The Disorders Induced by Iodine Deficiency

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ABSTRACT

This paper reviews present knowledge on the etiology, pathophysiology, complications, prevention, and therapy of the disorders induced by iodine deficiency. The recommended dietary allowances of iodine are 100 μg/day for adults and adolescents, 60–100 μg/day for children aged 1 to 10 years, and 35–40 μg/day in infants aged less than 1 year. When the physiological requirements of iodine are not met in a given population, a series of functional and developmental abnormalities occur including thyroid function abnormalities and, when iodine deficiency is severe, endemic goiter and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death, and infant mortality. These complications, which constitute a hindrance to the development of the affected populations, are grouped under the general heading of iodine deficiency disorders (IDD). At least one billion people are at risk of IDD. Iodine deficiency, therefore, constitutes one of the most common preventable causes of mental deficiency in the world today. Most of the affected populations live in montainous areas in preindustrialized countries, but 50 to 100 million people are still at risk in Europe. The most important target groups to the effects of iodine deficiency from a public health point of view are pregnant mothers, fetuses, neonates, and young infants because the main complication of IDD, i.e., brain damage resulting in irreversible mental retardation, is the consequence of thyroid failure occurring during pregnancy, fetal, and early postnatal life. The main cause of endemic goiter and cretinism is an insufficient dietary supply of iodine. The additional role of naturally occurring goitrogens has been documented in the case of certain foods (milk, cassava, millet, nuts) and bacterial and chemical water pollutants. The mechanism by which the thyroid gland adapts to an insufficient iodine supply is to increase the trapping of iodide as well as the subsequent steps of the intrathyroidal metabolism of iodide leading to preferential synthesis and secretion of triiodothyronine (T3). They are triggered and maintained by increased secretion of TSH, which is ultimately responsible for the development of goiter. The acceleration of the main steps of iodine kinetics and the degree of hyperstimulation by TSH are much more marked in the pediatric age groups, including neonates, than in adults, and the development of goiter appears as an unfavorable side effect in the process of adaptation to iodine deficiency during growth. The most serious complication of iodine deficiency is endemic cretinism, a syndrome characterized by irreversible mental retardation together with either a predominant neurological syndrome or predominant hypothyroidism, or a combination of both syndromes. The prophylactic action of iodine on the incidence of both types of cretinism demonstrates the fundamental etiological role of iodine deficiency. The possible additional roles of thyroid growth-blocking immunoglobulins and of selenium deficiency have been suggested. The pathogenetic roles of maternal and fetal hypothyroidism or a combination of both as well as of hypothyroidism present during the postnatal period are clearly established, but the relative importance of the three mechanisms in the pathogenesis of the various clinical manifestations of endemic cretinism is not entirely clearly established. A particularly important issue established both in severe and moderate conditions of iodine deficiency is that obvious neurointellectual deficits due to the deficiency are also frequently observed in individuals who do not present any of the other signs of endemic cretinism. The status of iodine nutrition was recently reevaluated in all European countries, including those in the Eastern part of the continent. Iodine deficiency is presently under control in only 5 countries (Austria, Finland, Norway, Sweden, and Switzerland). All other countries are still affected to varying degrees, especially in the southern and central parts of the continent. The public health consequences of iodine deficiency in Europe are an elevated thyroidal uptake of radiiodine that aggravates the risk of thyroid cancer in case of a nuclear accident, the occasional presence of neurointellectual deficits in schoolchildren, elevated
frequencies of transient primary hypothyroidism and of transient hyperthyrotropinemia in young infants. Neonatal screening for congenital hypothyroidism using serum TSH as primary screening test appears as a particularly sensitive index of the effects of iodine deficiency at a population level and as a monitoring tool in the evaluation of the effects of iodine prophylaxis. Although theoretically entirely preventable, IDD still prevail in the world because of various socioeconomical, cultural, and political limitations to adequate programs of iodine supplementation, especially in Europe. Prevention of iodine deficiency in Western countries is most efficiently achieved by programs of salt iodization at the level of one part of iodide to 10,000–50,000 parts salt, depending on the degree of the deficiency and on salt intake. Iodized salt should be made available not only for household salt but also in industrial food production including cheese and bread as well as for animal consumption. As a matter of fact, milk appears as the main source of iodine in many industrialized countries. In preindustrialized countries where food fortification with iodine is impossible to organize, prophylaxis and therapy of IDD can be achieved extremely efficiently by the administration of large quantities of iodine (20–960 mg) in the form of slowly resorbable iodized oil administered by intramuscular injections or orally. This approach not only corrected thyroid function on a long-term basis with progressive disappearance of goiter but also prevented the occurrence of endemic cretinism and endemic mental retardation.

INTRODUCTION

IODINE IS A TRACE ELEMENT present in the human body in minute amounts (15–20 mg, i.e., 0.02 × 10^-3% of body weight). Iodine is an essential substrate for synthesis of thyroid hormones. Thyroxine is approximately 60% iodine by weight and the daily requirement of iodine is at least equal to the amount of hormonal iodine degraded and unrecovered daily by the thyroid gland. In adolescents and adults, this amount is 50–100 μg/day. Consequently, the classical recommended dietary allowance (167) of iodine is 100 μg/day for adolescents and adults (150 μg/day in pregnant and lactating women). It is 60–100 μg/day for children aged 1–10 years, 40 μg/day for infants aged 6–12 months, and 35 μg/day for infants 6 months of age or younger, which represents about 8 μg/kg/day, 5 μg/dL/milk and 7 μg/100 kcal. However, a reevaluation of the iodine requirements in young infants based on iodine balance studies showed that, at least in conditions of marginally low iodine intake as observed in Europe, the recommended dietary allowance should be increased to 90 μg for infants aged less than 1 year (47).

When the physiological requirements of iodine are not met in a given population, a series of functional and developmental abnormalities occur (Table 1), including thyroid function abnormalities and, when iodine deficiency is severe, endemic goiter and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death, and infant mortality. These complications, which constitute a hindrance to the development of the affected population, are grouped under the general heading of iodine deficiency disorders (IDD) (112, 113).

Broad geographic areas exist in which the population daily intake of iodine is below the recommended dietary allowance and in which the population is affected by IDD (116, 182). These areas usually are mountainous because the soils lowest in iodine are those that were covered longest by the quaternary glaciers. When these glaciers melted, most of the iodine leached out of the ground beneath (124). The most important goitrous areas in the world today include the Himalayas and the Andes. Iodine deficiency also occurs in lowlands far from the oceans such as the central part of Africa or, to a lesser extent, of Europe.

The data available in 1987 (116), probably underestimated, indicated that at least 800 million people were at high risk of developing IDD, including approximately 190 million with goiter and 3.2 million with endemic cretinism. Recent figures from Europe should probably increase this number by another 50–100 million (65, 68, 105, 168). Iodine deficiency disorders therefore constitute a major public health issue and constitute one of the most common preventable cause of mental deficiency in the world today (113). Although theoretically entirely preventable, these disorders still prevail because of various socioeconomical, cultural, and political limitations to adequate programs of iodine supplementation (188).

**Table 1. The Spectrum of Iodine Deficiency Disorders (IDD)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>Abortions</td>
</tr>
<tr>
<td></td>
<td>Stillbirths</td>
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<tr>
<td></td>
<td>Increased perinatal and infant mortality</td>
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<tr>
<td></td>
<td>Endemic cretinism</td>
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<tr>
<td></td>
<td>Neurological</td>
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<td></td>
<td>Mental deficiency</td>
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<td></td>
<td>Deafmutism</td>
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<td></td>
<td>Spastic diplegia</td>
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<tr>
<td></td>
<td>Squint</td>
</tr>
<tr>
<td></td>
<td>Myxedematous</td>
</tr>
<tr>
<td></td>
<td>Mental deficiency</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Dwarfism</td>
</tr>
<tr>
<td>Neonate</td>
<td>Goiter</td>
</tr>
<tr>
<td>Infant–child</td>
<td>Overt or subclinical hypothyroidism</td>
</tr>
<tr>
<td>Adolescent</td>
<td>Goiter</td>
</tr>
<tr>
<td></td>
<td>Juvenile hypothyroidism</td>
</tr>
<tr>
<td>Adult</td>
<td>Impaired mental and physical development</td>
</tr>
<tr>
<td></td>
<td>Goiter and its complications</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Endemic mental retardation</td>
</tr>
<tr>
<td></td>
<td>Decreased fertility rate</td>
</tr>
</tbody>
</table>

*Adapted from Hetzel (112, 113).
This paper reviews present knowledge on the disorders induced by iodine deficiency. As indicated in Table 2, three different degrees of severity of IDD have been considered. Although the basic mechanisms of adaptation to iodine deficiency are similar in the three degrees, we will consider separately the problem of severe IDD complicated by cretinism as seen typically in remote areas in preindustrialized countries and mild or moderate IDD as seen typically in Europe. In the three degrees of severity of IDD, special attention will be devoted to the prenatal period and the pediatric age groups as they constitute the most important target groups regarding the main complication of iodine deficiency, i.e., brain damage and mental retardation (71, 114). Extensive review papers with exhaustive bibliographies are available on endemic goiter and the other disorders induced by iodine deficiency, including their pediatric aspects (16, 39, 40, 42, 45, 53, 67, 71, 79, 113, 116, 143, 180–183).

### SEVERE IODINE DEFICIENCY DISORDERS: ENDEMIC GOITER AND CRETINISM

#### Epidemiology

The following definitions were proposed by the Pan American Health Organization (PAHO) for public health studies conducted in the field (62):

Goiter. A thyroid gland with lateral lobes that have a volume greater than the terminal phalanges of the thumbs of the person examined is considered goitrous. In these conditions the thyroid is enlarged by a factor of 4–5.

Type of goiter. The following stages classify goiter according to the size of the thyroid gland:

- **Stage 0:** no goiter.
- **Stage Ia:** goiter detectable only by palpation and not visible when the neck is fully extended.
- **Stage Ib:** goiter palpable and visible only when the neck is fully extended; this stage also includes nodular glands, even if not goitrous.
- **Stage II:** goiter visible with the neck in normal position; palpation is not needed for diagnosis.

- **Stage III:** very large goiter that can be recognized at a considerable distance (Fig. 1).

The total goiter rate is the prevalences of stages I, II, and III; the visible goiter rate is the prevalence of stages II and III.

This classification can be simplified into stages 0, no goiter; I, palpable but not visible goiter, and II, visible goiter when the neck is in a normal position (WHO/UNICEF/ICCIDD consultation on IDD indicators, unpublished).

These clinical classifications are appropriate for field surveys in remote areas where no other methods are available. However,

![FIG. 1. Stage III nodular goiter in Nepal.](image-url)
the availability and the use of transportable ultrasonographic equipment in field studies have shown that in such studies the clinical assessment of thyroid size is imprecise for small goiters, especially in children (104). In these conditions, the distinction between absence of goiter (stage 0) and the presence of small goiter (stage I) is difficult and, consequently, the overall prevalence of goiter can be incorrect. Therefore, the frequency distribution of thyroid volume measured by ultrasonography is highly recommended (106), especially in endemic areas where the visible goiter rate is low.

**Endemic goiter.** According to PAHO (62), an area is arbitrarily defined as endemic with respect to goiter if more than 10% of the children aged 6 to 12 years are found to be goitrous. The figure 10% was chosen because a higher prevalence usually implies an environmental factor, while a prevalence of several percent is common even when all known environmental factors are controlled.

A WHO/UNICEF/ICCIDD consultation on IDD indicators recently proposed to decrease the threshold of prevalence of goiter from 10 to 5% (unpublished).

In epidemiologic surveys, the most rigorous methods for evaluating the prevalence of goiter consists of examination of the entire population of a likely area. This is occasionally difficult to organize, especially in urban areas. Many surveys are limited, therefore, to particular age groups, most typically to children in school (187). The prevalence of goiter is critically influenced by age and sex with a maximal frequency in females during puberty and child bearing age (Fig. 2).

The most serious areas of endemic goiter and cretinism are located in remote areas with a self-subsistence economy system in the Himalayas and the Andes and in the Central part of the African continent. An accurate description of the status of iodine nutrition and goiter in Africa, Latin America, Asia, Oceania, and Europe is presently available (68, 113, 116, 182) as a result of the combined efforts of national authorities in all countries in the world, the International Council for Control of Iodine Deficiency Disorders (ICCIDD), the United Nations Children’s Fund (UNICEF), and the World Health Organization (WHO).

**Etiology**

An insufficient dietary supply of iodine is the main cause of endemic goiter and cretinism. Its role has been demonstrated by numerous epidemiological, clinical, and experimental data reported in details elsewhere (7, 53, 67, 113).

Measurement of iodine in food is technically difficult and tedious (123). Adults are in equilibrium with their iodine environment and the fecal excretion of iodine is usually considered as negligible (137). Therefore, most estimates of the dietary supply of iodine are based on the measurements of the excretion of iodine in urines. Complete 24-h collection of urines is often difficult to achieve in field investigations. An alternative procedure is the measurement of the ratio between the concentrations of iodine and creatinine in casual urine samples (119) or even just the concentration of iodine, provided that the observation covers at least 50 to 100 randomly selected urine samples in one given population sample (11).

Goitrogenic factors in the diet or environment other than iodine deficiency can play a role in the etiology of IDD. The role of these substances had to be considered as endemic goiter has been found in regions with no iodine deficiency (30, 36, 154) and, conversely, as endemic goiter can be absent in areas with severe iodine deficiency (28, 48, 170). The role of these goitrogenic factors has been extensively reviewed elsewhere (53, 67, 95, 129, 162, 198). Natural goitrogens were first found in vegetables of the genus *Brassica* (the Cruciferae family), which possess goitrogenic properties in animals (162). Their antithyroid action is related to the presence of thioglicosides, which, after digestion, release thiocyanate and isothiocyanate (87, 99, 129). Another important group of naturally goitrogenic is the cyanogluicosides, which have been found in several staples (cassava, maize, bamboo shoots, sweet potatoes, lima beans) (59, 87, 198). After ingestion, these glucosides release cyanide, which is detoxified by conversion to thiocyanate, a powerful goitrogenic agent that actively acts by inhibiting thyroid iodide transport and, at higher doses, competes with iodide in the organification process (86, 206, 207). Cassava (manioc in French, Yuca in Spanish), is one of the basic foodstuffs in tropical areas. Its role in the etiology of endemic goiter, in association with iodine deficiency, has been clearly demonstrated in Africa (10, 43, 49, 59, 86) and confirmed in Malaysia (136). The determining factor involved in the goitrogenic action of cassava is the balance between the dietary supplies of iodine and thiocyanate (59). Goiter develops when the urinary iodine/thiocyanate ratio, used as index of this balance, decreases below a critical threshold of about 3 μg iodine per mg thiocyanate. This can occur when thiocyanate is elevated in the presence of overt

![FIG. 2. Changes of the prevalence of goiter as a function of age and sex in severe endemic goiter (Idjwi Island, Zaire). From Delange and Ermans (67), with permission.](image)
iodine deficiency or even in the presence of an almost normal iodine supply when thiocyanate overload is excessive (56).

Other aspects of environmental goitrogenesis are reviewed and discussed in depth in the classical textbook of Gaitan (95), which contains an exhaustive bibliography on the topic: in addition to milk and cassava, other foodstuffs are involved in the etiology of endemic goiter. The role of millet was demonstrated in Sudan. The goitrogens appear to be C-glycosylflavones and thiocyanate. The nut of Araucaria (Pinon) has been suspected to have a role in the pathogenesis of endemic goiter in an Indian reservation in Chile. The role of a palm-tree fruit was suspected in Brazil. The goitrogen involved is a potent inhibitor of thyroid peroxidase. An excess intake of iodine, arbitrarily defined as 2 mg or more per day, inhibits the proteolysis and release of thyroid hormones and eventually produces "iodide goiter." The endemic coast goiter described in Japan and China is caused not only by the high quantity of iodine contained in seaweeds but also by phloroglucinol and other polyhydroxphenols contained in large quantities in the seaweeds and which are potent antithyroid compounds.

Bacterial and chemical pollution of water supplies also play a role: lithium containing water in Venezuela, microorganisms containing water supplies in Greece and in Richmond County, Virginia. The classical studies of Gaitan and colleagues (95) in Colombia and Eastern Kentucky demonstrated the role of water pollutants (resorcinol, phalate ester derivatives, and disulfides) originating from shales and coals, humic substances, and gram-negative bacteria.

**Pathophysiology: Adaptation of thyroid function to iodine deficiency**

*In adults.* Endemic goiter is an adaptive disease that develops in response to an insufficient supply of dietary iodine. This classic concept was established in 1954 by Stanbury and colleagues (180) and has been confirmed since by an enormous amount of clinical and experimental observations (7, 53, 116, 143, 183).

When iodine intake is abnormally low, adequate secretion of thyroid hormones may still be achieved by marked modifications of thyroid activity. These adaptive processes include stimulation of the trapping mechanism as well as of the subsequent steps of the intrathyroidal metabolism of iodine, leading to preferential synthesis and secretion of triiodothyronine (T3). They are triggered and maintained by increased secretion of TSH.

Increased stimulation by TSH. Elevated serum TSH levels have been reported repeatedly but not systematically in humans with chronic iodine deficiency (22, 27, 50, 90, 110, 111, 153). Moreover, within a given area, striking and large variations in serum TSH levels are observed in adults independently of the presence or absence of goiter (27, 50, 153). Differences in the duration of elevated TSH levels or in thyroid responsiveness as well as other factors, including thyroid autoregulation independent of TSH, may determine whether goiter develops (17, 77, 82, 184). Experimental studies indicate that growth hormone, perhaps through IGF1, as an intermediate, induces thyroid growth. Human chorionic gonadotropin at high concentrations activates the cAMP cascade, and consequently proliferation, in FRTL-5 cells and human thyroid cells. Several growth factors have been shown to be mitogenic for thyrocytes: epidermal growth factor (EGF), fibroblast growth factor (FGF), and insulin like growth factor 1 (IGF1) (77). However, the role of these growth factors in the pathogenesis of endemic goiter is not demonstrated. Similarly, the possible role of thyroid autoimmunity in the goitrogenesis in endemic goiter remains largely unknown.

Increase in iodide trapping. The fundamental mechanism by which the thyroid gland adapts to an insufficient iodine supply is to increase the trapping of iodide. This results in the accumulation within the gland of a larger percentage of the ingested exogenous iodide and a more efficient reuse of iodide directly released by the thyroid or generated by the degradation of thyroid hormones (180, 183, 204). The increased iodide trapping is the result of both TSH-independent augmentation of membrane iodide trapping and TSH stimulation of the iodide pump (17, 77, 184).

Increased thyroidal uptake of 131I and reduction of urinary iodine excretion are the markers of a goiter endemia caused by iodine deficiency. A clearcut inverse relationship between both parameters was demonstrated in 1954 (180), has been confirmed in a large number of goiter endemias (7), and is further illustrated in Figure 3. This figure indicates that as soon as the iodine supply decreases below the physiological requirement of 100 μg iodine/day in adults, there is an increase in the thyroidal uptake of radioiodine, indicating an increase in the clearance rate of iodide by the thyroid.

In these conditions, in spite of a decrease in the serum concentration of iodide, the absolute uptake of iodide by the thyroid remains normal and the organic iodine content of the

![FIG. 3. The relationship between the daily urinary excretion of iodine and the prevalence of goiter, the hormonal iodine content of the thyroid (thyroid exchangeable organic iodine pool, determined by kinetic studies), and the 24-h thyroidal uptake of radioiodine. From Delange and Ermans (67), with permission.](attachment:image)
thyroid remains within the limits of normal (i.e., 10–20 mg) as long as the iodine intake remains above a threshold of about 50 μg/day. Below this critical level of iodine intake, in spite of a further increase of thyroid clearance, the absolute uptake of iodide diminishes and the iodine content of the thyroid decreases. Goiter, the visible consequence of iodine deficiency by public health standards starts to develop usually when the iodine intake is still lower.

Modifications of intrathyroid iodine metabolism and alterations of circulating thyroid hormones. Studies in the rat show that thyroid hyperplasia induced by iodine deficiency is associated with an altered pattern of tracer iodine distribution in the gland characterized by increased poorly iodinated compounds, moniodotyrosine (MIT) and triiodothyronine (T₃), and a decrease in diiodotyrosine (DIT) and thyroxine (T₄) (2, 82, 127, 183). These severely iodine-deficient animals have a low serum concentration of T₄ and a high serum concentration of T₃ (2). Similarly, the pattern of circulating thyroid hormones in clinically euthyroid adults in areas of severe iodine deficiency (Table 3) is characterized by low serum T₄, elevated TSH, and normal or supranormal T₃ (27, 50, 51, 111, 120, 153, 156). The mechanisms responsible for this pattern are unclear but may include thyroidal secretion of T₄ and T₃ in the proportion in which they exist within the gland (2, 82, 127), preferential secretion of T₃ (101) or increased peripheral conversion of T₄ to T₃. The shift to increased T₃ secretion and increased serum T₃/T₄ ratios play an important role in the adaptation to iodine deficiency, since T₃ possesses about four times the metabolic potency of T₄ but requires only 75% as much iodine for synthesis (101). Thyroidal uptake of radiiodine is elevated, the thyroid organic iodine exchangeable pool is low, and the markedly accelerated turnover rate of this pool is evidenced by an elevated apparent hormonal secretion rate and an elevated serum protein bound ¹³¹I.

In severe endemic goiter, there is an inverse relationship between serum T₄ and TSH but this correlation is not found for serum T₃, which is the most active thyroid hormone (82). This paradoxical finding is explained by the fact that the direct effect of T₄ on TSH suppression results from intrapituitary T₄ to T₃ conversion and the subsequent binding of T₃ to the nucleus of the thyrotropes; in other tissues, the largest part of intracellular T₃ originates from circulating T₃ (130, 131). These findings account for the observation in endemic goiter that normal serum T₃ levels enable a patient to maintain an overall euthyroid status, but pituitary stimulation persists as long as the serum T₄ level is depressed. In less severe goiter endemias, serum T₄ and T₃ levels are only slightly modified or even remain normal. In these conditions, basal TSH is slightly increased and the TSH response to intravenous injection of thyrotropin-releasing hormone is often exaggerated, indicating an increase in TSH pituitary reserves (145), a condition often reported as subclinical hypothyroidism (89).

Morphologic changes. Diffuse enlargement of the thyroid is found in severe endemic goiter only in young subjects. At this stage, parenchyma is abundant, follicular epithelium is high with papillary infolding, and colloid is rare. A later stage is the formation of small nodules that dissect the entire thyroid tissue by formation of nodules of very different size and consistency. At this time, histologically, the major part of the gland is occupied by extremely distended vesicles with a flattened

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**Table 3. Comparison of Epidemiological and Biochemical Data Exploring Thyroid Function**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Brussels Euthyroid adults</th>
<th>Zaire Euthyroid adults</th>
<th>Myxedematous cretins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily urinary excretion of iodine (μg/day)</td>
<td>51.2 ± 5.8 (38)</td>
<td>15.5 ± 1.3 (243)</td>
<td>—</td>
</tr>
<tr>
<td>Prevalence of goiter (%)</td>
<td>3</td>
<td>76.8</td>
<td>—</td>
</tr>
<tr>
<td>Serum concentration of T₄ (μg/dL)</td>
<td>8.1 ± 0.1 (125)</td>
<td>4.9 ± 0.2 (358)</td>
<td>0.5 ± 0.01 (120)</td>
</tr>
<tr>
<td>T₃ (ng/dL)</td>
<td>144 ± 3 (124)</td>
<td>166 ± 3 (299)</td>
<td>46 ± 3 (109)</td>
</tr>
<tr>
<td>TSH (μU/mL)</td>
<td>1.7 ± 1.1 (255)</td>
<td>18.6 ± 2.1 (365)</td>
<td>302 ± 20 (122)</td>
</tr>
<tr>
<td>Protein-bound ¹³¹I 24 h (% dose/mL)</td>
<td>0.06 ± 0.01 (27)</td>
<td>0.17 ± 0.02 (105)</td>
<td>1.09 ± 0.18 (19)</td>
</tr>
<tr>
<td>Thyroidal uptake of ¹³¹I 24 h (% dose)</td>
<td>46.4 ± 1.1 (255)</td>
<td>65.2 ± 0.9 (167)</td>
<td>28.3 ± 2.6 (6)</td>
</tr>
<tr>
<td>Thyroidal exchangeable organic iodine pool (mg)</td>
<td>15.8 ± 3.5 (12)</td>
<td>1.6 ± 0.2 (30)</td>
<td>0.01–0.1 (8)</td>
</tr>
<tr>
<td>“Apparent” hormonal secretion rate (%/day)</td>
<td>0.39 ± 0.04 (12)</td>
<td>1.92 ± 0.12 (24)</td>
<td>—</td>
</tr>
</tbody>
</table>

*In Brussels, Belgium and in the Idjwi Island and Ubangi endemic goiter areas, Zaire. Results given as mean ± SEM or range. (*) The number of patients is given in parentheses. The differences between the three groups are highly significant (p < 0.0001) for all variables. Adapted from Ermans et al. (84), Dumont et al. (76), Camus et al. (24), Delange et al. (52), Delange et al. (58).
epithelium filled with colloid. A few patches of thyroid follicles, on the contrary, show a typical pattern of stimulation (143, 183, 184).

In the pediatric age groups. Sequential development of the mechanisms of adaptation to iodine deficiency during growth. The metabolic pattern observed in adults in severe endemic goiter represents the final stage of an adjustment process, which is critically influenced by age: a study on the time course as a function of age from 3 to 22 years of the changes in thyroid function in goitrous and nongoitrous inhabitants of the Idjwi Island endemic goiter area in Zaire (39, 40) (Fig. 4) showed that thyroidal uptake of radioiodine reached its maximum value in the earliest years of life and then declined progressively until adulthood. Uptake was systematically higher in goitrous than in nongoitrous patients. The thyroid exchangeable hormonal iodine pool was about 0.5 mg iodine in young infants; it increased progressively with age but reached only 2.5 mg in adults, which is 4 to 10 times lower than in adults in nonendemic areas. Conversely, the renewal rate of intrathyroidal radioactive iodine (apparent secretion rate, K'4) decreased drastically with age.

This study demonstrates that the acceleration of the main steps of iodine kinetics is much more marked in childhood and adolescence than in adulthood and progressively decreases during growth. Similar studies conducted in the area of Idjwi Island with a similar degree of iodine deficiency but without goiter showed that in this area, (a) radioiodine uptake also was increased but to a lesser extent, (b) iodine stores in the thyroid were much lower, and (c) the plasma PBI was higher. These data suggest that goiter is by no means the optimal mechanism of adaptation to environmental goitrogens but constitutes a rather unfavorable side-effect of such a mechanism.

Age-related modifications of TSH regulation. By studying the time course as a function of age of the serum concentrations of TSH, T4, and T3 in clinically euthyroid patients in severe endemic goiter in the Ubangi area in Zaire (40), it was shown (Fig. 5) that, unexpectedly, the highest values of serum TSH were observed in the youngest infant in spite of the fact that they also had the highest serum T4 values. Consequently, for a given value of T4, the level of TSH was roughly twice as high in the 4 to 15 year age group as in the 16 to 20 year age group. These variations of the TSH/T4 ratio as a function of age are poorly understood: they could reflect the increase in the iodine stores within the thyroid as a function of age. They also could be explained by modifications with age of the turnover rate of T4 (138) and/or by modifications in thyroid gland sensitivity to TSH including progressive development of thyroid tissue autonomy (4).

Thyroid function in early life. One of the major achievements of recent years is the results obtained by pilot studies on systematic screening for congenital hypothyroidism in the newborn in iodine-deficient areas. The studies have shown that, in such areas, the alterations of thyroid function in neonates are much more frequent and severe than in adults.

The most extreme situation has been reported from Zaire (54, 58, 186) (Table 4 and Fig. 6) where thyroid failure in neonates results from the combined action of iodine deficiency and thiocyanate overload during fetal life. In this area (Fig. 6), cord serum TSH and T4 in unselected newborns showed an important variability between individuals and were frequently distinctly outside the normal range. Eleven percent of the newborns had both a cord serum TSH above 100 μU/ml and a cord serum T4

**FIG. 4.** Changes with age of the 6-h thyroidal uptake of radioiodine (U6), the thyroid exchangeable organic iodine pool (QG), and the apparent hormonal secretion rate by the thyroid (K'4) in goitrous (G+1) and nongoitrous (Go) inhabitants of the Idjwi Island endemic goiter area, Zaire. Values recorded as mean ± SEM. The number of patients is shown in parentheses. Adapted from Delange and Ermans (67), with permission.

**FIG. 5.** Changes with age of the serum concentrations of T4 and TSH in the Ubangi endemic goiter area, Zaire (○) and in Brussels (●). Values recorded as mean ± SEM. The number of patients is shown in parentheses. Adapted from Delange and Ermans (67), with permission.
TABLE 4. COMPARISON OF BIOCHEMICAL FINDINGS IN MOTHERS AT DELIVERY AND NEWBORNS a

<table>
<thead>
<tr>
<th>Variables</th>
<th>Brussels, Belgium</th>
<th>Ubangi area, Zaire</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mothers at delivery</td>
<td>Newborns (cord)</td>
</tr>
<tr>
<td>Urinary concentration of I (µg/day)</td>
<td>4.4 ± 0.3 (119)</td>
<td>—</td>
</tr>
<tr>
<td>SCN (mg/dL)</td>
<td>1.03 ± 0.05 (120)</td>
<td>—</td>
</tr>
<tr>
<td>Serum concentration of T₄ (µg/dL)</td>
<td>12.7 ± 0.3 (112)</td>
<td>11.4 ± 0.2 (204)</td>
</tr>
<tr>
<td>T3 (ng/dL)</td>
<td>182 ± 5 (109)</td>
<td>50 ± 1 (202)</td>
</tr>
<tr>
<td>TSH (µU/mL)</td>
<td>3.6 ± 0.2 (111)</td>
<td>8.2 ± 0.4 (201)</td>
</tr>
<tr>
<td>SCN (mg/dL)</td>
<td>0.35 ± 0.03 (111)</td>
<td>0.27 ± 0.01 (200)</td>
</tr>
</tbody>
</table>

a In Brussels, Belgium and in the Ubangi endemic goiter area, Zaire. Results are given as mean ± SEM. The number of patients is shown in parentheses. The differences for each variable between Brussels and Ubangi are highly significant (p < 0.0001). Modified from Delange et al. (58).

below 3 µg/dL, indicating severe congenital hypothyroidism according to the criteria used in western countries, where the incidence of the condition is only 0.025% (57). A similar frequency of biochemical hypothyroidism has been found in the same area in young infants (38), indicating that the situation found in neonates was not due to a nonspecific factor such as the stress of delivery. The picture of congenital hypothyroidism was only transient in some infants but remained unchanged in others (40). The abnormalities of neonatal thyroid function were prevented by correcting iodine deficiency in mothers before or during pregnancy (186, 191) (Fig. 6).

A similar prevalence of congenital hypothyroidism in severe endemic goiter has been reported from the Himalayas in Northern India, Nepal, and Bhutan (121). Alterations of thyroid function in neonates have been subsequently reported from other less severe endemic areas, even when thyroid function in adults was barely or even not modified (172). The alterations are characterized by a shift of the frequency distributions of neonatal TSH and T₄ toward elevated and low values, respectively.

Complications

In addition to the mechanical complications of goiter and the increased mortality rate due to thyroid cancer in endemic goiter, principally due to the late diagnosis of the condition in a population where thyroid enlargement and nodules are the rule (109, 169, 202), the main complication of endemic goiter is brain damage due to a lack of thyroid hormone at the cellular level during the critical period of brain development.

Endemic cretinism and endemic mental retardation. In severe endemic goiter, an abnormally high number of patients exhibit irreversible anomalies of intellectual and physical development. These anomalies are extremely polymorphous and have been grouped under the general heading of endemic cretinism. The prevalence of the disease may attain 5 to 15% of the population. It is by far the most serious complication of endemic goiter and represents a veritable scourge, both medically and socially (41, 45, 113, 158, 183).

The etiopathogenesis of endemic cretinism is only partly understood and information on its pathology is scanty (73, 122). For these reasons, the diagnosis of endemic cretinism is only descriptive and is made on epidemiological grounds. In 1986, a study group of the Pan American Health Organization (PAHO) formulated the following definition of endemic cretinism (62):

The condition of endemic cretinism is defined by three major features:

A. Epidemiology. It is associated with endemic goiter and severe iodine deficiency.

FIG. 6. Comparison of the frequency distributions of the serum concentrations of TSH and T₄ in cord blood in Brussels and in new borns in the Ubangi endemic goiter area in Zaire born to untreated mothers or to mothers treated with a single injection of iodized oil during pregnancy. The values within the interval mean ± 2 SD in Brussels are not given as individual symbols but as percentages of the total number of cases. The number of newborns is shown in parentheses. The dotted lines correspond to the values considered as suggestive (hypo?) or characteristic (hypo) of permanent sporadic congenital hypothyroidism in the neonatal thyroid screening program in Brussels. From Delange and Ermans (67), with permission.
B. **Clinical features.** These comprise mental deficiency, together with either:

1) A predominant neurological syndrome including defects of hearing and speech and characteristic disorders of stance and gait of varying degree; or

2) Predominant hypothyroidism and stunted growth.

Although in some regions, one of the two types may predominate, in other areas a mixture of the two syndromes will occur.

C. **Prevention.** In areas in which iodine deficiency has been adequately corrected, endemic cretinism has been prevented.

**Epidemiology, clinical features and laboratory data.** The clinical features of endemic cretinism summarized in the PAHO definition correspond to the two extreme types of endemic cretinism clearly defined from the pioneer work of McCarrison in 1908 (144) and repeatedly reported in subsequent epidemiological and clinical descriptions of endemic cretinism: the first type is marked by dominant neurological disorders (neurological cretinism) and the second by signs of severe thyroid insufficiency (myxedematous cretinism).

Figure 7 illustrates the picture of neurologic cretinism as seen in Nepal: the endemic cretins are extremely mentally retarded and most of them are reduced to a vegetative existence. Almost all are deaf mutes and are afflicted with the following neurological defects: (a) impaired voluntary motor activity, usually involving paresis or paralysis of pyramidal origin, chiefly in the lower limbs, with hypertonia, clonus, and plantar cutaneous reflexes in extension. Extrapyramidal signs are occasional, (b) spastic or ataxic gait. In the severest cases, walking or even standing is impossible, and (c) strabismus.

Subsequent detailed clinical studies in Ecuador (69, 70, 93) and China (12, 107, 108, 133, 174, 203) emphasized the impairment of the extrapyramidal tract in neurological endemic cretinism. In these areas, the pattern of neurological deficit included proximal spasticity and rigidity involving the lower extremities more than the upper, with increased knee jerks and adductor jerks. By contrast, increased reflexes or spasticity were usually absent or mild in the lower extremities with Babinski sign only in 20% of the cretins. According to DeLong (70), this clinical picture suggests dysfunction of the basal ganglia, especially putamen and globus pallidus, thus of the extrapyramidal tract, rather than dysfunction of the pyramidal tract with spastic diplegia. Unfortunately, recent accurate data on brain pathology in neurological cretinism are missing. Computerized tomographic scans of cretins from Ecuador demonstrated widespread atrophy including the cerebral cortex and subcortical structures and the brainstem, with corresponding enlargement of the basal cisterns, the lateral ventricles, and the sulci over the surface of the cerebral cortex (165).

The prevalence of goiter in neurological cretins is as high as the noncretin population of the area and they are clinically euthyroid. Thyroid function is usually normal (12, 23, 29, 171, 177) but can indicate subclinical hypothyroidism with elevated basal TSH or exaggerated TSH response to TRH (173, 209).

Figure 8 show the clinical aspects of the myxedematous type

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**FIG. 8.** Myxedematous endemic cretinism. Ubangi, Zaire. On the left a euthyroid 21-year-old man with a height of 162 cm. On the right, a 15-year-old female cretin with a height of 88 cm. Dwarfism. Severe myxedema and puffy features. No puberty. Immature nasoorbital configuration with flat and broad nose, hypoplastic mandible, dry and scaly skin, dry and brittle hair, prominent abdomen. Severe mental retardation. No deafmutism. Unpalpable thyroid gland. From Delange (46), with permission.
of endemic cretinism as the most typically seen in Zaire (5, 39, 52, 75, 76, 197). These cretins show less mental retardation than the neurological cretins; they are often capable of performing simple manual tasks. All exhibit major clinical symptoms of long-standing hypothyroidism: dwarfism, myxedema, dry skin, sparseness of hair and nails, retarded sexual development, and retarded maturation of body proportions and of nascobital configuration. Myxedematous cretins in Zaire occasionally exhibit neurological signs including spasticity of the lower limbs, jerky movements and Babinski sign, shifting gait, as observed in long-standing unrecognized sporadic congenital hypothyroidism (175).

The prevalence of goiter in the myxedematous cretins is much lower than in the noncretin population. Many of them have nonpalpable thyroid tissue although thyroid scintigrams show small residues of thyroid tissue located in normal position (39, 52), precluding thyroid dysgenesis (agenesis, ectopic thyroid) as the cause of hypothyroidism. The iodine pool of the thyroid is drastically reduced with a particularly fast turnover rate of iodine as indicated by elevated serum \( \text{PB}^{131}\text{I} \). The diagnosis of severe and long-standing hypothyroidism is further confirmed by a very important retardation in bone maturation and epiphyseal dysgenesis indicating hypothyroidism of perinatal onset, and by characteristic changes in the electrocardiogram (39).

The frequency distribution of the two extreme types of endemic cretinism markedly varies from one endemic to another. In most, the neurological type predominates while in others, especially in Zaire, myxedematous endemic cretinism is most frequently encountered (see pathogenesis).

Finally, it is widely agreed that between the two extreme types of cretinism, there are a number of mixed forms characterized by dominant neurological disorders or dominant hypothyroidism in the same individual (37, 118, 126, 133, 177, 203, 209). Some authors have suggested that deafness may be the only manifestation of cretinism in certain patients (118).

Table 5 summarizes the data available in the literature on the neuromotor and intellectual development in noncretinous individuals in areas with severe endemic goiter and cretinism. The same tests, optimally with no, or as little as possible, "cultural bias" were administered to two groups of noncretinous individuals living in the same environmental conditions except for the goitrogenic factors; a test group was exposed to these factors while in a control group, exposure was prevented by iodine prophylaxis, or these factors had never been present.

Table 5 indicates that in severe endemic goiter, neuromotor and intellectual deficits are also frequently observed in individuals who do not present any of the other signs of endemic cretinism.

Thus, endemic cretinism constitutes only the extreme expression of a spectrum of abnormalities in physical and intellectual development and in the functional capacities of the thyroid gland observed in the inhabitants of severe endemic goiter areas.

**Etiology.** Iodine deficiency. Iodine deficiency is fundamental in the etiology of endemic cretinism. This conclusion rests on (a) the correlation between the degree of iodine deficiency and the frequency of cretinism (158, 164), (b) the prophylactic action of iodine on the incidence of cretinism (41, 54, 115, 117, 158, 164, 166, 185, 186, 191), and (c) the emergence of cretinism in previously unaffected populations as a consequence.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Tests</th>
<th>Findings</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecuador</td>
<td>Goodenough Draw-a-Man</td>
<td>Low DQ, IQ and visual-motor performances</td>
<td>Fierro-Benitez et al. (92)</td>
</tr>
<tr>
<td></td>
<td>Stanford–Binet</td>
<td></td>
<td>Ramirez et al. (166)</td>
</tr>
<tr>
<td></td>
<td>Gesell</td>
<td></td>
<td>Dodge et al. (74)</td>
</tr>
<tr>
<td></td>
<td>Leiter</td>
<td></td>
<td>Trowbridge (194)</td>
</tr>
<tr>
<td></td>
<td>Bender–Gestalt</td>
<td></td>
<td>Greene (100)</td>
</tr>
<tr>
<td>Bolivia</td>
<td>Stanford–Binet</td>
<td>Low IQ and visual-motor performances</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bender–Gestalt</td>
<td></td>
<td>Bautista et al. (6)</td>
</tr>
<tr>
<td>Chile</td>
<td>Wechsler</td>
<td>Low IQ</td>
<td>Muzzo et al. (151)</td>
</tr>
<tr>
<td></td>
<td>Bender Kopitz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papua-New Guinea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaire</td>
<td>Brunet–Lezine</td>
<td>Motor performances</td>
<td>Connolly et al. (31)</td>
</tr>
<tr>
<td>Java</td>
<td>Locally adapted “culture free” intelligence tests</td>
<td>Low motor skill</td>
<td>Pharoah et al. (159)</td>
</tr>
<tr>
<td></td>
<td>Wechsler</td>
<td>Low DQ</td>
<td>Thilly et al. (190)</td>
</tr>
<tr>
<td></td>
<td>Catell</td>
<td>Low IQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raven</td>
<td>Low perceptual and neuromotor abilities</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Griffiths</td>
<td>Low IQ-relationship between IQ and nerve deafness and abnormal neurological signs</td>
<td>Boyages et al. (13)</td>
</tr>
<tr>
<td></td>
<td>Hiskey–Nebraska</td>
<td></td>
<td>Ma et al. (134)</td>
</tr>
<tr>
<td>India</td>
<td>Bhatia</td>
<td>Low IQ</td>
<td>Kochupillai et al. (121)</td>
</tr>
</tbody>
</table>

*Adapted from Delange (45), with permission.*
of iodine deficiency of recent onset, as observed in the Jimi valley in New Guinea after replacement of natural rock salt rich in iodine with low iodine industrial salt (157).

Finally, iodine deficiency during gestation in animals results in thyroid deficiency in the offspring. All the models used mimic the myxedematous type of cretinism; none was able to reproduce the neurological type (113, 163, 176).

Naturally occurring goitrogens. Thiocyanate overload resulting from chronic consumption of poorly processed cassava plays an additional role in the etiology of myxedematous cretinism (86). This role has been suggested from the observation that people in areas with severe but uniform iodine deficiency exhibit cretinism only when a certain critical threshold in the dietary supply of SCN is reached (59). The action of SCN is entirely due to an aggravation of iodine deficiency resulting in fetal hypothyroidism. SCN freely crosses the placenta (18) and its concentration in cord blood is three times higher in Ubangi than in Brussels (58) (Table 4). The role played by this SCN overload in the impairment of thyroid function of the newborn is strongly suggested by the observation that, in severely iodine-deficient pregnant women, elevated urinary SCN values are accompanied by a further increase of TSH and decrease of \( T_4 \) levels in cord serum (58). The antithyroid action of SCN in the newborn probably results from the fact that this ion interferes with the trapping of iodide by the placenta and by the neonatal thyroid gland. These two factors probably critically reduce the buildup of iodine stores within the thyroid gland during fetal and early postnatal life.

This mechanism is consistent with the very low iodine content of the thyroid gland reported in the myxedematous cretins (76). Thiocyanate overload aggravating the effect of iodine deficiency also explains the postnatal occurrence of juvenile hypothyroidism developing after weaning (148, 195).

Thyroid autoimmunity. Boyages et al. (14) showed that purified IgG fractions of serum from patients with myxedematous endemic cretinism inhibited thyrotropin-induced DNA synthesis and, consequently, thyroid growth, in guinea pig thyroid segments in a sensitive cytotoxic assay. On the contrary, no growth-blocking effect was observed with IgGs from euthyroid subjects or neurological cretins from the same area. It was concluded that the IgGs identified specifically in myxedematous cretinism were responsible for the condition by inhibiting thyroid growth. These IgGs, often called thyroid growth blocking immunoglobulins (TGBIs), are similar to the ones found by the same authors in sporadic congenital hypothyroidism (14). The antigenic stimulus is unknown as well as the timing of appearance in action of these IgGs in the course of pregnancy, fetal or postnatal life.

Serum TGBI were also identified using the FRTL5 system in cretins in Brazil with atrophic thyroids (147).

However, TGBI could not be found in sporadic congenital hypothyroidism by other authors (19, 26) and, consequently, the possible role of thyroid autoimmunity in the etiology of endemic cretinism remains controversial.

Trace elements. One quite stimulating new concept in the etiology of both myxedematous and neurologic endemic cretinism is the role of combined iodine and selenium deficiencies; selenium is present in high concentrations (0.72 \( \mu g/g \)) in the normal thyroid (1). It is present in glutathione peroxidase (GPX) and superoxide dismutase (35). It is also present in the type 1 5'-deiodinase (8). The following scheme has been proposed to explain the frequency of myxedematous cretinism and the relative rarity of neurologic cretinism in areas such as Zaire where both iodine and selenium are deficient (103, 197): iodine deficiency results in hyperstimulation of the thyroid by TSH and consequently in increased production of \( H_2O_2 \) within the cells. Selenium deficiency results in GPX deficit and consequently in accumulation of \( H_2O_2 \). Excess of \( H_2O_2 \) could induce thyroid cell destruction, and finally thyroid fibrosis resulting in myxedematous cretinism (33, 35). The recent observation of thyroid cell necrosis in severely selenium- and iodine-deficient rats submitted to acute iodide overload (34) is consistent with this hypothesis. On the other hand, deficiency in the selenoenzyme 5'-deiodinase in pregnant mothers induced by selenium deficiency causes decreased catabolism of \( T_4 \) to \( T_3 \) and thus increased availability of \( T_3 \) for the fetus and its brain. This mechanism could prevent the development of neurologic cretinism, which is due to fetal hypothyroxinemia during early gestation. Combined iodine and selenium deficiencies in Zaire could thus explain the large predominance of the myxedematous type of endemic cretinism, rather than the neurological type, as seen typically in this area.

Pathogenesis. Fetal and maternal hypothyroidism or a combination of both has been proposed as a pathogenic mechanism.

Fetal hypothyroidism. Several observations clearly demonstrate that myxedematous endemic cretinism results from severe thyroid failure occurring during fetal or early postnatal life. Chinese data have indicated that hypothyroidism is present in human fetuses from the fourth month of gestation in regions of severe iodine deficiency and myxedematous endemic cretinism (132). Thyroid failure at birth due to iodine deficiency has been evidenced in several endemic areas with myxedematous endemic cretinism such as Zaire (54, 58, 186), India (121), Algeria (25), and even in some parts of Europe such as Sicily (172). In addition, about 10% of infants aged less than 12 months in Ubangi, Zaire are clinically hypothyroid, and nearly half have a marked delay in bone maturation, which is directly correlated to serum TSH and inversely correlated to serum \( T_4 \) (54). The presence of epiphysyal dysgenesis in X-ray studies of the knees of some adult myxedematous endemic cretins in Zaire with clinical, biochemical, and radiologic signs of long-standing hypothyroidism suggests that hypothyroidism was present before or around birth (3, 205); this provides indirect evidence of perinatal hypothyroidism. Also the direct correlations observed in these cretins between mental retardation and both height retardation and retardation in bone maturation indicate that hypothyroidism present in early life would account for the mental deficiency of the dwarfs (75, 126).

In some young infants in the Ubangi area in Zaire, the biochemical signs of thyroid failure disappeared spontaneously within 6 to 10 weeks (38). The hypothesis has been proposed that permanent thyroid failure from birth results in myxedematous endemic cretinism, while transient hypothyroxinemia occurring during the critical period of brain development could at least partly explain the endemic mental retardation observed in noncretin individuals in this population (40).

In contrast to the situation reported for myxedematous endemic cretinism, there is no evidence that fetal hypothyroidism is involved in the pathogenesis of neurologic endemic cretinism; there is no evidence of hypothyroidism in the newborn in

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areas where neurological cretinism predominates (42, 146, 179). Conversely, there is no clinical picture similar to that of neurological endemic cretinism in sporadic thyroid agenesis, which results in the most severe degree of fetal hypothyroidism (3, 81).

However, the well-documented preventive action of correction of iodine deficiency in pregnant mothers on the incidence of endemic cretinism indicates that maternal thyroid function plays a role in the pathogenesis of endemic cretinism.

Maternal hypothyroidism. Maternal hypothyroxinemia is rare in nonendemic areas. It can result in impaired neurointellectual development in the offspring (122, 139). In contrast, maternal hypothyroxinemia is extremely frequent in endemic areas (58, 159, 179). It is associated with increased mortality and morbidity in offspring (159, 189) and increased incidence of hypothyroidism in neonates (186). In addition, data collected in rats showed that maternal hypothyroxinemia due to iodine deficiency results in lack of thyroid hormones in fetal tissues during early pregnancy, even before the onset of fetal thyroid function, and also later on during fetal development (88, 149, 150, 208). These data indicate that in rats, there is a substantial transfer of thyroid hormones from mother to fetus during early gestation, which plays a role in fetal development, especially in the brain. In contrast, the rate of transfer of thyroid hormones across the placenta in humans is largely unknown. The classical concept that there is no or only minimal transfer (18, 94) has been recently challenged by the observation that infants born without any thyroid (thyroid agenesis) or with nonfunctioning thyroids (dyshormonogenesis) still have detectable serum concentrations of thyroid hormones at birth (cord blood), which rapidly decrease thereafter (64, 201). For these reasons, the consequences of maternal hypothyroxinemia and iodine deficiency for fetal development in humans are still largely unknown.

In an attempt to present a unifying hypothesis for the etiopathogenesis of endemic cretinism, and based on very careful and extensive studies of endemic cretinism as seen in China and Indonesia (16, 69, 70, 107, 108), it has been proposed that the clinical picture of endemic cretinism results from the product of two pathophysiological events, both resulting from iodine deficiency: the first event is maternal or/and fetal hypothyroidism. It occurs in all cretins and results in the neurological features of the disorder. The second event is postnatal hypothyroidism. This event does not occur in all cretins and is determined by the thyroid gland’s functional capacity of the individual. Postnatal hypothyroidism is responsible for growth, mental and sexual retardation, and for the myxedematous appearance of the cretins.

The hypothesis is attractive and is probably satisfying for explaining the situation as seen in China and Java, but, in the opinion of the author, cannot be considered as universal. As a matter of fact, as indicated earlier, maternal or/and fetal hypothyroidism are much more severe and frequent in areas in the world where the myxedematous component of cretinism predominates than in areas where the neurological component predominates, and not the reverse.

Therapy. There is no specific therapy of neurological endemic cretinism. These patients need rehabilitation like patients with cerebral palsy in Western countries.

Thyroid function can be improved by iodine supplementation in myxedematous cretins aged less than 4 years but not in older defectives, indicating that in this type of cretinism, the atrophic thyroid progressively loses its functional capacity (15, 196). As in unrecognized sporadic congenital hypothyroidism, substitution therapy with 1-thyroxine will restore euthyroidism but will not correct the neuropsychointellectual sequelae.

Figure 9 shows that injections of iodized oil during pregnancy in Zaire will prevent hypothyroidism not only at birth but until the age of 2–3 years.

The fact that in some children, hypothyroidism starts after the age of 3 years is consistent with the observation of Goslings et al. (102) that hypothyroid patients in severe endemic goiter are not necessarily affected by severe and irreversible mental retardation and of Boyages et al. (12) that cretins with thyroid failure may have only moderate retardation in height and bone maturation.

Treatment and prophylaxis of iodine deficiency disorders

Prolonged administration of iodide or of thyroid hormones has been found highly effective in reducing the size of the goiter. Surgical treatment is often justified in large goiters with pressure symptoms. Nevertheless, such types of treatment administered at an individual level are, in practice, impossible to apply to a general population in view of the epidemiologic size of the problem and the general lack of adequate medical infrastructure in the most severely affected populations. The single logical medical attitude is the introduction of iodine prophylaxis.

For almost 50 years, iodized salt has been used as the simplest most effective way of providing extra iodine in the diet (72, 140, 142, 181). Iodine is most often added in the form of potassium iodide, but iodate is preferred in humid regions owing to its greater stability. The first large scale successful campaign to
DISORDERS INDUCED BY IODINE DEFICIENCY

TABLE 6. ADMINISTRATION OF IODIZED OIL IN THE PREVENTION OF THE DISORDERS INDUCED BY IODINE DEFICIENCY*

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral (mg iodine)</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
</tr>
<tr>
<td>Women of child bearing age (nonpregnant)</td>
<td>100–200</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>50–100</td>
</tr>
<tr>
<td>Infants–children</td>
<td>20–40</td>
</tr>
<tr>
<td>0–1 year</td>
<td>40–100</td>
</tr>
<tr>
<td>1–5 years</td>
<td>100–200</td>
</tr>
<tr>
<td>6–15 years</td>
<td>100–200</td>
</tr>
<tr>
<td>Males 16–45 years</td>
<td>100–200</td>
</tr>
</tbody>
</table>


prevent endemic goiter by iodized salt was carried out in the United States in 1917 (141). Later epidemiologic surveys demonstrated the successful result of this program (143). The effectiveness of the method was later confirmed by a number of similar campaigns in Switzerland, India, Mexico, Guatemala, Greece, Argentina, Switzerland, Austria, and Finland (188). These brought not only a dramatic reduction of the prevalence of goiter but also progressive disappearance of endemic cretinism (117, 160, 166, 191).

The recommended levels of iodine supplementation vary widely. In the United States, one part iodide is added to 10,000 parts salt. In other countries, the ratio is one in 100,000. A salt consumption of 5 g/day being presumed, extra iodine supply would vary therefore from 500 μg to 50 μg/day. A reasonable recommendation is one part in 20,000 to 50,000 (72, 80).

Iodide has been used as a supplement in bread alone in Holland and in Tasmania, but wide variations in the amount of bread consumption make this a less than satisfactory technique (181). Iodination of water has been successfully used in some areas with adequate water supply and control of iodination of water (135, 178).

However, in many developing countries with severe problems of endemic goiter, iodination of salt, bread, or water failed to prevent or eradicate the disease because various socioeconomic, climatic, or geographic conditions made systematic iodine supplementation difficult or even impossible, including areas where iodized salt does not reach the endemic areas or in areas where house salt is not available (72, 142, 188).

In such conditions, prophylaxis and therapy can be achieved extremely effectively by the administration of large quantities of iodine in the form of slowly resorbable iodized oil administered by intramuscular injections or orally (72, 80, 116, 161). The method is cheap and can be easily implemented through local health services using existing facilities or by small teams. The method appears as most convenient for isolated communities beyond the reach of commercial channels.

In light of investigations completed in various countries by injection of iodized oil (72, 80, 116, 182), it appears necessary to inject the entire population from 0 to 45 years for females and 0 to 20 years for males. This sex distinction is not, however, always applied for psychological reasons (188). The long-term effectiveness and safety of this procedure are now extensively documented for at least 7 years in adults and 2–3 years in young children (Fig. 9).

The recommended doses of iodine administered as iodized oil are shown in Table 6. Smaller doses of oral iodized oil are, however, equally effective at least for 1 year (193).

The principal complication of iodine prophylaxis is the occurrence of thyrotoxicosis (142). This complication was first noticed in the early days after the introduction of iodide supplementation. An increased incidence of thyrotoxicosis was observed in Tasmania following bread iodination in 1966 or/and following contamination of dairy products by iodine containing disinfectants (iodophores). The complication was most evident in the older age groups (32). It was attributed to the presence of autonomous nodules often observed in these subjects. Patients with thyrotoxicosis were occasionally reported after administration of iodized oil in Ecuador, Peru and Argentina but not in New Guinea and Zaire (181). In all reports the disease was mild and easily managed. The question may arise whether this development of thyrotoxicosis is to be considered as a complication of iodine prophylaxis or an ineluctable consequence of the normalization of the iodine intake. Even in nongoitrous areas, it has been shown that the shift from a low normal iodine intake (100 μg/day) to a high normal one (500 μg/day) may induce clear-cut thyrotoxicosis in euthyroid subjects with an autonomous thyroid nodule (85).

The large amount of information now available from all over the world clearly establishes that the occurrence of thyrotoxicosis is exceptional and does not put in question the enormous benefit that follows the introduction of iodine prophylaxis in endemic goiter regions.

MILD TO MODERATE IODINE DEFICIENCY: THE SITUATION IN EUROPE

Epidemiology

Endemic goiter, occasionally complicated by endemic cretinism, has been reported in Europe up to the turn of the twentieth
TABLE 7. COMPARISON OF THE RESULTS OBTAINED IN EUROPEAN COUNTRIES OR REGIONS FOR URINARY IODINE EXCRETION IN ADULTS, FOR THE IODINE CONTENT OF BREASTMILK AND OF URINE OF INFANTS ON DAY 5 OF LIFE

<table>
<thead>
<tr>
<th>Country or region</th>
<th>Urinary excretion of iodine in adults (μg/day)</th>
<th>City</th>
<th>Iodine concentration (μg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Breast milk</td>
<td>Urine infants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mean ± SEM)</td>
<td>day 5 (median)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>88–140</td>
<td>Rotterdam</td>
<td>16.2 (64)</td>
</tr>
<tr>
<td>Finland</td>
<td>238–270</td>
<td>Helsinki</td>
<td>11.2 (39)</td>
</tr>
<tr>
<td>Sweden</td>
<td>91–140</td>
<td>Stockholm</td>
<td>9.3 (60)</td>
</tr>
<tr>
<td>Sicily (nonendemic area)</td>
<td>113</td>
<td>Catania</td>
<td>7.1 (14)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>126–141</td>
<td>Zürich</td>
<td>6.2 (62)</td>
</tr>
<tr>
<td>Spain</td>
<td>89</td>
<td>Madrid</td>
<td>7.7 ± 0.9 (69)</td>
</tr>
<tr>
<td>France</td>
<td>55–126</td>
<td>Paris</td>
<td>8.2 ± 0.5 (68)</td>
</tr>
<tr>
<td>Belgium</td>
<td>51</td>
<td>Brussels</td>
<td>9.5 ± 0.6 (91)</td>
</tr>
<tr>
<td>Italy</td>
<td>37</td>
<td>Rome</td>
<td>4.7 (114)</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>35</td>
<td>Berlin</td>
<td>2.8 (87)</td>
</tr>
<tr>
<td>South</td>
<td>20</td>
<td>Freiburg</td>
<td>1.2 (41)</td>
</tr>
<tr>
<td>Sicily (endemic area)</td>
<td>16</td>
<td>Jena</td>
<td>0.8 (54)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>San Angelo</td>
<td>2.7 ± 0.3 (59)</td>
</tr>
</tbody>
</table>

Note: The number of determinations is shown in parentheses. Adapted from Delange et al. (63).

Iodine deficiency is presently under control in only five countries, namely Austria, Finland, Norway, Sweden, and Switzerland. Iodine deficiency is marginal or present mainly in "microfoci" (pockets of goiter or even of cretinism) in Belgium, the former Czechoslovakia, Denmark, France, Hungary, Ireland, Portugal, and the United Kingdom. IDD have recurred after transitory resolution in Croatia, the Netherlands, and possibly some Eastern European countries. Finally, iodine deficiency persists and ranges from moderate to severe in all the other European countries, namely Bulgaria, the Commonwealth of Independent States (CIS), Germany, Greece, Italy, Poland, Romania, Spain, and also Turkey. In some of these countries, such as Bulgaria and Romania, the prevalence of goiter in

FIG. 10. Updated evaluation of iodine intake in Europe (μg/day). Range of the values observed during regional or national surveys. The figures correspond to the measurement of the daily urinary excretion of iodine or to the extrapolation to 1 L of urine per day when the results were expressed as iodine concentrations or iodine/creatinine ratios. N, Norway; S, Sweden; SF, Finland; DK, Denmark; IRL, Ireland; UK, United Kingdom; B, Belgium; NL, The Netherlands; G, Germany; PL, Poland; CS, Former Czechoslovakia; CIS, The Commonwealth of Independent States; F, France; CH, Switzerland; A, Austria; H, Hungary; Ro, Romania; P, Portugal; E, Spain; I, Italy; CRO, Croatia; Y, Yugoslavia; BG, Bulgaria; GR, Greece, AL, Albania; TR, Turkey. Compiled from Delange et al. (68).
TABLE 8. VALUES OF 24 THYROIDAL UPTAKE OF RADIOIODINE IN EUTHYROID SUBJECTS*

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of centers</th>
<th>No. of subjects</th>
<th>24 h (^{131}I) thyroidal uptake (% dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td>2</td>
<td>162</td>
<td>32.6 ± 0.8</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>3</td>
<td>411</td>
<td>39.9 ± 0.5</td>
</tr>
<tr>
<td>France</td>
<td>8</td>
<td>938</td>
<td>40.9 ± 0.6</td>
</tr>
<tr>
<td>Italy</td>
<td>10</td>
<td>1510</td>
<td>42.2 ± 0.4</td>
</tr>
<tr>
<td>Belgium</td>
<td>14</td>
<td>1232</td>
<td>47.0 ± 0.5</td>
</tr>
<tr>
<td>Germany</td>
<td>7</td>
<td>1055</td>
<td>59.6 ± 0.5</td>
</tr>
</tbody>
</table>

*Subjects are from six European countries listed according to decreasing dietary intake of iodine (see also Fig. 10). Results are given as mean ± SEM. From Thilly et al. (192), with permission.

School children in Tuscany and Sicily of the most severely affected areas in the center of the African continent.

Public health consequences

In adults. The frequency of simple goiter is elevated in many countries and the cost of therapy of thyroid problems in the adult population is enormous (155). As shown in Table 8, thyroidal uptake of radioiodine varies markedly from one European country to another and is inversely related to the iodine intake. Elevated thyroidal uptake due to iodine deficiency aggravates the risk of thyroid irradiation and development of thyroid cancer in case of a nuclear accident (44). The best prophylaxis of nuclear hazards in case of radioiodine fallout is to increase the basal intake of iodine of the population (83).

Thyroid function is usually normal in adults in Europe. In contrast, it is frequently altered in pregnant women. During pregnancy, the thyroid is submitted to a triple challenge resulting in thyroid hyperstimulation by TSH, which can potentially induce thyroid disorders (98): there is an increase in the serum concentration of thyroxin binding globulin (TBG) under the influence of the estrogens accompanied by a desaturation of the binding protein; there is increased stimulation, at least during early pregnancy, by the human chorionic gonadotrophin (hCG), and, finally, there is an increased loss of iodine in the urine. It has been shown that, at least in conditions of borderline iodine intake as seen in Belgium (50–70 μg/day), pregnancy is accompanied by a progressive decrease of serum-free T₄ and consequently by an increase of serum TSH. This state of chronic TSH hyperstimulation results in the development of goiter in about 10% of the pregnant women and in a progressive increase in the serum concentration of thyroglobulin. Goiter can persist after pregnancy in an important number of women (98). Pregnancy, especially in conditions of borderline iodine intake, at least partly explains the higher frequency of thyroid problems in women than in men.

In adolescents and children. Euthyroid pubertal goiter is especially frequent in adolescents and occasionally requires substitutive therapy by T₄ or iodide. Iodine metabolism is accelerated during this period of life (138).

A very important issue is the demonstration that even in Europe today, clinically euthyroid schoolchildren born and living in an iodine-deficient environment exhibit subtle or even overt neuropsychointellectual deficits as compared to controls living in the same ethnic, demographic, nutritional, and socioeconomic system, except that they are not submitted to iodine deficiency (Table 9). These deficits are of the same nature, although less marked, than those found in schoolchildren in areas with severe iodine deficiency and endemic mental retardation. These deficits could result, as demonstrated in severe endemic goiter, from thyroid failure occurring during fetal or early postnatal life, i.e., during the critical period of brain development.

In neonates. The most important and frequent alterations of thyroid function due to iodine deficiency in Europe occur in neonates and young infants:

1. The frequency of transient primary hypothyroidism is almost 8 times higher in Europe than in North America (21). As shown in Figure 11, this syndrome is characterized by postnatally acquired severe primary hypothyroidism lasting for a few weeks and requiring substitutive therapy (55). The risk of transient hypothyroidism in the neonates increases with the degree of prematurity (60). The specific role played by iodine deficiency in the etiology of this type of hypothyroidism is demonstrated by the disappearance of neonatal transient thyroid failure in Belgian preterms since they were systematically supplemented with 30 μg potassium iodide/day.

TABLE 9. NEUROPSYCHOINTELLECTUAL DEFICITS IN INFANTS AND SCHOOLCHILDREN IN CONDITIONS OF MILD TO MODERATE IODINE DEFICIENCY IN EUROPE

<table>
<thead>
<tr>
<th>Regions</th>
<th>Tests</th>
<th>Findings</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Locally adapted</td>
<td>Lower psychomotor and mental development</td>
<td>Bleichrodt et al. (9)</td>
</tr>
<tr>
<td></td>
<td>Bayley</td>
<td>than controls</td>
<td></td>
</tr>
<tr>
<td></td>
<td>McCarthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cattell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sicily</td>
<td>Bender-Gestalt</td>
<td>Low preceptual integrative motor ability</td>
<td>Vermiglio et al. (199)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuromuscular and neurosensory abnormalities</td>
<td></td>
</tr>
<tr>
<td>Tuscany</td>
<td>Wechsler</td>
<td>Low verbal IQ, perception, motor, and attentive</td>
<td>Fenzi et al. (91)</td>
</tr>
<tr>
<td></td>
<td>Raven</td>
<td>functions</td>
<td></td>
</tr>
<tr>
<td>Tuscany</td>
<td>Wisc</td>
<td>Lower velocity of motor response to visual</td>
<td>Vitti et al. (200)</td>
</tr>
<tr>
<td></td>
<td>Reaction time</td>
<td>stimuli</td>
<td></td>
</tr>
</tbody>
</table>
used as a monitoring tool in the evaluation of the effects of iodine prophylaxis at a population level (152).

The reasons for the particular sensitivity of the newborn, especially of the preterm infant, to the effects of iodine deficiency are shown in Figure 13 and Table 10. In an area such as Belgium, with a borderline iodine intake, the iodine content of the fetal thyroid is extremely low and increases progressively with gestational age (Fig. 13). Table 10 shows that this content found in full-term infants is related to the iodine intake of the population and thus probably of the mother during gestation. The iodine content of the thyroid in full-term infants is almost 300 µg in Canada; it is only 82 µg in Belgium where the iodine intake is borderline and is as low as 43 µg in Germany where the iodine intake is severely insufficient. In these conditions, the turnover rate of intrathyroidal iodine is markedly accelerated and, therefore, thyroid failure is more likely to occur. These neonatal data contrast with adult data that have shown that the iodine stores of the thyroid are not affected by iodine deficiency unless there is an extreme degree of deficiency (Fig. 3).

Prevention and therapy of IDD in Europe

It is hard to understand and impossible to admit that iodine deficiency, the most common preventable cause of mental deficiency in the world to day (113), is still so prevalent in Europe. The most probable cause of the phenomenon is the insufficient awareness of the problem by the health authorities, including the medical and paramedical world, and by the public. The consequence is the absence of programs of health education focusing on the use of sea products, milk, and iodized salt and the absence, except in some countries such as the Scandinavian countries, Switzerland, and Austria, of efficient and well-controlled and monitored programs of iodized salt. As a matter of fact, iodized salt is available in many European countries. However, it has been reported that the iodination of household salt alone can raise urinary iodine excretion far below expectation (65). This apparent failure of programs of salt iodization can result from the fact that, even in Europe today, many of the iodized salt analyses were grossly inadequate with respect to their iodine content (65). It also could result from a gross overestimation of household salt consumption, as the actual

FIG. 11. Time course of the serum concentrations of TSH, total T4, and T3 in 11 infants with transient primary hypothyroidism. Values recorded as mean ± SEM. SCR, screening; DIAG, diagnosis. From Delange et al. (60), with permission.

FIG. 12. Relationship between the urinary iodine concentration and the recall rate at the time of screening for congenital hypothyroidism in newborn populations in Europe. Each points results from the analysis of 50 to 200 urine samples and from 200,000 to 300,000 screening tests. From Delange and Ermans (67), with permission.

FIG. 13. Changes in the iodine content of fetal thyroid as a function of gestational age in Brussels (Belgium).
TABLE 10. RELATIONSHIP BETWEEN THE IODINE CONTENT OF URINES IN ADULTS AND NEONATES

<table>
<thead>
<tr>
<th>Cities</th>
<th>Adults Urinary excretion of iodine (µg/day)</th>
<th>Iodine concentration in urines</th>
<th>Values below 5 µg/dL (%)</th>
<th>Neones</th>
<th>Throids</th>
<th>Estimated turnover rateb (%/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (µg/dL)</td>
<td></td>
<td></td>
<td>Weight (g)</td>
<td>Iodine content (µg)</td>
<td></td>
</tr>
<tr>
<td>Toronto Canada</td>
<td>600–800</td>
<td>14.8 (81)</td>
<td>11.9</td>
<td>1.00 ± 0.12 (13)</td>
<td>292 ± 47</td>
<td>17</td>
</tr>
<tr>
<td>Brussels Belgium</td>
<td>51</td>
<td>4.8 (196)***</td>
<td>53.2</td>
<td>0.76 ± 0.25 (4)</td>
<td>81 ± 9**</td>
<td>62</td>
</tr>
<tr>
<td>Leipzig Germany</td>
<td>16</td>
<td>1.6 (70)***</td>
<td>97.2</td>
<td>3.27 ± 0.39 (10)**</td>
<td>43 ± 6**</td>
<td>125</td>
</tr>
</tbody>
</table>

*Relationship used as an index of iodine supply and thyroid weight, iodine content, and estimated turnover rate of thyroidal iodine (b) based on a requirement of 77 µg/day in neonates in three areas in Europe with markedly different iodine intake. Results given as mean ± SEM. The number of patients is shown in parentheses. Levels of significance as compared to Toronto **p < 0.01, ***p < 0.001. Adapted from Delange et al. (66) and from Delange and Erman (67), with permission.

ingestion of household salt measured by the lithium marker technique indicates that it is only about 15% of the total salt intake. Therefore, iodized salt should be made available not only for household salt but also industrial food production including cheese and bread as well as for animal consumption. As a matter of fact, milk appears as the main source of iodine in many industrialized countries (78).

Because of the obvious effects of iodine deficiency in Europe on the main target groups including pregnant women, fetuses, neonates, and young infants and before the introduction of generalized programs of fortification of food including iodized salt, pregnant and lactating women and young infants should be supplemented with iodine. In addition, the iodine content of formula milk should be increased in Europe above the classical recommendation of 5 µg/dL milk. The present recommendation, endorsed by the European Thyroid Association (ETA) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), is 10 µg/dL for full-term and 20 µg/dL for preterm infants (47).

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