

# 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  $\mu\text{g}/\text{d}$  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)

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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<sub>4</sub>; IDD, iodine deficiency disorder; IGF1, IGF binding protein; IHH, iodine-induced hyperthyroidism; IMR, infant mortality rate; MIT, monoiodotyrosine; NIS, sodium/iodide symporter; PI, 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.

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## 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  $\mu\text{g/liter}$ . 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  $\mu\text{g/kg}$  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  $\mu\text{g}$  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  $\mu\text{g/d}$  for men and 190 to 210  $\mu\text{g/d}$  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  $\mu\text{g/d}$ , 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 ( $\leq 10\%$ ) 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  $\mu\text{g}/\text{d}$  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  $\text{T}_4$  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).

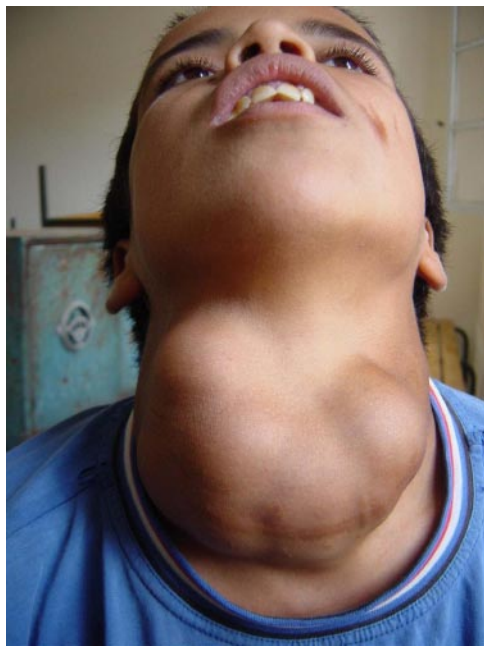
The body of a healthy adult contains 15 to 20 mg of iodine, of which 70 to 80% is in the thyroid (18). In chronic iodine deficiency, the iodine content of the thyroid may fall below 20  $\mu\text{g}$ . In iodine-sufficient areas, the adult thyroid traps approximately 60  $\mu\text{g}$  of iodine per 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  $\text{T}_4$ , and linkage of a MIT and DIT produces  $\text{T}_3$ . Thus,  $\text{T}_3$  is structurally identical to  $\text{T}_4$  but has one less iodine (at the 5' position on the outer ring). Iodine comprises 65 and 59% of the weights of  $\text{T}_4$  and  $\text{T}_3$ , 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  $\text{T}_4$  and  $\text{T}_3$  into the circulation. Degradation of  $\text{T}_4$  and  $\text{T}_3$  in the periphery—the half-life of circulating  $\text{T}_4$  is 5–8 d, and for  $\text{T}_3$ , 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  $\mu\text{g}/\text{d}$ , 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  $\text{T}_3$  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  $\mu\text{g}/\text{d}$ , 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 ( $\approx 10\text{--}20$  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 countries. 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<sub>4</sub> 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 TSH $\beta$  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.

### 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  $\mu\text{g}/\text{d}$  (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  $\mu\text{g}/\text{d}$  (8). The corresponding RDA (defined as the EAR plus twice the coefficient of variation in the population, rounded to the nearest 50  $\mu\text{g}$ ) is 150  $\mu\text{g}/\text{d}$  (8). This agrees with the WHO recommendation for adequate daily iodine intake of 150  $\mu\text{g}/\text{d}$  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<sub>4</sub> 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  $\mu\text{g}/\text{kg} \cdot \text{d}$  (56, 57); the mean retention of a healthy fetus with a weight of 3 kg would be approximately 22  $\mu\text{g}/\text{d}$ . Estimated daily fetal iodine retention added to the EAR of 95  $\mu\text{g}/\text{d}$  for nonpregnant women would yield an EAR of 117  $\mu\text{g}/\text{d}$ , but this would not take into account the iodine needed to increase maternal T<sub>4</sub> production and balance additional urinary losses. Dworkin *et al.* (49) found five pregnant women were at balance when consuming approximately 160  $\mu\text{g}/\text{d}$ , 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

**TABLE 1.** Recommendations for iodine intake ( $\mu\text{g}/\text{d}$ ) by age or population group

| Age or population group | IOM |           | Age or population group | WHO RNI |
|-------------------------|-----|-----------|-------------------------|---------|
|                         | EAR | AI or RDA |                         |         |
| 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 $\geq$ 14 yr     | 95  | 150       | Adults >12 yr           | 150     |
| Pregnancy               | 160 | 220       | Pregnancy               | 250     |
| Lactation               | 200 | 290       | Lactation               | 250     |

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

pregnancy; in studies by Romano *et al.* (58) and Pedersen *et al.* (59), total daily iodine intakes of approximately 200  $\mu\text{g}/\text{d}$  and 250–280  $\mu\text{g}/\text{d}$ , respectively, during pregnancy prevented an increase in thyroid volume, whereas in a study of Glinoe (60), total daily iodine intake of approximately 150  $\mu\text{g}/\text{d}$  was insufficient to prevent an increase in thyroid size. On the basis of the above data, the IOM set the EAR at 160  $\mu\text{g}/\text{d}$  for pregnancy in women at least 14 yr of age and the RDA, set at 140% of the EAR rounded to the nearest 10  $\mu\text{g}$ , at 220  $\mu\text{g}/\text{d}$  (8). WHO recommends a daily iodine intake of 250  $\mu\text{g}/\text{d}$  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  $\mu\text{g}/\text{liter}$  in iodine-sufficient women from the United States, the average daily loss of iodine in breast milk has been estimated to be approximately 115  $\mu\text{g}/\text{d}$  (8). Added to the EAR for nonpregnant women of 95  $\mu\text{g}/\text{d}$ , the EAR for lactating women at least 14 yr of age is set at 209  $\mu\text{g}/\text{d}$  by the IOM (8). The RDA is 140% of the EAR rounded to the nearest 10  $\mu\text{g}$ , or 290  $\mu\text{g}/\text{d}$  of iodine. WHO recommends a daily iodine intake of 250  $\mu\text{g}/\text{d}$  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  $\mu\text{g}/\text{liter}$  (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  $\mu\text{g}/\text{d}$  (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  $\mu\text{g}/\text{d}$ , respectively (8), and WHO recommends a daily iodine intake of 90  $\mu\text{g}/\text{d}$  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  $\mu\text{g}/\text{liter}$  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  $\mu\text{g}/\text{kg} \cdot \text{d}$  of iodine found that iodine retention was 7.3  $\mu\text{g}/\text{kg} \cdot \text{d}$  (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  $\mu\text{g}$ .

#### E. Childhood

In a balance study in children aged 1.5 to 2.5 yr (63), the median iodine intake was 63.5  $\mu\text{g}/\text{d}$ , and the average iodine balance was +19  $\mu\text{g}/\text{d}$ . Children 8 yr of age who consumed approximately 40  $\mu\text{g}/\text{d}$  of iodine were in negative iodine balance (–23 to –26  $\mu\text{g}/\text{d}$ ), indicating that the average minimum requirement is approximately 65  $\mu\text{g}/\text{d}$  (64). No other studies for assessing iodine requirements for young children are available; therefore an EAR of 65  $\mu\text{g}/\text{d}$  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  $\mu\text{g}$  for preschool children (0 to 59 months) and 120  $\mu\text{g}$  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).

## 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.

**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 ( $\mu\text{g/liter}$ )     | 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 |  |
| $\geq 500^a$                   | Excessive          |  |
| Lactating women <sup>b</sup>   |                    |  |
| <100                           | Insufficient       |  |
| $\geq 100$                     | Adequate           |  |
| Children less than 2 yr of age |                    |  |
| <100                           | Insufficient       |  |
| $\geq 100$                     | 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.

<sup>a</sup> The term excessive means in excess of the amount needed to prevent and control iodine deficiency.

<sup>b</sup> In lactating women, the numbers for median UI are lower than the iodine requirements because of the iodine excreted in breast milk.

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  $\mu\text{g/liter}$  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 ( $\mu\text{g/liter}$ )  $\times$   $0.0235 \times$  body weight (kg) = daily iodine intake (8). Using this formula, a median UI of 100  $\mu\text{g/liter}$  corresponds roughly to an average daily intake of 150  $\mu\text{g}$ .

### 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  $\mu\text{g/liter}$  (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  $\mu\text{g/liter}$ ) 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 se-

rum  $T_4$  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  $\mu\text{g}$  (8, 54) would correspond to a UI of approximately 135–150  $\mu\text{g/liter}$ . 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  $\mu\text{g}$  would correspond to a UI of approximately 185–215  $\mu\text{g/liter}$ .

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  $\mu\text{g/liter}$  (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  $\mu\text{g/liter}$ , 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  $\mu\text{g}/\text{liter}$ , whereas the median UI in their pregnant mothers was only 108  $\mu\text{g}/\text{liter}$  (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  $\mu\text{g}/\text{liter}$  reported a median BMIC of 155  $\mu\text{g}/\text{liter}$  (range, 3–1968  $\mu\text{g}/\text{liter}$ ) (96).

Based on the balance studies of Delange *et al.* (57), the full-term infant's requirement for iodine is approximately 7  $\mu\text{g}/\text{kg}$ . 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  $\mu\text{g}/\text{liter}$  would likely cover the infant's iodine requirement (approximately 50  $\mu\text{g}/\text{d}$ ) 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  $\mu\text{g}/\text{liter}$ . 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  $\mu\text{g}/\text{liter}$  in Finland to 270  $\mu\text{g}/\text{liter}$  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  $\mu\text{g}/\text{d}$ ), 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  $\mu\text{g}/\text{liter}$  in infants is sufficient (54). At the same time, they recommend an iodine intake of 90  $\mu\text{g}/\text{d}$  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  $\mu\text{g}/\text{liter}$ . 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]  $\mu\text{g}/\text{liter}$ , suggesting that the current WHO median UI cutoff for iodine sufficiency in infancy ( $\geq 100$   $\mu\text{g}/\text{liter}$ ) 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  $\mu\text{g}/\text{d}$ . 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  $\mu\text{g}/\text{kg} \cdot \text{d}$ , and the estimated infant requirement of 40  $\mu\text{g}$  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  $\mu\text{g}/\text{d}$  (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.** IDD by age group (Refs. 3 and 4)

| Age groups           | Health consequences of iodine deficiency  |
|----------------------|---|
| All ages             | Goiter<br>Increased susceptibility of the thyroid gland to nuclear radiation  |
| Fetus                | Abortion<br>Stillbirth<br>Congenital anomalies<br>Perinatal mortality   |
| Neonate              | Infant mortality<br>Endemic cretinism   |
| Child and adolescent | Impaired mental function<br>Delayed physical development  |
| Adult                | Impaired mental function<br>Reduced work productivity<br>Toxic nodular goiter; iodine-induced hyperthyroidism<br>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 gesta-



**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.

tion 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.

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,  $91 \pm 13$  vs.  $82 \pm 14$ ), and treatment resulted in far fewer children with low psychomotor scores (0.5% with a score  $\leq 60$  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 ( $\pm$ SD) developmental quotient at 2 yr of age was higher in the treated than in the untreated children ( $90 \pm 14$  vs.  $75 \pm 18$ ) (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 ( $85.6 \pm 13.9$  vs.  $74.4 \pm 4.8$ ) (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 ( $83.7 \pm 13.4$  vs.  $72.7 \pm 14.0$  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  $\mu\text{g}$  iodine as iodized salt or control daily beginning in the first trimester to healthy pregnant Italian women ( $n = 35$ ; median UI, 31–37  $\mu\text{g}/\text{liter}$ ). 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  $\mu\text{g}$  iodine/d as KI solution or no supplement from 17 wk to term. Median UI increased from 55 to 90–110  $\mu\text{g}/\text{liter}$  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, Glinioer *et al.* (60) supplemented pregnant Belgian women ( $n = 120$ ; median UI, 36  $\mu\text{g}/\text{liter}$ ; biochemical criteria of excess thyroid stimulation) with 100  $\mu\text{g}$  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  $\mu\text{g}$  iodine/d from 11 wk to term in pregnant German women ( $n = 108$ ; median UI, 53  $\mu\text{g/g}$  creatinine; goiter rate, 42.5%). Median UI increased to 104  $\mu\text{g/g}$  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<sub>3</sub>, T<sub>4</sub>, 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  $\mu\text{g}$  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, FT<sub>4</sub>, 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  $\mu\text{g/g}$  creatinine) with 50 or 200  $\mu\text{g}$  iodine/d from 18–26 wk to 29–33 wk. Median UI was significantly higher in the 200- $\mu\text{g}$  group than in the 50- $\mu\text{g}$  group (230 *vs.* 128  $\mu\text{g/g}$  creatinine). However, there were no differences in maternal FT<sub>4</sub>, FT<sub>3</sub>, 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<sub>4</sub> 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  $\mu\text{g/liter}$ , 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  $\mu\text{g/liter}$ , 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  $\mu\text{g}/\text{liter}$ , 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 sub-

types 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 ( $\approx 90\%$ ). The highest prevalence of iodine deficiency is in Europe (52.0%), where the household coverage with iodized salt is the lowest ( $\approx 25\%$ ), 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  $\mu\text{g}/\text{liter}$  (95% CI, 146–172), still adequate but half the median value of 321  $\mu\text{g}/\text{liter}$  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 <sup>a</sup> | Population with UI < 100 µg/liter <sup>b</sup> |                     | Households with access to iodized salt (%) <sup>c</sup> |
|--------------------------|--|---------------------|---|
|                          | 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  |

<sup>a</sup> Regions consist of 193 WHO member states.

<sup>b</sup> Based on population estimates for 2006.

<sup>c</sup> 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 health-care 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).

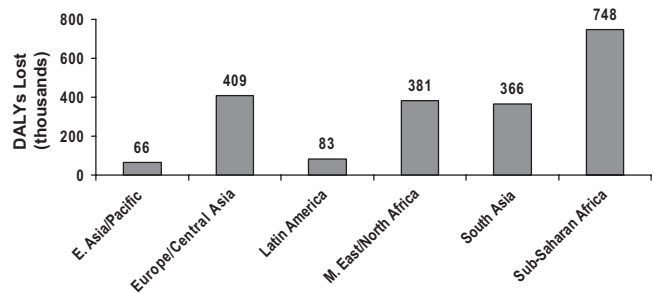
## IX. Treatment and Prevention

### 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<sub>3</sub>). Because KIO<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> 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



**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).

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  $\mu\text{g}/\text{liter}$  in schoolchildren (from Ref. 89)

|                                     |   |
|-------------------------------------|---|
| Women of childbearing age           | A single annual oral dose of 400 mg of iodine as iodized oil<br>OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the RNI of 150 $\mu\text{g}/\text{d}$ of iodine  |
| Women who are pregnant or lactating | A single annual oral dose of 400 mg of iodine as iodized oil<br>OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the new RNI of 250 $\mu\text{g}/\text{d}$ iodine<br>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<br>OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the RNI of 90 $\mu\text{g}/\text{d}$ of iodine<br>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<br>OR A daily oral dose of iodine as KI should be given so that the total iodine intake meets the RNI of 90 $\mu\text{g}/\text{d}$ 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  $\text{KIO}_3$  in drops or tablets. Single oral doses of KI monthly (30 mg) or bi-weekly (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  $\mu\text{g}/\text{d}$ ) 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  $\mu\text{g}/\text{liter}$  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)  $\mu\text{g}/\text{liter}$ , within the

adequate range recommended by WHO of 150–249  $\mu\text{g/liter}$ , the lower 95% CI was less than 150  $\mu\text{g/liter}$  (222). Because of this uncertainty, until additional data are available, the American Thyroid Association recommends that women receive 150  $\mu\text{g}$  iodine supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150  $\mu\text{g}$  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  $\mu\text{g/liter}$ , 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  $\mu\text{g/liter}$ , compared with 2  $\mu\text{g/liter}$  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  $\mu\text{g/liter}$ ) in those receiving supplementation with 150  $\mu\text{g/d}$  of oral iodine, compared with those not supplemented (34  $\mu\text{g/liter}$ ) (225). In Germany, 60 mothers who received 200  $\mu\text{g/d}$  of oral iodine had significantly higher mean iodine concentrations in breast milk (76  $\mu\text{g/liter}$ ) than untreated (55  $\mu\text{g/liter}$ ) (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  $\mu\text{g/kg}$  body weight/d are required to maintain positive balance, and experts generally recommend iodine intakes of 30 to 60  $\mu\text{g/kg} \cdot \text{d}$  for this group (227–229). Formula milks for preterm infants contain 20 to 170  $\mu\text{g}$  iodine/liter, and, depending on the dietary iodine intake of the mother, breast milk generally contains 50 to 150  $\mu\text{g/liter}$  (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 con-

tain much less iodine than breast milk or preterm formula milks (230). U.S. and European clinical nutrition societies recommend parenteral iodine intakes of 1  $\mu\text{g/kg}$  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  $\mu\text{g}$  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  $\mu\text{g}$  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  $\mu\text{g/kg}$  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  $\mu\text{g}$  iodine/liter) or the same formula without iodine supplementation (68  $\mu\text{g}$  iodine/liter) until 40 wk postconceptional age. These provided daily iodine intakes of approximately 40–50 and 12–16  $\mu\text{g}$  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<sub>4</sub> 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  $\mu\text{g}$  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  $\mu\text{g}/\text{liter}$ , with eight less than 50  $\mu\text{g}/\text{liter}$  (moderate deficiency) and seven less than 20  $\mu\text{g}/\text{liter}$  (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  $\mu\text{g}/\text{ml}$  KI equivalent to 1  $\mu\text{g}$  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  $\mu\text{g}$  iodine per serving (245). Daily iodine requirements in adult patients receiving total enteral nutrition or total PN are estimated to be 70–150  $\mu\text{g}$  (246). A recent technical review of PN by the American Gastroenterological Association recommended iodine in-

takes of 70–140  $\mu\text{g}/\text{d}$  (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, Schaumburg, IL) contains 100  $\mu\text{g}$  iodine/ml. According to the manufacturer's specifications (252), the usual adult dosage for prophylaxis or treatment of iodine deficiency is 1 to 2  $\mu\text{g}$  iodine/kg of body weight/d. For children and pregnant/lactating women, the recommended dosage is 2 to 3  $\mu\text{g}$  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  $\mu\text{g}/\text{liter}$ , whereas in Chile it is above 500  $\mu\text{g}/\text{liter}$  (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  $\mu\text{g}/\text{liter}$  (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 ( $\mu\text{g}/\text{d}$ )

| 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 iododerma, 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  $\mu\text{g}/\text{d}$ ) and Iceland, an area of high iodine intake (approximately 400–450  $\mu\text{g}/\text{d}$ , based on urinary iodine excretion around 300  $\mu\text{g}$  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  $\mu\text{g}/\text{d}$ . 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  $\mu\text{g}/\text{liter}$ , the mean UIs were 1235 and 428  $\mu\text{g}/\text{g}$  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  $\mu\text{g}/\text{liter}$  resulted in UIs greater than 900  $\mu\text{g}/\text{liter}$  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  $\mu\text{g}/\text{d}$ . 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  $\mu\text{g}/\text{d}$  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  $\mu\text{g}/\text{d}$ —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  $\mu\text{g}/\text{g}$  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  $\mu\text{g}/\text{liter}$ , 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  $\mu\text{g}/\text{liter}$ ; and Copenhagen, median UI, 61  $\mu\text{g}/\text{liter}$ ) 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 IHH 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  $\mu\text{g}/\text{d}$  for adults) can minimize the amount of thyroid dysfunction in populations (285). Iodine prophylaxis with periodic mon-

itoring 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).

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## References

1. Baumann F 1896 Ueber das normale Vorkommen von Jod im Thierkörper. *Z Physiol Chem* 21:319–330
2. Marine D, Kimball OP 1917 The prevention of simple goiter in man. *J Lab Clin Med* 3:40–48
3. Hetzel BS 1983 Iodine deficiency disorders (IDD) and their eradication. *Lancet* 2:1126–1129
4. Zimmermann MB, Jooste PL, Pandav CS 2008 The iodine deficiency disorders. *Lancet* 372:1251–1262
5. Goldschmidt VW 1954 *Geochemistry*. Oxford, UK: Oxford University Press
6. Pennington JAT, Schoen SA, Salmon GD, Young B, Johnson RD, Marts RW 1995 Composition of core foods in the U.S. food supply, 1982–1991. *J Food Comp Anal* 8:171–217
7. Haldimann M, Alt A, Blanc A, Blondeau K 2005 Iodine content of food groups. *J Food Comp Anal* 18:461–471
8. Institute of Medicine, Academy of Sciences 2001 Dietary reference intakes for vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press
9. Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE 2004 Sources of dietary iodine: bread, cows' milk, and infant formula in the Boston area. *J Clin Endocrinol Metab* 89:3421–3424
10. Chavasi V, Malaivongse P, Judprasong K 2002 Study on stability of iodine in iodated salt by use of different cooking model conditions. *J Food Comp Anal* 15:265–276
11. Alexander WD, Harden RM, Harrison MT, Shimmins J 1967 Some aspects of the absorption and concentration of iodide by the alimentary tract in man. *Proc Nutr Soc* 26: 62–66
12. Nicola JP, Basquin C, Portulano C, Reyna-Neyra A, Paroder M, Carrasco N 2009 The  $\text{Na}^+/\text{I}^-$  symporter mediates active iodide uptake in the intestine. *Am J Physiol Cell Physiol* 296:C654–C662



13. Hays MT, Nielsen KR 1994 Human thyroxine absorption: age effects and methodological analyses. *Thyroid* 4:55–64
14. DeGroot LJ 1966 Kinetic analysis of iodine metabolism. *J Clin Endocrinol Metab* 26:149–173
15. Stanbury JB, Brownell GL, Riggs DS, Perinetti H, Itoiz J, Del Castillo EB 1954 Endemic goiter. In: Stanbury JB, ed. *The adaptation of man to iodine deficiency*. Cambridge, MA: Harvard University Press; 1–209
16. Wayne EJ, Koutras DA, Alexander WD 1964 Clinical aspects of iodine metabolism. Oxford, UK: Blackwell Scientific
17. Weaver JC, Kamm ML, Dobson RL 1960 Excretion of radioiodine in human milk. *J Am Med Assoc* 173:872–875
18. Fisher DA, Oddie TH 1969 Thyroid iodine content and turnover in euthyroid subjects: validity of estimation of thyroid iodine accumulation from short-term clearance studies. *J Clin Endocrinol Metab* 29:721–727
19. Eskandari S, Loo DD, Dai G, Levy O, Wright EM, Carrasco N 1997 Thyroid Na<sup>+</sup>/I<sup>-</sup> symporter. Mechanism, stoichiometry, and specificity. *J Biol Chem* 272:27230–27238
20. Smanik PA, Ryu KY, Theil KS, Mazzaferri EL, Jhiang SM 1997 Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. *Endocrinology* 138:3555–3558
21. Eng PH, Cardona GR, Fang SL, Previti M, Alex S, Carrasco N, Chin WW, Braverman LE 1999 Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. *Endocrinology* 140:3404–3410
22. Dunn JT 1995 Thyroglobulin, hormone synthesis and thyroid disease. *Eur J Endocrinol* 132:603–604
23. Dunn JT, Dunn AD 2001 Update on intrathyroidal iodine metabolism. *Thyroid* 11:407–414
24. Oppenheimer JH, Schwartz HL, Surks MI 1975 Determination of common parameters of iodothyronine metabolism and distribution in man by noncompartmental analysis. *J Clin Endocrinol Metab* 41:319–324
25. Taki K, Kogai T, Kanamoto Y, Hershman JM, Brent GA 2002 A thyroid-specific far-upstream enhancer in the human sodium/iodide symporter gene requires Pax-8 binding and cyclic adenosine 3',5'-monophosphate response element-like sequence binding proteins for full activity and is differentially regulated in normal and thyroid cancer cells. *Mol Endocrinol* 16:2266–2282
26. Abrams GM, Larsen PR 1973 Triiodothyronine and thyroxine in the serum and thyroid glands of iodine-deficient rats. *J Clin Invest* 52:2522–2531
27. Delange F 2000 Iodine deficiency. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the thyroid: a fundamental and clinical text*. 8th ed. Philadelphia: JD Lippincott; 295–316
28. Dumont JE, Ermans AM, Maenhaut C, Coppée F, Stanbury JB 1995 Large goitre as a maladaptation to iodine deficiency. *Clin Endocrinol (Oxf)* 43:1–10
29. Kopp P, Kimura ET, Aeschmann S, Oestreicher M, Tobler A, Fey MF, Studer H 1994 Polyclonal and monoclonal thyroid nodules coexist within human multinodular goiters. *J Clin Endocrinol Metab* 79:134–139
30. Laurberg P, Bülow Pedersen I, Knudsen N, Ovesen L, Andersen S 2001 Environmental iodine intake affects the type of nonmalignant thyroid disease. *Thyroid* 11:457–469
31. Delange F, Camus M, Ermans AM 1972 Circulating thyroid hormones in endemic goiter. *J Clin Endocrinol Metab* 34:891–895
32. Van Herle AJ, Hershman JM, Hornabrook RW, Chopra IJ 1976 Serum thyroglobulin in inhabitants of an endemic goiter region of New Guinea. *J Clin Endocrinol Metab* 43:512–516
33. Dumont JE, Ermans AM, Bastenie PA 1963 Thyroid function in a goiter endemic. V. Mechanism of thyroid failure in the Uele endemic cretins. *J Clin Endocrinol Metab* 23:847–860
34. Morreale de Escobar G, Obregon MJ, Escobar del Rey F 2004 Role of thyroid hormone during early brain development. *Eur J Endocrinol* 151(Suppl 3):U25–U37
35. Gaitan E 1989 *Environmental goitrogenesis*. Boca Raton, FL: CRC Press
36. Ermans AM, Delange F, Van der Velden M, Kinthaert J 1972 Possible role of cyanide and thiocyanate in the etiology of endemic cretinism. *Adv Exp Med Biol* 30:455–486
37. Laurberg P, Nøhr SB, Pedersen KM, Fuglsang E 2004 Iodine nutrition in breast-fed infants is impaired by maternal smoking. *J Clin Endocrinol Metab* 89:181–187
38. Messina M, Redmond G 2006 Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *Thyroid* 16:249–258
39. Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL 2006 Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environ Health Perspect* 114:1865–1871
40. Braverman LE, Pearce EN, He X, Pino S, Seeley M, Beck B, Magnani B, Blount BC, Firek A 2006 Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. *J Clin Endocrinol Metab* 91:2721–2724
41. Zimmermann MB, Köhrle J 2002 The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. *Thyroid* 12:867–878
42. Zimmermann MB 2006 The influence of iron status on iodine utilization and thyroid function. *Ann Rev Nutr* 26:367–389
43. Zimmermann MB, Burgi H, Hurrell RF 2007 Iron deficiency predicts poor maternal thyroid status during pregnancy. *J Clin Endocrinol Metab* 92:3436–3440
44. Zimmermann MB, Wegmüller R, Zeder C, Chaouki N, Torresani T 2004 The effects of vitamin A deficiency and vitamin A supplementation on thyroid function in goitrous children. *J Clin Endocrinol Metab* 89:5441–5447
45. Zimmermann MB, Jooste PL, Mabapa NS, Schoeman S, Biebinger R, Mushaphi LF, Mbhenyane X 2007 Vitamin A supplementation in iodine-deficient African children decreases TSH stimulation of the thyroid and reduces the goiter rate. *Am J Clin Nutr* 86:1040–1044
46. Fisher DA, Oddie TH 1969 Thyroidal radioiodine clearance and thyroid iodine accumulation: contrast between random daily variation and population data. *J Clin Endocrinol Metab* 29:111–115
47. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Tong Y, Wang



- W, Gao T, Li C 2006 Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 354:2783–2793
48. Oddie TH, Fisher DA, Long JM 1964 Factors affecting the estimation of iodine entering the normal thyroid gland using short-term clearance studies. *J Clin Endocrinol Metab* 24:924–933
  49. Dworkin HJ, Jacquez JA, Beierwaltes WH 1966 Relationship of iodine ingestion to iodine excretion in pregnancy. *J Clin Endocrinol Metab* 26:1329–1342
  50. Harrison MT 1968 Iodine balance in man. *Postgrad Med J* 44:69–71
  51. Harrison MT, Harden R, Alexander WD, Wayne E 1965 Iodine balance studies in patients with normal and abnormal thyroid function. *J Clin Endocrinol Metab* 25:1077–1084
  52. Malamos B, Koutras DA, Marketos SG, Rigopoulos GA, Yataganas XA, Binopoulos D, Sfountouris J, Pharmakiotis AD, Vought RL, London WT 1967 Endemic goiter in Greece: an iodine balance study in the field. *J Clin Endocrinol Metab* 27:1372–1380
  53. Vought RL, London WT 1967 Iodine intake, excretion and thyroidal accumulation in healthy subjects. *J Clin Endocrinol Metab* 27:913–919
  54. World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders 2007 Assessment of iodine deficiency disorders and monitoring their elimination. 3rd ed. Geneva: WHO
  55. Glinoe D 1997 The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 18:404–433
  56. Delange F 1989 Iodine nutrition and congenital hypothyroidism. In: Delange F, Fisher DA, Glinoe D, eds. *Research in congenital hypothyroidism*. New York: Plenum Press; 157–161
  57. Delange F, Bourdoux P, Vo Thi LD, Ermans AM, Senterre J 1984 Negative iodine balance in preterm infants. *Ann Endocrinol* 45:77
  58. Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P, Cappa F, D'Armiento M 1991 The effects of iodoprophylaxis on thyroid size during pregnancy. *Am J Obstet Gynecol* 164:482–485
  59. Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Larsen KR, Eriksen GM, Johannesen PL 1993 Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. *J Clin Endocrinol Metab* 77:1078–1083
  60. Glinoe D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grün JP, Kinthaert J, Lejeune B 1995 A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. *J Clin Endocrinol Metab* 80:258–269
  61. Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ 1998 Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* 83:3401–3408
  62. Zimmermann MB 2007 The impact of iodized salt or iodine supplements on iodine status during pregnancy, lactation and infancy. *Public Health Nutr* 10:1584–1595
  63. Ingenbleek Y, Malvaux P 1974 Iodine balance studies in protein-calorie malnutrition. *Arch Dis Child* 49:305–309
  64. Malvaux P, Beckers C, De Visscher M 1969 Iodine balance studies in nongoitrous children and in adolescents on low iodine intake. *J Clin Endocrinol Metab* 29:79–84
  65. Zimmermann M, Saad A, Hess S, Torresani T, Chaouki N 2000 Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. *Eur J Endocrinol* 143:727–731
  66. Zimmermann MB, Hess SY, Molinari L, De Benoist B, Delange F, Braverman LE, Fujieda K, Ito Y, Jooste PL, Moosa K, Pearce EN, Pretell EA, Shishiba Y 2004 New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. *Am J Clin Nutr* 79:231–237
  67. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC 1981 Volumetrie der Schilddrüsenlappen mittels Real-time-Sonographie. *Dtsch Med Wochenschr* 106:1338–1340
  68. Zimmermann MB, Molinari L, Spehl M, Weidinger-Toth J, Podoba J, Hess S, Delange F 2001 Toward a consensus on reference values for thyroid volume in iodine-replete schoolchildren: results of a workshop on inter-observer and inter-equipment variation in sonographic measurement of thyroid volume. *Eur J Endocrinol* 144:213–220
  69. Aghini-Lombardi F, Antonangeli L, Pinchera A, Leoli F, Rago T, Bartolomei AM, Vitti P 1997 Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. *J Clin Endocrinol Metab* 82:1136–1139
  70. Zimmermann MB, Hess SY, Adou P, Toresanni T, Wegmüller R, Hurrell RF 2003 Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Cote d'Ivoire. *Am J Clin Nutr* 77:663–667
  71. Yu X, Fan C, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Tong Y, Wang W, Gao T, Li C, Teng W 2008 A five-year follow-up study of goiter and thyroid nodules in three regions with different iodine intakes in China. *J Endocrinol Invest* 31: 243–250
  72. Andersen S, Karmisholt J, Pedersen KM, Laurberg P 2008 Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. *Br J Nutr* 99:813–818
  73. Knudsen N, Christiansen E, Brandt-Christensen M, Nygaard B, Perrild H 2000 Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24h values. *Eur J Clin Nutr* 54:361–363
  74. Delange F 1997 Neonatal screening for congenital hypothyroidism: results and perspectives. *Horm Res* 48:51–61
  75. Zimmermann MB, Aeberli I, Torresani T, Bürgi H 2005 Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. *Am J Clin Nutr* 82:388–392
  76. Spencer CA, Wang CC 1995 Thyroglobulin measurement.

- Techniques, clinical benefits, and pitfalls. *Endocrinol Metab Clin North Am* 24:841–863
77. Knudsen N, Bülow I, Jørgensen T, Perrild H, Ovesen L, Laurberg P 2001 Serum Tg: a sensitive marker of thyroid abnormalities and iodine deficiency in epidemiological studies. *J Clin Endocrinol Metab* 86:3599–3603
  78. Benmiloud M, Chaouki ML, Gutekunst R, Teichert HM, Wood WG, Dunn JT 1994 Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. *J Clin Endocrinol Metab* 79:20–24
  79. Missler U, Gutekunst R, Wood WG 1994 Thyroglobulin is a more sensitive indicator of iodine deficiency than thyrotropin: development and evaluation of dry blood spot assays for thyrotropin and thyroglobulin in iodine-deficient geographical areas. *Eur J Clin Chem Clin Biochem* 32:137–143
  80. Zimmermann MB, Moretti D, Chaouki N, Torresani T 2003 Development of a dried whole-blood spot thyroglobulin assay and its evaluation as an indicator of thyroid status in goitrous children receiving iodized salt. *Am J Clin Nutr* 77:1453–1458
  81. Zimmermann MB, de Benoist B, Corigliano S, Jooste PL, Molinari L, Moosa K, Pretell EA, Al-Dallal ZS, Wei Y, Zu-Pei C, Torresani T 2006 Assessment of iodine status using dried blood spot thyroglobulin: development of reference material and establishment of an international reference range in iodine-sufficient children. *J Clin Endocrinol Metab* 91:4881–4887
  82. Zimmermann MB, Moretti D, Chaouki N, Torresani T 2003 Introduction of iodized salt to severely iodine-deficient children does not provoke thyroid autoimmunity: a one-year prospective trial in northern Morocco. *Thyroid* 13:199–203
  83. Loviselli A, Velluzzi F, Mossa P, Cambosu MA, Secci G, Atzeni F, Taberlet A, Balestrieri A, Martino E, Grasso L, Songini M, Bottazzo GF, Mariotti S 2001 The Sardinian autoimmunity study: 3. Studies on circulating antithyroid antibodies in Sardinian schoolchildren: relationship to goiter prevalence and thyroid function. *Thyroid* 11:849–857
  84. Mattsson S, Lindström S 1995 Diuresis and voiding pattern in healthy schoolchildren. *Brit J Urol* 76:783–789
  85. Larsson G, Victor A 1988 Micturition patterns in a healthy female population, studied with a frequency/volume chart. *Scand J Urol Nephrol Suppl* 114:53–57
  86. Dafnis E, Sabatini S 1992 The effect of pregnancy on renal function: physiology and pathophysiology. *Am J Med Sci* 303:184–205
  87. Aboul-Khair SA, Crooks J, Turnbull AC, Hytten FE 1964 The physiological changes in thyroid function during pregnancy. *Clin Sci* 27:195–207
  88. Liberman CS, Pino SC, Fang SL, Braverman LE, Emerson CH 1998 Circulating iodide concentrations during and after pregnancy. *J Clin Endocrinol Metab* 83:3545–3549
  89. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J 2007 Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the technical consultation. *Public Health Nutr* 10:1606–1611
  90. Caldwell KL, Miller GA, Wang RY, Jain RB, Jones RL 2008 Iodine status of the U.S. population, National Health and Nutrition Examination Survey 2003–2004. *Thyroid* 18:1207–1214
  91. Ategbro EA, Sankar R, Schultink W, van der Haar F, Pandav CS 2008 An assessment of progress toward universal salt iodization in Rajasthan, India, using iodine nutrition indicators in school-aged children and pregnant women from the same households. *Asia Pac J Clin Nutr* 17:56–62
  92. Gowachirapant S, Winichagoon P, Wyss L, Tong B, Baumgartner J, Melse-Boonstra A, Zimmermann MB 2009 Urinary iodine concentrations indicate iodine deficiency in pregnant Thai women but iodine sufficiency in their school-aged children. *J Nutr* 139:1169–1172
  93. Moleti M, Lo Presti VP, Campolo MC, Mattina F, Galletti M, Mandolino M, Violi MA, Giorgianni G, De Domenico D, Trimarchi F, Vermiglio F 2008 Iodine prophylaxis using iodized salt and risk of maternal thyroid failure in conditions of mild iodine deficiency. *J Clin Endocrinol Metab* 93:2616–2621
  94. Vermiglio F, Lo Presti VP, Finocchiaro MD, Battiato S, Grasso L, Ardita FV, Mancuso A, Trimarchi F 1992 Enhanced iodine concentration capacity by the mammary gland in iodine deficient lactating women of an endemic goiter region in Sicily. *J Endocrinol Invest* 15:137–142
  95. Dorea JG 2002 Iodine nutrition and breast feeding. *J Trace Elem Med Biol* 16:207–220
  96. Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L, Braverman LE 2007 Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocrinol Metab* 92:1673–1677
  97. Semba RD, Delange F 2001 Iodine in human milk: perspectives for human health. *Nutr Rev* 59:269–278
  98. Dorey CM, Zimmermann MB 2008 Reference values for spot urinary iodine concentrations in iodine-sufficient newborns using a new pad collection method. *Thyroid* 18:347–352
  99. National Research Council 1989 Recommended dietary allowances. 10th rev. ed. Washington, DC: National Academy Press; 215
  100. Delange F, Heidemann P, Bourdoux P, Larsson A, Vigneri R, Klett M, Beckers C, Stubbe P 1986 Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. *Biol Neonate* 49:322–330
  101. Nordenberg D, Sullivan K, Maberly G, Wiley V, Wilcken B, Bamforth F, Jenkins M, Hannon H, Adam B 1993 Congenital hypothyroid screening programs and the sensitive thyrotropin assay: strategies for the surveillance of iodine deficiency disorders In: Delange F, Dunn J, Glinoe D, eds. Iodine deficiency in Europe: a continuing concern. New York: Plenum Publishing; 211–217
  102. Carta Sorcini M, Diodato A, Fazzini C, Sabini G, Carta S, Grandolfo ME, Guidi M, Vasta M, Locatelli De Maestri J, Donati L 1988 Influence of environmental iodine deficiency on neonatal thyroid screening results. *J Endocrinol Invest* 11:309–312
  103. Sullivan KM, May W, Nordenberg D, Houston R, Maberly GF 1997 Use of thyroid stimulating hormone testing in newborns to identify iodine deficiency. *J Nutr* 127:55–58
  104. Copeland DL, Sullivan KM, Houston R, May W, Mendoza J, Salamatullah Q, Solomons N, Nordenberg D, Maberly GF 2002 Comparison of neonatal thyroid-stimulating hormone levels and indicators of iodine deficiency in school children. *Public Health Nutr* 5:81–87
  105. Glinoe D 2004 The regulation of thyroid function during

- normal pregnancy: importance of the iodine nutrition status. *Best Practice Res Clin Endocrinol Metab* 18:133–152
106. Zimmermann MB 2009 Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr* 89:668S–672S
  107. Elnagar B, Eltom A, Wide L, Gebre-Medhin M, Karlsson FA 1998 Iodine status, thyroid function and pregnancy: study of Swedish and Sudanese women. *Eur J Clin Nutr* 52:351–355
  108. Morreale de Escobar G, Obregon MJ, Escobar del Rey F 2004 Role of thyroid hormone during early brain development. *Eur J Endocrinol* 151(Suppl 3):U25–U37
  109. McCarrison R 1908 Observations on endemic cretinism in the Chitral and Gilgit Valleys. *Lancet* 2:1275–1280
  110. Halpern JP, Boyages SC, Maberly GF, Collins JK, Eastman CJ, Morris JGL 1991 The neurology of endemic cretinism. *Brain* 114:825–841
  111. Delange F 1974 Endemic goitre and thyroid function in Central Africa. *Monographs in pediatrics*. Basel, Switzerland: S. Karger; 1–171
  112. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O’Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 341:549–555
  113. Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulmsa T, Wiersinga WM, Drexhage HA, Vader HL 1999 Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 50:149–155
  114. Pharoah POD, Buttfield IH, Hetzel BS 1971 Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* 1:308–310
  115. Pharoah PO, Connolly KJ 1987 A controlled trial of iodinated oil for the prevention of endemic cretinism: a long term follow up. *Int J Epidemiol* 16:68–73
  116. Pharoah PO, Connolly KJ 1991 Effects of maternal iodine supplementation during pregnancy. *Arch Dis Child* 66:145–147
  117. Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H, Ermans AM 1978 Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *J Clin Endocrinol Metab* 47:354–360
  118. Thilly C, Lagasse R, Roger G, Bourdoux P, Ermans AM 1980 Impaired fetal and postnatal development and high perinatal death rate in a severe iodine deficient area. *Thyroid Research VIII. Proc 8th International Thyroid Congress, Australian Academy of Research, Sydney, Australia, 1980*, pp 20–23
  119. Thilly CH, Swennen B, Moreno-Reyes R, Hindlet JY, Bourdoux P, Vanderoas JB 1994 Maternal, fetal and juvenile hypothyroidism, birthweight and infant mortality in the etiopathogenesis of the IDD spectrum in Zaire and Malawi. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York: Cognizant Communication; 241–250
  120. Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O’Donnell K, Ma T, Amette K, DeLong N, DeLong GR 1994 Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *N Engl J Med* 331:1739–1744
  121. O’Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, DeLong N, Brenner G, Tai M, Dong W, DeLong GR 2002 Effects of iodine supplementation during pregnancy on child growth and development at school age. *Dev Med Child Neurol* 44:76–81
  122. Pretell EA, Palacios P, Tello L, Wan M, Utiger RD, Stanbury JB 1974 Iodine deficiency and the maternal/fetal relationship. In: Dunn JG, Medeiros-Neto GA, eds. *Endemic goiter and cretinism. Continuing threats to world health*. Pan American Health Organization Science Publication 292. Washington, DC: WHO; 143–155
  123. Pretell EA, Caceres A 1994 Impairment of mental development by iodine deficiency and its correction. A retrospective view of studies in Peru. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York: Cognizant Communication; 187–191
  124. Fierro-Benitez R, Cazar R, Stanbury JB, Rodriguez P, Garces F, Fierro-Renoy F, Estrella E 1988 Effects on schoolchildren of prophylaxis of mothers with iodized oil in an area of iodine deficiency. *J Endocrinol Invest* 11:327–335
  125. Greene LS 1994 A retrospective view of iodine deficiency, brain development and behavior from studies in Ecuador. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York: Cognizant Communication; 173–185
  126. Liesenkötter KP, Göpel W, Bogner U, Stach B, Grüters A 1996 Earliest prevention of endemic goiter by iodine supplementation during pregnancy. *Eur J Endocrinol* 134:443–448
  127. Nøhr SB, Jørgensen A, Pedersen KM, Laurberg P 2000 Postpartum thyroid dysfunction in pregnant thyroid peroxidase antibody-positive women living in an area with mild to moderate iodine deficiency: is iodine supplementation safe? *J Clin Endocrinol Metab* 85:3191–3198
  128. Antonangeli L, Maccherini D, Cavaliere R, Di Giulio C, Reinhardt B, Pinchera A, Aghini-Lombardi F 2002 Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study. *Eur J Endocrinol* 147:29–34
  129. Pedersen IB, Laurberg P, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Rasmussen LB 2007 An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab* 92:3122–3127
  130. Glinoe D, Lemone M, Bourdoux P, De Nayer P, DeLange F, Kinthaert J, LeJeune B 1992 Partial reversibility during late postpartum of thyroid abnormalities associated with pregnancy. *J Clin Endocrinol Metab* 74:453–457
  131. Rotondi M, Amato G, Biondi B, Mazziotti G, Del Buono A, Rotonda Nicchio M, Balzano S, Bellastella A, Glinoe D, Carella C 2000 Parity as a thyroid size-determining factor in areas with moderate iodine deficiency. *J Clin Endocrinol Metab* 85:4534–4537
  132. Knudsen N, Bülow I, Laurberg P, Ovesen L, Perrild H, Jørgensen T 2002 Parity is associated with increased thyroid volume solely among smokers in an area with moderate to mild iodine deficiency. *Eur J Endocrinol* 146:39–43
  133. Pharoah PO, Ellis SM, Ekins RP, Williams ES 1976 Ma-



- ternal thyroid function, iodine deficiency and fetal development. *Clin Endocrinol (Oxf)* 5:159–166
134. DeLong GR, Leslie PW, Wang SH, Jiang XM, Zhang ML, Rakeman M, Jiang JY, Ma T, Cao XY 1997 Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. *Lancet* 350:771–773
  135. Thilly CH, Swennen B, Moreno-Reyes R, Hindlet J-Y, Bourdoux P, Vanderpas JB 1994 Maternal, fetal and juvenile hypothyroidism, birth weight and infant mortality in the etiopathogenesis of the IDD spectra in Zaire and Malawi. In: JB Stanbury, ed. *The damaged brain of iodine deficiency*. New York: Cognizant Communication; 241–250
  136. Chaouki ML, Benmiloud M 1994 Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol* 130:547–551
  137. Semba RD, de Pee S, Hess SY, Sun K, Sari M, Bloem MW 2008 Child malnutrition and mortality among families not utilizing adequately iodized salt in Indonesia. *Am J Clin Nutr* 87:438–444
  138. Cobra C, Muhilal, Rusmil K, Rustama D, Djatnika, Suwardi SS, Permaesih D, Muherdiyantiningsih, Martuti S, Semba RD 1997 Infant survival is improved by oral iodine supplementation. *J Nutr* 127:574–578
  139. Boyages SC, Collins JK, Maberly GF, Jupp JJ, Morris J, Eastman CJ 1989 Iodine deficiency impairs intellectual and neuromotor development in apparently-normal persons. A study of rural inhabitants of north-central China. *Med J Aust* 150:676–682
  140. Choudhury N, Gorman KS 2003 Subclinical prenatal iodine deficiency negatively affects infant development in Northern China. *J Nutr* 133:3162–3165
  141. Gao TS, Teng WP, Shan ZY, Jin Y, Guan HX, Teng XC, Yang F, Wang WB, Shi XG, Tong YJ, Li D, Chen W 2004 Effect of different iodine intake on schoolchildren's thyroid diseases and intelligence in rural areas. *Chin Med J* 117:1518–1522
  142. Amarra MS, Bongga DC, Peñano-Ho L, Cruz FB, Solis JS, Barrios EB 2007 Effect of iodine status and other nutritional factors on psychomotor and cognitive performance of Filipino schoolchildren. *Food Nutr Bull* 28:47–54
  143. Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F 1990 Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily. *J Clin Endocrinol Metab* 70:379–384
  144. Fenzi GF, Giusti LF, Aghini-Lombardi F, Bartalena L, Marcocci C, Santini F, Bargagna S, Brizzolara D, Ferretti G, Falciglia G 1990 Neuropsychological assessment in schoolchildren from an area of moderate iodine deficiency. *J Endocrinol Invest* 13:427–431
  145. Vitti P, Aghini Lombardi F, Antonangeli L, Rago T, Chiovato L, Pinchera A, Marcheschi M, Bargagna S, Bertucelli B, Ferretti G 1992 Mild iodine deficiency in fetal/neonatal life and neuropsychological performances. *Acta Med Austriaca* 19(Suppl 1):57–59
  146. Aghini Lombardi FA, Pinchera A, Antonangeli L, Rago T, Chiovato L, Bargagna S, Bertucelli B, Ferretti G, Sbrana B, Marcheschi M 1995 Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. *J Endocrinol Invest* 18:57–62
  147. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F 2004 Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 89:6054–6060
  148. Santiago-Fernandez P, Torres-Barahona R, Muela-Martínez JA, Rojo-Martínez G, García-Fuentes E, Garriga MJ, León AG, Soriguer F 2004 Intelligence quotient and iodine intake: a cross-sectional study in children. *J Clin Endocrinol Metab* 89:3851–3857
  149. Azizi F, Sarshar A, Nafarabadi M, Ghazi A, Kimiagar M, Noohi S, Rahbar N, Bahrami A, Kalantari S 1993 Impairment of neuromotor and cognitive development in iodine-deficient schoolchildren with normal physical growth. *Acta Endocrinol (Copenh)* 129:501–504
  150. Azizi F, Kalani H, Kimiagar M, Ghazi A, Sarshar A, Nafarabadi M, Rahbar N, Noohi S, Mohajer M, Yassai M 1995 Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. *Int J Vitam Nutr Res* 65:199–205
  151. Salarkin N, Mirmiran P, Azizi F 2004 Timing of the effect of iodine supplementation on intelligence quotient of schoolchildren. *Int J Endocrinol Metab* 2:95–102
  152. Tiwari BD, Godbole MM, Chattopadhyay N, Mandal A, Mithal A 1996 Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. *Am J Clin Nutr* 63:782–786
  153. Huda SN, Grantham-McGregor SM, Rahman KM, Tomkins A 1999 Biochemical hypothyroidism secondary to iodine deficiency is associated with poor school achievement and cognition in Bangladeshi children. *J Nutr* 129:980–987
  154. Ojule AC, Osotimehin BO 1998 The influence of iodine deficiency on the cognitive performance of school children in Saki, south-west Nigeria. *Afr J Med Sci* 27:95–99
  155. Sameroff AJ, Seifer R, Baldwin A, Baldwin C 1993 Stability and intelligence from preschool to adolescence: the influence of social and family risk factors. *Child Dev* 64:80–97
  156. Bleichrodt N, Born MP 1994 A metaanalysis of research on iodine and its relationship to cognitive development. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York: Cognizant Communications; 195–200
  157. Qian M, Wang D, Watkins WE, Gebiski V, Yan YQ, Li M, Chen ZP 2005 The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pacific J Clin Nutr* 14:32–42
  158. Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL 1982 The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am J Clin Nutr* 35:127–134
  159. Shrestha RM 1994 Effect of iodine and iron supplementation on physical, psychomotor and mental development in primary school children in Malawi. Doctoral thesis, Wageningen Agricultural University, Wageningen, The Netherlands
  160. Huda SN, Grantham-McGregor SM, Tomkins A 2001 Cognitive and motor functions of iodine deficient but euthyroid children in Bangladesh do not benefit from iodized poppy seed oil (Lipiodol). *J Nutr* 131:72–77
  161. Isa ZM, Alias IZ, Kadir KA, Ali O 2000 Effect of iodized



- oil supplementation on thyroid hormone levels and mental performance among Orang Asli schoolchildren and pregnant mothers in an endemic goitre area in Peninsular Malaysia. *Asia Pac J Clin Nutr* 9:274–281
162. Zimmermann MB, Connolly K, Bozo M, Bridson J, Rohner F, Grimci L 2006 Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. *Am J Clin Nutr* 83:108–114
  163. Koutras DA, Christakis G, Trichopoulos D, Dakou-Voutetaki A, Kyriakopoulos V, Fontanares P, Livadas DP, Gatsios D, Malamos B 1973 Endemic goiter in Greece: nutritional status, growth, and skeletal development of goitrous and nongoitrous populations. *Am J Clin Nutr* 26:1360–1368
  164. Bautista A, Barker PA, Dunn JT, Sanchez M 1977 Lack of correlation between thyroid size and body growth in an area of endemic goiter. *Am J Clin Nutr* 30:275–279
  165. Ali O, Tan TT, Sakinah O, Khalid BA, Wu LL, Wan Nazaimoon WM, Ng ML 1994 Thyroid function and pubertal development in malnutrition. *Ann Acad Med Singapore* 23:852–855
  166. Neumann CG, Harrison GG 1994 Onset and evolution of stunting in infants and children. Examples from the Human Nutrition Collaborative Research Support Program. Kenya and Egypt studies. *Eur J Clin Nutr* 48(Suppl 1): S90–S102
  167. Lal RB, Srivastava VK, Chandra R 1996 A study of the spectrum of iodine deficiency disorders in rural area of Uttar Pradesh. *Indian J Public Health* 40:10–12
  168. Mason JB, Deitchler M, Gilman A, Gillenwater K, Shuaib M, Hotchkiss D, Mason K, Mock N, Sethuraman K 2002 Iodine fortification is related to increased weight-for-age and birthweight in children in Asia. *Food Nutr Bull* 23: 292–308
  169. van Stuijvenberg ME, Kvalsvig JD, Faber M, Kruger M, Kenoyer DG, Benadé AJ 1999 Effect of iron-, iodine-, and beta-carotene-fortified biscuits on the micronutrient status of primary school children: a randomized controlled trial. *Am J Clin Nutr* 69:497–503
  170. Rivera JA, González-Cossío T, Flores M, Romero M, Rivera M, Téllez-Rojo MM, Rosado JL, Brown KH 2001 Multiple micronutrient supplementation increases the growth of Mexican infants. *Am J Clin Nutr* 74:657–663
  171. Moreno-Reyes R, Mathieu F, Boelaert M, Begaux F, Suetens C, Rivera MT, Nève J, Perlmutter N, Vanderpas J 2003 Selenium and iodine supplementation of rural Tibetan children affected by Kashin-Beck osteoarthropathy. *Am J Clin Nutr* 78:137–144
  172. Hernández-Cassis C, Cure-Cure C, López-Jaramillo P 1995 Effect of thyroid replacement therapy on the stature of Colombian children with minimal thyroid dysfunction. *Eur J Clin Invest* 25:454–456
  173. Crew MD, Spindler SR 1986 Thyroid hormone regulation of the transacted rat growth hormone promoter. *J Biol Chem* 261:5018–5022
  174. Samuels MH, Wierman ME, Wang C, Ridgway EC 1989 The effect of altered thyroid status on pituitary hormone messenger ribonucleic acid concentration in the rat. *Endocrinology* 124:2277–2282
  175. Hochberg Z, Bick T, Harel Z 1990 Alterations of human growth hormone binding by rat liver membranes during hypo- and hyperthyroidism. *Endocrinology* 126:325–329
  176. Burstein PJ, Draznin B, Johnson CJ, Schalch DS 1979 The effect of hypothyroidism on growth, serum growth hormone, the growth hormone-dependent somatomedin, insulin-like growth factor, and its carrier protein in rats. *Endocrinology* 104:1107–1111
  177. Nántö-Salonen K, Muller HL, Hoffman AR, Vu TH, Rosenfeld RG 1993 Mechanisms of thyroid hormone action on the insulin-like growth factor system: all thyroid hormone effects are not growth hormone mediated. *Endocrinology* 132:781–788
  178. Miell JP, Zini M, Quin JD, Jones J, Portioli I, Valcavi R 1994 Reversible effects of cessation and recommencement of thyroxine treatment on insulin-like growth factors (IGFs) and IGF-binding proteins in patients with total thyroidectomy. *J Clin Endocrinol Metab* 79:1507–1512
  179. Iglesias P, Bayón C, Méndez J, Gancedo PG, Grande C, Díez JJ 2001 Serum insulin-like growth factor type 1, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 concentrations in patients with thyroid dysfunction. *Thyroid* 11:1043–1048
  180. Wan Nazaimoon WM, Osman A, Wu LL, Khalid BA 1996 Effects of iodine deficiency on insulin-like growth factor-I, insulin-like growth factor-binding protein-3 levels and height attainment in malnourished children. *Clin Endocrinol (Oxf)* 45:79–83
  181. Aydin K, Bideci A, Kendirci M, Cinaz P, Kurtoglu S 2002 Insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels of children living in an iodine- and selenium-deficient endemic goiter area. *Biol Trace Elem Res* 90:25–30
  182. Alikapıfođlu A, Ozön A, Yordam N 2002 Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency. *Turk J Pediatr* 44:215–218
  183. Ozön A, Alikapıfođlu A, Yordam N 2004 Influence of iodine supplementation on serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels in severe iodine deficiency. *Turk J Pediatr* 46:303–308
  184. Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, Chaouki N, Bozo M, Grimci L, Bridson J 2007 Treatment of iodine deficiency in school-age children increases IGF-1 and IGFBP-3 concentrations and improves somatic growth. *J Clin Endocrinol Metab* 92:437–442
  185. Biondi B, Cooper DS 2008 The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29:76–131
  186. Paoli-Valeri M, Guzman M, Jimenez-Lopez V, Arias-Ferreira A, Briceno-Fernandez M, Arata-Bellabarba G 2005 Atherogenic lipid profile in children with subclinical hypothyroidism. *An Pediatr (Barc)* 62:128–134
  187. Elnagar B, Eltom M, Karlsson FA, Ermans AM, Gebre-Medhin M, Bourdoux PP 1995 The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid-related hormones. *J Clin Endocrinol Metab* 80: 891–897
  188. Rönnefarth G, Kauf E, Deschner F, Forberger M 1996 Therapy of iodine deficiency goiter in adolescents with iodine or a combination of iodine and levothyroxine with special reference to lipid parameters. *Klin Padiatr* 208:123–128
  189. Zimmermann MB, Aeberli I, Melse-Boonstra A, Grimci L,

- Bridson J, Chaouki N, Mbhenyane X, Jooste PL 2009 Iodine treatment in children with subclinical hypothyroidism due to chronic iodine deficiency decreases TSH and C-peptide concentrations and improves the lipid profile. *Thyroid*, in press
190. Delange F, Bürgi H, Chen ZP, Dunn JT 2002 World status of monitoring iodine deficiency disorders control programs. *Thyroid* 12:915–924
  191. de Benoist B, McLean E, Andersson M, Rogers L 2008 Iodine deficiency in 2007: global progress since 2003. *Food Nutr Bull* 29:195–202
  192. Li M, Eastman CJ, Waite KV, Ma G, Zacharin MR, Topliss DJ, Harding PE, Walsh JP, Ward LC, Mortimer RH, Mackenzie EJ, Byth K, Doyle Z 2006 Are Australian children iodine deficient? Results of the Australian National Iodine Nutrition Study. *Med J Aust* 184:165–169
  193. UNICEF 2002 Fact sheet. IDD: achievements and challenges. Available at: <http://www.unicef.org/media/14946.html>
  194. Ministry of Health and Family Welfare, Government of India 2007 2005–06 National Family Health Survey (NFHS-3). New Delhi: Government of India
  195. Sankar R, Pandav CS 2005 Ban on sale of non-iodized salt for human consumption: A step in the right direction. *Natl Med J India* 18:169–171
  196. UNICEF 2007 The State of the world's children 2007. Available at: [www.unicef.org/SOWC/](http://www.unicef.org/SOWC/)
  197. Egbuta J, Onyezili F, Vanormelingen K 2003 Impact evaluation of efforts to eliminate iodine deficiency disorders in Nigeria. *Public Health Nutr* 6:169–173
  198. Okosieme OE 2006 Impact of iodination on thyroid pathology in Africa. *J R Soc Med* 99:396–401
  199. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA; International Child Development Steering Group 2007 Child development: risk factors for adverse outcomes in developing countries. *Lancet* 369:145–157
  200. UNICEF Nutrition Section, Eastern and Southern Africa Regional Office 2007 Protecting children's brain development: a strategic review on sustained universal salt iodization in Eastern and Southern Africa. Nairobi: UNICEF; 1–40
  201. Dunn JT 2000 Complacency: the most dangerous enemy in the war against iodine deficiency. *Thyroid* 10:681–683
  202. Zimmermann MB, Wegmüller R, Zeder C, Torresani T, Chaouki N 2004 Rapid relapse of thyroid dysfunction and goiter in school-age children after discontinuation of salt iodization. *Am J Clin Nutr* 79:642–645
  203. WHO 2005 The 58th World Health Assembly WHA58.24: Sustaining the elimination of iodine deficiency disorders. Available at: [http://www.who.int/gb/ebwha/pdf\\_files/WHA58/WHA58\\_24-en.pdf](http://www.who.int/gb/ebwha/pdf_files/WHA58/WHA58_24-en.pdf).
  204. Diosady LL, Alberti JO, Venkatesh Mannar MG, Stone TG 1997 Stability of iodine in iodized salt used for correction of iodine-deficiency disorders, I. *Food Nutr Bull* 18:388–396
  205. Diosady LL, Alberti JO, Venkatesh Mannar MG, FitzGerald S 1998 Stability of iodine in iodized salt used for correction of iodine-deficiency disorders, II. *Food Nutr Bull* 19:240–250
  206. Engle PL, Black MM, Behrman JR, Cabral de Mello M, Gertler PJ, Kapiriri L, Martorell R, Young ME; International Child Development Steering Group 2007 Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. *Lancet* 369: 229–242
  207. Aguayo VM, Scott S, Ross J; PROFILES Study Group 2003 Sierra Leone—investing in nutrition to reduce poverty: a call for action. *Public Health Nutr* 6:653–657
  208. Caulfield LE, Richard SA, Rivera JA, Musgrove P, Black RE 2006 Stunting, wasting, and micronutrient deficiency disorders 2006. In: Dean T, Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P, eds. *Disease control priorities in developing countries*. 2nd ed. New York: Oxford University Press; 551–568
  209. Horton S 2006 The economics of food fortification. *J Nutr* 136:1068–1071
  210. Seal JA, Doyle Z, Burgess JR, Taylor R, Cameron AR 2007 Iodine status of Tasmanians following voluntary fortification of bread with iodine. *Med J Aust* 186:69–71
  211. Cao XY, Jiang XM, Kareem A, Dou ZH, Abdul Rakeman M, Zhang ML, Ma T, O'Donnell K, DeLong N, DeLong GR 1994 Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet* 344:107–110
  212. Squatrito S, Vigneri R, Runello F, Ermans AM, Polley RD, Ingbar SH 1986 Prevention and treatment of endemic iodine-deficiency goiter by iodination of a municipal water supply. *J Clin Endocrinol Metab* 63:368–375
  213. Dunn JT 2003 Iodine should be routinely added to complementary foods. *J Nutr* 133:3008S–3010S
  214. Untoro J, Schultink W, West CE, Gross R, Hautvast JG 2006 Efficacy of oral iodized peanut oil is greater than that of iodized poppy seed oil among Indonesian schoolchildren. *Am J Clin Nutr* 84:1208–1214
  215. Bülow Pedersen I, Laurberg P, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Rasmussen LB 2006 Increase in incidence of hyperthyroidism predominantly occurs in young people after iodine fortification of salt in Denmark. *J Clin Endocrinol Metab* 91:3830–3834
  216. Delange F 1996 Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull World Health Organ* 74:101–108
  217. Todd CH, Dunn JT 1998 Intermittent oral administration of potassium iodide solution for the correction of iodine deficiency. *Am J Clin Nutr* 67:1279–1283
  218. Azizi F 2007 Iodine nutrition in pregnancy and lactation in Iran. *Public Health Nutr* 10:1596–1599
  219. Yan YQ, Chen ZP, Yang XM, Liu H, Zhang JX, Zhong W, Yao W, Zhao JK, Zhang ZZ, Hua JL, Li JS, Yu XQ, Wang FR 2005 Attention to the hiding iodine deficiency in pregnant and lactating women after universal salt iodization: a multi-community study in China. *J Endocrinol Invest* 28: 547–553
  220. Berghout A, Wiersinga W 1998 Thyroid size and thyroid function during pregnancy: an analysis. *Eur J Endocrinol* 138:536–542
  221. Zimmermann M, Delange F 2004 Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr* 58:979–984
  222. Public Health Committee of the American Thyroid Association, Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, Hollowell JG, Lamm SH, Mitchell ML, Pearce E, Robbins J, Rovet JF 2006 Iodine supplementation for pregnancy and lactation—United States and Can-

- ada: recommendations of the American Thyroid Association. *Thyroid* 16:949–951
223. Gushurst CA, Mueller JA, Green JA, Sedor F 1984 Breast milk iodine: reassessment in the 1980s. *Pediatrics* 73:354–357
  224. Pretell EA, Moncloa F, Salinas R, Kawano A, Guerra-Garcia R, Gutierrez L, Beteta L, Pretell J, Wan M 1969 Prophylaxis and treatment of endemic goiter in Peru with iodized oil. *J Clin Endocrinol Metab* 29:1586–1595
  225. Nøhr SB, Laurberg P, Børlum KG, Pedersen KM, Johansen PL, Damm P, Fuglsang E, Johansen A 1994 Iodine status in neonates in Denmark: regional variations and dependency on maternal iodine supplementation. *Acta Paediatrica* 83:578–582
  226. Seibold-Weiger K, Wollmann H, Rendl J, Ranke M, Speer C 1999 Iodine concentration in the breast milk of mothers of premature infants. *Z Geburtshilfe Neonatol* 203:81–85
  227. Delange F, Bourdoux P, Chanoine JP, Ermans AM 1988 Physiology of iodine nutrition during pregnancy, lactation, and early postnatal life. In: Berger H, ed. *Vitamins and minerals in pregnancy and lactation: Nestle nutrition workshop series*. New York: Vevey/Raven Press; 16:205–214
  228. Ares S, Escobar-Morreale HF, Quero J, Durán S, Presas MJ, Herruzo R, Morreale de Escobar G 1997 Neonatal hypothyroxinemia: effects of iodine intake and premature birth. *J Clin Endocrinol Metab* 82:1704–1712
  229. Ibrahim M, de Escobar GM, Visser TJ, Durán S, van Toor H, Strachan J, Williams FL, Hume R 2003 Iodine deficiency associated with parenteral nutrition in extreme preterm infants. *Arch Dis Child Fetal Neonatal Ed* 88:F56–F57
  230. Ares S, Quero J, Durán S, Presas MJ, Herruzo R, Morreale de Escobar G 1994 Iodine content of infant formulas and iodine intake of premature babies: high risk of iodine deficiency. *Arch Dis Child Fetal Neonatal Ed* 71:F184–F191
  231. Greene HL, Hambidge KM, Schanler R, Tsang RC 1988 Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr* 48:1324–1342
  232. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR) 2005 Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 41(Suppl 2):S1–S87
  233. Moukarzel AA, Buchman AL, Salas JS, Vargas J, Guss W, Baron HL, Reyen L, Ament ME 1992 Iodine supplementation in children receiving long-term parenteral nutrition. *J Pediatr* 121:252–254
  234. Smerdely P, Lim A, Boyages SC, Waite K, Wu D, Roberts V, Leslie G, Arnold J, John E, Eastman CJ 1989 Topical iodine containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 2:661–664
  235. Mimoz O, Villeminey S, Ragot S, Dahyot-Fizelier C, Laksiri L, Petitpas F, Debaene B 2007 Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care. *Arch Intern Med* 167:2066–2072
  236. Reuss ML, Leviton A, Paneth N, Susser M 1997 Thyroxine values from newborn screening of 919 infants born before 29 weeks' gestation. *Am J Public Health* 87:1693–1697
  237. Lucas A, Morley R, Fewtrell MS 1996 Low triiodothyronine concentration in preterm infants and subsequent intelligence quotient (IQ) at 8 year follow up. *BMJ* 312:1132–1133
  238. Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M 1996 The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. *N Engl J Med* 334:821–827
  239. Rogahn J, Ryan S, Wells J, Fraser B, Squire C, Wild N, Hughes A, Amegavie L 2000 Randomised trial of iodine intake and thyroid status in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 83:F86–F90
  240. Ibrahim M, Sinn J, McGuire W 2006 Iodine supplementation for the prevention of mortality and adverse neurodevelopmental outcomes in preterm infants. *Cochrane Database of Syst Rev* 2:CD005253
  241. van Wassenaeer AG, Kok JH, de Vijlder JJ, Briët JM, Smit BJ, Tamminga P, van Baar A, Dekker FW, Vulsma T 1997 Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. *N Engl J Med* 336:21–26
  242. Osborn DA, Hunt RW 2007 Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 24:CD005948
  243. Cicalese MP, Assante L, Vicinanza A, Terlizzi V, Squeglia V, Bruzzese E, Guarino A, Spagnuolo MI 2008 Asking for iodine supplementation in children on parenteral nutrition. *Dig Liver Dis* 40:A115
  244. Fresenius Kabi AG 2009 Peditrace: Bad Homburg, Germany. <http://www.fresenius-kabi.com/internet/kabi/corp/fkintpbn.nsf>
  245. Hopkins B 1994 Enteral nutrition products. In: Zaloga GP, ed. *Nutrition in critical care*. St. Louis, MO: Mosby; 439–468
  246. Atkinson M, Worthley LI 2003 Nutrition in the critically ill patient: part II. Parenteral nutrition. *Crit Care Resusc* 5:121–136
  247. Koretz RL, Lipman TO, Klein S, American Gastroenterological Association 2001 AGA technical review on parenteral nutrition. *Gastroenterology* 121:970–1001
  248. Grant JP 1992 Handbook of total parenteral nutrition. Philadelphia: W.B. Saunders Company; 280
  249. Gough DC, Laing I, Astley P 1982 Thyroid function on short-term total parenteral nutrition without iodine supplements. *JPEN J Parenter Enteral Nutr* 6:439–440
  250. Leung FY 1995 Trace elements in parenteral micronutrition. *Clin Biochem* 28:561–566
  251. Navarro AM, Suen VM, Souza IM, De Oliveira JE, Marchini JS 2005 Patients with severe bowel malabsorp-



- tion do not have changes in iodine status. *Nutrition* 21: 895–900
252. Iodopen (Sodium Iodide Injection) 2008 APP Pharmaceuticals, Schaumburg, IL. [http://www.apppharma.com/ProductDetail.aspx?Id=63&name=Iodopen\\_Sodium\\_Iodide\\_Injection](http://www.apppharma.com/ProductDetail.aspx?Id=63&name=Iodopen_Sodium_Iodide_Injection)
  253. Suzuki H, Higuchi T, Sawa K, Ohtaki S, Horiuchi Y 1965 “Endemic coast goitre” in Hokkaido, Japan. *Acta Endocrinol (Copenh)* 50:161–176
  254. Nagataki S 2008 The average of dietary iodine intake due to the ingestion of seaweeds is 1.2 mg/day in Japan. *Thyroid* 18:667–668
  255. Li M, Liu DR, Qu CY, Zhang PY, Qian QD, Zhang CD, Jia QZ, Wang HX, Eastman CJ, Boyages SC 1987 Endemic goitre in central China caused by excessive iodine intake. *Lancet* 2:257–259
  256. Zhao J, Chen Z, Maberly G 1998 Iodine-rich drinking water of natural origin in China. *Lancet* 352:2024
  257. Sigurdsson G, Franzson L 1988 Urine excretion of iodine in an Icelandic population. *Icelandic Med J* 74: 179–181
  258. London WT, Vought RL, Brown FA 1966 Bread—dietary source of large quantities of iodine. *N Engl J Med* 223:338
  259. Scientific Committee on Food, Health and Consumer Protection Directorate-General 2002 Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine. Brussels: European Commission
  260. Pennington JA 1990 A review of iodine toxicity reports. *J Am Diet Assoc* 90:1571–1581
  261. Parsad D, Saini R 1998 Acneform eruption with iodized salt. *Int J Dermatol* 37:478
  262. Chow CC, Phillips DI, Lazarus JH, Parkes AB 1991 Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable? *Clin Endocrinol (Oxf)* 34:413–416
  263. Gardner DF, Centor RM, Utiger RD 1988 Effects of low dose oral iodide supplementation on thyroid function in normal men. *Clin Endocrinol (Oxf)* 28:283–288
  264. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G 1991 High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves’ disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *J Intern Med* 229:415–420
  265. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A, Pinchera A 1999 The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab* 84:561–566
  266. Laurberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E, Knudsen PR 1998 Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *J Clin Endocrinol Metab* 83: 765–769
  267. Seck T, Scheidt-Nave C, Ziegler R, Pfeilschifter J 1997 Prevalence of thyroid gland dysfunctions in 50- to 80-year-old patients. An epidemiologic cross-sectional study in a southwestern community. *Med Klin (Munich)* 92: 642–646
  268. Hintze G, Burghardt U, Baumert J, Windeler J, Köbberling J 1991 Prevalence of thyroid dysfunction in elderly subjects from the general population in an iodine deficiency area. *Aging (Milano)* 3:325–331
  269. Szabolcs I, Podoba J, Feldkamp J, Dohan O, Farkas I, Sajgó M, Takáts KI, Góth M, Kovács L, Kressinszky K, Hnilica P, Szilágyi G 1997 Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis and abundant iodine intake. *Clin Endocrinol (Oxf)* 47:87–92
  270. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K 1994 Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *J Clin Endocrinol Metab* 78:393–397
  271. Roti E, Gardini E, Minelli R, Bianconi L, Braverman LE 1992 Prevalence of anti-thyroid peroxidase antibodies in serum in the elderly: comparison with other tests for anti-thyroid antibodies. *Clin Chem* 38:88–92
  272. Ozbakir O, Dođukan A, Kelestimir F 1995 The prevalence of thyroid dysfunction among elderly subjects in an endemic goiter area of Central Anatolia. *Endocr J* 42:713–716
  273. Nygaard B, Gideon P, Dige-Petersen H, Jespersen N, Solling K, Veje A 1993 Thyroid volume and morphology and urinary iodine excretion in a Danish municipality. *Acta Endocrinol (Copenh)* 129:505–510
  274. Knudsen N, Jorgensen T, Rasmussen S, Christiansen E, Perrild H 1999 The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin Endocrinol (Oxf)* 51:361–367
  275. Knudsen N, Bülow I, Jørgensen T, Laurberg P, Ovesen L, Perrild H 2000 Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. *Eur J Endocrinol* 143:485–491
  276. Knudsen N, Bulow I, Jørgensen T, Laurberg P, Ovesen L, Perrild H 2000 Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. *Clin Endocrinol (Oxf)* 53:479–485
  277. Tajiri J, Higashi K, Morita M, Umeda T, Sato T 1986 Studies of hypothyroidism in patients with high iodine intake. *J Clin Endocrinol Metab* 63:412–417
  278. Sato K, Okamura K, Hirata T, Yamasaki K, Ikenoue H, Kuroda T, Mizokami T, Inokuchi K, Fujishima M 1996 Immunological and chemical types of reversible hypothyroidism; clinical characteristics and long-term prognosis. *Clin Endocrinol (Oxf)* 45:519–528
  279. Safran M, Paul TL, Roti E, Braverman LE 1987 Environmental factors affecting autoimmune thyroid disease. *Endocrinol Metab Clin North Am* 16:327–342
  280. Harach HR, Escalante DA, Onativia A, Lederer Outes J, Saravia Day E, Williams ED 1985 Thyroid carcinoma and thyroiditis in an endemic goitre region before and after iodine prophylaxis. *Acta Endocrinol (Copenh)* 108:55–60
  281. Sehestedt T, Knudsen N, Perrild H, Johansen C 2006 Iodine intake and incidence of thyroid cancer in Denmark. *Clin Endocrinol (Oxf)* 65:229–233
  282. Feldt-Rasmussen U 2001 Iodine and cancer. *Thyroid* 11: 483–486



283. **Zimmermann MB, Ito Y, Hess SY, Fujieda K, Molinari L** 2005 High thyroid volume in children with excess dietary iodine intakes. *Am J Clin Nutr* 81:840–844
284. **Roti E, Uberti ED** 2001 Iodine excess and hyperthyroidism. *Thyroid* 11:493–500
285. **Zimmermann MB** 2008 Iodine requirements and the risks and benefits of correcting iodine deficiency in populations. *J Trace Elem Med Biol* 22:81–92
286. **Bourdoux PP, Ermans AM, Mukalay wa Mukalay A, Filetti S, Vigneri R** 1996 Iodine-induced thyrotoxicosis in Kivu, Zaire. *Lancet* 347:552–553
287. **Todd CH, Allain T, Gomo ZA, Hasler JA, Ndiweni M, Oken E** 1995 Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe. *Lancet* 346:1563–1564
288. **Delange F, de Benoist B, Alnwick D** 1999 Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 9:545–556
289. **Bürgi H, Kohler M, Morselli B** 1998 Thyrotoxicosis incidence in Switzerland and benefit of improved iodine supply. *Lancet* 352:1034
290. **Yang F, Shan Z, Teng X, Li Y, Guan H, Chong W, Teng D, Yu X, Fan C, Dai H, Yu Y, Yang R, Li J, Chen Y, Zhao D, Mao J, Teng W** 2007 Chronic iodine excess does not increase the incidence of hyperthyroidism: a prospective community-based epidemiological survey in China. *Eur J Endocrinol* 156:403–408