune thyroid disease, subacute thyroiditis, postpartum thyroiditis, type 2 amiodarone-induced thyrotoxicosis, hemithyroidectomy, or concomitant use of lithium therapy, the thyroid may not escape from the transient inhibitory effect of iodine on hormone synthesis. As a result, hypothyroidism may result after prolonged ingestion of excess iodine. The hypothyroidism is usually transient, and

thyroid function returns to normal after iodine withdrawal.

TABLE 15-7. Commonly Used Iodine-Containing Drugs

Drugs	Iodine Content
Amiodarone	75 mg/tablet
Benziodarone	49–100 mg/tablet
Calcium iodide	26 mg/mL
Echothiophate iodide for ophthalmic solution	5–41 mg/drop
Hydriodic acid syrup	13–15 mg/mL
Iodochlorhydroxyquin	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol	15 mg/tablet, 25 mg/mL
Idoxuridine ophthalmic solution	18 mg/drop
Isopropamide iodide	1.8 mg/tablet
Lugol solution	6.3 mg/drop
Niacinamide hydroiodide + KI	115 mg/tablet
Ponaris nasal emollient	5 mg/0.8 mL
Saturated solution of potassium iodide (SSKI)	38 mg/drop
Parenteral Preparations	
Sodium iodide, 10% solution	85 mg/mL
Topical antiseptics	
Iodide tincture	40 mg/mL
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 g gauze
Povidone iodide	10 mg/mL
Radiology Contrast Agents	

Diatrizoate meglumine sodium	370 mg/mL
Iodized oil	380 mg/mL
Iopanoic acid	333 mg/tablet
Ipodate	308 mg/cap
Iothalamate	480 mg/mL
Metrizamide	483 mg/mL

Adults

Iodine-induced goiter occurs in about 10% of the population of Hokkaido, a Japanese island where large quantities of iodine-rich seaweed are consumed, and the quantity of iodine ingested daily may exceed 200 mg (169,170). In another study, goiter due to iodine-rich drinking water was observed in 10% of the subjects residing in 19 Chinese counties (161). Despite the high prevalence of goiter in these studies, nearly all individuals had normal thyroid function, suggesting physiologic adaptation to the high intakes (161,169,170). However, other studies have demonstrated the adverse effects of high iodine intake on thyroid function. For example, in Chinese subjects with mildly deficient iodine intake (UIC of 84 to 88 µg/L), those with more than adequate iodine intake (UIC of 214 to 243 µg/L), and those with excessive iodine intake (UIC of 634 to 651 µg/L), the prevalence of subclinical hypothyroidism was 0.9%, 2.9%, and 6.1%, of overt hypothyroidism was 0.3%, 0.9%, and 2.0%, and of autoimmune thyroiditis was 0.5%, 1.2%, and 2.8%, respectively (93). These findings were confirmed in another survey showing that subjects with a median UIC of 200 to 300 µg/L and those with >300 µg/L had a prevalence of subclinical hypothyroidism of 1.99% and 5.03%, respectively (171), while a median UIC of 100 to 200 µg/L reflected a safe dietary iodine intake (172). A group of American volunteers working in West Africa had a median UIC of >5 mg/L due to a faulty iodination system. Some developed goiter and serum TSH concentrations were above 4.2 mU/L in 29% (164).

In an elderly Icelandic population, a high median UIC (150 µg/L, range 33 to 703 µg/L) was accompanied by a high prevalence (18%) of serum TSH >4 mU/L (173). In contrast, in subjects residing in Jutland with lower median

UIC (38 μg/L, range 6 to 770 μg/L), serum TSH was low (<0.4 mU/L) in 10%; the incidence of positive thyroid antibodies was similar in both populations (173). It has been observed in Denmark that after mandatory iodine fortification of salt, the incidence of hypothyroidism slightly increased, but only in young and middle-aged subjects (174). In Brazil, it has been observed that after 5 years of excessive iodine intake the prevalence of autoimmune thyroiditis was 16.9%, and hypothyroidism was present in the 8% of subjects with autoimmune thyroiditis (175). However, as noted above, chronic high iodine intakes may be associated with higher reference intervals for TSH (27,143). Thyroid radioactive iodine uptake would be expected to be very low in patients with iodine-induced hypothyroidism; however, about 30% have a normal or high thyroid radioactive iodide uptake (176). Similar findings have been observed in European but not U.S. patients who developed iodine-induced hypothyroidism after amiodarone administration (177,178).

Skin application of povidone iodide for 3 to 133 months resulted in subclinical hypothyroidism in 3 of 27 patients without antithyroid antibodies (179). Gargling with povidone iodide induced overt and subclinical hypothyroidism in two subjects without antithyroid antibodies. These subjects became euthyroid after gargling was discontinued (180). Histologic examination of the thyroid of patients with iodide-induced hypothyroidism revealed the presence of lymphocytic infiltration in only half the specimens examined. In the other specimens, hyperplastic changes in the follicles with papillary folding, cuboidal or columnar change of cells with clear and vesicular cytoplasm, and markedly reduced colloid in the distended follicles were seen. These changes were reversible after iodine withdrawal (181). In contrast, a single dose of 50 to 70 mg of potassium iodide (KI) given to children and adults for iodide prophylaxis following the Chernobyl accident did not increase the incidence of hypothyroidism (182).

Pregnancy and Infancy

Iodine readily crosses the placenta and is concentrated by the fetal thyroid. Large quantities of iodine administered to pregnant women may result in goiter in the newborn, probably because the fetal thyroid is highly sensitive to the inhibitory effect of iodine on hormone synthesis (183). The thyroid of the

fetus and newborn can be exposed to iodine from various routes. Large quantities of kombu, an iodine-rich seaweed consumed by pregnant Japanese women caused neonatal transient hypothyroidism; the neonates had a median UIC ≥300/L, serum TSH higher than control, and 12 of 15 required temporary LT4 treatment (184). Goiter and hypothyroidism have been diagnosed in a fetus whose asthmatic mother consumed two to three tablespoons per day of a syrup containing 130 mg/15 mL of iodine (185). Severe goitrous hypothyroidism was reported in a newborn infant with a history of iodine exposure in utero derived from an expectorant used by the mother (186).

Vaginal douching with iodine-containing solutions in nonpregnant women results in an increase of serum iodide and a small increase in serum TSH (187). Transient hypothyroidism of the newborn, as indicated by an increased serum TSH, has been reported to follow the application of vaginal solutions of povidone iodide and in a few cases after povidone iodide cream application during labor (188). In pregnant women treated with amiodarone, transient hypothyroidism was detected in 17% of the newborns (189). Other reports of newborn hypothyroidism due to amiodarone administration suggest hypothyroidism was transient (190). Maternal exposure to iodinated contrast media during pregnancy caused neonatal hypothyroidism in 18.2% of preterm and term neonates (191). Topical application of povidone iodide to the skin of the newborns may induce transient neonatal hypothyroidism, more frequently in premature, low-birthweight infants (192,193). Serum TSH >20 mU/L occurred in 25% of the cases, and serum TSH normalized after the iodide-containing antiseptic was discontinued (194). The administration of a single dose of 15 mg of KI to newborn infants for iodine prophylaxis after the Chernobyl nuclear reactor accident resulted in a transient increase of serum TSH concentrations in 0.4% (182). In the same population, the exposure to iodine in utero due to maternal iodine prophylaxis did not result in an increase in congenital hypothyroidism (182). Iodine is actively transported by breast tissue and secreted into the milk. Perinatal hypothyroidism and high infant urinary iodine levels were observed in newborns whose mothers consumed a large amount of seaweed soup during pregnancy and the postpartum period (195). Although maternal thyroid function was normal, transient iodine-induced hypothyroidism has been diagnosed in breastfed premature neonates whose mothers were medicated with iodoform gauze or

were exposed to topical iodine treatment (196,197).

Childhood

Endemic iodine-induced goiter has also been observed in 64% of children residing in a village in central China where the drinking water contained 462-mg iodine/L (159); however, there was no increase in lymphocytic thyroiditis and thyroid autoantibodies were negative (160). In Chinese children consuming iodine-rich drinking water, UIC increased to >1,500 μg/L and goiter prevalence was 3.7 times higher than in children with UIC of 100 to 199 μg/L (162). The administration of 40- to 65-mg iodine daily to euthyroid children residing in Greece resulted in serum TSH concentrations above 4.2 mU/L in 75%; in contrast, adult subjects did not have an increase in serum TSH concentrations (198). These findings suggest autoregulatory mechanisms within the thyroid are not fully mature in children, and the thyroid may be particularly susceptible to the inhibitory effects of excess iodine.

Chronic Nonthyroidal Illness

Certain diseases may predispose the patient to iodine-induced thyroid dysfunction. Children with cystic fibrosis, especially those treated with sulfisoxazole, are particularly susceptible to iodine-induced hypothyroidism (199). In children and adults with thalassemia major and requiring chronic blood transfusions, iodine administration (60 mg/day) resulted in subclinical hypothyroidism (TSH >5 mU/L) in 60% (200). TSH returned to basal levels 2 to 3 weeks after iodine withdrawal. It appears that hemosiderosis renders the thyroid of these patients susceptible to the inhibitory effects of iodine (200). Patients with chronic renal failure frequently have thyroid dysfunction, including thyroid enlargement and abnormal thyroid function tests, which may be due to iodine-containing antiseptics (201,202).

IODINE AND THYROIDITIS

Animal studies suggest that iodine administration may play a role in the

development of autoimmune thyroid disease (203–205). The mechanism by which iodine excess increases the occurrence of autoimmune thyroiditis may be due to the enhanced immunogenicity of iodide-rich Tg (206,207). An essential requirement for the development of iodine-induced thyroiditis is the uptake and metabolism of iodine within the gland (208). Other mechanisms for the development of iodine-induced thyroiditis, such as cellular damage due to elevated oxygen-free radicals, direct cytotoxic effects of iodine, autoregulation of major histocompatibility class I gene expression, and increased expression of intrathyroidal TNF-α, have been proposed (206,209–211).

Chronic Lymphocytic Thyroiditis

Patients with chronic lymphocytic (Hashimoto) thyroiditis often develop hypothyroidism due to thyroid destruction by the autoimmune process or rarely due to the presence of TSH receptor-blocking antibodies. In rats genetically susceptible to chronic lymphocytic thyroiditis, pharmacologic quantities of iodine enhanced the development of lymphocytic thyroiditis without inducing hypothyroidism (212). In a study in the United States, administration of pharmacologic quantities of iodine (180 mg/day) resulted in hypothyroidism in more than 60% of patients with Hashimoto thyroiditis; the iodide-perchlorate discharge test was positive in these individuals, indicating a defect in the intrathyroidal organification of iodine (213). Japanese patients with primary hypothyroidism due to lymphocytic thyroiditis and high dietary iodine intakes became euthyroid when the iodine intake was restricted (214,215). In another study, 8 of 40 patients with high TPO antibody levels residing in an area of mild iodine deficiency developed subclinical or overt hypothyroidism following the ingestion of 250 μg KI/day for 4 months (216). In contrast, the administration of 1.5-mg iodine daily for 3 months to patients with Hashimoto thyroiditis did not induce hypothyroidism (217) and 150 μg/day of iodine given to moderately iodine-deficient TPO-positive pregnant women did not induce or worsen postpartum thyroid disease (218). In patients with autoimmune thyroiditis residing in an area of mild iodide deficiency, small quantities of iodine caused a transient increase in serum T4 and T3 (219). Overall, the available data suggest that the administration of iodine to patients with autoimmune thyroiditis may precipitate

hypothyroidism in some patients but not all; the environmental or genetic factors that determine whether this occurs remain uncertain.

The relationship of iodine intake with the occurrence of Hashimoto thyroiditis in humans is controversial. Some studies (220,221) have suggested increased iodine intake is associated with an increased incidence of Hashimoto thyroiditis, especially when iodine is introduced into endemic goiter regions. In a randomized, double-blind, placebo-controlled study conducted in patients with endemic goiter, administration of 0.5 mg/day of KI for 6 months induced high serum anti-Tg antibody and antimicrosomal antibody levels in 19%. Fine-needle aspiration biopsy confirmed the presence of lymphocytic infiltration of the thyroid gland (222). These signs of thyroid autoimmunity disappeared after iodine withdrawal. Injection of 1-mL iodized oil intramuscularly in patients with nontoxic goiter living in Greece was accompanied by an increase in thyroid lymphocytic infiltration in the thyroid from 25% to 68% (223). In contrast, other studies did not find a relationship between iodine intake and the prevalence of thyroid autoimmunity (141,224). A lower prevalence of anti-TPO antibodies in children and adolescents following 5 years of iodine prophylaxis has also been reported (225). Possible explanations for these discrepant findings on the effect of iodine supplementation on thyroid autoimmunity are suggested by studies from Morocco and Sri Lanka (226–228), where the prevalence of thyroid antibodies increased following iodide prophylaxis, but decreased later to baseline or lower values.

Graves Disease

When patients with Graves disease treated with iodine-^{131}I were given iodine (250 mg/day) 1 to 2 weeks after ^{131}I therapy, 60% developed transient hypothyroidism (229). Euthyroid patients treated years earlier either with ^{131}I or thyroidectomy developed severe hypothyroidism during the administration of pharmacologic quantities of iodine. The hypothyroidism was transient, and thyroid function returned to normal after iodine withdrawal (230). All patients who developed hypothyroidism had a positive iodine-perchlorate discharge test, indicating an organification defect. In 10 euthyroid subjects previously treated with antithyroid drugs for Graves disease, the chronic administration of 10 drops of a saturated solution of potassium iodide (SSKI)

(350-mg iodine per day) induced an increase in basal or TRH-stimulated serum TSH concentrations irrespective of the iodide-perchlorate discharge test (231). Basal and TRH-stimulated serum TSH concentrations returned to normal 60 days after SSKI withdrawal. However, 2 of the 10 women developed recurrent hyperthyroidism requiring antithyroid drug therapy.

Postpartum Thyroiditis

Euthyroid women with a previous episode of postpartum thyroid dysfunction are prone to developing iodine-induced hypothyroidism. In 9 of 11 women, the administration of 300-mg iodine daily for 3 months induced hypothyroidism and, in some, goiter. As observed in patients with other thyroid diseases prone to developing iodine-induced hypothyroidism, a positive iodine-perchlorate discharge test was common (232). Two months after the iodine was withdrawn, thyroid function returned to normal (232). Similarly, small doses of iodine administered to patients expected to develop postpartum thyroiditis may intensify rather than ameliorate the disease (233). In China, higher iodine intakes were associated with an increase in the frequency of postpartum thyroiditis (234).

Subacute Thyroiditis

The chronic administration of large quantities of iodine (300 mg/day) to 18 euthyroid patients long after an episode of painful subacute thyroiditis resulted in a significant increase in serum TSH in 10 subjects. Most of these patients had mild increases in the serum TSH concentration, but two had values >50 mU/L and developed goiter. A positive iodine-perchlorate discharge test was highly predictive for the occurrence of iodine-induced hypothyroidism (235). Persistent mild autoimmunity has been reported to be present up to 3 years after the onset of subacute thyroiditis (236); however, the serum of these patients was negative for anti-Tg and antimicrosomal antibodies.

IODINE-INDUCED THYROTOXICOSIS

Since the initial description by Coindet in 1821 (237) and the subsequent definition by Breuer and Kocher in 1904, iodine-induced thyrotoxicosis has been reported in patients with a variety of underlying thyroid diseases. Hyperthyroidism following administration of iodine is termed the Jod-Basedow effect, which is named for the German word for iodine, "Jod," plus the name of Karl Adolph von Basedow, a German physician who described the effect. Iodine-induced thyrotoxicosis may occur in patients with iodine deficiency goiter, in euthyroid patients with Graves disease after antithyroid drug therapy, in patients with multinodular goiters who reside in areas of iodine sufficiency or deficiency, and in people with no evidence of underlying thyroid disease (238,239). The pathogenesis and epidemiology of iodine-induced thyrotoxicosis have been thoroughly reviewed (224,239) and is summarized in the following paragraphs.

Iodine-Induced Thyrotoxicosis in Endemic Iodine-Deficient Areas

The incidence of iodine-induced thyrotoxicosis after salt iodization in areas previously iodide deficient is variable, but may be predicted by the severity of iodine deficiency before prophylaxis and to the amount of iodine intake during prophylaxis (224). Single oral doses of 200-, 400-, and 800-mg iodized oil administered to severely iodine-deficient goitrous Sudanese adults induced four cases of thyrotoxicosis, and serum TSH concentrations <0.1 mU/L were present in 6% to 17%, 12 months after iodine administration (240). After iodized salt distribution in Zaire, among 190 adult subjects with nodular goiter, 7% developed severe thyrotoxicosis and 2 required antithyroid drug treatment (241). In Zimbabwe, following the iodization of salt at a level of 30 to 90 ppm, there was a threefold increase in iodine-induced thyrotoxicosis (242). Thyrotoxicosis can also be precipitated by lower doses of iodine provided to less iodine-deficient populations. For example, in Denmark, in a population with moderate iodide deficiency, the prevalence of thyrotoxicosis slightly increased after iodine intake was increased by only 50 μg/day (243); most patients had multinodular goiters and were elderly.

It appears that thyroidal autonomy and thyrotoxicosis occur when iodine

repletion permits the autonomous tissue to synthesize and release excess quantities of thyroid hormone. The importance of thyroid autonomy for the development of iodine-induced thyrotoxicosis is strengthened by a report of iodine-induced thyrotoxicosis in a woman with a multinodular goiter treated with suppressive doses of T4 and simultaneously exposed to high quantities of iodine (244). These observations suggest that the increased incidence of thyrotoxicosis in endemic areas after iodine exposure is due to underlying macro- or micronodular disease with autonomous thyroid nodules or latent Graves disease. In studies in Belgium and Greece (245,246), the administration of small quantities of iodine (0.5 mg/day) to euthyroid patients with autonomous nodules induced thyrotoxicosis in about 50%. In Austria in 1990, an increase in salt iodization from 10 to 20 ppm was accompanied by an increase in the incidence of overt thyrotoxicosis from 30.5 to 41.7 cases per 100,000 in 1992 and an increase in overt Graves thyrotoxicosis from 10.4 to 20.9 cases per 100,000 (247). The increased incidence of iodine-induced hyperthyroidism observed in Denmark after introduction of the salt iodization led to a transient increase in therapeutic use of antithyroid drugs in the population, which fell to a rate lower than before salt iodization after about 10 years (248).

Radiography Contrast Media–Induced Thyrotoxicosis

Iodine-induced thyrotoxicosis was reported in elderly persons in Australia (249) and Germany (250), who had undergone nonionic contrast radiography. These individuals did not have TPO antibodies, and thyroid scans revealed the presence of multinodular goiters. In a prospective study in elderly patients, frank thyrotoxicosis was uncommon following the administration of nonionic contrast agents, whereas subclinical thyrotoxicosis was observed in 8% (251). A case control study in U.S. adults suggested that iodinated contrast media exposure increases risk of subsequent development of incident hyperthyroidism and incident overt hypothyroidism (252). An expert report of the European Society of Urogenital Radiology concluded that iodine-induced thyrotoxicosis following iodinated contrast media can occur but is a rare phenomenon, and does not require prophylactic treatment (253,254).

Latent Graves Disease

Antithyroid drug therapy for Graves disease reduces thyroidal iodine content, and the thyroid is modestly iodine depleted. Overt thyrotoxicosis can develop only if sufficient iodine is available. A small increase in dietary iodine from either iodine ingestion or thyroid hormone administration increases the frequency of recurrence of thyrotoxicosis after antithyroid drug therapy. More than 30 years ago, the difference in remission rates between the United States and Europe were attributed, at least in part, to the higher recurrence rate of Graves disease in the United States due to higher iodide intake (255). However, in an 8-year prospective study, prevalence of thyroid dysfunction in the first-degree relatives of Graves disease patients did not differ from that in the general population with similar iodine status (256). Administration of large quantities of iodine to patients with latent Graves disease may result in worsening thyrotoxicosis. In one study (257), simultaneous administration of methimazole and ipodate, an iodinated oral cholecystographic agent, reduced the effectiveness of the antithyroid drug. Excess iodine administered to thyrotoxic patients with Graves disease significantly increased anti-TSH receptor antibody levels, suggesting that this phenomenon might be responsible for iodine-induced thyrotoxicosis in these patients (258).

AMIODARONE-INDUCED THYROID DISEASE (SEE Chapter 11)

Amiodarone, a benzofuranic derivative containing 75-mg iodine per 200-mg tablet, is widely used for the long-term treatment of cardiac arrhythmia. About 9-mg iodine is released daily during the metabolism of the drug (300-mg dose), which has a prolonged half-life of at least 100 days. Beyond its effects on the heart, amiodarone is a potent inhibitor of type I and type II deiodinase and is frequently associated with iodine-induced thyroid dysfunction (259). In view of the high incidence of thyroid dysfunction, amiodarone should be administered with caution to patients with pre-existing goiter or a history of thyroid disease. Before beginning amiodarone treatment, a careful examination is required; serum TSH, FT4, and TPO antibodies' values should be obtained. During amiodarone treatment, the

measurement of serum TSH should be carried out approximately every 6 months in order to detect the development of thyroid dysfunction. Should the TSH become abnormal, measurement of circulating thyroid hormones should be done.

Hypothyroidism

The etiology of amiodarone-induced hypothyroidism can be partially explained by the excess iodine released during the metabolism of the drug. Evidence for the essential role of iodine in the pathogenesis of amiodarone-associated hypothyroidism stems from the observation that administration of potassium perchlorate, which prevents thyroid iodide uptake and increases the release of inorganic iodine from the thyroid, restored euthyroidism (260). Iodine-induced hypothyroidism occurs most frequently in patients with pre-existing thyroid autoimmunity during amiodarone treatment (261). When LT4 treatment is indicated, higher than usual doses may be required to normalize serum TSH levels because of a decrease in conversion of T4 to T3 within the pituitary gland. Amiodarone-induced hypothyroidism does not require interruption of amiodarone therapy (259,262).

TABLE 15-8. Features of Amiodarone-Induced Thyrotoxicosis

	Iodine-Induced Thyrotoxicosis (Type 1)	Destructive Thyrotoxicosis (Type 2)
Underlying thyroid abnormality	Yes	No
Pathogenesis	Excessive thyroid hormone synthesis and release	Excessive thyroid hormone release
Thyroidal RAIU	Low, rarely normal or elevated	Low
Ultrasound	Diffuse/nodular goiter	Hypoechoic small gland
Color-flow Doppler sonography	Normal or increased blood flow	Decreased blood flow
Preferred medical therapy	Thionamides, perchlorate if necessary	Glucocorticoids

Subsequent hypothyroidism	Unlikely	Possible
Effect of excess iodine following the thyrotoxic phase	Possible recurrence of thyrotoxicosis	Likely iodine-induced hypothyroidism

Thyrotoxicosis

Amiodarone-induced thyrotoxicosis results from two different mechanisms (245,248). The iodine released during the metabolism of the drug is responsible for the thyrotoxicosis (amiodarone-induced thyrotoxicosis type 1 [AIT type 1]) in many cases. Predisposing factors include micro- and macronodular goiter, which are common in older patients who most often require amiodarone and, far less common, thyroid-stimulating antibodies (i.e., latent Graves disease). Amiodarone may also induce destructive thyroiditis (type 2), resulting in thyrotoxicosis, which is likely not related to the drug's iodine content. The clinical and pathologic characteristics of types 1 and 2 amiodarone-induced thyrotoxicosis are described in Table 15-8. Distinction between the two forms is important for determining therapy. Large doses of antithyroid drugs are recommended for amiodarone-induced thyrotoxicosis type 1 (259). If this treatment fails, potassium perchlorate may be added, if available (263). The latter drug blocks thyroid iodine uptake, thereby decreasing the intrathyroidal iodine content. In patients with destructive thyrotoxicosis, administration of large doses of glucocorticoids is effective (259,264). Relapses are frequent as the glucocorticoid dose is tapered. Surgery has been successfully used for the treatment of amiodarone-induced thyrotoxicosis (259,265).

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