17 Iodine Deficiency Disorders

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17.1 INTRODUCTION

Iodine, a nonmetallic solid in the halogen family, is an essential constituent of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Thyroid hormones are involved in a wide range of biological functions and modulate gene expression through specific nuclear receptors. Iodine is present in small amounts in soil, water, plants, and animals, and insufficient dietary intake of iodine is generally related to lack of iodine in the environment.

The iodine deficiency disorders consist of a wide spectrum, including mental retardation, impaired physical development, increased perinatal and infant mortality, hypothyroidism, cretinism, and goiter. *Goiter* is defined as an enlargement of the thyroid gland, and *cretinism* is a term used for a severe form of iodine deficiency characterized by severe mental retardation. The effects of iodine deficiency are most pronounced during periods of rapid growth, that is, in the fetus, neonate, infant, and young children, and this may have a major effect on brain development. The ongoing global effort to eliminate iodine deficiency disorders through iodization of salt represents one of the largest public health efforts of the 20th century.

17.2 PUBLIC HEALTH SIGNIFICANCE

It was estimated that in 1990, there were 1,572 million people worldwide who consumed inadequate amounts of iodine and were at risk for iodine deficiency disorders [1–3]. Iodine deficiency is the leading cause of preventable mental retardation in the world [4]. The prevalence of iodine deficiency is related to the local availability of iodine in water and iodine in plants and foods, and the problem of iodine deficiency is global, with mountainous regions and large river deltas the most well-known areas for endemic iodine deficiency disorders.

17.3 HISTORICAL BACKGROUND

Descriptions of goiter and cretinism have been found in written records and iconography since antiquity, and seaweed or thyroid extracts were empirically known to be effective treatments for goiter [5]. Iodine was discovered by a saltpeter manufacturer

* *deceased*

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near Paris, Bernard Courtois (1777–1838) in 1811. Seaweed ash from Normandy was used in the production of saltpeter, and Courtois observed violet vapors and formation of black crystals when an extract of this burned seaweed was heated [5, 7]. This substance was named iodine by the French chemist Joseph Louis Gay-Lussac (1778–1850) after the Greek word for "violet." Further investigations by chemists showed that iodine was found in various seaweeds, algae, and marine sponges but was present only in trace quantities in other sources in nature. The qualitative estimation of iodine was facilitated by the discovery of the iodine–starch reaction, in which free iodine formed a blue color when combined with starch. A physician in Geneva, Jean-François Coindet (1774–1834), found that pure iodine was a remedy for goiter [8]. While working in Bogota, Colombia, Jean Baptiste Boussingault (1802–1887) noted that goiter was not endemic in communities that utilized iodine-containing salt from certain salinas, and before his return to France in 1831, he advised the Colombian government to provide for distribution of this naturally iodized salt for the health of the community [9].

During the mid-19th century, Gaspard Adolphe Chatin (1813–1901), a professor in the School of Pharmacy of Paris, conducted investigations of iodine in plants, water, and animals, and he concluded that lack of iodine in the drinking water could be the cause of goiter and cretinism [10]. Public health authorities in three departments (Bas-Rhin, Seine-Inférieure, Haute-Savoie) started prophylactic measures of giving schoolchildren daily iodine tablets, and a large reduction in goiter was noted [11]. The French program of iodine prophylaxis used high doses of 0.1 to 0.5 mg/kg for iodization of salt and daily iodine tablets containing 0.01 g potassium iodide. Although schoolchildren seemed to have tolerated the doses well, some adults with goiter may have experienced iodine-induced hyperthyroidism (Jod-Basedow reaction), and consequently the iodine prophylaxis program was abandoned [5]. The French Goitre Commission was also skeptical about Chatin's theory that iodine deficiency caused goiter and cretinism, noting that some of the 420,000 individuals with goiter in France lived in places where the air and soil contained iodine; instead, the Commission implicated toxins in the water and food as the cause of goiter [12].

By the late 19th century, the geographical distribution of endemic goiter and cretinism was recognized to extend around the world, with detailed accounts available from many countries in Europe [13]. In detailed studies in northwest India, Robert McCarrison (1878–1960) distinguished neurological, or "nervous" cretinism from hypothyroid or "myxoedematous" cretinism [14].

In the United States, large-scale trials of iodine for goiter prophylaxis were conducted by David Marine (1880–1976) and Oliver P. Kimball among schoolgirls in Akron, Ohio, between 1916 and 1920 [15–19]. Sodium iodide was found to be effective in preventing goiter and in treating existing goiter, and by 1924, iodized salt was introduced in Michigan for general prophylaxis [20]. Iodized salt for prophylaxis of goiter was implemented in various cantons in Switzerland in the early 1920s, an effort that had to overcome many difficulties, including disagreement among scientists and local opposition [5, 21]. With more widespread use of iodized salt, there was a decline in goiter and cretinism in parts of Europe.

Goiter and cretinism gained renewed attention in studies conducted in Papua New Guinea in the 1950s and 1960s. These studies showed that injections of iodized oil could prevent goiter and cretinism in isolated mountain villages [22, 23].

Although various international organizations called for the eradication of iodine deficiency from 1974 to 1983, little action took place during this decade [24]. The term

Table 17.1
Spectrum of iodine deficiency disorders

Fetus	Abortions
	Stillbirths
	Congenital anomalies
	Increased perinatal mortality
	Increased infant mortality
	Neurological cretinism: mental deficiency, deaf mutism, spastic diplegia, squint
	Myxoedematous cretinism: dwarfism, mental deficiency
	Psychomotor defects
Neonate	Neonatal goiter
	Neonatal hypothyroidism
Child and adolescent	Goiter
	Juvenile hypothyroidism
	Retarded physical development
Adult	Goiter with its complications
	Hypothyroidism
	Impaired mental function
	Iodine-induced hyperthyroidism

Source: After [25].

iodine deficiency disorders was introduced in 1983 to encompass the wide spectrum of the effect of iodine deficiency on health, including physical impairment and mental retardation (Table 17.1) [25]. A report by a special committee of the European Thyroid Association showed that iodine deficiency disorders were still a serious problem in many European countries in the 1980s, contrary to the general impression that the problem had largely been eradicated in Europe [26]. The International Council for Control of Iodine Deficiency Disorders (ICCIDD) was established in 1985 with the support of United Nations International Children's Emergency Fund (UNICEF) [24], and this expert council remains a driving force behind the global eradication of iodine deficiency disorders.

17.4 EPIDEMIOLOGY

17.4.1 Geographical Distribution

There is a natural cycle of iodine in nature between the ocean, the atmosphere, rainfall, and runoff of rainfall into streams and rivers (Fig. 17.1) [24]. The ocean contains most of the iodine on the earth's surface, with a concentration of iodide of 50–60 µg/L. Sunlight oxidizes iodide in seawater to elemental iodine, which is volatile and evaporates from the surface of the ocean. The concentration of iodine in the air is about 0.7 µg/m^3. Iodine in the atmosphere is returned to the surface of the earth by rain, which has iodine concentrations of 1.8 to 8.5 µg/L. Iodine is leached from the soil by rain, flooding, deforestation, and glaciation. Crops and animals raised on iodine-poor soils will have low iodine content. Thus, iodine deficiency disorders tend to occur most commonly in areas where the soil is poor in iodine, especially mountainous regions such

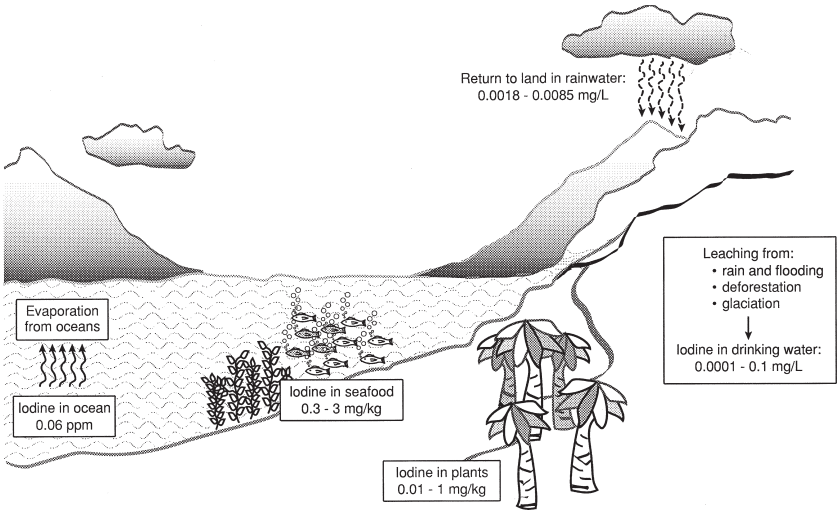

Fig. 17.1. Natural cycle of iodine.

as the Alps, Andes, and Himalayas, and large river floodplains and deltas, such as that of the Ganges and Irawaddy. The iodine content of the soil is usually reflected in the concentration of iodine in drinking water. For example, in India the iodine content of drinking water in iodine-deficient areas is 0.1–1.2 µg/L, and in the city of New Delhi, which is not iodine deficient, it is 9.0 µg/L [24].

17.4.2 Prevalence

The largest populations at risk of iodine deficiency disorders used to be in the eastern Mediterranean region, followed by Africa and Latin America (Table 17.2). It was estimated in 1990 that there were 655 million individuals in the world with goiter. In Asia, goiter prevalence was highest in China, Indonesia, and countries along the Himalayan mountains, such as India, Bhutan, Nepal, and Pakistan. Among countries with a high prevalence of goiter in Africa were Zaire, Tanzania, Sudan, and Cameroon. Goiter remained a major problem in countries along the Andean chain, such as Peru, Bolivia, Colombia, and Ecuador.

Long-term iodine prophylaxis has contributed to the decline of goiter in some parts of Europe [27], but even as late as the mid-1980s, goiter was a major problem in some European countries, such as Germany, Spain, Portugal, Italy, Turkey, and Greece, where national programs to iodize salt did not exist [28–31]. Even by 1992, iodine deficiency was considered to be under control in Europe only in several northern European countries and Switzerland [32]. The global prevalence of goiter and cretinism has markedly decreased in most regions and countries in the face of efforts to iodize salt worldwide, but because of a more accurate evaluation of the status of iodine nutrition in many parts of the world, the prevalence of iodine deficiency worldwide was still 38% in 1999 [33] and was 36.5% in school-aged children in 2003 [34].

Table 17.2
Total number of people and percent of regional population living in areas at risk of iodine deficiency disorder (IDD) or affected by IDD and cretinism in 1990

	Total	*At risk of IDD*		*Affected by goiter*		*Affected by cretinism*	
WHO region	*Population (millions)*	*Millions*	*% of region*	*Millions*	*% of region*	*Millions*	*% of region*
Africa	550	181	32.8	86	15.6	1.1	0.2
Americas	727	168	23.1	63	8.7	0.6	0.9
Eastern Med	406	173	42.6	93	22.9	0.9	2.3
Europe	847	141	16.7	97	11.4	0.9	1.1
Southeast Asia	1,355	486	35.9	176	13.0	3.2	1.3
Western Pacific	1,553	423	27.2	141	9.0	4.5	2.9
Total	5,438	1,572	28.9	655	12.0	11.2	2.0

Source: After [3].

17.4.3 Risk Factors

The most important risk factor for iodine deficiency disorders is residence in an area where soil and water are poor in iodine and where the primary sources of plant and animal foods are locally derived. Substances known as goitrogens are widely found in some vegetables and can interfere with the metabolism of iodine [35]. Cabbage, sweet potato, brussel sprouts, and turnips contain goitrogens. Cassava contains high concentrations of thiocyanates (SCNs) and has been implicated in the pathogenesis of goiter in Zaire [36]. Women of reproductive age, pregnant women, and young children are at the highest risk of iodine deficiency because of the impact of iodine deficiency on brain development. Among schoolchildren, girls appear to be at a higher risk of goiter than boys.

17.5 METABOLISM OF IODINE

17.5.1 Iodine Absorption and Transport

Dietary iodide (inorganic, bound form of iodine) is rapidly absorbed in the stomach and intestine. Iodate, the form of iodine used in iodized salt, is reduced in the blood and rapidly absorbed. The normal requirement for iodine is 100 to 150 µg per day [37]. Iodide circulates freely in the blood, not bound to proteins, and it is trapped by the thyroid and kidney. Iodine is excreted by the kidney, and the concentration of urinary iodine correlates well with the intake of iodine. Small amounts of iodine are excreted in saliva, sweat, and tears.

17.5.2 Iodine Storage

The human body contains about 15 to 20 mg of iodine, of which 70–80% is found in the thyroid gland. The thyroid traps iodine through an active transport mechanism known as the *iodine pump*, and iodine trapping is regulated by thyroid-stimulating hormone (TSH), or thyrotrophin, released from the pituitary gland. More trapping of iodine

occurs if an individual has had long-standing iodine deficiency rather than in a situation of adequate iodine intake. The thyroid must trap about 60 µg of iodine per day to maintain an adequate supply of thyroxine [24]. The iodine content of the thyroid is generally related to iodine intake. If the iodine supply has been abundant, the thyroid may contain 10–20 mg of iodine, but in a situation of chronic iodine deficiency, the thyroid may contain as little as 200 µg of iodine.

17.5.3 Synthesis of Thyroid Hormones

The thyroid is a highly vascularized organ that contains many follicles. The follicles consist of thyroid cells surrounding colloid, and the main constituent of the colloid is thyroglobulin, a storage form of thyroid hormones. Iodine is an essential constituent of thyroid hormones 3,5,3′,5′-tetraiodothyronine, thyroxine (T_4) and triiodothyronine (T_3). Thyroglobulin is synthesized from amino acids in thyroid cells and moves into the colloid. Iodide moves into the colloid of the thyroid by passive diffusion. In the colloid, iodide is oxidized by hydrogen peroxide from the thyroid peroxidase system, combines with tyrosine in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT continue oxidation and couple to form iodotyrosines. The iodinated thyroglobulin is absorbed back into the thyroid cell by pinocytosis and subsequently undergoes proteolysis, and T_3 and T_4 are released into the blood.

Iodine metabolism and the synthesis of thyroid hormones are regulated by complex interactions involving the brain, pituitary, thyroid, and iodine intake. Iodine uptake by the thyroid, synthesis of MIT and DIT, and secretion of T_3 and T_4 are regulated by TSH, which is secreted by the pituitary. Secretion of TSH in turn is regulated by the level of circulating T_4 and by thyrotrophin-releasing hormone (TRH) secreted by the hypothalamus. TRH release is influenced by neurotransmitters such as adrenalin, noradrenalin, serotonin, and dopamine. Further details of this complex regulation can be found elsewhere [38].

17.5.4 Transport and Turnover of Thyroid Hormones

In the blood, T_3 and T_4 are bound by different proteins produced in the liver, such as transthyretin, albumin, and thyroid-binding globulin (TBG). About three quarters of T_4 is normally bound to TBG. T_4 is found in much higher concentrations in the blood than T_3, and most of the T_3 in plasma is derived from peripheral tissues, where it is generated by monodeiodination of T_4. Other metabolic derivatives of thyroid hormones, such as rT_3 and 3,3′-diiodo-L-thyronine, are also found in the blood. Three deiodinases have been identified that catalyze monodeiodination of the outer ring [39]. Further deiodination of the inner ring deactivates T_3 and T_4. The three deiodinases contain selenocysteine; thus, selenium status may have an important influence on thyroid hormone metabolism, as discussed elsewhere in this chapter (see Section 17.8).

17.5.5 Thyroid Hormones and Gene Expression

Thyroid hormones are involved in the regulation of development and differentiation of nearly all organs and systems through their influence on gene expression. T_3 influences gene expression through thyroid hormone receptors (TRs), nuclear receptors that belong to a superfamily of DNA-binding proteins that includes receptors for retinoic acid (RAR; retinoic X receptor [RXR]), vitamin D (VDR), and steroids. Different isoforms of TRs

($TR\alpha_1$,$TR\alpha_2$, $TR\beta_1$, and $TR\beta_2$) have been described [40], and the expression of the TR isoform varies by organ type [41]. Specific sequences of DNA that bind TRs are known as thyroid hormone response elements (TREs) [42]. TRs bind T_3 and form heterodimers with retinoid X receptors (RXRs) in the form of RXR-TR [43]. The ligand for RXR is 9-*cis* retinoic acid. In addition, RXR can form heterodimers with the VDR [44]. T_3-responsive genes can be repressed by RXR-RXR homodimers [45]. A complex network of interaction exists among TRs, retinoid receptors, and other nuclear receptors. Thyroid hormone coactivators, corepressors, and cointegrators are involved in regulation of transcription by TR, and transcriptional activities are regulated by the relative presence or absence of T_3 [46, 47].

17.6 ROLE OF IODINE IN BIOLOGICAL FUNCTIONS

17.6.1 Metabolism

Thyroid hormones have major effects on the metabolism of proteins, carbohydrates, and lipids and are prime regulators of the basal metabolic rate. Thus, a wide variety of physiological activities, including heart rate, respiration, oxygen consumption, and nutrient metabolism are affected. Much of this regulation occurs through modulation of gene transcription by thyroid hormones. Thyroid hormones may also influence energy metabolism through direct and indirect regulation of mitochondrial activities [48].

17.6.2 Growth and Development

The synthesis of growth hormone is regulated in part by thyroid hormones [49], and physiological concentrations of circulating thyroid hormones appear to be necessary to maintain normal secretion of growth hormone by the pituitary [50]. Thyroid hormones play a role in normal bone cell growth and development [51], and in vitro studies suggested that thyroid hormones influence osteoblastic differentiation [52].

17.6.3 Brain Development

Thyroid hormones are involved in the early growth and differentiation of the brain and nervous system of the fetus [53–57]. The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. An insufficient supply of thyroid hormones to the developing brain may result in mental retardation. Thyroid hormones appear to ensure the coordination of developmental events through regulation of oligodendroglial and neuronal differentiation and cell death [58]. T_3 has been shown to regulate several specific brain genes [58].

Brain growth is characterized by two periods of maximal growth velocity [59]. The first one occurs during the first and second trimesters between the third and the fifth months of gestation. This phase corresponds to neuronal multiplication, migration, and organization. The second phase takes place from the third trimester onward up to the second and third years postnatally. It corresponds to glial cell multiplication, migration, and myelization. The first phase occurs before fetal thyroid has reached its functional capacity. It is now largely agreed that during this phase, the supply of thyroid hormones to the growing fetus is almost exclusively of maternal origin, while during the second phase, the supply of thyroid hormones to the fetus is essentially of fetal origin [60].

As a matter of fact, an important recent issue on thyroid function and regulation in the fetus is the concept that thyroid hormones are transferred from mother to fetus both

before and probably after the onset of fetal thyroid function, contrasting with the previous dogma that this transfer is minimal or does not exist [61]. In humans, T_4 can be found in the first trimester coelomic fluid from 6 weeks of gestational age, a long time before the onset of secretion of T_4 by the fetal thyroid, which occurs at the 24th week of gestation [62]. Nuclear T_3 receptors and the amount of T_3 bound to these receptors increase about six- to tenfold between 10 and 16 weeks, also before the secretion of hormones by the fetal thyroid [63]. The T_4 and T_3 found in early human fetuses up to midgestation are likely to be entirely or mostly of maternal origin. This transfer is decreasing but persists during later gestation as Vulsma et al. [64] suggested that up to 30% of serum T_4 in cord blood at birth could be of maternal origin, although a much lower percentage was reported by Delange et al. [65].

17.6.4 Iodine and Immune Function

There is some indirect evidence that iodine deficiency may contribute to abnormalities in immune function, but research in this area has largely been limited to animal studies of hypothyroidism and studies of the in vitro effects of thyroid hormones on immune effector cells. Thyroid hormones appear to be essential for normal lymphopoiesis and generation of antibody responses. Removal of the thyroid gland in rats resulted in the reduction of circulating peripheral blood lymphocytes, depression of antibody responses to experimental antigens, and reduced proliferative responses of spleen cells to mitogen, and abnormal immune responses could be restored by injections with thyroxine [66]. Antibody responses to sheep erythrocytes were depressed by a thyroid block in an avian model [67]. T_3-treated mice had higher antibody responses to sheep red blood cells [68]. Natural killer cell activity was enhanced by T_4 administration in mouse studies [69, 70]. Decreased proliferative responses of thymocytes to mitogen have been noted in chicks with hypothyroidism [71]. T_3 enhanced proliferation of murine lymphocytes to phytohemagglutinin in vitro [72] and enhanced differentiation of human B lymphocytes in vitro [73, 74]. In western India, the seroprevalence of toxoplasmosis was significantly higher among children with grade II goiter than children with no goiter or grade I goiter [75].

17.7 PATHOPHYSIOLOGY OF IODINE DEFICIENCY

17.7.1 Dietary Sources and Intake of Iodine

The richest dietary sources of iodine are seafood and seaweeds. Meat from animals that have grazed in areas with sufficient iodine in the soil can also constitute a significant source of iodine. Crops grown in iodine-sufficient soils may supply some dietary iodine. In most populations, iodized salt is the primary source of dietary iodine. Iodine in drinking water is usually only a small part of total iodine intake, providing less than 10% of daily iodine in the most iodine-rich areas. Some iodine is usually lost from foods during cooking; for example, during frying or boiling, as much as half the iodine content of fish may be lost.

17.7.2 Goitrogens

Environmental goitrogens are substances found in foods and water that interfere with the metabolism of iodine and in some circumstances will exacerbate iodine deficiency. These goitrogens include cyanogenic glycosides, thioglycosides, isothiocyanates, and

SCNs [76], and goitrogens can compete with iodine at the site of the iodine pump of the thyroid [24]. Several goiter endemias have been attributed to environmental goitrogens, for example, in Tasmania, eastern Nigeria, Colombia, and Greece [77]. It has been shown in Zaire that cassava plays a definite role in the development of endemic goiter. Cassava contains linamarin, a cyanogenic glucoside that is converted into SCN in the liver. Elevated serum levels of SCN were found in all age groups in the affected populations. SCN aggravates the effects of iodine deficiency by inhibiting the trapping of iodide by the thyroid gland [36, 78]. In general, iodized salt or other interventions with iodine can overcome the negative effects of environmental goitrogens

17.7.3 Iodine Dietary Requirements

Recommended intakes of iodine have been made by the World Health Organization (WHO), and recommendations are highest for pregnant and lactating women (Table 17.3) [79]. Very recently, the recommended iodine intake for pregnant and lactating women was increased to 250 µg/day [80].

17.8 CLINICAL MANIFESTATIONS OF IODINE DEFICIENCY DISORDERS

17.8.1 Goiter

Goiter, an enlargement of the thyroid gland, usually represents thyroid hyperplasia in response to insufficient iodine intake [81]. With iodine deficiency, T_4 concentrations in the blood fall, and the feedback of low T_4 on the pituitary leads to increased production of TSH. TSH stimulates hyperplasia of the thyroid with increased uptake of iodide, and the size of the thyroid increases, resulting in a goiter. By palpation on physical examination, *goiter* is defined as enlargement of the thyroid such that the lateral lobes are larger than the terminal phalanx of the thumb of the person who is being examined. The severity of goiter is usually proportional to the severity of iodine deficiency, and with persistent enlargement of the thyroid, nodules can form. Extremely large goiters may compress the trachea and interfere with respiration. In areas of goiter endemics, the daily iodine intake is usually well below 100 µg/day, and in the most severe goiter endemics, iodine intakes as low as 10 µg/day are known [82].

Endemic goiter has been occasionally associated with malnutrition [83, 84], although protein calorie malnutrition decreases the prevalence of goiter, to be expected on the basis of iodine intake [36]. Nutritional status and blood retinol concentrations were lower among individuals with goiter [85]. Impaired intestinal absorption of iodine has

Table 17.3
Recommended daily intakes of iodine

Age/state	*Micrograms/day*
0–59 months	90
7–12 years	120
12 years to adulthood	150
Pregnancy	250
Lactation	250

Source: From refs. 79 and 80.

been described in children with malnutrition [86]. In Senegal, preschool children with acute malnutrition had lower serum T_3 concentrations than controls, and levels returned to normal after 2 weeks of refeeding [87]. Selenium deficiency has been implicated in the pathogenesis of goiter and cretinism, and this may be related to the selenocysteine involved in thyroid hormone metabolism [88–90]. Multiple micronutrient deficiencies have been associated with poor iodine status in children [91].

17.8.2 Cretinism

Endemic cretinism is usually found where the prevalence of endemic goiter is higher than 30% and the median urinary iodine concentration is less than 25 µg/g creatinine [92]. Endemic cretinism is characterized by mental retardation, which may be mild to severe, and a continuous spectrum of growth and neurological manifestations [93]. Two extreme types of cretinism have been described: neurological cretinism and myxoedematous, or hypothyroid, cretinism [24, 93]. In neurological cretinism, stature is usually normal, mental retardation is often severe, and deaf-mutism and cerebral diplegia are often present. In hypothyroid cretinism, severe growth retardation is present, mental retardation is less severe, and coarse, dry skin, and husky voice are present, but deaf-mutism and cerebral diplegia are absent. Intermediate forms between the two extreme types of cretinism are frequently reported [24, 93].

Neurological signs of endemic cretinism appear to be the result of hypothyroxinemia in the mother and fetus occurring during early pregnancy [56, 94]. Iodine treatment to the mother up to the end of the second trimester of pregnancy can prevent fetal brain damage due to iodine deficiency [95], but iodine treatment is probably most effective in preventing endemic cretinism when given prior to conception [96]. The hypothyroid signs in cretinism are due to thyroid failure acquired lately during pregnancy and early in the postnatal period, for example, under the influence of combined iodine and selenium deficiencies [88, 90, 93].

Sporadic cretinism, or sporadic congenital hypothyroidism, is not related to iodine deficiency and is used to describe a congenital defect in thyroid hormones or congenital absence or defect of a thyroid gland. Its incidence is 3 in 10,000 in industrialized countries that are receiving adequate iodine [97, 98].

17.8.3 Growth and Development

Maternal iodine deficiency during pregnancy causes retarded development of the fetus, and the more severe consequences include cretinism, as mentioned in the preceding section. Other, more insidious effects include impaired psychomotor and cognitive development [57, 99]. Children growing in iodine-deficient areas appear to have impaired psychomotor development and lower school performance. Impaired psychomotor development was found in apparently normal schoolchildren from an area of iodine deficiency in Iran [100]. Lower school performance and significant differences in IQ have been reported in various studies comparing children from iodine-deficient and iodine-sufficient areas [101]. In a case-control study of preschool children in northern Zaire, endemic goiter without cretinism was not associated with any major growth impairment, but no studies of thyroid status were performed in either cases or controls [102]. Thyroid function was evaluated in children with short stature in north India, and nearly half the children had abnormal thyroid function [103].

17.8.4 Reproductive Failure

Iodine deficiency in women is associated with infertility [104] and impaired fetal development [105]. Higher rates of spontaneous abortions and stillbirths have been reported from areas of iodine deficiency [24], and correction of hypothyroidism in pregnant women reduces these adverse outcomes [106]. Treatment with oral iodized oil during pregnancy significantly lowered the rates of abortions, stillbirths, and premature births in a mountainous area in Algeria [107]. Trends in salt iodization suggested that improvement of iodine status was associated with reductions in stillbirth and congenital anomalies [108].

17.8.5 Perinatal, Infant, and Child Mortality

High perinatal mortality has been associated with goiter during pregnancy [109]. Clinical trials conducted in different parts of the world suggested that iodine supplementation, in the form of iodized oil injections, oral iodized oil, or iodinated water supply, can reduce neonatal, infant, and child mortality (Table 17.4). Infant mortality was lower among infants born to women who were treated with intramuscular iodized oil around the 28th week of pregnancy compared with infants born to control women in Zaire [110]. In a controlled clinical trial in Papua New Guinea, cumulative long-term survival of children was significantly higher among those whose mothers received iodinated oil before conception (Fig. 17.2) [111]. The causes of death of children in this study were not known. In a rice-farming community in West Java, Indonesia, oral iodized oil, 100 mg, given directly to 6-week-old infants reduced mortality between 6 weeks and 6 months by about 50% compared with placebo (Fig. 17.3) [112]. Comparison of infant mortality rates between villages that received iodine in irrigation water versus control villages that did not in rural China suggested that iodinated water could reduce infant mortality by approximately half (Fig. 17.4) [113].

17.9 ASSESSMENT OF IODINE STATUS

Several indicators exist for the assessment of iodine status, both on the individual and population levels. WHO has developed criteria for iodine deficiency as a public health problem in populations [3] (Table 17.5).

Table 17.4
Controlled trials of iodine supplementation and perinatal, infant, and child mortality

Location	*Subjects*	*n*	*Treatment effect*	*Reference*
Zaire	Pregnant women	5,471	One-third reduction in infant mortality	109
Papua New Guinea	Women, infants	522	50% reduction in 15-year mortality	111
Indonesia	Infants, 6 weeks old	617	50% reduction in mortality to 6 months	112
China	Villages, all population	37,000	50% reduction in infant mortality	113

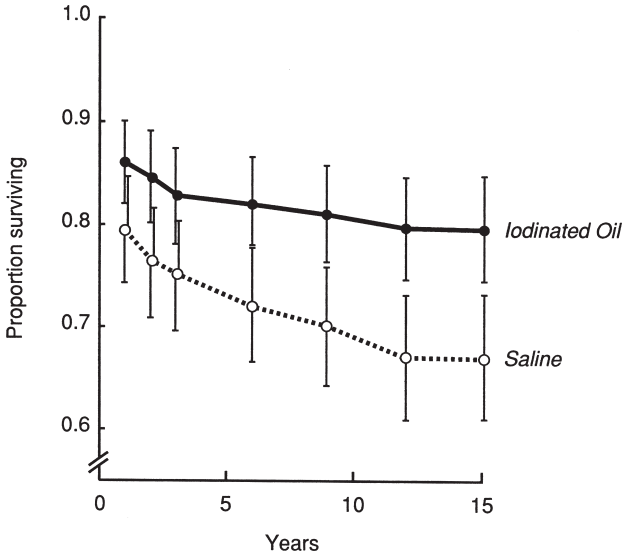

Fig. 17.2. Cumulative survival rates of children whose mothers received either iodinated oil or saline (bars indicate 95% confidence interval) [111].

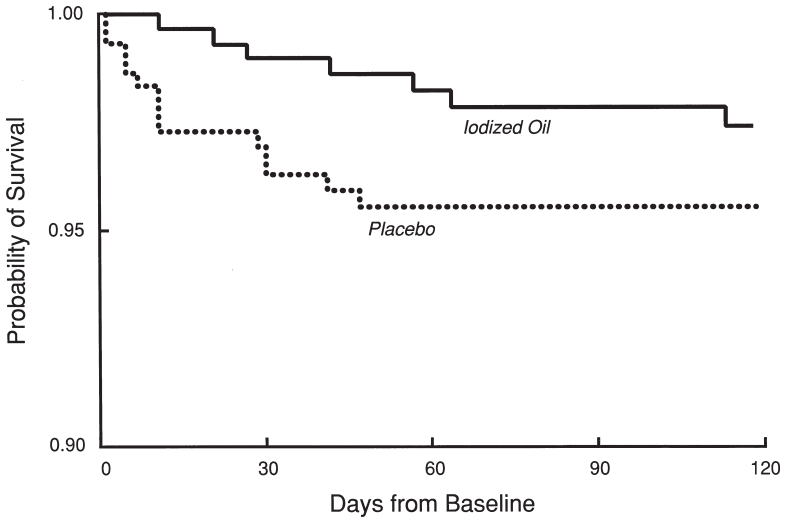

Fig. 17.3. Survival curves of infants receiving oral iodized oil or placebo in West Java, Indonesia [112].

17.9.1 Goiter Rate

The goiter rate is often used for the assessment of iodine status in a population, and the goiter rate includes both visible and palpable goiter. WHO has adopted a grading classification for goiter (Table 17.6) [3]. Determination of thyroid size by ultrasonography is more accurate than palpation, especially in areas where iodine deficiency is mildly

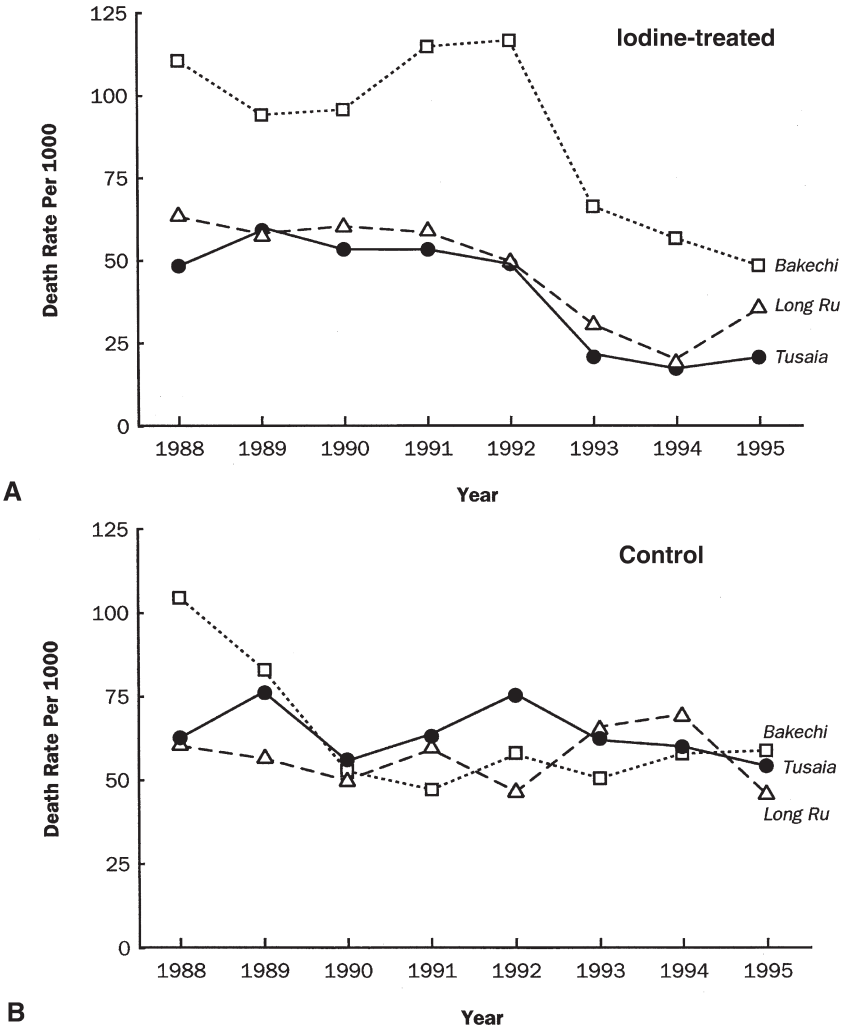

Fig. 17.4. Infant mortality rates in rural villages in China that received iodinated irrigation water (**A**) or were control villages (**B**). (Adapted with permission from [113].)

Table 17.5
World Health Organization criteria for iodine deficiency as a public health problem in populations

Indicator	*Population assessed*	*Mild*	*Moderate*	*Severe*
Goiter by palpation (%)	School children	5–19.9	20–30	>30
Thyroid volume by ultrasound (>97th percentile) (%)	School children	5–19.9	20–30	>30
Median urinary iodine (μg/L)	School children	50–99	20–49	<20
Thyroid-stimulating (>5 mU/L whole blood) hormone	Neonates	3–19.9	20–40	>40

Source: From [3].

Table 17.6
Classification for goiter

Grade 0	No palpable or visible goiter
Grade 1	A mass in the neck that is consistent with an enlarged thyroid that is palpable but not visible when the neck is in the normal position; it moves upward in the neck as the subject swallows; nodular alterations can occur even when the thyroid is not enlarged
Grade 2	A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated

Source: From [3].

endemic and goiters in children are small. Health workers who are well trained in ultrasonography can conduct up to 200 examinations per day [114]. WHO and ICCIDD has recently recommended reference values for thyroid volume in school-aged children [114] based on variation in thyroid size varies by age, height, and weight [115] and data from a survey from 12 European countries [116]. These reference values were subsequently updated by a WHO working group [117].

17.9.2 Urinary Iodine Concentrations

Urinary iodine concentrations are a good indicator of iodine status in representative groups of subjects [3], and iodine can be easily measured in large numbers of samples [118]. Because urinary iodine concentrations tend to be skewed, the median value is usually used in describing urinary iodine concentrations in a population. Urinary iodine concentrations are classified as less than 20 µg/L (severe deficiency), 20–49 µg/L (moderate deficiency), 50–99 µg/L (mild deficiency), and 100–200 µg/L (adequate) [3]. A large study conducted among schoolchildren in Indonesia [119] and many others confirmed that urinary iodine concentrations are the best indicator for field studies for the assessment of iodine deficiency.

17.9.3 Blood Thyroid-Stimulating Hormone

Blood TSH can be used as an indirect indicator of iodine status [120] and has been used for screening of neonatal hypothyroidism. Heel-stick blood samples can be collected from neonates, spotted on filter paper, dried, and later eluted and measured using enzyme-linked immunosorbent assay [121]. A normal range of TSH is 0.17–2.90 µU/mL. The degree of iodine deficiency in a population can be evaluated on the basis of the frequency of neonatal blood TSH above the cutoff point of 3 µU/mL (Table 17.5).

17.10 PREVENTION OF IODINE DEFICIENCY DISORDERS

Iodized salt is currently the primary strategy for the prevention of iodine deficiency disorders worldwide, and oral iodized oil is being used in some areas to target specific communities at risk of iodine deficiency disorders. Intramuscular iodized oil injections were used in earlier investigations of iodine deficiency disorders. Iodination

of the water supply has been a useful strategy in some communities but is limited to conditions where the whole population and the livestock have access to a single source of water.

17.10.1 Iodized Salt

Iodized salt is a term used to describe two different forms of iodine in salt: iodide, such as potassium iodide (KI), and potassium iodate (KIO_3) [24]. Potassium iodide was first used in salt iodization, but iodate is more stable under different climatic conditions and is now the recommended form for salt iodization. *Universal salt iodization* is defined as fortification of all salt for human and animal consumption [122, 123]. The goal of salt iodization is to provide about 150 µg of iodine per day in dietary salt, taking into account factors such as heat and humidity. Warm and humid conditions can influence the retention of iodate in salt. In typical circumstances, in which about 20% of the iodine is lost from salt from the production site to the household and another 20% is lost during cooking before consumption, and the average individual salt intake is 10 g/day, the iodine concentration in salt at the point of production should be within the range of 20–40 mg of iodine per kilogram of salt (20–40 ppm of iodine) [124]. This is estimated to provide 150 µg of iodine per person per day. In countries where iodized salt is used in processed foods, the iodine content in salt should be closer to the lower end of this range and vice versa [124]. The usual salt intakes can vary from country to country, but the usual consumption levels are 5–15 g/day for children and adults [3, 125].

Some studies suggested that the level of iodine in salt is often below the minimum required by local governments. A survey of iodine in salt samples across the country in Guatemala showed that more than 60% of samples were below the legally mandated level for iodized salt [126]. A national survey in Kenya in 1990 and 1991 showed that most samples of iodized salt did not reach the minimal iodine concentrations as required by government regulation [127]. Under the National Iodine Deficiency Disorder Control Programme in India, iodized salt containing at least 15 ppm iodine is supposed to be provided to beneficiaries; however, a survey of salt samples showed that nearly a fifth of samples did not contain adequate iodine [128]. On the other hand, it occurred occasionally that, on the contrary, the iodine content of salt largely exceeded the recommended level. This resulted in the occurrence of sporadic cases of iodine-induced hyperthyroidism (IIH) [129]. Therefore, adequate monitoring of the level of salt iodization and of the status of iodine nutrition of the populations has to be strictly organized [130].

In spite of these regrettable side effects, it is recognized that the benefits of correcting iodine deficiency by iodized salt by far outweigh the risks [131, 132]. Salt iodization appears as a particularly successful public health program as the access to iodized salt in households increased from 5–10% in 1990 to 68% in 1999 [33] and was accompanied by a spectacular decrease in the occurrence of brain damage and mental retardation due to iodine deficiency [34, 133].

17.10.2 Oral Iodized Oil

Oral iodized oil has been used to prevent iodine deficiency disorders in populations located where iodized salt is difficult to procure and where certain groups (i.e., pregnant women) are at high risk [134, 135]. In adults, a single dose of 460 mg of iodine is

recommended [134], and a single annual dose of 240 mg of iodine seems to be adequate for children [135]. Lower doses of 47 mg and 118 mg of iodine in oral iodized oil were also found to be effective in reducing hypothyroidism in children in Zaire [136]. Among schoolchildren in western Sudan, oral iodized oil was as effective as an iodized oil injection in reducing goiter and preventing the recurrence of goiter [137], and in a clinical trial in eastern Zaire, oral iodized oil was also found to be an effective alternative to iodized oil injections [138, 139]. Oral iodized oil seemed to increase the mental performance of school-aged girls in a trial conducted in Bolivia [140].

For correction of iodine deficiency in children, single oral doses of 240 mg iodine in poppy seed oil appeared to be the optimal dose for 6-month coverage [141]. A trial conducted among schoolchildren in Malawi suggested that intestinal parasitic infections may interfere with the absorption of oral iodized oil [142]. Oral iodized oil is considered to be safe for pregnant women and can be given any time during pregnancy [143, 144].

Childhood immunization programs may provide infrastructure for the delivery of oral iodized oil to infants in areas where iodine deficiency disorders are a public health problem and iodized salt is not readily available [145]. There was initial concern that oral iodized oil might theoretically interfere with trivalent oral poliovirus vaccine when given together because the iodide could potentially inactivate the live poliovirus. In vitro studies suggested that there was no interference [146], and a clinical trial in Indonesia demonstrated that oral iodized oil given at 6 weeks of age did not interfere with seroconversion to trivalent oral poliovirus vaccine [147]. WHO recommends the following doses of oral iodized oil every 12–18 months in areas where iodine deficiency disorders are a serious problem: for children younger than 1 year, 0.5 mL (240 mg); for children older than 1 year and for women of childbearing age, 1.0 mL (480 mg) [148].

17.10.3 Iodized Oil Injections

Much knowledge about the use of iodized oil injections came from studies conducted in Papua New Guinea, Latin America, and Zaire from the late 1960s and 1970s [24, 149, 150]. In part because of concern over the AIDS pandemic and use of needles, oral iodized oil has largely replaced iodized oil injections.

17.10.4 Other Strategies

Monthly administration of 30 mg iodine in the form of a 10% potassium iodide oral solution was effective in the prophylaxis of iodine deficiency in schoolchildren in Zimbabwe [151]. Iodization of drinking water has been used as a strategy to reduce iodine deficiency disorders in developing countries such as Malaysia [152] and Mali [153]. Iodization of irrigation water improved iodine content of soil, crops, and animals in an area of rural China, and the annual costs of the project ranged from $0.05/person in the first year to $0.12/person in the second year [154]. In a study in western Sudan, iodine-saturated silicon matrices placed in wells and hand pumps significantly increased media urinary iodine concentrations and greatly reduced the prevalence of goiter [155].

Other strategies that have been proposed for prevention of iodine deficiency disorders include iodine fortification of flour [156], addition of iodine to fertilizers, and incorporation of iodine into school snacks and beverages. Increasing the dietary iodine consumption by chickens and livestock by the use of fish flour, seaweed, or iodine supplementation may

be another strategy to increase the iodine content of meat, poultry, and dairy products. However, because of the difficulties in controlling the iodine intake by means of these different procedures, the current recommendation is to focus on the strategy of universal salt iodization with possible additional programs of iodine supplementation in pregnant and lactating women and young infants, that is, in the most susceptible age groups to the effects of iodine deficiency as long as the programs of salt iodization have not yet adequately covered the whole population [80].

17.11 CONCLUSIONS

Iodine deficiency is the leading cause of preventable mental retardation in the world and is a preventable cause of morbidity and mortality. Great progress has been made in providing access to iodized salt. As indicated by a WHO/UNICEF/ICCIDD report to the World Health Assembly in 1999 [33], of 5 billion people living in countries with iodine-deficiency disorders, 68% now have access to iodized salt. Of 130 countries affected by iodine deficiency disorders, 104 countries (81%) now have an intersectoral coordinating body, and 98 (75%) have legislation in place for iodized salt.

Major challenges remain in ensuring the sustainability of salt iodization through monitoring and enforcement. The goals for monitoring include salt iodine at a level of 90% effectively iodized and urine iodine in the normal range (median excretion of 100–300 µg/L). The lower level of 100 µg/L is necessary to ensure normal brain development in the fetus and young infant, and the upper level of 300 µg/L is to minimize the occurrence of iodine-induced hyperthyroidism. Further momentum on the governmental level and in the scientific and medical communities should help ensure the practical elimination of iodine deficiency disorders worldwide.

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