

NUTRITIONAL EPIDEMIOLOGY AND THYROID HORMONE METABOLISM

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■ **Abstract** Severe iodine deficiency was the main cause of endemic goiter and cretinism. Most of the previously iodine-deficient areas are now supplemented, mainly with iodized salt. The geographical distribution of severe endemic areas has been progressively reduced, and at present, approximately 200 million people living in remote places are still at risk of severe iodine deficiency. International public health programs should be focused first on reaching these populations, and second on auditing and monitoring the operational work of supplementation programs. This second point is essential to prevent iodine-induced hyperthyroidism or interruptions of iodine supplement distribution, which could be catastrophic for the fetus and the young infant. Echography brings a complementary tool to clinical assessment of goiter by palpation. Inductively coupled plasma–mass spectrometry brings at least a definitive gold standard for iodine measurement and thyroid hormone measurement. Thiocyanate overload has been clearly documented as a goitrogen in Central Africa, and when associated with selenium deficiency, it may be included as risk factor for endemic myxedematous cretinism. Variable exposure to different environmental risk factors is likely the explanation of the variable distribution of two types of endemic cretinism (neurological and myxedematous), and the clinical overlap of the pathogeny of both syndromes is more important than previously described. It is possible that Kashin-Beck osteoarthropathy is another evanescent endemic disease that will disappear with the correction of iodine deficiency.

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MODERN ASSESSMENT OF NUTRITIONAL IODINE SUPPLY

Iodine deficiency is well characterized as the main nutritional risk factor for thyroid dysfunction. The causality criteria have been fulfilled since the pioneering iodine supplement trials in Switzerland in 1922 (reviewed in Reference 47), and were not invalidated by many observations in various countries. Median urinary iodine concentrations in various human groups show a threshold for endemic goiter when the value is below 50 $\mu\text{g/L}$ [World Health Organization (WHO) criteria for moderate iodine deficiency] and for endemic cretinism when the value is below 20 $\mu\text{g/L}$ (WHO criteria for severe iodine deficiency). Mild deficiency is in the range of 50–99 $\mu\text{g/L}$, and no endemic goiter is found in populations with urinary iodine excretion >100 $\mu\text{g/L}$, corresponding to a median intake of >150 μg iodine/day in the adult population (82).

In the past ten years, important technological progress has permitted the development of definitive and accurate reference material for measurement of iodine and iodothyronines (thyroxine, or T4, and triiodothyronine, or T3) by inductively coupled plasma–mass spectrometry (ICP-MS). Echography technologies bring a method to assess thyroid volume that is more sensitive and more precise than the clinical inspection and palpation of goiter, particularly when the increase of volume is moderate. In remote areas of developing countries, where the more severe clinical consequences of iodine deficiency still occur, such technological advances likely have little impact. By contrast, in developed countries where mild iodine deficiency is still present (3a), well-standardized clinical assessment of thyroid volume with echography represents a major improvement.

Goiter Measurement: Echography as a Complement to Palpation

International multicentric studies have been conducted to obtain reference values for thyroid volume by ultrasound in the target population of young children, a group that is sensitive to recent change in iodine supply. Thyroid volume was measured in 3529 children (6 to 12 years old) living in areas of long-term iodine sufficiency in North and South America, central Europe, the eastern Mediterranean, Africa, and the western Pacific. Thyroid volume was adjusted for body surface area. The proposed reference values should be considered the best valuable ones at this time (86). It should be emphasized that the sources of variability were minimal: (a) two observers have been trained together and have conducted the examinations in the various countries; (b) the same echography instrument was used for all

the measurements. It remains to be shown whether a consensus can be reached concerning the procedure at an international level between various expert groups.

By contrast, simple clinical estimation by visual inspection and palpation offers the advantage of methodological stability over decades: Some criteria (e.g., the lobes are greater than the last phalange of the thumb of the patient) (58) will remain valid over time and throughout the world. Clinical estimation of goiter remains a good instrument in areas with severe endemic goiter.

In areas with a low prevalence of endemic goiter, interobserver standardization is more difficult to attain for clinical evaluation (visual inspection and palpation) than it is for ultrasound measurement, and the method lacks sensitivity and specificity (88). Nevertheless, the clinical data of palpation should be systematically combined with volume measurements by ultrasound (or by any other method) because this information is easily obtained, and the simple clinical criteria of goiter persist over time and over place.

Another problem of definition arises with ultrasound methodology: It detects increases of thyroid volume that are not yet clinically detectable. When palpation detects goiter, the volume of thyroid is already increased by a factor greater than 3 as compared with a normal iodine-sufficient gland. The diagnostic threshold, then, is much more sensitive with ultrasound technology. The use of the same word “goiter” for both approaches (clinical and ultrasound) may be a source of confusion: The term “goiter” should be reserved for clinical judgment (visual inspection and palpation), whereas “increase of volume” would more appropriately differentiate the small increases of volume—not yet clinically evident from true goiters—that are detected when echography is used. It is likely that when small increases of volume are subclinically determined, they are mainly an adaptation of the thyroid gland to the environmental conditions. This does not mean that public health resources should not be allocated to resolve this problem in some developing countries, but it is difficult to argue that the subclinical increases of thyroid volumes observed by echography alone are a health priority in the poorest developing countries in comparison with competing concerns (malaria, HIV, and other infectious diseases).

Gold Standard for Iodine and Iodothyronine Measurements

Historically, iodine measurement in biological samples (essentially in urine for epidemiological purposes) was based on a colorimetric method Sandel-Kolthoff reaction (61), in which iodine has a catalytic effect on the reaction between cerium (IV) and arsenic (III). Automation of this method in 1963 (with the Technicon Autoanalyzer II) considerably improved the analytical precision. Nevertheless, the autoanalyzer has fallen into disuse, and progressively, manual methods were again introduced (28).

In the 1990s, ICP became a method for the determination of trace elements. The coupling of ICP with a mass spectrometer allows the determination of iodine (12). The ICP-MS method for iodine measurement is now considered as

a reference method in specialized laboratories (34). The difference between the two methods (Sandel-Kolthoff and ICP-MS) was not significant for the mean urinary iodine concentrations over a wide range, from 1 to 1000 $\mu\text{g/L}$. Nevertheless, individual values could differ for more than 100 $\mu\text{g/L}$, and differences between the two methods were concentration dependent. The authors (12) conclude that the National Health and Examination Survey III data (obtained with the Sandel-Kolthoff method) should be compared cautiously with the National Health and Examination Survey 2000 data (obtained with ICP-MS). One of the main advantages of ICP-MS over Sandel-Kolthoff methodology is the addition of an internal standard (Tellurium) with which loss of recoveries during the pre-analytical phase can be corrected, thus improving the accuracy of the method. Because the equipment cost is prohibitive for developing countries, the less precise spectrophotometric method will remain sufficient for iodine monitoring in human populations. Even a visual test is sufficient to evaluate in the field the adequacy of iodine salt content (promoted by the United Nations Children's Fund and described in detail on the Web site www.iodinenetwork.net/documents/iodine_deficiency.pdf).

The new interest in high technology for an old measurement has brought additional insights into iodine metabolism. For example, a diurnal variation of urinary iodine has been observed, with a nadir around 11 AM and a peak around 6 PM; the variation is likely linked with nutritional intakes (3).

More than 90% of dietary iodine is excreted in urine (71a). Data on urinary iodine excretion are variously expressed as a concentration ($\mu\text{g/L}$), in relation to creatinine excretion (μg iodine/g creatinine) in populations with adequate general nutrition, or as a 24-hour urine collection. Due to interday variation (interday intraindividual CV >20%), the concentration in a casual sample of urine has little clinical significance at the individual level, and the results should mainly be interpreted to appreciate the iodine intake of a specific population.

One epidemiological consideration is that a relatively small sample of subjects ($N < 100$) in a homogeneous population is sufficient to obtain a good index of the distribution of urinary iodine concentrations. Urinary iodine measurement is not a marker of hypothyroidism at the individual level, and its usefulness is limited to determine the profile of this variable in the population. Within a homogeneously iodine-deficient population, there is no correlation of urinary iodine and biochemical parameters of thyroid function (personal data; the same observation for selenium concentration is discussed in Reference 73). The distribution of urinary iodine measurements is clearly skewed to the elevated values, so, transformed values are necessary to perform parametric statistical tests on approximately normal (Gaussian) distributed values.

The recommendations by the U.S. National Academy of Sciences are described in Table 1.

The immunoassay methodology is well established for the clinical chemistry measurements of thyroid function [thyroid-stimulating hormone (TSH), T4, free T4, T3, free T3, reverse T3, thyroglobulin, thyroid-binding globulin, and

TABLE 1 Recommended dietary allowance (RDA) and upper limit (UL) of iodine intake (microgram/day). Recommendation by the U.S. National Academy of Sciences (71a)

	Age (years)	RDA ($\mu\text{g/day}$)	UL ($\mu\text{g/day}$)
Infants	-0.5	110	Not possible to establish; source of intake should be from food and formula only
	0.5-1.0	130	
Children	1-3	90	200
	4-8	90	300
	9-13	120	600
Adolescents	14-18	150	900
Adults	19 \rightarrow >70 years	150	1100
Pregnant women	18-50	220	1100
Lactating women	18-50	290	1100

transthyretin]. The replacement of the radioactive isotope as a marker by a non-radioactive one in the immunoassay (chemiluminescent, enzymatic, fluorescent) has brought the development of automation for these measurements.

A major advance is the introduction of a reference method for total thyroid hormone measurement (T4, T3, and reverse T3) in serum and other biological matrices with isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS) (66). A precise and accurate (unbiased) measurement of the total thyroid hormones in various liquids allows a definitive standardization and validation of the commercial reagents used for thyroid hormone measurements. This is an important improvement in the accuracy of total thyroid hormone measurements.

IODINE DEFICIENCY AND ADAPTIVE MECHANISMS

Iodine is uniquely incorporated in iodothyronines (T4, thyroxine; T3, triiodothyronine) in the thyroid. The biochemical steps (Figure 1) are described below.

Iodine uptake occurs through a poorly specific Na (sodium) iodide symporter, NIS, which is competitively inhibited by perchlorate (ClO_4^-) or thiocyanate (SCN^-). This active transport mechanism allows thyroid cells to concentrate iodine at 20- to 40-fold above its level in the extracellular space. The transporter is located in the basal membrane of the follicular thyroid cell. The NIS protein increases in parallel with TSH-induced iodide transport, and this effect of TSH is reduced by moderate doses of I- (exogenous regulation of the thyroid through TSH and autoregulation of the gland through iodide). The same transporter is found in the breast, and inhibition at that site by SCN^- has been proposed as another factor favoring iodine deficiency in breastfed infants (44).

Iodine organification and coupling of iodotyrosines: Thyroglobulin (Tg) is a 660 kDa protein accumulating in the thyroid follicles. In the presence of thyroperoxidase (TPO) and H₂O₂, iodine is incorporated in mono- and diiodotyrosil (MIT and DIT) residues of thyroglobulin. The same enzyme TPO couples DIT and MIT to form T₄ and T₃. In iodine-sufficient conditions, 30% of Tg's iodine is in T₄ and T₃. The 70% of Tg's iodine in MIT and DIT are recycled within the thyroid and are virtually not secreted. TSH stimulates TPO activity while moderate doses of iodide reduce it. Tg is absorbed through coated pits on the apical pole of thyroid cells, and lysosomal degradation cuts the iodothyronines T₄ and T₃ from its protein support.

The amount of available iodine is critical for successful Tg iodination. When the iodine supply is low, thyroid hormone synthesis diminishes for lack of this ingredient, and circulating T₄ is low. The pituitary is stimulated to produce TSH, which activates most of the steps of thyroid hormone synthesis. In the case of iodine-deficient conditions, T₃ is produced relatively more than T₄, sparing one atom of iodine. Actually, in the euthyroid adult, serum T₃ has a half-life of less than one day, in contrast to serum T₄, with a half-life of seven days (42). Thus, the equilibrium is unstable and the preferential synthesis of T₃ can compensate the iodine supply for only a limited time: In the case of persistent extreme deficiency, serum T₃ also decreases and clinical hypothyroidism occurs.

Excess iodine, on the other hand, inhibits H₂O₂ synthesis and makes it unavailable for oxidation (the Wolff-Chaikoff phenomenon).

T₃ is the active hormone; T₄ is a precursor. At the cellular level, T₃ binds to four types of T₃ receptor proteins (α 1, α 2, β 1, and β 2) and these complexes bind on specific nuclear thyroid receptors of DNA. T₃ active at the nuclear level has two sources: (a) circulating serum T₃, which is synthesized and secreted by the thyroid gland or which results from the conversion of T₄ to T₃ in the liver; and (b) local (intracellular) conversion of the prohormone T₄ to the active hormone T₃. This conversion (deiodination) of T₄ to T₃ is regulated by deiodinases, which are selenium-containing enzymes (5). The reader is referred to recent comprehensive reviews for more details (4, 5, 7, 39). Only a few general points are summarized here in direct relationship with the topic. Three different enzymes (D1 through D3) with essential roles in thyroid hormone metabolism have been identified.

D1 is mainly present in peripheral tissues (thyroid, liver, kidney, heart, and muscle), and its activity is decreased in the case of hypothyroidism, except in thyroid, where it increases (48). It catalyzes 5'-deiodination (prohormone T₄ is converted to active hormone T₃ and reverse T₃ to 3-3'-T₂) and 5-deiodination (prohormone T₄ is converted to inactive reverse T₃ and T₃ is converted to 3, 3'-diiodothyronine T₂). In kidney, muscle, and heart, half of active hormone T₃ is derived from local conversion of T₄ to T₃, the other half is derived from circulating plasma T₃, which is mainly produced through deiodination of T₄ in T₃ in the liver.

D2 is mainly present in central tissues (central nervous system, including pituitary) and in the thyroid, and the pituitary activity is increased in the case of

hypothyroidism. It has only 5'-deiodinase activity, converting T4 to T3 and reverse T3 to 3-3'-T2. In the pituitary, the proportion of T3 derived from local conversion of T4 is around 80%; the other 20% is derived from circulating plasma T3. These differences between peripheral and central tissues explain the following well-known observations (29, 64):

- In iodine-deficient conditions, serum TSH is inversely associated with serum T4 or free T4, but not with serum T3 or free T3 [inverse linear association of serum TSH (log scale) with serum T4 (normal scale)].
- Serum T3 increases while serum T4 decreases in iodine deficiency. The relative part of increased production of T3 by the thyroid and of increased conversion of serum T4 to T3 by deiodinases remains to be determined.

D3 is present in the central nervous system, placenta, endothelium and epithelium. Its only 5-deiodinase activity inactivates thyroid hormones by producing reverse T3 from T4 and 3-3'-T2 from T3. It regulates the supply of T4 and T3 from the mother to the fetus (52). An excess of D3 has been documented as the cause of severe "consumption" hypothyroidism in the case of massive liver hemangioma in a three-month-old infant (low T4-T3 and increased TSH-reverse T3) that required combined T4 and T3 in high doses to correct hypothyroidism (35): Retrospectively, elevated TSH (at least twice the upper limit of normal) was documented in three more cases among 92 neonatal hemangiomas (35).

As Long as Adaptation is Effective

Most adult people in iodine-deficient areas (even in areas with severe deficiency) maintain a sufficient production of thyroid hormones through efficient adaptive mechanisms (Figure 2) and do not present signs of clinical hypothyroidism:

- Increased TSH stimulation
- Increased iodide trapping by the thyroid
- Preferential thyroid synthesis of T3 and apparent euthyroid state despite low or extremely low circulating serum T4
- Preferential conversion of T4 to T3 in central nervous system
- Increased volume of the thyroid

As long as adaptation is effective, increased thyroid volume may be considered as a mechanism to store iodine during periods of increased supply to provide for less favorable periods. The adaptive mechanism has its limits: Voluminous goiters have a decreased functional capacity, resulting sometimes in hypothyroidism and in anatomical complications (trachea compression). These cases are relatively uncommon.

This relatively good adaptation to extreme environmental conditions in most adults is in contrast with the irreversible consequences of severe iodine deficiency

on the general health of fetuses, neonates, infants, and children, when iodine stores are not yet constituted. A snapshot of the thyroid function in neonates or children during a cross-sectional study can only describe the state at a precise time. Actually, in severe endemic areas, the individual clinical state is unstable, and it can be considered that the whole population goes through periods of hypothyroidism of variable duration, of variable timing, and of variable severity, particularly during the critical period of thyroid hormone-dependent brain development, i.e., during fetal life, the neonatal period, and childhood. This concept of generalized disease at a population level may explain why the development of a priori normal subjects (i.e., without obvious clinical signs of hypothyroidism) is clearly delayed (decreased intellectual development and stunted growth). In severe endemic areas, the consequences of iodine deficiency affect to some degree every subject, in the absence of a correction of iodine deficiency (for a review of iodine deficiency disorders, see Reference 37).

When Adaptation is Defective

This adaptation to iodine deficiency is precarious, at least in a significant proportion of young subjects:

- The capacity to synthesize thyroid hormones is not proportional to the increase of volume, and particularly in voluminous goiter, the thyroid function is inefficient. When expressed by gram of tissue, the capacity of the thyroid to synthesize thyroid hormones decreases according to the thyroid volume (29), which results in an auto-aggravating increase of thyroid volume.
- In some subjects (endemic myxedematous cretins), the thyroid has been hyperstimulated since early life by a very elevated TSH, and the gland does not evolve normally; an involution develops in the thyroid gland, and the subjects are unable to recover a normal thyroid status even when iodine supply is increased (77). A clear distinction of cretins—supposed to be hypothyroid since fetal life or at least since early life—and children with transient hypothyroidism is impossible on the baseline thyroid function tests T4 and TSH, while baseline serum T3 concentration in myxedematous cretins is definitely lower than that in noncretin hypothyroid subjects or in euthyroid subjects, these last two groups being similar for T3 (Table 2). Multiple databases were brought together from surveys in northern Congo between 1974 and 1985. Of 235 clinically defined cretins, 182 had severe biochemical hypothyroidism ($TSH \geq 40$ mU/L and $T4 \leq 5$ $\mu\text{g/dL}$). In a survey of 591 young, apparently normal persons, 156 hypothyroid subjects had serum TSH and T4 values within the same range as those defined for cretins, and 260 euthyroid subjects had serum TSH ≤ 10 mU/L and $T4 \geq 6$ $\mu\text{g/dL}$. Apparently normal subjects with moderately hypothyroid hormonal values [(TSH > 10 mU/L and $T4 > 5$ $\mu\text{g/dL}$) or (TSH < 40 mU/L and $T4 < 6$ $\mu\text{g/dL}$)] were not included in the analysis (175

cases). Radiological age was determined according to specific tables for the knee (59a) and the wrist (32a). Psychomotor development was determined for subjects less than 7 years of age by Gesell tests modified by Brunet-Lezine and adapted to rural Africa (59b). Table 2 shows that a diagnostic test of responsiveness to iodine differentiates both groups (myxedematous cretins with irreversible loss of thyroid function and hypothyroid children with responsiveness to iodine). Clinically, myxedematous cretins have growth retardation, lower bone maturation, and lower psychomotor development in comparison with noncretin hypothyroid subjects and euthyroid subjects. A less-severe degree of growth retardation and lower bone maturation, but not lower psychomotor development, was documented in noncretin hypothyroid subjects versus euthyroid subjects: These data strongly suggest that severe longstanding hypothyroidism was not definitively installed since birth in noncretin hypothyroid subjects, but developed transiently during development. Such a distinction of myxedematous cretins and hypothyroid children has been observed in Indonesia (31) and in Congo (77). The presence of some thyroid tissue still responsive to iodine in endemic myxedematous cretinism could explain the old observations of subclinical hypothyroidism (low T₄, elevated TSH, and likely normal T₃) in subjects who are phenotypically cretins (mental deficiency, disproportionate nanism), but who are living in an area where iodine deficiency has been corrected (see page 128 of Reference 67 for Degrossi's description of a group of 15 cretins, in the previously severe endemic area of Salta in the Andean mountains of Argentina, who became clinically euthyroid after prophylaxis with iodized salt).

The involution—or alternatively lack of development—of thyroid gland in endemic myxedematous cretinism has been further documented by a relatively moderately increased concentration of Tg (21), in contrast to a marked increase classically observed in endemic goiter (78, 80, 87).

Myxedematous features (mental deficiency, stunted growth, and myxedema) and neurological features (mental deficiency, deafness, and characteristic neurological impairment) should be considered as a spectrum of two overlapping endemic syndromes. The neurological impairment of neurological cretins in Central Java, Indonesia was similar to the one observed in myxedematous cretins of Qinghai province, China, when the clinical examination was conducted by the same neuropediatrician (34a). Even in northern Congo, considered to be the typical endemic area with predominant myxedematous cretinism, examination of 80 cretins disclosed neurological impairment in 26 myxedematous cretins (32.5% of the total being, then, a “mixed” form of cretinism with neurological and myxedematous features), and 18 cases (22% of the total) of cretins were classified as neurological. “Pure” myxedematous cretinism represented 36 cases (45% of the total) (25c). In their typical and more extreme form, the epidemiological distribution of two types of cretinism differ from one endemic area to the other—even though the overlap of clinical pattern in both types of cretinism was less recognized before the mid-1980s (25a). Such a variable distribution results likely from a different timing of severe

TABLE 2 Comparison of thyroid function tests before and after iodine administration (20 µg KI/kg per os) virgule of physical and psychomotor development in myxedematous cretins, noncretin hypothyroid subjects, and euthyroid subjects of Ubangi, northern Congo*

	A: Cretins	B: Hypothyroid subjects	C: Euthyroid subjects	Probability	
				A/B:	B/C: A/C:
Baseline thyroid function tests (age: 0–38 yrs)					
Serum TSH (mU/L), geometric mean (±SD) (number)	218 (102–469) (182)	156 (70–345) (156)	2.1 (0.7–5.8) (260)	<10 ⁻⁵	<10 ⁻⁵
Serum T4 (µg/dL), mean ±SD (number)	1.2 ± 1.1 (182)	1.6 ± 1.2 (156)	11.8 ± 3.6 (260)	<10 ⁻⁵	<10 ⁻⁵
Serum T3 (ng/dL), mean ±SD (number)	115 ± 71 (178)	198 ± 75 (152)	202 ± 64 (248)	<10 ⁻⁵	NS
Serum T3 <120 ng/dL, percentage (ratio)	59% (105/178)	17% (26/152)	9.7% (24/248)	<10 ⁻⁵	0.03
Thyroid function tests 7 days after oral iodine administration (20 µg KI/kg, once) (age: 2.5–15 yrs)					
Serum TSH (mU/L), geometric mean (±SD) (number)	59 (20–176) (23)	13 (7.8–22) (14)	3.8 (1.1–13) (9)	<10 ⁻⁵	<10 ⁻⁵
Serum TSH >20 mU/L, percentage (ratio)	74% (17/23)	14% (2/14)	0% (0/9)	0.004	NS
Serum T4 (µg/dL), mean ±SD (number)	3.9 ± 3.0 (23)	4.8 ± 1.9 (15)	9.9 ± 3.7 (9)	0.04	<10 ⁻⁵
Serum T3 (ng/dL), mean ±SD (number)	103 ± 68 (23)	258 ± 70 (6)	170 ± 23 (4)	<10 ⁻⁵	0.001
Physical development (age: 0–18 yrs)					
Height, mean percentage of median ± SD (number)	78 ± 9 (149)	85 ± 6 (123)	91 ± 5 (223)	<10 ⁻⁵	<10 ⁻⁵
Height <80% of median reference height for age, percentage (ratio)	58% (86/149)	20% (25/123)	2.2% (5/223)	<10 ⁻⁵	<10 ⁻⁵
Bone age/chronological age ratio, mean percentage ±SD (number)	34 ± 17 (78)	53 ± 16 (46)	65 ± 14 (34)	<10 ⁻⁵	<10 ⁻⁵
Bone age/chronological age ratio <50%, percentage (ratio)	76% (59/78)	50% (23/46)	15% (5/34)	0.003	<10 ⁻⁵
Psychomotor development (age: 0–7 yrs)					
Psychomotor development score, mean percentage of normal ±SD (number)	62 ± 25(64)	91 ± 15 (90)	93 ± 16 (197)	<10 ⁻⁵	0.03
Psychomotor development score <80% of normal, percentage (ratio)	72% (46/64)	17% (15/90)	20% (39/197)	<10 ⁻⁵	NS

*The probabilities were calculated with univariate analysis: student t-test for continuous variables expressed as means ± 1 standard deviation (SD) and Barvais-Pearson X2 tests with 1 degree of freedom for discrete values expressed as percentages and ratios. NS, not statistically significant (probability > 0.05).

iodine deficiency that affects mainly the mother-fetus unit during the first and second trimester of pregnancy in neurological cretinism and the infant and young child in myxedematous cretinism (Figure 3). Thyroid gland differentiates only after 10 weeks of gestation, and it is considered that maternal thyroid hormones are essential around the end of the first trimester and during the second trimester of pregnancy to guarantee a normal neurological development. This classical concept is still in contradiction with the paucity of neurological symptoms observed in the rare disease of generalized resistance to thyroid hormones (19). In this last case, it would be anticipated from observations in iodine-deficient areas that the children suffer of severe neurological impairment because the fetal central nervous system is resistant to the limited transfer of maternal thyroid hormones during the critical period of neurological development. Mental deficiency and hearing loss are observed in only 2.7% and 8%, respectively, of 439 cases of complete resistance to thyroid hormones (19). The discrepancy of this observation with the data of neurological cretinism in severe endemic goiter areas remains paradoxical and unexplained. In the observational longitudinal epidemiological study in Xinjiang province, China (14), mothers were treated with an iodine supplement at various times during pregnancy and children were treated in a similar way during the first two years. Iodine was shown to prevent cretinism (neurological cretinism) only when administered during the first two trimesters of pregnancy. This corroborates the historical therapeutic trial of iodized oil (in a randomized study) of Pharoah et al. in New Guinea (59).

CORRECTION OF IODINE DEFICIENCY: INTERNATIONAL AUDITING AND MONITORING REMAIN ESSENTIAL

The public health progress in most countries with endemic goiter during the past 25 years is impressive. The implementation of iodine supplement is based essentially on universal iodized salt, and in a few remote places where iodized salt is not easily distributed, there is interest in iodized oil or iodized water. In 84% of the 130 countries affected by iodine deficiency disorders, national legislation to establish iodine supplement programs was in place or in draft form in 2001, according to WHO (83).

Where does salt iodization stand on an international scale in 2006? Many countries now have vast programs of universal salt iodization. The literature should be examined cautiously for two biases:

- Misclassification bias with overestimation of cases: Because financial support from international agencies is directly proportional to the severity of the public health problem, there is a risk that its magnitude will be exaggerated, for example by extending local problems of iodine deficiency to an entire country (extrapolation by excess).
- Misclassification bias with underestimation of cases: Another risk is overestimation of the efficacy of a public health program.

By definition, there is no way to precisely measure biases once they occur. Nevertheless, biases can be prevented by sound methodology. International cooperation is needed to conduct auditing and monitoring, and such a program has been implemented (36).

- **Auditing:** Independent experts (usually foreign to the country audited) analyze the way the public health program works in a specific area by supervising the processes of iodine deficiency disorders prevention (internal audit) or by conducting personal control on the field (external audit).
- **Monitoring:** As long as major economic progress will develop, a public health program of iodine deficiency correction remains to be maintained against obstacles such as:
 - Sociopolitical troubles that divert attention from the iodine deficiency problem and assign it a low priority.
 - National programs that depend on very few people or on very small teams, as well as uncertainties regarding personal freedom (such a fragility has also been described for HIV prevention programs in developing countries) (15).
 - International programs that local experts, who are in a dependency relationship with their foreign colleagues, find difficult to accept (moreover, the wage difference is frequently on a geometric scale, which does not encourage frank and open cooperation based on nondiscrimination).

Despite these difficulties, which have been well described for other international public health challenges (15), iodine deficiency has receded at high speed on the world map, and it is not realistic to estimate that 1.5 billion people are at risk of iodine deficiency (47) at present. Although it is not possible to obtain precise data, a more likely estimate is that 200 million people currently live in severe endemic areas without efficient programs of iodine supplementation (3a, 42).

The work of a nongovernmental organization, the International Control Center for Iodine Deficiency Disorders (ICCIDD), should be mentioned (36). It plays an essential role in promoting iodine deficiency control on a world scale, and it has an intermediate role with international agencies such as WHO or the United Nations Children's Fund and with sponsoring private organizations such as Kiwanis. Besides the possible misclassification bias cited above, a publication bias also exists: The countries do not disseminate the information relative to the iodine deficiency problem at home, and, for example, objective recent data are lacking after 1993 for Argentina and Congo (Congo-Brazzaville, formerly République populaire), despite the official language describing elimination of the iodine deficiency problem. A Web site is available for up-to-date information (www3.who.int/whosis/micronutrient).

Efforts should be concentrated on two priorities:

1. Improving the strategy of supplying iodine to isolated, severely iodine-deficient populations essentially in remote areas, and

- auditing and monitoring national programs at the international level, where iodine deficiency is controlled, to prevent two risks:

Excess iodine: Excess iodine has been shown in Tasmania and in Congo after the use of iodized oil (1, 46), and even transient hyperthyroidism has been documented in Brazil after the introduction of iodized salt in iodine-deficient areas (63). Unfortunately, only case reports are described, and no incidence data are available to estimate the frequency of this complication.

Recurrence of iodine deficiency: The reappearance of juvenile hypothyroidism was documented in Morocco a few months after interruption of the program of iodization of salt (89). Even after 50 years of mandatory iodine supplementation, mild iodine deficiency was still present in Tasmania (33). Surveillance of iodine availability should remain a public health priority in all countries known for past iodine deficiency, even in the developed world (25, 43).

SOME OTHER NUTRITIONAL FACTORS MODULATING THYROID FUNCTION

Thiocyanate and Perchlorate as Competitive Inhibitors of Iodine Uptake

THIOCYANATE Antithyroid sulfur-containing organics have been identified in vegetable foodstuffs. Thiocyanate and cyanide do not occur in the intact plant as free anions. They result from the hydrolysis of a thioglucoside by specific enzymes such as the couple linamarine–linamarase in the cassava plant when the roots are crushed. In most populations, crushed roots are detoxified by sinking them for a few days in river water or by exposing them to the sun. The principal vegetables containing thioglucosides are kale, cabbage, sprouts, broccoli, kohlrabi, turnips, swedes, rapeseed, and mustard. The main vegetables containing cyanogenic glucosides are cassava, lima beans, linseed, bamboo shoots, and sweet potatoes. One of the most widespread mustard oils is allylthiocyanate ($\text{CH}_2=\text{CH}-\text{CH}_2-\text{N}=\text{C}=\text{S}$), which is the principal mustard oil in cabbage.

The inhibitory action of thiocyanate on iodine uptake is due to a competitive effect of pseudohalide with the mechanism of iodide concentration. However, under experimental conditions, rather high plasma concentrations of thiocyanate are required for inhibiting the iodine uptake by the thyroid gland. In the ethnic groups with the highest prevalence of goiter, cassava is not soaked; the roots are peeled, dried in the sun for one or two days, and then bruised in a mortar with corn that has been steeped for 12–24 hours in water. The flour is eaten as a gruel (*fuku*) prepared in boiling water. In other ethnic groups of Central Africa where goiter prevalence is lower, the roots of cassava are soaked for two to six days and then mashed into a purée, which is simmered to form a paste of firm and elastic consistency. The paste is enveloped in a palm or banana leaf (*chikwangue*). The cassava leaves are ground and extensively boiled before consumption (*mpondu*).

Thiocyanate overload in northern Congo (R.D., ex-Zaire) is present at birth, resulting from the placental transfer of maternal serum thiocyanate. In contrast to a group of mothers who did not consume cassava, thiocyanate was not present in excess in maternal milk. Lack of thiocyanate overload associated with a stable iodine deficiency (mammary gland does not concentrate iodine in humans) could explain the relative mitigation of endemic hypothyroidism in infants of Ubangi during the breast-feeding period (74), and the deterioration of thyroid function after weaning is chronologically associated with the introduction of cassava meals in the food. Nevertheless, recent data show that thiocyanate can decrease the iodine content of maternal milk by blocking the mammary iodine pump (44). At birth and during childhood, thiocyanate overload and iodine deficiency act in synergy to produce low serum thyroxine concentrations.

There is interaction of iodine deficiency and thiocyanate overload: Populations exposed to the same risk of iodine deficiency do not suffer of goiter or cretinism when they are not eating poorly detoxified cassava ("Gens d'eau," i.e., people living along the rivers). Also, in one of the most severe endemic areas (Ueles in the northern part of Congo), people living in the forest (Pygmies) clearly have iodine deficiency according to urinary iodine excretion, but have neither huge goiter nor cretinism (2).

Whatever the importance of cassava and of cyanogenic glucosides, thyroid dysfunction is entirely preventable by correction of iodine deficiency in the population.

Tobacco smoking is another cause of thiocyanate overload. In a country with borderline iodine deficiency (Belgium), the risk of neonatal hypothyroidism seems to be higher in neonates from smoking mothers (17). Impaired action of thyroid hormone associated with smoking in women with hypothyroidism has also been shown: Smoking was associated with greater serum TSH, total and LDL cholesterol, creatine kinase concentrations, and prolonged ankle-reflex time. These effects suggest an interaction of smoking with thyroid hormone receptors, different from the effects of thiocyanate.

PERCHLORATE Perchlorate was used at pharmacological doses (600–2000 mg/day) to treat Graves-Basedow disease in the 1960s. For this purpose, the therapeutic approach has been abandoned owing to the toxic effect of the drug on bone marrow (agranulocytosis). Its use has been maintained for short-term (one month) treatment of iodine-induced hyperthyroidism (antiarrhythmic amiodarone treatment, X-ray contrast agents in coronary angiography).

Surveys of wells and drinking water in the United States found maximum concentrations of 18 $\mu\text{g/L}$, corresponding to the ingestion of 36 μg daily (55). A no-observed-adverse-effect level of perchlorate was sought by testing the thyroid function (45), including ^{123}I uptake (radioactive uptake, or RAIU) in nine euthyroid male volunteers (22 to 30 years old) consuming 10 mg perchlorate daily (i.e., 300 times greater than the potential exposure from drinking water) during 14 days. After 14 days, circulating thyroid hormones (T4 and T3) and TSH remained stable, while 24th-hour RAIU decreased significantly from $23.6 \pm 2.6\%$ to

14.0 ± 1.6% after perchlorate (10 mg/day). Normal 24th-hour RAIU was recovered two weeks after administration of perchlorate was stopped. The effect of perchlorate can be explained entirely by its competitive inhibition of iodine uptake through NIS blockade. In conclusion, in the presence of sufficient iodine intake, perchlorate at much higher concentration than that found in water does not seem to involve hypothyroidism (stable thyroid hormones and TSH), even if RAIU decreased significantly. This has yet to be validated in countries with mild iodine deficiency, where the effect on thyroid function could be more evident.

Workers in an ammonium perchlorate production facility in Cedar City, Utah, have been shown to be exposed to perchlorate ClO₄⁻ (41). In the same plant, serum thiocyanate, perchlorate, and nitrate, biochemical profiles of thyroid function and thyroid RAIU were measured after three days off ("Pre") and during the last three 12-hour night shifts in the plant ("During") and in 12 volunteers ("Controls") (8). Serum thiocyanate and nitrate were similar in all groups. Serum and urine ClO₄⁻ were not detected in Controls. Urine ClO₄⁻ was not detected in 12 of 29 workers and was 0.27 mg/g creatinine in 17 Pre workers. It was markedly elevated during ClO₄⁻ exposure to 43 mg/g creatinine. Thyroid RAIUs were markedly decreased in the During period compared with Pre (13.5% versus 21.5%; *P* < 0.01). Serum T₄, free T₄ index, and T₃ were slightly increased in the During workers in comparison with the Pre workers. Serum TSH and Tg concentrations and thyroid volume by ultrasound were not affected by ClO₄⁻. Although much higher than doses potentially achieved from environmental exposure, these absorbed doses are still significantly lower than the 600–2000 mg/day doses previously used to treat hyperthyroidism. Intermittent, high exposure to ClO₄⁻ for many years in workers employed in an ammonium ClO₄⁻ production plant did not induce goiter or any evidence of hypothyroidism because serum TSH and Tg concentrations were unaffected, even though ¹²³I uptakes were decreased during exposure to ClO₄⁻.

Goitrin (Thio-Oxazolidone) and Aliphatic Disulfides

Upon enzyme hydrolysis, a particular thioglucoside gives rise to progoitrin, which is rapidly converted to form goitrin. Progoitrin is present in swedes and turnips. Administration of goitrin to rats for 20 days induces an enlargement of the thyroid, decreases iodine uptake by the gland, and decreases thyroxine synthesis. Other sources of goitrin-like compounds have been detected in various species of herbs and shrubs of the *Barbarea* and *Residea* families.

The role of goitrin has been advocated in the development of endemic goiter in schoolchildren of Tasmania; this goiter could not be prevented by iodine supplementation. The endemism was attributed to a goitrogenic factor ingested by cattle from thousand-headed kale and transmitted by milk. However, only 0.05% of goitrin appears in the milk, and it is rapidly denatured unless the milk is heated immediately. Goitrin has also been involved as an environmental goitrogen in Finland.

The major component of the volatile compounds from onion and garlic are small aliphatic disulfides that depress uptake of radioactive iodide by the thyroid

of rats on a low-iodine diet. Disulfides are also present in high concentrations (0.3–0.5 g/L) in aqueous effluents from coal-conversion processes; it is possible that these water contaminants intervene in the etiology of endemic goiter in the Cauca districts of Colombia (30).

Flavonoids

Flavonoids are a broadly distributed class of plant pigments and are universally present in vascular plants. They are not synthesized in animal tissues. Their number exceeds 3000 and new structures have been reported at a rapid rate. All classes of flavonoids derive their carbon skeleton from cinnamic acid; chalcone is the first common intermediate. More than 1 g of various flavonoids is ingested daily in the Western diet.

Since most flavonoids in foodstuffs are β -glucosides, they are not hydrolyzed by intestinal digestive enzymes and pass largely unaltered into the lower bowel. Microflora in the large intestine hydrolyze the flavonoid glucosides to their corresponding aglycone, and cleave the heterocyclic pyrane ring. Pharmacokinetic investigations in humans showed that 3% of an ingested dose of flavonoids (catechin) is absorbed, with peak plasma levels of 17 mg/ml after 1 hour and biexponential disappearance from plasma with mean half-lives of 8.8 minutes and 2.4 hours.

The effect of flavonoids on thyroid hormone metabolism was discovered in studies of several substances of plant origin, chemically different from ascorbic acid, which have been reported as "vitamin P." The ability of flavonoids to induce goiter was suggested from many studies involving various plants, e.g., peanuts (arachidoside) and millet (vitexin, glucosylorientine). Millet flavonoids are potent inhibitors of iodine organification, and flavonoids and thiocyanate interact synergistically. By their structural homology with thyroid hormones, the flavonoids displace the hormones from their natural transporters in human serum (transthyretin and thyroxine-binding globulin) (40).

In human populations, pearl millet (*Pennisetum americanum*) is the staple food for millions of people and livestock in Africa and Asia. Because of its perennial growth, it constitutes the main source of food energy for the very poor in the semiarid tropics. In Darfur province of western Sudan, the goiter prevalence in schoolchildren is closely linked to the level of consumption of millet (56).

Selenium Deficiency

ENDEMIC CRETINISM At the end of the 1980s, selenium deficiency evidence was found in the eastern and northern part of Congo (32, 75), and the construction of a map showed that selenium-deficient areas were overlapping iodine-deficient areas (54). The elevated frequency of a peculiar clinical feature (endemic myxedematous cretinism) was proposed to be associated with combined iodine and selenium deficiency. The initial hypothesis was that selenium deficiency decreases antioxidant protection in the thyroid (glutathione peroxidase had been known since 1973 to be a selenium enzyme). Thyroid cells synthesize hydrogen peroxide during the

TABLE 3 Geographical association of endemic diseases with exposure to nutritional risk factors in various countries [Darfur, Sudan (49), Tibet (51), Malawi and Vietnam (68), and Congo (R.D.) (75)]. Proposed causality hypothesis (60): Severe iodine deficiency is a necessary condition for all three endemic diseases. It is a sufficient condition only for endemic neurological cretinism. For the two other conditions, other exposure factors have to be present. For Kashin-Beck disease, combined iodine and selenium deficiency is not sufficient, as the same nutritional profile is documented in Congo (R.D.) without the disease. Epidemiologically, the potential role of elevated toxic concentrations of mycotoxins is still undetermined, as its concentration has not been determined in other endemic areas where the two other necessary environmental factors are present (iodine and selenium deficiency). Combined severe iodine and selenium deficiency and thiocyanate overload could be necessary and sufficient conditions for the occurrence of endemic myxedematous cretinism in Congo (R.D.). This hypothesis remains valid as long as there is no endemic place with the same environmental characteristics without the corresponding endemic disease

Exposure factor	Tibet	Vietnam	Malawi	Darfur (Sudan)	Congo (R.D.)
Iodine deficiency	3+	3+	3+	3+	3+
Selenium deficiency	3+	0	0	0	2+
Thiocyanate overload	0	0	0	0	3+
Elevated thyroid-stimulating hormone	+	+	+	+	3+
Mycotoxins					
Endemic diseases	3+	Unknown	Unknown	Unknown	Unknown
Endemic myxedematous cretinism	few	few	few	few	3+
Endemic neurological cretinism	2+	2+	2+	2+	2+
Kashin-Beck disease	3+	0	0	0	0

process of hormone synthesis (Figure 1), and it was proposed that this hydrogen peroxide could be toxic for the thyroid gland and explain the thyroid involution characteristic of endemic myxedematous cretinism. Nevertheless, this hypothesis seems too simplistic: Tibetan children are still much more iodine- and selenium-deficient than are Congolese children, and myxedematous cretinism is seven times less frequent than neurological cretinism in Tibet (51). So, if in the good direction, the hypothesis should include thiocyanate overload as a third risk factor of myxedematous cretinism in Congolese children (68)—thiocyanate overload is not present in Tibet. Epidemiologically (Table 3), the general geographical association shows that the association of endemic diseases with nutritional factors is multifactorial, and at least three risk factors have to be taken into account to explain the variable distribution of both types of cretinism and of Kashin-Beck osteoarthropathy (see Kashin-Beck Disease section below). With the same degree of iodine deficiency, thiocyanate overload characterizes the endemic goiter areas of Congo versus other endemic places in Tibet (51), Sudan (49), Vietnam (26), and Malawi (68), and could interact with iodine deficiency to provoke a particularly marked increase of serum TSH that is so frequent in Congo in comparison with the other places. This extremely elevated TSH could well be the *primum movens* of excessive

stimulation of the gland, including increased synthesis and production of hydrogen peroxide.

Experimental models of thyroid involution have been tested by submitting rats to nutritional stress. Contempré et al. (22) have obtained evidence of necrosis and fibrosis in the thyroid by giving excess iodine intraperitoneally to 30-day-old selenium-deficient rats with elevated TSH induced by perchlorate (to reproduce the effect of iodine deficiency). According to the glutathione peroxidase values and to the T4 and T3 values, the rats were in an extremely severe hypothyroid state and were selenium deficient. In these conditions, necrosis and fibrosis were obtained in the thyroid. Rat TSH was not measured (but it could be presumed that it was extremely elevated). The possible irreversible loss of thyroid functional capacity was not tested either: It is, then, not possible to conclude up to now that the lesions observed are sufficient to involve large sizes of thyroid damage, sufficient to involve irreversible hypothyroidism even after correction of iodine deficiency. Colzani et al. (20) also led studies on combined selenium and iodine deficiency in rats. In a first experiment, combined deficiency was obtained by diet, and an increase of serum TSH, a decrease of serum T4, and normal serum T3 reflected compensated hypothyroidism; goiter was present; no sign of fibrosis or necrosis was observed in the thyroid. In a second experiment, rats were given either a selenium-sufficient or a selenium-deficient diet for at least six weeks prior to mating. At conception and until day 19, dams were begun either on 0.5% perchlorate in their drinking water or on tap water. On days 20, 21, and 22, dams received either NaI (2 mg/rat) or saline. Paradoxically, hypothyroidism was not observed according to the biochemical values of TSH, T4, and T3 in the various groups of rats, and lesion of fibrosis, necrosis, inflammatory infiltration, or follicle disruption was not observed—goiter was present in fetuses and dams. In a third experiment, rats were given either a selenium-sufficient or a selenium-deficient diet for at least six weeks prior to mating. At conception and until pups were 30 days of age, dams and their pups were begun either on 0.5% perchlorate in their drinking water or on tap water. On day 30, perchlorate was withdrawn, and either NaI (1 mg/pup) or saline was administered for three days. As in the second experiment, serum TSH and T3 paradoxically did not differ in pups after NaI or saline—goiter was present and serum T4 was lower in pups receiving perchlorate. No conclusion can be attained in regard to the mechanism of endemic myxedematous cretinism in humans, as marked hyperthyrotropinemia (excessive TSH) seems to be a prerequisite for thyroid involution, and it was not obtained in the second and third experiments of Colzani et al. before acute iodine overload. From his first experiment, it can be concluded that prolonged administration of elevated quantity of iodine to hypothyroid rats having consumed an iodine- and selenium- deficient diet does not involve irreversible insult to the thyroid: These rats recovered normal thyroid function tests once iodine deficiency was corrected. Previous experiments submitted 11-day-old rats to a combined iodine- and selenium-deficient diet: Serum thyroid function tests clearly reflected severe hypothyroidism. In these conditions, no evidence of thyroid atrophy, fibrosis, or necrosis was observed (48).

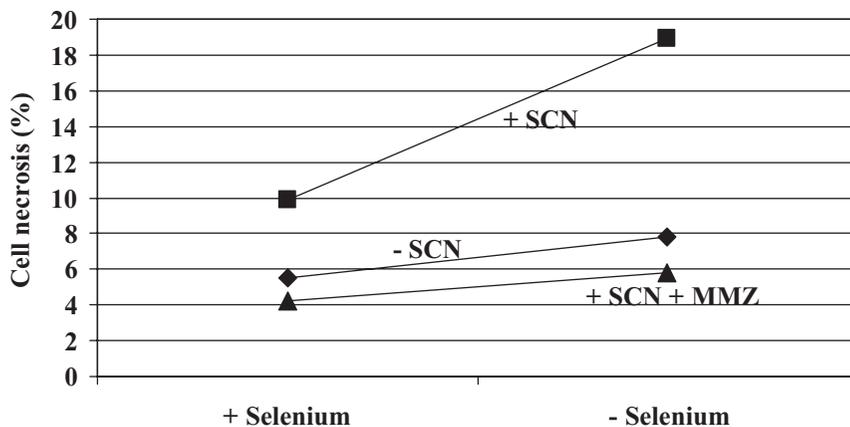


Figure 4 Twenty-one-day-old Wistar rats were exposed to a perchlorate \pm selenium-deficient diet for five weeks before intraperitoneal injection of iodine (1 mg) \pm 20 mg thiocyanate (SCN) injected again 24 h and 48 h after the first injection with 1% SCN in tap water. To test the effect of thyroperoxidase, methimazole (MMZ) was given as an enzyme inhibitor in an SCN-treated group. The results show the interaction of selenium deficiency and SCN overload on the percentage of necrosis in thyroid and the inhibition of the effect through MMZ. In selenium-sufficient rats not exposed to perchlorate, the percentage of necrotic cells is $<0.3\%$. Adapted from the experimental data published by Contempré et al. (23).

Contempré et al. (23) have performed an experimental model still closer to the environmental conditions of endemic myxedematous cretinism in Congo by submitting rats to perchlorate (as substitute for long-term iodine deficiency and iodine depletion of the thyroid gland) and selenium deficiency before administering to the animals an acute suprathysiologic dose of iodine. The effect of acute administration of thiocyanate in these conditions on thyroid histology and thyroid function tests was measured (see Figure 4).

In perchlorate-treated rats with a selenium-sufficient diet, 5.5% of the thyroid cells were necrotic after acute administration of iodine. The percentage of cell necrosis increased to 7.8% in selenium-deficient rats, to 9.9% in thiocyanate-treated rats receiving a selenium-sufficient diet, and to 18.9% in thiocyanate-treated rats receiving a selenium-deficient diet. Methimazole blocked in great part the necrotizing effect of thiocyanate on thyroid cells, a finding that suggests this compound has to be organified to become toxic. Fibrosis of the thyroid gland was, also, much more severe in selenium-deficient rats. These experimental conditions are extreme when compared with the natural environment of Congo: Acute thiocyanate overload in rats resulted in a serum concentration more than three times greater than the one observed in the human population. It is known that with increasing thiocyanate overload, plasma thiocyanate concentration reaches an upper

limit, whereas urinary thiocyanate concentration continues to increase and is a better index of huge overload (29a). In other, previous studies, rats were treated with perchlorate and were administered a more moderate thiocyanate overload resulting in serum concentration similar to the one of human population living in Northern Congo. They were also submitted to acute iodine overload (200 μg). In these conditions, the goitrogen effect of thiocyanate was well documented, but no necrosis of thyroid tissue was observed (25b). Nevertheless, Contempré et al.'s model possibly could reproduce in a short term what happens in a long term in the real world.

Up to now, thyroid dysfunction has not been put in evidence in selenium protein P experimental knockout animals (the knockout involves a profound decrease in activity of all selenium-dependent enzymes, including deiodinases) (11). No abnormal thyroid hormone metabolism has been described in this model (61b), but no experiment with iodine-deficient diet has been published up to now with these genetically modified rodents.

In humans, no genetic deficiency of any of the three selenium-deiodinases has been documented up to now. In October 2005, a genetic link of selenium with a human disease was published (27), with evidence of altered thyroid hormone metabolism (slightly increased serum TSH and T4 and slightly decreased serum T3 and reverse T3). The defect involves a binding protein that epigenetically modulates the linking of tRNA (selenocysteine) on specific UGA codons on mRNA. Clinically, these subjects have moderate growth retardation before puberty.

PHENYLKETONURIC CHILDREN AND POPULATION WITH MARGINAL SELENIUM AND IODINE STATUS In areas without iodine deficiency, the relationship of thyroid hormone metabolism with selenium has been studied in phenylketonuric children supplemented with a special diet. These children lack selenium as a result of diets that are poor in phenylalanine and they have isolated selenium deficiency. Although selenium nutrition could conceivably affect thyroid function in infants, children, and adolescents, available data (13, 72) suggest that the effect of selenium deficiency on thyroid function is relatively modest, and likely without any clinical consequence on intellectual or somatic development. Peripheral thyroid hormone metabolism is biochemically impaired, but there are no changes in TSH or clinical signs of hypothyroidism, a finding that suggests these patients are euthyroid.

CONGENITAL HYPOTHYROIDISM In patients who have absent or decreased production of thyroid hormones and who rely solely on deiodination of exogenous L-thyroxine for generation of the active triiodothyronine (such as patients with congenital hypothyroidism due to aplasia of the gland), selenium supplementation may optimize the feedback loop at the pituitary level. This optimization is reflected by a decrease of serum TSH during selenium supplementation (16). This unique study was conducted in Belgium, with a marginal selenium deficiency; it was a longitudinal observation follow-up with no untreated control group. The biochemical changes seem minimal, and may be due to variations of substitutive

hormone intake. Perhaps the most important conclusion of this study is that congenital hypothyroidism (sporadic form) is not associated with altered metabolism of selenium and of selenium-enzymes (at least, plasma glutathione peroxidase and deiodinases seem unaltered).

OTHER POPULATION STUDY OF COMBINED IODINE AND SELENIUM DEFICIENCY A minimal effect of selenium on thyroid hormonal profile was also observed in New Zealand in a population with marginal deficiency of selenium and iodine (70). Lack of significant associations between plasma selenium and thyroid status, and only minimal changes in T₄, suggest that the selenium status in New Zealand is close to adequate for the optimal function of deiodinases. The results suggest that plasma selenium of about 65–70 $\mu\text{g/L}$ may be adequate for optimal function of the deiodinases, reflecting a daily dietary intake of 30–35 μg . This compares with a plasma selenium concentration of 85–90 $\mu\text{g/L}$ and dietary selenium intake of 45–55 $\mu\text{g/day}$ for maximal glutathione peroxidase (69). These data suggest that deiodinases rank high in the hierarchy of selenium supply and are therefore less likely to be affected by marginal selenium deficiency than is glutathione peroxidase, which is lower on the hierarchy (6).

IODINE-INDUCED HYPERTHYROIDISM

Universal salt iodization was the WHO plan for iodine-deficient African, Asian, and South American countries previously known as endemic. The marked decrease in the prevalence of goiter during the following years was a striking confirmation of the effectiveness of universal salt iodization. Nevertheless, iodine-induced hyperthyroidism was clearly documented in some cases (46, 63, 71, 81). A balance has to be reached between the desirable daily iodine supply necessary to prevent goiter ($>100 \mu\text{g/day}$) and excessive iodine ($>1100 \mu\text{g/day}$ in adults; see Table 1). The risk of developing iodine-induced hyperthyroidism is small ($<1\%$ in the general population), a precise incidence rate being impossible to obtain up to now; this rate is increased in the subgroup of women over 40 years of age with longstanding, nodular, and potentially autonomous goiter. From experimental data, it is considered that autonomy of the gland results from a mutation of TSH receptor in thyroid tissue, which renders the hormonal synthesis independent of its control by thyrotropin (79). As long as iodine deficiency is present, the multinodular goiter is functionally inefficient. With iodine supplementation, the autonomous parts of the gland become active, and the patient develops hyperthyroidism (sometimes named Jod-Basedow hyperthyroidism). Although the number of cases is low and the clinical signs are asymptomatic or moderate most of the time, some deaths occurred in relationship with the introduction of universal salt iodization in Africa. It is likely that the problem is transient in public health terms, as the *primum movens* cause—presence in the population of autonomous thyroid gland due to iodine deficiency—will decrease with time.

KASHIN-BECK DISEASE

Kashin-Beck disease is an endemic degenerative osteoarthropathy that affects rural villages in a belt crossing China from its northeastern to southwestern extremities and extending to the Tibet autonomous region. From its geographical distribution, it is clearly an environmental disease. Historically, a similar clinical picture has been described in Siberia (Urov disease).

In the 1970s, it was observed that cereals of endemic areas provoked a liver necrosis in rats. This observation called to mind the effect of selenium deficiency on liver necrosis in rats (9, 10, 62). Since that period, one of the largely tested hypotheses was that extreme selenium deficiency is a major risk factor for developing the disease. An English review from Xi'An Medical University (Shaanxi province) summarizes 110 Chinese papers on that subject (38). Eleven epidemiological studies are reviewed—six were longitudinal observations and five were community therapeutic trials—without random allocation. Two of these community therapeutic trials are described in more detail (24, 85). In the first one (24), selenium fertilizer applied to soil increased the selenium content in children's hair from 82 ng/g to 215 ng/g within 10 months ($n = 473$) and increased further to 295 ng/g one year later. The 448 children of unsupplemented villages remained at a low concentration (between 65 and 70 ng/g) during the whole period (the threshold of minimal selenium concentration in hair for the prevention of Kashin-Beck disease is considered to be around 110 ng/g). Fifty-five percent (94/173) of patients with Kashin-Beck disease recovered or were improved in the supplemented villages, versus 8% (15/184) in the unsupplemented villages; the diagnosis was based on hand X-ray. In the second of these cited therapeutic trials (85), selenium supplement was introduced in salt (16 mg sodium selenite per kilo), and evolution of Kashin-Beck disease after one year was compared in 46 children supplemented with the salt (treated group) and in 89 children receiving unsupplemented salt (control group). In the treated group, 18 of the 30 children with Kashin-Beck disease improved (versus 6 of 24 children with Kashin-Beck disease in the control group). It should be noted that in this study, at baseline, the proportion of children with Kashin-Beck disease was greater in the treated group (63%; 30/46) than in the control group (41%; 18/44), suggesting the interference of major confounding variables. No double-blind, controlled, monitored, randomly allocated trial with selenium versus placebo was apparently conducted by the Xi'An Medical University.

In 1995, extremely severe iodine and selenium deficiency was documented in 11 Tibetan villages affected by endemic goiter, cretinism, and Kashin-Beck osteoarthropathy (51). Interestingly, the prevalence of the disease was significantly associated with iodine deficiency in the villages, but the selenium deficiency was homogeneously extremely severe in all groups independent of whether Kashin-Beck osteoarthropathy was present. In the same villages, a blind, controlled, randomized therapeutic intervention was tested (iodine with/without selenium) during one year (50). Despite the excellent compliance as reflected by the monitoring of urinary selenium concentration, no clinical benefit was evident. This negative



Figure 5 With universal salt iodization, endemic cretinism and maybe Kashin-Beck osteoarthropathy become evanescent. In a few decades, the clinical experience with these diseases will be over, and the syndrome will look as exotic as the baby in this painting, who could present a morphological appearance compatible with sporadic cretinism. “The Soothsayer” of Jan Lievens, a close collaborator of Rembrandt, around 1631 at Leyden, Holland, courtesy of reproduction from the Staatliche Museen zu Berlin. Artistic information from Professor J.F. Lhotte, Faculté des Arts et des Sciences, Université de Montréal.

result casts doubt on the causal nature of the association of Kashin-Beck disease with iodine and/or selenium deficiency. Studies conducted by colleagues of the Xi'An Medical University cited above were based on a radiological definition of Kashin-Beck disease, whereas the inclusion criteria in Tibet were based on a clinical definition of the disease (joint pain, deformity, and limited mobility). At baseline, only 27 of the 133 Tibetan children presented radiological lesions; these results suggest that the radiological criteria of the disease were more sensitive in the studies conducted by the Xi'An Medical University.

Besides iodine and selenium deficiency, organic matter in drinking water and mycotoxin contamination have also been proposed as risk factors for Kashin-Beck disease (57): The contamination of cereals (mainly barley) by mesophilic fungi *Trichothecium roseum*, *Dreschlera Ito*, and *Alternaria Nees* was, indeed, consistently greater in endemic villages of Tibet (18) and of Yulin, Shaanxi province in China (84). A multifactorial origin of the disease is progressively emerging (65).

Few experimental data on the effect of selenium deficiency on bone development in animals are available. Rats submitted for 3 to 11 months to a selenium-deficient diet lost weight and showed decreased bone density (61a). Cartilage was microscopically normal and only electronic microscopy revealed some cellular lesions. Rats submitted for two generations to a selenium-deficient diet presented growth retardation, impaired bone metabolism, and osteopenia (49b). Curiously, iodine deficiency with compensated hypothyroidism (elevated TSH, low T4, normal T3) mitigates growth retardation and osteopenia in selenium-deficient rats (49a). Up to now, specific bone development impairment of Kashin-Beck disease—such as disproportionate short femur and short humerus with chondrodysplasia in the extremities—has not been reproduced experimentally.

In the long term, this endemic disease—whatever the pathogenesis—disappears in parallel with improvement of environmental conditions (including iodine supplementation) (personal observation in Angkan village, Shaanxi province, where Kashin-Beck disease disappeared soon after introduction of iodized salt) (76).

Like endemic cretinism, Kashin-Beck osteoarthropathy is an evanescent endemic disease. It recedes at the speed of socioeconomic progress of China. In a few years, this syndrome will be considered a historical souvenir, and scientists will be puzzled by the description of these cases, in the same manner we may now be perplexed in viewing an old Flemish picture (see Figure 5) of a suspected young myxedematous cretin on the back of his mother.

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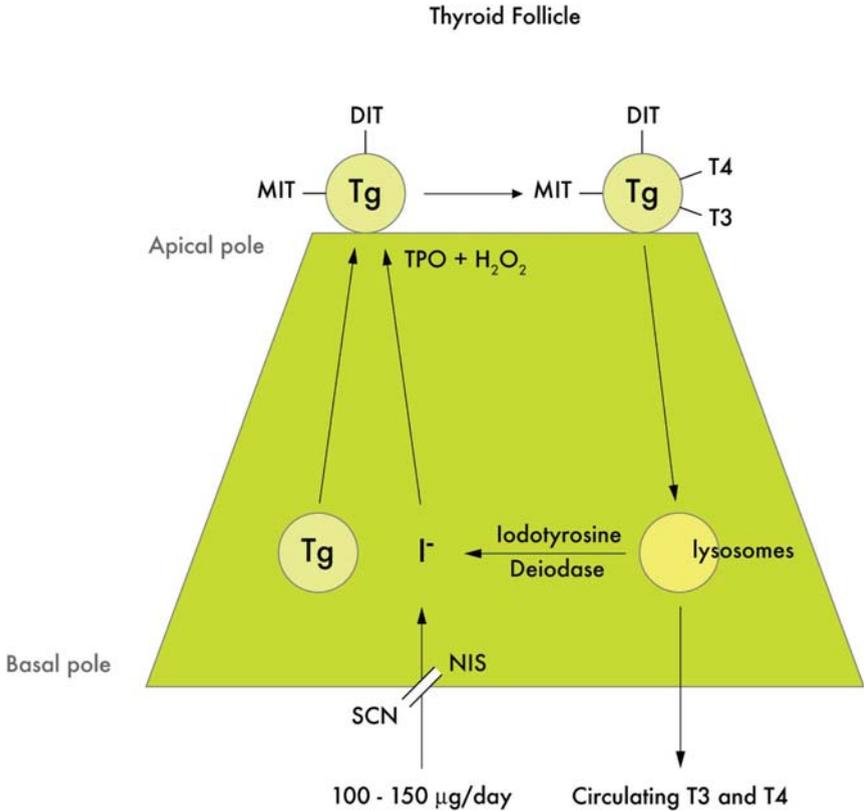


Figure 1 Biochemical steps of iodine (I) uptake and hormone synthesis (T4, thyroxine; T3, triiodothyronine) in the thyroid involving natrium-iodine symporter (NIS) at the basal membrane and hydrogen peroxide (H_2O_2) generation at the apical membrane. Thyroid peroxidase (TPO) oxidizes iodine in the presence of H_2O_2 and incorporates it on tyrosyl residues of thyroglobulin to form mono- and diiodotyrosyl (MIT and DIT) residues. The same enzyme TPO is coupling MIT and DIT to form T4 and T3. Thyroglobulin (Tg) is directed from the follicle space to intracellular lysosomal degradation, and T4 and T3 are secreted in the circulation. MIT and DIT are deiodinated through a deiodinase process different from the selenium deiodinases.

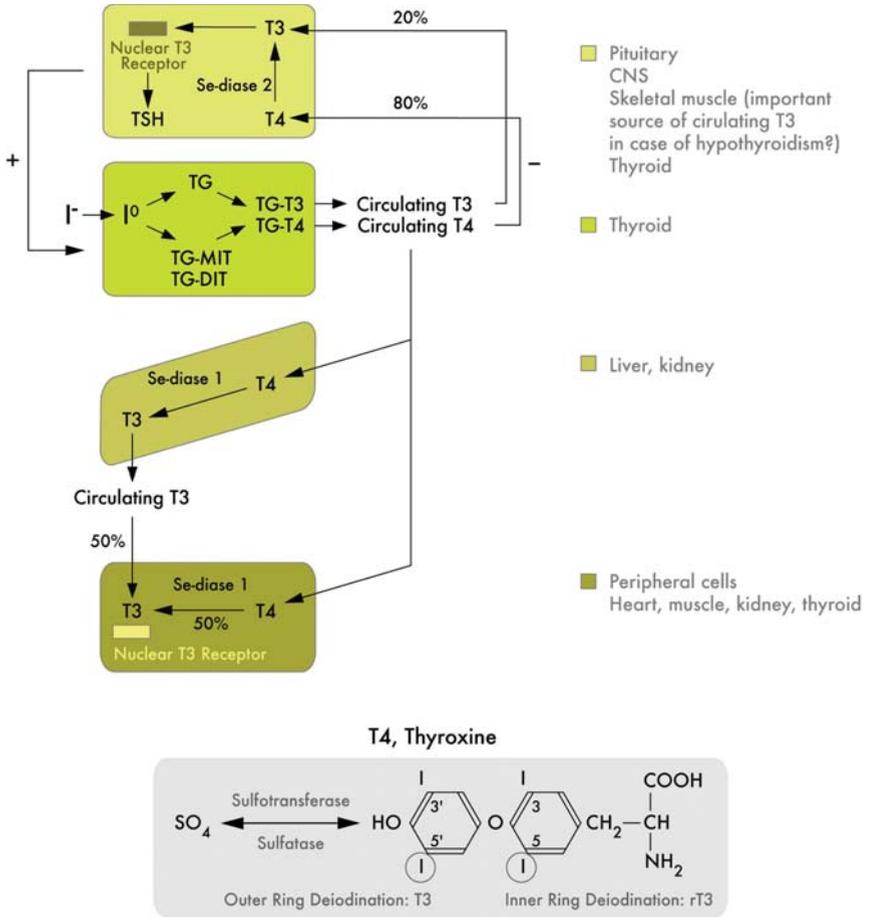


Figure 2 Modulation of thyroid hormone metabolism through selenium-dependent deiodinases (5' selenium-deiodinases 1 and 2) and pituitary control. CNS, central nervous system; TSH, thyroid-stimulating hormone.

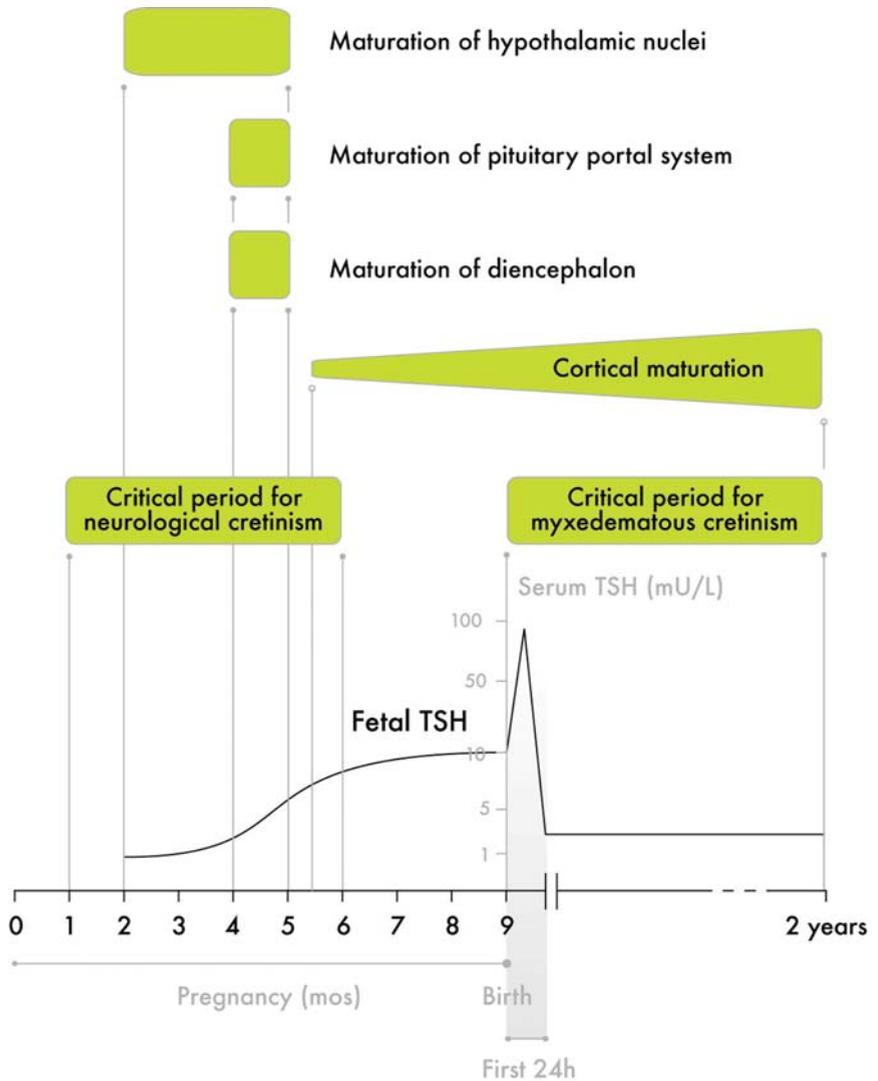


Figure 3 Timing of alterations of the central nervous system in endemic cretinism as a function of clinical features of neurological cretinism and myxedematous cretinism. TSH, thyroid-stimulating hormone. The profile of serum human TSH evolution (logarithmic scale) during fetal life, around birth and during infancy, is the physiological one observed in a population with normal iodine supply. The characteristic neonatal serum TSH surge is maximal approximately 30 minutes after birth (29b).



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ERRATA

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