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cassava toxicity and thyroid: research and public health issues

proceedings of a workshop held in Ottawa, Canada, 31 May – 2 June 1982

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RESEARCH AND PUBLIC HEALTH ISSUES

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Editors: F. Delange[1] and R. Ahluwalia[2]

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Résumé

Cette publication est un résumé des actes d'un atelier qui a porté sur les relations entre la consommation de manioc et les troubles thyroïdiens chez l'homme. L'atelier a rassemblé des spécialistes de la médecine, de l'agriculture et de l'hygiène publique pour (1) examiner les résultats des études subventionnées par le CRDI sur le rôle du manioc dans l'étiologie du goitre endémique et du crétinisme ; (2) passer en revue les travaux de recherche sur les aspects du manioc intéressant l'agriculture ; (3) échanger des informations sur la méthodologie et les résultats d'études dans des domaines connexes ; et (4) définir les priorités de recherche et faire des recommandations touchant les programmes d'hygiène publique. La poursuite des travaux de recherche dans ces domaines contribuera grandement à prévenir et à contrôler le goitre endémique qui, par les anomalies de développement dont il est la cause constitue toujours un grand danger pour les populations des pays en développement.

Resumen

Esta publicación informa sobre las exposiciones presentadas en un seminario dedicado a la relación entre el consumo de yuca y el problema de la tiroides en los humanos. El seminario reunió científicos de los sectores médico, agrícola y de salud pública con el objeto de (1) reseñar los resultados de los estudios financiados por el CIID sobre el papel de la yuca en la etiología del bocio endémico y el cretinismo, (2) reseñar las actividades investigativas sobre aspectos agrícolas de la yuca, (3) intercambiar información sobre metodologías y hallazgos de otros estudios relacionados, y (4) identificar prioridades específicas para la investigación y hacer recomendaciones para los programas de salud pública. Los esfuerzos continuos en estas áreas de la investigación se dezicarán en buena parte a prevenir y controlar el bocio endémico y sus anormalidades acompañantes en el desarrollo, las cuales siguen constituyendo un problema serio de salud pública entre las poblaciones del mundo en desarrollo.

Contents

Nutritional Factors Involved in the Goitrogenic Action of Cassava[1]

F. Delange, P. Bourdoux, E. Colinet, P. Courtois, P. Hennart, R. Lagasse, M. Mafuta, P. Seghers, C. Thilly, J. Vanderpas, Y. Yunga, and A.M. Ermans[2]

Previous studies in Zaire have shown that cassava has a definite antithyroid action in humans and animals, resulting in the development of endemic goitre and cretinism. This action is due to the endogenous release of thiocyanate (SCN) from linamarin, a cyanogenic glucoside contained in cassava, in particular in the tuberous roots. Despite the fact that cassava is consumed on a large scale within the tropics, however, goitre and cretinism are not found in all populations whose staple food is cassava.

One possible explanation for the lack of goitrogenic action by cassava in some populations may be that they have a high iodine intake. Indeed, in Idjwi Island, Kivu, and Ubangi, Equateur, the antithyroid action of cassava was observed in the presence of severe iodine deficiency. Moreover, the correction of iodine deficiency through injections of slowly resorbable iodized oil resulted in the eradication of endemic goitre and cretinism and the normalization of thyroid function.

Studies conducted in Sicily proved that SCN may have a goitrogenic action even when the iodine supply is not as dramatically reduced as that observed in Zaire. The question, therefore, is "At what level of iodine intake does ingestion of SCN precursors, such as those found in cassava, alter the iodine metabolism of the thyroid gland and play a decisive role in the etiology of endemic goitre?"

Another nutritional factor that may be involved in the goitrogenic action of cassava in humans is the protein calorie intake, because the endogenous conversion of cyanide (HCN) into SCN requires sulfur amino acids. Experiments with pigs have indicated that protein deficiency protects against the antithyroid action of cassava by reducing the quantity of SCN arising from HCN. It has also been shown experimentally that the presence of protein calorie deficiency impairs the development of goitre due to a goitrogenic diet.

The observation in the Ubangi endemic goitre area of retarded psychomotor development in young infants who do not show the other features of endemic cretinism is probably explained by the mechanism involved in the etiology of endemic cretinism, i.e., thyroid insufficiency occurring during the critical period of brain development covering the fetal life and the first years of life. According to such a concept, cassava toxicity for the brain should be mediated by an elevated production of SCN, as described for the pathogenesis of goitre. However, the large amount of HCN present in several cassava-based foodstuffs evokes the question of whether mental retardation in endemic goitre could result from a direct toxic action of HCN on the central nervous system.

In summary, two main questions arose from previous observations on the role of cassava in the etiology of endemic goitre and cretinism (Ermans et al. 1980):

(1) What are the nutritional prerequisites for cassava to induce the development of endemic goitre and cretinism in humans? More specifically, what are the respective roles of iodine and

[1]The information in this paper has been summarized from *Nutritional factors involved in the goitrogenic action of cassava*, IDRC-184e. An extensive reference list can be found in this publication.

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protein calorie intake in the presence of a cassava-based diet?

(2) What mechanisms are responsible for the mental retardation observed in endemic goitre? Is it caused indirectly, by congenital thyroid failure, or directly, by the toxic action of HCN on the central nervous system?

The first objective of the current study, therefore, was to evaluate the nutritional conditions required in humans for cassava to induce endemic goitre and cretinism. This objective was reached by means of field studies performed in three rural areas of Zaire (Bas Zaire, Kivu, and Ubangi) where cassava was the staple food and which were characterized by the presence or absence of goitre and malnutrition and by different intake levels of iodine. Kinshasa and Brussels were used as control areas. In the three areas investigated in Zaire, epidemiological, clinical, nutritional, and biochemical studies were conducted in the general population, adults, young infants, mothers at delivery, and newborns. Extensive biochemical analyses of the HCN content of cassava products and of the processes used to detoxify cassava were also performed.

The second objective was to evaluate the respective roles played by thyroid failure and the toxic effect of HCN on the central nervous system. This was achieved by feeding groups of pregnant rats various diets characterized by the presence or absence of iodine deficiency, and HCN and SCN overload. The study included the estimation of the growth of the litter, weight of the thyroid and brain, serum levels of thyroxine and SCN, and brain content of total proteins, DNA, RNA, and lipids to assess the cellularity and myelinization process.

The successive steps of the work included: (1) epidemiological studies of goitre and malnutrition, and nutritional surveys and estimation of dietary supplies of iodine, thiocyanate, and proteins in Bas Zaire, Kivu, and Ubangi; (2) study of the influence of dietary goitrogens and proteins on thyroid function in adults and young infants; (3) study of the influence of dietary goitrogens during pregnancy on thyroid function of the newborn; (4) study of the HCN content of cassava products and the influence of the detoxification processes; (5) studies on the influence of breast-feeding on thiocyanate metabolism and thyroid function in young infants in severe endemic goitre; (6) further assessment of the role of the balance between the dietary supplies of iodine and thiocyanate in the etiology of endemic goitre in the Ubangi area; (7) study of the serum levels of free amino acids in adult males, mothers at delivery, and newborns; and (8) experimental study of the mechanisms responsible for mental retardation resulting from chronic cassava ingestion.

Methods

The methods used in these studies have been described extensively in Ermans et al. (1980) and Delange et al. (1982).

Results

Table 1 summarizes the epidemiology of goitre and malnutrition, nutritional habits, dietary supplies of iodine and thiocyanate, and concentrations of serum TSH observed in Bas Zaire, Kivu, and Ubangi. The ratio of the urinary excretion of iodine and thiocyanate has been used as an index of the exposure to dietary goitrogens and serum TSH was used as an index of impairment of thyroid function. Brussels served as the control area. Goitre was absent in Bas Zaire, slightly endemic in Kivu, and hyperendemic in Ubangi, where 51.1% of the population had visible goitre and 18.8% had nodular goitre. Endemic cretinism was found only in Ubangi, where 91% of the cretins were of the myxedematous type. Clinically detectable malnutrition was extremely frequent in Kivu, less frequent in Bas Zaire, and only occasional in Ubangi.

Within the three areas, a similarly high percentage of the inhabitants surveyed had consumed cassava at least once during the 24 hours preceding the interview. However, the methods of preparing food items containing cassava varied greatly among the three areas. In Ubangi, the preferred food was a cassava gruel (*fuku*), prepared from sun-dried but unsoaked bitter cassava. In Kivu, cassava products were consumed mainly as a cassava paste, prepared from sun-dried and fermented cassava. In Bas Zaire, the most popular foodstuff was a cassava paste prepared from soaked bitter cassava.

The marked increase in the prevalence of goitre from Bas Zaire, to Kivu, to Ubangi was not related to differences in the iodine supply, which was similarly low within each of the three areas, but was inversely related to the progressive decrease of the urinary I/SCN ratio.

Chronic exposure to cassava throughout the

Table 1. Comparison of epidemiological, nutritional, and biochemical data from Brussels, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM.[a] Numbers of patients are shown in parentheses.)

Variables	Brussels	Bas Zaire	Kivu	Ubangi
Epidemiological				
Prevalence (%):				
Endemic goitre	<3	1.5	12.5	76.8
Endemic cretinism	0	0	0	4.7
Weight-to-height <80% of median of standard curve	—	16.0	26.0	8.5
Depigmentation	—	0.0	7.2	0.7
Nutritional				
Daily consumption of cassava (% of inhabitants)	0	96	93	91
Biochemical				
Daily urinary excretion:				
I (μg)	51.2 ± 5.8 (38)	20.5 ± 2.9 (22)***	14.7 ± 1.0 (153)***	15.5 ± 1.3 (243)***
SCN (mg)	5.37 ± 1.07 (38)	7.24 ± 1.09 (24)^{ns}	5.88 ± 0.31 (1.52)^{ns}	10.75 ± 0.61 (140)***
Urinary I/SCN ratio (μg/mg)	8.8 ± 0.4 (38)	3.8 ± 0.7 (23)***	2.6 ± 0.1 (156)***	1.9 ± 0.2 (121)***
Serum concentration				
Adults:				
SCN (mg/dL)	0.26 ± 0.01 (113)	0.80 ± 0.04 (87)***	0.74 ± 0.05 (118)***	1.05 ± 0.04 (292)***
TSH (μU/mL)	1.7 ± 0.1 (125)	2.7 ± 0.2 (183)***	1.7 ± 0.1 (178)^{ns}	18.6 ± 2.1 (365)***
Infants 1–3 years:				
TSH (μU/mL)	2.2 ± 0.2 (94)	3.1 ± 0.3 (41)*	1.1 ± 0.1 (64)***	40.2 ± 9.5 (129)***

[a]Levels of significance refer to a comparison with the results from Brussels: ^{ns}, nonsignificant; *, $P<0.05$; ***, $P<0.001$.

three rural areas was reflected by elevated concentrations of serum SCN, with the highest values being found in Ubangi.

The concentrations of serum TSH in clinically euthyroid adults and in infants aged 1–3 years were normal in Bas Zaire and Kivu, in spite of a lower I/SCN ratio in these two areas than in Brussels and the presence of goitre in Kivu. In contrast, serum TSH was markedly elevated in Ubangi. The TSH levels found in young infants in Ubangi were markedly higher than those found in adults, in spite of the fact that the infants also had higher serum T_4 levels than the adults.

The severity of malnutrition in Kivu was also evidenced by markedly lower concentrations of serum albumin than in the Belgian controls, principally in infants between 1 and 5 years of age.

It has to be pointed out that the prevalence of goitre found in Kivu in this study was seven times greater than the figure of 1.8% reported in 1972 from the same villages. In contrast, the degree of iodine deficiency was unchanged. This evolution corresponds to a marked increase in the consumption of cassava in Kivu due to the dramatic food shortage occurring within the area.

Table 2 presents the urinary concentrations of iodine and thiocyanate and urinary I/SCN ratios found in pregnant women at the time of delivery in Bas Zaire, Kivu, and Ubangi. In this study, Kinshasa was used as the control area because the nutritional status of pregnant women there was better than in Brussels. The I/SCN ratio was lower in the three rural areas than in Kinshasa but the differences were significant only for Kivu and Ubangi. Within the three areas, the I/SCN ratios were higher in women at delivery than in the adult population in general (cf. Table 1).

Figure 1 compares the mean concentrations of serum T_4, T_3, TSH, and SCN in mothers at delivery in the three rural areas and in Kinshasa. In the controls, T_4 and T_3 levels were higher than in nonpregnant adults, whereas the TSH level was similar, as classically observed in pregnancy. When compared with the control group, total T_4 was slightly lower in Bas Zaire and Kivu and markedly lower in Ubangi. TSH

Table 2. Comparison of concentrations of urinary iodine and SCN, and the urinary I/SCN ratios in pregnant women at delivery in Kinshasa, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM.[a] Numbers of patients are shown in parentheses.)

Variables	Kinshasa	Bas Zaire	Kivu	Ubangi
Urinary concentration				
I (μg/dL)	6.1 ± 0.5 (64)	4.6 ± 0.4 (41)*	3.9 ± 0.2 (140)***	3.5 ± 0.2 (181)***
SCN (mg/dL)	0.84 ± 0.04 (99)	0.89 ± 0.09 (51)^{ns}	1.14 ± 0.05 (146)**	1.52 ± 0.09 (193)***
Urinary ratio				
I/SCN (μg/mg)	12.1 ± 2.8 (64)	7.0 ± 0.5 (41)^{ns}	3.5 ± 0.1 (139)***	3.7 ± 0.5 (176)***

[a]Levels of significance refer to a comparison with the results from Kinshasa: ^{ns}, nonsignificant; **, $P<0.01$; ***, $P<0.001$.

was significantly higher than in the controls only in Ubangi, where it was greater by a factor of 3. T_3 was barely modified. As a consequence of chronic intake of cassava, mean SCN was higher in the three rural areas than in the controls, with the highest value being found in Ubangi.

Figure 2 compares the mean concentrations of serum T_4, T_3, TSH, and SCN in cord blood in newborns in Bas Zaire, Kivu, Ubangi, and Kinshasa. The differences observed between the four areas for T_4 and SCN were similar to those observed in the mothers. In contrast, TSH was significantly higher in Bas Zaire and Kivu than in the control area, whereas TSH was unmodified in the mothers. Moreover, mean cord TSH in Ubangi was 68 μU/mL, which is 10 times higher than in the controls.

Figure 3 presents the individual results obtained for cord TSH and T_4 in Ubangi. The newborns were divided into two groups on the basis of the maternal urinary concentrations of SCN, with a cutoff point of 1.2 mg/dL, which corresponds to the mean value plus one standard deviation in the control group, being used. Group A was born to mothers with a low SCN concentration, whereas group B was born to mothers with elevated SCN concentrations. Both groups of mothers were subjected to a similar degree of extreme iodine deficiency.

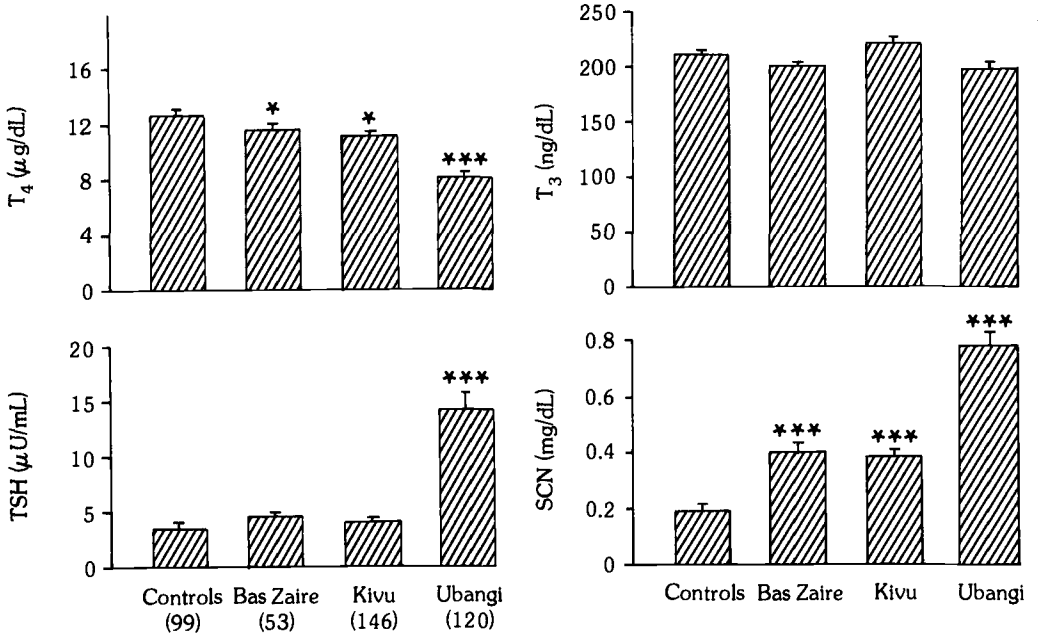

*Fig. 1. Comparison of concentrations of T_4, T_3, TSH, and SCN in mothers at delivery in Kinshasa, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM. Numbers of patients are shown in parentheses. Levels of significance refer to a comparison with the results from Kinshasa, which was used as the control area: *, $P<0.05$; ***, $P< 0.001$).*

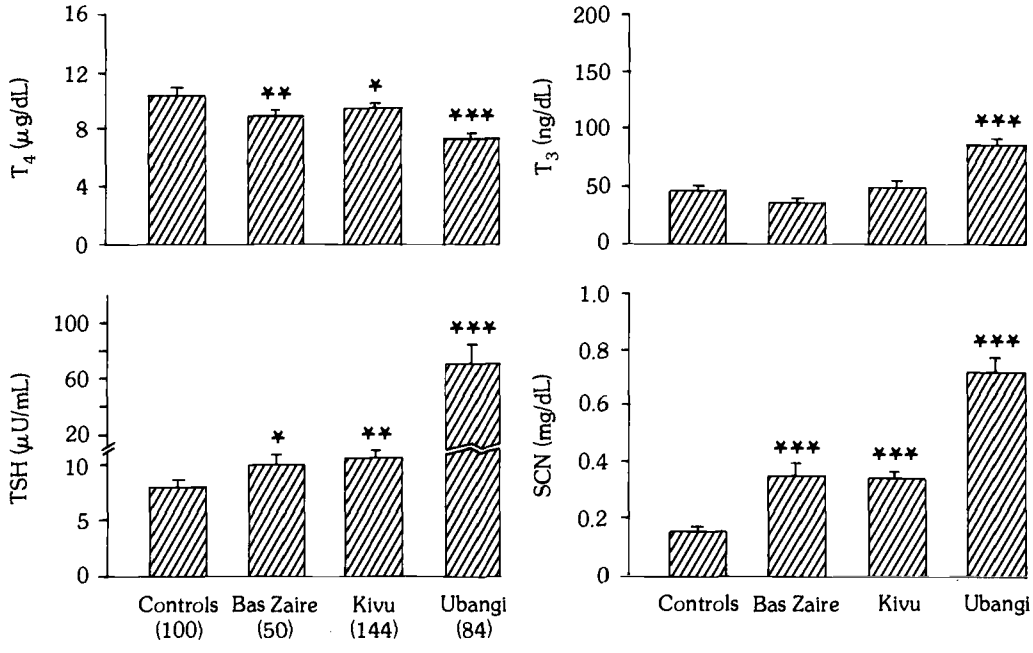

*Fig. 2. Comparison of concentrations of serum T_4, T_3, TSH, and SCN in newborns (cord blood) in Kinshasa, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM. Numbers of patients are shown in parentheses. Levels of significance refer to a comparison with the results from Kinshasa, which was used as the control area: *, P<0.05; **, P<0.01; ***, P<0.001).*

Within the two groups of newborns, both cord TSH and T_4 showed an extremely important variability between individuals. Using cutoff points of 50 μU/mL for TSH and 5 μg/dL for T_4, the frequencies of high TSH and low T_4 were significantly higher in group B, with high thiocyanate, than in group A, with low thiocyanate ($P<0.05$). Considering the Ubangi newborns as a whole, 11.2% had both a cord TSH higher than 100 μU/mL and a cord T_4 lower than 3 μg/dL. These values are characteristic of severe congenital hypothyroidism in western countries.

For the total population of 610 mothers at delivery and newborns investigated in Brussels and Zaire, there was a highly significant correlation between the concentrations of serum SCN in the mothers and in cord blood ($r = 0.908$, $P<0.00001$), indicating that SCN freely crosses the placenta.

Exclusively breast-fed infants had lower concentrations of serum SCN than breast-fed and supplemented infants and infants that had been weaned. They also had a lower prevalence of goitre, although they were submitted to a similar degree of iodine deficiency. Infants aged 0.2–83 months had geometric mean TSH levels that were systematically higher than the Belgian controls. Weaning was accompanied by a further elevation of serum TSH and lowering of serum T_4.

An epidemiological, biochemical, and nutritional study performed along two road axes situated at the southwestern limit of the Ubangi endemic goitre area allowed the respective roles of iodine deficiency and SCN overload in the etiology of endemic goitre to be defined further. Along the two road axes, each approximately 100 km long, the prevalence of goitre increased progressively from 20 to 80% of the population. Serum TSH increased steeply and T_4 decreased when the prevalence of goitre reached 60% of the total population. Along one road (Fig. 4), urinary iodine remained nearly constant and was very low. In contrast, urinary SCN increased as a consequence of increasing consumption of poorly processed cassava with a high content of cyanide. Along the second road, urinary SCN remained constantly high, whereas urinary iodine progressively decreased, probably as a consequence of decreasing consumption of fish. Consequently, along the two roads, the urinary I/SCN ratio decreased from 3.1 in the villages with a low prevalence of goitre to 0.60 and 0.75 in hyperendemic villages.

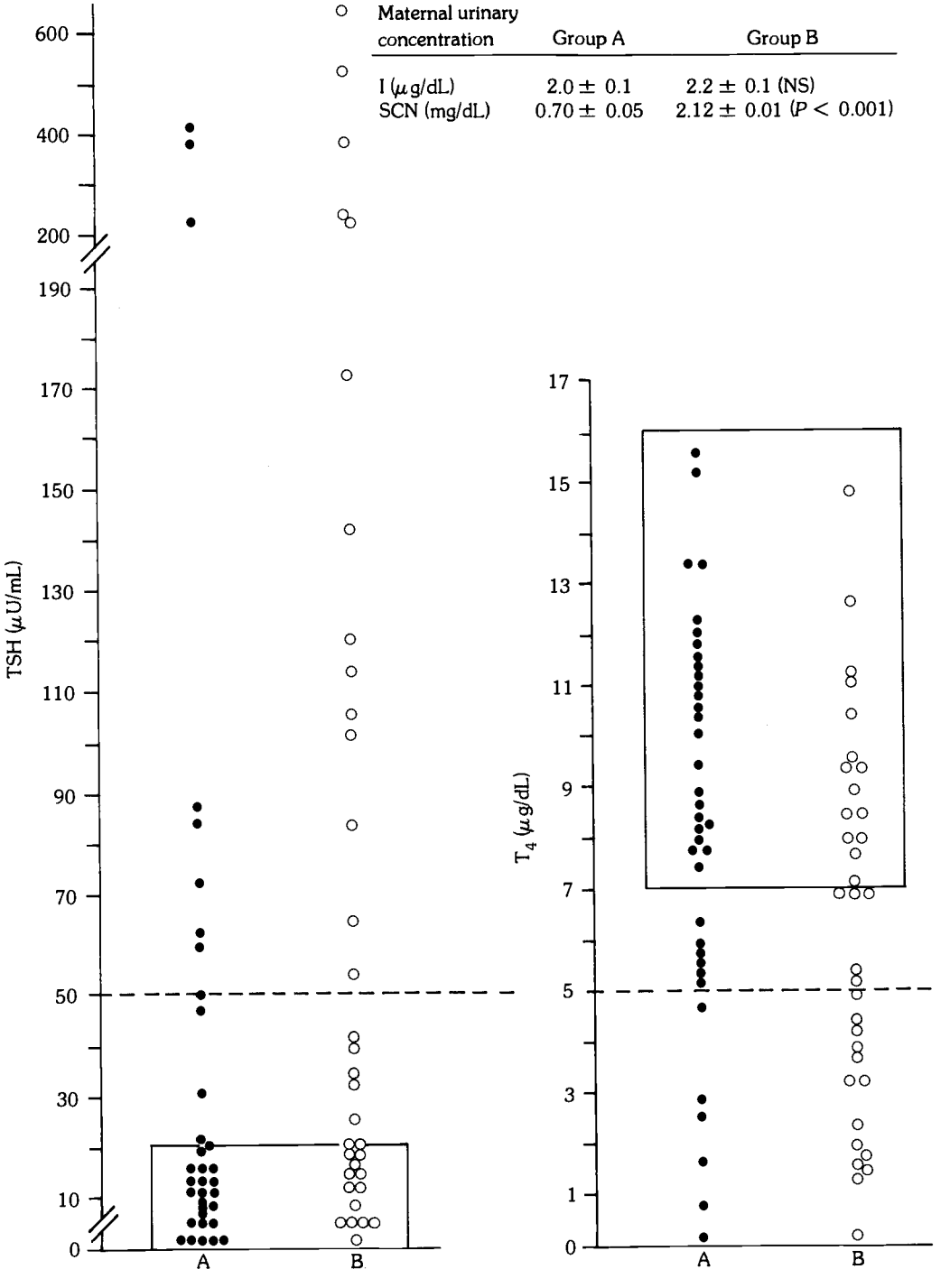

Fig. 3. Comparison of concentrations of serum TSH and T_4 in cord blood in Ubangi as a function of the concentrations of urinary SCN at delivery in severely iodine-deficient mothers. The columns indicate the normal limits for these variables in a Belgian newborn population.

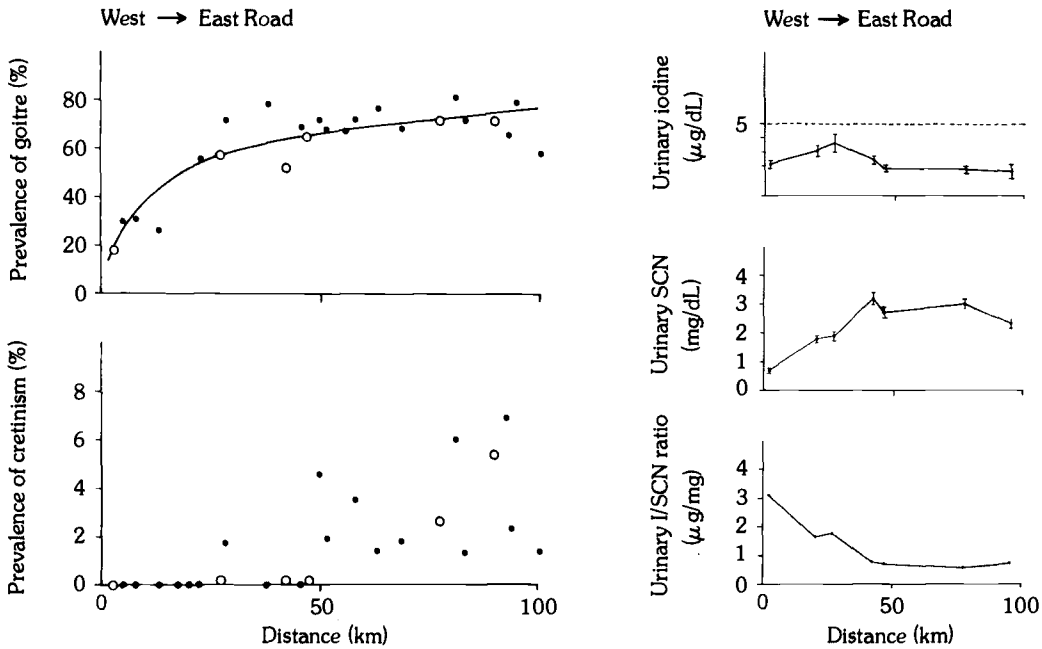

Fig. 4. Changes in prevalence of goitre and cretinism (each point represents one village; open circles represent those where metabolic investigations were carried out), concentrations of urinary iodine and SCN, and urinary I/SCN ratio along one of the two roads. (Mean ± SEM. Broken line represents normal limits for Belgian adults.)

The serum levels of sulfur amino acids, particularly methionine, in adult males, mothers at delivery, and newborns in Kivu and Bas Zaire were not lower than those found in the Belgian controls. In adult males in Kivu, there were low levels of serum branched amino acids, valine, leucine, and isoleucine. This pattern of serum amino acids is characteristic of severe protein calorie malnutrition and is consistent with the low serum levels of albumin found in these patients.

In the experimental study to determine the mechanism responsible for mental retardation resulting from cassava ingestion, it was observed that administration of an iodine-deficient diet alone or an iodine-deficient diet supplemented with HCN or SCN to pregnant and nursing rats induced marked thyroid hyperplasia and decreased serum T_4 in both the mothers and offspring, indicating a state of thyroid insufficiency.

The effect of iodine deficiency plus HCN was greater than that of iodine deficiency alone. HCN-induced hypothyroidism was accompanied by a striking decrease in the protein, RNA, and cholesterol contents of the cerebellum of the pups at the end of the lactation period, indicating a slowing of cellular growth.

The changes induced by HCN overload were not apparent when the overload was associated with a normal iodine supply. HCN overload, with or without iodine supplementation, was accompanied by a highly significant increase in serum SCN concentration.

Figure 5 shows that, for all of the experimental groups studied, regardless of the diet, brain RNA, used as an index of the process of cellular growth, was remarkably constant both in the cerebral hemispheres and in the cerebellum, in spite of variations in serum T_4 concentrations ranging from a normal of about 7 μg/dL to as low as 1 μg/dL in rats at 16 days of age. When serum T_4 fell below this critical threshold, however, RNA content dropped sharply.

Discussion, Summary, and General Conclusions

Field studies conducted in Zaire have demonstrated the following points:

(1) Chronic consumption of large quantities of cassava does not necessarily result in the development of endemic goitre.

(2) In the presence of a cassava-based diet,

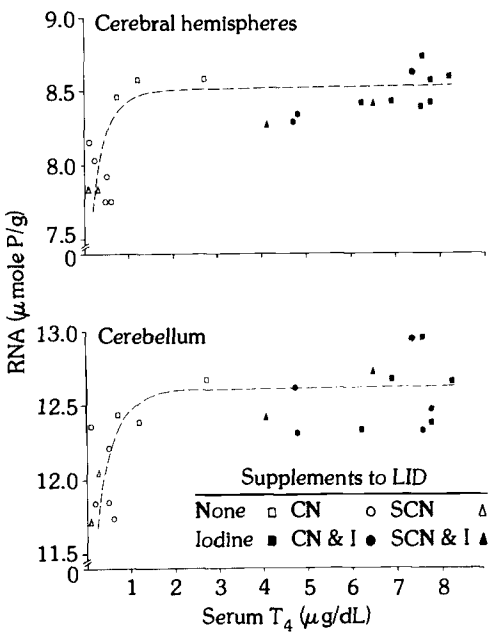

Fig. 5. Relationship between concentration of serum T_4 and RNA content for the cerebral hemispheres and cerebellum in rats 16 days of age and different groups of pregnant and nursing rats subjected to a low-iodine diet (LID) alone or a low-iodine diet supplemented with cyanide (CN), thiocyanate (SCN), or iodine (I). Each point represents the mean for a group of 3-7 animals.

the development of goitre is critically related to the balance between the dietary supplies of iodine and SCN.

(3) Under normal conditions, the I/SCN ratio is higher than 7. Endemic goitre develops when it reaches a critical threshold of about 3 and becomes hyperendemic, complicated by endemic cretinism, when it is lower than 2. The validity of this ratio as an index of the risk of development of goitre has been demonstrated by comparative studies conducted in different regions of Zaire (Fig. 6) and at the limit of the hyperendemic goitre area of Ubangi, as well as previous studies in Sicily. The four factors that determine the I/SCN ratio are: level of iodine intake in the diet; HCN content of fresh cassava roots and leaves; efficiency of the detoxification processes used during the preparation of cassava-based foods; and frequency and quantity of consumption of these foods.

The critical threshold of the I/SCN ratio for the development of goitre may be reached either in the presence of a subnormal iodine supply with markedly elevated SCN supply, as in Sicily, or in the presence of severe iodine deficiency and the periodic utilization of poorly detoxified cassava, as in Kivu. When a similar iodine deficiency is associated with a more frequent and more extreme ingestion of poorly detoxified cassava with a very high content of HCN before detoxification, as in Ubangi, this ratio reaches extremely low values, resulting in the development not only of endemic goitre but also endemic cretinism. When the iodine supply is higher than about 60 μg/day, goitre is not abnormally prevalent, even in the presence of a high SCN supply, as reported previously for some parts of Sicily. Under such conditions, the I/SCN ratio is indeed higher than the previously mentioned critical threshold. Such a situation probably accounts for the absence of endemic goitre in many populations of the world for which cassava constitutes a staple food. Finally, the evolution of the epidemiological, nutritional, and biochemical situation observed in the Kivu area during the last 10 years indicates that the massive introduction of cassava, because of food shortage, in populations previously adapted to iodine deficiency without any abnormal prevalence of goitre results in the development of endemic goitre in these populations.

(4) There are important differences in the HCN content of cassava-based foods among populations in Zaire for whom cassava is the main staple. These differences may be partly

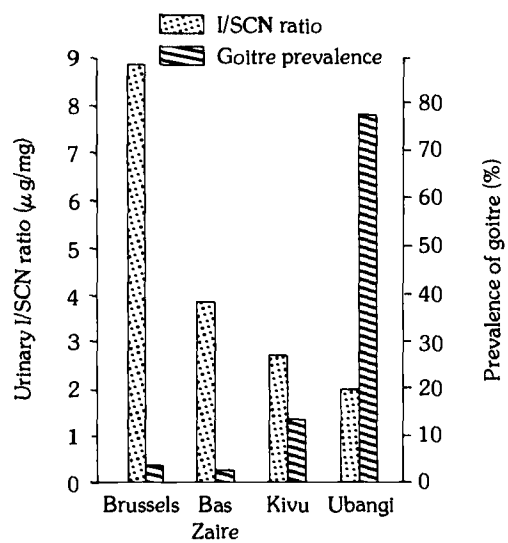

Fig. 6. Relationship between the urinary I/SCN ratio and the prevalence of goitre in Brussels and in the three rural areas investigated in Zaire.

explained by variations in the HCN content of fresh cassava due to genetic or environmental factors, or their interaction, involved in the biosynthesis of linamarin. They are explained mainly by differences in traditional detoxification processes. Soaking clearly appears to be the most efficient detoxification process. Sun-drying, most commonly used in Ubangi, results mainly in a loss of water from the fresh roots but only partial release of HCN.

(5) Even extreme protein calorie malnutrition does not appear to greatly impair the endogenous conversion of HCN into SCN in humans.

(6) In adults, a low urinary I/SCN ratio is accompanied by low concentrations of serum thyroid hormones. However, marked hypersecretion of TSH is observed only when the ratio is lower than a critical threshold of about 2. Adaptation of thyroid function to less severe goitrogenic conditions in the environment can take place without a marked increase in TSH stimulation. Similar observations have been reported in many endemic goitre areas in the presence of moderate iodine deficiency.

(7) Infants and children are more sensitive than adults to the antithyroid action of combined iodine deficiency and SCN overload because they have notably higher TSH than adults, in spite of higher concentrations of thyroid hormones, particularly T_4.

(8) Newborns and, to a lesser extent, pregnant women are still more sensitive to the antithyroid action of dietary goitrogens than infants and children. In populations in which the I/SCN ratio is only slightly decreased and thyroid function is unaffected in adults, TSH and T_4 concentrations in cord blood show a clear-cut shift toward high and low values respectively. When the I/SCN ratio is lower than 2 in the general population, the changes in the newborn are dramatic and about 10% of them exhibit a caricatural biochemical picture of severe congenital hypothyroidism.

The human placenta is permeable to SCN. The specific role played by SCN during fetal life on the development of hypothyroidism at birth is demonstrated by the comparison of thyroid function in newborns in Kivu and Ubangi, where the iodine supply to the mothers is similar but the higher SCN supply in Ubangi is accompanied by markedly higher TSH and lower T_4 in the newborns. In addition, in Ubangi, where two groups of mothers with a similar degree of iodine deficiency were studied, the higher SCN supply in one group of mothers was accompanied by a further increase of TSH and decrease of T_4 in the newborns.

Thus pregnant women and particularly newborns are the vulnerable target groups of the population for the toxic action of cassava on thyroid function.

(9) SCN is significantly lower in breast-fed infants than in newborns, children, and adults because SCN is not concentrated by the mammary gland in humans. Thus, breast-feeding appears to play a protective role against the development of endemic cretinism by not providing cassava to young infants.

In addition to the information obtained on the goitrogenic action of cassava in human beings, the present studies stressed the importance of two other points related to the problem of endemic goitre:

(1) Evaluation of the goitrogenic environment in a given area should be based systematically on the simultaneous assessment of the degree of iodine deficiency and SCN overload.

(2) The main targets of the effects of a goitrogenic environment are pregnant women and, especially, newborns.

Consequently, in endemic goitre areas, systematic screening for congenital hypothyroidism in the newborn constitutes the most sensitive index for detecting the risk of mental deficiency resulting from environmental goitrogenic factors.

Experimental studies on rats confirm that severe hypothyroidism during the neonatal period in the rat, regardless of its cause, produces alterations in the maturation of the central nervous system. The studies have demonstrated that HCN does not affect the process of maturation of the central nervous system in young rats directly but acts indirectly by inducing hypothyroidism after being converted to SCN.

These findings suggest that the cerebral anomalies induced by the consumption of poorly detoxified cassava are mediated by the induction of thyroid failure and, thus, also depend on a critical supply of iodine.

In conclusion, these studies have elucidated the nutritional prerequisite for cassava to induce endemic goitre and cretinism in humans and, more specifically, the respective roles of iodine and protein calorie intake in the presence of a cassava-based diet. They have also established the mechanism responsible for mental retardation observed in endemic goitre in the presence of a cassava-based diet.

These data have important practical implications for the health and development of millions of people in developing countries whose staple diet is cassava. In particular, the possibility

arises that overuse of cassava for nutritional purposes and economic reasons could create new diseases, including mental retardation, in currently unaffected areas by introducing a disequilibrium among the different constituents of the diet.

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