

Teratogen Update: Iodine Deficiency, a Community Teratogen

JOSEPH G. HOLLOWELL, JR.* AND W. HARRY HANNON

National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341

In the last decade, iodine deficiency disorders (IDD) have become recognized as the most common preventable cause of mental retardation worldwide. Iodine deficiency interferes severely with prenatal and postnatal growth and neurologic development of individuals. It has condemned tens of millions of children to cretinism—characterized by mental and growth retardation, rigid spastic motor disorders, deaf mutism, and severe hypothyroidism—and hundreds of millions of children to milder degrees of mental and physical impairments. Accompanying effects include increased rates of congenital anomalies, fetal wastage, infant mortality, goiter, and hypothyroidism in children and adults. Endemic cretinism has been classically divided into two types: a chronic neurological disorder and a condition with myxedema and severe hypothyroidism. Recent studies have shown considerable overlap in the findings of these two types, which are now thought to have a common etiology differing primarily by the timing and severity of the pre- and postnatal deficiency of iodine and maternal thyroxine. The severity of iodine deficiency and hypothyroidism in the mother during early and midgestation is related to the severity of the neural damage in the fetus. The most logical intervention for a community or population is the introduction of iodine prophylaxis. Although salt iodization is technically straightforward, community leadership is essential to any effort. The mobilization of global efforts through WHO, UNICEF, Program Against Micronutrient Malnutrition (PAMM), and International Council for Control of Iodine Deficiency Disorders (ICCIDD) since 1990 has led to goals to eliminate new cases of IDD by the year 2000. Most countries at great risk for IDD have met or are close to meeting the middecade goal of having iodized salt for 90% of households. This provisional success indicates that the goal of eliminating new IDD cases by the year 2000 may be achieved.

INTRODUCTION

Iodine, an essential trace element, was present during the primordial development of the earth, but it has been leached from the surface soil by snow, rain, and glaciation and carried into the sea. The ocean is now the primary source of iodine, with a concentration of 50–60 µg/l (Hetzel and Maberly, '86).

As a result, iodine deficiency became and continues to be a major public health problem affecting many millions of people worldwide. Although iodine nutrition has improved greatly over the past decade, it is esti-

mated that more than a billion people, concentrated largely in less developed countries and in the emerging nations of the former Soviet Union, are at risk for consuming insufficient amounts of iodine (Gerasimov, '93; Maberly, '94). Iodine deficiency rarely produces malformations identifiable at birth, but it interferes severely with prenatal and postnatal growth and neurologic development of individuals. It condemns millions of children to cretinism, tens of millions to mental retardation, and hundreds of millions to milder degrees of mental and physical impairments (UNICEF, '95a) (Fig. 1). It presents an intriguing pathophysiological problem involving complex interrelations between different micronutrient deficiencies and the timing of those deficiencies during development (Dumont et al., '94). Iodine deficiency can have devastating effects on entire communities. It could be considered a major teratogen at the community level, which can alter significantly the development and function of entire populations. Therefore, interventions are necessary at the community level. The effects of iodine deficiency are potentially 100% preventable simply by correcting the affected population's deficiency of iodine.

Iodine is important in human nutrition because it is a constituent of the thyroid hormones, 3,5,3',5' tetraiodothyronine (thyroxine or T₄) and 3,5,3' triiodothyronine (T₃), which are necessary for the growth and development of humans and animals. The healthy human body contains 15–20 mg iodine, of which 70–80% is present in the thyroid gland. Iodine exists in blood in both inorganic and organic forms. The normal range of plasma inorganic iodide is 0.08–0.60 µg/dL, with values <0.08 suggesting a deficiency and values >1.0 pointing to exogenous iodine administration. Organic iodine in blood is present mainly as T₄ bound to plasma proteins (Hetzel and Maberly, '86). The human requires ~50–150 µg of iodine daily to replace the hormonal iodine that is degraded and unrecovered daily (WHO/Nutrition, '97). The amount of iodine in drinking water often reflects the amount of iodine in soil, which also determines the level in crops and animals in the area. Iodine levels in drinking water in deficient areas is usually <2 µg/l (Hetzel and Maberly, '86).

*Correspondence to: Joseph G. Hollowell, Jr., M.D., National Center for Environmental Health, CDC, 4770 Buford Highway, MS F-28, Atlanta, GA 30341.

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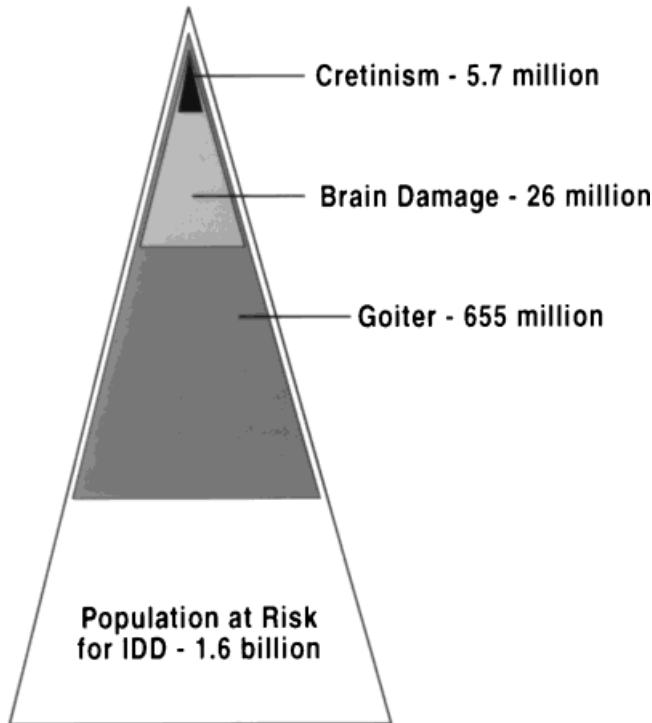


Fig. 1. Scope of iodine deficiency disorders. Cretinism is just one of many problems related to iodine deficiency. Until recently, the prevalence of cretinism and goiter defined the extent of the problem. (UNICEF, '95a)

Iodine deficiency can be assessed most directly by measuring urinary iodine excretion, either in 24-hr samples or in casual samples. In areas of endemic iodine deficiency, intake is usually below 100 $\mu\text{g}/\text{day}$, and goiter, the most commonly associated abnormality, is usually seen when the level is $<50 \mu\text{g}/\text{day}$. Goiter can be detected visually, by palpation, or by sonography. (Fig. 2). The prevalence of goiter increases as iodine excretion (reflecting intake) falls. The rate of goiter is nearly 100% among people who excrete $<10 \mu\text{g}$ iodine/day.

Historical observations

The record of goiter dates back to ~ 2700 BC with a reference to the use of seaweed sargassum to treat it. In the third and fourth centuries, goiter can be found in artwork and in the sculpture of Buddha and his disciples. In the thirteenth century, goiter and cretinism were associated in drawings, and the Renaissance art of Rubens, Weyden, and Durer contained many examples of goiter. Surgery for goiter was performed at the early medical schools of Italy in the twelfth and thirteenth centuries and noted by Paracelsus in the 16th century. It was not until the seventeenth century that the thyroid gland was first described (Merke, '84).

In the eighteenth century, the word "cretin" first appeared in print and was defined as "an imbecile who is deaf and dumb with a goiter hanging down to the waist" (Hetzel, '89a) In the 1820s, the French chemist

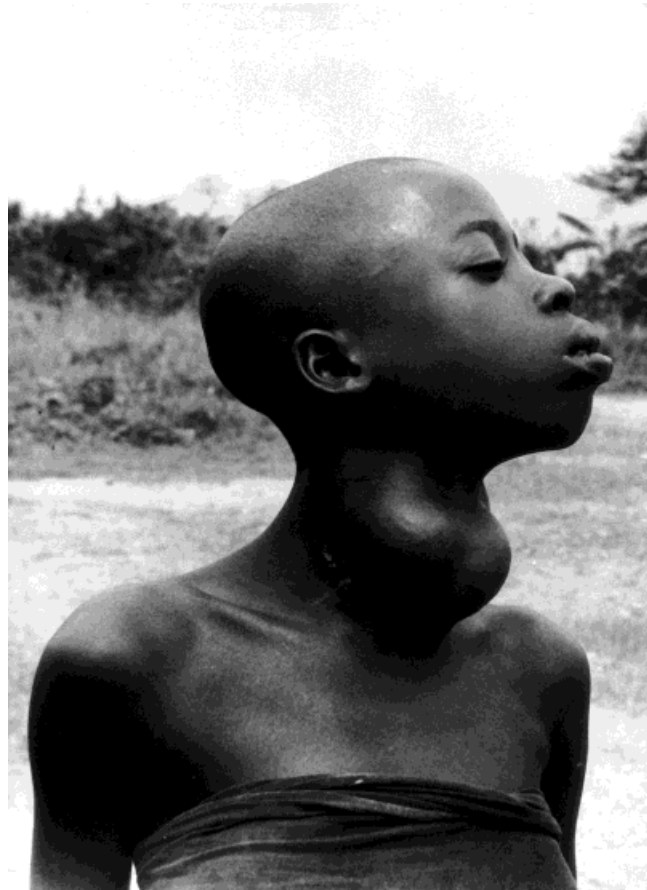


Fig. 2. Grade 3 nodular goiter. Photograph courtesy of F. Delange, M.D.

Bernard Courtois discovered the element iodine in the ashes of seaweed, which for centuries had been used as an efficacious treatment for goiter. The relationship of goiter to iodine deficiency became clearer during the nineteenth century. In 1846, Prevost and Maffoni first hypothesized that goiter was due to iodine deficiency. The concentration of goiter and cretinism in specific regions led to speculations on the environmental causes for these conditions. A survey for goiter commissioned in 1848 by the king of Sardinia revealed 370,403 people with goiter and 120,000 cretins or idiots out of a total population of 36 million and showed the relationship of goiter to cretinism (Hetzel, '89, '95). The relationship of iodine with the thyroid gland, the thyroid's role as an endocrine organ, and the relationship among the thyroid, iodine deficiency, and cretinism became better understood by the end of the nineteenth century. In 1883, Theodor Kocher found the relation between the thyroid and cretinism, for which he received the Nobel Prize in 1909 (Schlich, '94). McCarrison ('08) conducted a study in the Himalayan valleys of Chitral and Gilgit and distinguished two types of endemic cretinism (Figs. 3,4). The "neurologic" type is a severe chronic neurological disorder, and the "myxedematous" type is more associated with hypothyroidism.



Fig. 3. Neurologic endemic cretinism. Nepal. This clinically euthyroid 41-year-old man of normal height has severe mental retardation, deaf-mutism, spastic diplegia with hyperreflexia, clonus, and Babinski sign as well as Stage 2 goiter. Photograph courtesy of F. Delange ('94) with permission.

In the United States, goiter was endemic in all states bordering on the Great Lakes, but endemic cretinism was not observed (Kelly and Snedden, '60). In 1917, Marine and Kimball performed the first large-scale trial with iodine using iodized salt to prevent goiter in Ohio and Michigan (Marine and Kimball, '22). In the mountainous regions of Europe where the prevalence of goiter and cretinism was high, such cases declined precipitously after the introduction of iodized salt. The decline was aided also by the importation of foods from outside the areas of iodine-deficient soil (Burgi et al., '90; Hetzel, '94).

Iodine deficiency disorders (IDD) have been eliminated for >40 years in several countries, including the United States, England, Switzerland, New Zealand, and Australia. Other countries where iodine deficiency is severely endemic are eliminating IDD with the use of iodized salt and injections of iodized oil. However, Europe, once considered non-endemic, has reported dangerous IDD in certain areas (Delange et al., '93).

In the last few years, there has been a widespread awareness of the enormous global impact of iodine

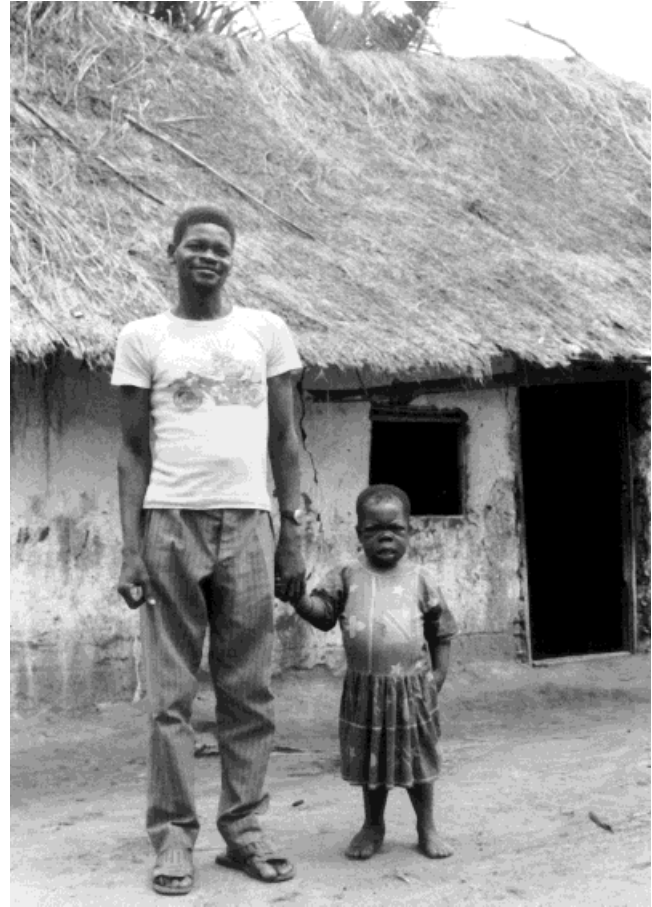


Fig. 4. Myxedematous endemic cretinism, Ubangi Zaire. The euthyroid man on the left, age 21, is with a 15-year-old female with cretinism. She had severe myxedema and puffy features, immature naso-orbital configuration, severe mental retardation, and dwarfism. She has not entered puberty. Her thyroid gland was not palpable, and she was not deaf-mute. Photograph courtesy of F. Delange ('94) with permission.

deficiency on brain development during prenatal and early postnatal life. The International Council for Control of Iodine Deficiency Disorders (ICCIDD) was formed in 1986 with support from UNICEF, WHO, and the Australian government. In 1990, the World Summit for Children set a goal to eliminate new cases of IDD by the year 2000 (Hetzel and Delange, '96).

PATHOPHYSIOLOGY OF IDD

Following studies in South America, Stanbury et al. ('54) re-established interest in studying the relationship between endemic goiters and an insufficient supply of iodine. This was soon followed by studies in New Guinea, China, Indonesia, India, Africa, and more detailed observations in South America. Researchers from Europe, Australia, and North America joined with scientists from the affected areas better to understand endemic cretinism (Hetzel, '89). Choufoer et al. (1965) suggested that the very low levels of protein-bound

iodine (PBI), an indirect measure of serum thyroxine found in pregnant women with severe iodine deficiency, probably played a major role in central nervous system (CNS) damage of their children with cretinism. Subsequently, the degree of maternal hypothyroxinemia was shown to be related to the severity of CNS damage in their offspring. The controversy over the role of iodine in the etiology of cretinism was resolved when Pharoah and colleagues (Pharoah et al., '71; Pharoah and Connolly, '87) conducted a double-blind trial, which began in 1966 in Papua, New Guinea, using intramuscular iodized oil, and confirmed earlier observations that endemic cretinism could be prevented by the administration of iodine. Studies in other areas were done showing the benefit of iodine supplementation on pregnancy outcomes (Fierro-Benitez et al., '72; Chaouki and Benmiloud, '94). Evidence has also shown that iodine supplementation given to women before conception is effective in preventing both varieties of endemic cretinism and possibly in preventing early fetal and infant death (Pharoah, '93).

With iodine deficiency, synthesis of thyroxine (T₄) is impaired, thus triggering the release of thyroid-stimulating hormone (TSH), which stimulates thyroid gland activity. Adaptation occurs in the trapping mechanism and in other steps of the intrathyroidal metabolism of iodine. These mechanisms that are stimulated by the increased secretion of TSH and other thyroïdal and systemic homeostatic mechanisms lead to the preferential secretion of 3,5,3' triiodothyronine (T₃). By increasing the efficiency in trapping of iodine, the thyroid gland accumulates a larger percentage of the ingested exogenous iodide and reuses endogenous iodide more efficiently, and in many instances adequate amounts of thyroxine can be secreted (Delange, '94). Under these conditions the thyroid gland increases in size, forming a goiter. Long-standing iodine deficiency causes some of the goiters to become nodular with some nodules functioning autonomously (Dremier et al., '96). More severe impairment of T₄ synthesis leads to hypothyroidism and in the developing fetus and newborn results in neurologic damage.

In 1971, three mechanisms were suggested to explain the effect of iodine deficiency on brain development: (1) fetal hypothyroidism, (2) maternal hypothyroidism, and iodine deficiency *per se* (Pharoah et al., '71; Hetzel, '94).

Roles of iodine and thyroxine

It was considered a paradox that in areas of iodine deficiency, children with cretinism, but with functioning thyroid glands, had more severe CNS damage than some children who were missing a thyroid gland. For prevention of CNS damage, iodine had to be supplied before conception or early in first trimester, a time in development before the fetal thyroid was known to be functioning. The finding that maternal thyroxine does reach the fetus (Vulsma et al., '89) made it understandable that CNS damage could occur if thyroid hormones

were necessary for brain development during its early developmental period, if the mother supplied the needed thyroxine, and if the mother were also hypothyroxinemic.

It is important to distinguish the role of maternal thyroxine from that of the fetal and embryonal thyroid hormone in the development of cretinism and to understand the difference between the neurological and the hypothyroid forms of the disease (Fig. 5). Early in pregnancy, before the fetal thyroid gland begins to function, maternal thyroxine has an important role in the development of the embryonic brain and neural tissues. A reduced level of thyroid hormone in utero subverts the molecular underpinnings of normal neuro-anatomical development. The alteration of specific molecular events follows the effects of diminished fetal thyroid hormone levels on specific thyroid hormone responsive genes after they interact with brain thyroid hormone receptors. These specific genes direct the synthesis of protein products that are critical for the normal development and maintenance of the nervous system (Stein, '94).

During pregnancy the thyroid status of the mother changes. There is increased stimulation by TSH, because estrogens result in an increase in serum concentration of thyroxine binding globulin (TBG), which shifts the binding equilibrium of T₄ away from free-T₄. In early pregnancy, the thyroid gland is stimulated by human chorionic gonadotrophin and there is increased loss of iodine in the urine (Burrow et al., '94; Delange, '94). Studies by Vermiglio et al. ('95) observed a critical decrease of free T₄ and a significant increase in the T₃/T₄ molar ratio in pregnant women in an area of iodine deficiency. Precarious iodine or euthyroid status may be shifted toward iodine deficiency and hypothyroidism in borderline situations with pregnancy (Glinier '93; Burrow et al., '94). In Belgium, Delange ('94) showed that borderline intake of 50–75 µg/day is accompanied by a progressive decrease in serum free-T₄ and increase in serum TSH. This leads to a state of chronic thyroid hyperstimulation and goiter in ~10% of women and a progressive increase in serum concentration of thyroglobulin. These processes set the stage for fetal deprivation of T₄ at a time when it may be needed for brain growth and maturation. This situation is especially precarious if the fetal thyroid gland is unable to produce adequate amounts of T₄, also because of iodine deficiency.

In the developing fetal brain, the availability of T₃ is highly dependent on a supply of T₄ for intracellular deiodination. Studies in rats showed that nuclear receptors are occupied by T₃ well before the beginning of fetal thyroid function, thus indicating that maternal thyroid hormones play a role in the maturation of the brain (de Escobar et al., '94). Maternal deficiency of iodine and the resulting maternal hypothyroidism appear to have their impact in the early stages of fetal brain development. In areas of endemic iodine deficiency, the severity of a mother's hypothyroidism dur-

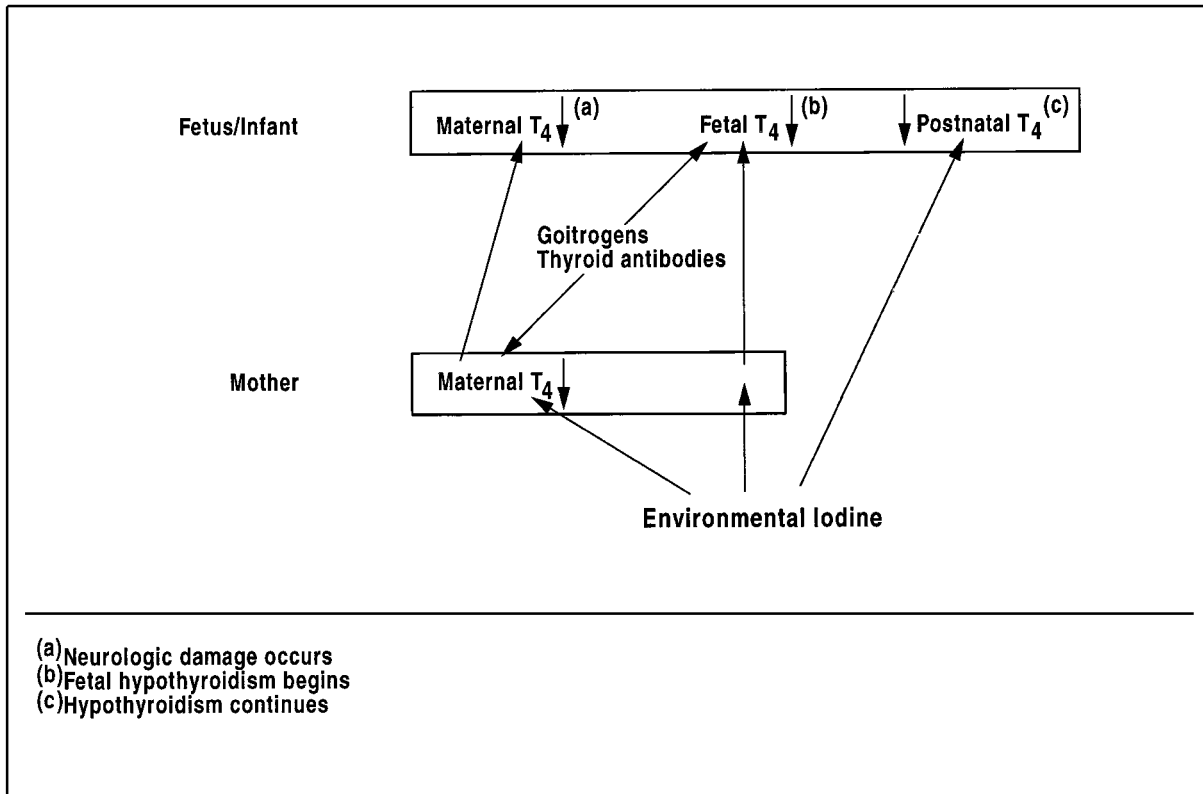


Fig. 5. Outcomes of iodine deficiency. Maternal iodine deficiency early in pregnancy leading to maternal hypothyroxinemia deprives the fetus of T₄ required for neural development and thus causes brain damage (a). With adequate maternal T₄ in early pregnancy neural damage may be avoided, but when accompanied by iodine deficiency later will result in fetal hypothyroidism (b).

ing early gestation is related to the severity of her fetus's neural damage (which is thought to require T₄ deficiency in both mother and fetus). It is believed that the characteristic neural damage of cretinism occurs in the face of fetal hypothyroxinemia from the 14th week of gestation into and probably through the third trimester. It is during these periods in gestation when the thyroid hormone has a major effect on neuronal differentiation and myelination (Eayrs, '60; Legrand, '84; De-long, '96). Thyroid hormone also influences neuronal cell multiplication, migration, and apoptosis at an earlier time in gestation (Behnam-Rassoli et al., '91; Pharoah and Connolly, '96a,b) making it likely that brain damage from thyroxine deficiency can occur throughout gestation. Regardless of the timing of specific pathogenetic neural outcomes seen in cretinism, when sufficient maternal thyroxine is delivered to the fetus during gestation, severe neural damage is not seen; instead iodine deficiency will interfere primarily with the production of thyroxine by the fetus, leading to a condition nearly indistinguishable from other forms of congenital hypothyroidism (CH). The myxedematous form of the condition, which is largely due to an infant's postnatal deficiency of iodine, results in hypothyroidism that can worsen with continuing iodine deficiency

and lack of thyroid replacement treatment during childhood and adulthood (Boyages and Halpern, '93).

Although the unifying hypothesis for the pathogenesis of endemic cretinism can be used to explain the situation in China and Java, Delange ('94) points out that it cannot be considered universal, because maternal and fetal hypothyroidism are much more severe and frequent in areas in the world where the myxedematous component of cretinism predominates over the neurological components. These neurological findings from areas of endemic iodine deficiency may be related to and shed light on clinical observations in iodine-sufficient areas.

The similarity of neurological and motor manifestations of endemic cretinism, some infants of mothers with thyroid disease, and sporadic hypothyroidism suggests a common effect of thyroid hormone deficiency during pregnancy on the developing nervous system. Pathologically these lesions of fetal hypothyroidism are similar to those observed in cerebral palsy (Stein, '94). Nelson and Ellenberg ('85,'86) report that children of women who were hypothyroxinemic or hyperthyroxinemic before or during pregnancy may have poor fine motor coordination, varying degrees of mental retardation, specific signs of cerebral palsy (including spastic-

ity, tone abnormalities, and hemiparesis), and a 20-fold increase of risk for later cerebral palsy (Stein, '94). Severe hypothyroxinemia among preterm infants weighing 2,000 g or less at birth has been shown to be strongly associated with impaired brain function and development, including disabling cerebral palsy among those children at 2 years of age (Reuss et al., '96).

Other pathogenic cofactors

The basic cause of endemic cretinism is iodine deficiency and the resulting hypothyroidism. In areas of iodine deficiency, myxedematous cretinism varies widely from one goiter-endemic area to another and is associated with varying degrees of thyroid damage. Aggravating cofactors (such as dietary goiterogens and autoimmune hypothyroidism) may explain some of these pathological and clinical variations. The overload of thiocyanate (SCN), a dietary goiterogen, results from chronic consumption of poorly processed cassava. The SCN level in cord blood among infants in one endemic area, the Ubangi in Zaire, was three times that in the cord blood of infants born in Brussels, Belgium. In the face of iodine deficiency, SCN, which freely crosses the placenta, can further compromise iodine transport and trapping by both the placenta and the thyroid gland and can critically reduce the buildup of iodine stores within the thyroid gland during fetal and early postnatal life. By also decreasing maternal thyroxine production, SCN further increases the risk for cretinism in iodine-deficient areas (Delange, '94).

Selenium deficiency, which has been described in areas where the prevalence of myxedematous cretinism is very high, has been investigated as a possible cofactor (with iodine deficiency) in its pathogenesis by contributing to thyroid destruction (Vanderpas et al., '90). The mechanism for this involves the antioxidant defenses offered by the selenoproteins, e.g., glutathione peroxidase, phospholipid hydro peroxide, and others, which like vitamin E have the ability to reduce either H_2O_2 , or other H_2O_2 -derived free radicals and lipid peroxides. These systems protect the lipophilic membrane and soluble fraction of the cell from attack. When stimulated, the thyroid gland produces large amounts of hydrogen peroxide. Contempre et al. ('95) showed that iodide challenged rats with selenium deficiency in conjunction with iodine deficiency exhibited increased necrosis, induced fibrosis, and impeded compensatory epithelial cell proliferation of the thyroid, findings compatible with the histological and functional descriptions of thyroid tissue from people with myxedematous cretinism. Because of the complex interactions involved here, Contempre et al. ('91) warned against selenium supplementation alone in areas of combined iodine and selenium deficiency. The role of selenium is not clear cut. (Maberly, pers. com.) pointed out that in northern China, where selenium deficiency is most severe, the neurologic form of cretinism predominates. Ma and Wang ('93) demonstrated that selenium-deficient areas also can be endemic for IDD, but that IDD can be severe

where selenium is considered to be adequate. The distribution of myxedematous cretinism was not related to selenium deficiency.

Selenium is also present in the active centers of two of the three iodothyronine deiodinases (ID), namely, types ID-1 (Arthur et al., '93; Berry and Larsen, '93) and ID-3 (Ramauge et al., '96) in the form of selenocysteine (Larsen and Berry, '95). ID-1, present in liver, kidney, and pituitary, converts T4 to T3 and provides T3 to plasma. ID-3, present in the CNS, placenta, and skin inactivates T3 and T4 and generates reverse T3 (rT3). The third iodothyronine deiodinase, ID-2, does not appear to require selenium (Meinhold et al., '93; Beckett and Arthur, '94). It is present in the CNS, pituitary, brown fat, and placenta and provides T3 to plasma and intracellular compartments. Of the T3 needed for brain development, 80% is dependent on its *in situ* conversion from T4. Thus selenium is required for the thyroid hormone dependent functions of normal growth and brain development (Larsen and Berry, '95). The relationship of selenium to the findings in cretinism is complex (Contempre et al., '94; Kohrle, '96). Its deficiency may contribute to the IDD phenotype and severity through a variety of possible mechanisms. Further research on selenium and its relationship to iodine deficiency is needed to elucidate the selenium contributions relative to growth and brain development in this condition.

IODINE DEFICIENCY DISORDERS (IDD)

The term "iodine deficiency disorders" is used to describe a broad spectrum of effects of iodine deficiency on growth and development (Hetzel et al., '88). These disorders range from the most severe form, endemic cretinism, which is characterized by mental and growth retardation, rigid spastic motor disorders, and deaf mutism, to endemic goiter and less severe forms of brain damage. Accompanying effects include increased rates of congenital anomalies, fetal wastage, infant mortality, goiter, and hypothyroidism in children and adults (Thilly et al., '92). In the last decade, IDD have become recognized as the most common preventable cause of mental retardation worldwide (Hetzel and Maberly, '86).

The impact of iodine deficiency differs depending on the age and life stage of the individual affected (see Table 1). The most severe problems caused by iodine deficiency are among fetuses, neonates, and infants because of the irreversible changes that can occur during this period of rapid structural and behavioral development. Cognitive impairment is the most common finding seen with iodine deficiency. Women who suffer from iodine deficiency and hypothyroidism during pregnancy risk causing neurologic damage in their offspring (Hetzel and Maberly, '86).

Neonatal screening used to identify sporadic cases of congenital hypothyroidism also may identify cases caused by iodine deficiency. In areas endemic for iodine deficiency, many neonates will have elevated TSH levels, which reflect the decrease in T4 synthesis. These

TABLE 1. Iodine deficiency disorders (IDD) over the life span¹

Time of life	Potential outcomes
Fetus	Abortions, stillbirths Congenital abnormalities Increased perinatal and infant mortality Endemic cretinism: neurological Endemic cretinism: neurological mental retardation; deafmutism spastic diplegia; squint Endemic cretinism: myxedematous hypothyroidism; dwarfism
Neonate-infant	Neonatal goiter Overt or subclinical hypothyroidism
Child-adolescent	Goiter Juvenile hypothyroidism Impaired mental and physical development
Adult	Goiter and its complications Hypothyroidism Impaired mental function Decreased fertility rate Iodine induced hyperthyroidism Risk for perpetuating endemic cretinism during pregnancy
All ages	Increased uptake for radioactive iodine in nuclear disaster Cognitive impairment

¹Modified from Hetzel, '94.

increases in TSH levels in turn cause an increase in the false-positive and recall rate for the detection of sporadic congenital hypothyroidism. As the sensitivity of newborn screening assays for TSH has improved with the new generation of methods, measuring the rate of TSH elevation in a population has become a way of assessing that population's degree of iodine deficiency (Nordenberg et al., '94). Clinical findings at birth are usually not remarkable; only later will hypothyroidism develop or neurologic findings become apparent.

Endemic cretinism

In the classification of cretinism described by McCarrison ('08), neurological cretinism is said to be characterized by the presence of goitre, speech and hearing defects, abnormalities of gait and posture, and often euthyroidism. Myxedematous cretinism is distinguished by thyroid atrophy and consequently prominent features of hypothyroidism with growth retardation and sexual immaturity. Recent studies reporting similar neurological patterns among all people with cretinism regardless of conventional classification and independent of current thyroid function have blurred this distinction (DeLong, '87).

Neurological findings. Halpern et al. ('91) studied and described the neurologic findings in people with endemic cretinism in western China, where myxedematous cretinism predominated and in central Java, Indonesia, where neurological cretinism predominated. Findings were similar in subjects from both areas. There was significant pyramidal dysfunction in a proximal

distribution with hyperreflexia and extensor plantar responses. There was a characteristic standing posture, characterized by flexion of the neck, and hips and knees were flexed with adductor tightness. The trunk tilted forward, feet were flat and everted, and the gait was broad-based and knock-kneed. Arms were often held in a curious posture with the shoulders abducted and the elbows and wrists flexed. No fasciculation was seen in the muscles. Bladder and bowel function was not usually affected. Peripheral sensory function appeared normal. Prolongation of the relaxation phase of the ankle jerk was found in those with hypothyroidism, but this response was not sufficiently sensitive to be used as a diagnostic test. Cerebellar function was normal in all subjects who could imitate the required movements, even those individuals who were severely hypothyroid. Many patients had a squint that was nonparalytic, with one or both eyes failing to abduct fully on lateral gaze. Nystagmus was seen in a few patients (Halpern et al., '91).

Musculoskeletal abnormalities were common and predominantly involved the weight-bearing joints. These abnormalities showed no relationship to current thyroid function. Excessive laxity of the hips, feet, and ankles was frequently seen. Excessive laxity of the upper limb joints was an infrequent finding. Fixed deformities of the joints and of the spine were occasionally seen (Halpern et al., '91).

Most subjects had a characteristic gait disturbance ranging from a mild disturbance of posture and rhythm to an inability to walk. In the mildest form of this disturbance, subjects walked on a widened base with a slight waddle and with reduced arm swing. Among more severely affected subjects, the gait was slow and shuffling, turning was effected in series, all movements tended to be stiff and jerky, and there was a pronounced waddle. Many of these people had an asymmetric arm swing, or none at all. These features also resemble those seen in Parkinson's disease (Halpern et al., '91).

Sankar et al. ('93) described similar findings among 100 people with endemic cretinism in the state of Sikkim. They also found visible goiters in 62%, deaf mutism in 74%, squint in 29%, and severe mental retardation in 16%. The others people without severe mental retardation were capable of performing simple tasks, such as herding sheep, cattle, and working in the fields. Most of the people with cretinism were cheerful and cooperative.

DeLong et al. ('94) studied 30 children with endemic cretinism in Xinjiang Province, China. They described five patterns of neurologic involvement in 28 of these children. Two of the children had myxedema without neurologic abnormalities. The "typical" pattern (exhibited by 17 children) was that of hearing and speech deficits, proximal spastic-rigid motor disorder, and mental retardation. Three children exhibited thalamic posturing, severe mental retardation, marked microcephaly, inability to sit, stand, or walk, and exaggerated primitive facial reflexes. One child with an "autistic"

pattern also had severe mental deficiency, exacerbated by deaf-mutism, poor visual attention, and absence of purposeful activity. Two children had a "cerebellar" pattern of neurologic findings, which is unusual in cretinism. Five other children had marked truncal hypotonia with delay in sitting, standing, and walking.

The report of DeLong et al. ('94) emphasized the degree of microcephaly found in the various groups. Except for the children with mild "typical" cretinism whose head circumferences approached American norms, the others had microcephaly with head circumferences from 2–9 SD below the mean. The "thalamic" group was the most severe.

Brain-imaging and neuropathological changes.

Hetzel et al. ('88) noted that moderate, widespread reduction in the number of brain cells and in brain size among people with cretinism and more recent studies in 1984 by Cruz et al., using computed tomography (CT) scans, show widespread atrophy of the cerebral cortex and subcortical structures of the brain stem (pons and mesencephalon) with corresponding enlargement of the basal cisterns, the lateral ventricles, and the cerebral cortical sulci (Hetzel et al., '88). Magnetic resonance images of three adult males with neurologic endemic cretinism were remarkably normal overall. However, each did show abnormalities in the region of the globus pallidus and the substantia nigra with hyperintensity on T₁ and hypointensity on T₂ weighted images. A CT scan showed no evidence of brain calcification. These observations are consistent with the extrapyramidal rigidity characteristic of the neuromotor defects of endemic cretins (Ma et al., '93; DeLong et al., '94). Halpern et al. ('91) also found basal ganglia calcification on CT scans that was positively associated with the hypothyroid state. Wang ('93) carried out pathological examinations of the brains of five patients with endemic cretinism. A computer image analysis showed that all five had hypoplasia of the pyramidal and granular cells of the hippocampus. A correlation was found between the weight of the thyroid gland and weight of the brain as well as the size of the hippocampus. Wang postulates that lesions found in the hippocampus constitute one of the morphologic bases of dementia in endemic cretinism.

Cognitive abnormalities. Although endemic cretinism with a cognitive deficit is the most severe and striking outcome from iodine deficiency, there is evidence that many more otherwise normal individuals can have impairments of cognitive functioning. The population of entire communities can be left with subnormal average intelligence and impaired motor functions. Mild iodine deficiency associated with a goiter rate of 10% has been reported to reduce the average IQ by 10–15% (Boyages et al., '89a; Fierro-Benitez et al., '72, Fierro-Benitez et al., '88, Trowbridge, '72). Studies in Ecuador, Bolivia, Chile, Papua New Guinea, Zaire, Java, China, and India also showed high

rates of low intelligence or developmental quotients in noncretin individuals from areas of severe endemic goiters (Delange, '94).

O'Donnell et al. ('94) report psychological assessment data from 131 children from an area of Xinjiang in the People's Republic of China in which cretinism is endemic. These children were given iodine supplements beginning at different times during development: in utero, in the newborn period, and after the first 3 months of life. The children whose mothers received iodine during their pregnancies had developmental quotient scores significantly higher than either of the other two groups at 24 months of age. Cao et al. ('94) extended the study to include 689 children and 885 women, 295 at each trimester of pregnancy. Among the groups whose mothers were given iodine in the first or second trimester, they found significantly fewer children with neurologic abnormalities (2%), less microcephaly (11%), and a higher developmental quotient (90 ± 14) than among those whose mothers were treated in the third trimester, or children who were given iodine only after birth. In the latter group, 9% had neurologic abnormalities, 27% had microcephaly, and the developmental quotient was 75 ± 18 . Cao et al. ('94) thus concluded that iodine treatment improved the children's neurologic outcome and that treatment up to the end of the second trimester protected the fetal brain from the effects of iodine deficiency. Iodine treatment may improve brain growth and developmental achievement slightly when given later in pregnancy or after delivery, but does not improve neurologic status.

Bleichrodt and Born ('94) reviewed 21 research studies on the relationship of iodine to cognitive development and found 18 suitable for meta-analysis. They found that iodine deficiency had a negative influence on cognitive scores of noncretinous individuals. They calculated that the mean IQ among those with insufficient iodine was 0.9 standard deviations lower than those individuals with adequate iodine, or 13.5 IQ points apart. Bleichrodt and Born ('94), however, point out that not all studies could be adequately traced, some publications did not include the statistical data needed for the metaanalysis, and only reported studies were included. Other limitations to the meta-analysis include the possible nonnormal distribution of group scores in the iodine-deficient group such that the mean was shifted because of a few children with "sub-clinical cretinism" (DeLong, '90). There is the additional difficulty of using tests of intellectual and motor ability developed in one culture to evaluate cognitive functioning of people from another culture (Pharoah, '93).

Audiological findings. From the time of the first written records of cretinism in the thirteenth century, deafness has been associated with the condition. Deaf-mutism has been reported in 80% of the people with endemic cretinism in the Himalayas (McCarrison, 1908) and as many as 92% of those with the "neurologic" form of cretinism in Java (Goslings et al., '75). In contrast, none of 88 people with severely "myxedematous" nongoi-

terous cretinism from Idjwi island in Zaire were deaf-mute. The results of audiometry suggested the deafness to be sensorineural (Fierro-Benitez et al., '70), which is at odds with findings of abnormalities of the middle ear and surrounding temporal bones in endemic cretinism (Koenig and Neiger, '72). The only data on brainstem auditory evoked potential were interpreted as showing impairment of middle ear function (Ramirez et al., '83).

In an attempt to determine better the nature of the deafness associated with endemic cretinism and the relationship between its type and severity and the severity of hypothyroidism, Halpern ('94) studied 59 patients with endemic cretinism in Qinghai Province, China, using brainstem auditory-evoked potentials and pure-tone audiometry combined with tympanography and testing of reflex sensory thresholds. He also obtained results from CT scans of the petrous temporal bones. Of the 59 patients studied, 37 were euthyroid (with serum TSH levels ≤ 10 mIU/l), and 22 were hypothyroid (TSH levels > 10 mIU/l), of whom 16 were severely hypothyroid (TSH > 60 mIU/l). All types of audiometric deficits were found: conductive, sensorineural, and sensorineural. Hearing was impaired in nearly all subjects, including those who were euthyroid, as well as those with severe hypothyroidism, some of whom were deaf and mute. The brainstem auditory-evoked potentials disclosed a high incidence of hearing abnormalities at both a peripheral and central level among both euthyroid and hypothyroid subjects. Auditory conduction abnormalities were more common in the hypothyroid group. Halpern interpreted these findings as supporting the concept that all expressions of endemic cretinism are caused by a prenatal neurological insult near the time when the fetal thyroid gland commences activity and exerts maximal effect on brain development.

Hypothyroidism. The clinical findings of myxedematous hypothyroidism due to iodine deficiency are indistinguishable at the time of birth from those of sporadic cases of CH due to other causes. The myxedematous form of cretinism seen in endemic areas of iodine deficiency with its onset in an early developmental period is a product of florid long-standing untreated hypothyroidism. This form of cretinism is marked by substantial growth failure, puffy features, immature naso-orbital configuration with a flat and broad nose, a hypoplastic mandible, dry and scaly skin, dry and brittle hair, a prominent abdomen, immature body proportions with a relatively short lower body segment, and retarded sexual development. Mental retardation may be severe, but usually not as severe as in the neurologic type of cretinism. The severity of neurologic findings may reflect the severity and onset of prenatal hypothyroxinemia. The prevalence of goiter is usually not as great as in the neurologic type (Delange, '94).

Severe protracted thyroid hormone deficiency may cause thyrotrophin adenomas of the pituitary gland that contribute to the disturbances of growth, puberty, and sexual function among people with endemic cretinism (Boyages et al., '89b).

Goiters found among people in areas of iodine deficiency are usually caused by the body's attempt to trap more iodine through increased TSH stimulation and other intrathyroidal mechanisms. This poses a particular risk for people exposed to nuclear disasters or mishaps such as the explosion in Chernobyl near Kiev, USSR (now Ukraine) on April 26, 1986, the world's worst nuclear accident. The iodine deficiency of that region could well have accounted for the excessive and particularly aggressive thyroid cancer among children that occurred there following the accident. By the fifth year following the explosion, the rate of cancer in children had increased more than 30 times the rate found in the decade (1975–1985) prior to the Chernobyl mishap (Astakhova et al., 1994). Stsjazhko et al. ('95) showed that by 1994, the rate had risen even higher.

Treatment of hypothyroidism or goiter. For the individual infant or child discovered clinically to have hypothyroidism, treatment should begin promptly with proper doses (10–14 $\mu\text{g}/\text{kg}/\text{day}$) of L-thyroxine (Fisher and Foley, '89). The hypothyroidism of patients with endemic hypothyroidism is no different from those with the hypothyroidism of sporadic CH, except possibly for the severity of neurological damage seen in the former. The dosage should elevate the patient's concentrations of circulating T4 to the upper half or upper third of the normal range and reduce serum TSH levels to the normal range (Sato et al., '88). Vanderpas et al. ('86) showed that iodized oil administered to young children with cretinism is capable of restoring the child to a biochemical euthyroid state within a few months of treatment. In view of the developmental changes occurring during infancy, it would be unwise to rely solely on iodine supplementation during this period when hypothyroidism is discovered.

Among older children and adults with hypothyroidism, prolonged use of iodides and thyroid hormone has been effective in reducing the size of goiters. Surgical treatment is often justified for large goiters that produce obstructive symptoms. Although these treatments are effective, surgery may not be a viable public health option when large portions of the population are affected and the affected communities do not have an adequate medical or public infrastructure (Delange, '94).

Prophylaxis in the event of nuclear hazards and radioactive iodine fallout is to increase the iodine intake of the population by administering potassium iodide shortly after a disaster or in preparation for imminent disaster by administering thyroxine and iodide over time in order to reduce the excessive uptake of ^{131}I by the thyroid gland (Ermans, '93).

ENDEMIC IODINE-DEFICIENT COMMUNITY

Areas can become deficient in iodine from the effects of heavy rain on steep mountain slopes and from floods caused by melting snow and rain. Areas involved in glaciation, such as the upper midwestern areas of the United States, also can be leached of iodine. Crops

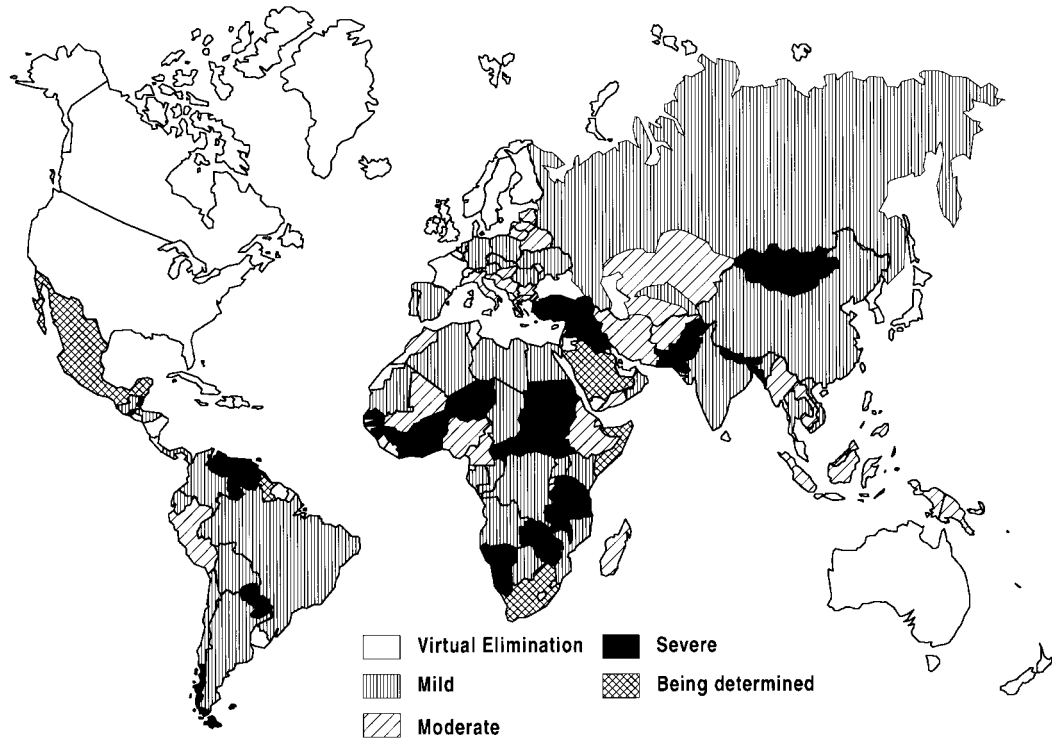


Fig. 6. Worldwide distribution of iodine deficiency disorders. Based on total goiter prevalence in school-age children. Data from the CIDDS database, ICCIDD, updated January 1995.

grown on iodine-deficient soils are iodine-deficient as well. As a result, animal and human populations totally dependent on such crops also will become iodine deficient. Such iodine-deficient soil accounts for the severe iodine deficiency seen throughout Asia among people living within a system of subsistence agriculture. The content of iodine in plants grown in iodine-deficient soil may be as low as 10 µg/kg dry weight, compared with an average of 1 mg/kg for plants grown in iodine-sufficient soils. The concentration of iodine in water in areas where goiter and IDD are endemic is <2 µg/l, whereas the concentration in nongoiter areas is 9.0 µg/l (Hetzel and Maberly, '86).

Geographical distribution and epidemiology

A 1995 UNICEF report estimated that 1.6 billion people (~30% of the world population) are at risk of IDD, nearly 900 million have IDD, >5 million have cretinism, and several million more suffer from mental and neurological defects (UNICEF, '95a). Less-developed countries were most affected. In these areas, the population grows rapidly, making it difficult to keep preventive measures abreast of the need. In some countries, mountainous terrain and jungles make it difficult successfully to implement iodine prophylaxis. IDD occurs in all parts of the world, hilly regions as well as lowlands (Fig. 6).

In Africa, the areas most severely affected by iodine deficiency had been in the Central African Republic, Zambia, Zimbabwe, Tanzania, and Namibia (WHO/

UNICEF/ICCIDD, '93). These areas had a goiter prevalence of up to 70–80% and a high rate of cretinism. In Asia, a goiter prevalence of 70–80% was found in areas of the countries along the Himalayan Mountains: Pakistan, India, Nepal, and Bhutan. In Indonesia and China, goiter also has had a high prevalence (Lamberg, '91).

Europe had been thought to be free of IDD, but a survey in the late 1980s under the sponsorship of the European Thyroid Association found that with the exception of the Scandinavian countries, Austria, and Switzerland, most of European nations, or at least certain areas of these countries, were still affected (Gutekunst and Scriba, '89). A recent study showed that iodine deficiency is presently under control in only five European countries: Austria, Finland, Norway, Sweden, and Switzerland. Iodine deficiency is marginal or present mainly in pockets in Belgium, the former Czechoslovakia (now Slovakia and the Czech Republic), Denmark, France, Hungary, Ireland, Portugal, and the United Kingdom. In Croatia, the Netherlands, and some Eastern European countries, IDD has recurred after a period of resolution. Moderate to severe iodine deficiency persists in all other European countries (Bulgaria, Commonwealth of Independent States (CIS), Germany, Greece, Italy, Poland, Romania, Spain, and Turkey). In some countries such as Bulgaria and Romania, the prevalence of goiter among schoolchildren varies from 16% to 81%, and levels of urinary iodine were found to be equivalent to that found in the most

severely affected areas in the center of the African continent (Delange et al., '93; Delange, '94). Studies had shown rates of goiter ranging from 30–80% in certain parts of the Mediterranean countries and in southern Germany and the presence of cretinism in certain communities in Spain (Sanchez-Franco et al., '87) and Sicily (Trimarchi et al., '90).

Since the 1991 breakup of the Soviet Union, problems associated with iodine deficiency appear to be getting worse. There has been no legislation aimed at reducing iodine deficiency including programs to iodize salt. Some countries of the former USSR have severe iodine-deficiency problems, with goiter rates from 10–60%. (WHO/UNICEF/ICCIDD, '93). In a 1995 study in Georgia, 73.8% of the infants born in Gori and 53.7% in Tbilisi were found to have TSH levels >5 mU/l (Cruse, pers. comm.).

PREVENTION OF IDD

The most logical single intervention for a community or population is the introduction of iodine prophylaxis. The most efficient method of delivering iodine to a population is by systematic iodine supplementation of food or water supplies. For almost 50 years iodized salt has been the most effective method of providing extra iodine in the diet (Stanbury et al., '74; Demaeyer et al., '79). The first successful large-scale intervention with iodized salt was carried out in the United States to prevent endemic goiter (Marine and Kimball, '22). Other population-based interventions with iodized salt were carried out in Switzerland, India, Mexico, Ecuador, Guatemala, Greece, Argentina, Austria, and Finland, resulting in reductions of both endemic goiter and endemic cretinism.

There has been a major achievement in the reduction of IDD in countries that have implemented universal salt iodization; however, in some countries, the iodine intake of some people has been unnecessarily high. This has been associated with hyperthyroidism in some instances (Todd et al., '95; Bourdoux et al., '96). A study conducted by the WHO, UNICEF, and ICCIDD in seven African countries showed that iodine-induced hyperthyroidism (IIH) may occur, primarily in older people, when severely iodine-deficient populations increase their iodine intake, even when the total amount is within the usually accepted range of 100–200 µg/day. On a population basis, IIH represents a transient increase in the incidence of hyperthyroidism, and it will disappear over time with the correction of the population's iodine deficiency. The occurrence of IIH is more likely in people with pre-existing autonomous nodular goiters, and the risk is directly proportional to the number of people with nodular goiters in the population. Individuals with latent Graves disease may be at risk. Although IIH has occurred when iodine intake was in the acceptable range, the risk of IIH was greatest following ingestion of larger amounts (WHO/Nutrition, '97).

TABLE 2. Recommended allowances for iodine¹

Age and status	Recommended daily allowance
Pregnant and lactating women	200 µg
Adults	150 µg
School children 7–12 years of age	100 µg
Children 2–6 years of age	90 µg
Infants <1 year of age	50 µg

¹WHO/Nutrition, '96.

Because of these findings, new recommendations for iodine levels in salt and for monitoring were developed. For nonpregnant, nonlactating adults, the daily intake of iodine should be 150 µg (Table 2). This should be reflected in population median urinary iodine excretion varying from 100–200 µg/l. To achieve this intake of iodine through fortification of salt, 20–40 mg iodine (or 34–66 mg potassium iodate) should be added per kg of salt, a ratio of 1:50,000 to 1:25,000. These recommendations are based on an average salt intake of 5 gm/day and are only slightly lower than previous recommendations (Demaeyer et al., '79; Dunn and Van der Haar, '90).

Further, it was recommended that the iodine excretion in the population be monitored as well as the iodine content of the salt supply. If the median urinary iodine excretion from a representative sample of the population at risk is not within the recommended range, salt iodization levels and factors affecting its production and use should be reassessed (Clugston et al., '96; WHO/UNICEF/ICCIDD, '97).

Global efforts at prevention

In 1990, the World Summit for Children was held at the headquarters of the United Nations in New York City. At this meeting, 71 heads of state and 80 other officials from 150 governments attended and adopted goals for children. Because of the attention given to iodine deficiency's global impact on brain development, the elimination of all new cases of iodine deficiency by the year 2000 became one of the 27 goals adopted by the governments (UN Children's Fund, '90). The work of the preceding few years had identified the enormous impact of iodine deficiency beyond cretinism and had set the stage for the coalition of science, public health, and political leaders to address the worldwide issues of iodine deficiency. At this and subsequent meetings, these leaders recommended universal iodization of salt as the best method of prevention iodine deficiency.

In response to this recommendation, most of the countries with IDD problems agreed to try to iodize 90% of all edible salt by the end of 1995. In 1994, of the 94 countries affected by iodine deficiency, 58 (with 60% of the developing world's children) had achieved this goal, or were on track toward achieving it. Another 32 countries could achieve the goal with extra effort. Achieving the goal appeared to be unlikely in four countries (UNICEF, '95a) (Table 3). In the Middle East and North Africa, 10 of 17 countries were on track to

TABLE 3. Countries with severe or moderate iodine deficiency,¹ and salt iodization status, 1995

Country	TGR ³	Salt iodization status ²
Sub-Saharan Africa		
Central African Republic	63.1	20
Zimbabwe	52.3	
Zambia	50.5	50
Tanzania	37.0	32
Namibia	34.5	0
Mali	28.5	0
Cameroon	26.3	100
Madagascar	24.1	
Benin	23.7	0
Togo	22.1	0
North Africa and Eastern Mediterranean		
Syria	73	18
Pakistan	32.4	11
Yemen	32	0
Iran	30	70
Morocco	20 ⁴	0
Sudan	20 ⁴	
Afghanistan	20 ⁴	
Southeast Asia		
Nepal	44.2	18
Bhutan	25.0	100
India	9.0	65
Western Pacific		
Fiji	47 ⁴	
New Guinea	30 ⁴	
Laos	25	
Vietnam	20	24
Malaysia	20	
Americas		
Paraguay	48.7	48
Peru	35.8	90
El Salvador	24.6	92
Bolivia	20.9	90
Europe		
Albania	40.8	
Turkey	35.6	

¹Prevalence of goiters in 1990 (WHO/UNICEF/ICCIDD, '93).
²Percent of salt iodized, many include salt that is exported (UNICEF, '95b).

³"Total Goiter Rate," schoollage population.

⁴Estimated values.

have all iodized salt; in Asia this was the case in 7 out of 20 countries (including Bangladesh and India). With the possible exception of Haiti, all Central and South American nations were expected to meet the 1995 goal (although acceleration of effort was required in Peru, Columbia, and Paraguay). The two South American countries with the worst history of IDD (Bolivia and Ecuador) were very close to eliminating the problem. Salt iodization was being achieved in 28 of the 39 affected nations in sub-Saharan Africa. (UNICEF, '95b).

The exception to this progress is seen in countries of the former Soviet Union because of the discontinuation of previously established systems designed to furnish iodized salt to the populations (Table 4). Data from the ICCIDD found: IDD to be marginal and mild in the Czech Republic, Hungary, and the Baltic states; IDD to

be moderate (with areas of severe and/or mild IDD) in Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Romania, Turkey, Turkmenistan, Uzbekistan, Croatia, Bosnia, Belarus, Bulgaria, Poland, and Ukraine, and severe or critical IDD in Albania and Tajikistan. However, IDD is virtually eliminated in Slovakia. Information was insufficient from Moldova, Macedonia, and Yugoslavia to assess the status of IDD. Effective programs of salt iodization have been put in place in Czech Republic, Slovakia, Hungary, and recently in Poland. There has been no program begun in Albania, Armenia, Azerbaijan, Moldova, Tajikistan, Uzbekistan, Belarus, Latvia, Lithuania, Russia, or Ukraine. Other countries have legislation in place or pending, by no enforcement (Gerasimov, '97).

Assessment of community iodine and IDD status

It is important to assess a community's iodine nutritional status in relation to public health programs of iodine supplementation. This assessment should be carried out both on the individuals living in a community and on the community's environment itself (Hetzel and Maberly, '86).

In 1994, WHO, UNICEF, and ICCIDD established criteria for monitoring progress toward eliminating IDD. These included levels of salt iodization, urinary iodine, thyroid size, and neonatal TSH (Table 5) (Pandav, '96).

Sensitive TSH assays (capable of low limits of analytic detection), when applied to whole blood collected on filter paper, can be a valuable screen for individuals with sporadic CH and also a screen for populations with iodine deficiency. The TSH analysis for these purposes requires a wide detection range to detect individuals with hypothyroidism in whom a high value will be found, but also for identifying populations and communities at risk, which will require the more sensitive test capable of discriminating among low values. Using the proportion of newborns with blood TSH levels >5 mu/l as a basis for classifying the severity of IDD in populations, WHO has defined mild IDD as 3–19.9%, moderate as 20–39.9%, and severe as >40%. In China and Indonesia, mild to moderate elevations of TSH were found in the newborns tested (Nordenberg et al., '94). Studies in the Philippines, Malaysia, Kyrgyzstan, and Pakistan recorded values ranging from 32% in Manila, Philippines, to 80% in Lahore, Pakistan (Sullivan et al., '97) (Fig. 7).

Supplying iodine to remote populations

When distribution of food or water is not uniform or household salt is not available, prophylaxis and therapy can be achieved by administering large quantities of iodine in the form of slowly absorbable iodized oil given intramuscularly or orally. This method is inexpensive and can be administered by local health units or special purpose teams. The method is most appropriate for use in isolated areas and is most effective when the entire population 45 years of age or younger is given the oil. It

TABLE 4. Status of IDD and iodization of salt in countries of the former Soviet Union (Central and Eastern Europe, Commonwealth of Independent States, and Baltic States)¹

Country	Goiter (%)	Median urine iodine (mcg/dL)	Iodization of salt	Comments
Albania	41		No	Localized evidence of cretinism
Armenia	10		Partial	Mild to moderate IDD
Azerbaijan	20		No	
Belarus	10–30	70–90	Partial	Regional survey in Minsk and a rural area
Bosnia/Herzegovina		49–113	Yes	Regional surveys, mild to severe IDD in mountains and near rivers
Bulgaria	29	20–60	Yes	Mild to severe endemic regions for IDD
Croatia	13–35	74	Yes	National survey, 30% salt iodized at 25 ppm
Czech Republic	low prevalence	85	Yes	Mild IDD
Estonia		65	No	Mild to moderate IDD
Georgia	20		No	65% of newborns had TSH >5 mU/L
Hungary	1.5–7	52–115	Partial	Marginal deficiency
Kazakhstan	63–92	32–70	No	Extensive evidence of IDD, sporadic cretinism
Kyrgyz Republic	38–49	30	No	60% of newborns and TSH >5 mU/L
Latvia	N/A	98	No	Mild IDD
Lithuania	N/A	75	No	Mild IDD
Macedonia	N/A	N/A	Yes	Mild ?
Poland	10–43	49–93	Yes	Mild to moderate IDD, elevated newborn TSH levels
Russia	12–60	23–80	Partial	Mild to severe
Slovakia	very low		Yes	Mild or no IDD, effective iodization program
Tajikistan	20–90	<10 in some areas	No	Critical–5% of the population in the Vanch Valley in Patnir classified as cretins
Turkemenistan	23–64	37–72	No	Mild to moderate
Ukraine	10		No	Mild and moderate IDD, more severe in Carpathian mountains
Uzbekistan	8–30	35	No	Mild to severe IDD

¹Adapted from communication prepared by G. Gerasimov for the Gore/Chernomyrdin Health Committee meeting, February 1997, Washington, DC. (Gerasimov, '97).

TABLE 5. Criteria for monitoring progress toward eliminating¹ IDD as a public health problem (WHO/Nutrition 1994)²

Indicator	Goal
1. Salt iodization	
Percentage of households consuming effectively iodized salt	>90%
2. Urinary iodine	
Percentage of population with levels 100 µg/L	<50%
Percentage of population with levels <50 µg/L	<20%
3. Thyroid size	
In school children 6–12 years of age	
Percentage with enlarged thyroid (indicated by population of ultrasound)	<5% ³
4. Neonatal TSH	
Percentage of neonates with levels >5 mU/L whole blood	<3%

¹For a country to be certified as “eliminated IDD,” the salt iodization criterion should be satisfied, if this is the main method of prevention. In addition, at least two of the remaining criteria should be fulfilled.

²Pandav ('96).

³In affected individuals from a community that was previously iodine deficient, but now with an adequate supply of iodine, the goiters may not rapidly regress. Thus the goiter rate in an iodine recently repleted community may be greater than the value given here (pers. comm., G.F. Maberly, '97).

is crucial that the iodine deficiency be corrected before or early in gestation. Correction of the maternal, fetal, and neonatal hypothyroidism can occur at any time during pregnancy, including the last trimester. The duration of postnatal correction of thyroid function depends on the dose of iodized oil administered to the mother, e.g., ~2 years for 1 ml (480 mg) iodized oil administered orally or IM, (Table 6), but only 6 months for half this dose. The potential benefits greatly outweigh the potential risks in areas of moderate and severe prevalence of iodine-deficiency disorders, where iodized salt is not available (Delange, '96).

Delange ('94) also points out that the mild to moderate IDD seen in Europe will require additional effort by health officials to understand the reasons for the occurrence and ensure the supply of adequate iodine to pregnant women, fetuses, neonates, and young infants. Various methods of iodine supplementation have been used around the world. Iodine has been added to salt in many countries, tea in Tibet, water supplies in certain parts of Asia and Africa, fish paste in Thailand, and bread in Australia. However, adding iodine to salt is probably the best method because salt is universally consumed in a consistent amount throughout the year,

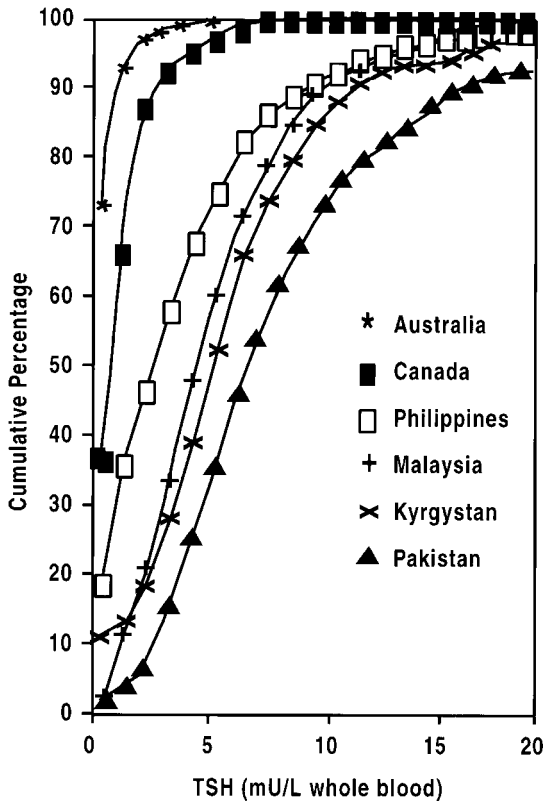


Fig. 7. Comparison of the distribution of newborn whole-blood TSH concentrations of infants from several countries. The cumulative percentage indicates the percentage of infants with TSH levels below a particular concentration. Canada and Australia are iodine-replete countries with 95% and 98% of infants having TSH <5 mU/l whole blood. Note the decrease in the percentage of infants with levels <5 mU/l in iodine deficient countries. (©J. Nutr., 127:57, 1997, American Institute of Nutrition with permission, Sullivan et al., '97.)

TABLE 6. Single-dosage of iodinated oil for an effective duration of 12 months of more to prevent IDD remote areas¹

Group to be treated	Oral	Intramuscular
Women of childbearing age		
Nonpregnant	400–960 mg	480 mg
Pregnant	300–480 mg	480 mg
Infants and children		
Birth to 1 year	100–300 mg	240 mg
1–5 years	300–480 mg	480 mg
6–15 years	400–960 mg	480 mg
Men		
16–45 years	400–960 mg	480 mg

¹Delange ('94).

the small cost is passed on to consumers, and the iodine in salt can be delivered in small quantities that produce no side effects or toxicity. Furthermore the cost would be only 2–4 cents per person per year (Maberly, '94).

Community development for prevention

Although salt iodization is technically straightforward, a successful program for a large population

requires policy support, adequate planning, the advocacy of salt manufacturers and traders, well-conceived educational and marketing programs, economic incentives, appropriate legislation and enforcement, and monitoring and evaluation systems for the iodine content of salt. Community leadership and cooperation are essential (Mannar and Dunn, '95).

Despite the low cost and uniform consumption associated with salt iodization, distributing salt with consistent content of adequate iodine may be logistically difficult in some circumstances. For remote, isolated populations without organized methods of food or water distribution, iodized oil taken either by injection or orally may be more useful. It is also reasonably inexpensive (~8 cents per person per year by mouth and 50 cents per year by injection), but its safety for women and fetuses during pregnancy is unclear. Any method of supplementation should be accompanied by adequate communication strategies to reinforce the messages so that the population understands the problem and the prevention objectives. Prevention should be accompanied by surveillance methods that can accurately assess micronutrient malnutrition IDD in affected countries worldwide. Data now available are for the most part outdated and collected from small selected studies in certain areas. More sensitive sonographic or biochemical tests have shown that, in some circumstances, clinical methods have greatly underestimated the extent and severity of the problem. Countries must invest the resources necessary to conduct surveys, process samples, and interpret and act upon the results. Better surveillance data on the severity and impact of the "milder" forms of iodine deficiencies will help to fully understand the extent of the problem. The elimination of iodine deficiency should be considered part of a nation's total public health efforts. Infrastructure and economic development, along with effective social marketing to change consumption patterns, will lead to more effective interventions. It is well to remember that iodine is only one of several micronutrient deficiencies that may occur simultaneously in a community (Maberly, '94; Maberly et al., '94).

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