Iodine Deficiency

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Iodine deficiency has multiple adverse effects in humans, termed iodine deficiency disorders, due to inadequate thyroid hormone production. Globally, it is estimated that 2 billion individuals have an insufficient iodine intake, and South Asia and sub-Saharan Africa are particularly affected. However, about 50% of Europe remains mildly iodine deficient, and iodine intakes in other industrialized countries, including the United States and Australia, have fallen in recent years. Iodine deficiency during pregnancy and infancy may impair growth and neurodevelopment of the offspring and increase infant mortality. Deficiency during childhood reduces somatic growth and cognitive and motor function. Assessment methods include urinary iodine concentration, goiter, newborn TSH, and blood thyroglobulin. But assessment of iodine status in pregnancy is difficult, and it remains unclear whether iodine intakes are sufficient in this group, leading to calls for iodine supplementation during pregnancy in several industrialized countries. In most countries, the best strategy to control iodine deficiency in populations is carefully monitored universal salt iodization, one of the most cost-effective ways to contribute to economic and social development. Achieving optimal iodine intakes from iodized salt (in the range of 150–250 μg/d for adults) may minimize the amount of thyroid dysfunction in populations. Ensuring adequate iodine status during parenteral nutrition has become important, particularly in preterm infants, as the use of povidone-iodine disinfectants has declined. Introduction of iodized salt to regions of chronic iodine deficiency may transiently increase the incidence of thyroid disorders, but overall, the relatively small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency. **(*Endocrine Reviews* 30: 376–408, 2009)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/er.2009-0011 Received March 23, 2009. Accepted May 8, 2009.
First Published Online May 21, 2009

Abbreviations: AI, Adequate intake; BMIC, breast milk iodine concentration; CI, confidence interval; DALY, disability-adjusted life year; DIT, diiodotyrosine; EAR, estimated average requirement; FT4, free T_4; IDD, iodine deficiency disorder; IGFBP, IGF binding protein; IIH, iodine-induced hyperthyroidism; IMR, infant mortality rate; MIT, monoiodotyrosine; NIS, sodium/iodide symporter; PII, plasma inorganic iodide; PN, parenteral nutrition; RDA, recommended dietary allowance; RIC, renal iodine clearance; RNI, recommended nutrient intake; Tg, thyroglobulin; TPO, thyroperoxidase; UI, urinary iodine concentration; USI, universal salt iodization.

I. Introduction

IODINE (atomic mass, 126.9 amu) is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. In 1811, Courtois discovered iodine as a violet vapor arising from seaweed ash while manufacturing gunpowder for Napoleon's army. Gay-Lussac identified it as a new element, and named it iodine, from the Greek for "violet." Iodine was found in the thyroid gland by Baumann in 1895 (1). In 1917, Marine and Kimball showed that thyroid enlargement (goiter) was caused by iodine deficiency and could be prevented by iodine supplementation (2). Goiter prophylaxis through salt iodization was first introduced in Switzerland and the United States in the early 1920s.

In 1980, the first global estimate from the World Health Organization (WHO) on the prevalence of goiter was reported; it estimated that 20–60% of the world's population was iodine deficient and/or goitrous, 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 1970–1990. Controlled studies in iodine-deficient regions showed that iodine supplementation not only eliminated new cases of cretinism but also reduced infant mortality and improved cognitive function in the rest of the population (3). The term "iodine deficiency disorders" (IDD) was coined, and IDD became widely recognized as a spectrum of related disorders potentially affecting 1.5 billion individuals. 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 IDD has been an integral part of many national nutrition strategies (4).

II. Ecology

Iodine (as iodide) is widely but unevenly distributed in the earth's environment. 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 sea water is approximately 50 μg/liter. Iodide ions in seawater are oxidized to elemental iodine, which volatilizes into the atmosphere and is returned to the soil by rain, completing the cycle (5). However, iodine cycling in many regions is slow and incomplete, leaving soils and drinking water iodine depleted. 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 with approximately 1 mg/kg in plants from iodine-sufficient soils.

Iodine-deficient soils are common in mountainous areas (*e.g.*, the Alps, Andes, Atlas, and Himalayan ranges) and areas of frequent flooding, especially in South and Southeast Asia (for example, the Ganges River plain of northeastern India). Although many inland areas, including central Asia and Africa and central and eastern Europe are iodine deficient, iodine deficiency may also affect coastal and island populations. Iodine deficiency in populations residing in these areas will persist until iodine enters the food chain through addition of iodine to foods (*e.g.*, iodization of salt) or dietary diversification introduces foods produced outside the iodine-deficient area. The current global prevalence of iodine deficiency is discussed in *Section VIII*.

III. Dietary Sources

The native iodine content of most foods and beverages is low. In general, commonly consumed foods provide 3 to 80 μg per serving (6, 7). Foods of marine origin have higher iodine content because marine plants and animals concentrate iodine from seawater. Iodine in organic form occurs in high amounts in certain seaweeds. Inhabitants of the coastal regions of Japan, whose diets contain large amounts of seaweed, have remarkably high iodine intakes amounting to 50 to 80 mg/d. In the United States, the median intake of iodine from food in the mid-1990s was estimated to be 240 to 300 μg/d for men and 190 to 210 μg/d for women (8). Major dietary sources of iodine in the United States are bread and milk (9). In Switzerland, based on direct food analysis, mean intake of dietary iodine is approximately 140 μg/d, mainly from bread and dairy products (7). In many countries, use of iodized salt in households for cooking and at the table provides additional iodine. Boiling, baking, and canning of foods containing iodated salt cause only small losses (≤10%) of iodine content (10).

Iodine content in foods is also influenced by iodine-containing compounds used in irrigation, fertilizers, and livestock feed. Iodophors used for cleaning milk cans and

teats can increase the native iodine content of dairy products. Traditionally, iodate was used in bread making as a dough conditioner, but it is being replaced by non-iodine-containing conditioners. Erythrosine is a red coloring agent high in iodine that is widely used in foods, cosmetics, and pharmaceuticals. Dietary supplements often contain iodine. Based on data from the Third National Health and Nutrition Examination Survey (NHANES III), 12% of men and 15% of nonpregnant women took a supplement that contained iodine, and the median intake of iodine from supplements was approximately 140 μg/d for adults (8). Other sources of iodine include water purification tablets, radiographic contrast media, medicines (*e.g.*, a 200-mg tablet of amiodarone, an antiarrhythmic drug, contains 75 mg), and skin disinfectants (*e.g.*, povidone-iodine contains approximately 10 mg/ml).

IV. Absorption and Metabolism

Iodine is ingested in several chemical forms. Iodide is rapidly and nearly completely absorbed in the stomach and duodenum. Iodate, widely used in salt iodization, is reduced in the gut and absorbed as iodide. In healthy adults, the absorption of iodide is greater than 90% (11). In animal models, the sodium/iodine symporter (NIS) is functionally expressed on the apical surface of enterocytes and mediates active iodine accumulation (12). Organically bound iodine is typically digested and the released iodide absorbed, but some forms may be absorbed intact; for example, approximately 70% of an oral dose of T_4 is absorbed intact (13).

The distribution space of absorbed iodine is nearly equal to the extracellular fluid volume (14). Iodine is cleared from the circulation mainly by the thyroid and kidney, and whereas renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. In conditions of adequate iodine supply, no more than 10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80% (14–16). During lactation, the mammary gland concentrates iodine and secretes it into breast milk to provide for the newborn (17). 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 iodine has a half-life of approximately 10 h, but this is shortened if the thyroid is overactive, as in iodine deficiency or hyperthyroidism (14–16).

The body of a healthy adult contains 15 to 20 mg of iodine, of which 70 to 80% is in the thyroid (18). In chronic iodine deficiency, the iodine content of the thyroid may fall below 20 μg. In iodine-sufficient areas, the adult thyroid traps approximately 60 μg of iodine per day to balance losses and maintain thyroid hormone synthesis (14–16). A transmembrane protein in the basolateral membrane, the NIS, transfers iodide into the thyroid at a concentration gradient 20 to 50 times that of plasma (19). The human NIS gene is located on chromosome 19 and codes for a protein of 643 amino acids (20). The NIS 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 (19). The decrease in thyroidal iodide transport from excess iodide administration is related to a decrease in NIS expression (21).

At the apical surface of the thyrocyte, the enzymes thyroperoxidase (TPO) and hydrogen peroxide oxidize iodide and attach it to tyrosyl residues on thyroglobulin to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), the precursors of thyroid hormone (22). TPO then catalyzes the coupling of the phenyl groups of the iodotyrosines through a diether bridge to form the thyroid hormones (22, 23). Linkage of two DIT molecules produces T_4, and linkage of a MIT and DIT produces T_3. Thus, T_3 is structurally identical to T_4 but has one less iodine (at the 5′ position on the outer ring). Iodine comprises 65 and 59% of the weights of T_4 and T_3, respectively. In the thyroid, mature thyroglobulin (Tg), containing 0.1 to 1.0% of its weight as iodine, is stored extracellularly in the luminal colloid of the thyroid follicle (22, 23). After endocytosis, endosomal and lysosomal proteases digest Tg and release T_4 and T_3 into the circulation. Degradation of T_4 and T_3 in the periphery—the half-life of circulating T_4 is 5–8 d, and for T_3, 1.5 to 3 d—releases iodine that enters the plasma iodine pool and can be taken up by the thyroid or excreted by the kidney (24). More than 90% of ingested iodine is ultimately excreted in the urine, with only a small amount appearing in the feces.

A. Thyroidal adaptation to iodine deficiency

The thyroid adapts to low intakes of dietary iodine by marked modification of its activity, triggered by increased secretion of TSH by the pituitary. In most individuals, if iodine intake falls below approximately 100 μg/d, TSH secretion is augmented, which increases plasma inorganic 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 (25). As a greater fraction of circulating iodide is cleared by the thyroid, there is a progressive reduction in renal iodide excretion. TSH also stimulates breakdown of Tg and preferential synthesis and release of T_3 into the blood (26). As long as daily iodine intake remains above a threshold of

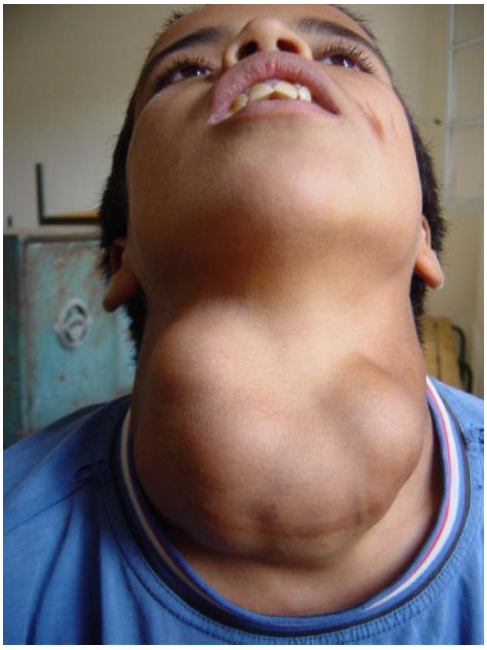

FIG. 1. Large nodular goiter in a 14-yr-old boy photographed in 2004 in an area of severe IDD in northern Morocco, with tracheal and esophageal compression and hoarseness, likely due to damage to the recurrent laryngeal nerves.

approximately 50 μg/d, despite a decrease in circulating plasma inorganic iodine, absolute uptake of iodine by the thyroid remains adequate, and the iodine content of the thyroid remains within normal limits (≈10–20 mg). Below this threshold, despite high fractional clearance of plasma inorganic iodine by the thyroid, absolute intake falls, the iodine content of the thyroid is depleted, and many individuals develop goiter (27).

In large colloid goiter, the configuration of Tg is abnormal, reducing the efficiency of thyroid hormone synthesis (28). Initially, goiters are characterized by diffuse, homogeneous enlargement, but over time, nodules often develop (Fig. 1). Many thyroid nodules derive from a somatic mutation and are of monoclonal origin (29); the mutations appear to be more likely in nodules under the influence of a growth promoter, such as iodine deficiency. Although iodine deficiency produces diffuse goiter in all age groups, it is also associated with a high occurrence of multinodular toxic goiter mainly seen in women older than 50 yr (30). The characteristic pattern of circulating thyroid hormones in children in areas of moderate-to-severe iodine deficiency is a variably elevated TSH, a low serum T_4, and a normal or high-normal T_3; this pattern is also seen in adults, but less predictably, and it may not be present (31). The serum Tg concentration is typically elevated (32). Thyroid failure and cretinism usually develop only in regions of chronic, severe iodine deficiency where individuals show low circulating T_4 and T_3 and dramatically elevated TSH (33, 34). 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.

B. Goitrogens

Dietary substances that interfere with thyroid metabolism can aggravate the effect of iodine deficiency, and they are termed goitrogens (35). 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 (36). 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 (37).

Soy and millet contain flavonoids that may impair TPO activity. Use of soy-based formula without added iodine can produce goiter and hypothyroidism in infants, but in healthy adults, soy-based products appear to have negligible effects on thyroid function (38). Unclean drinking water may contain humic substances that block thyroidal iodination, and industrial pollutants, including resorcinol and phthalic acid, may also be goitrogenic (35). Perchlorate is a competitive inhibitor of thyroidal iodine uptake (39), but 6-month exposure to perchlorate at doses up to 3 mg/d has no effect on thyroid iodide uptake or serum levels of thyroid hormones (40). It appears that most of these goitrogenic substances do not have a major clinical effect unless there is coexisting iodine deficiency.

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 metabolism, and these effects have been implicated in the etiology of myxedematous cretinism (41). Iron deficiency reduces heme-dependent TPO activity in the thyroid and impairs production of thyroid hormone. In goitrous children, iron deficiency anemia blunts the efficacy of iodine prophylaxis whereas iron supple-

mentation improves the efficacy of iodized oil and iodized salt (42). Pregnant women are highly vulnerable to iron deficiency anemia, and poor maternal iron status predicts both higher TSH and lower T_4 concentrations during pregnancy in an area of borderline iodine deficiency (43). 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 (44, 45).

V. Requirements

Several methods have been used to estimate the requirement for iodine. Daily uptake and turnover of radioactive iodine can be used to estimate the requirement for iodine, provided that the subjects tested have adequate iodine status and are euthyroid (18, 46, 48). Several studies have estimated iodine requirements from balance studies (49–53), but these have serious limitations: many ingested substances contain unrecognized iodine, and strict control of iodine intake is difficult. Moreover, because of the need to consider the iodine in the thyroidal compartment in addition to iodine intake and excretion, even in prolonged balance studies equilibrium may not be clearly established (49).

A. Definitions

The following definitions are from the U.S. Institute of Medicine (IOM) (8) (Table 1):

- The estimated average requirement (EAR) is the daily iodine intake that meets the requirement of half of the healthy individuals in a particular life stage. The EAR is not meant to be used in the assessment of intake in individuals, but it can be used for groups.
- The recommended dietary allowance (RDA) for iodine is the average daily intake sufficient to meet the iodine requirement of 97–98% of healthy individuals in a life stage. It can be used as a goal for daily iodine intake by individuals. The RDA is derived from the EAR, considering the estimated variability in individual requirements.
- The adequate intake (AI) is given if there is insufficient scientific evidence to calculate an EAR. For example, the AI for iodine in infancy is based on observed mean iodine intakes by healthy full-term breastfed infants in iodine-sufficient areas. The AI is expected to meet or exceed the amount of iodine needed in "essentially all" individuals in the specified population group, and it can be used as a goal for individual intake.

The following definition is from the WHO (54):

- The recommended nutrient intake (RNI) for iodine is the intake estimated to cover the needs of "nearly all" healthy individuals in the specified life stage.

TABLE 1. Recommendations for iodine intake (μg/d) by age or population group

Age or population group	IOM EAR	IOM AI or RDA	Age or population group	WHO RNI
Infants 0–12 months		110–130	Children 0–5 yr	90
Children 1–8 yr	65	90	Children 6–12 yr	120
Children 9–13 yr	73	120		
Adults ≥14 yr	95	150	Adults >12 yr	150
Pregnancy	160	220	Pregnancy	250
Lactation	200	290	Lactation	250

IOM, Ref. 8; WHO, Ref. 54.

B. Adulthood

Iodine turnover, thyroidal radioiodine uptake, and balance studies in euthyroid adults have suggested that the average daily requirement for iodine is 91–96 μg/d (18, 46, 50). 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 at least 14 yr of age from the IOM has been set at 95 μg/d (8). The corresponding RDA (defined as the EAR plus twice the coefficient of variation in the population, rounded to the nearest 50 μg) is 150 μg/d (8). This agrees with the WHO recommendation for adequate daily iodine intake of 150 μg/d for men and nonpregnant, nonlactating women (54).

C. Pregnancy and lactation

The iodine requirement during pregnancy is increased due to: 1) an increase in maternal T_4 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 renal iodine clearance (55). Balance studies have found that the average iodine retention of full-term infants is 7.3 μg/kg · d (56, 57); the mean retention of a healthy fetus with a weight of 3 kg would be approximately 22 μg/d. Estimated daily fetal iodine retention added to the EAR of 95 μg/d for nonpregnant women would yield an EAR of 117 μg/d, but this would not take into account the iodine needed to increase maternal T_4 production and balance additional urinary losses. Dworkin *et al.* (49) found five pregnant women were at balance when consuming approximately 160 μg/d, with no significant differences pre- and postpartum.

Several authors have roughly estimated iodine requirements during pregnancy by correlating the effects of iodine supplementation with changes in thyroid volume during

pregnancy; in studies by Romano *et al.* (58) and Pedersen *et al.* (59), total daily iodine intakes of approximately 200 μg/d and 250–280 μg/d, respectively, during pregnancy prevented an increase in thyroid volume, whereas in a study of Glinoer (60), total daily iodine intake of approximately 150 μg/d was insufficient to prevent an increase in thyroid size. On the basis of the above data, the IOM set the EAR at 160 μg/d for pregnancy in women at least 14 yr of age and the RDA, set at 140% of the EAR rounded to the nearest 10 μg, at 220 μg/d (8). WHO recommends a daily iodine intake of 250 μg/d for pregnant women, a value approximately 10% higher than the RDA (54).

Based on mean breast milk excretion of 0.78 and 0.6 liters/d in the first and second 6 months of infancy, respectively (8), and a mean breast milk iodine concentration (BMIC) of 146 μg/liter in iodine-sufficient women from the United States, the average daily loss of iodine in breast milk has been estimated to be approximately 115 μg/d (8). Added to the EAR for nonpregnant women of 95 μg/d, the EAR for lactating women at least 14 yr of age is set at 209 μg/d by the IOM (8). The RDA is 140% of the EAR rounded to the nearest 10 μg, or 290 μg/d of iodine. WHO recommends a daily iodine intake of 250 μg/d for lactating women (54).

D. Infancy

Because no functional criteria are available that reflect iodine intake in infants, recommended intakes are based on mean iodine intake of healthy full-term infants fed human milk. The IOM based their recommendation on the median BMIC of women in the United States in the early 1980s, that is 146 μg/liter (8). Based on estimates of mean daily breast milk excretion, the mean amount of iodine secreted in human milk is estimated to be approximately 115 μg/d (8). Considering these data, the AI for iodine for infants ages 0–6 and 6–12 months from the IOM has been set at 110 and 130 μg/d, respectively (8), and WHO recommends a daily iodine intake of 90 μg/d for infants (54). But because iodine intakes in the U.S. population were excessive in the early 1980s (61), the BMIC used was at the upper end of the range of 78–167 μg/liter reported for iodine-sufficient countries (62). Although high maternal iodine intakes can result in high BMIC, iodine intakes by the infant greater than his or her requirements will simply be excreted in the urine. Thus, iodine requirements during lactation should be based on infant balance studies rather than the measured but variable amount excreted in breast milk from women in iodine-sufficient countries. Balance studies in full-term infants fed 20 μg/kg · d of iodine found that iodine retention was 7.3 μg/kg · d (57). If the reference body weight at 6 months of age is 7 kg (8), daily retention of iodine in a 6-month-old infant in positive balance is approximately 50 μg.

E. Childhood

In a balance study in children aged 1.5 to 2.5 yr (63), the median iodine intake was 63.5 μg/d, and the average iodine balance was +19 μg/d. Children 8 yr of age who consumed approximately 40 μg/d of iodine were in negative iodine balance (−23 to −26 μg/d), indicating that the average minimum requirement is approximately 65 μg/d (64). No other studies for assessing iodine requirements for young children are available; therefore an EAR of 65 μg/d was set for ages 1–8 yr (8). For the remainder of childhood and adolescence, there are few data available for estimating an average requirement, so the EAR was set by extrapolating down from adult data (8). The RDAs for childhood were then set at 140% of the EAR. 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 yr) (54).

VI. Methods to Assess Status

Four methods are generally recommended for assessment of iodine nutrition in populations: urinary iodine concentration (UI), the goiter rate, serum TSH, and serum Tg. These indicators are complementary, in that UI 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).

A. Thyroid size

Two methods are available for measuring goiter: 1) neck inspection and palpation; and 2) 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 (54), 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 (65). Thyroid ultrasound is noninvasive, quickly done (2–3 min per subject), and feasible even in remote areas using portable equipment. However, interpretation of thyroid volume data requires valid references from iodine-sufficient children. In a recent multicenter study, thyroid volume was measured in 6- to 12-yr-old children (n = 3529) living in areas of long-term iodine sufficiency on five

continents. Age- and body surface area-specific 97th percentiles for thyroid volume were calculated for boys and girls (66). Goiter can be classified according to these international reference criteria, but the criteria are only applicable if thyroid volume is determined by a standard method (66, 67). Thyroid ultrasound is subjective and requires judgment and experience. Differences in technique can produce interobserver errors in thyroid volume as high as 26% (68).

In areas of endemic goiter, although thyroid size predictably decreases in children in response to increases in iodine intake, thyroid size may not return to normal for months or years after correction of iodine deficiency (69, 70). 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. Aghini-Lombardi *et al.* (69) suggested that enlarged thyroids in children who were iodine deficient during the first years of life may not regress completely after introduction of salt iodization. If true, this suggests that to achieve a goiter rate below 5% in children may require that they grow up under conditions of iodine sufficiency. A sustained salt iodization program will decrease the goiter rate by ultrasound to less than 5% in school-age children, and this indicates disappearance of iodine deficiency as a significant public health problem (54). WHO recommends that the total goiter rate be used to define severity of iodine deficiency in populations using the following criteria: below 5%, iodine sufficiency; 5.0–19.9%, mild deficiency; 20.0–29.9%, moderate deficiency; and above 30%, severe deficiency (54).

TABLE 2. Epidemiological criteria from the WHO for assessment of iodine nutrition in a population based on median or range of UI (Refs. 4 and 54)

UI (μg/liter)	Iodine intake	Iodine nutrition
School-aged children		
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimum
200–299	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible groups
>300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150	Insufficient	
150–249	Adequate	
250–499	More than adequate	
≥500[a]	Excessive	
Lactating women[b]		
<100	Insufficient	
≥100	Adequate	
Children less than 2 yr of age		
<100	Insufficient	
≥100	Adequate	

There is no information about iodine nutrition for pregnant and lactating women in the WHO assessment table, and the upper limits of the median UI for lactating women and children less than 2 yr of age were not specified.

[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 UI are lower than the iodine requirements because of the iodine excreted in breast milk.

B. Urinary iodine concentration

Because more than 90% of dietary iodine eventually appears in the urine (12, 53), UI is an excellent indicator of recent iodine intake. UI can be expressed as a concentration (micrograms per liter), in relationship to creatinine excretion (micrograms iodine per gram creatinine), or as 24-h excretion (micrograms per day). For populations, because it is impractical to collect 24-h samples in field studies, UI can be measured in spot urine specimens from a representative sample of the target group and expressed as the median, in micrograms per liter (54). Variations in hydration among individuals generally even out in a large number of samples, so that the median UI in spot samples correlates well with that from 24-h samples. For national school-based surveys of iodine nutrition, the median UI from a representative sample of spot urine collections from approximately 1200 children (30 sampling clusters of 40 children each) can be used to classify a population's iodine status (54) (Table 2). Although the median UI does not provide direct information on thyroid function, a low value suggests that a population is at higher risk of developing thyroid disorders.

However, the median UI is often misinterpreted. Individual iodine intakes and, therefore, spot UIs are highly variable from day to day (72), and a common mistake is to assume that all subjects with a spot UI less than 100 μg/liter are iodine deficient. To estimate iodine intakes in individuals, because of day-to-day variability, several 24-h collections are preferable but would be difficult to obtain. An alternative is to use the age- and sex-adjusted iodine:creatinine ratio in adults, but this also has limitations (73). Creatinine may be unreliable for estimating daily iodine excretion from spot samples, especially in malnourished subjects where creatinine concentration is low. Daily iodine intake for population estimates can be extrapolated from UI, using estimates of mean 24-h urine volume and assuming an average iodine bioavailability of 92% using the formula: urinary iodine (μg/liter) × 0.0235 × body weight (kg) = daily iodine intake (8). Using this formula, a median UI of 100 μg/liter corresponds roughly to an average daily intake of 150 μg.

C. Thyroid stimulating hormone

Because serum TSH is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake, TSH can be used as an indicator of iodine nutrition. However, in older children and adults, although serum TSH may be slightly increased by iodine deficiency, values often remain within the normal range (27, 31–34). TSH is therefore a relatively insensitive indicator of iodine nutrition in adults. In contrast, TSH is a sensitive indicator of iodine status in the newborn period (74, 75), as discussed in *Section VI.H*.

D. 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 less than 10 μg/liter (76). In areas of endemic goiter, serum Tg increases due to greater thyroid cell mass and TSH stimulation (43). Serum Tg is well correlated with the severity of iodine deficiency as measured by UI (77). Intervention studies examining the potential of Tg as an indicator of response to iodized oil and potassium iodide (KI) have shown that Tg falls rapidly with iodine repletion and that Tg is a more sensitive indicator of iodine repletion than TSH or T_4 (78, 79). However, commercially available assays measure serum Tg, which requires venipuncture, centrifugation, and frozen sample transport, which may be difficult in remote areas.

A new assay for Tg has been developed for dried blood spots taken by a finger prick (80, 81), 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 (80, 81). However, several questions need to be resolved before Tg can be widely adopted as an indicator of iodine status. One question is the need for concurrent measurement of anti-Tg antibodies to avoid potential underestimation of Tg; it is unclear how prevalent anti-Tg antibodies are in iodine deficiency or whether they are precipitated by iodine prophylaxis (82, 83). Another limitation is large interassay variability and poor reproducibility, even with the use of standardization (76). This has made it difficult to establish normal ranges and/or cutoffs to distinguish severity of iodine deficiency. However, recently an international reference range and a reference standard for dried blood spot Tg in iodine-sufficient schoolchildren (4–40 μg/liter) has been made available (81).

E. Thyroid hormone concentrations

In contrast, thyroid hormone concentrations are poor indicators of iodine status. In iodine-deficient populations, serum T_3 increases or remains unchanged, and serum T_4 usually decreases (27, 31). However, these changes are often within the normal range, and the overlap with iodine-sufficient populations is large enough to make thyroid hormone levels an insensitive measure of iodine nutrition (54).

F. Assessing status during pregnancy

The median UI is recommended by WHO/International Council for the Control of Iodine Deficiency Disorders (ICCIDD)/UNICEF (54) for assessing iodine nutrition in pregnant women. The expected UI in micrograms per liter can be extrapolated from a recommended daily iodine intake, assuming median 24-h urine volumes for girls aged 7–15 yr of 0.9 ml/h/kg (84) and for adult women of approximately 1.5 liters (85), and assuming a mean iodine bioavailability of 92%. Thus, the recommended daily iodine intakes for pregnancy of 220 to 250 μg (8, 54) would correspond to a UI of approximately 135–150 μg/liter. Pregnancy may occur in adolescence, particularly in developing countries; in a 15-yr-old girl weighing approximately 50 kg, daily iodine intake of 220 and 250 μg would correspond to a UI of approximately 185–215 μg/liter.

However, during pregnancy this estimation of intake from UI may be less valid due to an increase in glomerular filtration rate (86) and, possibly, renal iodine clearance (RIC) (87). If RIC increases in pregnancy, the daily iodine intake extrapolated from the UI in pregnancy would be lower than that in nonpregnancy. However, the evidence for an increase in RIC and a decrease in plasma inorganic iodide (PII) concentration during pregnancy is equivocal. One study (87) suggested an increase in RIC using an indirect method, whereas Liberman *et al.* (88) directly measured PII and reported no significant difference in PII or UI during pre- and postpartum in 16 women, but they were from an area of high iodine intake. The iodine balance study by Dworkin *et al.* (49) also found no differences in UI pre- and postpartum. It is unclear whether pregnancy *per se* significantly increases UI.

Considering this uncertainty, a recent WHO expert group recommended the median UI that indicates adequate iodine intake during pregnancy to be 150–249 μg/liter (54) (Table 2). However, WHO emphasized that the scientific evidence on which the recommendation is based is weak, and that more data are needed on the level of iodine intake (and the corresponding UI) that ensures maternal and newborn euthyroidism. Also, the median UI is a population indicator and should not be used for the purpose of individual diagnosis and treatment of pregnant women (89).

Using a median cutoff of 150 μg/liter, several recent studies have found marginal or deficient iodine status in pregnant women from areas with only partial household coverage with iodized salt, including Italy, India, Thai-

land, and the United States (90–93). Traditionally, the median UI in school-aged children is recommended for assessment of iodine nutrition in populations. If the median UI is adequate in school-aged children, it is usually assumed that iodine intakes are also adequate in the remaining population, including pregnant women. However, a recent Thai study within families eating from the same household food basket found that the median UI in schoolchildren was 200 μg/liter, whereas the median UI in their pregnant mothers was only 108 μg/liter (92). Thus, the median UI in school-aged children may not always be a good surrogate for monitoring iodine status in pregnancy; it may be prudent to monitor pregnant women directly. More studies in other populations are needed to clarify this issue.

G. Assessing status during lactation

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 (94, 95). This may help explain why, in areas of iodine deficiency, BMICs are often greater than expected based on the UI of the lactating mother (95–97). For example, a recent study in lactating women in the United States with a median UI of 114 μg/liter reported a median BMIC of 155 μg/liter (range, 3–1968 μg/liter) (96).

Based on the balance studies of Delange *et al.* (57), the full-term infant's requirement for iodine is approximately 7 μg/kg. Based on mean breast milk excretion of 0.78 liters in the first 6 months of infancy (8), and assuming that the iodine in breast milk is 95% absorbed, a BMIC of at least 80 μg/liter would likely cover the infant's iodine requirement (approximately 50 μg/d) until weaning foods are begun. Most infants begin weaning by the second half of the first year, and some of the iodine requirement during that period will be met by weaning foods. Semba and Delange (97) proposed that a potential indicator of iodine status in a population could be the proportion of lactating women whose BMIC is at least 100 μg/liter. There is no consensus on what an adequate BMIC is, and WHO has not made a recommendation on this issue. A review of BMIC among the iodine-sufficient countries reported a wide range of mean or median concentrations, from 50 μg/liter in Finland to 270 μg/liter in the United States, but sample sizes were small and not representative, making it difficult to draw conclusions (62).

For the mother, although the iodine requirement is high (200–290 μg/d), after accounting for iodine losses into breast milk, the median UI in lactating women that indicates adequate iodine nutrition is the same as that of nonpregnant, nonlactating women (54) (Table 2).

H. Assessing status during infancy

WHO recommendations state that a median UI of at least 100 μg/liter in infants is sufficient (54). At the same time, they recommend an iodine intake of 90 μg/d during infancy (54) and suggest extrapolating from this to a median UI assuming a urine volume of 300–500 ml/d, but this would produce a higher cutoff of at least 180 μg/liter. To clarify this, UI was recently measured in a representative national sample of healthy, full-term, iodine-sufficient, euthyroid, breastfeeding Swiss infants in the first week after birth (98). Median UI was 77 [95% confidence interval (CI), 76–81] μg/liter, suggesting that the current WHO median UI cutoff for iodine sufficiency in infancy (≥100 μg/liter) may be too high for the first week after birth. Extrapolating from this median UI, assuming a urine volume of 300–500 ml/d, suggests that the mean daily iodine intake in iodine-sufficient Swiss newborns in the first week is 30–50 μg/d. This estimated iodine intake is consistent with data from balance studies in infants that suggest that the mean iodine requirement is likely not more than 8–10 μg/kg · d, and the estimated infant requirement of 40 μg iodine/d in the 1989 U.S. RDA extrapolated from the relative energy requirements of adults (98, 99). These data suggest that the current recommendations for iodine intake in early infancy of 90–110 μg/d (8, 54) are too high. More data are needed to clarify this issue. Worldwide, access by health workers to newborns in the first few days after birth is generally good; establishing a firm UI reference range for iodine-sufficient newborns and a simple collection system would facilitate use of UI as an indicator of iodine status in this age group.

TSH screening in newborns may also be useful in assessing iodine status (100–105). 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 (54). 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 with 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, a condition termed transient newborn hypothyroidism. In areas of iodine deficiency, an increase in transient newborn hypothyroidism, indicated by more than 3% of newborn TSH values above the threshold of 5 mU/liter whole blood collected 3 to 4 d after birth, suggests iodine deficiency in the population (54). Recent data from a large representative Swiss study suggest that newborn TSH, obtained with the use of a sensi-

TABLE 3. IDDs by age group (Refs. 3 and 4)

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
	Delayed physical development
Adult	Impaired mental function
	Reduced work productivity
	Toxic nodular goiter; iodine-induced hyperthyroidism
	Increased occurrence of hypothyroidism in moderate-to-severe iodine deficiency; decreased occurrence of hypothyroidism in mild-to-moderate iodine deficiency

tive assay on samples collected 3–4 d after birth, is a sensitive indicator of even marginal iodine nutrition in pregnancy (75). This cutoff needs confirmation in other iodine-sufficient countries with newborn screening programs.

VII. Effects of Deficiency through the Life Cycle

Iodine deficiency has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency disorders (IDDs) (Table 3) and are one of the most important and common human diseases (3, 4). They result from inadequate thyroid hormone production due to lack of sufficient iodine.

A. Pregnancy and infancy

In areas of iodine sufficiency, healthy women maintain iodine stores of 15–20 mg in the thyroid. During pregnancy, to help meet the approximately 50% increase in maternal iodine requirements, women may draw on this significant iodine store (55, 106, 107). However, in areas of chronic iodine deficiency, women enter pregnancy with already depleted iodine stores. With little thyroidal iodine to draw on to meet the increased maternal iodine requirement, pathological changes—goiter and hypothyroidism—may occur that can adversely affect maternal and fetal health.

1. Neurological development of the offspring

In areas of severe chronic iodine deficiency, maternal and fetal hypothyroxinemia can occur from early gestation onward (108). Thyroid hormone is required for normal neuronal migration; myelination of the brain during fetal and early postnatal life and hypothyroxinemia during these critical periods causes irreversible brain damage, with mental retardation and neurological abnormalities (109). The consequences depend upon the timing and severity of the hypothyroxinemia.

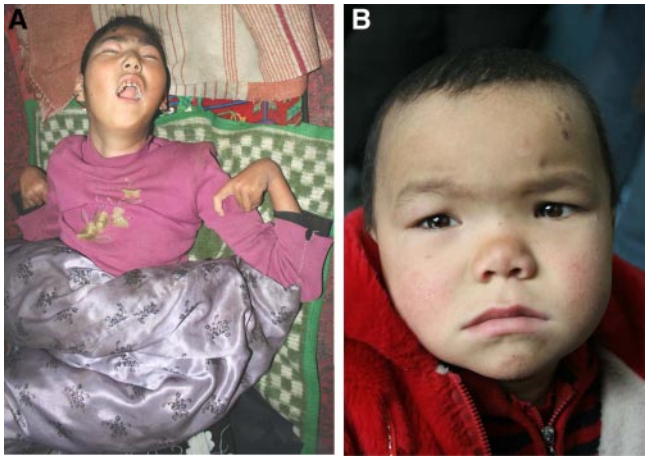

FIG. 2. Neurological cretinism. This 2007 photograph of a 9-yr-old girl from western China demonstrates the three characteristic features: severe mental deficiency together with squint, deaf mutism, and motor spasticity of the arms and legs. The thyroid is present, and frequency of goiter and thyroid dysfunction is similar to that observed in the general population. B, Myxedematous cretinism. This 2008 photograph of a 7-yr-old girl from western China demonstrates the characteristic findings: profound hypothyroidism, short stature (height, 106 cm), incomplete maturation of the features including the naso-orbital configuration, atrophy of the mandible, myxedematous, thickened and dry skin, and dry hair, eyelashes, and eyebrows. The thyroid typically shows atrophic fibrosis.

In McCarrison's (109) original description of cretinism in northern India, he delineated a neurological form, with predominantly neuromotor defects, and a myxedematous form, marked by severe hypothyroidism and short stature. His observations were expanded on by subsequent authors (110, 111). The three characteristic features of neurological cretinism in its fully developed form are severe mental retardation with squint, deaf mutism, and motor spasticity (Fig. 2A). The mental deficiency is characterized by a marked impairment of abstract thought, whereas autonomic and vegetative functions and memory are relatively well preserved, except in the most severe cases. Vision is unaffected, whereas deafness is characteristic. This may be complete in as many as 50% of cretins, as confirmed by studies of auditory brainstem-evoked potentials. The motor disorder shows proximal rigidity of both lower and upper extremities and the trunk, and corresponding proximal spasticity with exaggerated deep tendon reflexes at the knees, adductors, and biceps (100). 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 cre-

tinism from other forms of cerebral palsy commonly encountered in endemic areas, such as cerebral palsy from birth injury or meningitis.

The typical myxedematous cretin (Fig. 2B) has a less severe degree of mental retardation than the neurological cretin but has all the features of severe hypothyroidism present since early life, including severe growth retardation, incomplete maturation of the features including the nasoorbital configuration, atrophy of the mandibles, puffy features, myxedematous, thickened and dry skin, dry and rare hair, and delayed sexual maturation. In contrast to the general population and with neurological cretinism, goiter is usually absent, and the thyroid is usually atrophic (101). Circulating T_4 and T_3 are extremely low, often undetectable, and TSH is dramatically high. It may be difficult to differentiate between these two forms of cretinism; cretinism may present as a mixed form with features of both (100, 101).

Whether mild-to-moderate maternal iodine deficiency causes more subtle impairment of cognitive and/or neurological function in the offspring is uncertain. Two case-control studies in iodine-sufficient women with mild thyroid hypofunction have reported developmental impairment in their offspring. In the United States (112), the IQ scores of 7- to 9-yr-old children of mothers with subclinical hypothyroidism during pregnancy (an increased TSH in the second trimester) were 7 points lower compared with children from mothers with normal thyroid function during pregnancy. In The Netherlands (113), infant development to 2 yr was impaired in children of women with a free T_4 (FT4) below the 10th percentile at 12 wk gestation. These studies suggest that cognitive deficits may occur in the offspring even if maternal hypothyroidism is mild and asymptomatic. However, the maternal thyroid dysfunction in these studies was presumably not due to iodine deficiency because they were done in iodine-sufficient populations. It is unclear whether maternal hypothyroxinemia and/or subclinical hypothyroidism occurs in otherwise healthy pregnant women with mild-to-moderate iodine deficiency (see discussion in *Section VII.A*).

2. Controlled interventions in severe deficiency

In a landmark trial in an area of severe iodine deficiency in Papua New Guinea (114, 115), alternate families received saline (control) or iodized oil injection. The primary outcome was the prevalence of cretinism at 4- and 10-yr follow-up, with more sensitive diagnostic tests applied at the 10-yr follow-up. Iodine supplementation was associated with a significant reduction in the prevalence of endemic cretinism: at 4 yr of age, the relative risk (95% CI) was 0.27 (0.12–0.60), and at 10 yr of age, the relative risk (95% CI) was 0.17 (0.05–0.58). The authors carried out a long-term follow-up on a small subsample of noncretinous children at 11 and 15 yr of age (116) and found no significant differences in motor and cognitive function between the children born to supplemented families and controls.

In a study in Zaire, participants were pregnant women attending antenatal clinics in an area of severe iodine deficiency with a 4% cretinism rate (117–119). Pregnant women were randomly allocated to two groups: one received iodized oil injection, the other an injection of vitamins. Women were on average 28 wk pregnant when they were treated. Psychomotor development scores were measured in the offspring at approximately 72 months of age, but there was a loss to follow-up of approximately 50% in both groups. The psychomotor development scores were significantly higher in the iodine group (mean psychomotor development score, 91 ± 13 *vs.* 82 ± 14), and treatment resulted in far fewer children with low psychomotor scores (0.5% with a score ≤.60 *vs.* 9.7% in the control group).

In a study in western China, an area of severe iodine deficiency and endemic cretinism, participants were groups of children from birth to 3 yr and women at each trimester of pregnancy (120). Untreated children 1–3 yr of age, who were 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 yr. The main outcomes were neurological examination, head circumference, and indexes of cognitive and motor development. A small subsample was followed to approximately 7 yr of age (121). The prevalence of moderate or severe neurological 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 neurological status, but head growth and developmental quotients improved slightly. Treatment at the end of the first trimester did improve neurological outcome. The prevalence of microcephaly was 27% in the untreated children compared with 11% in the treated children. The mean (±SD) developmental quotient at 2 yr of age was higher in the treated than in the untreated children (90 ± 14 *vs.* 75 ± 18) (120).

In the long-term follow-up study (121), development of children (range, 4 to 7.3 yr) whose mothers received iodine during pregnancy and children who received iodine first in their second year was examined. A second group of children (range, 5.8 to 6.9 yr) whose mothers received iodine while pregnant were examined 2 yr later. Head circumference was improved for those who received iodine dur-

ing pregnancy (compared with those receiving iodine at age 2) and for those supplemented before the end of the second trimester (relative to those supplemented during the third trimester). Iodine before the third trimester predicted higher psychomotor test scores for children relative to those provided iodine later in pregnancy or at 2 yr (121).

In a randomized Peruvian trial (122, 123), women of childbearing age from three Andean villages in an area of severe iodine deficiency with a 1–3% cretinism rate were studied. The treatment group received iodized oil injection either before conception or during pregnancy; the control group did not receive an injection. Cognitive development scores were done in a subsample of their children between 1 and 4 yr of age. The initial publication did not find a statistical difference in cognitive outcomes (122). A subsequent reanalysis reassigned children to two groups, iodine-deficient or iodine-sufficient at time of cognitive testing, based on their UI and concentration of T_4. This analysis found a significantly higher IQ score in the iodine-sufficient group compared with the iodine-deficient group (85.6 ± 13.9 *vs.* 74.4 ± 4.8) (123).

In two villages in Ecuador with severe iodine deficiency and a cretinism rate of up to 8%, one village received iodine treatment, and one did not and served as an iodine-deficient control (124). Participants were all women of childbearing age, pregnant women, and children, and coverage with iodine was estimated to be about 90%. The treatment group received one iodized oil injection at baseline and were followed at 4-yr intervals for approximately 20 yr. A series of follow-up studies was done to look at the effects in offspring (124, 125). No more cretins were born in the treated village. Two years after treatment began, the mean developmental quotient in infancy was not significantly different between villages. However, mean IQ measured in first- and second-grade children was higher by approximately 10 points in the treated village than in the control village. Five years after treatment began, the treated group was divided into three subgroups: 1) children born after treatment had begun; 2) children whose mothers had received iodine during pregnancy; and 3) children whose mothers had received iodine before conception. The latter subgroup had significantly higher IQ than the first two groups (72.3 *vs.* 65.2 *vs.* 76.8, respectively). Studies done several years later in these children also suggested that iodine treatment late in pregnancy or afterward had no benefits for children's IQ at 3–5 yr of age, but treatment early in pregnancy or before conception improved IQ (83.7 ± 13.4 *vs.* 72.7 ± 14.0 in treated *vs.* control villages) (125).

These five intervention trials were groundbreaking studies done under difficult conditions in remote areas (1114–125). The Papua New Guinea study had the strongest design and clearly demonstrates that iodine treatment in a population with high levels of endemic cretinism sharply reduces or eliminates incidence of the condition. The Zaire and China trials report that developmental scores were 10–20% higher in young children born to mothers treated during pregnancy or before. The studies in Peru and Ecuador were less well controlled but also suggest modest cognitive benefits for infants and children of maternal iodine treatment. Although the data from the Zaire trial indicate that correction of iodine deficiency even at mid-to-late pregnancy improves infant cognitive development, data from the other trials suggest that the neurological deficits can only be prevented when iodine is given before or early in pregnancy.

3. Controlled interventions in mild-to-moderate deficiency

The cognitive deficits associated with iodine deficiency may not be limited to remote, severely iodine-deficient areas. Several authors have argued that even mild-to-moderate iodine deficiency in pregnancy, still present in many countries in Europe, may affect cognitive function of the offspring (58–60, 126–128). The controlled trials of iodine treatment in mild-to-moderately iodine-deficient pregnant women discussed in the following paragraphs did not report data on infant or child development. However, several reported measures might be surrogate markers of future infant development, including maternal and newborn thyroid function.

Romano *et al.* (58) gave 120–180 μg iodine as iodized salt or control daily beginning in the first trimester to healthy pregnant Italian women (n = 35; median UI, 31–37 μg/liter). In the treated group, median UI increased 3-fold, and thyroid volume did not change. In the controls, there was no change in UI, but a 16% increase in thyroid volume. Treatment had no effect on maternal TSH. Pedersen *et al.* (59) randomized pregnant Danish women (n = 54) to receive either 200 μg iodine/d as KI solution or no supplement from 17 wk to term. Median UI increased from 55 to 90–110 μg/liter in the treated group. Maternal thyroid volume increased 16% in the treated group *vs.* 30% in controls. Maternal Tg and TSH and cord Tg were significantly lower in the treated group. No significant differences were found between groups comparing maternal or cord T_4, T_3, and FT4. In a double-blind, placebo-controlled trial, Glinoer *et al.* (60) supplemented pregnant Belgian women (n = 120; median UI, 36 μg/liter; biochemical criteria of excess thyroid stimulation) with 100 μg iodine/d or control from approximately 14 wk gestation to term. Treatment had no significant effect on maternal or cord T_3, FT4, and T_3/T_4 ratio. The treated women had significantly higher UI, smaller thyroid volumes, and lower TSH and Tg concentrations, compared

with controls. Newborns of the treated group also had significantly higher UI, smaller thyroid volumes, and lower Tg concentrations compared with controls.

Liesenkötter *et al.* (126) reported results from a quasi-random, controlled trial of 230 μg iodine/d from 11 wk to term in pregnant German women (n = 108; median UI, 53 μg/g creatinine; goiter rate, 42.5%). Median UI increased to 104 μg/g creatinine in the treated group, and median thyroid volume was significantly lower in the newborns of the treated women compared with controls (0.7 *vs.* 1.5 ml, respectively). Treatment had no significant effect on maternal TSH, T_3, T_4, thyroid volume, or Tg, and had no effect on newborn TSH. In a placebo-controlled, double-blind trial, Nøhr *et al.* (127) gave a multinutrient supplement containing 150 μg iodine/d or control to pregnant Danish women positive for anti-TPO antibodies (n = 66) from 11 wk gestation to term. Median UI was significantly higher in the treated women at term, but there were no differences in maternal TSH, FT4, or Tg between groups. Finally, in a prospective, randomized, open-label trial, Antonangeli *et al.* (128) supplemented pregnant Italian women (n = 67; median UI, 74 μg/g creatinine) with 50 or 200 μg iodine/d from 18–26 wk to 29–33 wk. Median UI was significantly higher in the 200-μg group than in the 50-μg group (230 *vs.* 128 μg/g creatinine). However, there were no differences in maternal FT4, FT3, TSH, Tg, or thyroid volume between groups.

These studies 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 (106). Although supplementation was generally effective in minimizing an increase in thyroid size during pregnancy, only two of the six studies reported that maternal TSH was lower (within the normal reference range) with supplementation, and none of the studies showed a clear impact of supplementation on maternal and newborn total or free thyroid hormone concentrations. Thyroid hormone concentrations may be the best surrogate biochemical marker for healthy fetal development (111). Thus, the results of these trials are reassuring (106). However, because none of the trials measured long-term clinical outcomes such as maternal goiter or infant development, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy remain unclear.

In areas of mild-to-moderate iodine deficiency, pregnancy has often been suggested as an environmental factor contributing to a higher prevalence of goiter and thyroid disorders in women, compared with men. But the data to support this are scarce. In European studies, an uncontrolled prospective study in 10 women (130), a retrospective study (131), and a cross-sectional study in smoking women (132) suggest that goiters formed during pregnancy may only partially regress after parturition.

4. Infant mortality

Infant survival is improved in infants born to women whose iodine deficiency is corrected before or during pregnancy. In areas of severe iodine deficiency, there is an inverse relationship between levels of maternal T_4 during pregnancy and death rates in the offspring (133). DeLong *et al.* (134) added potassium iodate to irrigation water over a 2- to 4-wk period in three areas of severe iodine deficiency in China and found a large reduction in both neonatal and infant mortality in the following 2–3 yr compared with areas that did not receive iodine. The median UI increased in women of childbearing age from less than 10 to 55 μg/liter, whereas the infant mortality rate (IMR) decreased in the three treated areas from a mean of 58.2 to 28.7/1000 births, from 47.4 to 19.1/1000, and from 106.2 to 57.3/1000. Similar results were also observed for neonatal mortality; the odds of neonatal death were reduced by about 65% in the population who had iodine treatment.

Iodized oil given im to iodine-deficient pregnant women in Zaire at approximately 28 wk gestation decreased infant mortality (135). In severely iodine-deficient women, the IMR in infants of treated and untreated mothers was 113/1000 and 243/1000 births, respectively, and in women with mild or moderate iodine deficiency, the IMR with and without treatment was 146/1000 and 204/1000 births, respectively. In Algeria, rates of abortion, stillbirth, and prematurity were significantly lower among women given oral iodized oil 1–3 months before conception or during pregnancy than among untreated women (136).

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 an area of presumed iodine deficiency in Indonesia to evaluate the effect on mortality (137). The iodine or placebo was given in conjunction with oral poliovirus vaccine; infants (n = 617) were treated at approximately 6 wk of age and were followed to 6 months of age. There was a significant 72% decrease in risk of infant death during the first 2 months of follow-up (137). In a large cross-sectional study in Indonesia, use of adequately iodized salt was associated with a significantly lower prevalence of child malnutrition and mortality in neonates, infants, and children younger than 5 yr of age (138). Taken together, these results suggest that iodine repletion in severely iodine-deficient pregnant women or infants may reduce the IMR by at least 50%.

B. Childhood

1. Cognition

There have been many cross-sectional studies comparing cognition and/or motor function in children from chronically iodine-deficient and iodine-sufficient areas, including children from Asian and European backgrounds (139–154). These cross-sectional studies, with few exceptions, report reduced intellectual function and motor skills in children from iodine-deficient areas. However, observational studies are often confounded by other factors that affect child development (155). Also, these studies could not distinguish between the persistent effects of *in utero* iodine deficiency and the effects of current iodine status.

Two meta-analyses have been reported on this issue (156, 157). The first was done for 21 observational and experimental studies including a control group of the effect of iodine deficiency on mental development (156). Of these, 16 studies were in children, four included adults, and two included infants; the age range was 2–45 yr. The final meta-analysis included 2214 participants (mainly children), and IQ was used as the main outcome measure. The studies were all done in areas of moderate-to-severe iodine deficiency. The IQs of non-iodine-deficient groups were on average 13.5 IQ points higher than those of the iodine-deficient groups. However, the studies included in this analysis were of varying quality; much of the data came from observational studies, and only six of the papers cited were published in peer-reviewed journals. Inclusion criteria for the second meta-analysis (157) included all studies conducted in China, comparing children (<16 yr old) living in naturally iodine-sufficient areas with those: 1) in severely iodine-deficient areas; 2) children in iodine-deficient areas born before the introduction of iodine prophylaxis; and 3) children in iodine-deficient areas born after the introduction of iodine prophylaxis. IQ was measured using the Binet or Raven's scales. The effect size was an increase of 12.45, 12.3, and 4.8 IQ points, respectively, for the iodine-sufficient group and the latter two groups, compared with those in iodine-deficient areas. Compared with severely iodine-deficient children, there was an increase of approximately 12 IQ points for children born more than 3.5 yr after iodine prophylaxis was introduced. Although it is stated that the iodine-sufficient control groups were comparable socially, economically, and educationally, it is difficult to judge the overall quality of the studies reported in Chinese included in this meta-analysis. Despite the clear limitations of the mainly cross-sectional data included in these two meta-analyses (156, 157), their overall conclusions are similar. They estimate that populations, and particularly children, with chronic, severe iodine deficiency experience a mean reduction in IQ of 12–13.5 points.

For a child born and raised under conditions of iodine deficiency, is iodine treatment at school age beneficial? Several randomized, controlled trials in school-aged children have tried to measure the effect of iodized oil on cognition (158–161). Three of the studies found no effect (158, 160, 161), whereas one found that cognition improved with treatment (159). However, methodological problems limit their interpretation because two of the studies were confounded by a significant improvement in iodine status in the control group (158, 161), whereas in the other two, the treated group remained iodine deficient at retesting (159, 160). In a recent placebo-controlled, double-blind, 6-month intervention trial, moderately iodine-deficient 10- to 12-yr-old children (n = 310) in Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo. The children were given a battery of seven cognitive and motor tests that included measures of information processing, working memory, visual problem solving, visual search, and fine motor skills. Treatment with iodine markedly improved iodine and thyroid status: at 24 wk, median UI in the treated group was 172 μg/liter, and mean circulating T_4 increased approximately 40%. Compared with placebo, iodine treatment significantly improved performance on tests of information processing, fine motor skills, and visual problem solving. These findings need to be confirmed in other populations, but it appears that in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion (162).

2. Somatic growth

Severe iodine deficiency *in utero* causes cretinism and dwarfism, and iodized oil given during pregnancy in areas of moderate iodine deficiency increases birthweight by 100–200 g (134, 163). Less clear is the relationship between iodine deficiency and postnatal growth. Data from cross-sectional studies on iodine intake and child growth are mixed (164–167), with most studies finding modest positive correlations. In five Asian countries, household access to iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy (168). However, controlled intervention studies of iodized oil alone (158, 159) and iodine given with other micronutrients (169–171) generally have not found child growth to be affected.

Iodine status may influence growth through its effects on the thyroid axis. Administration of T_4 to hypothyroid children increases their growth (172). Thyroid hormone promotes GH secretion and modulates the effects of GH at its receptor (173–175). IGF-I and IGF binding protein (IGFBP)-3 are also dependent on thyroid status (176, 177). In humans, hypothyroidism decreases circulating IGF-I and IGFBP-3 levels, and thyroid hormone replace-

ment increases them (178, 179). In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-I and IGFBP-3 concentrations (180–182). However, in an uncontrolled trial, oral iodized oil paradoxically decreased IGF-I and IGFBP-3 concentrations in Turkish children (183).

The aim of a recent study (184) was to determine whether iodine repletion improves growth in school-age children and to investigate the role of IGF-I and IGFBP-3 in this effect. Three prospective, double-blind intervention studies were done in areas of varying iodine deficiency: in severely iodine-deficient Moroccan children; in moderately iodine-deficient Albanian children; and in mildly iodine-deficient South African children. In all three studies, iodine treatment increased median UI to more than 100 μg/liter, whereas median UI in the controls remained unchanged. In South Africa, iodine repletion modestly increased IGF-I but did not have a significant effect on IGFBP-3, total T_4, or growth. In Albania and Morocco, iodine repletion significantly increased total T_4, IGF-I, IGFBP-3, weight-for-age z scores, and height-for-age z scores. These controlled studies clearly demonstrate that iodine repletion in school-age children increases IGF-I and IGFBP-3 concentrations and improves somatic growth (184).

3. Subclinical hypothyroidism due to iodine deficiency

Chronic iodine deficiency increases the TSH concentration and produces a thyroid hormone pattern consistent with subclinical hypothyroidism (45), and subclinical hypothyroidism may be associated with cardiovascular disease risk factors (185). Subclinical hypothyroidism in children may be associated with a more atherogenic lipid profile (186). Iodized oil rapidly normalizes the increased TSH concentrations found in iodine-deficient individuals (187) and thus corrects subclinical hypothyroidism. An uncontrolled study reported iodine treatment of goitrous German adolescents decreased plasma cholesterol concentrations (188). A recent controlled study reported iodine treatment of moderately iodine-deficient children with elevated TSH concentrations due to iodine deficiency improves their lipid profile and reduces their insulin (C-peptide) levels compared with control (189). If these findings are confirmed in other populations, this previously unrecognized benefit of iodine prophylaxis may be important because iodine deficiency remains common in many rapidly developing countries with increasing rates of obesity and cardiovascular disease.

C. Adulthood

In adults, mild-to-moderate iodine deficiency appears to be associated with higher rates of more aggressive subtypes of thyroid cancer, increases risk for diffuse goiter, and increases risk of nontoxic and toxic nodular goiter and associated hyperthyroidism (4, 30) (see detailed discussion in *Section XI*). Observational studies also suggest subtle but widespread adverse effects in adults secondary to hypothyroidism, including impaired mental function with decreased educability, apathy, and reduced work productivity (3).

VIII. Epidemiology

Only a few countries—Switzerland, some of the Scandinavian countries, Australia, the United States, and Canada—were completely iodine sufficient before 1990. Since then, globally, the number of households using iodized salt has risen from less than 20% to more than 70%, dramatically reducing iodine deficiency (190). This effort has been spurred by a coalition of international organizations, including the ICCIDD, WHO, the Micronutrient Initiative, and UNICEF, working closely with national IDD control committees and the salt industry; this informal partnership was established after the World Summit for Children in 1990. It has been funded by Kiwanis International, the Gates Foundation, and country aid programs.

Currently, WHO estimates that nearly 2 billion individuals have an insufficient iodine intake, including one third of all school-age children (191) (Table 4). The lowest prevalence of iodine deficiency is in the Americas (10.6%), where the proportion of households consuming iodized salt is the highest in the world (≈90%). The highest prevalence of iodine deficiency is in Europe (52.0%), where the household coverage with iodized salt is the lowest (≈25%), and many countries have weak or nonexistent IDD control programs. The number of countries where iodine deficiency remains a public health problem is 47. However, there has been progress since 2003; twelve countries have progressed to optimal iodine status, and the percentage of school-aged children at risk of iodine deficiency has decreased by 5% (191). In Australia and the United States, two countries previously iodine sufficient, iodine intakes are falling. Australia is now mildly iodine deficient (192), and in the United States, the median UI is 160 μg/liter (95% CI, 146–172), still adequate but half the median value of 321 μg/liter found in the 1970s (90). On the other hand, iodine intake is more than adequate, or even excessive, in 34 countries, an increase from 27 in 2003. These changes emphasize the importance of regular monitoring of iodine status in countries to detect both low and excessive intakes of iodine.

There are several limitations to these WHO prevalence data. First, extrapolation from a population indicator (median UI) to define the number of individuals affected is

TABLE 4. Prevalence of iodine deficiency, as total number (millions) and percentages, in general population (all age groups) and in school-age children (6–12 yr) in 2007 (Ref. 191) and the percentage of households with access to iodized salt (Ref. 196)

WHO regions[a]	Population with UI <100 μg/liter[b]		Households with access to iodized salt (%)[c]
	General population	School-age children	
Africa	312.9 (41.5%)	57.7 (40.8%)	66.6
Americas	98.6 (11.0%)	11.6 (10.6%)	86.8
Eastern Mediterranean	259.3 (47.2%)	43.3 (48.8%)	47.3
Europe	459.7 (52.0%)	38.7 (52.4%)	49.2
Southeast Asia	503.6 (30.0%)	73.1 (30.3%)	61.0
Western Pacific	374.7 (21.2%)	41.6 (22.7%)	89.5
Total	2000.0 (30.6%)	263.7 (31.5%)	70.0

[a] Regions consist of 193 WHO member states.

[b] Based on population estimates for 2006.

[c] These figures do not include data for non-UNICEF countries (*e.g.*, the United States and Western Europe).

problematic, *e.g.*, a country in which children have a median UI of 100 μg/liter would be classified as being iodine sufficient, yet at the same time 50% of children would be classified as having inadequate iodine intakes. Second, nationally representative surveys represent only 60% of the global population included in the WHO data, and subnational data may under- or overestimate the extent of iodine deficiency (191). Finally, there are insufficient data from nearly all countries to estimate the prevalence of iodine deficiency in pregnant women.

Household coverage by iodized salt in South Asia is only 49%. Over 17 million newborns in this region are born annually unprotected from brain damage due to iodine deficiency; this is about 40% of all unprotected births globally (193). There are major challenges to increasing iodized salt coverage in the region, including the presence of a large number of small local salt producers, inadequate monitoring, and/or a lack of political commitment. In India, despite intensive efforts to promote iodized salt, only about half of the population is covered, and coverage is especially poor in low socioeconomic populations (194, 195). Iodized salt is unavailable in many rural markets, and/or salt claiming to be iodized is poorly or incompletely iodized. In 1997, in a move to increase the consumption of iodized salt, the Government of India banned the sale of noniodized salt for human consumption. However, in September 2000, the Government of India lifted the ban on the sale of noniodized salt, stating, "On point of principle, compulsions in the matter of individual choice are undesirable," resulting in a 12% decrease in the coverage of iodized salt nationwide (195). Only after intense advocacy by international and national partners did the Government of India reimpose the ban in May 2006.

Sixty-seven percent of households in sub-Saharan Africa are using iodized salt, but coverage varies widely from country to country (196). In countries like Sudan, Mauritania, Guinea-Bissau, and Gambia, coverage is less than 10%, whereas in Burundi, Kenya, Nigeria, Tunisia, Uganda, and Zimbabwe it is more than 90%. Several countries have absent or weak legislation on iodized salt, and in those with legislation, the stipulated iodine content for salt ranges from 20 to 100 ppm. As a consequence, iodine status in sub-Saharan Africa varies from clear iodine deficiency in countries like Ethiopia, Sierra Leone, and Angola to iodine excess in Uganda and Kenya. A number of sub-Saharan countries have outstanding programs, including Nigeria, recently recognized as the first African country to successfully eliminate iodine deficiency (197).

There are several challenges to the control of IDD in sub-Saharan Africa. In many countries, attempts to effectively implement and/or enforce iodized salt programs have been derailed by conflict, famine, and political instability. Emphasis should be placed on education of government leaders and the public, the formation of national IDD coalitions, and the generation of country-specific information on iodine status. Countries with legislation requiring 80 to 100 ppm of iodine in salt should reduce those levels to 20 to 40 ppm and improve their monitoring of iodine status (198).

The International Child Development Steering Group identified iodine deficiency as one of four key global risk factors for impaired child development where the need for intervention is urgent (199). But controlling IDD in the remaining one third of the global population at risk will not be easy. Although the key contributors to successful national programs have been identified, reaching economically disadvantaged groups living in remote areas and convincing small-scale salt producers to iodize their salt are major challenges (200). 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 and require a

long-term commitment from governments. In several countries where iodine deficiency had been eliminated, salt iodization programs fell apart, and iodine deficiency recurred (201). Children in iodine-deficient areas are vulnerable to even short-term lapses in iodized salt programs (202). To this end, countries should monitor the state of their iodine nutrition every 3 yr and report to the World Health Assembly on their progress (203).

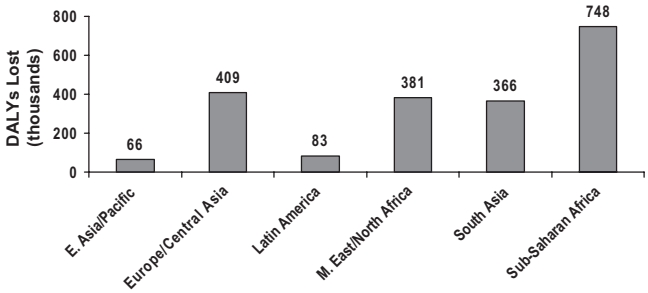

FIG. 3. DALYs (thousands) lost due to iodine deficiency among children under age 5, by region. A DALY is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or cases of disability occurring in a particular year (data from Ref. 208).

IX. Treatment and Prevention

A. Salt fortification with iodine

In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodization (54). Universal salt iodization (USI) is a term used to describe the iodization of all salt for human (food industry and household) and livestock consumption. Although the ideal, even in countries with successful salt iodization programs, USI is rarely achieved because food industries are often reluctant to use iodized salt, and many countries do not iodize salt for livestock. 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 throughout 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 monitored at the production, retail, and household levels.

WHO/UNICEF/ICCIDD recommends that iodine is added at a level of 20–40 mg iodine/kg salt, depending on local salt intake (54). Iodine can be added to salt in the form of KI or potassium iodate (KIO_3). Because KIO_3 has higher stability than KI in the presence of salt impurities, humidity, and porous packaging (204, 205), it is the recommended form in tropical countries and those with low-grade salt. Iodine is usually added after the salt has been dried. Two techniques are used: 1) the wet method, where a solution of KIO_3 is dripped or sprayed at a regular rate on to salt passing by on a conveyor belt; and 2) the dry method, where KI or KIO_3 powder is sprinkled over the dry salt. Optimally, packaging should be in low-density polyethylene bags. In a multicountry study, high humidity combined with porous packing resulted in up to 90% losses of iodine in 1 yr of storage through sublimation in high-density polyethylene bags, compared with 10–15% from low-density polyethylene bags (205).

Salt iodization remains the most cost-effective way of delivering iodine and of improving cognition in iodine-deficient populations (206). For example, in Sierra Leone, if current levels of iodine deficiency remain unchanged over the next 5 yr, the present value of future productivity losses due to intellectual impairment from *in utero* iodine deficiency will exceed US $42.5 million (207). Worldwide, the annual costs of salt iodization are estimated at US $0.02–0.05 per child covered; the costs per child death averted are US $1000 and per disability-adjusted life year (DALY) gained are US $34–36 (Fig. 3) (208). Looked at in another way, before widespread salt iodization, the annual potential losses attributable to iodine deficiency in the developing world have been estimated to be US $35.7 billion as compared with an estimated US $0.5 billion annual cost for salt iodization, *i.e.*, a 70:1 benefit:cost ratio (209). However, USI must be sustained to be effective, and this is a major challenge.

B. Other fortification vehicles

Bread can be an effective vehicle for iodine by including baker's salt enriched with iodine (210). Although iodizing drinking water or irrigation water can also be effective (211, 212), the higher cost and the complexity of monitoring are disadvantages. Iodine-containing milk is a major adventitious source in countries such as Switzerland and the United States (7, 9), due to the use of iodophors in the dairy industry, rather than to the deliberate addition of iodine. In Finland, iodine-fortified animal fodder has increased the iodine content of foods derived from animal sources. In countries affected by IDD, whenever possible, iodine should be routinely added to complementary foods for weaning infants to provide approximately 90 μg of iodine per day (213).

C. Iodine supplementation

In some regions, iodization of salt may not be practical for control of iodine deficiency, at least in the short term.

TABLE 5. Recommendations for iodine supplementation in pregnancy and infancy in areas where <90% of households are using iodized salt and the median UI is <100 μg/liter in schoolchildren (from Ref. 89)

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 KI should be given so that the total iodine intake meets the RNI of 150 μg/d 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 KI should be given so that the total iodine intake meets the new RNI of 250 μg/d iodine Iodine supplements should not be given to a woman who has already been given iodized oil during her current pregnancy or up to 3 months before her current pregnancy started
Children aged 0–6 months	A single oral dose of 100 mg of iodine as iodized oil OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the RNI of 90 μg/d of iodine Should be given iodine supplements only if the mother was not supplemented during pregnancy or if the child is not being breast-fed
Children aged 7–24 months old	A single annual oral dose of 200 mg of iodine as iodized oil as soon as possible after reaching 7 months of age OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the RNI of 90 μg/d of iodine

This may occur in remote areas where communications are poor or where there are numerous small-scale salt producers. In these areas, iodized oil supplements can be used (54). Iodized oil is prepared by esterification of the unsaturated fatty acids in seed or vegetable oils, and addition of iodine to the double bonds (214). It can be given orally or by im injection (78). The im route has a longer duration of action, but oral administration is more common because it is simpler. Usual doses are 200–400 mg iodine/yr (54), and it is often targeted to women of childbearing age, pregnant women (216), and children (Table 5). Its disadvantages are an uneven level of iodine in the body over time and the need for direct contact with individuals with the accompanying increased costs.

Iodine can also be given as KI or KIO_3 in drops or tablets. Single oral doses of KI monthly (30 mg) or biweekly (8 mg) can provide adequate iodine for school-age children (217). Lugol's iodine, containing approximately 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.

D. Strategies to prevent or correct deficiency during pregnancy and lactation

For nearly all countries, the primary strategy for sustainable elimination of iodine deficiency in pregnancy remains USI (89). In countries or regions where a salt iodization program covers at least 90% of households and has been sustained for at least 2 yr and the median UI indicates iodine sufficiency (Table 2), pregnant and lactating women do not need iodine supplementation (89). Several countries with long-standing, successful iodized salt programs—China, Iran, Switzerland—have reported an optimal median UI in pregnant women (90, 218, 219). Also, in countries affected by mild or moderate iodine deficiency (Ireland, Germany, Belgium, Italy, Denmark), thyroid volume increases 15–31% during pregnancy, whereas in iodine-sufficient countries (Finland, The Netherlands), there is little or no increase in thyroid volume during pregnancy (220). These data suggest that effective salt iodization can provide adequate iodine intake during pregnancy, but iodine-containing supplements taken during the prenatal period may have contributed to iodine intakes in these studies (221).

However, implementation of USI is not always feasible, and this may result in insufficient access to iodized salt for women of childbearing age and pregnant women. When this happens, supplementation of these groups should be considered. WHO recommends that countries assess their salt iodization programs and then decide whether supplementation is indicated (89). Highly populated countries should use disaggregated data and categorize areas of the country according to subnational (region, province, district, *etc.*) data. To ensure adequate iodine supply during pregnancy, women should ideally be provided with ample iodine intake (at least 150 μg/d) for a long period before conception to ensure plentiful intrathyroidal iodine stores (93). In Italy, thyroid function in pregnant women from a mildly iodine-deficient area who had regularly used iodized salt for at least 2 yr before becoming pregnant was compared with women who began using iodized salt upon becoming pregnant (93). The findings suggested that prolonged use of iodized salt is associated with better maternal thyroid function, possibly due to greater intrathyroidal iodine stores to draw on during pregnancy.

In iodine-deficient countries or regions that have weak iodized salt distribution, that is, in countries or areas where less than 90% of households are using iodized salt and the median UI is less than 100 μg/liter in schoolchildren, supplements should be given to pregnant women, lactating women, and infants, according to the strategy shown in Table 5 (54). In the United States, where iodized salt use is not universal although the median UI of pregnant women is 173 (95% CI, 75–229) μg/liter, within the

adequate range recommended by WHO of 150–249 μg/liter, the lower 95% CI was less than 150 μg/liter (222). Because of this uncertainty, until additional data are available, the American Thyroid Association recommends that women receive 150 μg iodine supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 μg of iodine (222).

Adequate iodine supply should continue after parturition because the iodine requirement of a woman who is fully breastfeeding her infant is likely even higher than that during pregnancy. Gushurst *et al.* (223) reported that the median BMIC in U.S. women who used noniodized salt or consumed low or high amounts of iodized salt was 113, 143, and 270 μg/liter, respectively. Pretell *et al.* (224) administered 950 mg iodine as injected iodized oil to pregnant women; median BMIC at 18–36 months postpartum increased to 70 μg/liter, compared with 2 μg/liter in untreated women. In Algeria, Chaouki and Benmiloud (136) gave 240 mg iodine as oral iodized oil either 1–3 months before pregnancy or in the first or third trimester. At delivery and 6 months postpartum, mean BMIC increased significantly compared to untreated women. In Danish mothers (n = 147), median BMIC on the fifth day postpartum was significantly higher (57 μg/liter) in those receiving supplementation with 150 μg/d of oral iodine, compared with those not supplemented (34 μg/liter) (225). In Germany, 60 mothers who received 200 μg/d of oral iodine had significantly higher mean iodine concentrations in breast milk (76 μg/liter) than untreated (55 μg/liter) (226). Thus, iodine supplementation of breastfeeding women can significantly improve iodine supply to the newborn.

X. Enteral and Parenteral Nutrition

A. Infancy

Balance studies in healthy preterm infants have suggested that iodine intakes of at least 30 μg/kg body weight/d are required to maintain positive balance, and experts generally recommend iodine intakes of 30 to 60 μg/kg · d for this group (227–229). Formula milks for preterm infants contain 20 to 170 μg iodine/liter, and, depending on the dietary iodine intake of the mother, breast milk generally contains 50 to 150 μg/liter (97, 226, 230). Thus, particularly during the first postnatal weeks when feed volumes are often low, enterally fed preterm infants may not achieve the recommended intake of iodine (228, 230).

Oral absorption of iodine is efficient; in adults, oral iodine bioavailability is typically 90–95% (11, 12). This suggests that iodine dosages via the enteral or parenteral route should be nearly equivalent. However, commercially available parenteral nutrition (PN) solutions contain much less iodine than breast milk or preterm formula milks (230). U.S. and European clinical nutrition societies recommend parenteral iodine intakes of 1 μg/kg body weight/d (231, 232), far below fetal accretion rates (228, 229). This conservative recommendation assumes that 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. This assumption is supported by the study of Moukarzel *et al.* (233), who found in 18 infants receiving long-term total PN without iodine supplementation that thyroid function test results were normal and serum iodide concentrations were significantly higher than in control children. The authors estimated that adventitious iodine in total PN solutions and fat emulsions accounted for about 50% of the iodine intake and assumed that skin absorption of topical iodinated disinfectant accounted for the remaining intake. They concluded that it was unnecessary to supplement iodine even in children receiving long-term total PN without added iodine. Moreover, frequent use of iodinated antiseptics in infants can result in transcutaneous absorption of at least 100 μg iodine per day, iodine excess, and neonatal hypothyroidism (234).

Because of concerns over possible iodine excess and the potential advantages of chlorhexidine-based antiseptics (235), use of iodinated antiseptics in infants may be decreasing, putting infants at risk of iodine deficiency. If parentally fed preterm infants are not exposed to adventitious sources of iodine, they may receive only 1–3 μg iodine/kg body weight/d and be in negative iodine balance during the first few postnatal weeks (228, 229). In the study of Ibrahim *et al.* (229), preterm infants (n = 13) had a mean iodine intake of 3 μg/kg body weight/d at PN rates of 150 ml/kg/d. All 13 infants had negative iodine balances on d 1, 12 remained in negative balance at d 6, but only three infants remained in negative balance on d 28.

Several authors have argued that iodine deficiency should be avoided during this period because it may transiently lower thyroid hormone levels in the first weeks of life (228, 229). Transient hypothyroxinemia in preterm infants has been linked to impaired neurodevelopment (236–238), but the potential role of iodine in this phenomenon has been investigated in only one randomized controlled trial (239). Infants born before 33 wk gestation (n = 121) were randomized to receive either iodine-supplemented formula milk (272 μg iodine/liter) or the same formula without iodine supplementation (68 μg iodine/liter) until 40 wk postconceptional age. These provided daily iodine intakes of approximately 40–50 and 12–16 μg per kg body weight in the treatment and control groups, respectively. There was no statistically significant

effect on thyroid function or in the incidence of chronic lung disease (239).

However, the study had several limitations. Although transient hypothyroxinemia is most closely associated with adverse outcomes in extremely preterm infants, only 14% of subjects had a birth weight below 1000 g. Second, the intervention began only after the infants had established enteral feeding, usually 2 wk after birth, but in preterm infants iodine balance is often negative, and transient hypothyroxinemia is established in the first 1–2 postnatal weeks. Finally, the trial was likely underpowered to assess a potential effect on neurodevelopment. A recent review concluded that the available data are insufficient to support supplementation of preterm infants with iodine (240). Moreover, although subgroup analyses in a single controlled trial suggested that T_4 replacement may prevent neurodevelopmental morbidity in extremely preterm infants (241), the overall data are insufficient to recommend prophylactic thyroid hormone treatment in preterm infants (242).

B. Childhood

A daily dose of 1 μg iodine/kg body weight is also recommended for children receiving PN (231, 232). A recent study assessed the iodine and thyroid status of children aged 1 to 17 yr (n = 15; mean age, 76 months) on long-term PN (243). Nine children had short bowel syndrome, and six had other intestinal diseases. Ten were on total PN, and five were on partial PN for 14 to 84 wk. There was a significant inverse correlation between duration of PN and UI, and after 12 wk all children had a UI less than 100 μg/liter, with eight less than 50 μg/liter (moderate deficiency) and seven less than 20 μg/liter (severe deficiency). However, despite apparently low iodine intakes, there was no significant increase in thyroid size or signs of thyroid dysfunction in the children. If needed, parenteral trace element additives containing iodine are available for pediatric use. An example is Peditrace solution (Fresenius Kabi, Bad Homburg, Germany), which contains KI (1.3 μg/ml KI equivalent to 1 μg iodide/ml). The manufacturer's recommended dosage (244) for infants and children weighing 15 kg or less and 2 d old or older is 1 ml/kg body weight/d; the recommended daily dose is 15 ml for children weighing more than 15 kg.

C. Adulthood

Commercially available products for enteral nutrition generally supply 75–110 μg iodine per serving (245). Daily iodine requirements in adult patients receiving total enteral nutrition or total PN are estimated to be 70–150 μg (246). A recent technical review of PN by the American Gastroenterological Association recommended iodine intakes of 70–140 μg/d (247). Although most PN formulations do not contain iodine, deficiency is not likely to occur because of cutaneous absorption from iodine containing disinfectants and other adventitious sources of iodine. Iodine deficiency symptoms have not been reported with in-hospital iv nutrition support (248). Thyroidal iodine stores may be adequate to meet the needs of patients requiring total PN for less than 3 months (246); in iodine-sufficient adults, thyroidal iodine content is 15–20 mg (18). Iodine status and thyroid hormone levels were adequate in Brazilian adults with intestinal malabsorption secondary to short gut syndrome who were receiving long-term total PN without iodine (251). For these reasons, many experts do not recommend supplemental iodine routinely for subjects receiving total PN (249, 250). If needed, iv sodium iodide solutions are available. For example, Iodopen (APP Pharmaceuticals, Schaumberg, IL) contains 100 μg iodine/ml. According to the manufacturer's specifications (252), the usual adult dosage for prophylaxis or treatment of iodine deficiency is 1 to 2 μg iodine/kg of body weight/d. For children and pregnant/lactating women, the recommended dosage is 2 to 3 μg iodine/kg of body weight/d.

XI. Increasing Iodine Intakes in Populations and Iodine Excess

More than two thirds of the 5 billion people living in countries affected by iodine deficiency now have access to iodized salt (4). Iodine excess is occurring more frequently, particularly when salt iodine levels are too high or are poorly monitored. For example, in Brazil, Armenia, and Uganda, median UI is more than 300 μg/liter, whereas in Chile it is above 500 μg/liter (191). High dietary iodine can also rarely come from natural sources, such as seaweed in coastal Japan (253, 254), iodine-rich drinking water in China (255, 256), and iodine-rich meat and milk in Iceland from fish products used for animal feed (257). The median UI in primary school-aged children in the United States is 229 μg/liter (90), as a result of iodine-containing agents used in dairying and food preparation (9, 258), together with iodine from fortified salt.

European (259) and U.S. (8) expert committees have recommended tolerable upper intake levels for iodine (Table 6) but caution that individuals with chronic iodine deficiency may respond adversely to intakes lower than these. In monitoring populations consuming iodized salt, the WHO/ICCIDD recommendations (54) for the median UI that indicates more than adequate and excess iodine intake are shown in Table 2. Acute iodine poisoning caused by ingestion of many grams causes gastrointestinal irritation, abdominal pain, nausea, vomiting, and diar-

TABLE 6. Tolerable upper intake level for iodine (μg/d)

Age group	European Commission/Scientific Committee on Food (Ref. 259)	IOM (Ref. 8)
1–3 yr	200	200
4–6 yr	250	300
7–10 yr	300	300
11–14 yr	450	300
15–17 yr	500	900
Adult	600	1100
Pregnant women	600	1100

rhea, as well as cardiovascular symptoms, coma, and cyanosis (260). Excess iodine intake may very rarely precipitate iodermia, a skin disorder consisting of acneiform eruptions, pruritic rash, and urticaria (261).

In areas of iodine sufficiency, most healthy adults are remarkably tolerant to iodine intakes up to 1 mg/d because the thyroid is able to adjust to a wide range of intakes to regulate the synthesis and release of thyroid hormones (262). Large amounts of iodine given for days to months in small groups of healthy subjects have shown few adverse effects (263). However, increasing doses of iodine in the microgram range may cause hyper- or hypothyroidism in those with past or present thyroid abnormalities. This occurs because, in a damaged thyroid gland, the normal down-regulation of iodine transport into the gland may not occur. Thus, changes in population iodine intake may be an important determinant of the pattern of thyroid diseases. This has been demonstrated in epidemiological studies that have examined the relationship between iodine intake and the incidence and prevalence of thyroid diseases.

A. Cross-sectional studies: the epidemiology of thyroid disorders in areas of low and high intakes

Danish investigators compared the incidence and prevalence of hyperthyroidism and hypothyroidism in Jutland, Denmark, an area with low iodine intake (approximately 40 to 70 μg/d) and Iceland, an area of high iodine intake (approximately 400–450 μg/d, based on urinary iodine excretion around 300 μg per 24 h in young subjects) (264). There was a distinctly different pattern of thyroid dysfunction in the two areas: there was a higher prevalence of hyperthyroidism but a lower prevalence of hypothyroidism in Jutland, compared with Iceland. The lifetime risk for developing hyperthyroidism was 2.3 times higher in Jutland than in Iceland. Multinodular toxic goiter was the most common cause of hyperthyroidism in Jutland, but relatively rare in Iceland. In contrast, nearly all cases of hyperthyroidism in Iceland were Graves' disease in young and middle-aged subjects (264). Other populations with long-standing mild to moderate iodine deficiency also demonstrate a high prevalence of thyroid hyperfunction with low serum TSH but a low prevalence of thyroid hypofunction, whereas populations in areas of high iodine intake show the opposite pattern (265–274). In mildly iodine-deficient areas, there is an increase in thyroid multinodularity in females with advancing age that is associated with a decrease in serum TSH (275, 276). Together, these data argue that higher rates of hyperthyroidism in populations with mild iodine deficiency are likely due to a higher rate of multinodular toxic goiter. Thus, like diffuse goiter, thyroid hyperfunction should be included in the spectrum of disorders caused by mild-to-moderate iodine deficiency.

Two mechanisms may be responsible for the increase in hypothyroidism in a population where the iodine intake is chronically high. One mechanism is the inhibitory effect of iodine on thyroid hormone synthesis and secretion. This autoregulatory process is thought to protect against thyroid hormone hypersecretion in the face of high iodine intake. However, this autoregulation is not perfect and commonly induces some degree of thyroid hypofunction. In Japanese adults with chronic excess iodine intakes, many with overt hypothyroidism will become euthyroid if their iodine intakes are normalized (277, 278). The other proposed mechanism is induction of thyroid hypofunction due to iodine-induced autoimmune thyroiditis (279), although not all studies agree (82, 83). The frequency of histological thyroiditis in surgical thyroid specimens is increased in an area of endemic goiter after iodine prophylaxis (280).

The overall incidence of thyroid carcinoma in populations does not appear to be influenced by iodine intake. A study in Denmark suggested that modest differences in iodine intake between regions did not affect thyroid cancer incidence or the distribution of its subtypes (281). However, other studies have suggested that the distribution of the subtypes of thyroid carcinoma is related to iodine intake; in areas of higher iodine intake, there appear to be fewer of the more aggressive follicular and anaplastic carcinomas, but more papillary carcinomas (280, 282). When iodine prophylaxis is introduced in populations, this shift toward less malignant types of thyroid cancer, as well as a lower radioactive iodine dose to the thyroid in case of nuclear fallout, are benefits of the correction of mild-to-moderate iodine deficiency.

In children, excess dietary iodine has been associated with goiter and thyroid dysfunction. In the reports of "endemic coast goiter" in Hokkaido, Japan (253), the traditional local diet was high in iodine-rich seaweed. UI excretion in children consuming the local diet was approximately 23,000 μg/d. The overall prevalence of visible goiter in children was 3–9%, but in several villages

approximately 25% had visible goiter. Most of the goiters responded to administration of thyroid hormone and/or restriction of dietary iodine intake. TSH assays were not available, but it was suggested that an increase in serum TSH was involved in generation of goiter. No cases of clinical hypo- or hyperthyroidism were reported.

Goiter in children may also be precipitated by iodine intake well below that consumed in the studies from Hokkaido (253). In Chinese children (n = 171) from two villages where the iodine concentrations in drinking water were 462 and 54 μg/liter, the mean UIs were 1235 and 428 μg/g creatinine, mean serum TSH was 7.8 and 3.9 mU/liter, and the goiter rate was above 60% and 15–20%, respectively (255). In other reports from China, drinking water with iodine concentrations above 300 μg/liter resulted in UIs greater than 900 μg/liter and a goiter rate above 10% (256). These Chinese studies suggest that goiter and thyroid dysfunction may occur in children at iodine intakes in the range of 400-1300 μg/d. This contention is supported by a study in a large international cohort of 6- to 12-yr-old children where chronic iodine intakes of at least 500 μg/d in children were associated with an increase in thyroid size as determined by ultrasonography (283). Although overall these findings suggest moderately high dietary intakes of iodine—in the range of 300–400 μg/d—are well-tolerated by healthy children, iodine intakes in this range are of no benefit and may have adverse effects not detected in these studies.

B. Longitudinal studies: the effects of increasing intakes in populations on thyroid function

Increasing iodine intakes in iodine-deficient populations is typically accompanied by a clear rise in the incidence of hyperthyroidism, the magnitude of the increase depending on the amount of iodine administered and the severity of the preexisting iodine deficiency. Subjects at high risk of developing iodine-induced hyperthyroidism (IIH) have preexisting multinodular thyroid disease, and although most are euthyroid, they may have radioactive iodine uptakes that are not suppressible, low serum TSH concentration values, and a serum TSH that does not respond to TRH (284). Thyrocytes in these nodules may be insensitive to TSH control, and if the iodine supply is suddenly increased, they may overproduce thyroid hormone.

In iodine-deficient, goitrous Sudanese adults, 3% developed overt hyperthyroidism after receiving iodized oil, and serum TSH concentrations were less than 0.1 mU/liter in 6–17% of subjects 12 months after iodine treatment (187). After iodized salt was introduced to adults in Zaire with nodular goiter, 7.4% developed severe thyrotoxicosis, and in many the disorder persisted longer than 1 yr (286). Similarly, in Zimbabwe, introduction of overiodized salt produced a 3-fold increase in IIH (287). The increase in the incidence of IIH after a properly monitored introduction of iodine is transient, probably because the resulting iodine sufficiency in the population reduces the future risk of developing autonomous thyroid nodules (288). In Switzerland in 1980, when the iodine content of salt was raised from 7.5 to 15 ppm, the UI increased from approximately 80 to 150 μg/g creatinine. In the first 2 yr after this increase, the incidence of toxic nodular goiter rose by 12% but gradually regressed to a stable level of only 25% of the initial incidence (289).

To investigate the effects of iodine intake on thyroid disorders in China (47, 71, 290), a 5-yr, prospective community-based survey was done in three rural Chinese communities with mildly deficient, more than adequate (previously mild iodine deficiency corrected by iodized salt), and excessive iodine intake from environmental sources; the median UI was 88, 214, and 634 μg/liter, respectively. For the three communities, the cumulative incidence of hyperthyroidism was 1.4, 0.9, and 0.8%; of overt hypothyroidism, 0.2, 0.5, and 0.3%; of subclinical hypothyroidism, 0.2, 2.6, and 2.9%; and of autoimmune thyroiditis, 0.2, 1.0, and 1.3%. In most individuals, these latter two disorders were not sustained. Among subjects with euthyroidism and antithyroid antibodies at baseline, the 5-yr incidence of elevated serum TSH levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. In all three communities, independent of iodine intake, either positive TPO antibodies (odds ratio, 4.2; 95% CI, 1.7–8.8) or goiter (odds ratio, 3.1; 95% CI, 1.4–6.8) in originally healthy participants was associated with the occurrence of hyperthyroidism. For the three communities, the cumulative incidence of diffuse and nodular goiter was 7.1, 4.4, and 6.9% and 5.0, 2.4, and 0.8%, respectively, suggesting that the relationship between iodine and the risk for the occurrence of diffuse goiter shows a U-shaped curve, whereas nodular goiters are more prevalent in iodine-deficient areas.

Denmark has documented the pattern of thyroid disease after careful introduction of iodized salt (129, 215). New cases of overt hypothyroidism were identified in two areas of Denmark with previous moderate and mild iodine deficiency, respectively (Aalborg, median UI, 45 μg/liter; and Copenhagen, median UI, 61 μg/liter) before and for the first 7 yr after introduction of a national program of salt iodization. The overall incidence rate of hypothyroidism modestly increased during the study period: baseline, 38.3/100,000/year; after salt iodization, 47.2/100,000/year (*vs.* baseline, relative risk, 1.23; 95% CI, 1.07–1.42). There was a geographic difference because hypothyroid-

ism increased only in the area with previous moderate iodine deficiency. The increase occurred in young and middle-aged adults. Similarly, new cases of overt hyperthyroidism in these two areas of Denmark before and for the first 6 yr after iodine fortification were identified. The overall incidence rate of hyperthyroidism increased [baseline, 102.8/100,000/year; after salt iodization 138.7/100,000/year (P for trend <0.001)]. Hyperthyroidism increased in both sexes and in all age groups, but in contrast to IIH where most cases occur in older individuals, many of the new cases were observed in young subjects—the increase was highest in adults aged 20–39 yr—and were presumably of autoimmune origin. The authors suggested that further monitoring is expected to show a decrease in the number of elderly subjects suffering from nodular hyperthyroidism.

XII. Conclusions

Concerns about potential increases in iodine-induced thyroid disease continue to delay or limit the implementation of iodine prophylaxis in iodine-deficient populations. Are these concerns justified? Looking at the benefits *vs.* the risks of iodine prophylaxis, it is clear that severe iodine deficiency in pregnancy can cause hypothyroidism, poor pregnancy outcome, cretinism, and irreversible mental retardation. Mild-to-moderate iodine deficiency *in utero* and in childhood results in less severe learning disability, poor growth, and diffuse goiter. In adults, mild-to-moderate iodine deficiency appears to be associated with higher rates of more aggressive subtypes of thyroid cancer and increases risk for nontoxic and toxic nodular goiter and associated hyperthyroidism.

However, increasing iodine intakes in deficient populations is not without risk. Mild iodine deficiency may be associated with a decreased risk of overt and subclinical hypothyroidism, as well as autoimmune thyroiditis. In China, chronic excess iodine intakes are associated with a small increase in subclinical hypothyroidism and autoimmune thyroiditis, but not overt hypo- or hyperthyroidism. In contrast, in Denmark, correcting mild-to-moderate deficiency modestly increased rates of hypo- and hyperthyroidism. The differing effects of varying iodine intakes in these studies may be related to differences in underlying thyroid autonomy, genetic susceptibility, or other environmental variables.

More prospective data on the epidemiology of thyroid disorders caused by changes in iodine intake in other countries would be valuable. But it appears that achieving optimal iodine intakes (in the range of 150–250 μg/d for adults) can minimize the amount of thyroid dysfunction in populations (285). Iodine prophylaxis with periodic monitoring is an extremely cost-effective approach to help control thyroid disorders, compared with clinical diagnosis and treatment. If programs of iodine prophylaxis are carefully monitored for both iodine deficiency and excess, the relatively small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency—pregnancy loss, goiter, and mental retardation, which continue to affect up to one third of the global population (191).

Acknowledgments

I would like to thank the families for their permission to use the photographs included in this review.

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The Swiss Federal Institute of Technology in Zürich provided financial support during the researching and writing of this manuscript.

Disclosure Summary: The author has nothing to disclose.

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