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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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CASSAVA TOXICITY AND THYROID:

RESEARCH AND PUBLIC HEALTH ISSUES

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Proceedings of a workshop held in Ottawa, Canada, 31 May - 2 June 1982

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.

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Foreword

This publication reports on the proceedings of a meeting that represents the culmination of long-term support, provided by the Health Sciences Division of the International Development Research Centre (IDRC), for research on the relationship between the consumption of cassava and thyroid condition in humans.

Over the past decade, significant investments and research efforts at the international level have been devoted toward improved production and processing of cassava. Millions of low-income populations in developing countries rely on this crop as a major staple. However, cassava contains a cyanogenic glucoside, linamarin, which in humans is converted primarily to thiocyanate (SCN) — a known goitrogenic agent. Despite this, very little attention has been paid to cassava toxicity and human health.

Based upon 7 years of research conducted in Zaire, Zairian and Belgian scientists confirmed the role of cassava in the etiology of endemic goitre and cretinism. Even more importantly, they established critical threshold values of the dietary supply of iodine and thiocyanate (I/SCN) as they relate to endemic goitre and hyperendemic cretinism. The studies emphasized the need for appropriate prophylactics and treatment of high-risk groups such as pregnant women and their offspring, a high percentage of whom may suffer from congenital hypothyroidism. The development of new varieties of cassava that contain minimal amounts of linamarin, and effective detoxification techniques at the village level, were underscored. The results of these studies were reported in two previous IDRC monographs and highlighted important public health implications.

Consequently, the Health Sciences Division organized a workshop on cassava toxicity and thyroid, which brought together scientists from the medical, agricultural, and public health sectors, as well as IDRC staff. The objectives of the meeting were to: (1) review results of IDRC-supported studies on the role of cassava in the etiology of endemic goitre and cretinism; (2) review research activities on agricultural aspects of cassava; (3) exchange information on methodologies and findings of other related studies; and (4) identify specific priorities for research and make recommendations for public health programs.

The quality of the individual presentations and active discussions by the participants were instrumental in ensuring the success of the meeting and reflected the keen interest in and commitment to carry out further research and implement appropriate interventions related to cassava toxicity and endemic cretinism. The prompt submission of papers and the assistance of some of the participants who kindly agreed to act as chairpersons and rapporteurs greatly facilitated publication of the proceedings of this meeting.

It is sincerely hoped that the deliberations of the meeting and this publication will serve as a strong catalyst for promoting collaborative research efforts aimed at preventing and controlling endemic goitre and its accompanying developmental abnormalities, which remain a major public health problem for populations in developing countries.

Dr John Gill, former director of this division, and Rashim Ahluwalia, former associate director, played key roles in the success of the workshop, and provided strong support in recent years for cassava toxicity research.

Elizabeth Charlebois
Director
Health Sciences Division
International Development Research Centre

Role of Cassava in the Etiology of Endemic Goitre and Cretinism[1]

A.M. Ermans, P. Bourdoux, J. Kinthaert, R. Lagasse, K. Luvivila, M. Mafuta, C.H. Thilly, and F. Delange[2]

The goitrogenic role of cassava has been evinced through studies carried out in severe endemic goitre areas of Zaire: Idjwi Island, Kivu, and Ubangi. These studies were initially devoted to the adaptation mechanisms of the thyroid function to iodine deficiency, in order to define an adequate method of iodine prophylaxis. The existence, in these areas, of marked iodine deficiency has been extensively documented and most of the observed abnormalities of thyroid function have been satisfactorily explained on this basis. However, some findings have not been consonant with generally accepted views concerning the physiopathology and management of endemic goitre and its associated complications.

The first area of disagreement involves the lack of parallelism between the degree of iodine deficiency and the severity of the goitrous endemias. For instance, on Idjwi Island, very high (60–70%) or very low (<5%) prevalences of goitre were observed in communities with similarly low iodine intake levels. In both goitrous and nongoitrous regions of Idjwi Island, urinary iodine was found to be extremely low, and nearly identical high values were observed for ^{131}I thyroid uptake. The discrepancy between goitre prevalence and iodine deficiency was first reported by Delange et al. (1968) and subsequently confirmed by Thilly et al. (1972). Similar findings had previously been reported by Roche (1959), in Venezuela, and Choufoer et al. (1963), in New Guinea. Therefore, although iodine deficiency could be considered as the major causative factor of endemic goitre on Idjwi Island, an additional goitrogenic factor was obviously intervening and producing important epidemiological variations.

A second unexplained finding was the dramatically high incidence observed in these regions of a particular form of cretinism, myxedematous cretinism, which so far has not been reported in other severe endemic goitre areas of the world. The disease was similar to the untreated congenital hypothyroidism observed in industrial countries. In previous descriptions of endemic cretinism the syndrome was characterized mainly by very severe mental retardation and several neurological abnormalities; no specific impairment of thyroid function has been reported in neurological cretinism. The question, therefore, arose: Is the myxedematous cretinism observed in Central Africa related to the goitrogenic environment and, if so, by what specific mechanism?

The third point developed as a consequence of local socioeconomic conditions, which suggest the uselessness of a program of iodine prophylaxis based upon the distribution of iodized salt. This view was supported mainly by the lack of convenient commercial networks for salt distribution and also because of the instability of iodized salt under tropical climatic conditions. Failure of this type of program has been reported in several countries of the Third World. It appears necessary, therefore, to develop a new method of iodine prophylaxis that could

[1]The information in this paper has been summarized from *Role of cassava in the etiology of endemic goitre and cretinism*, IDRC-136e. An extensive reference list can be found in this publication. The work was supported by the International Development Research Centre (IDRC), Canada; l'Administration Générale de la Coopération au Développement (AGCD), Belgium; and the Fonds de la Recherche Scientifique Médicale (FRSM), Belgium.

[2]Centre Scientifique et Médical de l'Université Libre de Bruxelles pour ses Activités de Coopération (CEMUBAC), Belgium, and Institut de Recherche Scientifique (IRS), Zaire, Goitre Program; Departments of Radioisotopes, Pediatrics, and Public Health, University of Brussels, Belgium.

be readily adapted to local conditions.

This paper will attempt to provide answers to these medical and physiopathological problems. The research was performed on a multidisciplinary basis in the field, in endemic areas, or in Brussels, where all experimental studies were carried out.

Role of Cassava in the Pathogenesis of Endemic Goitre

To define the additional goitrogenic factor which, in association with iodine deficiency, could account for the particular epidemiological findings observed, the study initially focused on the goitrogenic properties of certain foodstuffs in humans, paying particular attention to cassava. Earlier, Ekpechi et al. (1966) established the antithyroid properties of cassava in rats, and Ermans et al. (1969) demonstrated that cassava intake was higher in goitrous areas than in nongoitrous areas, although cassava is a mainstay in the diet of the inhabitants of Idjwi Island.

The influence of the principal foodstuffs consumed on Idjwi Island on the distribution of a tracer dose of ^{131}I was tested. Following a cassava meal, ^{131}I uptake by the thyroid was clearly reduced, accompanied by increased urinary output of ^{131}I and stable iodine. This finding suggested that cassava contained a thiocyanate-like substance producing a transitory inhibition of the thyroid iodide pump.

Experimental Studies on the Goitrogenic Action of Cassava

As a result of the clinical observations, experiments involving iodine-deficient rats fed on fresh cassava roots were undertaken. Within a short period of time, a rapid and sustained increase in serum thiocyanate concentration, associated with inhibition of ^{131}I uptake by the thyroid, was observed (Fig. 1). Thus, the experimental model reproduced the results of the clinical investigation and confirmed that the inhibition of thyroid iodide uptake was due to endogenous production of thiocyanate.

Despite these results, the hypothesis that the

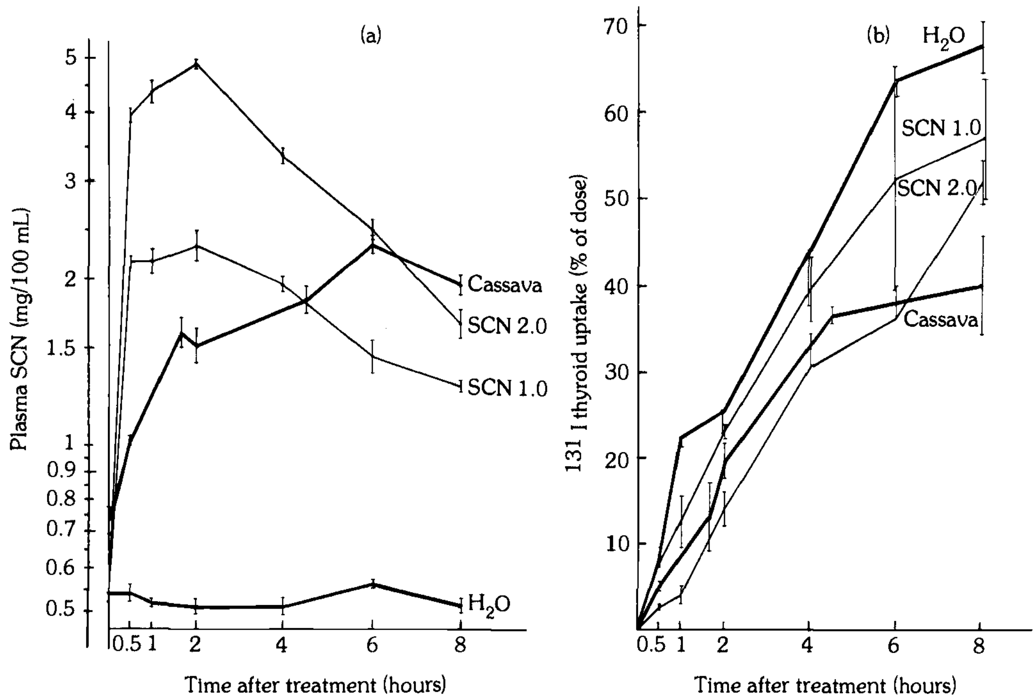

Fig. 1. Short-time effects of the ingestion of crude cassava tubers compared with those due to the absorption of a single thiocyanate dose (1.0 or 2.0 mg) in rats: (a) modifications of SCN plasma concentrations and (b) concomitant ^{131}I thyroid uptake values. Control animals received distilled water; ^{131}I was injected intraperitoneally at time 0.

goitrogenic action of cassava was uniquely due to repeated inhibition of thyroid iodide uptake was not entirely satisfying. Mean serum thiocyanate concentrations in the inhabitants of Idjwi Island were elevated, approximately 1 mg/dL compared with 0.2 mg/dL in Belgians, but these values were not high enough to account for inhibition of the thyroid. In addition, serum thiocyanate levels were equally elevated in nongoitrous and goitrous regions. Therefore, thiocyanate did not appear to be the discriminating factor. Finally, in view of the extremely high ^{131}I uptake observed in the Idjwi Island population, inhibition of uptake, induced by a large cassava meal, probably represented an exceptional rather than normal situation. At this stage, the completion of an iodine prophylaxis campaign rendered further studies impossible on Idjwi Island.

Before initiating new studies in another goitrous region, attempts were made to define more clearly the effects of chronic administration of cassava and thiocyanate to rats. Data were available on the effects of thiocyanate but mainly on its acute effects. The principal results of prolonged administration of cassava or thiocyanate included:

(1) Oral administration of thiocyanate (0.2–10 mg/day) did not induce serum thiocyanate levels higher than 1.0–1.2 mg/dL. This same serum concentration was observed following a single injection of 0.2 mg of thiocyanate. Above a critical threshold of 1 mg/dL, a renal adaptive mechanism ensured rapid elimination of the administered doses in the urine. Thus, circulating thiocyanate concentration is not a quantitative measure of thiocyanate load.

(2) The prolonged administration of high doses of thiocyanate did not cause inhibition of ^{131}I uptake by the thyroid. On the contrary, an increase in uptake was frequently observed.

(3) Daily ingestion of fresh cassava roots (10 g/day) led to modifications in thiocyanate levels and abnormalities in thyroid iodine metabolism. These modifications were identical, qualitatively and quantitatively, to those induced by 1–2 mg thiocyanate ingested daily. Thus, the antithyroid effect of cassava is directly linked to endogenous thiocyanate production following cassava ingestion.

(4) The abnormalities in thyroid metabolism induced by cassava or thiocyanate ingestion were characterized by decreased thyroid iodine reserves and alterations in intrathyroidal hormone production (increased MIT/DIT ratio and decreased T_4 synthesis), peripheral distribution of thyroid hormones (reduction of $PB^{127}I$), and thyroid size (goitrogenic action). These abnormalities were identical to those caused by an increase in iodine deficiency.

(5) In the absence of any inhibition of thyroid iodine uptake, the underlying cause of iodine wastage was not clear. Increased renal iodine clearance could be demonstrated but only for thiocyanate doses of 5 mg/day or higher.

The methods of preparing cassava in Kivu and Ubangi result in partial or complete denaturation of the enzyme linamarase. This enzyme hydrolyzes linamarin, resulting in the production of cyanide. To determine the effect of linamarin in the absence of its specific enzyme, synthetic linamarin was administered to rats in the presence and absence of the enzyme. In its presence, the expected elevation of serum and urinary thiocyanate was observed. In its absence, these effects were not seen — a finding that suggests that linamarin hydrolysis only occurs when substrate and enzyme are simultaneously present. The hypothesis that linamarin could be degraded nonspecifically by intestinal bacteria was also tested. *Klebsiella* were found to degrade linamarin completely. The possible role of intestinal breakdown of linamarin in cassava toxicity in humans has not yet been determined.

Clinical Evidence of the Goitrogenic Role of Cassava

At this stage of the studies, despite the lack of definitive evidence supporting the causative role of cassava in endemic goitre, experimental findings favoured this hypothesis. Therefore, clinical studies were initiated in Ubangi in northwestern Zaire. Endemic goitre in this population of more than 2 million people is even more widespread than on Idjwi Island. Cassava intake is also very high. In the goitrous population, mean serum thiocyanate concentrations of 1.0 mg/dL were observed, and some subjects had serum thiocyanate values of 2–3 mg/dL, i.e., 10 times the normal value.

Plasma and urinary thiocyanate concentrations were compared in a large number of people. The concentrations increased in parallel up to a serum level of 1.0–1.2 mg/dL, but a renal adaptive mechanism prevented an increase in serum thiocyanate concentration beyond this critical level.

Various cassava preparations were tested, calculating their cyanide content and their effect on thiocyanate load in humans. Ingestion of large amounts of cassava for 3 days produced a significant increase in serum and urinary thiocyanate concentrations. Complete cessation of cassava intake induced a marked decrease in these values. These observations confirmed that cassava is responsible for the abnormal thiocyanate load in this population.

Particularly favourable conditions allowed for a demonstration of the effect of cassava on thyroid metabolism. The investigation involved a group of adolescents at a boarding school. Their food was prepared from local sources but contained less cassava than that consumed by the general population. In addition, the methods of preparation were quite different because of the special kitchen equipment adapted for the large group. Compared with a similar ethnic group living in a rural environment, the boarding school group had lower serum and urinary thiocyanate concentrations. Urinary iodide excretion and ^{131}I thyroid uptake were identical. These data indicate that the two groups were subject to the same degree of iodine deficiency, but the students at the boarding school had practically normal serum T_4 and TSH levels, whereas those in the rural environment had decreased T_4 and increased TSH values. These observations clearly suggest that severe iodine deficiency triggers adaptive mechanisms to ensure nearly normal thyroid hormone production. However, the added hindrance from thiocyanate compromises thyroid adaptation and diminishes thyroid secretory capacity even in the presence of intense TSH stimulation.

The goitrogenic action of cassava was also demonstrated in a comparative study of cassava intake and preparation methods in five different ethnic populations of Ubangi. In three of these populations, the Ngbaka, Ngbaka-Mabo, and Mbanza (group I), cassava is consumed principally in the form of *fuku* and *mpondu*. *Fuku* is a gruel of cassava flour mixed with corn. *Mpondu* consists of ground boiled cassava leaves. These two preparations contain an average of 13.5 and 8.5 mg HCN/kg respectively. The Mongwandi (group II) and "Gens d'eau" (group III) populations consume cassava mainly as *chickwangue*, which is soaked and then mashed into a puree. This preparation contains an average 3.5 mg HCN/kg. The "Gens d'eau" eat large quantities of fish and, thus, have a higher iodine intake than the rest of the Ubangi population. They are not affected by severe endemic goitre.

Serum and urinary thiocyanate levels in populations consuming *fuku* and *mpondu* (group I) are 1.5–2 times higher than in populations consuming *chickwangue* (Table 1). There is a highly significant correlation between *fuku* and *mpondu* intake and the prevalence of goitre and cretinism. In groups I and II iodine intake is identical, but the prevalence of goitre is 60% in group I and only 34% in group II. This difference is associated with thiocyanate excretions of 2.57 mg/dL in group I and 1.32 mg/dL in group II. Urinary thiocyanate concentrations are similar in groups II and III, although the "Gens d'eau" (group III) have a lower prevalence of goitre (17%) due to their higher iodine intake.

These results clearly indicate that the prevalence of goitre is linked to the balance between thiocyanate and iodine intake. In each community, prevalence is directly proportional to thiocyanate load and inversely proportional to iodine supply. On the basis of this relationship, an index corresponding to the ratio between urinary thiocyanate and iodine concentrations has been calculated. The indices are 2.1 (group I), 0.75 (group II), and 0.39 (group III), corresponding to goitre prevalence of 60, 34, and 17% respectively (Table 1). A study in Sicily confirmed the importance of the balance between thiocyanate and iodine supply. There, iodine intake was at the lower limit of normal, but urinary thiocyanate concentrations were markedly elevated, apparently because of cabbage intake.

Table 1. Epidemiological and metabolic indicators for three groups investigated.[a]

Group	Prevalence of goitre (%) (mean ± SE)	Prevalence of cretinism (%) (mean ± SE)	6-hour ^{131}I thyroid uptake (%) (mean ± SE)	Serum levels: T_4 (µg/dL) (mean ± SE)	Serum levels: TSH (µU/mL) (mean ± SE)	Serum levels: SCN (mg/dL) (mean ± SE)	Urinary levels: SCN (mg/dL) (mean ± SE)	Urinary levels: ^{127}I (µg/dL) (mean ± SE)	Urinary SCN/I ratio (mg/µg) (mean ± SE)
I	60 ± 4	6.1 ± 1.0	55 ± 2	4.4 ± 0.1	27.0 ± 4.0	1.24 ± 0.03	2.57 ± 0.10	1.9 ± 0.1	2.10 ± 0.21
	(8)	(8)	(142)	(408)	(409)	(406)	(379)	(254)	(250)
II	34	1.1	42 ± 3	6.4 ± 0.4	3.8 ± 0.6	0.42 ± 0.04	1.32 ± 0.11	2.5 ± 0.3	0.75 ± 0.08
	(2)	(2)	(46)	(43)	(44)	(44)	(49)	(49)	(49)
III	17 ± 5	0	23 ± 1	6.8 ± 0.2	3.3 ± 0.5	0.78 ± 0.04	1.60 ± 0.07	4.9 ± 0.3	0.39 ± 0.02
	(3)	(3)	(75)	(77)	(76)	(76)	(77)	(77)	(77)

[a]Figures in parentheses are the number of villages or subjects.

Nature of the Antithyroid Action of Cassava

In spite of experimental and clinical data collected on the role of cassava, one important point remains to be clarified before the real intervention of cassava as a causative agent of goitre in humans can be established. Indeed, the main antithyroid action of thiocyanate is thought to be the inhibition of the thyroid gland's ability to concentrate iodine. With the exception of an inhibitory effect on the thyroid pump, observed after the ingestion of exceptionally large amounts of cassava, it was not possible to detect any abnormality in iodide transport in the thyroid glands of these populations. In fact, the high values observed for their ^{131}I thyroid uptake seemed to demonstrate the tremendous effectiveness of the iodide concentrating mechanism.

To clarify this point, the situation observed in the population of Ubangi was mimicked in rats (Table 2). Therefore, small amounts of thiocyanate, 0.25 mg per day, were administered to iodine-deficient rats, which resulted in serum thiocyanate concentrations of the order of 0.8-1.0 mg/dL. The control group was fed an identical iodine-deficient diet without thiocyanate. The uptake of ^{131}I was identical in the two groups; however, thyroid uptake of ^{99m}Tc was reduced 50-60% in the rats receiving thiocyanate, compared with the controls. Technetium ion is concentrated in the thyroid but is not organified. A decreased ^{99m}Tc uptake indicates accelerated discharge of technetium from the gland. An identical effect on iodine exit has been demonstrated in rats in which organification is blocked by previous administration of propylthiouracil. These results confirm the hypothesis of Wollman (1962) and Scranton et al. (1969) that small doses of thiocyanate selectively affect the rate of iodine discharge without influencing the concentrating capacity of the thyroid.

It was important to determine why iodine uptake was unchanged despite its rapid exit from the thyroid. One could postulate that when the iodine organification mechanism is intact intrathyroidal iodide concentration is negligible. Under these conditions, even a very rapid iodine exit would have no significant effect on iodine uptake. However, this explanation was not supported by experiments in which thiocyanate administration was abruptly interrupted. Serum thiocyanate concentrations decreased rapidly

Table 2. Influence of prolonged supplementation (3-11 weeks) with thiocyanate (0.25 mg/day) in low-iodine diet (LID) rats on the ^{125}I thyroid uptake and the ^{99m}Tc-T/S ratio.[a]

	Experiment[b]			
Parameter	A	B	C	D
Serum thiocyanate (μg/mL)				
LID	1.9 ± 0.5	2.1 ± 0.6	3.7 ± 1.1	3.9 ± 1.3
LID + SCN	12.3 ± 0.6**	8.9 ± 1.5**	11.0 ± 0.8**	11.8 ± 0.8**
4-hour thyroid uptake (% of dose)				
LID	27.6 ± 4.8	24.5 ± 3.6	33.1 ± 8.6	76 ± 5
LID + SCN	30.0 ± 3.9	29.2 ± 7.3	38.1 ± 3.0	76 ± 5
^{99m}Tc-T/S ratio				
LID	195 ± 30	177 ± 20	205 ± 64	
LID + SCN	64 ± 18**	62 ± 8**	85 ± 26**	
Serum thyroxine (μg/dL)				
LID	5.2 ± 1.2	4.1 ± 0.7	4.8 ± 1.1	2.2 ± 0.3
LID + SCN	3.1 ± 1.0*	3.9 ± 0.9	3.4 ± 1.0**	1.6 ± 0.5*
Serum TSH (μU/dL)				
LID	10.7 ± 6.0	6.3 ± 4.2		
LID + SCN	11.9 ± 5.4	14.0 ± 8.1*		
Iodine content (μg)				
LID			1.27 ± 0.37	0.60 ± 0.11
LID + SCN			1.14 ± 0.35	0.77 ± 0.31

[a]The mean values ±SD were calculated for 9 rats in experiment A and 20 rats in B, C, and D.
[b]Significance: * = $P<0.01$; ** = $P<0.005$.

and ^{99m}Tc uptake returned to normal, but ^{131}I was also markedly increased. These observations demonstrate that if ^{131}I uptake remains unchanged in the presence of thiocyanate overload this value represents a new equilibrium between increased iodine uptake and accelerated iodine exit from the thyroid. This new equilibrium is only attained at a price of increased TSH stimulation of the gland.

These findings satisfactorily account for the observations that, under clinical conditions, specific antithyroid action of cassava (and of thiocyanate) has so far been neither detected by conventional exploratory methods or distinguished from the effects of iodine deficiency.

Cretinism and Congenital Hypothyroidism in Central Africa

Myxedematous cretinism, in the endemic areas of Central Africa, constitutes a real medical and social scourge. It is found in 2–7% of the population and is characterized by dwarfism, mental retardation, severe hypothyroidism, and several developmental abnormalities (Fig. 2). Other victims, presenting subtle signs that do not correspond to classic criteria for cretinism, also exhibit various degrees of developmental retardation and hypothyroidism. Observations indicate that there exists a continuous spectrum between normal subjects and the most severe forms of cretinism. The similarity of this disease with congenital hypothyroidism, as observed in industrial countries, led to investigations of thyroid function in newborns in goitrous areas. In a maternity located in Karawa, concentrations of thyroxine (T_4) and thyrotropic hormones (TSH) were measured in cord blood in unselected newborns. Similar measurements were also carried out in a group of infants whose mothers were treated with a single injection of iodized oil during the last 3 months of pregnancy. In the latter group, levels of T_4 and TSH in cord blood were found to be in the range of the concentrations observed in the Belgian controls (Fig. 3). In the cord blood of infants born to untreated mothers, approximately 15% of the T_4 and TSH values showed definite congenital hypothyroidism on the basis of the criteria used in industrialized countries. Deficient thyroid function at birth usually persists for several months and is, in all likelihood, directly responsible for the developmental abnormalities and mental retardation characteristics of endemic cretinism. The

Fig. 2. Myxedematous cretin girl from the village of Bokuda (Ubangi, Zaire); she was 9 years old, 92 cm tall, with a bone age of 1½ years. She had no goitre; her T_4 was undetectable; her T_3 was 9 ng/dL; and TSH was 510 µU/mL. The picture shows lumbar lordosis with prominent abdomen and umbilical hernia, as well as the configuration of her face and skull and dryness of skin. She scored 7 a.u. in the Raven test and 12 a.u. in the Gesell test.

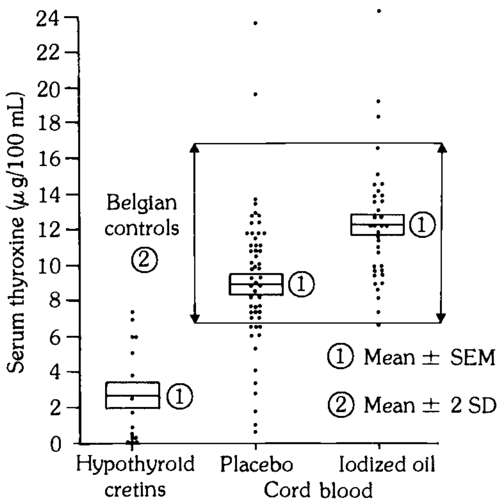

Fig. 3. Serum thyroxine levels in the cord blood of newborns of treated and untreated mothers compared with levels for 15 myxedematous cretins and for newborns in Belgium.

pathogenesis of this syndrome is linked to iodine deficiency, as indicated by the fact that administration of iodine to the population eliminates congenital hypothyroidism and cretinism. Myxedematous cretinism is only rarely encountered in other endemic goitre areas of the world, even in areas where iodine deficiency is as severe as that in Ubangi. The question, then, is whether or not the incidence of myxedematous cretinism is also influenced by cassava ingestion.

In Ubangi, elevated serum thiocyanate concentrations were observed in pregnant and nursing women as well as in newborns and breast-fed infants. Thiocyanate concentration in cord blood was strictly proportional to the maternal serum concentration — a finding that proves the transplacental passage of this ion. In contrast, thiocyanate content in breast milk was low and was not influenced by elevated serum levels in nursing mothers. The elevated thiocyanate levels in breast-fed infants are probably due to a supplement of cassava juice, which is frequently given to babies. Thiocyanate ion may have a direct deleterious effect on the thyroid of the fetus and newborn, mediated by the same mechanism as proposed for adults. In addition, thiocyanate inhibits active transport of iodide in the placenta and mammary glands.

An experimental model was developed in which pregnant rats were fed an iodine-deficient diet supplemented with propylthiouracil and large doses of thiocyanate. Marked thyroid hyperplasia was observed in the newborns that became even more marked on the 16th day after birth, i.e., at weaning. Administration of supplementary iodide to the mother 2 days before delivery induced nearly complete normalization of thyroid size in the newborns; however, iodide supplementation during lactation did not produce this effect. These observations suggest that thiocyanate inhibition of the iodide pump in the mammary glands could be an important mechanism in the development of thyroid abnormalities in nurslings.

Thus, epidemiological surveys in Ubangi have revealed that endemic goitre is only an indicator of an overall public health problem of unsuspected enormity. Iodine deficiency together with ingestion of goitrogenic substances produces not only goitre and abnormal thyroid metabolism but also severe abnormalities in pregnant women and in their offspring, particularly during fetal and early life. The following observations document the importance of the problem:

(1) The incidence of endemic cretinism, essentially myxedematous, is very high, ranging from 1–7%. In addition, numerous children are "cretinoid," exhibiting clinical, neurologic abnormalities similar to, but less striking than, cretins.

(2) Congenital hypothyroidism is present in 15% of newborns. This incidence rate is 500 times that observed in industrialized countries.

(3) Birth weight is reduced by as much as 200 g. This reduction is as marked as that seen in protein calorie malnutrition, which is known to be associated with a high frequency of malformations and neurologic abnormalities.

(4) Mortality from birth to 24 months is increased by 7%.

(5) In Ubangi, psychomotor retardation during the first 2 years of life is demonstrable in infants without outward signs of cretinism. This observation is in keeping with the findings of Fierro-Benitez et al. (1974) in older children in Ecuador. The concept of widespread psychomotor deficiency in children living in goitrous zones appears to be confirmed.

Prevention of Endemic Goitre and Cretinism

In regions where salt intake is small or variable, iodized salt prophylaxis has little chance of succeeding. In Third World countries, the lack of central facilities to distribute salt and the tropical climate are additional reasons for failure of this mode of prophylaxis. The systematic administration of slowly absorbable iodized oil to whole populations was first tested in a pilot project on Idjwi Island and then administered on a large scale in Ubangi. This method of prophylaxis was effective, cheap, and well-accepted. The population was protected for 3-7 years, depending upon age and sex. No cases of secondary hyperthyroidism were observed. No adverse effects were seen in pregnant women to whom iodized oil was given at least 1 month before delivery. Iodized oil administration produced a spectacular decrease in the prevalence and size of goitres. All parameters of thyroid function were corrected for a period longer than 5 years. At birth, children of treated mothers showed normal thyroid function, which persisted for more than 6 months. No cases of cretinism were seen among the offspring of mothers who had received iodized oil.

The cost of the program was approximately U.S.$20/person for each year of protection. The injections were carried out by mobile units administering 500-1000 injections per day and averaging 85% coverage of the population. Such a campaign can be organized with moderate means in regions of low socioeconomic development with only two prerequisites. One is that the populations must be sensitized to the gravity of endemic goitre through close collaboration between medical personnel and local administrative authorities, and the other is that the program must be carefully planned and monitored through systematic evaluation of the results of samples taken at random. Such control requires specially trained medical and nursing personnel, with careful records being kept by a central programing organization.

Conclusions

The principal contribution of the clinical and experimental studies described is the demonstration that cassava ingestion, together with iodine deficiency, is a key factor in the etiology of endemic goitre and cretinism in Central Africa. Thiocyanate is the goitrogenic factor directly involved. The principal difficulty encountered in this study was to distinguish between the goitrogenic effects of thiocyanate and those of iodine deficiency. A chronic thiocyanate overload induces abnormalities in thyroid metabolism identical to those observed as a result of iodine deficiency. The observed abnormalities in thyroid function are directly related to the ratio of thiocyanate to iodine.

Cassava is and will continue to be a primary source of nutrition in the Third World. It is, therefore, important to determine iodine supply and goitre prevalence in all regions of high cassava intake. In addition, the necessity of reducing the toxicity of cassava preparations must be emphasized. Two approaches are needed. The populations in affected areas should be shown how to prepare cassava in a way that ensures complete liberation of hydrocyanic acid, and agricultural researchers should develop subspecies of cassava that have minimal concentrations of linamarin. Also, further research is needed to establish more precisely the thiocyanate/iodine ratio at which prophylactic measures are essential.

Choufoer, J.C., van Rhijn, M., Kassenaar, A.A.H., and Querido, A. 1963. Endemic goiter in Western New Guinea: iodine metabolism in goitrous and non-goitrous subjects. Journal of Clinical Endocrinology and Metabolism, 23, 1203-1217.

Delange, F., Thilly, C., and Ermans, A.M. 1968. Iodine deficiency, a permissive condition in the development of endemic goitre. Journal of Clinical Endocrinology and Metabolism, 28, 114-116.

Ekpechi, O.L., Dimitriadou, A., and Russell Fraser, T. 1966. Goitrogenic activity of cassava (a staple Nigerian food). Nature (London), 210, 1137-1138.

Ermans, A.M., Thilly, C., Vis, H.L., and Delange, F. 1969. Permissive nature of iodine deficiency in the development of endemic goitre. In Stanbury, J.B., ed., Endemic Goitre. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 101-117.

Fierro-Benitez, R., Ramirez, I., Estrella, E., and Stanbury, J.B. 1974. The role of iodine in intellectual development in an area of endemic goiter. In Dunn, J.T. and Medeiros-Neto, G.A., ed., Endemic Goiter and Cretinism: Continuing Threats to World Health. Pan American Health Organization, Washington, DC, USA, Scientific Publication 292, 135-140.

Roche, M. 1959. Elevated thyroidal ^{131}I uptake in the absence of goiter in the isolated Venezuelan Indians. Journal of Clinical Endocrinology and Metabolism, 19, 1440-1445.

Scranton, J.R., Nissen, W.M., and Halmi, N.S. 1969. The kinetics of the inhibition of thyroidal iodide accumulation by thiocyanate: a reexamination. Endocrinology, 85, 603-607.

Thilly, C.H., Delange, F., and Ermans, A.M. 1972. Further investigations of iodine deficiency in the etiology of endemic goiter. American Journal of Clinical Nutrition, 25, 30-40.

Wollman, S.H. 1962. Inhibition by thiocyanate of accumulation of radioiodine by thyroid gland. American Journal of Physiology, 203, 517-524.

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

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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.

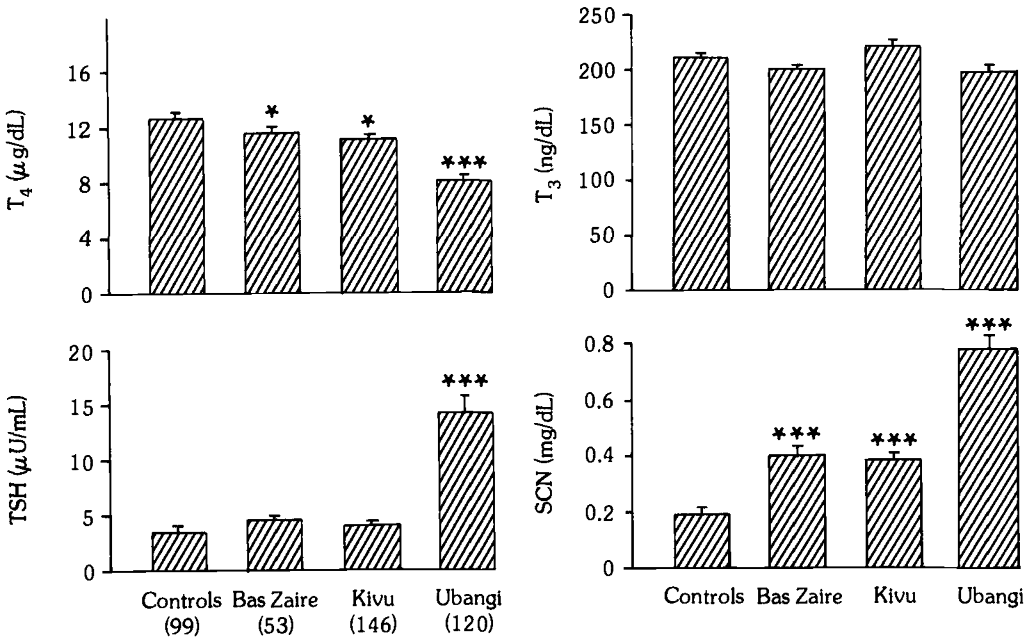

*Fig. 1. Comparison of concentrations of T_4, T_3, TSH, and SCN in mothers at delivery in Kinshasa, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM. Numbers of patients are shown in parentheses. Levels of significance refer to a comparison with the results from Kinshasa, which was used as the control area: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

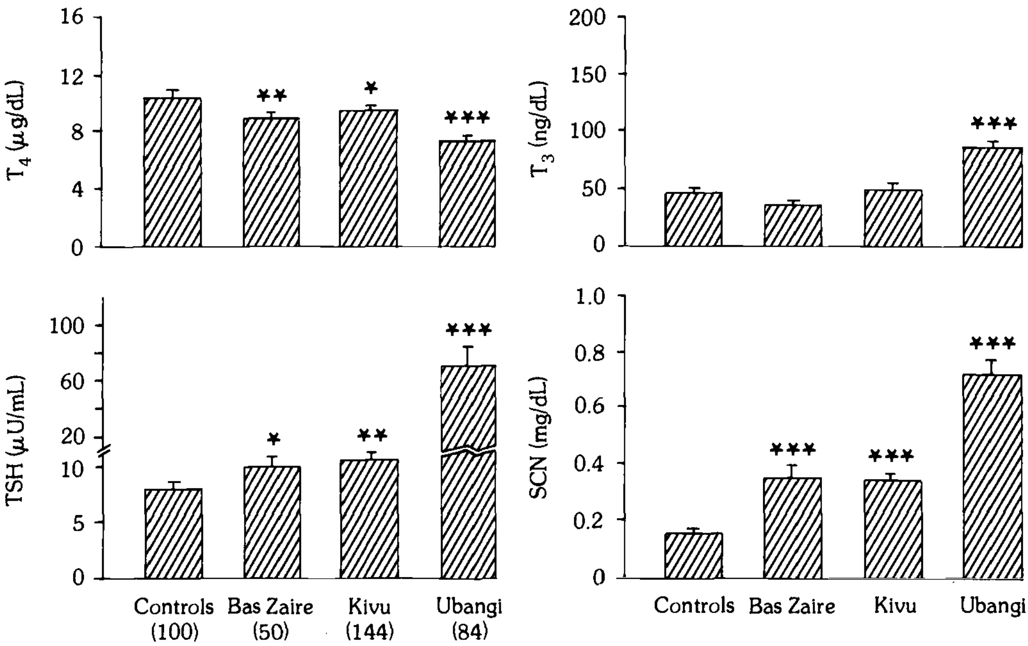

*Fig. 2. Comparison of concentrations of serum T_4, T_3, TSH, and SCN in newborns (cord blood) in Kinshasa, Bas Zaire, Kivu, and Ubangi. (Mean ± SEM. Numbers of patients are shown in parentheses. Levels of significance refer to a comparison with the results from Kinshasa, which was used as the control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

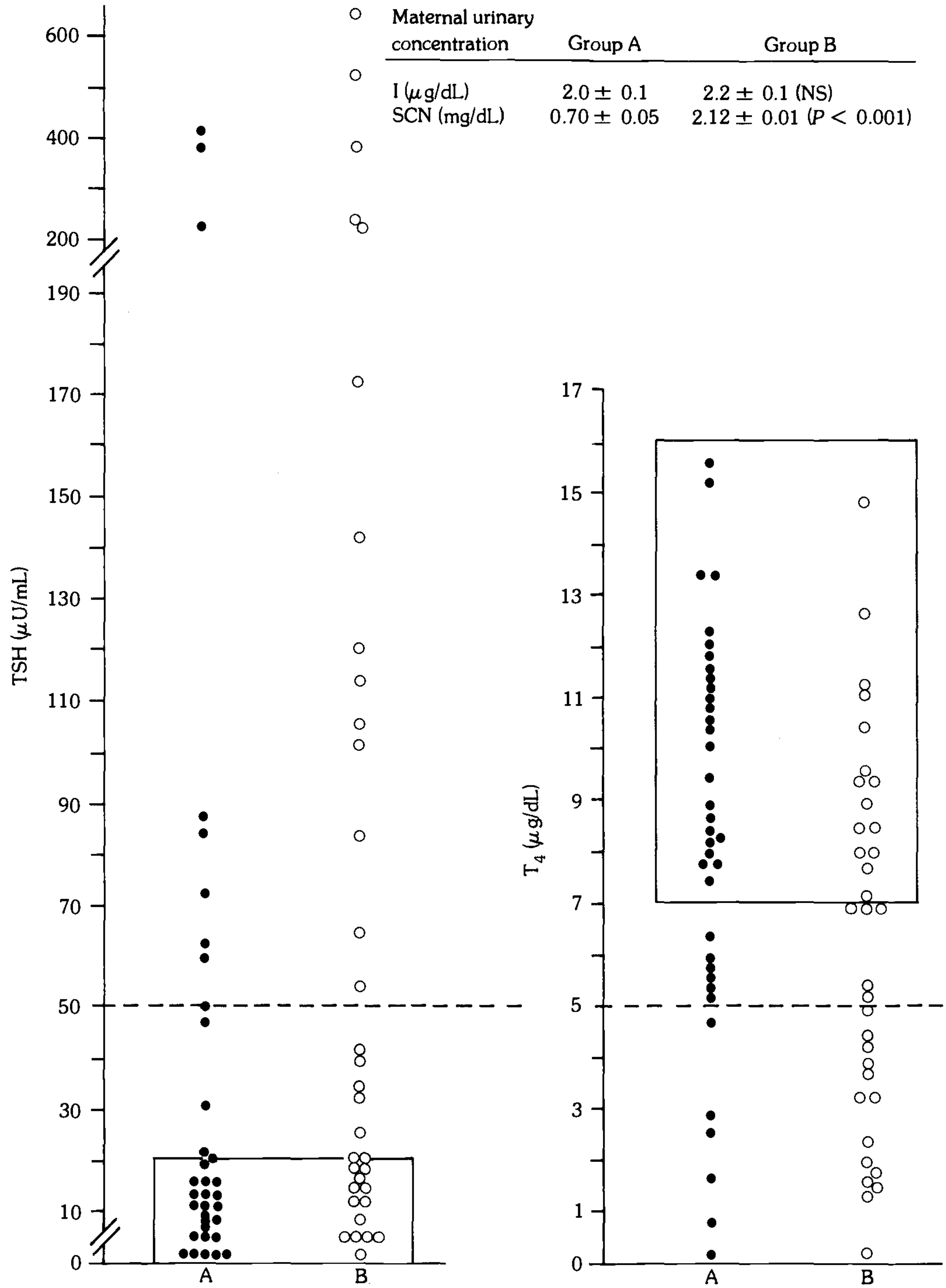

Fig. 3. Comparison of concentrations of serum TSH and T_4 in cord blood in Ubangi as a function of the concentrations of urinary SCN at delivery in severely iodine-deficient mothers. The columns indicate the normal limits for these variables in a Belgian newborn population.

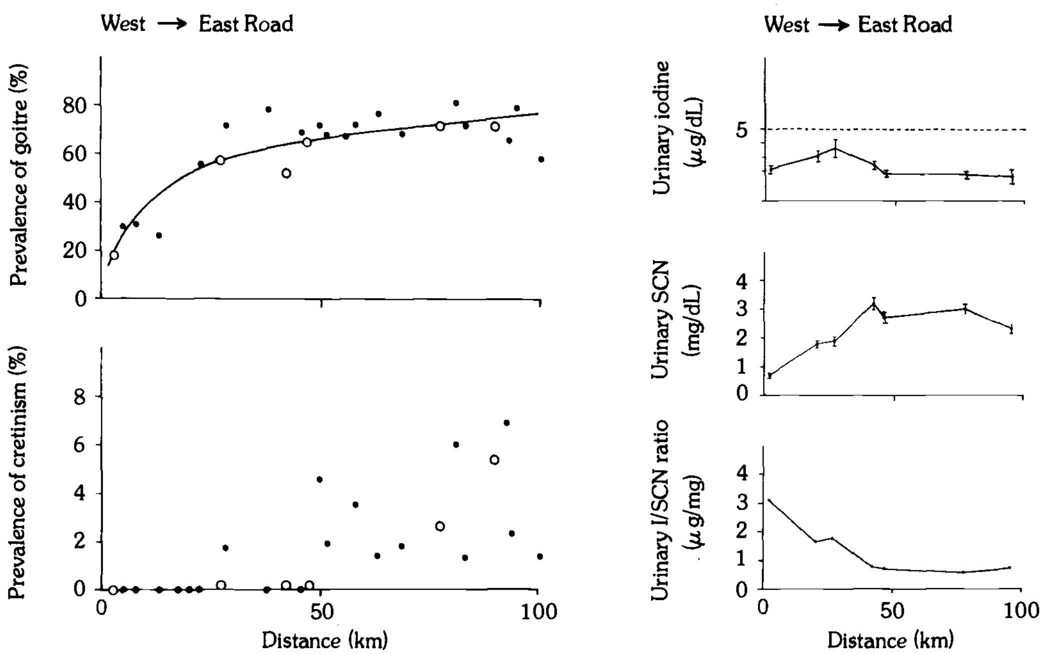

Fig. 4. Changes in prevalence of goitre and cretinism (each point represents one village; open circles represent those where metabolic investigations were carried out), concentrations of urinary iodine and SCN, and urinary I/SCN ratio along one of the two roads. (Mean ± SEM. Broken line represents normal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

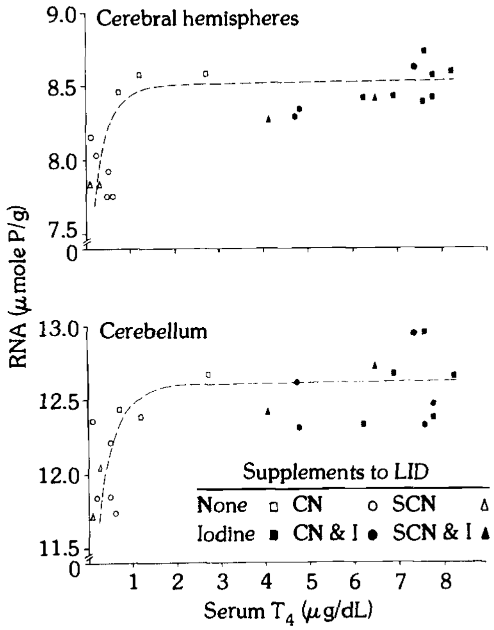

Fig. 5. Relationship between concentration of serum T_4 and RNA content for the cerebral hemispheres and cerebellum in rats 16 days of age and different groups of pregnant and nursing rats subjected to a low-iodine diet (LID) alone or a low-iodine diet supplemented with cyanide (CN), thiocyanate (SCN),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

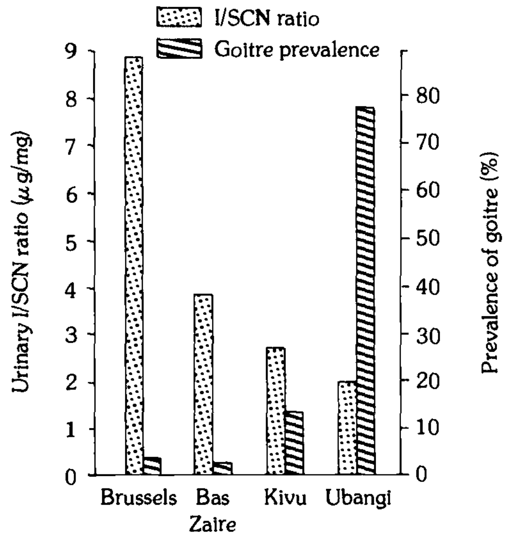

Fig. 6. Relationship between the urinary I/SCN ratio and the prevalence of goitre in Brussels and in the three rural areas investigated in Zaire.

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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Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Delange, F., Iteke, F.B., and Ermans, A.M., ed. 1982. Nutritional factors involved in the goitrogenic action of cassava. International Development Research Centre, Ottawa, Canada, IDRC-184e, 100 p.

Role of Other Naturally Occurring Goitrogens in the Etiology of Endemic Goitre

Eduardo Gaitan[1]

This paper reviews the evidence implicating environmental goitrogens as etiological factors of endemic goitre (Gaitan 1980; Langer and Greer 1977; Ermans et al. 1980).

During the last few years, several groups of investigators have reported situations in which neither goitre or endemic cretinism were evident despite severe dietary iodine deficiency (<25 μg/day). These reports challenge the concept that iodine deficiency by itself invariably results in endemic goitre and cretinism. Thus, it was logical to postulate the existence of other factors that, in conjunction with iodine deficiency, determine the development of these two pathological entities.

The important role of iodine deficiency as a permissive factor in endemic goitre and cretinism has been firmly established by several observations indicating that iodine supplementation consistently results in a marked decrease in the prevalence of endemic goitre and the disappearance of endemic cretinism. It has been found, however, that adequate iodine intake (75–300 μg/day) does not always eradicate goitre, as a prevalence rate of 6–40% persists in some areas. Therefore, environmental factors other than nutritional iodine deficiency are thought to be responsible for the persistence of old cases and development of new cases, as well as for differences in goitre prevalence among localities where iodine intakes are similar.

Under these circumstances, goitrogens in staple foods and water appear to be most important as environmental factors in the etiology of endemic goitre. Environmental goitrogens may, normally, be ineffective when low in concentration, but may become significant when the supply of iodine is restricted. In other situations, they may be sufficiently potent in themselves to cause goitre despite an abundance of iodine.

Overview of Other Naturally Occurring Goitrogens in Foodstuffs and Endemic Goitre

Although the existence of goitrogenic substances in foodstuffs has been suspected for many years, it was not until 1928 that this was firmly established, when the development of goitre in rabbits fed on cabbage was demonstrated. Since then, other vegetables of the genus *Brassica* (Cruciferae family) have been found to possess goitrogenic properties (Langer and Greer 1977). During the past 30 years, thiocyanates and isothiocyanates have been demonstrated as the principal goitrogens in Cruciferae. In 1949, the potent antithyroid compound goitrin, a thioglycoside, was isolated from yellow turnips and from *Brassica* seeds (Langer and Greer 1977). Cyanogenic glucosides have also been found in several staple foods, such as cassava, maize, bamboo shoots, sweet potatoes, and lima beans, from the Third World. After ingestion, these glucosides can be readily converted to thiocyanate by a widespread tissue enzyme (Ermans et al. 1980). The presence of polysulfides in several vegetables of the Cruciferae family has also been described, but these exert only a weak antithyroid effect. The major volatile components of onions and garlic have been identified as small aliphatic disulfides, which have marked antithyroid activity in rats (Gaitan 1980).

Extensive reviews on sources, metabolic pathways, and action of cyanogenic glycosides,

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thioglycosides, isothiocyanates, and thiocyanates have been published recently (Gaitan 1980; Langer and Greer 1977; Ermans et al. 1980; Van Etten 1969).

There have been several goitre endemias attributed to environmental goitrogens. Two goitre endemias have been ascribed to the presence of goitrogenic substances in milk. One was in Tasmania (Gibson et al. 1960; Clements 1968), where a seasonal variation in goitre prevalence in schoolchildren was noted in spite of adequate iodine intake, and in which an isothiocyanate, cheilorine, was suspected as the principal goitrogen. The other occurred in Finland (Peltola 1965), where goitrin, a thioglycoside present in cow's milk from the region of endemic goitre, was considered as the causative factor. Rats fed for 1–2 years on milk produced in endemic goitre districts developed thyroid glands almost twice as large as those in control rats given milk from nongoitrous districts (Peltola and Krusius 1960). The concentration of 1,5-vinyl-2-thio-oxazolidone (goitrin), in the range of 35–100 μg/L in milk specimens from goitre districts, exceeded the level necessary to explain the goitrogenic effect of this milk when fed to rats in long-term experiments. Thus, the authors concluded that goitrin might well be responsible, at least in part, for the goitre endemia in those areas of Finland (Peltola and Krusius 1960; Krusius and Peltola 1966). On the other hand, available data from the Tasmanian endemia failed to establish the goitrogenic properties of milk (Trikojus 1974).

Goitrogenic substances in cassava have also been implicated in the etiology of two other endemias. In eastern Nigeria (Ekpechi 1973), goitrogenic and thionamide-like antithyroid activity was demonstrated in cassava from endemic areas. The second case, Central Africa (Ermans et al. 1980), involved the presence of the cyanogenic glucoside linamarin in cassava, which is then converted to thiocyanate.

The nut of the *Araucaria araucana* (Pinon) has been suspected as having a role in the pathogenesis of endemic goitre in an Indian reservation in Chile (Barzelatto et al. 1967). A Pinon diet showed goitrogenic activity in rats that was not due to iodine deficiency (Tellez et al. 1969).

An excess intake of iodine, arbitrarily defined as 2 mg or more per day, inhibits the proteolysis and release of thyroidal hormones and eventually produces "iodide goitre" and hypothyroidism. Sustained ingestion of seaweeds rich in iodine causes "endemic coast goitre," as described among natives in Hokkaido, Japan (Suzuki 1980).

Naturally Occurring Goitrogens in Water and Endemic Goitre

Table 1 indicates that goitre endemias have been attributed or related to goitrogenic substances in drinking water.

Epidemiological evidence from western Colombia shows that environmental factors other than nutritional iodine deficiency are responsible for the persistence of goitre. A relationship between drinking water and goitre prevalence rates has been reported previously (Gaitan 1973, 1980; Gaitan et al. 1978). These studies indicated that antithyroid and goitrogenic organic compounds with thionamide-like antithyroid activity contaminate the water supply and appear to be the main factor underlying the endemia.

Chemical Characterization of Goitrogens in Water

Physicochemical analysis of goitrogenic water extracts disclosed the presence of sulfur-bearing organic compounds with potent antithyroid activity (Gaitan 1973; Gaitan et al. 1973). Disulfides of saturated and unsaturated aliphatic hydrocarbons were tentatively identified by mass spectrometry (Gaitan 1973). Recent studies (Table 2) indicate that treatment of goitrogenic water extracts with reducing agents sodium borohydride and dithiothreitol (Cleland's reagent) (Cleland 1964) decreases their antithyroid activity. Activity was also found in the fraction containing Di-n-butyl phthalate, which was presumed, at the time, to be a contaminant of the extracts (Gaitan 1973). Phthalic acid esters are ubiquitous in their distribution and have been frequently identified as water pollutants (Marx 1972; Mayer et al. 1972; Peakall 1975; Junk and Stanley 1975; Shackelford and

Table 1. Goitre endemias attributed to goitrogens in water.

Locality	Source	Active principal
West Virginia	*E. coli*	5×10^4 to 10×10^4 (molecular weight)
Greece	*E. coli*	—
Colombia	Sedimentary rock	Sulfurated and other organic compounds (disulfides?)

Table 2. Effect of reducing agents on antithyroid activity of water extracts from endemic goitre areas.

	Antithyroid activity	
	µg/mL (as MMI[a])	%
Water extract	340	100
0.5 mL (water extract) + 0.5 mL (0.1 m*M* $NaBH_4$ in 1 *N* NaOH[b])	106	31
0.5 mL (water extract) + 0.5 mL (0.1 *M* $NaBH_4$ in 1 *N* NaOH)	28	8
Deionized distilled water	<2	<1
0.5 mL (deionized distilled water) + 0.5 mL (0.1 m*M* $NaBH_4$ in 1 *N* NaOH)	0	0
0.5 mL (deionized distilled water) + 0.5 mL (0.1 *M* $NaBH_4$ in 1 *N* NaOH)	<2	<1
0.5 mL (water extract) + 0.5 mL Cleland's reagent (0.1 m*M*)	46	14
1 mL Cleland's reagent	0	0

[a]Methyl-mercaptoimidazole.
[b]Changes in pH do not affect antithyroid activity.

Keith 1976). Most commonly, they result from industrial pollution or artificial contamination, but phthalates are also reported to occur naturally in shale, crude oil, petroleum, plants, and as fungal metabolites (Peakall 1975). Like phthalates, organic disulfides have also been identified as water contaminants (Junk and Stanley 1975; Shackelford and Keith 1976). The most frequently isolated compounds are dimethyl, diethyl, and diphenyl disulfides, but dimethyl trisulfide, dimethyl sulfoxide, and diphenylene sulfide have also been isolated. Small aliphatic disulfides, as already mentioned, have been shown to have potent antithyroid activity in rats (Gaitan 1980).

That environmental goitrogens in water might affect animal species as well as humans has been emphasized in reports on the increasing frequency of goitres in coho salmon in the Great Lakes (Sonstegard and Leatherland 1976; Moccia et al. 1977). Epizootiological data suggest that organochlorines, which have a widespread distribution within the Great Lakes and have been shown to alter thyroid activity in fish (Sonstegard and Leatherland 1976), birds (Jefferies and French 1972; Jefferies and Parslow 1972), and mammals (National Research Council 1977; Bastomsky 1977), may be involved in the etiology of these cases. Organochlorines and organothiochlorines, as a result of chlorination treatment or industrial pollution, have been isolated with increasing frequency in waters from many areas of the United States (National Research Council 1977; Jolley et al. 1978). Recently, 4-chlororesorcinol, one of several chloro-organics detected in chlorinated domestic sewage treatment plant effluent (Jolley et al. 1975), was shown to have pronounced antithyroid activity in studies conducted at the University of Mississippi.

Physical State and Geocycle of Waterborne Goitrogens

Some knowledge has been gained on the physical state of organic goitrogens in water. Ultrafiltration of water extracts from a goitrogenic well in Colombia (Table 3), with a cutoff at 12 000 molecular weight, produced filtrates containing 60% of the antithyroid activity; the other 40% remaining in the dialyzed fraction. With the cutoff at 5000 molecular weight, 20% of the activity was present in the ultrafiltrate and 80% remained in the dialyzed fraction. This result indicated that the material was heterogeneous and pointed to the possibility that the active organic compounds were forming easily dissociable complexes with larger organic molecules. Further evidence was provided from studies using thin-layer chromatography (TLC), slab-gel electrophoresis in polyacrylamide, and high pressure liquid chromatography (HPLC), which showed one or two spots or a large unresolved peak, respectively, suggestive of "humic materials." These findings suggest that the organic goitrogens contaminating water supplies, although of low solubility in water, are effectively held in solution and transported in water by their association with humic materials (Jolley et al. 1978; Schnitzer and Kahn 1972;

Table 3. Ultrafiltration of goitrogenic water extracts and antithyroid activity.[a]

	Antithyroid activity	
	µg/mL (as MMI)[b]	%
Cutoff, 12 000 molecular weight: Dialyzed	68	40
Filtrate	102	60
Cutoff, 5000 molecular weight: Dialyzed	220	79
Filtrate	60	21

[a]Amicon-Diaflo ultrafilter (UM membranes); 2 mL extract at 4°C for 22 hours.
[b]Methyl-mercaptoimidazole.

Ogner and Schnitzer 1970). Humic materials are high molecular weight polymeric and complex nonprotein organic substances present in sedimentary rock, soils, and water. Their spheroidal or linear colloidal conformation provides them with adsorption and surface-active properties to complex with organic chemicals such as phthalates, herbicides, and chlorinated hydrocarbons (Schnitzer and Kahn 1972; Ogner and Schnitzer 1970).

Additional information on the possible geocycle of these natural goitrogens was obtained from epidemiological studies in 37 localities of western Colombia (Gaitan et al. 1978; Meyer et al. 1978). Goitre prevalence ranged from 1-42% and average daily urinary iodine excretion ranged from 65-295 μg. It is worth noting that in the presence of adequate iodine supplementation, as was the case under which these studies were conducted, a positive and significant correlation was found between goitre prevalence and urinary iodine excretion ($r = 0.333$, $P<0.05$). This is contrary to what has been observed in iodine-deficient areas. As indicated in Table 4, a high statistical correlation ($P<0.005$ to $P<0.0005$) exists between the geological composition of watersheds and prevalence of goitre. Towns located downstream from sedimentary rock, which is rich in organic matter, have the highest prevalence of goitre. In contrast, those populations taking their drinking water from streams flowing across igneous rock, which is devoid of organic matter, show a low goitre prevalence. Watersheds containing mixed lithologies are associated with intermediate levels of goitre. Because the development of soils is dependent upon elevation and because the statistical tests did not select elevation of communities as an important variable, it appears that the goitrogens are not soil derived but originate in the rock below. These results support the hypothesis that sedimentary rock (e.g., shales, coal, etc.), which is rich in organic matter, is the main source of waterborne goitrogens.

Malamos et al. (1971), studied the distribution of goitre in Greece, where nutritional iodine deficiency is still a major factor related to goitre, and observed that the distribution of different rock types correlates with goitre prevalence. Communities located on limestone terrain are associated with low goitre prevalence, whereas those located on shales and schists have a high incidence of goitre. On the basis of soil and rock analyses, the authors imply that the low concentration of exchangeable cations and the ability of soils to absorb iodine are related to a high prevalence of goitre. I would like to suggest that those particular shales and schists in Greece are, possibly, rich in organic material, whereas the limestone may be deficient in these substances. Geological studies on Idjwi Island showed that the type of terrain existing in the localized area of the southwest, where there is no endemic goitre or cretinism, is made up solely of basalt, an igneous rock, whereas the terrain of the endemic area has a different geological composition (Ermans et al. 1969).

Table 4. Results of a stepwise regression analysis on 35 localities, establishing a relationship between goitre prevalence and geological and urinary iodine variables.

Step	Variable	F	df	P
1	Sedimentary rock	16.62	1,33	<0.0005
2	Igneous rock	9.98	1,32	<0.005
3	Urinary iodine	4.44	1,31	<0.05

To verify the above epidemiological observations, a specific, sensitive, and reproducible in vitro assay has been utilized to investigate antithyroid activity in rocks and small water samples (Gaitan et al. 1982). Assays were performed using porcine thyroid slices. Antithyroid activity was expressed as the percentage decrement of ^{125}I uptake by thyroid slices and the inhibition of ^{125}I organification. Iodide and the different organic iodocompounds were separated in small columns by means of molecular sieve, adsorption, and ion exchange chromatography. A significant positive correlation ($r = 0.49$, $P<0.05$) was observed between goitre prevalence (2-29%) and antithyroid activity in water collected from the pipelines (households and schools) in 16 of the 37 localities. This antithyroid activity could not be explained on the basis of total hardness (ppm) or concentrations of Ca, Mg, sulfates, chlorides, silicates, nitrates, and iodine. Antithyroid activity was also present in black shale extracts from the watershed supplying a locality of high endemic goitre (42%) in western Colombia as well as in shale extracts from Chattanooga, Tennessee. In contrast, lava extracts from a watershed supplying an area of low endemicity (6%) were devoid of antithyroid activity. These results emphasize the need for a more systematic and extensive study of antithyroid activity in different rock types. The findings from these assays provide additional evidence that organic antithyroid compounds derived from sedimentary rocks (shales, coal, etc.) contaminate water supplies in areas where goitre persists despite adequate iodine supplementation. It is interesting to note that 50 years ago Twort and Twort (1932) observed that painting shale oil on the skin of mice produced goitre in a large number of the mice and that the "petrol goitre" harboured carcinomas in a few mice.

Bacterial Contamination of Water Supplies and Endemic Goitre

Microorganisms contaminating water supplies have been implicated as causative factors in at least two instances of endemic goitre (Gaitan 1980; Malamos et al. 1971; Vought et al. 1967; Koutras 1980). In bacteriological studies of some villages in Greece, the drinking water in villages with a high prevalence of goitre was polluted with *E. coli* and coli-like organisms significantly more often than water from nongoitrous localities (Malamos et al. 1971; Koutras 1980). A similar relationship had been demonstrated previously by Vought et al. (1967) in Richmond County, Virginia, where goitre exists despite adequate iodine supplementation. Vought et al. (1974) also showed antithyroid activity in cultures of *E. coli* isolated from a polluted stream in an area of high endemia. Antithyroid activity, reflected as reduced uptake of ^{131}I by the rat thyroid, was present in the 5×10^4 to 10×10^4 molecular-weight fraction of the cell-free extract of the *E. coli*. More recent studies (Koutras 1980; Gaitan 1980) in endemic and nonendemic areas of Greece showed that concentrations of both *E. coli* antibodies and IgG were higher in the goitrous population than in the nongoitrous population of the endemic area, and that IgG concentrations were higher in the endemic area, where drinking water was subject to pollution, than in the nonendemic area, which had a nonpolluted water supply. These results were interpreted as providing further support to the hypothesis that microorganisms (i.e., *E. coli*) are involved in the pathogenesis of endemic goitre.

In earlier studies (Gaitan et al. 1978; Meyer et al. 1978), the statistical correlation ($P<0.005$ to $P<0.0005$) between goitre prevalence and rock type accounted for 57% of the variation in goitre prevalence, and it was hypothesized that bacterial contamination of water supplies could be one factor involved in the remaining 43%. Therefore, bacteriological studies were performed to incorporate this variable into the statistical model in 34 of the 37 localities previously surveyed (Gaitan et al. 1980). Only two variables demonstrated significant relationships with goitre prevalence: the overall concentration of bacteria in the pipeline system (associated with increased goitre prevalence) ($P<0.05$) and *K. pneumoniae* in the water source (associated with decreased goitre prevalence) ($P<0.01$). A model fitted with the geological ($P<0.005$) and bacteriological variables ($P<0.025$) accounted for 80% of the variability in goitre prevalence (Table 5).

Increased goitre prevalence in the presence of bacterial contamination in the pipeline system agrees with the findings of other investigators (Malamos et al. 1971; Vought et al. 1967, 1974; Koutras 1980) and provides further support for the hypothesis that microorganisms (i.e., *E. coli*) are involved in the pathogenesis of endemic goitre. In contrast, the lower goitre prevalence found when *K. pneumoniae* was present in the water source perhaps provides an example of natural biodegradation of the organic contaminants that produce goitre. This hypothesis is supported by experiments in which pesticides and other hazardous organic materials were degraded by microorganisms present in the soil (Maugh 1979). Recently, strains of klebsiella were shown to hydrolize the cyanogenic glucoside linamarin, with an associated liberation of cyanide; the extent of hydrolysis being proportionate to the number of microorganisms added (Ermans et al. 1980). As well, there is ample evidence to demonstrate that bacteria (gram-negative rods) are major elements in the biodegradation of phthalate esters (Keyser et al. 1976; Engelhardt et al. 1975).

Nutritional Status and Goitre

Because general nutrition appears to influence

Table 5. Relationships between goitre prevalence and rock types, urinary iodine, *K. pneumoniae*, and bacteria concentration in a group of 16 localities.

Variable	Coefficient	t(9 df)	P
Constant	0.127		
Presence of sedimentary rock	0.097	3.92	<0.005
Presence of metamorphic rock	0.018	0.71	NS
Presence of igneous rock	-0.012	0.24	NS
Urinary iodine	0.00013	0.51	NS
Presence of *K. pneumoniae* in water source	-0.083	2.77	<0.025
Bacterial concentration in pipeline	6.45×10^{-7}[a]	2.12	$0.05 < P < 0.10$

[a] $R^2 = 0.80$.

Table 6. Relationship between goitre prevalence and geologic variables (adjusting for age and arm skinfold thickness), based upon a stepwise multivariate analysis using the logistic model.

Step	Variable	Likelihood ratio test χ^2	P
1	Age	0.6526	NS
2	Skinfold thickness	0.4824	NS
3	Igneous rock	7.8434	<0.01
4	Sedimentary rock	4.1426	<0.05
5	Metamorphic rock	0.2594	NS

goitre prevalence rates in humans (Medeiros-Neto 1980) and experimental animals (Gaitan and Merino 1976), the hypothesis being that poor nutrition is associated with increased risk of goitre, a nutritional status variable was also included in the statistical model of the previously mentioned epidemiological studies. Results of univariate analyses showed that in 929 schoolchildren (551 females, 378 males) none of the nutritional variables, i.e., height, weight, arm skinfold thickness, and a nutrition index (weight/height^2), were significantly related to goitre prevalence. In a stepwise multivariate analysis, height (taller children had a greater incidence of goitre; $P<0.01$) and arm skinfold thickness (goitre was more prevalent in thinner children; $P<0.05$) were significantly associated with goitre prevalence. However, in the final step of the analysis (Table 6), the geological variables remained significantly related to goitre prevalence after adjusting for the nutritional variables. Therefore, differences in nutritional status among this group of children of similar socioeconomic background did not account significantly for the variations observed in goitre prevalence.

In summary, the presence of sedimentary rock was the best indicator of disease; goitrous and nongoitrous children are found in areas in which the geology of the watersheds differ significantly. The second best indicator of disease was the concentration of *K. pneumoniae* in the water source. The highly significant relationship between bacteria and the presence of sedimentary rock and goitre prevalence emphasizes the complex and multifactorial etiology of endemic goitre and also provides insight into the geobiological cycle of waterborne goitrogens.

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Barzellato, J., Beckers, C., Stevenson, C., Covarrubias, E., Gianetti, A., Bobadilla, E., Pardo, A., Donoso, H., and Atria, A. 1967. Endemic goiter in Pedregoso (Chile). I. Description and function studies. Acta Endocrinologica, 54, 577.

Bastomsky, C.H. 1977. Goiters in rats fed polychlorinated biphenyls. Canadian Journal of Physical Pharmacology, 55, 288.

Cleland, W.W. 1964. Dithiothreitol, a new protective reagent for SH groups. Biochemistry Journal, 3, 480.

Clements, F.W. 1968. Goiter studies in Tasmania, 16 years prophylaxis with iodide. Bulletin of the World Health Organization, 38, 297.

Ekpechi, O.L. 1973. Endemic goitre and high cassava diets in Eastern Nigeria. In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 139-145.

Engelhardt, G., Wallnofer, P.R., and Hutzinger, O. 1975. The microbial metabolism of Di-n-butyl phthalate and related dialkyl phthalates. Bulletin of Environmental Contamination and Toxicology, 13, 342.

Ermans, A.M., Thilly, C., Vis, H.L., and Delange, F. 1969. Permissive nature of iodine deficiency in the development of endemic goitre. In Stanbury, J.B., ed., Endemic Goitre. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 101.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Gaitan, E. 1973. Water-borne goitrogens and their role in the etiology of endemic goitre. In Bourne, G.H., ed., World Review of Nutrition and Dietetics. Vol. 17. S. Karger, New York, NY, USA, 53-90.

1980. Goitrogens in the etiology of endemic goitre. In Stanbury, J.B. and Hetzel, B., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, Inc., New York, NY, USA, 219-236.

Gaitan, E. and Merino, H. 1976. Antigoitrogenic effect of casein. Acta Endocrinologica, 83, 763.
Gaitan, E., Merino, H., Rodriguez, G., Sanchez, G., and Meyer, J.D. 1973. Environmental goitrogens. In Scow, R.D., ed., Endocrinology. Excerpta Medical Foundation, Amsterdam, Netherlands, International Congress Series 273, 1143-1149.
Gaitan, E., Merino, H., Rodriguez, G., Medina, P., Meyer, J.D., DeRouen, T.A., and MacLennan, R. 1978. Epidemiology of endemic goitre in western Colombia. Bulletin of the World Health Organization, 56, 403.
Gaitan, E., Medina, P., DeRouen, T.A., and Zia, M.S. 1980. Goitre prevalence and bacterial contamination of water supplies. Journal of Clinical Endocrinology and Metabolism, 51, 957.
Gaitan, E., Cooksey, R.C., Matthews, D., and Presson, R. 1982. *In vitro* detection of antithyroid activity in rocks and small water samples from supplies of endemic goitre areas. In Hemphill, D.P., ed., Trace Substances in Environmental Health. 15th Annual Conference, University of Missouri, Columbia, MO, USA.
Gibson, H.B., Howlerer, V.F., and Clements, F.W. 1960. Seasonal epidemics of endemic goitre in Tasmania. Medical Journal of Australia, 1, 875.
Jefferies, D.J. and French, M.C. 1972. Changes induced in the pigeon thyroid by pp'DDT and Dieldrin. Journal of Wildlife Management, 36, 24.
Jefferies, D.J. and Parslow, J.L.F. 1972. Effect of one polychlorinated biphenyl on size and activity of the gull thyroid. Bulletin of Environmental Contamination and Toxicology, 8, 306.
Jolley, R.L., Pitt, W.W. Jr., Scott, C.K., Jones, G. Jr., and Thompson, J.E. 1975. Analysis of soluble organic constituents in natural and processed waters by high-pressure liquid chromatography. In Hemphill, D.P., ed., Trace Substances in Environmental Health. 9th Annual Conference, University of Missouri, Columbia, MO, USA, 247-253.
Jolley, R.L., Gorchev, H., and Hamilton, D.H. Jr. 1978. Water chlorination: environmental impact and health effects. Vol. 2. Ann Arbor Science Publishers, Inc., Ann Arbor, MI, USA.
Junk, G.A. and Stanley, S.E. 1975. Organics in drinking water. Part I. Listing of identified chemicals. Ames Laboratory, ERDA, Iowa State University, Ames, IA, USA.
Keyser, P., Basayya, G.P., Eaton, R.W., and Ribbons, D.W. 1976. Biodegradation of the phthalates and their esters by bacteria. Environmental Health Perspectives, 18, 159.
Koutras, D.A. 1980. Trace elements, genetic and other factors. In Stanbury, J.B. and Hetzel, B., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, Inc., New York, NY, USA, 255-268.
Krusius, F.E. and Peltola, P. 1966. The goitrogenic effect of naturally occurring L-5-vinyl- and L-5-phenyl-2-thio-oxazolidone in rats. Acta Endocrinologica, 53, 342.
Langer, P. and Greer, M.A. 1977. Antithyroid substances and naturally occurring goitrogens. S. Karger, New York, NY, USA.
Malamos, P., Koutras, D.A., Rigopoulos, G.A., and Papapetrou, P.D. 1971. Endemic goitre in Greece: Some new epidemiologic studies. Journal of Clinical Endocrinology, 32, 130.
Marx, J.L. 1972. Phthalic acid esters: Biological impact uncertain. Science, 178, 46.
Maugh, T.H. 1979. Hazardous wastes technology is available. Science, 204, 903.
Mayer, F.L., Stalling, D.L., and Johnson, J.L. 1972. Phthalate esters as environmental contaminants. Nature, 238, 411.
Medeiros-Neto, G.A. 1980. General nutrition and endemic goitre. In Stanbury, J.B. and Hetzel, B., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, Inc., New York, NY, USA, 269-283.
Meyer, J.D., Gaitan, E., Merino, H., and DeRouen, T.A. 1978. Geologic implications on the distribution of goitre in Colombia, S.A. International Journal of Epidemiology, 7, 25.
Moccia, R.D., Leatherland, J.H., and Sonstegard, R.A. 1977. Increasing frequency of thyroid goitres in coho salmon (*Oncorhynchus kisutch*) in the Great Lakes. Science, 198, 425.
National Research Council. 1977. Drinking water and health. Prepared for the U.S. Environmental Protection Agency by the Safe Drinking Water Committee, National Academy of Sciences, Washington, DC, USA.
Ogner, G. and Schnitzer, M. 1970. Humic substances: Fulvic acid - dialkyl phthalate complexes and their role in pollution. Science, 170, 317.
Peakall, D.B. 1975. Phthalate esters: Occurrence and biological effects. Residue Reviews, 54, 1-41.
Peltola, P. 1965. The role of L-5-vinyl-2-thio-oxazolidone in the genesis of endemic goitre in Finland. In Cassano, C. and Andreoli, M., ed., Current Topics in Thyroid Research. Academic Press, London, UK, 872-876.
Peltola, P. and Krusius, F.E. 1960. Effect of cow's milk from the goitre endemia district of Finland on thyroid function. Acta Endocrinologica, 33, 603.
Schnitzer, M. and Kahn, S.U. 1972. Humic substances in the environment. Marcel Dekker, Inc., New York, NY, USA.
Shackelford, W.M. and Keith, L.H. 1976. Frequency of organic compounds identified in water. Analytical Chemistry Branch, Environmental Research Laboratory, Athens, GA, USA.
Sonstegard, R. and Leatherland, J.F. 1976. The epizootiology and pathogenesis of thyroid hyperplasia in coho salmon (*Oncorhynchus kisutch*) in Lake Ontario. Cancer Research, 36, 4467.
Suzuki, H. 1980. Etiology of endemic goitre and iodide excess. In Stanbury, J.B. and Hetzel, B., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, Inc., New York, NY, USA, 237-253.
Tellez, M., Gianetti, A., Covarrubias, E., and Barzelatto, J. 1969. Endemic goitre in Pedegroso (Chile). Experimental goitrogenic activity of "Pinon." In Stanbury, J.B., ed., Endemic Goitre. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 245.

Trikojus, V.M. 1974. Some observations of endemic goitre in Tasmania and southern Queensland. New Zealand Medical Journal, 80, 491.

Twort, J.M. and Twort, C.C. 1932. Disease in relation to carcinogenic agents among 60,000 experimental mice. Journal of Pathology and Bacteriology, 35, 219-242.

Van Etten, C.H. 1969. Goitrogens. In Liener, I.E., ed., Toxic Constituents of Plant Foodstuffs. Academic Press, New York, NY, USA, 103-134.

Vought, R.L., Brow, F.A., and Sibinovic, K.H. 1974. Antithyroid compound(s) produced by *Escherichia coli*: Preliminary report. Journal of Clinical Endocrinology, 38, 861.

Vought, R.L., London, W.T., and Stebbing, G.E.T. 1981. Endemic goitre in northern Virginia. Journal of Clinical Endocrinology, 27, 1381.

Discussion: Cassava and Endemic Goitre

Kochupillai: Some time ago, Dr de Groot and one of my colleagues in Dr Stanbury's laboratory in Boston showed that manganese interacts with thyroidal peroxidase, enhancing its activity for organification of iodide. It has also been demonstrated that manganese is present in higher concentrations in the thyroid than in any other tissues. You have referred to studies on chemical composition and oligo-element content conducted on Idjwi Island, where the soil and plants and, in particular, the cassava cultivated in the nonendemic southern part of the island have higher manganese contents than in the endemic region to the north. Do you think the higher manganese content in the diet could exert a protective effect on the thyroid of people living in the south?

Ermans: We have addressed that question in experiments with rats involving chronic administration of manganese. A definite antigoitrogenic effect of manganese was observed in one experiment involving some 300 rats. However, we were unable to reproduce the results in subsequent experiments. We don't have an answer for the discrepancy in the results, but it might be due to accidental contamination with iodide in the case of the manganese-treated rats. Repeated observations, for 2 years, have not revealed any action by manganese on thyroid function.

Cooke: Your studies have focused primarily on the detoxification product of cyanide, thiocyanate, and its effects on the development of goitre and cretinism. When I first became involved with cassava and cyanide, the medical profession seemed more concerned with the effect on the detoxification substrate, namely, the sulfur-containing amino acids. Therefore, concerns focused primarily on weight gains, height for age, and pathologic conditions, such as tropical ataxic neuropathy in Nigeria and Mozambique. Could you tell us the importance you attach to the problem of detoxification substrates, i.e., the sulfur-containing amino acids? This is especially important because your studies indicate that even in protein calorie malnutrition the cyanide still has first call on these essential amino acids, which in many of the countries we are concerned with are the limiting essential amino acids.

Delange: We were concerned, as are others, by the possibility that protein intake, particularly the sulfur-containing amino acids, could be a limiting factor in the conversion of cyanide to thiocyanate but, surprisingly, in Zaire, we found normal sulfur-containing amino acid levels, such as cysteine. This was observed even in the Kivu area, where there is extreme protein calorie malnutrition. These findings are in contrast to reports from Nigeria, where these amino acids are actually undetectable. I cannot explain the difference between the two countries. It might be related to the quality of the proteins, with its very low intake by the populations of both Nigeria and Zaire. It would make sense to ascribe the neuropathy in Nigeria to chronic cyanide poisoning due to a lack of substrates for its conversion, whereas the toxic action of cassava in Zaire is predominantly due to thiocyanate.

Cooke: Do you think that this part of Zaire is one of the exceptions, in that the sulfur-containing amino acids are not limiting?

Delange: All I can say is that, in this area with malnutrition, sulfur-containing amino acids are not a limiting factor. Besides, I am not aware of other studies, except those in Nigeria, in which precise chromatographic analyses of amino acids have been conducted.

Dussault: I would like to address this question to the group from Brussels. It was mentioned that the incidence of congenital hypothyroidism in the study area was between 2 and 10% and that about 400 000 people were treated with iodized oil. Have you noticed any effect of this treatment on the incidence of this disorder?

Thilly: We have data on a trial conducted in Ubangi indicating that the incidence of myxedematous endemic cretinism is nil from birth to 2 years of age after having corrected the iodine deficiency in the mothers during pregnancy. This figure compares with an incidence of about 10% at the same age in children born to untreated pregnant mothers. It is clear, therefore, that iodine supplementation prevents the appearance of myxedematous endemic cretinism. However, this does not exclude the possibility that congenital hypothyroidism in this area is due to two factors, namely, iodine deficiency and thiocyanate overload.

Dussault: With a large population sample, you would expect to obtain the same incidence of sporadic congenital cretinism as in nonendemic, iodine-sufficient areas.

Delange: Definitely, but in these field studies we do not have the technical facilities, including thyroid scans, that would allow us to distinguish between sporadic and endemic congenital hypothyroidism.

Geevarghese: Have any of the participants looked into or found a higher incidence of diabetes mellitus associated with cassava consumption? I have found such an association and believe this might be a new entity related to cassava consumption.

Kabamba: Research on the incidence of diabetes mellitus and cassava consumption has been started at our university. We hope to publish the results in the next year. Have you, Dr Delange, observed a relationship between cassava consumption and this particular form of diabetes in some areas of Zaire?

Delange: We have not carried out an exhaustive investigation on this aspect in our study areas. However, we have been aware of the data of Dr Geevarghese and have looked clinically and epidemiologically into this problem to some extent. Although we did not conduct systematic measurements of blood sugar levels in the inhabitants of these areas, there were no obvious cases. Thus, it appeared to us that this was not a prevalent problem.

Burrow: Based upon your ratios of iodide and thiocyanate excretion in urine and their relationship to goitre prevalence, and knowing that thiocyanate is a competitive inhibitor of iodide transport into the gland, it seems that what is really important is the level of absolute iodide uptake by the gland. This value should really be a direct measure of the goitrogenic effect of cassava. If you calculate the I/SCN ratio on a molar basis, moles of iodide versus moles of thiocyanate, rather than micrograms versus milligrams, one should be able to arrive at a figure that would express the inhibitory factor.

Ermans: We have not measured absolute thyroidal uptake of iodide; however, we have answered that question indirectly by measuring the iodine content of the gland in rats after prolonged administration of small amounts of thiocyanate. Under these conditions, thiocyanate does not modify, statistically, the iodine content of the gland. Decreased thyroid iodine content was observed in previous studies when larger amounts of thiocyanate were given. I do not have data on the equivalence of iodide and thiocyanate in terms of molar concentrations, but I guess that it is much higher for thiocyanate than for iodine.

Kochupillai: Your data indicate that, in the presence of high levels of circulating thiocyanate, which suppresses the thyroidal uptake of iodine, there is no corresponding increase in the urinary excretion of this element. This looks anomalous to me. Do you have an explanation?

Ermans: In individuals given acutely large amounts of cassava, which induce inhibition of thyroid iodide uptake, an increase in urinary iodide excretion corresponding to the degree of inhibition of the thyroidal uptake was actually observed, permitting us to conclude that, in this particular situation, cassava exerts a thiocyanate-like effect.

Kochupillai: I was referring to your observations in the field, where, in the population with high goitre prevalence and high circulating thiocyanate levels, the thyroidal iodide uptake at 24 hours was significantly lower than in the population of the nongoitrous area, but still there was not a statistically significant increase in daily urinary iodine excretion.

Delange: I agree that even in the chronic state one would expect an increase in urinary iodine proportional to the high thiocyanate concentrations in the blood, and suppression of thyroidal uptake of radioiodine. I do not have a definite explanation, but can suggest two possibilities. The first is that the goitrous group was more iodide deficient than the nongoitrous group and that in the presence of higher circulating thiocyanate levels both groups excreted similar amounts of urinary iodine. I believe that this is a poor explanation, however. The second possibility is that individuals chronically exposed to thiocyanate overload periodically, perhaps after each meal, lose additional iodide in the urine. Actually, in inhabitants where observations have been made under acute conditions, there is a consistent transient increase in urinary iodine. On the other hand, under basal conditions and for large groups, it is difficult to quantify these differences properly. Furthermore, in experimental animals under acute conditions there is a consistent loss of iodide in the urine.

Kochupillai: In the areas studied, Dr Delange has shown that endemic goitre is not found as long as the iodide to thiocyanate ratio is higher than 4, appears in mild to moderate form with ratios between 2 and 4, and only becomes hyperendemic when the ratio is less than 2. One sees a sort of sigmoidal distribution in this phenomenon. On the basis of what is known of the biology of the thyroid gland function, is there an explanation for this phenomenon?

Delange: No, except that this suggests a threshold effect, which has been demonstrated for most of the goitrogenic substances.

Ramirez: The etiopathogenesis of cretinism still remains obscure and controversial. For instance, in the Andean endemic regions, there are many individuals who do not fit the clinical criteria for cretinism but have permanent impairment of neuromotor development. In our area, we found a high percentage of those individuals who are not typical cretins but show some impairment. Is the same true in your study areas?

Delange: Yes, we have also found many intermediate situations between what is called clinically myxedematous endemic cretinism and normal subjects. We have also found exactly the same situation as yours for the neurological type of cretinism. The unanswered question that remains is: Why is the clinical spectrum of endemic cretinism so different in various parts of the world?

Van Middlesworth: I would like to ask two questions. The first is: Have you studied the thyroglobulin of goitres in humans or, if not available, have you studied it in goitres of indigenous animals such as rats? This is important with respect to the total iodine content of the thyroid. If you find an abnormal thyroglobulin, it may not be accounted for as part of the total iodine content in your equilibrium studies because you are only measuring metabolically active pools. If there is a nonactive thyroglobulin, you will not know the total iodine content unless you isolate, digest, and analyze it. The second question is: In endemic hypothyroidism, is there a chance that the neuropathy is due to amino propionitryl in the diet? It was shown years ago that amino propionitryl could produce neuropathy in hypothyroidism more severely than in the euthyroid state.

Ermans: In answer to your first question, we were aware of your observation in rats fed on thiocyanate in which you found that iodine in particular spots does not exchange with the rest of the gland. In view of this observation, we systematically studied both the total iodine content and the thyroglobulin fraction in our last experiment and were unsuccessful in obtaining evidence of any difference in the thyroglobulin fraction and total iodine content of the glands. We did not conduct morphological studies and were unable to repeat your experiment, probably because your observations were made after a very long period of thiocyanate administration. We have no answer to your second question.

Tewe: We have heard that the etiology of endemic goitre and cretinism is multifactorial, and this seems evident from the nutritional and environmental factors mentioned. Regarding the effect of cassava on mental retardation in rats, however, the impression was left that it was principally mediated by hypothyroidism and consequent abnormal cellular growth of the brain. I would think that in the presence of protein deficiency there is less detoxification of cyanide, which might act directly, and in addition to the hypothyroid effect of thiocyanate, on the brain. In cases of protein deficiency, the combined action of these two factors might well explain neurological and brain abnormalities and would reconcile some of the different views on this aspect. Have you investigated the effect of protein malnutrition in your experiments on rats?

Delange: We have not investigated the specific action of protein malnutrition. We are aware of the work being done in this area, including your own, and I quite agree with all of your comments; however, in our experiments, body weight was not affected in rats put on cassava. This suggests that they were not in malnutrition and that the cerebral anomalies resulted from hypothyroidism.

Benmiloud: I would like to go back to the iodide–thiocyanate ratio. You have shown severe endemic goitre and cretinism in the presence of extremely low levels of iodide and very high levels of thiocyanate. What do you think will happen in areas with moderate iodine deficiency and moderately elevated thiocyanate levels, as seen, for instance, in smokers? Do you think that smokers would have goitres more often than nonsmokers?

Delange: Yes, we believe that with borderline iodine deficiency and borderline thiocyanate overload you might develop goitre problems, as has been shown in Sicily. There, with a daily iodide intake of 50 μg, similar to that in Brussels, and with a borderline thiocyanate overload due to cabbage consumption, you find an iodide-thiocyanate ratio of 3.4 and a goitre prevalence of 45% among schoolchildren. Whether or not this population presents subtle brain problems we don't know, but it would be fascinating to investigate it. Consequently, heavy smokers would be at risk of thyroid dysfunction, including goitre, if they were also relatively iodine deficient.

Benmiloud: You have indicated the presence of antithyroid compounds in rocks rich in organic content. It is also said that the iodine content of the soil and rocks increases with their organic content. Would you please comment on this?

Gaitan: You are right in that the iodine content of soils and rocks increases in proportion to their organic content. The iodine concentration in most igneous, metamorphic, and sedimentary rocks has generally been given as 0.2–5.8 ppm, with 5 to 10 times this amount in shales, coals, and soils rich in organic matter. Thus, igneous or volcanic rocks devoid of organic matter have the lowest iodine content. All of the geological studies in endemic goitre areas prior to our investigation were conducted in the presence of dietary iodine deficiency. For instance, Malamos and collaborators, who studied the distribution of goitre in Greece, where nutritional iodine deficiency is still a factor in the development of goitre, also observed that the distribution of different rock types correlates with the prevalence of goitre. Communities located on limestone terrain are associated with low goitre prevalence, whereas those located on shales and schists have a high incidence of goitre. On the basis of soil and rock analyses, these investigators implied that the low concentration of exchangeable cations and the ability of soils to absorb iodine are related to a high prevalence of goitre. I would like to suggest that those particular shales and schists in Greece may be rich in organic material, whereas the limestone may be deficient in organic material. We were fortunate to conduct our studies in areas with adequate iodine supplementation. Therefore, we were able to cancel out the iodine deficiency variable, and to explain the variation in goitre prevalence based on the differences in the geological composition of watersheds. I would also like to point out that geological studies on Idjwi Island showed that the type of terrain existing in the localized area of the southwest, where there is no endemic goitre or cretinism, is made up solely of basalt, an igneous rock devoid of organic matter, whereas that of the endemic area has a different geological composition. These results are entirely in accordance with our findings in western Colombia.

Dussault: I am not sure about your experiments on rats with respect to the effect of thiocyanate in low-iodine diets. It is very difficult to render a pup truly hypothyroid on a low-iodine diet. There is always a circulating triiodothyronine (T_3) level that is even higher than normal. Therefore, I would pursue that experiment and, in particular, would measure other parameters of brain development. I would also like to ask: What do you think of the role of iodine deficiency in the development of the central nervous system? There seems to be a popular feeling in the literature that iodine deficiency plays a role in sheep and rats. I don't believe it myself, but I would like to have your opinion on this issue.

Delange: I agree with your first comment, particularly in view of the fact that we have no measurements of T_3. Regarding other parameters of brain development in newborn rats, I only showed data for RNA, but it worked just as well for DNA, protein content, cholesterol, and cerebrosides. I agree that one should investigate this further. In answer to your question on the direct effect of iodine deficiency on brain development, I am not completely convinced of such a direct effect based on the data presently available. I might regret saying that but, at present, neither clinical nor epidemiological data unequivocally support that view, and, as far as the experimental approach, it is extremely difficult to make sheep and rat fetuses severely iodine deficient without also making them hypothyroid. Therefore, the evidence presented for a direct effect of iodine on brain development might be smeared by the concomitant occurrence of fetal hypothyroidism.

Ramirez: Dr Gaitan, in your studies in the Candelaria area of western Colombia, endemic cretinism was not found even though endemic goitre was present. This is due to the fact that iodine has been supplemented in that area since 1954. This observation would support the hypothesis of a direct effect of iodine in the prevention of endemic cretinism. Do you have any other hypotheses to explain the absence of endemic cretinism in this endemic area.

Gaitan: It is interesting to look at the history of goitre and endemic cretinism in Colombia. It is identical to that of Ecuador and Peru. Colombia had rampant high endemic cretinism before iodization began. Actually, pre-Colombian sculptures of cretin dwarfs from the Tumaco culture, which existed in the southwestern Andean region of Colombia from 400 BC to 500 AD, constitute historical proof of the existence of the myxedematous type of endemic cretinism in this region long before iodine supplementation began. Thus, iodine supplementation certainly eradicates endemic cretinism. We probably have, at present, the same incidence of sporadic congenital hypothyroidism as in most countries with adequate iodine intake. Whether iodine exerts a direct or indirect effect on the prevention of cretinism, however, I really don't know. I tend to agree with Drs Ermans and Delange that endemic cretinism is the result of more than a single factor. I opened my presentation this morning by stating that the level of iodine intake in endemic goitre areas determines the magnitude of the endemia and the nature of its complications. Once iodine is supplemented, hyperthyroidism becomes apparent, whereas the incidence of endemic cretinism becomes negligible.

Unidentified participant: I understood Dr Ramirez's question in a different way. I guess he feels that endemic goitre in the Candelaria area is related to a mechanism that has nothing to do with iodine deficiency, because it is related to antithyroid compounds blocking the organification of iodine and becomes worse if you continue adding iodine. The fact that in this situation there is no cretinism is proof of the role played by iodine in its pathogenesis. I also think that the endemia of Candelaria is, in fact, moderate and cretinism only occurs in very severe situations.

Gaitan: There is no question, at present, that the magnitude of the goitre endemia in Colombia is moderate. It decreased from an overall prevalence of

54% before iodization to 15% after the prophylaxis program was established. Therefore, we have not observed that adding iodine makes the goitre problem worse. There is also no question that goitres among schoolchildren are relatively small, corresponding to grades 1 and 2 based upon WHO criteria. We no longer see giant goitres in schoolchildren. On the other hand, goitre prevalence in western Colombia ranges from 1–42% in various localities that are equally supplemented with iodine. This clearly indicates that goitrogenic factors other than iodine deficiency are present in these areas. Whether it is the direct effect of iodine that prevents cretinism or the fact that the blockage of organification in the gland by the antithyroid agents is not complete, so that adequate synthesis and release of thyroid hormones is possible, thus maintaining the euthyroid state, is not known. We have published extensively on the pathophysiology and thyroid gland function of these goitrous individuals. Consistently, we have found normal concentrations of thyroid hormones with both serum T_4 and T_3, as well as TSH within the normal range. These individuals, therefore, are clinically and chemically euthyroid, with varying degrees of thyroid enlargement. Goitres were not observed in children under 5 years of age, indicating that it takes at least that amount of time to decrease thyroid iodine stores to a threshold level, at which time the gland enlarges. One can argue, then, that the reason that endemic cretinism is not observed in this area is because fetal hypothyroidism does not occur. Thus, we return again to the question of the role of iodine in the prevention of endemic cretinism.

Ermans: I was a little surprised by your classification of the various goitrogens in foodstuffs. You mentioned cyanogenic glycosides, which act through thiocyanate, and thioglycosides, which act as "goitrin." In my opinion, "goitrin" is a very peculiar example of a thioglycoside. Thioglycosides are found, generally, in the Cruciferae family and most of them have the production of isothiocyanates and thiocyanates in common. Actually, there is a lot of work being done by the Bratislava group indicating that the amount of thiocyanate in the urine is the best indicator of the presence of thioglycosides in food. I also believe that "goitrin" constitutes a particular type of thioglycoside that acts on the organification and coupling of iodotyrosines and not on the kinetics of iodide. Thus, I don't agree with your concept.

Gaitan: I agree with Dr Ermans that most thioglycosides are transformed to isothiocyanates and eventually a fraction becomes thiocyanate. I also agree that "goitrin" is unique in that it does not degrade like other thioglycosides. It is also true, however, that "goitrin" acts in vitro on the thyroidal peroxidase and in vivo exerts a thionamide-like effect. For this reason and because "goitrin" is a well-known naturally occurring goitrogen and has been implicated as the causative factor in at least one goitre endemia, that of Finland, I gave it a special place as a thioglycoside in the group of naturally occurring compounds that affect organification and coupling. Isothiocyanates ingested as such or as by-products of thioglycosides were similarly placed with "goitrin." It has been shown that isothiocyanates use not only the thiocyanate-metabolic pathway but react spontaneously with amino groups forming di-substituted thiourea derivatives, which produce a thiourea-like antithyroid effect. Langer and Greer demonstrated the thionamide antithyroid action in vitro of some naturally occurring isothiocyanates. They also demonstrated an additive antithyroidal effect of thiocyanate, isothiocyanate, and "goitrin" in groups of rats force-fed various combinations of these naturally occurring goitrogens. As you can see, this is a complex issue.

de Bruijn: I understand that whenever the iodide–thiocyanate ratio decreases goitre will appear first and then, with a further decline in the ratio, endemic cretinism becomes apparent. This would mean that all endemic cretins should also have goitre, but this does not seem to be the case. Is it because they are two different entities but somewhat closely related to each other?

Delange: You are correct. The reason why myxedematous endemic cretins usually have no goitre in spite of very low I/SCN ratios is unknown. Our impression is, although we do not have supportive data, that sometime between birth and late childhood the thyroid gland of these patients is anatomically damaged by some unknown factor. We have no histologic data and a prospective study is unthinkable on ethical grounds, because you cannot follow up a newborn with extremely high serum TSH and very low T_4 levels until the individual becomes an adult cretin without providing adequate treatment.

Phillips: Dr Gaitan pointed out that, in Candelaria, when water from goitrogenic well "A" was mixed with water from nongoitrogenic well "B" and the whole town was supplied through a common pipeline, the goitre in area "B" increased significantly over a 1-year period. Therefore, if the process was reversed, goitres should disappear. Would that be your assumption?

Gaitan: Yes. Actually, the incidence or "attack" rate of goitre was 13%, over an 8-month period, among 242 schoolchildren from Candelaria, at the time the water from both wells was combined. Recent epidemiological studies have documented the reverse situation. As mentioned earlier, the prevalence of goitre in Candelaria has been constant at around 30% since 1959. In June 1974, 6 months after the closure of goitrogenic well "A," the prevalence decreased to 8%. In December of the same year, another survey revealed that the prevalence was still as low as 10% in children from the urban area, but in children living in rural areas the prevalence remained at 28%. A survey carried out 5 months after well "A" had been reinstalled disclosed that the goitre prevalence in children living in the urban area again reached 32%, a significant increase from the two previous studies during which the well was not in use. Thus, it is a reversible condition, at least in schoolchildren, taking about 6 months to disappear in significant numbers.

Phillips: In many parts of the world, cassava is consumed on a seasonal basis, as sometimes suggested in the literature. In such a case, there should be variability in the incidence of goitre, and I wonder whether or not this is as serious a problem as a continuous or persistent goitre.

Delange: We have no data on that particular aspect. It is obvious, for instance, that in the Kivu area there is a marked seasonal variation in cassava consumption and I suspect that it should affect goitre prevalence. This is very difficult to document, however, in large field studies. Similarly, we have observed, in the Ubangi area, seasonal fluctuations in the serum concentration of thiocyanate in adults, which should be reflected in changes in the incidence of goitre. Again, this is difficult to evaluate because the problem is so severe from the beginning. Nevertheless, I agree that this is an aspect that must be taken into account.

Phillips: In view of what Dr Gaitan said, that it takes about 6 months for the effect of goitrogenic water to wear off, we could, perhaps, say that the same time period would be required for the effects of cassava to wear off. The cycle is too repetitive, however, in terms of the amount of cassava eaten. Therefore, you never see a significant decrease in goitre prevalence.

Public Health and Nutritional Aspects of Endemic Goitre and Cretinism in Asia

N. Kochupillai[1] and V. Ramalingaswami[2]

Endemic goitre and cretinism are common nutritional disorders in Asia, particularly in south and southeast Asia. India, Burma, Thailand, Nepal, Indonesia, and Bangladesh are among the worst affected countries in Asia. The prevalence of endemic goitre and cretinism in China is not known.

An estimated 400 million people in Asian countries are exposed to the risk of goitre, which, in the main, has been shown to be linked with environmental iodine deficiency (Ramalingaswami 1973). The actual number of people suffering from goitre is estimated to be approximately 80 million. In regions where goitre is prevalent in more than 50% of the general population, the prevalence of cretinism and other related developmental defects is reported to vary from 3–17% (Kochupillai et al. 1980).

This paper will review the problem of endemic goitre and cretinism in Asia, India in particular. Special emphasis will be placed on the prevalence, etiology, and health consequences, as observed in India and other countries of the region. The contributory role played by dietary goitrogens, particularly cassava intake, will be examined in the available literature.

Recent observations, using modern techniques, show that more than half of the population living in severely goitrous areas may have subclinical hypothyroidism (Kochupillai et al. 1973), which could have an adverse effect on the general health and economic productivity of the people living in these areas (Kochupillai et al. 1980).

Endemic Goitre and Cretinism in India

Prevalence

Goitre has been an age old health problem in the southern slopes of the Himalayas. Recent observations show that goitre is also distributed widely in the subcontinent with varying degrees of severity (Pandav and Kochupillai 1980). The world's most classic and intense endemic belt occurs along the slopes and foothills of the Himalayas, extending over 2400 km from Kashmir in the west to the Naga Hills in the east. The endemic belt involves the northern states of Jammu and Kashmir, Himachal Pradesh, Punjab, Haryana, Uttar Pradesh, Bihar, West Bengal, Sikkim, Assam, Mizoram, Meghalaya, Tripura, Manipur, Nagaland, and Arunachal Pradesh. Table 1 provides recent data on the prevalence of endemic goitre in different states of India.

According to the latest available estimates, about 120 million people in India live in known regions of endemic goitre. Nearly one-third of these are actually goitrous. More recent studies have demonstrated the existence of endemic goitre in numerous foci away from the traditionally endemic zones (Pandav and Kochupillai 1982) (Fig. 1). There is a growing impression among researchers that the present estimates of goitre prevalence within the country are, at best, underestimations.

Etiology

The primacy of environmental iodine deficiency as the underlying cause of Himalayan endemic goitre was established through a series of investigative efforts, spanning more than a

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Fig. 1. Distribution of endemic goitre in India.

decade, by Professor V. Ramalingaswami and his research team at the All India Institute of Medical Sciences, New Delhi (Kochupillai et al. 1980). It has been found that the level of iodine in drinking water is extremely low in the endemic zone, with no values being higher than 3 μg/L, and most values being considerably below this figure. Marked elevations in 24-hour thyroidal ^{131}I uptake, coupled with low urinary iodide excretion of less than 40 μg per gram of creatinine, clearly demonstrate iodine deficiency in the goitrous individuals. Plasma inorganic iodide, estimated by the isotope dilution technique, was low. Protein bound ^{131}I, at 48 hours, was markedly elevated, demonstrating a rapid turnover rate of intrathyroidal iodine. The majority of the goitrous patients studied showed suppressibility of the high ^{131}I uptake by T_3. A TSH stimulation test did not reveal any further enhancement of ^{131}I uptake, suggesting

Table 1. Goitre prevalence in India.

State	Goitre prevalence (%)
Assam	1.5-31.5
Bihar	3.6-64.5
Chandigarh	45.9
Delhi	55.0
Gujrat	22.8-36.7
Haryana	6.5-26.0
Himachal Pradesh	23.7-41.6
Jammu and Kashmir	25.4-38.2
Kerala	32.3
Madhya Pradesh	21.3-55.6
Maharashtra	8.8-55.3
Manipur	32.0
Meghalaya	2-3
Mizoram	68.6
Punjab	9.3-40.3
Sikkim	37.8
Tripura	17.0
Uttar Pradesh	16.9-65.9
West Bengal	11.6-35.6

Source: Government of India and medical research conducted in India, 1981.

Table 2. Iodine metabolism in schoolchildren, Delhi.

Study group	Percentage of children with urinary iodine <50 μg/g creatinine	Percentage of children with ^{131}I uptake >35% at 24 hours
Kalkaji schools		
Boys	61	58
Girls	70	78
Chandni Chowk schools		
Boys	66	79
Girls	83	92

maximum endogenous stimulation by TSH (Ramalingaswami 1973). Studies designed to demonstrate iodine organification defects did not yield positive results.

Similar studies conducted in several other goitrous areas of the country confirmed iodine deficiency as the major etiological factor (Pandav and Kochupillai 1982). Recently, endemic goitre has been shown to exist in several parts of Delhi (Pandav and Kochupillai 1980). Epidemiological, as well as quantitative studies on iodine metabolism (summarized in Tables 2 and 3), indicate that severe iodine deficiency exists in goitrous patients from these pockets (Pandav and Kochupillai 1980; Kochupillai et al. 1977).

Although iodine deficiency is a necessary and important condition for goitrogenesis, several other contributory factors seem to be operative, and may explain the observed variability in the prevalence and health consequences of goitre from one area to another. As early as 1908, the role of polluted drinking water in the genesis of endemic goitre, based on epidemiological observations in the Gilgit valley of the Himalayas, has been pointed out. Earlier, McClelland observed an association between goitre prevalence and lime-rich drinking water, through extensive medico-topographic studies along a wide belt of northern India extending from northwestern frontier provinces to Bengal. These observations are relevant to numerous endemic goitrous areas in northern India today. Recent observations (Pandav and Kochupillai 1982) in the Gangetic plains of Uttar Pradesh and Bihar seem to bring out the relationship between flooding and goitre prevalence (Table 4). It is folklore in several of these areas that goitre is most noticeable in flood-prone hamlets nestled particularly along the bends of rivers. For example, in the Gonda district of Uttar Pradesh, goitre in its most severe form was observable in the hamlets situated on the strip of land between the rivers Ghaghra and Sarayu. The village of Katra Shahwajpur, situated on the banks of the river Sarayu, is flooded annually. Goitre prevalence in this village was observed to be over 80%, most belonging to grades II–IV. Cretinism, deaf-mutism, and other clinically detectable oligophrenic states, with related developmental defects attributable to severe environmental iodine deficiency, were present in 4% of the population of this village. In addition,

Table 3. Parameters of iodine kinetics in simple goitre.

Study group	^{131}I thyroidal clearance rate (mL/min)	^{131}I renal clearance rate (mL/min)	Plasma inorganic iodine (μg %)	Absolute iodine uptake (μg/hour)	Urinary iodine creatinine (μg/g)
Goitrous patients	88.39 ± 13.1	23.33 ± 1.96	0.0696 ± 0.0075	2.532 ± 0.257	20.0 ± 1.85
Control	22.2 ± 3.43	21.675 ± 2.2	0.1372 ± 0.0183	1.6463 ± 0.00183	76.4 ± 10.18
	(P<0.001)	(P<0.07)	(P<0.01)	(P<0.05)	(P<0.001)

Source: Kochupillai et al. (1977).
NOTE: Values are mean ± SE.

Table 4. Relationship between goitre prevalence and flooding in India.

District	Village	Flooding	Percentage goitre prevalence
Gonda (Uttar Pradesh)	Katara Shahwajpur	Yes	80
	Saideva	No	50
Sitamarhi (Bihar)	Riwari	Yes	90
Madhubani (Bihar)	Pandaul	No	22

93% of the primary schoolchildren examined were goitrous and 20% of them showed thyroid insufficiency (Table 5). In contrast, in the village of Zaideva, Gonda district, where there is no flooding, goitre prevalence was 50%, most belonging to grade Ob and grade I. Only one adult cretinous individual was found in this village. Similar contrasting pictures related to flooding are observable within the iodine deficient endemic belt.

Poverty and attendant nutritional problems have long been held to coexist with severe endemic goitre in several parts of northern India (Stott et al. 1931). The present study seemed to bear this out. It was observed that goitre and its associated disabilities occurred in their worst form in the backward impoverished villages of northeastern Uttar Pradesh and Bihar states. Clinical features of protein calorie malnutrition are widely observable in these villages. In addition, due to extreme poverty, populations living in these backward villages often resort to eating unconventional seeds, cereals, and other plant products growing under wild conditions. In the Colonelgunj Primary Health Centre area of Gonda district, people living in several severely goitrous villages consume fried *Petua* (*Hibiscus cannabinus* Linn.) regularly, in large quantities, to supplement their diet. In several other villages in Uttar Pradesh and Bihar, people consume the flower of *Hibiscus subduriffa* Linn., a related plant. Both these plants contain anthocyanins, such as gossipefin and hibiscin, in addition to containing useful nutrients such as fatty acids (essential and nonessential) and rich quantities of vitamin C. It remains to be investigated whether or not these unconventional sources of food contain any naturally occurring goitrogens, and whether or not they contribute to the variability observed in goitre prevalence.

These observations suggest that a number of poverty-related factors contribute to goitre formation, aggravating the biological consequences of environmental iodine deficiency. Also, poor economic productivity can result from a generalized suboptimal function of the thyroid in goitrous areas. There is already evidence for this (Kochupillai et al. 1973). The vicious cycle of environmental iodine deficiency impinging adversely on the thyroidal function of an impoverished population, which in turn renders these populations economically less productive, thus aggravating the very poverty conditions that make them susceptible to the scourges of environmental iodine deficiency, is a phenomenon widely observable in the endemic foci of India. To add to this burden is the significant number of mentally retarded individuals, with varying degrees of physical disabilities, that are seen among them.

Cassava and Goitre in India

Kerala, in southern India, is the only state in India where cassava (*Manihot utilissima*) is used as a dietary component. Although its use in the diet is widespread throughout the state, it is mainly consumed by poorer people, particularly along the coastal districts, where poverty is at a maximum.

Recently, goitre prevalence has been studied along the coastal strips of two districts in this state (Kochupillai et al. 1976). A total of approximately 19 000 people was surveyed between these two districts. The overall goitre prevalence was 1.3–1.4%. Nodular goitre, and particularly uninodular lesions, were predominant, accounting for 68% of the overall goitre prevalence. Diffuse goitre accounted for only 12% of all the detected goitres. The maximum preva-

Table 5. Thyroid status of 30 schoolchildren from highly endemic goitrous villages of Colonelgunj, Gonda district, Uttar Pradesh.

Thyroid status	TSH (μU/mL) (mean ± SE)	T_4 (μg/dL) (mean ± SE)	T_3 (ng/dL) (mean ± SE)	r-T_3 (ng/dL) (mean ± SE)
Euthyroid (23)	9.10 ± 1.83	4.0 ± 0.53	170.5 ± 5.56	27.90 ± 2.64
Hypothyroid (7)	>80 in all	1.51 ± 1.10	110.48 ± 17.37	38.33 ± 2.88

NOTE: Numbers in parentheses indicate the number of schoolchildren studied.

lence of goitre was observed in women 40–60 years of age. Goitre prevalence was negligible among schoolchildren. Thirty-six nodular lesions from these areas were subjected to surgery. Most of the uninodular lesions resected turned out to be adenomas upon histopathological examination. Thus, it is clear that endemic goitre is not prevalent along coastal Kerala, where cassava is widely consumed.

Endemic goitre, however, is reported from the hilly tracts of Kerala. Basu et al. (1976) observed 32.28% goitre among the workers of the tea estates of Munnar. There were no reports of an associated prevalence of cretinism in these areas. Personal observations on goitre prevalence in several midland villages of Quilon and Kottayam districts, where cassava is consumed liberally, did not reveal endemic goitre. However, nodular goitres were observable sporadically, especially in women, in 3–4% of the people examined. Although further studies are required to evaluate the role of cassava in the genesis of endemic goitre in the eastern hills of Kerala, cassava consumption does not seem to be associated with endemic goitre in the coastal and midland districts of this state.

Endemic Goitre: Attendant Disabilities in India

Large-sized goitre, with multiple nodules, is the most dramatic and frequently encountered effect of severe environmental iodine deficiency. However, the real health problems that ensue from iodine deficiency and goitre are due to functional failures of the thyroid gland at different stages of an individual's development. Although goitre is considered to be an adaptive response, recent evidence suggests that large goitres are, in fact, maladaptive. It has been shown recently (Kochupillai et al. 1973), in a severely goitrous village of Uttar Pradesh, that there is an inverse relationship between goitre size and circulating thyroxine, on the one hand, and a direct relationship between goitre size and pituitary TSH reserve, as indicated by the TRH test. Data also suggest that, in areas with a high prevalence of severe grades of goitre, as much as 60% of the population may show laboratory evidence of subclinical failure of the thyroid.

A more disturbing recent observation has been the unexpectedly high prevalence of hypothyroidism among newborns from severely endemic goitrous areas. Preliminary findings in this regard show an incidence that varies from 2–5% in endemic foci of differing severity (Kochupillai et al., in preparation). These alarming observations make prophylactic measures for goitre prevention a necessary and urgent requirement to be implemented immediately in India, and elsewhere, where goitre is prevalent in significant proportions.

Endemic Goitre in Other Parts of Asia

Table 6 summarizes known information on goitre prevalence, its etiology, and health

Table 6. Goitre and cretinism in other parts of Asia.

Country	Reported prevalence (%)	Population affected	Etiology	Role of cassava	Health consequence
Afghanistan	10–65	700000–1000000	Iodine deficiency	Nil	?
Bangladesh	25	25% of the population	?	Nil	?
Burma	44–91	Chin-special division, Kachin state, Shan state	Iodine deficiency ?Mustard-green goitrogen	Nil	4–17% cretins in severely affected areas
Indonesia	20–63	Java, Sumatra, Kalimanthan, Sulawesi, Irian, Barat	Iodine deficiency	?	8% cretins in severely goitrous areas
Malaysia	Up to 40	Pahang, Sarawak	Iodine deficiency	?	Nil
Nepal	7–100	Entire country	Iodine deficiency	Nil	11.5% cretins in severely affected areas
Sri Lanka	7–54	70%	Iodine deficiency ?Due to high rainfall	?	Nil
Thailand	42–84	Prae province, Cheng Rai province, Cheng Mai province	Iodine deficiency	?	4% cretins in severely affected villages

consequences in other countries of the Asian continent (Kochupillai et al. 1980). Broadly, the situation is similar to that observed in India. Dietary goitrogens are implicated as a cause of endemic goitre in Burma, due to consumption of green mustard in some areas. Iodine deficiency is the principal etiological factor for goitre in all the countries studied in the area. Nothing is known about other contributory factors. No information is available about the role of cassava in goitrogenesis in countries such as Thailand, Indonesia, and Malaysia, where it is grown. Cretinism and related developmental defects have variable prevalence rates ranging from 4–17% in severely affected areas. From countries such as Malaysia and Sri Lanka, where goitre prevalence is mild, no cretinism or related defects are reported.

Conclusions

Over 400 million people in the Asian countries, other than China, are exposed to the risk of endemic goitre and its health consequences. Approximately 20% of them are actually goitrous. Of the people living in severely goitrous areas, 3–17% suffer from cretinism and related developmental defects. Environmental iodine deficiency plays an important role in goitrogenesis in all countries studied. Although cassava is grown in countries such as India, Thailand, Indonesia, and Malaysia, there is no evidence to show that cassava consumption plays any role in goitrogenesis in Asia. However, several other ill-defined contributory factors seem to operate to generate the extreme variability in goitre prevalence observed in different endemia in Asia. Detailed studies are necessary to clarify the role of such contributory factors in different parts of Asia. Moreover, recent observations indicate that in severely goitrous areas as much as 2–5% of newborns may have thyroid insufficiency at birth. There is, therefore, an urgent need to implement iodine prophylaxis, at least in the severely endemic foci of the Asian continent.

Basu, P.K., Narayan, R., Yusuf, S., and James, K.K. 1976. Preliminary report of a survey of the prevalence of goitre in the tea estates of Munnar. Paper presented at the 6th All India Conference of Preventive and Social Medicine, Bangalore, India.

Kochupillai, N., Deo, M.G., Karmarkar, M.G., McKendrick, M., Weightman, D., Evered, D.C., Hall, R., and Ramalingaswami, V. 1973. Pituitary thyroid axis in Himalayan endemic goitre. Lancet, 12 May, 1021-1024.

Kochupillai, N., Thangavelu, M., and Ramalingaswami, V. 1976. Nodular lesions of the thyroid in an area of high background radiation in coastal Kerala, India. Indian Journal of Medical Research, 64(4), 537–544.

Kochupillai, N., Augustine, P., and Ahuja, M.M.S. 1977. Quantitative aspects of iodine metabolism in simple goitre seen in Delhi and neighbourhood areas. Journal of the All India Institute of Medical Sciences, 3(2), 159–164.

Kochupillai, N., Ramalingaswami, V., and Stanbury, J.B. 1980.Southeast Asia. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 101-121.

Kochupillai, N., Godbole, M.M., Karmarkar, M.G., and Ahuja, M.M.S. In preparation. Cord blood r-T_3 levels as an index of thyroid function in the newborn of iodine-deficient goitrous areas of India.

Pandav, C.S. and Kochupillai, N. 1980. Endemic goitre in Delhi. Indian Journal of Medical Research, 72, 81-88.

1982. Endemic goitre in India — current status. Prevalence, etiology, attendant disabilities and control measures. Indian Journal of Paediatrics, in press.

Ramalingaswami, V. 1973. Endemic goitre in Southeast Asia: New clothes on an old body. Annals of Internal Medicine, 78, 277-283.

Stott, H. et al. 1931. Distribution and causes of endemic goitre in the united provinces. Indian Journal of Medical Research, 18, 1069.

Public Health and Nutritional Aspects of Endemic Goitre and Cretinism in Africa[1]

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Endemic goitre is still a major public health problem in Africa, affecting several million people. Its benign appearance is deceptive enough that it ranks low in the hierarchy of acute and chronic diseases plaguing developing countries. Multiple complications may arise, however, all of them deleterious to the well-being of the population as well as to the health budget of the country involved. The most notable of these include: an increased rate of cretinism, whether myxedematous or neurological; severe postsurgical complications, such as hypoparathyroidism and laryngeal nerve paralysis; an association with impaired fertility and mental impairment of schoolchildren, which could be epiphenomenal rather than a consequence of endemic goitre; and a higher prevalence of cancer, although in many affected countries there is only a change in the distribution of the histological types of cancer.

Since the extensive review of Kelly and Snedden (1960), Beckers and Benmiloud (1980) have reviewed more recent reports on the subject (Adadevoh and Lukanmbi 1974; Boukhris et al. 1981; Kajubi and Okel 1970; Latham 1966; McGill et al. 1970; McGill and Svenssen 1980; Medeiros-Neto 1980; Osman and Fatah 1981; Singh and Etta 1978). The scarcity of reports reflects the absence of active research in a field where it is highly desirable.

A cursory look at a map of Africa (Fig. 1) demonstrates that, with the exception of a few Sahelian countries such as Mauretania and Niger and a few West African coastal countries such as Benin, Gabon, and Togo, goitre endemia is present everywhere. The incidence of goitre varies among countries and regions within the same country (Table 1). Severe endemias are found in Zaire and some of its neighbours, e.g., Angola, Chad, and Rwanda, with perhaps smaller populations being affected in Rwanda. Similarly, 20% (4 million) of the population of Algeria has a goitre incidence varying from 10–80%. Morocco has a smaller endemic area, but the incidence of goitre is quite high.

Although the areas involved are frequently found in the highlands or mountains, this is not always the case. In Senegal, Egypt, Zaire, and Algeria, goitrous areas can also be found at low altitudes. Although normally occurring inland, the endemia can also be found on the seashore in Algeria, Tanzania, Sudan, and Senegal. Climatic conditions can vary from semitemperate mediterranean to tropical. Only the Sahara Desert, with its small nomadic population, is spared.

Although the socioeconomic development of Africa is variable, none of these countries, with the exception of some areas in South Africa, are developed enough to ensure an adequate health environment.

The coexistence of endemic cretinism and endemic goitre reported in Cameroon, Kenya, and Zaire has been thoroughly studied only in Zaire (Pharoah et al. 1980). However, it is likely that endemic cretinism can often be detected in goitrous areas.

The clinical characteristics of endemic goitre are similar in most African countries; sex and age distribution, as with most endemias, are characterized by an increased incidence at puberty in both males and females, with a sustained elevation for females of childbearing age. The frequency of nodular forms increases with age.

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Fig. 1. Distribution of endemic goitre in Africa.

Table 1. Incidence of goitre in Africa.

Maximum percentage	Affected countries
<90	Zaire, Angola, Chad, Uganda, Sudan
<80	Kenya, Sierra Leone, Algeria, Morocco, Tanzania, Mali, Upper Volta
<70	Ethiopia, Cameroon, Ivory Coast, South Africa, Namibia
<60	Zambia, Egypt, Tunisia, Nigeria, Guinea
<50	Malagasy Republic, Central African Republic, Senegal, Gambia
<40	Rwanda, Zimbabwe

Sources: Beckers and Benmiloud (1980); Kajubi and Okel (1970); Kelly and Snedden (1960); Latham (1966); McGill et al. (1970); McGill and Svenssen (1980); Nwokolo (1974); Singh and Etta (1978).

In cases where biological data have been obtained, trends similar to those observed in other world endemias have been found. In Algeria, high serum TSH and T_3 and high RAI uptake and low serum T_4 and PBI values have been observed (Table 2). TRH response (Bachtarzi 1979) has been found to be exaggerated and sustained.

Incomplete data were obtained in other countries (Adadevoh and Lukanmbi 1974; Aquaron et al. 1977; Boukhris et al. 1981; Ghalioungui 1965; Greig et al. 1970; Kajubi and Okel 1970; McGill et al. 1970; Osman and Fatah 1981). In Zaire, in addition to the usual parameters studied (Beckers and Benmiloud 1980; Ermans 1980), TBG levels were found to be increased, whereas TBPA levels decreased, and

Table 2. Comparison of variables (mean ± 50) from two goitrous areas, Takana (population, 458; altitude, 1700 m; 30 km from the sea) and Messelmoune (population, 702; altitude, sea level; on the shore), with a nongoitrous area, Algiers.

	Urinary iodine (μg/24 hours)	Thiocyanate (μg/24 hours)	^{131}I uptake (% 6th hour)	PBI (μg per 100 mL)	T_4 (μg per 100 mL)	T_3 (ng/mL)	TSH (μU/mL)
Messelmoune	16.1 ± 5.40	12.1 ± 5.5	51.5 ± 6.6	3.6 ± 1.3	5.0 ± 2	2.40 ± 0.3	13.2 ± 16.3
	(17)	(20)	(13)	(153)	(123)	(134)	(152)
Algiers	185.9 ± 170.5	8 ± 3.3	14.6 ± 6.9	5.4 ± 0.5	8.3 ± 1.4	1.66 ± 0.30	5.3 ± 1.7
	(27)	(22)	(21)	(69)	(40)	(62)	(62)
Takana	10.3 ± 4.7	10.6 ± 6.4	41.4 ± 10.7	3.5 ± 0.1	5.6 ± 1.2	2.35 ± 0.7	10.0 ± 12.5
	(21)	(20)	(14)	(98)	(63)	(90)	(95)

NOTES: Number of people examined in parentheses. A comparison of goitrous and nongoitrous areas showed highly significant differences between the means of all variables ($P<0.001$).

in-depth biochemical studies demonstrated a reduction in intrathyroidal iodine (25–50%) and abnormalities in iodine kinetics, e.g., a heterogenous distribution of ^{131}I in the thyroid, abnormal iodoproteins, and high MIT/DIT ratios. These data are suggestive of iodine deficiency.

As demonstrated in Table 3, the main etiological factor of endemic goitre and cretinism is iodine deficiency. In countries where iodine levels were measured in urine, alimentary salts, and water, the mean levels in goitrous areas were found to be well below accepted normal limits. Unfortunately, studies of this nature have not been carried out in all of the affected countries and, in some cases, only indirect evidence is available.

The sea–air–land cycle of iodine is maintained by wind and rain. The iodine content of soil is related to its organic content, the permanency of its superficial layers, and the amount of rainfall received.

Geological factors may also be related to iodine deficiency. Although data are sometimes conflicting, there is general agreement on the association of Precambrian granite with very low iodine concentrations in the environment.

Figure 1 shows that a major portion of goitre endemias occurs in Precambrian regions. This is not the case in North Africa, however, where the Atlas Mountains are of Tertiary origin. Detailed studies of the Atlas Mountains have revealed a granite base and alkaline superficial layers washed out by water, with very little clay to retain iodine.

Iodine deficiency is not the only causal factor of endemic goitre and cretinism. Other possible etiological determinants of endemic goitre have been observed in Africa, which could be responsible for variations in goitre incidence at similar levels of iodine deficiency.

The role of fluoride in goitrogenesis is controversial in both experimental as well as epidemiological studies (Koutras 1980). It has been suggested as an etiological factor in South Africa, Tanzania, and Kenya (Kelly and Snedden 1960; McGill et al. 1970; McGill and Svenssen 1980). However, fluorosis and endemic goitre do not coexist in Algeria or Nigeria.

The goitrogenic action of calcium, on the

Table 3. Iodine content in water, urine, and alimentary salt samples from African countries.

	Alimentary salt (μg/g)	Water (μg/L)	Urinary iodine (μg/24 hours)	Source
Algeria	10	2–3	10–16	Bachtarzi (1979)
Tunisia		3.9		Boukhris et al. (1981)
Egypt		<5		Abdou and Awadalla (1969); Ghalioungui (1965)
Sudan	0.07	<5		Ghalioungui (1965); Greig et al. (1970)
Ivory Coast		<4		Angate et al. (1972)
Nigeria		0.7		Kelly and Snedden (1960)
Zaire		1	18	Beckers and Benmiloud (1980)
Cameroon		1–2.4	2.5	Aquaron et al. (1977)
Zambia	3	1–5		Nwokolo (1974)
Tanzania			10–16	McGill et al. (1970)
Sierra Leone		1–2.4		Kelly and Snedden (1960)
Uganda			<50	Kajubi and Okel (1970)

other hand, has been established under experimental conditions. Although epidemiological data are conflicting, this problem can be reconciled if one assumes that the goitrogenic effect of high calcium intake is unmasked only in presence of iodine deficiency. Some evidence of high calcium concentrations in water has been reported in Algeria, Egypt, Sudan, and Zambia (Bachtarzi 1979; Nwokolo 1974; Osman and Fatah 1981). Higher concentrations of other trace elements were observed in the water of goitrous areas, e.g., sulfides were high in Algeria (Bachtarzi 1979) and iron in Sudan (Osman and Fatah 1981).

Polluted drinking water is common in these isolated areas. Bacteriological analyses performed in Algeria (Bachtarzi 1979), Sudan, and Egypt (Ghalioungui 1965) have revealed the presence of *Clostridium perfringens* and *Escherichia coli*, both of which could be goitrogenic. They act either through production of myrosinase (Gaitan 1980), which converts progoitrin into goitrin, or production of a substance that has an effect similar to that of TSH.

A familial tendency of goitre has been documented in many countries, including Algeria, Sudan, Ivory Coast, Nigeria, etc. Endogamy is highly prevalent in these isolated areas, where it is favoured by religion and culture. Genetic factors, therefore, could play a direct role in the predisposition to endemic goitre, or the familial aggregation could be due to the microenvironment.

Nutrition may also play a role in goitrogenesis, either through protein caloric malnutrition (PCM) or through goitrogenic agents in food. Protein calorie malnutrition, occurring as marasmus, kwarshorkior, or adult protein malnutrition, is commonly found in less developed countries with goitre endemias. Medeiros-Neto (1980) and Ingenbleek (1977), as well as others, have observed decreased thyroid function by measuring T_4, T_3, and FT_4. TBG and TBPA were also decreased and TSH was found to be low, normal, or slightly elevated. TSH response to TRH was usually exaggerated and sustained. Even assuming that normal basal TSH levels could be explained on the basis of increased sensitivity of the thyroid cells, a goitrogenic effect of PCM is unlikely (Ingenbleek (1977) found no goitre in Senegal in malnourished children; furthermore, pathological examination revealed a hypoplastic thyroid tissue). In PCM, plasma iodine is increased through a reduction in thyroid uptake and kidney clearance. It is, therefore, plausible that iodine deficiency could be enhanced by PCM through several mechanisms: (1) the low iodine content associated with a low animal protein diet; (2) decreased iodine uptake by the thyroid; and (3) recycling of iodine could be diminished as the deiodination of the thyronines is decreased.

The existence of a goitrogenic agent in food has been well documented for cassava (Ermans 1980), a staple food in many countries with goitre endemias, e.g., Nigeria, Cameroon, Zaire, Zambia, Ivory Coast.

Since the work of Chesney et al. (1928), the goitrogenic effect of the genus *Brassica* has often been documented. It could be of importance in countries where turnips and cabbage are consumed in large amounts. Such could be the case in North Africa, Zambia, and Tanzania. Although these foods are rarely eaten raw, one cannot rule out the possibility of bacterial flora in the gut. Measurement of thiocyanates in Algeria revealed a slight elevation of urinary thiocyanate in endemic areas. The exact role of these agents is difficult to establish because many causative factors could intervene concomitantly.

According to Delange et al. (1980), the urinary I/SCN ratio is more significant than either parameter by itself; however, available data are limited on I/SCN ratios and goitre incidence from areas with slightly elevated urinary thiocyanate levels and variable degrees of iodine deficiency.

Osman and Fatah (1981) have demonstrated that millet (*Pennisetum typhoides*) has a goitrogenic effect. They found a high concentration of an unidentified thionamide in the serum of schoolchildren in a Sudanese village that had a goitre incidence of 75% and where millet was the main staple food. Experimental data on rats (Osman 1981), however, were inconclusive. The rats fed on millet had higher T_4 and T_3 levels and thyroid hyperplasia; in the absence of serum TSH values, however, interpretation remains difficult. Nonetheless, Osman points out that in many African countries with goitre endemia the population eats millet, herbs, or grains, as is the case in Kenya, Nigeria, Upper Volta, Mali, and Nigeria.

The known antithyroid activity of aliphatic disulfides, which are the volatile components of onion and garlic (Cowan et al. 1967; Saghir et al. 1966), has been incriminated by Abdou et al. (1971) as a causative factor in Egypt. These foods, used largely in North African diets, are consumed in both cooked and raw forms.

Olive oil, along with other vegetable oils, has been shown to be goitrogenic in rats (Kaunitz and Johnson 1967). In North Africa, the inhabitants of goitrous areas use a crudely refined olive oil as their main fat nutrient.

Endemic cretinism is defined as an association of mental deficiency with a neurological syndrome consisting of deficient hearing and speech and disorders of stance and gait or hypothyroidism and stunted growth. This is characteristically present with an abnormal incidence in goitrous areas and can be prevented by adequate correction of iodine deficiency.

A recent review of endemic cretinism in Zaire (Lagasse et al. 1980; Pharoah et al. 1980) revealed a high incidence of cretinism in association with severe goitre endemia. Compared with the Nepalese endemia, Zaire has a twenty-fold increase in the myxedematous form. The overall prevalence is 1-8%.

No other studies on endemic cretinism have been reported from Africa, although the subject has been mentioned in other surveys (Kelly and Snedden 1960), particularly in Cameroon. It is most likely that a thorough study would bring about new evidence in other countries. In Algeria, a house-to-house survey for endemic goitre (Bachtarzi 1979) revealed problems in areas previously reported as cretin free. A recent pilot study demonstrated 47 cases among the 3500 subjects examined. Of these, 27 could be classified as neurological cretins, 10 myxedematous, and 10 moderately hypothyroid. There were 12 subjects under the age of 10 years.

Pharoah et al. (1980) have suggested that iodine deficiency is responsible for endemic cretinism and that supplementation of dietary iodine is successful in its prevention. Iodine deficiency during pregnancy would be responsible for neurological damage. A similar survey was conducted in Zaire on the myxedematous cretins. Some doubts persist, however, on the etiopathogenesis of this syndrome, because the incidence decreased with improved economic conditions without iodine prophylaxis.

It is evident that endemic goitre and endemic cretinism are still major public health problems within African countries. It is also apparent that iodine deficiency is a common causative factor, compounded by others, some of which are nutritional. During the past 20 years, little has been done to eradicate this problem through prophylaxis; although methods of prevention by salt iodination or injection of iodinated oil are well standardized and simple. In Table 4, countries in which the government has taken measures toward iodine supplementation are presented. Although full implementation is uncommon, pilot studies on various scales have been reported from different countries, e.g., Senegal, Mali, Nigeria, and, more recently, Kenya and Zaire. Only the study from Zaire has been evaluated.

Except for some parts of South Africa and countries with small populations such as Kenya, Libya, and Lesotho, which import iodized salt, the salt itself is not always available. The cost of iodine supplementation is small; but to ensure adequate supplementation, the commercial network should be under state control, which is not always the case. When industrial production of salt exists within a country, the capacity for iodization could be inadequate. In all cases, the primary health care centres, when they exist, are unable to monitor the program. Thus, persistence of goitres indicating goitrogenic factors other than iodine deficiency, or the occurrence of hyperthyroidism, will escape notice.

Recently, the World Health Organization and the African Unity Organisation have tried to promote national policies within African countries. Two meetings in Yaounde, in 1976, and in Addis Ababa, in 1980, have tried to outline a common African approach to this problem.

It is hoped that greater awareness on the part of African governments will lead to the implementation of active prophylaxis to eradicate totally, or at least reduce considerably, goitre endemias and endemic cretinism.

Table 4. Use of prophylactic iodine in African countries.

	Implementation of government regulation	Level of implementation	Iodized compound
South Africa	1954		Iodized salt
Algeria	1967	Partial	KIO_3 (20 mg/kg salt)
Libya			Imported iodized salt
Kenya	1970	Under evaluation	KI (20 mg/kg salt)
Nigeria			KI (20 mg/kg salt)
Zaire		Large pilot study	Iodinated oil
Senegal	1965	Pilot study	Iodized salt
Ivory Coast		Pilot study	Iodized food seasoning
Tanzania	1978	Pilot study	Iodinated oil

Abdou, I.A. and Awadalla, M.Z. 1969. Comparative study of iodine content of foods in goitrous and non-goitrous areas of Egypt. Journal of the Egyptian Public Health Association, 44, 587-598.

Abdou, I.A., Awadalla, M.Z., and Wassef, S.A. 1971. A biochemical and histopathological study of the effect of some dietary factors on the thyroid gland of experimental animals. Journal of the Egyptian Public Health Association, 46, 1-15.

Adadevoh, B.K. and Lukanmbi, F.A. 1974. Radioiodine metabolism in endemic goitre in Nigeria (significance of the perchlorate discharge test). East African Medical Journal, 51, 273-281.

Angate, Y., Massa, G., and Coulibaly, A.O. 1972. Aspects étiologiques du goître endémique en Côte d'Ivoire. Afrique Médicale, 11 (101), 525-530.

Aquaron, R., Poll-Gouater, E., Riviere, R., Le Bras, J., and Menard, J.C. 1977. Étude biologique du goître endémique dans le pays Bamoun (Cameroun). Médecine d'Afrique Noire, 24, 183-190.

Bachtarzi, H. 1979. Physiopathologie du goître endémique en Algérie. MD thesis, University of Algiers.

Beckers, C. and Benmiloud, M. 1980. The present status of endemic goitre as a problem of the public health: Africa. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 69-78.

Boukhris, R., Guedri, H., Hamza, M., and Ben Ayed, H. 1981. Le goître simple : Fréquence et évaluation biologique. La Tunisie Médicale, 59, 339-343.

Chesney, A.M., Clauson, T.A., and Webster, B. 1928. Endemic goitre in rabbits. I. Incidence and characteristics. Bulletin of the Johns Hopkins Hospital, 43, 261.

Cowan, J.W., Saghir, A.R., and Salji, J.P. 1967. Antithyroid activity of onion volatiles. Australian Journal of Biological Sciences, 20, 683.

Delange, F., Vigneri, R., Trimarchi, F., Filetti, S., Pezzino, V., Squatrito, S., Bourdoux, P., and Ermans, A.M. 1980. The iodine/thiocyanate ratio. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 143-145.

Ermans, A.M. 1980. Etiopathogenesis of endemic goitre. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 287-302.

Gaitan, E. 1980. Goitrogens in the etiology of endemic goitre. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 219-236.

Ghalioungui, P. 1965. Endemic goitre in Africa. Cairo National Information and Documentation Centre, Report No. 77-117.

Greig, W.R., Gray, H.W., McGirr, E.M., Kambal, A., and Rahman, I.A. 1970. Investigations of endemic goitre in Sudan. British Journal of Surgery, 57, 11-16.

Ingenbleek, Y. 1977. La malnutrition protéino-calorique chez l'enfant en bas âge. Répercussions sur la fonction thyroïdienne et les protéines vectrices du sérum. Acco Publisher, Louvain, Belgium.

Kajubi, S.K. and Okel, P.M. 1970. Possible existence of iodine deficiency in Uganda. East African Medical Journal, 47, 453-456.

Kaunitz, H. and Johnson, R.E. 1967. Thyroid and pituitary pathology in iodine deficient rats fed fresh and oxidized fats and oils. Journal of Nutrition, 91, 55-62.

Kelly, F.C. and Snedden, W.W. 1960. Prevalence and geographical distribution of endemic goitre. In Endemic Goitre. World Health Organization, Geneva, Switzerland, Monograph Series No. 44, 117-153.

Koutras, D.A. 1980. Trace elements, genetic and other factors. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 255-268.

Lagasse, R., Luvivila, K., Yunga, Y., Gerard, M., Hanson, A., Bourdoux, P., Delange, F., and Thilly, C.H. 1980. Endemic goitre and cretinism in Ubangi. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 45-60.

Latham, M.C. 1966. Endemic goitre in Tanzania. Journal of Tropical Medicine and Hygiene, 69, 167-170.

McGill, P.E. and Svenssen, E.O. 1980. Goitre in Kenya: Qualitative studies of iodine metabolism. Transactions of the Royal Society of Tropical Medicine and Hygiene, 74, 197-200.

McGill, P.E., Taylor, J.R., and Spoerry, A. 1970. A new focus on endemic goitre in Mwezi, Tanzania. East African Medical Journal, 47, 66-72.

Medeiros-Neto, G.A. 1980. General nutrition and endemic goitre. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 269-283.

Nwokolo, U. 1974. Endemic goitre in Zambia. Medical Journal of Zambia, 8 (77), 233-238.

Osman, A.K. 1981. Bulrush millet (*Pennisetum typhoides*): A contributory factor to the endemicity of goitre in Western Sudan. Ecology of Food and Nutrition, 11, 121-128.

Osman, A.K. and Fatah, A.A. 1981. Factors other than iodine deficiency contributing to the endemicity of goitre in Darfur province (Sudan). Journal of Human Nutrition, 35, 302-309.

Pharoah, P., Delange, F., Fierro-Benitez, R., and Stanbury, J.B. 1980. Endemic cretinism. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 395-421.

Saghir, A.R., Cowan, J.W., and Salji, J.P. 1966. Goitrogenic activity of onion volatiles. Nature, 211, 87.

Singh, A. and Etta, M. 1978. Thyroid hormone levels in Nigerians living in endemic goitrous and non-goitrous areas. Tropical and Geographical Medicine, 30, 235-240.

Nutritional and Public Health Considerations Relating to Endemic Goitre and Cretinism in South America

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The relationship between health and socioeconomic development is complex: the distinction between health, socioeconomic, and cultural factors is artificial and, in practical terms, impossible (Beghin et al. 1980). It is much easier to be healthy and well-nourished in a developed country than in a society "in transition."

The nutritional category of most South American countries is average, deficient, or highly deficient. One of the disorders associated with this situation is goitre.

Epidemiology of Endemic Goitre and Cretinism

In 65% of Latin American countries, endemic goitre is a public health problem and, in South America, the entire continent is affected. The major etiological factor is iodine deficiency (Delange et al. 1968).

Studies on goitre (conducted in accordance with recommendations made by the World Health Organization in 1960) have been carried out by national organizations and operational research groups directed by North American and European researchers. Table 1 shows studies undertaken prior to the implementation of programs using iodized salt as a prophylactic and is based on the surveys with the most representative samples. With the exception of Chile, which has a percentage just at the prevalence threshold, all countries have a rate of over 20%. Endemic afflictions show varying rates, 80% being the highest, indicating that some regions (particularly rural regions) are severely affected. Most communities in which the urinary ratio of iodine to creatinine is less than 50 μg/g — corresponding to the second and third degrees of severity established by the Pan American Health Organization (Querido et al. 1974) — are in the Andean countries: Bolivia, Ecuador, and Peru.

Table 2 contains a list of the regions in South America where the inhabitants suffer from varying degrees of mental retardation associated with a predominantly neurological syndrome. Studies of thyroid function in these zones of endemic cretinism support the clinical evidence: it is indeed neurological cretinism, as hypothyroidism was found in less than 10% of these cases. Hormone levels are normal and some parameters of iodine metabolism are altered.

All developing countries present two images in this regard: the positive image, whether real or apparent, in urban centres where goitre is not endemic and almost everyone uses iodized salt; and the negative image, in the countryside where there is endemic goitre and the inhabitants live in isolated areas and do not have access to health programs or iodized salt.

Throughout South America, internal migrations and the colonizing process have resulted in the migration of populations with goitre to nonendemic zones, as happened with the population of El Corazón in Ecuador, or the reverse, as in the case of Rondonia, Brazil. Both situations affect the results of studies on prevalence among the general population.

Geochemical Environment

It is interesting to analyze the biotic interaction between humans and their environment in relation to iodine and its effects on thyroid physiology.

As a result of geomorphic variations, iodine is deposited quite unevenly throughout the soil of South America. Thus, although iodine appears in very low concentrations in ancient glacial valleys, it can be abundant in land that is formed from marine deposits.

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Table 1. Main studies: Prevalence of goitre in South America prior to prophylaxis by iodized salt.

Country (year)	Regions	Number of subjects examined	Prevalence (%)	References
Argentina (1968)	Córdova, Corientes, Jujuy, La Pampa, La Rioja, Neuquen, Santa Fé, Santiago, Tucumán	52710[a]	7.2-53.6	Altschuler et al. (1968)
Bolivia (1962)	Cochabamba	10000[a]	40.9	Pardo-Subieta (1974)
	Chuquisaca	5787[a]	14	Pardo-Subieta et al. (1971);
	Santa Cruz, Berin		0.3-57	Sotelo (1970)
Brazil (1956)	East, centre, south, west	886217[b]	30-55	Pellón et al. (1956)
Chile (1954)	Province of Santiago	39433[b]	11	Donoso (1967)
	Province of Coquimbo	8332[b]		Donoso et al. (1958)
Colombia (1950)	Antioquía, Atlántico, Bolívar, Boyacá, Caldas, Cauca, Cundinamarca, Magdalena, Avila, Nariño, North and South Santander, Tolima, Valle	183243[b]	53	Góngora et al. (1952)
Ecuador (1969)	Carchi, Esmeraldas, Los Rios, Chimborazo, Cotopaxi, Imbabura, Pichincha	28639[b]	23.7	Varea (1978)
Paraguay (1946)	Caacupé	44000[b]	26.5	Peña and Fleitas (1964);
		1457[b]	33.7	Altschuler et al. (1969)
Peru (1954)	Coast, highlands, montaña	181000[b]	22	Pretell (1977)
			12-80	
Uruguay (1955)	North, centre, south	—	22-50	Banza et al. (1955)
Venezuela (1951)	North, centre, south	641[b]	83	De Venanzi et al. (1954); Villez-Boza (1966)
		—	15	
		—	38-57	
		470207[a]	13.4	

[a]Schoolchildren.
[b]General population.

The Andes Mountains are formed primarily from the decomposition of andesites (a name derived from "Andes") and ash (tuff), both of which are made of silicates that are deficient in a number of elements, including iodine. This formation has been continually altered by deforestation, the washing of the soil by percolating water, and glaciation.

The glacial valleys, however, contain the most fertile soil in the Andes and are, therefore, densely populated. Hence, the majority of the population does not have access to geological or natural sources of iodine and, furthermore, because of socioeconomic conditions, does not eat animal protein, which is the prime nutritional source of this valuable metalloid.

Apart from iodine deficiency, which is the principal etiological cause of endemic goitre in South America, other causal agents have also been discovered (Delange and Ermans 1976). In Chile, for example, it has been shown in experiments on rats that nuts from the *Araucaria araucana* tree, or pinon, are goitrogenic; these nuts are consumed by the indigenous population (Tellez et al. 1969). In one area of Colombia, it has been discovered that the water consumed by the inhabitants comes from sedimentary rocks rich in organic matter and that this water contains sulfurated hydrocarbons that have an antithyroid action (Gaitan and Wahner 1969; Gaitan et al. 1969).

Very little research has been conducted on microorganisms polluting the water through their production of goitrogenic substances.

Biochemical Profile

Table 3 presents a few parameters of thyroid function in endemic goitre. Except for the inhabitants of Candelaria, Colombia, uptake of ^{131}I is very high. The levels of hormones T_3 and T_4 are normal, and the TSH concentration is high to normal. The response of TSH to TRH is normal or excessive. In a private experiment conducted on inhabitants of high-altitude areas, the response was less marked (Paredes et al. 1982).

Table 2. Endemic cretinism in South America.

Country (references)	Regions	Number of patients	Prevalence (%)	Goitre (%)	Metabolic and clinical characteristics: ^{131}I uptake (24 hours)	PBI (μg) (%)	TSH (μU) (mL)	EUI[a] (μg)	Neurological cretinism (%)
Argentina (Stanbury et al. 1954)	Mendoza	50	—	—	—	4.6	4	—	100
Bolivia	Cegezal del Rosario	—	11.8	63	—	—	—	—	—
(Mendoza 1936; Pardo-Subieta et al. 1971)	Chuquisaca	—	11.8						
Brazil	Luziana Balsas			80.5					
(Lobo et al. 1963, 1964; Medeiros-Neto	Goiaz	16	0.17	34		5.7			
and Dunn 1980; Rosenthal et al. 1969)	Mato Grosso	24	0.5	69	24	3.1	—	47–100[b]	90
Chile (Barzelatto et al. 1967; Beckers et al. 1967)	Pedregoso	1	—	66.8	—	—	—	8.6–26[b]	—
Colombia (Callejas et al. 1966)	Guaduas	—	2	83.1	—	Normal	3.3	—	—
Ecuador	Tocachi	74	—	60	79	2.76	—	10.4	90
(Fierro-Benítez 1969)	La Esperanza				47–87	2.8–5		17.7[c]	
Peru (Burga-Hurtado 1956; Pretell 1977)	Mountains and jungle	—	1–3.6	55	75	5.5	—	12–17[b]	100
Venezuela (Roche et al. 1955, 1956)	Bailadores	18	1.3	83	75	5.5	—	—	100

[a]Urinary excretion of iodine.
[b]μg/day.
[c]μg/0.9 g creatinine.

Table 3. Parameters of thyroid function in endemic goitre in South America.

Country (year) (references)	Regions	^{131}I uptake (percentage per 24 hours)	T_3 (μg/dL)	T_4 (μg/dL)	TSH (μU/mL)	Protein bound ^{127}I (μg) (%)	Response of TSH to TRH
Argentina (1969)	Chiquillihuin	64.4	—	—	—	4.5	Excessive
(De Grossi et al. 1969)	Nehuquen	59	—	—	4.0	—	—
Bolivia (1971) (Moscoso et al. 1974)	Cocuabamba	—	—	—	—	4.0	—
Chile (1940, 1970)	Pedregoso	68	—	—	—	—	—
(Stevenson et al. 1970,	Pisque	Low	—	—	—	5.0	Excessive
1974)	Plumo	High	—	—	—	—	Excessive
	Maipo	—	219	—	—	—	—
Colombia (1969) (Gaitan and Wahner 1969; Gaitan et al. 1969)	Candelaria	17.2	—	—	3.3	6.85	—
Ecuador (1972)	Mulalo	60	—	6.60	12.2	—	Diminished
(Fierro-Benítez et al. 1968; Paredes et al. 1982; Varea et al. 1977)	Tocachi	79	—	6.2	—	2.76	Normal
Paraguay (1969) (Altschuler et al. 1969)	Caacupe	56-79	—	—	—	5.6	—
Peru (1977) (Pretell 1977)	Tarma	74.7	150	4.1	3.6	—	—
Venezuela (1955) (Roche et al. 1955, 1956)	Bailadores	70.8	—	—	—	—	—

Prophylactic Programs

Goitre has been identified as a medical problem in South American countries since the last century, but it is only during the past 30 years that iodine deficiency has been considered a public health problem. The implementation of prophylactic programs has had setbacks for cultural, sociopolitical, and legal and economic reasons that are beyond the scope of this paper. Moreover, since the passage of legislation providing for the iodization of salt, and even the establishment of programs, problems related to the production, marketing, and consumption of these prophylactic products have curtailed their effectiveness in almost all countries.

In 1980, some 5×10^6 t of salt was available to the 246 million inhabitants of South America. The population of the Andes region alone grew from 55.4 million inhabitants in 1970 to 75 million in 1980 — an increase of 29% in 10 years.

Table 4 shows the year goitre was identified as a medico-social problem and the year salt iodization legislation was passed, in each country, along with data on the prevalence of goitre before and after a few years of consumption.

Iodized oil has been used as a prophylactic in South America in several pilot programs: nearly 20 000 people have received it orally or intramuscularly in Argentina, Bolivia, Brazil, and Ecuador. The low cost of this method makes it viable in light of these countries' socioeconomic conditions. Moreover, no side effects have been detected. The neuromotor disorders and mental retardation of endemic cretinism can be averted if iodine is administered to the mother prior to pregnancy (Medeiros-Neto and Dunn 1980; Pretell 1972, 1974; Querido et al. 1974; Ramirez et al. 1972).

The scope of iodized salt prophylactic programs has been limited because sociocultural factors have led to mistaken attitudes toward goitre by two groups: the government and the marginal rural population. On the one hand, politicians have not realized the seriousness of the problem — particularly the neurological and mental repercussions. The rural population, on the other hand, owing to its isolation and low educational level, has resisted programs centring on the consumption of iodized salt. Work in Ecuador has shown that 46.6% of the population is unaware of the cause of goitre, and that for 49.7% this affliction has ancestral and mystical significance (Varea 1978).

Conclusions

Iodine deficiency in the diet, along with protein calorie malnutrition and poor conditions

Table 4. Prevalence of endemic goitre in South America following prophylaxis by iodized salt.

Country and year problem identified (references)	Year legislation promulgated (concentration)	Regions	Prevalence (%) Before	After	References
Argentina, 1820	1968	—	1940	1968	Salvaneschi and De Grossi (1974)
(Schidtmeyer 1824)	(1:30000)		40	3.2	
Bolivia, 1569	1968	—	—	—	—
(Kelly and Snedden 1960)	(1:20000)				
Brazil, 1819	1953	All	1956	1975	Medeiros-Filho (1977)
	(10-20 mg/kg)		30-55	14.7	
Colombia, 1974	1955	Cauca Valley	1959	1967	Gaitan et al. (1968)
(Mutis 1974)			80	30	
Chile	1968	—	1954	—	—
(Barzelatto 1969; Beckers et al. 1967)			11		
Ecuador, 1824	1968	Central	1969	1978	Varea (1978)
(Caldas 1942)		provinces of the Ecuadorean Andes	23.7	12	
Paraguay, 1820	1958	—	1946	—	—
(Schidtmeyer 1824)	(1:10000)		26.5		
Peru, 1886	1960	Coast, Andes	1967	1975	Pretell (1977)
		highlands,	12	0	
		montaña	48	21	
			80	50	
Uruguay	1963	North	1953	1970	Salveraglio (1974); Salveraglio
(Banza et al. 1955)			50.7	20.9	et al. (1976)
			28.3	24.4	
			34.5	23.0	
Venezuela, 1946	—	—	1966	—	—
(Bengoa 1946)			13.4		

of hygiene and sanitation, induces progressive delays in the growth, weight, height, and maturity of children in developing countries.

Nutrition is unique, in comparison with other

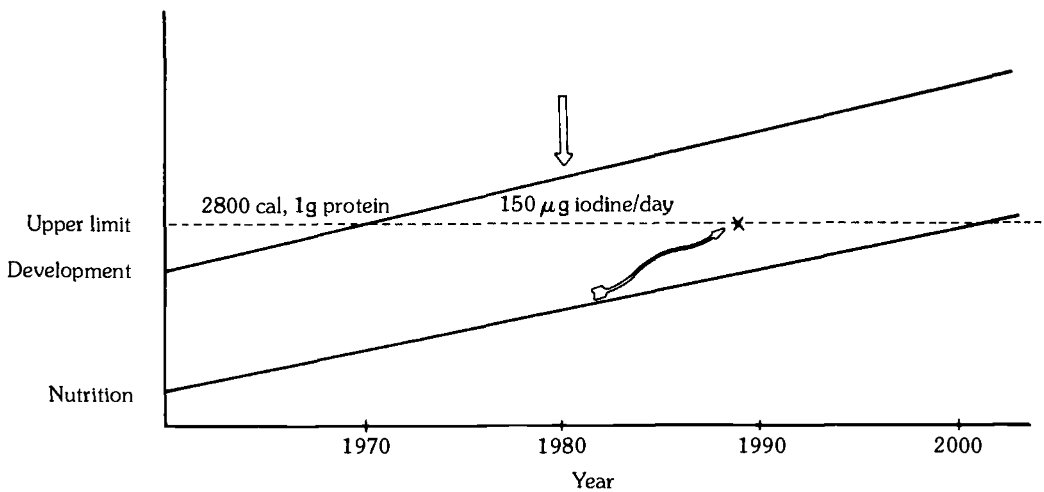

Fig. 1. Improvement in nutrition and endemic goitre in relation to development.

components of social development, such as education, health, and recreation, in that it has a practical upper limit. Figure 1 shows that if adequate nutritional measures are adopted now (arrow), the proposed limit may be reached by the end of the century.

To increase the rate of nutritional improvement, it is necessary to: (1) establish better iodized salt prophylactic programs, in terms of production, marketing, and consumption; (2) create iodized oil prophylactic programs in marginal rural zones; (3) detect and initiate rapid treatment of congenital hypothyroidism in endemic zones; and (4) study and, in time, treat the psychomotor and mental disorders associated with goitre.

Altschuler, N., De Grossi, O.J., and Pecorini, V., ed. 1968. Primer Coloquio Argentino de Hormonas Tiroideas. Buenos Aires, Asociación Argentina Biol. Med. Nucl.

Altschuler, N., De Grossi, O.J., Ceriani, R., Forcher, H., Mayor, V., and Eurori, C.L. 1969. Endemic goiter in the Republic of Paraguay. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 168-176.

Banza, J., Cervino, J.M., and Salveraglio, F.J. 1955. Epidemiología del bocio endémico en el Uruguay. Dia Medico Uruguay, 22(262), 454.

Barzelatto, J. 1969. Endemic goiter in Chile. Paper prepared for the meeting of the Pan American Health Organization Scientific Group on Research in Endemic Goiter, Puebla, Mexico, 27-29 June 1968. Pan American Health Organization, Washington, DC, USA.

Barzelatto, J., Beckers, C., Stevenson, C., Covarrubias, E., Gianetti, A., Pobadilla, E., Pardo, A., Donoso, F., and Atria, A. 1967. Endemic goiter in Pedregoso (Chile). I. Description and function studies. Acta Endocrinologica, 54, 577-590.

Beckers, C., Barzelatto, J., Stevenson, C., Gianetti, A., Pardo, A., Pobadilla, E., and de Visscher, M. 1967. Endemic goiter in Pedregoso (Chile). II. Dynamic studies on iodine metabolism. Acta Endocrinologica, 54, 591-603.

Beghin, I., Del Canto, J., and Teller, Ch. 1980. Desnutrición, Desarrollo nacional y planificación. Boletín de la Oficina Sanitaría Panamericana, 89(6), 505-515.

Bengoa, J.M. 1946. Medicina social en el medio rural venezolano. Caracas, Venezuela, Editorial Grafolit.

Burga-Hurtado, B. 1956. Nueva contribución al estudio del bocio endémico en el Perú. Revista Peruana de Salud Pública, 5, 3-16.

Caldas, F.J. 1942. El influjo del clima sobre les seres organizados. Semanario del Nuevo Reino de Granada. Bogotá, Biblioteca de Cultura Popular.

Callejas, L., Gómez-Afanador, J., Almanzán, R., and Ucrós, A. 1966. Bocio endémico. Revista de la Sociedad Colombiana de Endocrinología, IV(1), 56-84.

De Grossi, O.J., Altschuler, N., Forcher, H., Zaninovich, A., Mutchinick, O.M., and Eurori, C.L. 1969. Characteristics of endemic goiter in a Mapuche Indian tribe in Chiquillihuin El Malles, Province of Neuquen, Argentine Republic. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 149-158.

Delange, F. and Ermans, A.M. 1976. Endemic goitre and cretinism. Naturally occurring goitrogens. Pharmacology and Therapeutics, C-1, 57.

Delange, F., Thilly, C., and Ermans, A.M. 1968. Iodine deficiency, a permissive condition in the development of endemic goitre. Journal of Clinical Endocrinology and Metabolism, 28, 114-116.

De Venanzi, F., Musm, F., Musm, M., Gorra, G., Lamberti, J., and Arocha, R. 1954. Investigaciones preliminares sobre el bocio endémico de los Andes. Acta Medica Venezolana, 2, 124.

Donoso, F. 1967. Bocio endémico en Chile. Revista Medica de Chile, 95, 164.

Donoso, F., Jadresic, A., Lennon, H., Carrasco, M., and Vallejo, J. 1958. Encuesta de bocio en escolares de la Provincia de Coquimbo. Revista Medica de Chile, 86, 744.

Fierro-Benítez, R. 1969. Endemic goiter in Ecuador. In Stanbury, J.B., ed., Endemic Goiter. World Health Organization, Geneva, Switzerland, 305-359.

Fierro-Benítez, R., Paredes, M., and Peñatiel, W. 1968. Endemiologic aspects of goiter in the Ecuadorian Andean Region. Revue Européenne d'Endocrinologie, 3, 367-369.

Gaitan, E. and Wahner, H.W. 1969. Studies on the pathogenesis of endemic goiter in the Cauca Valley, Colombia. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 267.

Gaitan, E., Wahner, H.W., Correa, P., Bernal, R., Judiz, W., and Gaitan, J.E. 1968. Endemic goiter in the Cauca Valley. I. Results and limitations of twelve years of iodine prophylaxis. Journal of Clinical Endocrinology, 28, 1730.

1969. Endemic goiter in the Cauca Valley. II. Studies of thyroid pathophysiology. Journal of Clinical Endocrinology, 29, 765.

Góngora y López, J. and Mejía, C.F. 1952. Endemic goiter in school children in Colombia. Revista de Medicina Cirujia (Bogotá), 16, 357.

Kelly, F.C. and Snedden, W.W. 1960. Prevalence and geographic distribution of endemic goiter. In Stanbury, J.B., ed., Endemic Goiter. World Health Organization, Geneva, Switzerland, Monograph Series 44, 27.

Lobo, L.C.G., Pompeu, F., and Rosenthal, D.L. 1963. Endemic cretinism in Goiaz, Brazil. Journal of Clinical Endocrinology, 23, 407.

Lobo, L.C.G., Rosenthal, D.L., Pompeu, F., Fridman, J., and Figueiredo, J.G. 1964. Studies on endemic cretinism in Brazil. Archives Brasileiros de Endocrinología, 13, 65.

Medeiros-Filho, A. 1977. Report of the 1975 survey on endemic goiter prevalence in Brazil. Ministry of Health, Brazil.

Medeiros-Neto, G.A. and Dunn, J.T. 1980. The pre-

sent status of endemic goitre as a problem of public health: Central and South America. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goitre and Endemic Cretinism. John Wiley and Sons, New York, NY, USA, 3-29.
Mendoza, J. 1936. Apuntes de un médico. Tipografía Salesiana Sucre.
Moscoso, G., Garrido, J., Bautista, A., Corrales, J., and Corrales, H. 1974. Bocio endémico en la población escolar en Cochabamba. Boliv. Soc. Ped., 3, 79.
Mutis, J.C. 1974. Reflexiones sobre la enfermedad que vulgarmente se llama coto. Papel Periódico de Santa Fé de Bogotá, 137, 669-767.
Parades, M., Varea, J., Garcés, G., Avila, C., Coy, D.G., and Schally, A. 1982. Pituitary response to luteinizing hormone. Releasing hormone analog at sea level and high altitudes. Obstetrics and Gynecology, 59, 52-57.
Pardo-Subieta, A. 1974. Training program in endemic goiter for medical personnel. Pan American Health Organization, Washington, DC, USA, Scientific Publication 292, 191.
Pardo-Subieta, A., Loayza, H., and Guardini, R. 1971. El bocio endémico en el Departamento de Chuquisaca (Bolivia). Prensa Medica, 23, 4.
Pellón, A.B., Silva, W., Borges, P., and Gualberto, V. 1956. Endemic goiter in Brazil. Results of the 1955 survey. Ministry of Health, Brazil.
Peña, R. and Fleitas, D.I. 1964. Endemic goiter in school children in Paraguay. Boletín de la Oficina Sanitaría Panamericana, 25, 1090.
Pretell, E.A. 1972. The optimal program for prophylaxis of endemic goiter with iodized oil. In Stanbury, J.B., ed., Human Development and the Thyroid Gland: Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 249.
1974. Simposium sobre nutrición, carencia de yodo en la gestación y su repercusión en el desarrollo infantil. Revista Viernes Medica, 25, 195.
1977. Bocio y cretinismo endémico. In Medeiros et Nicolau, ed., Temas Atuais em Tireodologia. Sao Paulo, 67-75.
Querido, A., Delange, F., Dunn, J.T., Fierro-Benítez, R., Ibbertson, J.K., Kontras, D.A., and Perinetti, H. 1974. Definitions of endemic goiter and cretinism, classification of goiter size and severity of endemias and survey techniques. Pan American Health Organization, Washington, DC, USA, Scientific Publication 292, 267.
Ramirez, J., Fierro-Benítez, R., Estrella, E., Gómez, A., Jaramillo, C., Hermida, C., and Moncayo, F. 1972. The results of prophylaxis of endemic cretinism with iodized oil in rural Andean Ecuador. In Stanbury, J.B., ed., Human Development and the Thyroid Gland: Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 203-237.
Roche, M., De Venanzi, F., Spinetti, M., Vera, J., Coll-García, E., and Ríos-Teppa, A. 1955. Un estudio de bocio endémico. I. Prevalencia en la Región Andina. Revista de la Policlínica (Caracas), 23, 213-226.
Roche, M., De Venanzi, F., Spinetti, M., Berti, M., Gerardi, A., Mendez Martínez, J., and Forrero, J. 1956. Iodine metabolism in a region of endemic goiter. Proceedings of the Society for Experimental Biology and Medicine, 91, 661-664.
Rosenthal, D.L., Lobo, L.C.G., Rbvello, M.A., and Fridman, J. 1969. Studies on endemic goiter and cretinism in Brazil. III. Thyroid function studies. Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 217-226.
Salvaneschi, J.P. and De Grossi, J. 1974. The program for surveillance of salt iodization in Argentina. Pan American Health Organization, Washington, DC, USA, Scientific Publication 292, 205.
Salveraglio, F.J. 1974. Gaining public acceptance of prophylaxis: experience from the campaign against endemic goiter in Uruguay. Pan American Health Organization, Washington, DC, USA, Scientific Publication 292, 198.
Salveraglio, F.J., Cerviño, J.M., Massiolo, J., Buena, J.P.S., and Denis, C.F.S. 1976. Aspectos médico-sociales de la lucha contra el bocio endémico en el Uruguay. Arch. Inst. Endocr. Fournier, I(1), 17-39.
Schidtmeyer, P. 1824. Travels into Chile over the Andes in the years 1820 and 1821. With some sketches of the productions and agriculture, mines and metallurgy, inhabitants, history and other features of America, particularly of Chile and Arauco. London, 188-194.
Sotelo, L.V. 1970. Consideraciones sobre el problema de bocio endémico en Bolivia. Primer Seminario Nacional de Nutrición. La Paz, Bolivie.
Stanbury, J.M., Brownell, G.L., Riggs, D.S., Perinetti, H., Itoiz, J., and Del Castillo, E.B. 1954. Endemic goiter. The adaptation of man to iodine deficiency. Harvard University Press, Cambridge, MA, USA, 209 p.
Stevenson, C., Pineda, G., and Silva, E. 1970. Role of triodothyronine in endemic goiter. VII Congr. Pan-Am Endocrinol Symposium, Sao Paulo, Brazil. Excerpta Medica, 238, 142.
Stevenson, C., Silva, E., and Pineda, G. 1974. Thyroxine (T_4) and triodothyronine (T_4): effects of iodine on the serum concentrations and disposal rates in subjects from an endemic goiter area. Journal of Clinical Endocrinology and Metabolism, 38, 390.
Tellez, M., Gianellu, A., Covarrubias, E., and Barzelatto, J. 1969. Experimental goitrogenic activity of "piñon." Pan American Health Organization, Washington, DC, USA, Scientific Publication 193, 245.
Varea, J. 1978. Bocio y sal yodada en el Ecuador. Quito, Ecuador, Artes Graficas.
Varea, J., Garcés, G., Paredes, M., Avila, C., and Urresta, J. 1977. The adaptation syndrome in the biologically underdeveloped individual. In Proceedings of the Western Hemisphere Nutrition Congress. Nutrition Transition. Quebec, V. Am. Med. Assoc., 334-340.
Villez-Boza, F. 1966. Encuesta nacional del bocio en Venezuela en niños de 5 a 14 años. Caracas, Venezuela, Instituto Nacional de Nutrición.

Public Health and Nutritional Aspects of Endemic Goitre in Nepal — Summary

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Endemic goitre and cretinism have been reported in the Himalayas since the turn of the century (McCarrisson 1908). However, only a few studies have been conducted in the Nepalese Himalayas, namely, in the Khumbu area (Ibbertson et al. 1971, 1972, 1974), lower Trisuli valley and Jumla area (Karmakar et al. 1974), upper Rolwaling valley (Skjerven 1975), upper Trisuli valley (Delange et al. 1981), and Raswa and Jumla districts (Berghmans, L. et al., unpublished data). More limited studies have shown that endemic goitre is also found along the east-west highway (Cunningham 1970) in the central part of Nepal and even in the lowlands (Terai), where pockets of goitre have been reported (Worth and Shah 1969).

It has been shown that in the endemic areas, goitre is complicated by endemic cretinism, whose prevalence can be as high as 5-10% of the total population (Ibbertson et al. 1974; Delange et al. 1981). The clinical picture of the defectives in Nepal corresponds principally to the neurologic type of endemic cretinism (Querido et al. 1974), with severe mental retardation, deaf-mutism, and disturbance of stance and gait. Myxedematous endemic cretinism, with stunted growth and hypothyroidism, is also found, although with a much lower prevalence. A large number of the defectives show a mixed pattern of neurological and myxedematous endemic cretinism (Ibbertson et al. 1974; Delange et al. 1981). Thus, it appears that endemic goitre and cretinism constitute the major public health problems in Nepal.

The role played by iodine deficiency in the etiology of endemic goitre and cretinism in Nepal has been demonstrated repeatedly (Ibbertson et al. 1974; Karmakar et al. 1974; Delange et al. 1981). The role played by other naturally occurring goitrogens, such as buckwheat (Ibbertson et al. 1971) and turnip (Delange et al. 1981), has been considered but has not been demonstrated conclusively.

A goitre control program began in Nepal in 1972, with the import of iodized salt from India. The impact of this program, however, was not significantly visible due to a shortage of transport facilities and, consequently, the unavailability of iodized salt in remote and hyperendemic areas (Delange et al. 1981). Moreover, poor packing of the iodized salt, open storage, and the long transportation process from India to Nepal contributed to depletion of the iodine from the salt.

In 1979, His Majesty's Government of Nepal recognized endemic goitre and cretinism as a major public health problem and instituted, under the Expanded Project for Immunization (EPI), the semiautonomous Goitre and Cretinism Eradication Project, with support from the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO). This project initiated prophylaxis and treatment of endemic goitre by intramuscular injections of slowly resorbable iodized oil. Between 1978 and 1982, 440 399 inhabitants in goitrous regions received the injections. It is envisaged that, by the end of 1985, 70% of the eligible population of 20 hilly districts will have been treated through this mass injection program.

[1]Expanded Project for Immunization and Goitre and Cretinism Eradication Project, Kathmandu, Nepal.

Cunningham, J.S. 1970. Goitre incidence in workers and their families on the east-west highway (British section). Journal of the Nepalese Medical Association, 8, 37-39.

Delange, F., Valeix, P., Bourdoux, P., Lagasse, R., Ermans, J.P., Thilly, C., and Ermans, A.M. 1981. Comparison of the epidemiological and clinical aspects of endemic cretinism in central Africa and in the Himalayas. In Hetzel, B.S. and Smith, R.M., ed., Fetal Brain Disorders. Recent Approaches to the Problem of Mental Deficiency. Elsevier North Holland Publishers, Amsterdam, Netherlands, 243-263.

Ibbertson, H.K., Pearl, M., McKinnon, J., Tait, J.M., Lim, T., and Gill, M.B. 1971. Endemic cretinism in Nepal. In Hetzel, B.S. and Pharoah, P.O.D., ed., Endemic Cretinism. Institute of Human Biology, Papua, New Guinea, Monograph Series No. 2, 71-88.

Ibbertson, H.K., Tait, J.M., Pearl, M., Lim, T., McKinnon, J.R., and Gill, M.B. 1972. Himalayan cretinism. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland, Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 51-69.

Ibbertson, H.K., Gluckman, P.D., Croxson, M.S., and Strang, L.J.W. 1974. Goiter and cretinism in the Himalayas. A reassessment. In Dunn, J.T. and Medeiros-Neto, G.A., ed., Endemic Goiter and Cretinism: Continuing Threats to World Health. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 292, 129-134.

Karmakar, M.G., Deo, M.G., Kochupillai, N., and Ramalingaswami, V. 1974. Pathophysiology of Himalayan endemic goiter. American Journal of Clinical Nutrition, 27, 96-103.

McCarrison, R. 1908. Observations on endemic cretinism in the Chitral and Gilgit valleys. Lancet, 2, 1275-1280.

Querido, A., Delange, F., Dunn, T., Fierro-Benitez, R., Ibbertson, H.K., Koutras, D.A., and Perinetti, H. 1974. Definitions of endemic goiter and cretinism, classification of goiter size and severity of endemias, and survey techniques. In Dunn, J.T. and Medeiros-Neto, G.A., ed., Endemic Goiter and Cretinism: Continuing Threats to World Health. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 292, 267-272.

Skjerven, O. 1975. A demographic study and nutritional survey of two villages in the upper Rolwaling valley. Kailash (Kathmandu), 3, 295-301.

Worth, R.M. and Shah, N.K. 1969. Nepal health survey, 1965-1966. University of Hawaii Press, Honolulu, HI, USA, 1-158.

Endemic Goitre in the State of Sarawak, Malaysia

Tan Yaw Kwang[1]

Epidemiology of Endemic Goitre and Cretinism in Sarawak

There has been no formal epidemiological survey to systematically investigate the distribution, prevalence, and severity of goitre in Sarawak since it was first reported. In the early 1950s, a high incidence was first noted in central Sarawak in communities along the Rejang River about 80 km up the coast. In response to the problem, iodization of coarse salt, destined for the interior, was introduced as being the most practical and well-known preventive measure and effective treatment. Even then, it was not possible, due to prevailing resource constraints, to undertake baseline as well as follow-up surveys on the problem.

Recent data on the presence of goitre within the state have been obtained from studies undertaken by different groups of researchers (Fig. 1; Table 1). Polunin (1970) tried to cover all three regions of Sarawak (west coast, east coast, interior) but his study was limited to those communities in more accessible areas, highlighting goitre prevalence in women aged 15 years and above. Although this represented a cross section of the women, it did not constitute "a random sample of the whole community" (Polunin 1970). Polunin concluded that Sarawak, at the time of his study, had the highest and most extensive incidence of goitre within any of the states of Malaysia.

Subsequent studies focused on certain remote localities known for their high endemicity and associated low socioeconomic, health, and nutritional status, which may not be representative of all of the remote inland areas of Sarawak. In one community in the Lubok Antu district, the incidence of goitre in 167 persons examined was reportedly 99%. This was reported to be the world's highest incidence rate (Maberly and Eastman 1976). Although these findings indicated a high and fairly extensive prevalence of goitre in the inland regions, Alexander (1979) reported that goitre was not a problem in inland towns. On the other hand, Maberly and Eastman (1976) observed a goitre incidence of 74% in a coastal community, possibly due to the consumption of large quantities of cassava, which is a known goitrogen.

Endemic cretinism has also been reported in Sarawak. In a severely goitrous community (99% goitre incidence), 6 of the 167 people surveyed (3.6%) were classified as neurological cretins (Maberly 1975). Alexander (1979), however, found no cretins in the areas she studied (Table 1).

Based upon these findings, as well as current reports and observations, 12 of Sarawak's 25 districts have been identified as goitrous, with varying rates of prevalence and occurring mainly in the inland areas. Current estimates indicate that there are at least 20 000 cases of endemic goitre in Sarawak, representing about 1.5% of its total population.

Control of Endemic Goitre

Etiology

Endemic goitre in Sarawak is caused primarily by insufficient iodine in the diet. The natural source of dietary iodine seems to be limited to seafoods. This is because the iodine content in water from rivers and soils, which are depleted of iodine (and other minerals) through constant leaching due to heavy rainfall, are reported to be very low or negligible. Water analyses of the Upper Rajang River and its tributaries by

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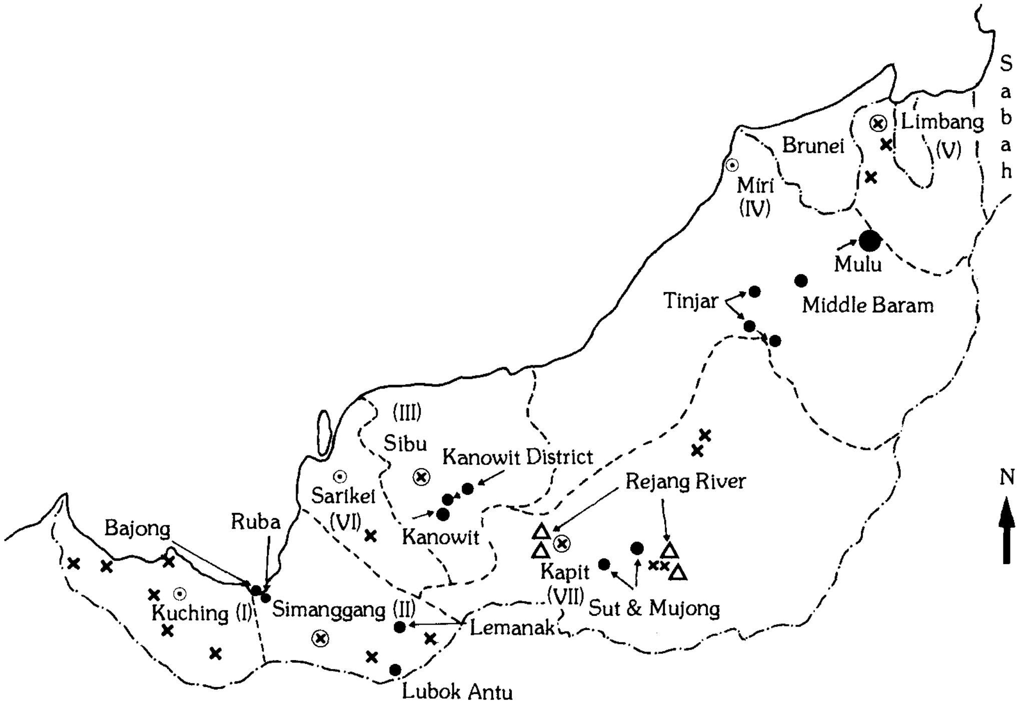

Fig. 1. Goitre surveys and prevalence, Sarawak (1970–1982). ⊙, main towns in divisions. ⊗, main towns in divisions II, III, V, and VII studied by Polunin (1970). **X**, *areas studied by Polunin (1970). Δ, areas studied by Ogihara (1971). ●, areas studied by Maberly (1975), Anderson (1974–1978), Alexander (1979), and Chen and Lim (1982).*

Ogihara et al. (1972) revealed a mean iodine content of 0.3 μg/L compared with a mean tap water iodine content of 3.4 μg/L in the Honshun district of Japan. In a hilly, inland area of Division I, Anderson (1975) reported iodine levels ranging from nil to 0.8 μg/L, with a mean of 0.1 μg/L in drinking water from regular sources. The low iodine intake levels could be aggravated further due to the fact that consumption of seafoods in Sarawak (and Sabah) was less than in Peninsular Malaysia (Polunin 1970). Although the price of seafoods is higher in the inland areas due to high transportation costs, the demand for the expensive seafood (fish) could easily be offset by supplies of fish from the rivers. Therefore, it is not surprising to observe goitre among many communities in the interior, hilly, and mountainous regions, where the inhabitants tend to have less access to iodine-rich seafoods.

Endemic Goitre Control Program

In view of the need to provide the required dietary iodine, the production of iodized salt was initiated as a preventive measure to control goitre. In 1957, the state Medical Services Department established salt iodization plants in Kuching and Sibu to iodize coarse salt, at a concentration of one part potassium iodate in 10 000, for wholesale salt dealers to redistribute to retailers in rural areas. The iodized salt was dyed green to distinguish it from uniodized salt. The salt iodization program decreased the incidence of goitre in some districts but was not successful in others due to poor distribution, especially in divisions I, II, IV, and V, where there seemed to be a lack of demand from the people, who were disappointed at not seeing immediate results, and also due to insufficient supplies of salt from the dealers because of transportation difficulties. In 1979, in order to assist in its distribution and further extend the use of iodized salt, the state Medical Services Department undertook the provision of iodized salt through statewide medical and health facilities, with emphasis on reaching the affected areas and groups.

In a more recent step toward controlling endemic goitre, legislation was passed in

Table 1.Goitre surveys conducted in Sarawak.

Source	Location (refer to Fig. 1)	Ethnic groups	Respondents: Age (years)	Respondents: Total number	Prevalence of goitre (%)
Polunin (1970)	First division	Chinese, Malay, Bidayuh	10–14 (female)	273	49.8
			⩾15 (female)	157	52.2
	Second division	Iban, Malay, Chinese	10–14 (female)	147	38.8
			⩾15 (female)	161	80.7
	Third, sixth, and seventh divisions	Iban, Chinese, Malay, Kejaman	10–14 (female)	252	34.5
			⩾15 (female)	589	55.2
	Fifth division	Malay, Chinese, Iban	10–14 (female)	20	45.0
			⩾15 (female)	151	45.0
		Total	⩾10 (female)	1750	50
			⩾15 (female)	1058	58
Ogihara et al. (1972)	Third division Rejang River (interior)	Iban	All ages (both sexes)	608	8 (male) 33 (female)
Maberly (1975)	Second division Lubok Antu (interior)	Iban	>11 (both sexes)	167	99.5
	Ruba (coastal)	Iban	>11 (both sexes)	38	74.1
	Bajong (coastal)	Iban	>11 (both sexes)	122	3.0
Anderson (1974–1978)	Second division Lemanak River (interior)	Iban	5–8 (both sexes)	388	76.5
			Mothers only	116	90.5
	Fourth division Middle Baram (intermediate)	Kayan/Kenyah	<7 (both sexes)	556	30.4
			4–8 (both sexes)	372	55.1
			Mothers only	142	50.0
	Mulu area (interior)	Punan (nomadic tribe)	All ages (both sexes)	334	59.3
	Seventh division Sut/Mujong River (interior)	Iban	<7 (both sexes)	414	7
			Mothers only	106	30.2
Alexander (1979)	Second division Upper Lemanak River (interior)	Iban	⩾15 (female)	75	93.3
			8–12 (both sexes)	152	21.7
	Third division Kanowit District (Rejang River interior)	Iban	⩾15 (female)	137	38.7
	Kanowit Town	Iban, Chinese	7–12 (both sexes)	542	0.7
Chen and Lim (1982)	Fourth division Tinjar River	Kayan, Kenyah Iban	10–14 (female)	110	78.0
			⩾15 (female)	157	77.7
			10–14 (male)	114	78.6

NOTE: The only data reported on percentage cretinism come from Maberly (1975), who reported 3.6% for the second division, Lubok Antu (interior).

January 1982 making the import of iodized table salt compulsory. This would ensure a readily available source of dietary iodine for the population. It is expected that some problems in terms of meeting the needs of populations in interior and remote communities will occur.

In addition to salt iodization, two other methods of treating and controlling endemic goitre were tested, over a period of 1–2 years, in several communities in which endemic goitre occurred. The first method involved the use of iodized salt injections. This method was found to be unsuitable because of the high prevalence of the Jod Basedow phenomenon and the rapid depletion of iodine stores from the body within 2 years (Maberly et al. 1978). This method also required close biochemical supervision of the patients and, therefore, was not practical in remote areas.

The second method, which utilized an iodinator fitted into the existing gravity-fed village water supply, produced encouraging results — within 9 months, the prevalence of goitre was reduced from 61–30%, with 79% of goitres showing visible signs of reduction in size. This particular method was also reported to have a beneficial sterilizing effect on the water supply (Maberly et al. 1978).

Role of Cassava in the Etiology of Endemic Goitre

In many rural communities, cassava (*Manihot utilissima*, Pohl), known locally as tapioca, is an important food crop for human consumption as well as for livestock feed. Cassava, a hardy and productive plant, which flourishes even in poor soils, is the inevitable crop to be cultivated in areas where rice, being the staple, is intermittently in short supply. Even though other sources of calories may be used, e.g., the cultivated swamp sago (*Metroxylon* spp.) or wild hill sago (*Eugeissona utilis*), cassava (root) remains a traditional caloric supplement or substitute at certain times of the year. Cassava leaves, on the other hand, are frequently used in side dishes in family meals. Being relatively rich in protein, calcium, lipids, carotene, B-vitamins, and vitamin C (Yeoh and Chew 1974), cassava leaves provide an important nutritional contribution to the diet.

Data from food consumption studies in two inland communities (one of which was in Lemanak, which is considered a goitrous area) indicated an average intake of 400 g of cassava leaves and 900 g of the cassava roots per household. The percentage of households consuming cassava was 20-60%. It was reported that cassava is prominent in the diet (Anderson 1978). However, at the time of the survey, most of the roots given to the livestock were raw. There was no preparation of the roots prior to consumption except for peeling off the skin and boiling the root until soft. It was only in one or two households, where cassava roots were consumed as a rice substitute, that an elaborate preparation was carried out. The roots were grated, sun-dried, and pounded into flour, which was then made into a stiff round dough and dipped into boiling water to become a brownish, starchy product, ready for consumption. At other times, the roots were sliced and cooked together with rice as the main part of the family meal. Leaves were either shredded or pounded before cooking, mainly by boiling. In most cases the water in which the cassava was boiled was discarded.

Evidence that cassava could be another contributory factor of endemic goitre was observed in a coastal area, where, with near dependence on cassava roots and leaves (as a result of frequent rice shortage) and minimal consumption of seafoods and other common food crops, the incidence of goitre was reported to be 74% (Maberly et al. 1976).

Some attempts to determine the cyanogenic content of local cassava varieties have been made by the Agricultural Research Centre (ARC) in Sarawak in 1967-1969. The results indicated that the cyanide content changes from one variety to another. Also, cyanide levels were found to be higher in the leaves than in the roots (Table 2). It was recently reported that the variation of cyanide content in cassava is influenced more by production practices than by variety (Phillips 1974; Yeoh and Chew 1974).

Preliminary evidence of cyanogenic activity in goitrous subjects in Sarawak (G.F. Maberly, personal communication) showed levels of urinary thiocyanate that are among the highest reported (Table 3). In view of these very preliminary findings, serious attention to cassava

Table 2. Total cyanides in local cassava varieties (expressed as prussic acid content, ppm) studied in 1965 and 1967.

Variety	Flesh (tuber) 1965	Flesh (tuber) 1967	Leaves (1967)
Bitter variety			
Black Twig	141	11	303
Sweet varieties			
Berat	44	8	176
Baloi	45	24	269
Kapok	19	10	231
Buloh	80	11	84
Sawah	54	17	69
Kekabu	29	7	80
Betawi	94	55	266
Ubi Putih	47	12	194
Putih	109	25	364

Source: Agricultural Research Centre, Sarawak (1967).

Table 3. Mean urinary thiocyanate (SCN) levels in subjects from goitrous regions of Zaire (Africa), Sarawak (Malaysia), and Belgian and Australian controls.[a]

Region	Number of subjects	Mean ± SE urinary SCN (mg/100 mL)
Zaire[b]	102	1.9 ± 0.06
Belgian controls[b]	78	0.6 ± 0.07
Sarawak	14	2.1 ± 0.09
Australian controls	8	0.85 ± 0.07

[a]Source: G.F. Maberly (personal communication).
[b]Source: Ermans et al. (1980).

(and related food) and its goitrogenic implications are very much required in Sarawak.

Need for Research

The problem of endemic goitre has long been realized and urgent measures have been taken to alleviate it. Endemic goitre has not been studied extensively due to a lack of personnel, expertise, and other pressing priorities. The need to establish a clear understanding of this public health problem, its true magnitude, causes, and consequences is apparent. The Malaysian health authorities, in proposed collaborative efforts with Australian research organizations, are embarking on studies to assess the current statewide prevalence of endemic goitre, neonatal hypothyroidism, and cretinism; evaluate the effectiveness of iodized salt as a method of controlling goitre; and measure and test further water iodination as an alternative method of control. Another major part of the studies would focus on cassava consumption, its role in the etiology of endemic goitre, and analysis of goitrogenic toxicity in local cassava varieties and other related foods. It is envisaged that these lines of research would establish a long-term program toward the effective treatment and prevention of endemic goitre and its associated problems in Malaysia.

Agricultural Research Centre, Sarawak. 1967. Annual report.

Alexander, G.H. 1979. Endemic goitre and salt iodization in Sarawak, Malaysia. World Health Organization, Geneva, Switzerland, Report MAA/NUT/001.

Anderson, A.J.U. 1974. Nutrition surveys and food consumption surveys. Sarawak Medical Services, Internal Report.

1975. Nutrition surveys and food consumption surveys. Sarawak Medical Services, Internal Report.

1976. Nutrition surveys and food consumption surveys. Sarawak Medical Services, Internal Report.

1977. Nutrition surveys and food consumption surveys. Sarawak Medical Services, Internal Report.

1978. Nutrition surveys and food consumption surveys. Sarawak Medical Services, Internal Report.

Chen, C.Y. and Lim, P.E. 1982. The prevalence of endemic goitre in the Tinjar area, Sarawak. Malaysian Medical Journal, in press.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Maberly, G.F. 1975. The significance of endemic goitre in Sarawak, Borneo. BSc (Med) thesis.

Maberly, G.F. and Eastman, C.J. 1976. Endemic goitre in Sarawak, Malaysia. I. Somatic growth and etiology. Southeast Asian Journal of Tropical Medicine and Public Health, 7(3), 434-442.

Maberly, G.F., Eastman, C.J., and Corcoran, J.M. 1976. Endemicity and consequences of goitre in Sarawak, Malaysia. In Current Thyroid Problems in Southeast Asia and Oceania: Proceedings of a Workshop on Endemic Goitre and Thyroid Testing, Singapore. Asia and Oceania Thyroid Association, 21-27.

1978. The effect of iodized oil on goitre size, thyroid function and the development of Jod Basedow phenomenon in endemic goitrous subjects in Sarawak, Malaysia. Proceedings of the Endocrinology Society, 21, 9.

Maberly, G.F., Corcoran, J.M., and Eastman, C.J. 1978. The effect of iodination of a village water supply on goitre size and thyroid function. Lancet, in press.

Ogihara, T. et al. 1972. Endemic goitre in Sarawak, Malaysia (Island of Borneo). Endocrinology Japan, 119, 285.

Phillips, T.P. 1974. World market prospects for cassava and its products. In Araullo, E.V., Nestel, B., and Campbell, M., ed., Cassava Processing and Storage: Proceedings of an Interdisciplinary Workshop, Pattaya, Thailand, 17-19 April 1974. International Development Research Centre, Ottawa, Canada, IDRC-031e, 13-19.

Polunin, I.V. 1970. Endemic goitre in Malaysia. World Health Organization, Geneva, Switzerland, Report Malaysia 5602-E (0081).

Yeoh, H.H. and Chew, M.Y. 1974. Research in tapioca. A brief review. Malaysian Agricultural Journal, 49(3), 332.

Cassava Consumption, Endemic Goitre, and Malnutrition in Costa Rica

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Consumption of Cassava (Yuca)

More than 100 varieties of *Manihot esculenta* are grown in Costa Rica, a few of which are native. Three cultivars are popular: manggie, valencia, and guacimo, the latter being a bitter local variety. At present, sweet cultivars mex-59 and cmc-76 are being promoted because of their low cyanide content. In 1980 and 1981, national cassava production reached 17 000–18 000 metric tons for a population of 2.2 million.

Cassava is eaten by many Costa Ricans. Data on cassava consumption were obtained from the 1978 national nutrition survey (Díaz et al. 1978) and a field study of health and growth in Puriscal (Mata et al. 1981). Cassava is prepared in many different ways and is always well cooked. It is never, to the best of our knowledge, eaten raw. At least eight different ways of preparing cassava were observed in a survey of 30 families in Puriscal (Table 1). Boiled, alone or with other vegetables; eaten with salt; or eaten with other species are preferred. Cassava leaves are not consumed. Raw cassava is used in animal feed. Only 17% of the families in Costa Rica consume cassava according to the 1978 national nutrition survey (Table 2). People in sparsely populated rural areas consumed the least cassava, probably due to its low availability when not produced locally.

Table 1. Cassava consumption, 30 families of Puriscal, Costa Rica, 1982.

Form of preparation	Frequency (%)
Boiled	21(70)
Soup with vegetables	19(63)
Fried cakes	16(53)
Boiled-fried	14(47)
Soup with meat and vegetables	13(43)
Boiled with melazza	10(33)
Puree	2(7)
Boiled-fried stuffed with cheese or meat	1(3)

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Mean cassava consumption is rather low (Table 3) and contributes little to the total calorie and protein content of the diet, in contrast with observations in Africa (Ermans et al. 1980; Delange et al. 1982). Only 13% of children consume cassava, the intake being greater in urban areas than in rural areas (Table 4). Daily consumption of cassava among lactating women and neonates was found to be low (Table 5). A considerable proportion of the members in cassava-consuming families do not consume cassava on a regular basis. It was observed that 67% of family members consumed cassava every week and less than 1% consumed it daily.

Prevalence of Malnutrition and Goitre

The national nutrition survey of 1966 (INCAP-OIR 1969) revealed that a considerable number

Table 2. Frequency of cassava consumption, 253 families, Costa Rica, 1978.

Population	Number of families	Number (%) of families consuming cassava
Urban	91	17(18.6)
Rural dense	84	18(21.4)
Rural sparse	78	9(11.5)
National mean	253	44(17.3)

Table 3. Mean consumption of cassava in Costa Rica, 1978.

Population	Grams		Calories		Protein	
	Per family	Per capita	Total	%[a]	Grams	%[a]
Urban	402.8	67.2	89	4.6	0.7	1
Rural dense	622.6	98.8	130	6.3	1.0	1
Rural sparse	577.0	117.1	155	7.9	1.2	1
National mean	534.1	94.3				

[a]Percentage of total nutrient value of diet.

Table 4. Cassava consumption (frequency and amount) by children 1-6 years old, Costa Rica, 1978.

Population	Number of children	Number (%) of children consuming cassava	Grams per capita	Calories		Protein	
				Total	%[a]	Grams	%[a]
Urban	75	13(17.3)	62.6	83	5.7	0.6	1.2
Rural dense	82	10(12.1)	38.3	51	3.9	0.4	1.0
Rural sparse	71	6(8.4)	62.6	83	5.8	0.6	1.3
National mean	228	29(12.7)	54.4				

[a]Percentage of total nutrient value of diet.

Table 5. Daily consumption of cassava among lactating women and neonates, Puriscal, 1980.

Month of lactation	Months of age (neonates)	Number of persons	Number of persons (%) consuming cassava	Consumption of cassava in grams	
				Mean ± SD	Minimum–Maximum
1		40	9(22)	64.6 ± 25.3	34–123
3		29	6(21)	76.4 ± 22.4	50–104
5		29	12(41)	84.9 ± 31.4	30–120
7		23	9(39)	76.4 ± 28.4	31–120
9		13	4(31)	92.2 ± 31.8	56–120
	0-3	261	0		
	4-11	271	16(6)	32.0 ± 27.2	

of infants and preschool children were deficient in weight and height for their age (Table 6). Goitre was prevalent, especially among women (Table 7).

In retrospect, the health profile of Costa Rica shows a marked and constant improvement after 1940, based upon falling rates of infant mortality and death due to diarrheal diseases, and by a dramatic increase in life expectancy at birth (Mata and Mohs 1978; Villegas and Osuna 1979; Mohs 1980; Mata 1981). Other health parameters also reveal improvement. For instance, there have been no cases of polio or death due to diptheria during the last 8 years; the morbidity and mortality due to measles, whooping cough, and tuberculosis have decreased sharply; and a dramatic decline in energy-protein malnutrition and endemic goitre has been recorded (Tables 6, 7). Collaterally, hypothyroidism has also decreased during the last few years.

As expected from the prevalence of malnutrition and goitre, cretinism is not now a serious problem in Costa Rica. About half a dozen new cases are diagnosed each year at the National Children's Hospital, in contrast with the dozens of cases diagnosed annually before the iodination of salt began in 1974.

Comment

The decrease in malnutrition has been attributed to an overall improvement in the quality of life, especially through education, hygiene, and income (Mata and Mohs 1978). With regard to malnutrition, the most feasible explanation for the secular trends recorded during the last 16 years is the drastic reduction in acute infections, especially diarrhea and common communicable diseases such as measles and

Table 6. Evolution of the nutritional status of Costa Rican children 0–4 years old, 1966–1978.

Survey year	Number of children	Percentage stunted (<90% height/age)	Percentage wasted (<76% weight/age)	Reference
1966	791	16.9	14.2	INCAP-OIR (1969)
1975	1910	7.2	12.1	Díaz et al. (1975)
1978	2646	7.6	7.8	Díaz et al. (1978)

Table 7. Prevalence of endemic goitre in Costa Rica, 1952–1979.

Survey period	Age of population (years)	Number of persons	Percentage prevalence	Reference
1952–1955	7–18	10% of schoolchildren	18.4	Pérez et al. (1956)
1966	All ages	3735	18.0	INCAP-OIR (1969)
1975–1978	All ages	2012	11.9	INISA (unpublished data)
1975–1978	0–9	529	6.6	INISA (unpublished data)
1979	5–15	4883	3.6	Flores et al. (1981)

whooping cough. No striking changes in diet were noted, although there has been a trend toward a higher intake of animal protein (Díaz et al. 1975, 1978). Cassava does not contribute much to the nutrient value of the diet, and the present low level of consumption does not seem to increase the risk of goitre, cretinism, malnutrition, or other maladies associated with it.

The decline in goitre has been attributed to a government-supported salt iodation program, initiated in 1974. There is evidence that iodation of salt was not carried out properly in Costa Rica. For instance, monitoring of the iodine content in salt samples selected at random revealed suboptimal levels of iodine in most of them. However, iodine was detected in most of the samples, enough to induce a response in susceptible persons, as judged by an epidemic of hyperthyroidism (Jod Basedow phenomenon) (Quesada et al. 1976), and by improved iodine uptake (Estrada et al. 1975). Other contributory factors to the decline in goitre should be considered. Better methods of communication in the goitrogenic highland zones improved availability of foods from the lowlands and oceans. A decrease in the intake of cassava and other goitrogenic foods seems to have occurred, judging by the current low levels of consumption. One factor to consider is the increase in chlorinated piped water that, at present, serves almost 100% of the urban and about 70% of the rural populations of Costa Rica. The improvement in water supply began during the 1960s and has been responsible, in part, for the reduction of death due to diarrheal disease from about 100 per 100 000 inhabitants during the early 1960s to 4.5 in 1981 (Mata 1981). Water contaminated with certain bacteria seems to be a factor favouring goitre (Gaitán et al. 1978).

Goitre is still observed in certain families. The importance of studying the epidemiology of goitre in these families cannot be denied. The study should determine if cassava consumption is high in such families, and which cultivars of cassava and forms of preparation are used. The presence of other goitrogenic factors in food, and particularly in drinking water, must also be investigated.

Delange, F., Iteke, F.B., and Ermans, A.M., ed. 1982. Nutritional factors involved in the goitrogenic action of cassava. International Development Research Centre, Ottawa, Canada, IDRC-184e, 100 p.

Díaz, C., Brenes, H., Córdoba, M.I., García, P., and Quirós, J. 1975. Encuesta nutricional antropométrica y de hábitos alimentarios en Costa Rica. Ministry of Health, Costa Rica, 35 p.

Díaz, C., Rivera, M.L., Ulate, E., Bermúdez, D.G. et al. 1978. Encuesta nacional de nutricion. Evaluación dietética, 1978. Ministry of Health, Costa Rica, 45 p.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Estrada, Y., Loría, A.R., Iglesias, L., and Brenes, C. 1975. Bocio endémico infantil. Rev. Méd. Hosp. Nac. Niños (Costa Rica), 10, 1–18.

Flores, M.E., López, M.E., Santiesteban, I., and de

Céspedes, C. 1981. Epidemiología de bocio endémico en Costa Rica. Boletin de la Oficina Sanitaria Panamericana, 91, 531-539.

Gaitán, E., Merino, H., Rodríguez, G., Medina, P., Meyer, J.D., DeRoven, T.A., and Mackennan, R. 1978. Epidemiology of endemic goiter in Western Colombia. Bulletin of the World Health Organization, 56, 403.

INCAP-OIR. 1969. Evaluación nutricional de la población de Centro América y Panamá. Instituto de Nutrición de Centro América y Panamá, Guatemala, 133 p.

Mata, L. 1981. Epidemiologic perspective of diarrheal disease in Costa Rica and current efforts in control, prevention, and research. Rev. Lat-amer. Microbiol., 23, 109-119.

Mata, L. and Mohs, E. 1978. As seen from national levels. Developing world. In Margen, J. and Ogar, R.A., ed., Progress in Human Nutrition. Avi Publishing Co. Inc., Westport, CT, USA, 254-264.

Mata, L., Jiménez, P., Allen, M.A., Vargas, W., García, M.E., Urrutia, J.J., and Wyatt, R.G. 1981. Diarrhea and malnutrition: breast-feeding intervention in a transitional population. In Holme, T., Holmgren, J., Merson, M.H., and Mollby, R., ed., Acute Enteric Infections in Children. New Prospects for Treatment and Prevention. Elsevier/North Holland Biomedical Press, Netherlands, 233-251.

Mohs, E. 1980. Salud, Medicina y Democracia. El Surgimiento de una Nueva Era. Escuela de Medicina, Universidad de Costa Rica, Costa Rica, 186 p.

Pérez, C., Salazar, A., Tandon, D.B., and Scrimshaw, N.S. 1956. Endemic goiter in Costa Rican school children. American Journal of Public Health, 46, 1283-1286.

Quesada, O., Paéz, C.A., Zúñiga, N., Rosenstok, J., and Pucci, J. 1976. Tormenta tiroidea durante bocio inducido por yodo en Costa Rica. Acta Medica Costarricense, 19, 95-107.

Villegas, H. and Osuna, J. 1979. Extensión de los servicios de salud de Costa Rica. In Condiciones en Salud del Niño en las Américas. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 381, 168-183.

Endemic Cretinism in the Andean Region: New Methodological Approaches

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The term endemic cretinism refers to individuals born and living in severe endemic goitre areas and exhibiting severe mental retardation associated with either a neurological syndrome, including hearing defects and abnormalities in stance and gait (neurological endemic cretinism), or hypothyroidism and stunted growth (myxedematous endemic cretinism) (Querido et al. 1974).

That this definition is based on a clinical description results from the fact that the etiopathogenesis of endemic cretinism is only partly understood (Pharoah et al. 1980). In particular, the mechanism responsible for irreversible impairment of the central nervous system in neurological endemic cretinism is unknown. Epidemiological findings have suggested the role of elemental iodine lack on brain development during early fetal life (Pharoah et al. 1971). However, only limited information is available on the structure and function of the central nervous system in individuals affected by the neurological type of endemic cretinism. One of the reasons for this is that these individuals live in remote areas where sophisticated investigations are not normally possible.

At least two areas of endemic goitre have been reported in Ecuador: one is the area of Mulalo (Varea and Riva Deneira 1978) and the other is located in the Andes, 60 km north of Quito in the villages of Tocachi and La Esperanza (Fierro-Benitez et al. 1969a,b, 1970, 1972, 1974a,b; Ramirez et al. 1969, 1972; Stanbury et al. 1969; Stanbury 1972). A third area has recently been reported in the coastal region of Ecuador, where cassava consumption plays an important role in the nutritional habits of the local population. Prevalence of the neurological type of endemic cretinism is particularly high in the area of Tocachi and La Esperanza, where extensive studies have been carried out on the prophylaxis of this condition (Fierro-Benitez et al. 1972; Ramirez et al. 1969, 1972). One of the important observations made in this area is that impairment of intellectual capacity is also to be found in individuals who do not present the complete clinical entity of endemic cretinism (Fierro-Benitez et al. 1972, 1974b; Ramirez et al. 1969, 1972; Dodge et al. 1969; Trowbridge 1972). This observation confirms that there exists a whole spectrum of developmental abnormalities related to severe endemic goitre (Delange et al. 1972).

Recently, the authors of this paper had the opportunity to investigate neurological defectives by means of computerized cranial tomography (CT) and brainstem auditory evoked potentials (BAEP). These classical techniques for investigating the etiopathogenesis of cerebral palsy in neurologic clinics had never before been used in the investigation of neurological endemic cretins. Moreover, the authors performed electroencephalograms (EEGs) in young infants who did not show clinical signs of endemic cretinism. The aim of this paper, therefore, is to report the results of these investigations.

Patients and Methods

Cranial Tomography

Six defectives from Tocachi and La Esperanza were chosen by local physicians involved in the Andean Biopathology Research Program of the National Polytechnic School at Quito. All were mentally retarded and exhibited different degrees of deaf-mutism and dysarthria. They also had flexion dystonia. The patients were subjected to plain CT scanning of the head according to

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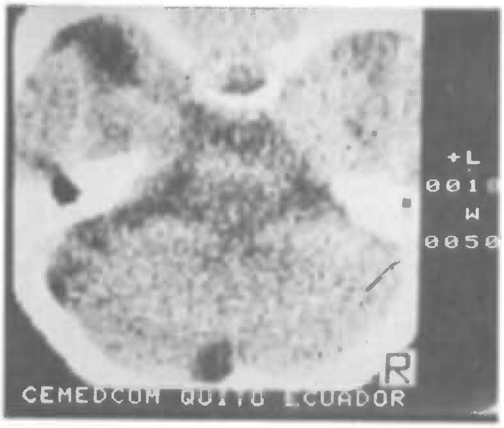

Fig. 1. Computerized cranial tomography. Findings on a 54-year old with the typical syndrome of endemic cretinism: the cistern magna is ample; the circumpenduncular cistern surrounded a brainstem of atrophic aspect; rostrally, the ambiens, retrothalamic and quadriacminal cisterns are equally dilated.

standard techniques within the EMI 5005-G CT scanner. Figure 1 illustrates the findings in one defective. Five of the six defectives presented a similar pattern: the subarachnoid spaces of the posterior fossa were dilated; the circumpenduncular cistern surrounding the brainstem was atrophic; the cisterns of the pontocerebellar angles were large; the fourth ventricle, however, was only moderately enlarged; rostrally, the ambiens, retrothalamic, and quadrigeminal cisterns were equally distended; the sylvian cisterns were also enlarged; the cortical sulci were wide, especially over the frontal region; and the third and lateral ventricles were moderately dilated.

These findings are consistent with a severe ponto-mesencephalic atrophic process, associated with a moderate cerebellar atrophy, especially of the vermis and middle cerebellar peduncles.

Brainstem Auditory Evoked Potentials

The investigation was conducted in eight defectives (three children and five adults). Using the method of Stockard et al. (1979), four silver electrodes were placed on the vertex, nation, and on each of the ear lobules. Monoaural clicks of 30–90 dB intensity, with 2000 readings and double register, were employed. The absolute latency of vertex waves I and IV were measured, as well as the interapical latencies between I and II, I-III, III-IV, I-IV.

The responses were normal in the defective children. In the adults, however, there was a total absence of the five positive sharp waves as shown in Figs. 2 and 3. This indicates progressive impairment of conductivity in the middle ear.

Electroencephalograms

Forty-eight children, between the ages of 12 and 14 months were studied. All of the children

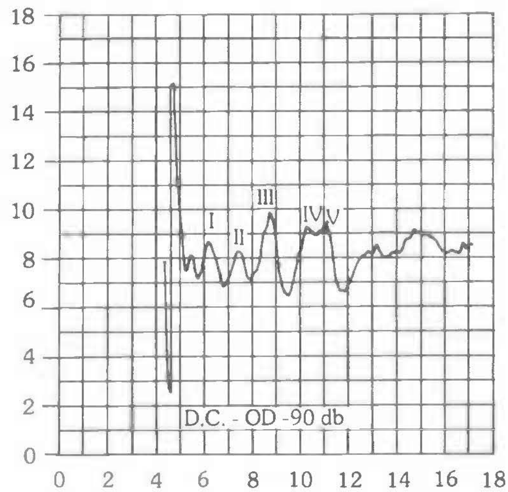

Fig. 2. Brainstem auditory evoked responses of a defective child from Tocachi. Normal wave V is the most reliable component.

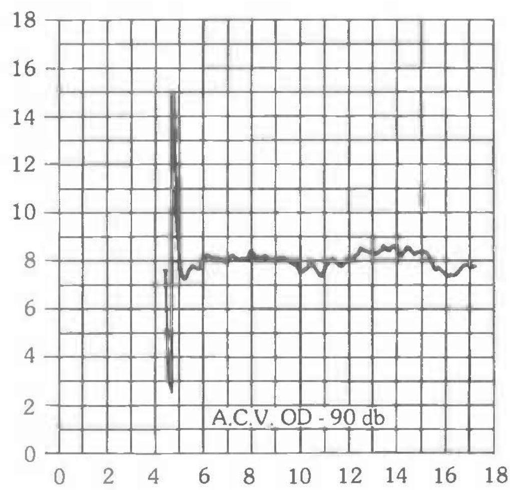

Fig. 3. Brainstem auditory evoked responses of a Tocachi adult cretin. Total absence of the V positive sharp waves of vertex.

were born under medical supervision and the deliveries were normal; none exhibited clinical features of cretinism. Similar investigations were conducted in a control group of children, from Quito, of the same age.

EEGs were recorded by means of a Beckman Accutrace-8 EEG. Twenty-two silver electrodes were applied to the head according to the International System and following the technical requirements suggested by the American Electroencephalographic Society. The EEGs were taken during induced sleep, after each child received chloral hydrate 74 mg/kg orally.

The EEGs were normal in the control group, except in a few infants who showed focal or paroxysmal abnormalities. In these infants, the background rhythm was normal. In contrast, 52% of the study group had EEG anomalies characterized by diffuse slowing of the background rhythm and increased high voltage slow activity (15 infants), paroxysmal discharges (8 infants), or focal changes (2 infants). The temporal area was affected more frequently by increased voltage. These anomalies indicate bioelectrical cerebral disturbances affecting both cortical and subcortical structures.

Discussion

The results of this study indicate that neurological endemic cretins have major anomalies in the structure of the brain, and impairment of the middle ear. They also suggest that clinically normal young infants in severe endemic goitre areas may frequently show signs of minimal brain damage.

The results of the CT scans suggest that in Ecuador the neurological endemic cretins have an irreversible abiothrophic disease of the type associated with olivo-pontocerebellar degeneration. It must be emphasized that these anomalies can also be found in the syndrome of cerebral palsy of various origins. This similarity is consistent with the proposal made by Pharoah (1981) to categorize neurological endemic cretinism as a specific form of cerebral palsy.

The BAEP data suggest impairment of the middle ear. In contrast, audiometric tests performed previously in the same type of defectives indicated perceptive deafness due to a central cause with lesions above the second neurone (Fierro-Benitez et al. 1970). We do not have explanations for this discrepancy because an audiometric evaluation was not performed in our study group. The EEG anomalies found in clinically noncretin young infants in the Equadorian endemic goitre area have similarities with the anomalies reported earlier in endemic cretins from the same area (Fierro-Benitez et al. 1970) and from Italy (Costa et al. 1974; Mortara and Rubino 1970). These anomalies are strikingly different from those found in congenital hypothyroidism (Shapiro and Martin 1976). They are consistent with the concept of minimal brain damage found in the noncretin part of the hyperendemic population. The frequency of anomalies found in the temporal zones may account for the speech disturbances found in the cretins.

In conclusion, the authors would like to emphasize the need for further investigation of the central nervous system's structure and function in severe endemic goitre areas.

Costa, A., Cottino, F., Mortara, M., and Vogliazzo, U. 1964. Endemic cretinism in Piedmont. Panminerva Medica, 6, 250–259.

Delange, F., Costa, A., Ermans, A.M., Ibbertson, H.K., Querido, A., and Stanbury, J.B. 1972. Clinical and metabolic patterns of endemic cretinism. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland. Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 175–187.

Dodge, P.R., Palkes, H., Fierro-Benitez, R., and Ramirez, I. 1969. Effect on intelligence of iodine in oil administered to young Andean children. A preliminary report. In Stanbury, J.B., ed., Endemic Goiter. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 193, 378–380.

Fierro-Benitez, R., Penafiel, W., De Groot, L.J., and Ramirez, I. 1969a. Endemic goiter and endemic cretinism in the Andean region. New England Journal of Medicine, 280, 296–302.

Fierro-Benitez, R., Ramirez, I., Estrella, E., Jaramillo, C., Diaz, C., and Urresta, J. 1969b. Iodized oil in the prevention of endemic goiter and associated defects in the Andean region of Ecuador. I. Program design, effects on goiter prevalence, thyroid function, and iodine excretion. In Stanbury, J.B., ed., Endemic goiter. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 193, 306–321.

Fierro-Benitez, R., Stanbury, J.B., Querido, A., De Groot, L., Alban, R., and Cordova, J. 1970. Endemic cretinism in the Andean region of Ecuador. Journal of Clinical Endocrinology and Metabolism, 30, 228–236.

Fierro-Benitez, R., Ramirez, I., and Suarez, J. 1972. Effect of iodine correction in early fetal life on intelligence quotient. A preliminary report. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland. Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 239–247.

Fierro-Benitez, R., Ramirez, I., Garces, J., Jaramillo, C., Moncayo, F., and Stanbury, J.B. 1974a. The clinical pattern of cretinism as seen in Highland Ecuador. American Journal of Clinical Nutrition, 27, 531-543.

Fierro-Benitez, R., Ramirez, I., Estrella, E., and Stanbury, J.B. 1974b. The role of iodine deficiency in intellectual development in an area of endemic goiter. In Dunn, J. and Medeiros-Neto, G.A., ed. Endemic Goiter and Cretinism: Continuing Threats to World Health. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 292, 135-142.

Mortara, M. and Rubino, R. 1970. Cretinismo endemico. La Malattia — I suoi aspetti neurologici. Quaderni de la "ricerca scientifica" n° 62, Consiglio Nazionale delle Ricerche (Roma) Publ, 1-59.

Pharoah, P.O.D. 1981. Epidemiology of cerebral palsy: a review. Journal of the Royal Society of Medicine, 74, 516-520.

Pharoah, P.O.D., Buttfield, I.H., and Hetzel, B.S. 1971. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1, 308-310.

Pharoah, P.O.D., Delange, F., Fierro-Benitez, R., and Stanbury, J.B. 1980. Endemic cretinism. In Stanbury, J.B. and Hetzel, B.S., ed., Endemic Goiter and Endemic Cretinism. Iodine Nutrition in Health and Disease. John Wiley & Sons Inc., New York, NY, USA, 395-421.

Querido, A., Delange, F., Dunn, T., Fierro-Benitez, R., Ibbertson, H.K., Koutras, D.A., and Perinetti, H. 1974. Definitions of endemic goiter and cretinism, classification of goiter size and severity of endemias, and survey techniques. In Dunn, J.T. and Medeiros-Neto, G.A., ed., Endemic Goiter and Cretinism: Continuing Threats to World Health. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 292, 267-272.

Ramirez, I., Fierro-Benitez, R., Estrella, E., Jaramillo, C., Diaz, C., and Urresta, J. 1969. Iodized oil in the prevention of endemic goiter and associated defects in the Andean regions of Ecuador. II. Effects on neuromotor development and somatic growth in children before two years. In Stanbury, J.B., ed., Endemic Goiter. Pan American Health Organization, Washington, DC, USA, Scientific Publication No. 193, 341-359.

Ramirez, I., Fierro-Benitez, R., Estrella, E., Gomez, A., Jaramillo, C., Hermida, C., and Moncayo, F. 1972. The results of prophylaxis of endemic cretinism with iodized oil in rural Andean Ecuador. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland. Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 223-237.

Shapiro, S.C. and Martin, G.I. 1976. Electroencephalogram in hypothyroidism in the neonate. Journal of Pediatrics, 89, 518.

Stanbury, J.B. 1972. The clinical pattern of cretinism as seen in Highland Ecuador. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland. Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 3-17.

Stanbury, J.B., Fierro-Benitez, R., Estrella, E., Milutinovic, P.S., Tellez, M.U., and Refetoff, S. 1969. Endemic goiter with hypothyroidism in three generations. Journal of Clinical Endocrinology and Metabolism, 29, 1596-1600.

Stockard, J.J., Stockard, J.E., and Sharbrough, F.W. 1979. Brainstem auditory evoked potentials in neurology: methodology, interpretation, clinical application. In Aminoff, M.J., ed., Electrophysiological Approaches to Neurological Diagnosis. Churchill Livingstone, New York, NY, USA, 524-527.

Trowbridge, F.L. 1972. Intellectual assessment in primitive societies, with a preliminary report of a study of the effects of early iodine supplementation on intelligence. In Stanbury, J.B. and Kroc, R.L., ed., Human Development and the Thyroid Gland. Relation to Endemic Cretinism. Plenum Press, New York, NY, USA, 137-150.

Varea, J. and Riva Deneira, M. 1978. Bocio y sol yodada en el Ecuador. Fundacion ciencia para estudios delhombre y la naturaleza. Quito, Ecuador, 1-126.

Cassava Diet, Tropical Calcifying Pancreatitis, and Pancreatic Diabetes

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In recent years, evidence has accumulated to show that cassava-based diets are related to the development of tropical calcifying pancreatitis (TCP) and pancreatic diabetes (PD). This disease starts in childhood with episodic abdominal pain, followed by the development of diabetes by puberty. The patients are young and lean, having bilateral parotosis and cyanosis of the lips and face. Scout films of the abdomen often show pancreatic calcification — a diagnostic sign of chronic pancreatitis. Histopathologically, there is dilatation of pancreatic ducts and ductules containing proteinaceous calcified material, acinar atrophy, and islet cell destruction in the pancreas.

TCP and PD is seen most frequently, and in its purest form in Kerala State, India (Sarles et al. 1979), where we have studied 1700 patients with pancreatic calcification and diabetes, admitted to the Medical College hospitals in Kerala, during the past 20 years. Operative findings, pancreatograms, and pancreatic biopsy in 375 patients and 38 postmortem cases have shown that there is a distal pancreatic ductal obstruction toward its duodenal end in the majority of cases. A ductal obstruction has also been described in many cases of alcoholic calcifying pancreatitis (ACP), seen in Western countries (Warren and Hoffman 1976).

The theory of primary pancreatic ductal obstruction as a cause of ACP has been refuted recently by Sarles and Laugier (1981), who have found that a high protein - high fat diet in the presence of alcoholism induces enzyme precipitation in pancreatic ductules, and the obstruction in the pancreatic duct system is only secondary to the formation of protein plugs. However, an international multicentre study of nutrition and pancreatitis conducted by Sarles (1973) has shown that in Trivandrum, Kerala, the protein intake of patients with TCP was comparatively low and that calcifying pancreatitis was common. Therefore, we looked for other dietetic factors that can cause pancreatic injury in the presence of protein deficiency. A high carbohydrate content in the diet might also cause precipitation of enzyme proteins in the pancreatic juice. This is supported by the observation of Sarles et al. (1979) that in centres of southern Europe, e.g., Marseille, France, the intake of carbohydrates was 429 ± 115 g/day in patients with ACP and the pattern of pancreatitis was of the calcifying type, whereas in northern Europe, e.g., Copenhagen, Denmark, where acute pancreatitis is more prevalent, the carbohydrate intake was only 290 ± 69 g/day. In our calcifying pancreatitis patients in Kerala, the intake of carbohydrates was high, 478 ± 100 g/day. The source of this carbohydrate, peculiar to Kerala, was found to be cassava. Cassava is rich in carbohydrates and poor in protein content. In addition, the presence of cyanogenic glycosides in cassava would cause further protein deficiency because sulfur-containing amino acids, such as methionine and cysteine, already deficient in cassava, are required for cyanide detoxification.

Epidemiological data in support of cassava as a cause of TCP show that this disease is most prevalent in countries such as Nigeria (Osuntokun 1970), Uganda (Shaper 1964), India (Geevarghese 1968), Indonesia (Zuidema 1959), and Brazil (Dani and Nogueira 1976), where cassava is eaten and the incidence of endemic goitre related to cassava toxicity is also common. That diabetes mellitus is more common in people eating cassava-based diets has also been pointed out by Davidson et al. (1969) who reported a 1% incidence of diabetes in inhabitants of Kalene Hill, Zambia, where people consume 340 g of carbohydrates per day in the form of cassava, making up 93% of their total caloric intake; whereas in areas of the adjoining coun-

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tries, i.e., Malawi and Zimbabwe in Central Africa, population surveys have shown the incidence of diabetes to be only 0.1–0.13%.

The experimental evidence (Pushpa 1980) in support of cassava-based diets as a cause of TCP is that rats on a diet containing 22.8 g of cassava containing 73 mg/g cyanide and sacrificed at 18 months showed pancreatic changes such as dilated ductules, papillary infoldings, eosinophilic material in ductular lumen, round cell infiltration, and atrophic acini as is seen in TCP.

McMillan and Geevarghese (1979) have shown that administration of cyanide (KCN), orally or intraperitoneally, to rats caused a peaking of plasma glucose up to 300 mg/dL within 30 min. This was associated with temporary glycosuria. After ingesting KCN for 1 month, the chronically cyanide ingesting rats developed a dusky colour of the fur somewhat similar to the cyanotic hue of the lips seen in our patients with TCP, possibly due to sulfur amino acid deficiency. It is possible that during the process of cyanide detoxification in the body, the pancreas, which has a high turnover of protein in the body, is affected if there is a deficiency of amino sulfur, as in cassava-based diets.

Although there is a high incidence of both endemic goitre and TCP in Kerala, where cassava is consumed in amounts varying from 100–300 g/day, making up 60% of caloric intake and 73% of carbohydrate intake, the two diseases are rarely associated. We have observed that goitre is more prevalent in better nourished individuals, whereas TCP is common in the undernourished. The incidence of goitre has remained steady over the past 10 years in the major teaching hospitals of Kerala, whereas TCP is declining. This is probably due to the increase in protein consumption of Keralites over the past decade as a result of the increased availability of fish, which is consumed with cassava. It is presumed that with protein deficiency the pancreas is affected; on the other hand, if enough sulfur amino acids are present in the diet the thiocyanate that is formed as a result of cyanide detoxification causes endemic goitre.

In summary, it may be stated that the high carbohydrate content of cassava may cause enzyme precipitates in the pancreatic ductules, causing TCP, just as a high protein - high fat diet is responsible for ACP. In addition, the cyanogenic glycosides present in cassava induce pancreatic injury. Protein deficiency aggravates the pancreatic damage. It is to be emphasized, however, that cassava-based diets alone may not cause TCP and PD. Other genetic factors, such as pancreatic ductal anomalies, are also present in this disease.

Dani, R. and Nogueira, C.E.D. 1976. Chronische kalzifizierende pankreatitis in Braselien — eine analyse von 92 fallen. Leber Magen Darm, 6, 272–275.

Davidson, J.C., Mcglashan, M.B., Nightingale, E.A., and Upadhyay, J.M. 1969. The prevalence of diabetes mellitus in the Kalene Hill area of Zambia. Medical Proceedings. Mediese Bydraes, 15, 426–432.

Geevarghese, P.J. 1968. Pancreatic diabetes. Popular Prakashan, Bombay, India.

McMillan, D.E. and Geevarghese, P.J. 1979. Dietary cyanide and tropical malnutrition diabetes. Diabetes Care, 2, 202–208.

Osuntokun, B.O. 1970. The neurology of non alcoholic pancreatic diabetes mellitus in Nigerians. Journal of the Neurological Sciences, 11, 17–47.

Pushpa, M. 1980. Chronic cassava toxicity. An experimental study. MD thesis (pathology), Kerala University.

Sarles, H. 1973. An international survey on nutrition and pancreatitis. Digestion, 9, 389–403.

Sarles, H. and Laugier, R. 1981. Alcoholic pancreatitis. Clinical Gastroenterology, 10, 401–415.

Sarles, H., Sahel, J., Staub, J.L., Bourry, J., and Laugier, R. 1979. In Exocrine Pancreas. W.B. Saunders Co., Philadelphia, PA, USA, 420–421.

Shaper, A.G. 1964. Aetiology of chronic pancreatic fibrosis with calcification seen in Uganda. British Medical Journal, 2, 1607–1609.

Warren, K.W. and Hoffman, G. 1976. Changing patterns in surgery of pancreas. Surgical Clinics of North America, 56, 615–629.

Zuidema, P.J. 1959. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Tropical and Geographical Medicine, 11, 70–74.

Discussion: Public Health and Nutritional Aspects of Endemic Goitre and Cretinism

Delange: I would like to ask about the high incidence of congenital hypothyroidism found in the endemic goitre areas you have studied in India because in other endemic areas where neonatal screening for congenital hypothyroidism has been performed, such as Algeria, Sicily, and Peru, no abnormally high incidence of congenital hypothyroidism has been found. In contrast, a particularly high incidence of congenital hypothyroidism in newborns has been found in the Ubangi endemic goitre area in Zaire. Consequently, my questions are: What are your biochemical criteria for defining congenital hypothyroidism based on cord blood? What is the balance between the dietary supplies of I and SCN in the mothers during pregnancy? What is the result of the control examinations in these newborns? Was hypothyroidism confirmed? Did they need permanent substitutive therapy?

Kochupillai: We have recently introduced neonatal thyroid screening in three areas in India: in villages with a very high prevalence of goitre in the Gangetic belt, Gonda district; in the Delhi area, where the prevalence of goitre in schoolchildren in several pockets can be as high as 50%; and in Kerala, where there is no endemic goitre. We have just finished standardizing the various techniques in our laboratory. We have highly sensitive radioimmunoassays for TSH, T_4, T_3, and reverse T_3.

We have preliminary results on 120 cord blood samples collected from moderately severe (Delhi) and severe endemic goitre areas. The results are:

	Cord serum (mean ± SEM)		
	TSH (μU/mL)	T_4 (μg/dL)	T_3 (ng/dL)
Moderately severe endemic goitre	9.8 ± 0.3	6.4 ± —	59.8 ± 2.5
Severe endemic goitre	14.6 ± 1.8	4.2 ± 0.3	96.9 ± 9.6

It is interesting to note that these newborns have elevated T_3 in cord serum. The highest values found were 168 and 174 ng/dL.

We have detected two infants with frank hypothyroidism out of the 120 infants screened, which gives a prevalence of 2.2%. The individual results were:

	Cord serum		
	TSH (μU/mL)	T_4 (μg/dL)	T_3 (ng/dL)
Patient 1	>200	2.6	43
Patient 2	>200	0.5	40

These hypothyroid patients also had cord blood hyper tri-iodothyronemia, which, in our opinion, may partly explain the neurological damage frequently found in endemic cretinism and deaf-mutism.

Thilly: Among the complications of endemic goitre, you mentioned decreased fertility in women. Along this line, we have shown that, in the Ubangi endemic goitre area, weight at birth is lower and perinatal mortality is higher in infants born to severely iodine-deficient mothers than in infants born to mothers who received injections of iodized oil during pregnancy. This difference could be due either to fetal hypothyroidism or to maternal hypothyroidism or to a combination of both factors. Have you any data on the thyroid status of pregnant women in endemic goitre areas of Algeria?

Benmiloud: We now have an ongoing study in which we are comparing the populations from a goitrous and a nongoitrous area in Algeria. At present, we do not feel that hypothyroidism during pregnancy is an important factor in the endemic area. There are probably prematurity and neonatal complications in this area but this could be due to many other factors, considering the poor health conditions in the area. We have no final data showing that the prevalence of these complications is higher than in the nongoitrous area, although the economic conditions are identical.

Ermans: You have made an extensive review of the programs of goitre prophylaxis in Africa. In Zaire, in collaboration with the health authorities, we have organized a prophylactic program utilizing injections of iodized oil because a program based on iodization of salt was not possible for the reasons reported by Dr Singh. What is your opinion on the optimal prophylactic programs in Africa today?

Benmiloud: The choice will depend upon local conditions. You should have a more flexible program than utilization of iodized salt or iodized oil alone. For example, in Algeria we have not been terribly successful with iodized salt during the last 10 years. We are planning to compare the efficiency of iodized oil administered intramuscularly in primary health-care centres and orally in schools. The two networks are different and sometimes the school network is better than in the health-care centres.

Van Middlesworth: Have the speakers who advocate iodine prophylaxis considered giving Teridax, the oral material used for X-ray visualization of the gall bladder? It sometimes has a half-life of 20–30 years in the body.

Benmiloud: I am afraid that Teridax is presently off the market.

Thilly: There are possibilities of technical research in the field of iodinated substances to be used in the prevention of endemic goitre. The X-ray iodinated contrast media, such as Lipiodol, that are commonly used are supposed to be excreted as rapidly as possible, whereas for the prophylaxis of goitre we are looking for substances that are excreted as slowly as possible.

Cooke: I have a comment related to Paraguay. Paraguay should be of interest to this workshop because not only does it have a high prevalence of goitre but also very high consumption of cassava. In 1979, the production was about 900 000 tonnes per year for a population of 3.5 million and cassava is the staple source of carbohydrates in the country. In the 1940s, the prevalence of goitre varied from 39–79%. An iodized salt program was introduced. However, by 1965, the mean prevalence of goitre was still 25% and was over 40% in pregnant women. There are a number of reasons for this: (1) Although the control of salt has been centralized, a recent survey indicated that one-third of the samples of iodized salt analyzed did not contain potassium iodate. (2) In Paraguay, the practice is to add the salt at the beginning of cooking, so that the amount of iodine in the prepared food is probably low. (3) The additional role of cyanide from cassava could also be considered.

Cock: Are there areas in the world where people have adequate amounts of iodine but still have thyroid problems because they also consume high amounts of cassava?

Delange: I am not aware of any such area. A good example is the Azolongo ethnic group in Zaire. They live close to the Atlantic Ocean, in the southwestern part of the republic, and eat seafoods but also large quantities of unsoaked bitter cassava. We determined the prevalence of goitre in the population, the urinary concentrations of iodine and thiocyanate, and the I/SCN urinary ratio in 55 randomly selected adults. The results were:

	Urinary I (μg/dL)	Urinary SCN (mg/dL)	Urinary I/SCN ratio	Prevalence of goitre
Azolongo	13.4 ± 1.5	1.45 ± 0.09	9.7 ± 0.9	2.5
Belgian controls	5.3 ± 0.7	0.60 ± 0.07	8.8 ± 0.4	3

The Azolongo patients have elevated urinary SCN, resulting from consumption of cassava. They also have elevated urinary I, resulting from consumption of seafoods. Consequently, they have an elevated urinary I/SCN ratio and no abnormal prevalence of goitre. Similar conclusions resulted from comparative studies conducted in four areas in Zaire with different intake levels of iodine and cyanide from cassava.

Ermans: I could add that, experimentally in rats, when you administer 10 mg SCN per day, which is a huge amount, there is no effect on the thyroid provided that the iodine supply is adequate.

Van Middlesworth: An adequate iodine supply is a relative thing. A low iodine supply can be adequate if you have no SCN, but as you increase SCN, you must increase iodide also.

Kochupillai: Cassava has a high content of fibre. Dr Van Middlesworth, did you publish evidence that fibres would inhibit absorption of iodine from the gut? Could this be a mechanism responsible for the goitrogenic action of cassava?

Van Middlesworth: Not exactly. Dietary fibre will increase the mass of the feces in rats and this will increase the excretion of thyroxine in the feces and thus the requirement for thyroxine.

Cock: I would like to stress that cassava is not rich in fibres.

Burrow: In humans, the amount of thyroxine excretion through the biliary tract is much lower than in rats. Therefore, fecal loss of thyroxine in humans is probably not a major problem.

Gaitan: You have reported that the prevalence of goitre is 74.1% in Ruba and only 3.0% in Bajong, yet these two areas are very close to one another. This is an ideal situation for evaluating the respective roles of iodine intake, water pollution, and other nutritional or socioeconomic factors in the etiology of endemic goitre. Could you identify the causal factors in this area?

Tan: We are planning to perform such investigations but they have not been possible yet.

Delange: I appreciated your neurological approach to the problem of neurological endemic cretinism. If you saw, in any clinic in the world, most of the defectives you described in Ecuador, the diagnosis would be cerebral palsy and you would investigate a large number of possible etiological factors, including consanguinity and prenatal, perinatal, and postnatal events, but you would not consider iodine deficiency or thyroid failure as a possible etiological factor. The major reason, however, for suggesting that this type of defect is related to endemic goitre is that it is preventable by iodine supplementation. In my opinion, in order to clarify the problem of neurological endemic cretinism, we need to reevaluate, entirely, the situation in adults, as you did, and we also need a longitudinal study of a newborn population in order to appreciate possible relationships of anomalies of thyroid function at birth and the subsequent appearance of developmental anomalies.

Ramirez: Because a well-trained neurologist shared our outlook on endemic cretinism, we started a new approach to the problem, including the investigations we have described. Moreover, relatively simple investigations such as an EEG in newborns appear to be contributive.

Gaitan: Water supply has been markedly improved in Costa Rica during the past few years. This resulted in a significant decrease in the prevalence of goitre, whereas pockets of goitre remained in areas where water sanitation was not available. This, again, underlines the multifactorial etiology of endemic goitre.

An Overview of Cassava Consumption and Production

Truman P. Phillips[1]

Cassava as a Human Food

Cassava production occurs in an equatorial belt bounded by latitudes 30°N and 30°S and is restricted to zones less than 2000 m above sea level and receiving an annual rainfall of 200–2000 mm. Within this region, cassava is an important staple for about 800 million people. With few exceptions, the human food market has been and continues to be the major outlet for cassava. This market, however, is highly localized, with the product usually being consumed in either fresh or processed form near the growing areas.

Cassava is generally regarded as a subsistence crop with a low market preference, as indicated by its small or even negative income elasticity.[2] For example, Food and Agriculture Organization of the United Nations (FAO) estimates of cassava income elasticities indicate that 43% are positive, but the values, generally, are 0.2 or less (R.J. Perkins, personal communication).

Annual per capita consumption of cassava is greatest in Africa, averaging 102 kg/year. In the Central African Republic, Congo, Gabon, and Zaire, consumption exceeds 300 kg/person/year. In Latin America, the average per capita consumption is substantially lower (35 kg/year). Only in Brazil and Paraguay does consumption exceed 50 kg/year (76 and 173 kg/year respectively). Nevertheless, in both Africa and Latin America cassava is the second or third most important calorie source. Consumption is lowest in Southeast Asia, averaging 24 kg/person/year (R.J. Perkins, personal communication).

Demand projections for cassava, based on expected population and income growth rates, have been made by FAO. These projections, for the major cassava consuming regions and six selected countries (which account for 56% of the human food market), are presented in Table 1.

At the regional level, Africa is expected to experience the greatest annual increase in demand and Latin America the least. At the national level, both Zaire and Colombia are expected to have demand growth rates of about 3% per year, whereas Brazil is expected to have a demand growth rate of only 1.5% per year.

Geographical Distribution of Cassava Production

Cassava is grown in about 80 countries. Ninety percent of production comes from 25 countries, with four countries accounting for 53.4% of world population, i.e., Brazil (21.3%); Indonesia (11.2%); Thailand (10.7%); and Zaire (10.2%) (FAO 1980). Of the remaining 21 countries, Nigeria, Tanzania, Viet Nam, Mozambique, People's Republic of China, Colombia, Ghana, Angola, Philippines, Paraguay, Madagascar, and Uganda each account for 1–10% of world production. Burundi, Central African Republic, Cameroon, Ivory Coast, Benin, Kenya, Sri Lanka, Guinea, and Congo each account for less than 1% of world production (FAO 1980).

Production trends over the past 20 years have remained stable, although those of the 1970s generally exhibited lower rates of increase than those of the 1960s (Fig. 1a, b), the exception being Southeast Asia.

On a national scale, certain dramatic changes

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[2]Income elasticity is the ratio of the percentage increase (decrease) in the demand for a commodity to a given percentage increase in income. In general terms, the larger the ratio, the more desirable the commodity.

Table 1. Cassava demand projections (1000 metric tons) for human consumption.

	1975	1985	1990	Annual percentage increase
World	61671	78809	88715	2.4
Africa	33744	44480	51216	2.8
Latin America	11783	14103	15212	1.7
South Asia	6587	8065	8770	1.9
Southeast Asia	7482	9418	10368	2.2
Nigeria	8400	10520	11771	2.3
Zaire	8713	11738	13676	3.1
Brazil	8806	10326	10992	1.5
Colombia	792	1072	1234	3.0
Indonesia	6379	7983	8767	2.1
Thailand	211	274	305	2.5

Source: R.J. Perkins, personal communication.

should be noted (Fig. 2). The rapid increase in cassava production in Thailand has been in response to growth in the European Economic Community (EEC) market for animal feed ingredients (Phillips 1981). Thailand's particular ability to respond to this market growth can be explained by several factors unique to Thailand: (1) cassava is not a popular local food crop; (2) the land base is relatively large; and (3) the marketing infrastructure is quite good. Also, when Thailand began exporting cassava, sea freight rates were very low, owing to excess capacity. The increase in cassava production in Zaire may be explained by the government's cassava promotion program. The decrease in Brazil's cassava production is somewhat unexpected, in light of the national alcohol program that is based on the assumption that cassava will provide 10% of alcohol feedstock. It can only be suggested that government efforts to stimulate cassava alcohol production have failed and that the relatively slow expansion of the human market (Table 1) has discouraged the expansion of production. As well, the substantial rural-to-urban migration during the past two decades has meant that the market is

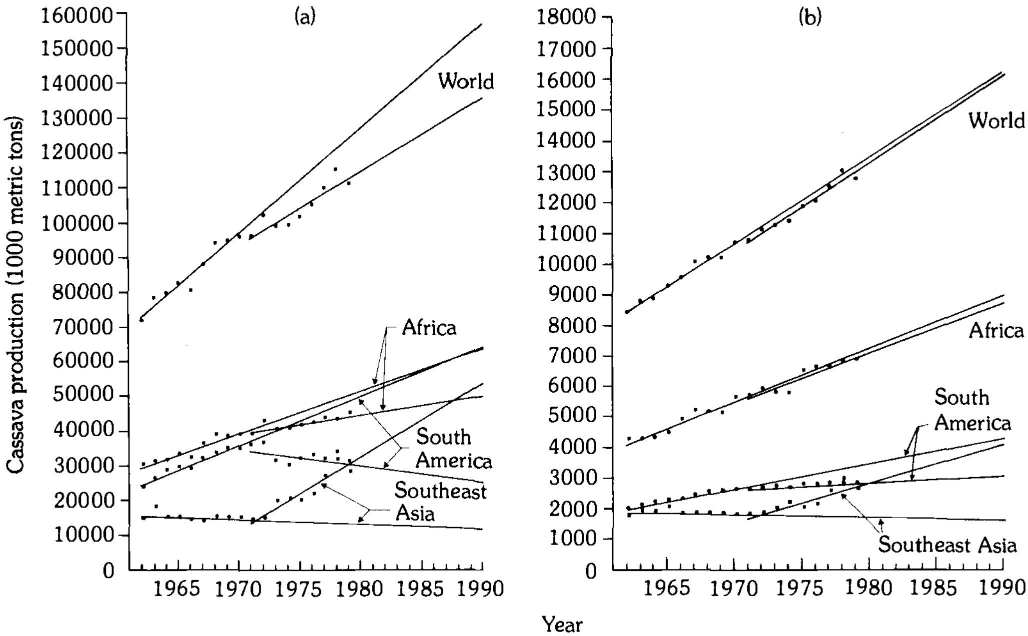

Fig. 1. (a) Pre- and post-1970 production trends. (b) Pre- and post-1970 area trends.

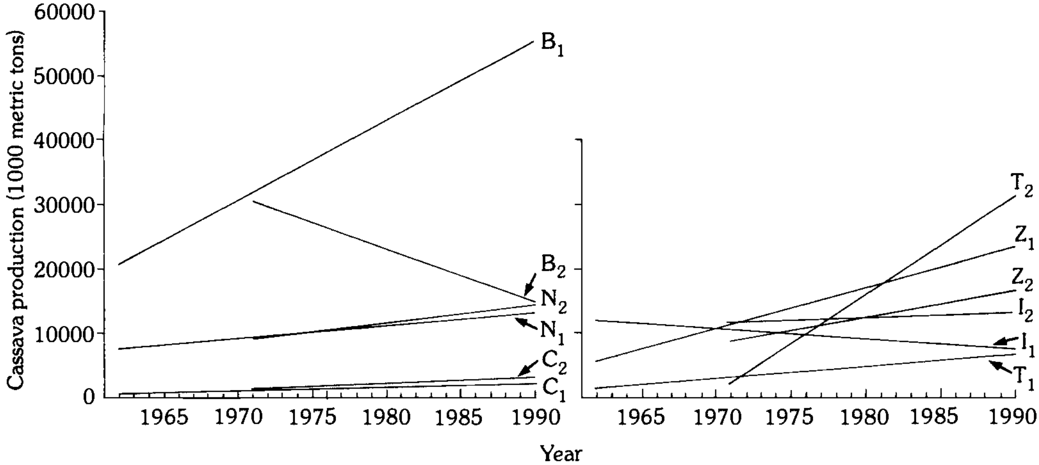

Fig. 2. National production trends. B, Brazil; C, Colombia; I, Indonesia; N, Nigeria; T, Thailand; Z, Zaire. Subscript 1 represents pre-1970; subscript 2 represents post-1970.

moving away from the producing areas, making it more difficult for farmers to market their products, and, consequently, making cassava a less attractive crop.

In all instances, production trends have evolved primarily to meet local food demands,[3] but within the constraints of subsistence resources. These constraints are substantial in spite of the positive attributes of cassava, i.e., relatively good resistance to diseases, pests, and drought. In Colombia, Brazil, and Paraguay, 41–52.3% of the land upon which cassava is grown occurs on farms with less than 10 ha total area (Lyman 1978). In Thailand, 92% of land devoted to cassava is located on farms with less than 8 ha total area (Phillips 1977). In eastern Nigeria, a detailed study of three villages showed that 100% of the cassava was produced on farms with total areas of 2.4 ha or less, including bush and grass fallow (Lagemann 1977).

As an additional constraint, production practices tend to be unmechanized,[4] requiring a labour input of 80–100 man-days/ha (Phillips 1977). In comparison with other staple crops, this requirement seems high. From the point of view of food energy output versus labour input, however, cassava appears to be very efficient (Chandra et al. 1974).

The fact that cassava production has kept pace with population growth is remarkable, especially when it is considered that this expansion has been achieved on small farms employing labour-intensive methods. It should be noted that this is in contrast to declining per capita cereal production in the tropics (Hadler and Yang 1976). Cassava expansion is even more impressive when it is realized that there have been no clear trends in terms of increased yields (Table 2). Thus, the bulk of the expansion has come from increasing the land dedicated to cassava production — not necessarily an easy achievement for a peasant farmer (FAO 1980).

Comparison of Projected Consumption and Production

The links between cassava production and consumption are processing and marketing. Processing is undertaken to detoxify the product and to convert it to a storable form. The present discussion is concerned mainly with the former aspect of processing. From the producer's point of view, however, the preservation of the harvested root is probably of greater interest, because a product with a good shelf life increases consumption and marketing alternatives.

Processing, like production, is carried out on a small scale, using time-honoured techniques. In northeastern Brazil, the production of *farinha de mandioca*, the major processed form of cassava in the region, is carried out at *casas de farinha*, which have an average capacity of 1 metric ton of roots per day (250 kg of *farinha de mandioca* per day) (Scholtz 1971). This is

[3]Thailand is the exception because its production is mainly oriented toward the European animal feed market.

[4]Again, the exception is Thailand, where 66% of the farmers hire tractors for land preparation (Phillips 1977).

Table 2. Cassava yields, 1960s and 1970s (tons/ha).

	1960s	1970s		1960s	1970s
World	8.9	8.8	Nigeria	9.5	9.9
Africa	7.2	6.7	Zaire	11.9	8.0
Latin America	13.2	12.0	Brazil	14.2	12.9
South Asia	11.2	14.0	Colombia	6.1	8.8
Southeast Asia	8.2	9.9	Indonesia	7.4	8.5
			Thailand	15.4	13.9

Sources: FAO (1980); author's calculations.

equivalent to the daily output of 4–5 ha. In eastern Nigeria, individual farmers process the cassava that they produce. A case study of farm activities found that farmers spend about 12% of their time processing cassava and 17% of their time marketing cassava and other products (Lagemann 1977). Even in Thailand, chipping and drying, which is the first stage of pellet production, is small scale, with an average chipping plant capacity of 10 tons of roots per day (about 990 tons of chips per year) (Boonjit 1974).

Thus, it is through the hands of small-scale processors, who often times are also producers and marketers, that about 69 million metric tons of cassava pass annually. It is these same processors who will continue to provide the link between production and consumption in the future. Production and consumption projections for 1985 and 1990 are presented in Table 3.

In general, cassava supply is expected to exceed demand, except for the 1990 African deficit and an insignificant deficit in South Asia. Indeed, if the projections for Nigeria and Zaire are correct, the rest of Africa could have a 1990 demand for 26 million tons, with a supply of only 19 million tons, resulting in a deficit of 7 million tons. In practice, demand cannot exceed supply for a nontraded commodity. Therefore, the projections suggest that for an equilibrium to be achieved the trends must change. This implies that there could be increasing pressure on other food crops or strong pressure to accelerate the rate of increase of cassava production. In the latter case, it may be assumed that this will be accompanied by increasing requirements for new technology to realize production expansion.

Southeast Asia's surplus is primarily a reflection of the surplus in Thailand. In all likelihood, this surplus will not occur because the EEC market (the main outlet for Thailand's production) will not continue to expand (Phillips 1981).

The 1990 Brazilian surplus is doubtful because it is based on FAO consumption estimates, which appear to underestimate actual consumption levels. For example, the 1975 FAO consumption estimate is ~8 million metric tons (R.J. Perkins, personal communication), whereas the Brazilian estimate for the same year is ~15 million metric tons. The problem with the FAO data is that they appear to relate either to the consumption of only *farinha de mandioca* (processed cassava), not fresh cassava, or to *mandioca mansa* only or *mandioca brava* only — even though both are consumed by humans. If it is assumed that the FAO demand projec-

Table 3. Projected cassava consumption and production (1000 metric tons).

	1985		1990	
	Consumption	Production	Consumption	Production
World	78809	124987	88715	135513
Africa	44480	47311	51216	50081
Latin America	14103	27693	15212	25229
South Asia	8065	7503	8770	7950
Southeast Asia	9418	43211	10368	53820
Nigeria	10520	12996	11771	14365
Zaire	11738	14585	13676	16671
Brazil	10326	19137	10992	15015
Colombia	1072	2656	1234	3124
Indonesia	7983	15865	8767	17821
Thailand	274	23721	305	31390

Sources: R.J. Perkins, personal communication; FAO (1980); author's calculations.

tions are low, Brazil may experience difficulty in meeting future cassava demands unless its decreasing production trend is reversed.

Cassava Consumption and Endemic Goitre and Cretinism

Studies have demonstrated that a relationship exists between iodine deficiency, human consumption of cassava, and endemic goitre and cretinism (Ermans et al. 1980; Delange et al. 1982).

Inadequately detoxified cassava can contain cyanide (HCN) that, when ingested by humans, is converted to thiocyanate (SCN), a goitrogenic agent. In most traditional practices, the enzyme linamarase and cyanogenic glucosides contained in cassava are brought into contact by cell rupture and the liberated HCN is then released through volatilization or solution in water. Some methods also involve fermentation as an initial means of glucoside hydrolysis (Coursey 1973).

Because HCN content varies with plant variety and detoxification methods vary by community, information on the precise geographical distribution of varieties and processing methods would be extremely useful. Unfortunately, such detailed information is not readily available on a global basis. Limited information on Brazil, however, is available.

In Brazil, the types of cassava consumed by humans normally are of the "sweet" or low HCN variety. It is known, however, that certain of the bitter varieties are also consumed (Rosenthal 1973). It has also been shown that although "bitter" varieties generally have higher HCN values than "sweet" varieties the division is inexact and considerable overlapping between classes exists (Coursey 1973). It should be pointed out that, judging from the paucity of literature on cassava toxicity in Brazil, the problem does not seem to be of major concern among Brazilian researchers.

The processing of cassava in Brazil, for human consumption, can be categorized as being either "one-step" or "multistep." One-step processing involves boiling, frying, or roasting fresh tubers; as well, young leaves are ground and boiled and served with various dishes. With multistep processing, the fresh root is converted to an intermediate foodstuff and then converted, through further preparation, into a final table product (e.g., *farofa*; tapioca-based dishes; dishes employing roots that are grated, soaked, and pressed; and baked products containing cassava flour).

The HCN content of different Brazilian cassava foods is not known, but it can be assumed that multistep processing probably liberates HCN better than one-step processing.

Iodine deficiency is a common problem in Brazil, and past surveys have shown that goitre is endemic throughout the country (Kelly and Snedden 1960; Medeiros-Neto and Dunn 1980). In 1953, iodization of salt became mandatory, but the law only affected refined salt and not the unrefined block salt commonly consumed in rural areas (Medeiros-Neto and Dunn 1980).

When 1960 cassava consumption figures (Getulio Vargas Foundation 1970) are compared with the findings of a goitre survey covering roughly the same time period (Kelly and Snedden 1960), a striking relationship between the two emerges (Table 4).

The incidence of goitre seems to be positively associated with the consumption of fresh roots (subjected to one-step processing, which liberates

Table 4. Percentage goitre and fresh cassava consumption.

Region[a]	Percentage goitre	Weighted zone average		Consumption (kg/capita/year) Fresh roots	Farinha
Zone 1			Zone 1		
North	9.4		Rural	10.259	64.666
Northeast	11.8 0.6	4.0	Urban	0.580	24.052
Zone 2			Zone 2		
Southeast	27.0	19.0	Rural	20.235	28.990
East	0.9		Urban	3.865	11.847
Zone 3			Zone 3		
South	27.7	27.7	Rural	45.983	12.140
			Urban	2.914	3.380

Sources: Kelly and Snedden (1960); Getulio Vargas Foundation (1970).
[a]The Central region had the highest incidence of goitre, 53.8%, but, unfortunately, data on fresh root consumption in this region were unavailable.

the least amount of HCN) but not to *farinha* consumption (a multistep processed food). Thus, although Brazil has a relatively low per capita cassava consumption rate, it may serve to illustrate the relationship between goitre and the type of processing of cassava foods. Furthermore, given that fresh root consumption is higher in rural areas than in urban areas, the 1953 law that made iodization of salt mandatory offers an example of legislated prophylaxis that (perhaps for lack of understanding of the potential link between cassava consumption and goitre) proved inadequate to the requirements of the situation.

Finally, it should be noted that rural income elasticities for fresh roots are generally negative, whereas those for urban areas are generally positive (Phillips 1974). Therefore, because incomes have risen during the past 20 years, it would be expected that consumption of fresh roots would have decreased in rural areas and increased in urban areas. An interesting question, therefore, is whether or not the incidence of goitre decreased in rural areas and increased in urban areas during the same time span. Unfortunately, detailed information on the incidence of goitre in rural and urban areas was not available to the author at the time this paper was prepared.

Conclusions

Global demand for cassava is primarily determined by the human food market, which in turn is largely determined by population. The size of the human food market is the principal determinant of the quantity of cassava that is produced. Moreover, this market is often geographically tied to highly localized production sites. Of the major producers, only Thailand does not depend on cassava as a staple.

Although the 1990 supply of cassava is expected to exceed demand, certain deficit or problem areas are projected. Cassava production is, generally, small scale and employs traditional techniques. Future expansion of production will have to occur within this context.

Processing and marketing are also small scale and also use traditional techniques. Often, the producer acts as both processor and marketer. Any attempt to alter processing methods or the type of product marketed should take these factors into consideration.

Boonjit, Titapiwatanakun. 1974. Cassava industry in Thailand. M. Econ. thesis, Thammasat University, Bangkok, Thailand.

Chandra, S., DeBoer, A.J., and Evenson, J.P. 1974. Economics and energetics: Sigataka Valley, Fiji. World Crops, 26 (1), 34-37.

Coursey, P.G. 1973. Cassava as food: Toxicity and technology. In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 27-36.

Delange, F., Iteke, F.B., and Ermans, A.M., ed. 1982. Nutritional factors involved in the goitrogenic action of cassava. International Development Research Centre, Ottawa, Canada, IDRC-184e, 100 p.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Food and Agriculture Organization of the United Nations (FAO). 1980. 1979 FAO production yearbook. Vol. 33. Rome, Italy.

Hadler, S. and Yang, Maw-Cheng. 1976. Developing country foodgrain projections for 1985. World Bank Staff Working Paper No. 247, Washington DC, USA.

Kelly, F.C. and Snedden, W.W. 1960. Prevalence and geographical distribution of endemic goitre. In Endemic Goitre. World Health Organization, Geneva, Switzerland, Monograph Series No. 44.

Lagemann, J. 1977. Traditional African farming systems in eastern Nigeria. Weltforum Verlag, München, Germany.

Lyman, J.K. 1978. Options for Latin American countries in the development of integrated cassava production programs. Centro Internacional de Agricultura Tropical, Cali, Colombia.

Medeiros-Neto, G.A. and Dunn, J.T. 1980. Central and South America. In Endemic Goiter and Endemic Cretinism. John Wiley,Toronto, Ontario, Canada.

1970. Food consumption of Brazil: Family budget surveys in the early 1960's. Getulio Vargas Foundation, Rio de Janeiro, Brazil.

Phillips, T.P. 1974. Cassava utilization and potential markets. International Development Research Centre, Ottawa, Canada, IDRC-020e, 182 p.

1977. A profile of Thai cassava production practices. In Cock, J., MacIntyre, R., and Graham, M., ed., Proceedings of the Fourth Symposium of the International Society for Tropical Root Crops held at CIAT, Cali, Colombia, 1-7 August 1976. International Development Research Centre, Ottawa, Canada, IDRC-080e, 228-232.

1981. Established markets and new possibilities for tapioca. Presented at the Seminar on Cassava and Cassava Products, Bangkok, Thailand, 7-10 December 1981.

Rosenthal, F.R.T. 1973. Industrialização do amido de mandioca: estado do Pará. Instituto Nacional de Tecnologia, Rio de Janeiro, Brazil.

Scholtz, H.K.B.W. 1971. Aspectos Industrias no Nordeste. Banco Nacional do Brasil, Fortaleza, Ceara, Brazil.

Utilization of Cassava in the European Community[1]

D. Renshaw[2]

Virtually all cassava, or manioc as it is commonly known, imported within the European Community is used in animal feed.

Animal products (meat, milk, eggs, etc.) represent about 60% of the Community's final agricultural output; consequently, the question of animal feed is of prime importance. The Community's approach to these feedstuffs is based on four main elements: (1) maximum effective use of natural forage crops such as grass, with permanent and semipermanent grasslands providing about half of the total feed used by the animal population; (2) maximum use of cereals in animal feed, thereby supporting the cereal growers; (3) free access to world supplies of protein in which the Community is deficient (it is the Community's import of soybean that is principally responsible for its large agricultural trade deficit with the USA); and (4) encouragement of the Community's own production of protein.

The increase in livestock production within the Community in recent years has led to the spectacular development of a new factor — that of cereal substitutes — to the extent that increased demand from the animal sector has been met largely by cheap substitutes, imported over nil or low levies, rather than by cereals. For example, during the period between 1975 and 1980, Community production of compound animal feed increased by 36%, but the use of grain in feedstuffs rose by only 9%.

The most important of these cereal substitutes has been maize gluten feed, the import of which rose from 700000 tons in 1974 to an estimated 3 million tons in 1981; cereal and rice brans, which rose from 1.2 million tons to just over 2 million tons over the same period; and manioc, the import of which has increased three times, from 2 million tons in 1974 to an estimated 6.5 million tons in 1981 (Table 1). All of this has taken place amid increased cereal production within the Community, which has necessitated expenditure on the disposal of grain on the world market.

Faced with this situation, the Community must try to balance the interests of its livestock producers and cereal growers as well as its budget. It is with all three interests in mind that the Commission of the European Communities had proposed that over the next few years, up to 1988, the Community narrow the gap between its own cereal prices and those applied by its main competitors. In the long term, this should make cereal substitutes less attractive; in the short and medium terms the Commission of the European Communities has proposed that arrangements be made to stabilize imports of these products at their present levels. In the past, there has been a tendency for both the nature and source of these substitute products to change. Originally from basic raw materials grown in developing countries, an increasingly large percentage of these substitute products are now residues and processed products coming from developed economies.

In Table 2, imports of manioc into the Community since 1974 and the principal sources of these imports are presented. The year 1974 has been chosen as a base year because this is the first year for which complete statistics are available for all nine member states of the European Community, i.e., after the accession of Denmark, Ireland, and the United Kingdom and before that of Greece.

Even the total import in 1974 of 2.1 million tons, although low by today's standards, represents a three- or fourfold increase over the

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Table 1. Imports of substitute products (1000 tons).

Product	1974	1975	1976	1977	1978	1979	1980	1981 (estimate)
Manioc	2073	2222	2984	3801	5976	5375	4866	6500
Sweet potatoes	177	115	55	9	6	81	324	75
Molasses[a]	1498	1731	2198	2648	2789	3317	2706	2100
Grape marc	13	10	19	17	7	9	38	70
Fruit waste								
Citrus peels	327	480	646	968	1000	1205	1571	1400
Other fruit waste	21	56	136	164	117	177	156	90
Maize gluten feed	700	930	1147	1486	1685	2021	2596	3000
Brans								
Maize, rice (max. 35% starch)	233	267	417	280	145	205	233	265
Maize, rice (>35% starch)				15	6	3	2	6
Wheat (max. 28% starch)	976	1237	1839	1903	1798	1806	1707	1750
Other brans				4	6	0.1	5	1
Brewers grains	64	57	94	116	161	204	290	340
Maize germ cake (<3% fat)	NA	465	564	709	790	869	822	750
Maize germ cake (3-8% fat)	NA	60	65	108	181	167	203	220

NOTE: NA = Not available.
[a]50% destined for human consumption.

Table 2. Imports of manioc by source (tons).

	Thailand	Indonesia	Brazil	China	Malawi	India	Tanzania
1974	1739487 (84)	259747 (13)	40581	4111	12644	—	—
1975	1873337 (84)	313893 (14)	7006	4211	6089	—	—
1976	2785727 (93)	179433 (6)	1638	7253	1757	—	—
1977	3639474 (96)	143920 (4)	1864	999	1026	7949	—
1978	5668254 (95)	218898 (4)	2032	1327	2059	37182	39508
1979	4528761 (84)	694214 (13)	27804	51449 (1)	3400	26799	34967
1980	4115816 (85)	372228 (8)	12316	335989 (7)	2087	11915	8074
1981 (estimate)	5500000 (84)	470000 (7)	2000	560000 (9)	NA	NA	NA

NOTES: Values in parentheses are percentages of total. NA = not available.

quantities imported during the mid-1960s, when Community imports were around 0.5 million tons, increasing in 1968 to about 1.0 million tons.

It was only after heavy investment by European companies in handling and shipping installations in Thailand, encouraged by the government, that Community imports, particularly those from Thailand, started their dramatic increase. Total imports rose from just over 2 million tons in 1974 to almost 3 million tons in 1976 and 6 million tons in 1978. Owing to supply difficulties, imports fell in 1979 to 5.4 million tons and decreased further in 1980 to 4.9 million tons, which, nevertheless, represented an increase of 135% over 1974 imports. Provisional figures for 1981 suggest an increase of 1.7 million tons, bringing the total quantity imported to over 6.5 million tons.

During the period under review, Thailand, although not the world's largest producer, with an output slightly less than that of Indonesia and only half that of Brazil, has been by far the principal source of manioc, supplying between 84% and 96% of imports. The increase of 189% in total supplies between 1974 and 1978 was easily surpassed by Thailand, whose exports rose by 225% over this period, thus boosting their share to 95% of total imports. Thailand's

1978 record of 5.67 million tons has not since been exceeded; in fact, imports from Thailand declined by 1.5 million tons within the next 2 years. Due to a large crop, however, imports from Thailand in 1981, at an estimated 5.5 million tons, will almost return to 1978 levels. This represents an increase of 216% over 1974 values, which is slightly higher than the increase for all imports.

Indonesia, the second most important source of manioc, has been a much more erratic supplier than Thailand. Its share of the market has ranged from as low as 4% in 1977 and 1978, with 144 000 and 219 000 tons, respectively, to 14% in 1975. A record tonnage of 694 000 in 1979 went a long way toward compensating for the decrease in supplies from Thailand. Shipments decreased to 372 000 tons in 1980 to reduce the Indonesian market share to 8%.

The only other supplier of manioc to the Community of any importance during recent years has been China, whose exports when added to those of Thailand and Indonesia account for more than 98% of total supplies. Imports from China have grown very rapidly over the last 2-3 years. During the period 1974-1976, China averaged 5000 tons per year. Quantities fell to a mere 1000 tons in 1977 and 1978 but increased to 51 000 tons in 1979, 336 000 tons in 1980, and an estimated 560 000 tons in 1981. Thus, in 1981 China will replace Indonesia (470 000 tons) as the second most important supplier of manioc and gain an 8.5% share of the market.

Smaller and more variable suppliers of manioc include Brazil, whose average quantity between 1978 and 1980 was 14 000 tons; Malawi, averaging 2500 tons between 1978 and 1980 but with 12 000 tons in 1974; India, averaging 25 000 tons between 1978 and 1980; and Tanzania, with almost 40 000 tons in 1978, nothing between 1974 and 1977, and a 1978-1980 average of 27 500 tons.

Total imports between 1974 and 1981 have been characterized by an overall increase of more than three times, with a similar rate of increase applying to Thailand; a variable performance by Indonesia, which currently has a smaller share of the market than was the case in 1974 and 1975; and a dramatic increase by China. Thailand's performance is due mainly to the fact that, unlike nearly all other producers, manioc cultivation in Thailand is geared and organized toward export and animal feed, whereas elsewhere the crop is intended primarily for domestic human consumption and forms a vital element in local diets. Consequently, a number of the world's largest producers, such as Brazil, Zaire, and Nigeria, are far from being the largest exporters.

Table 3 presents the destination countries for manioc imports within the Community. Three countries, Germany, the Netherlands, and Belgium/Luxembourg, usually take at least 90% of Community imports, with Germany and the Netherlands accounting for more than 70%.

The Netherlands, the Community's dominant importer, has seen its imports grow from an average of 1.15 million tons in 1974 and 1975 to 2.7 million tons in 1978. A downward trend in 1979 and 1980, caused by supply difficulties, resulted in a decrease in imports to about 2.4 million tons. Preliminary figures for 1981 indicate that imports will resume their upward movement and should reach about 3.4 million tons.

Germany usually accounts for between 20 and 25% of total imports. Quantities rose from 430 000 tons in 1974 to 1.44 million tons in 1978. Following a temporary drop to around 1.26 million tons in 1980, they are estimated to rise again to about 1.33 million tons in 1981.

Belgium/Luxembourg, the third largest user, regularly imports between 15 and 20% of the Community's total, with an average quantity for 1978-1980 of about 835 000 tons. Belgium imports a much larger proportion of its supplies from Indonesia and China than do the Netherlands and Germany. For example, in 1979 and 1980, an average 25% of Belgian imports were supplied by Indonesia, which was more than twice the Community average of 11%. As is the case with other major importers, quantities are estimated to rise in 1981 (to about 925 000 tons).

France tends to import a larger proportion of its supplies from Indonesia, partly because French ports find it easier to handle the smaller ships used in this trade. Over the last 3-4 years, France has taken just under 10% of total Community imports.

The United Kingdom, whose imports until recently were extremely small, has now started to use manioc in its compound feeds. Total imports for 1981 are estimated to reach about 140 000 tons, compared with an average of 14 000 tons during the previous 3 years.

Despite recent increases in the use of manioc in countries such as the United Kingdom and Italy, the Netherlands, Germany, and, to a lesser extent, Belgium/Luxembourg remain by far the biggest users in the Community.

As stated earlier, the Community's manioc imports are used almost entirely in animal feed

Table 3. Imports of manioc by importing country (tons).

	Germany	France	Italy	Netherlands	Belgium/ Luxembourg	United Kingdom	Ireland	Denmark
1974	429764 (21)	164588 (8)	596	1085923 (52)	357554 (17)	30848	5	3340
1975	483909 (22)	146399 (7)	—	1232037 (55)	352985 (16)	6876	—	—
1976	663912 (22)	173243 (6)	12857	1508392 (51)	611774 (21)	7082	927	6241
1977	908988 (24)	190997 (5)	26	2024988 (53)	617143 (16)	5198	1604	51737
1978	1437704 (24)	644504 (11)	219152	2687878 (45)	883042 (15)	12233	8270	83587
1979	1402118 (26)	527784 (10)	189817	2335090 (43)	867043 (16)	21431	9363	22210
1980	1260843 (26)	331814 (7)	98869	2388839 (49)	757486 (16)	8229	8223	11519
1981 (estimated)	1325000	590000	240000	3350000	925000	140000	NA	NA

NOTES: Values in parentheses are percentages of total. NA = not available.

and particularly in pig rations, which utilize about 75% of imports; poultry and cattle feed share the rest almost equally.

In those areas of the Community that have easy access to the large unloading ports on the North Sea, but are far from surplus grain areas, manioc comprises up to 30–40% of pig and poultry compounds. For dairy cattle, the maximum manioc content is lower, at about 20%, but only about 10% is normally used. The rate of incorporation of manioc varies widely across the Community. In all compounds in 1979, the Community average was 7%, ranging from 17% in the Netherlands and 15% in Belgium to 4% in France and 2% in Italy.

As to the future, particularly with respect to whether or not the dramatic rate of increase in the use of manioc in animal feed observed over the last decade will continue, sight must not be lost of two very important factors. First, the proposed reduction in the gap between Community cereal prices and those on the world market should make cereals more competitive for use in feed and, second, given current economic conditions, it is far from certain that the dynamic development in animal production achieved in the European Community during the 1970s will continue during the 1980s.

Cassava Research to Overcome the Constraints to Production and Use in Africa

S.K. Hahn[1]

Annual African production of 47 million tons of cassava, grown on 6 million ha, comprises 38% of the global production from 50% of the total world area under cultivation (FAO 1980). Cassava provides more than 50% of the caloric requirement for over 200 million inhabitants of Africa and is thus an important staple food crop in tropical Africa (Hahn et al. 1979). In addition, in Africa, cassava leaves are also used as the preferred vegetables in many countries.

Cassava adapts well to diverse environmental conditions and farming systems in Africa. It requires few skills and inputs and gives relatively good yield. Planting and harvesting are not seasonal and the crop can be kept in the ground for up to 24 months and harvested when required. Cassava is relatively drought tolerant and can survive even 4–6 months of dry weather.

Under favourable conditions, it can recover from the damage caused by a severe incidence of insect pests, disease, bush fires, or frost. For these reasons, it has played a vital role, since its introduction, in alleviating famine in Africa by providing a sustained food supply when other crops failed. Cassava is now widely grown from the humid to the semi-arid regions of tropical Africa.

In Africa, cassava tuberous roots are used mainly as food and are a major source of carbohydrates. Cassava leaves are used as a vegetable and are an important source of vitamins, minerals, and proteins. However, tuberous roots and leaves require tedious processing procedures to reduce their cyanide content and to meet consumer acceptance standards. Transportation of fresh tuberous roots and planting sticks is difficult because of the bulk and perishability. Even the processed products are not stored for long periods of time.

In Africa, the average cassava yield of 6.4 tons/ha is low compared with the world average yield of 8.8 tons/ha. This average yield has declined since 1975 due to severe diseases, and particularly insect pests, which were accidentally introduced from Latin America. As a result, the total acreage devoted to cassava has been increased to compensate for the lower yield per unit area. Cassava production costs and prices to consumers, consequently, have gone up in many African countries and are often higher than those for cereals.

Constraints to Production

Diseases

The major diseases affecting cassava in Africa are cassava mosaic (CMD), bacterial blight (CBB), and anthracnose (CAD) diseases. CMD is one of the most severe and widespread diseases in all of the cassava-growing areas in Africa and India, causing yield reductions of up to 90% in severely infected crops.

CBB has been reported to be very serious in the major cassava producing countries in Africa. Heavy infection with CBB can lead to total crop failure, because most local varieties are highly susceptible to the disease.

CAD, caused by *Colletotrichum* spp., is a stem disease in the grassland savanna regions of Central Africa, where soils are infertile and acidic and populations of the insect (*Pseudoteraptus devastans*), which is associated with transmitting the disease, are high.

Insect Pests

The important insect pests in Africa are the

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cassava mealybug (CMB) (*Phenacoccus manihoti*) and the green spider mite (CGM) (*Mononychellus tanajoa*).

CMB is native to Latin America, where it is a minor pest, but it has become the most serious pest of cassava in Africa since it was first reported in Zaire in 1973 (Hahn and Williams 1973). CMB now threatens cassava production in two-thirds of the cassava-growing areas in Africa. Usually, damage appears first on the growing points. The damaged leaves are bunched and stems are stunted. Severe attacks cause serious leaf loss and up to 60% reduction in tuberous root yield.

CGM, which is also indigenous to Latin America, was first reported in Uganda in 1972 (Nyiira 1972). It now occurs in almost all of the cassava-growing countries in Africa. The pest causes damage mainly to the young leaves, resulting in a dramatic leaf area reduction of 95%. CGM can cause die-back when the shoots are heavily attacked (Hahn et al. 1979). A yield loss in tuberous roots of more than 40% has been reported (Nyiira 1975). Leaf yield can also be severely affected.

Grasshoppers (*Zonocerus* spp.)

Grasshoppers are a dry-season pest and the only pest that feeds on the whole leaf. They have frequently been reported as being the cause of serious damage to cassava in West Africa (Bernays et al. 1977).

Nematodes

Cassava is very susceptible to root-knot nematodes (*Meloidogyne incognita* and *M. javanica*). Moderate to heavy infestations by these pests can cause yield losses of up to 50%. Inferior planting sticks are also produced due to the slender stems that develop as a result of root-knot nematode attack.

Weeds

Slow development and serious damage of plants by diseases and pests make cassava plants very susceptible to weed competition during the first 10–12 weeks of growth. Delaying the first weeding by more than 2 months has been reported to cause over 20% reduction in tuberous root yield. However, total crop failure has frequently been observed due to the compound effects of weeds, diseases, and pests.

Increasing population pressure, together with the attendant shortening of fallow periods, favours the growth and establishment of annual weeds, perennial grasses, and semi-woody perennial broad-leaved weed species. In addition, the growth cycle of cassava and the traditional practice of using cassava as the last crop before a bush fallow encourages perennials, which cannot be easily controlled (Hahn et al. 1979).

Soil and Cultural Factors

Some cassava varieties, particularly those that are susceptible to diseases and pests, promote soil erosion because of poor and slow canopy development. Soil loss of 3, 87, 125, and 221 tons/ha were reported in areas where cassava was grown on slopes of 1, 5, 10, and 15% respectively. Continuous cultivation of cassava, without adequate erosion control measures, can result in severe and irreversible soil degradation (Hahn et al. 1979).

Socioeconomic Factors

Increasing deficits in food production in tropical Africa have been met by larger imports of cereals, mainly in the form of food aid. Between 1970 and 1980, gross cereal imports by the countries of tropical Africa increased approximately 11% per year — equivalent to doubling every 6.5 years. The urban and, to some extent, rural populations are becoming accustomed to food made from cereals that cannot be grown in most of tropical Africa. The rate of urbanization in Africa is very high, at more than twice the overall rate of population growth. These factors are discouraging the production of cassava.

Most of the cassava produced in African countries is used for human consumption. Tedious and complicated processing of both storage roots and leaves into various forms is required and carried out by smallholders. Processing is still accomplished following traditional methods that are labour intensive. Jones and Akinrele (1976) note that labour is probably an even more binding constraint on *gari* production in Nigeria than it is on crop production. This makes cassava less competitive with cereals. One of the most neglected concerns in agriculture has been transportation, particularly that from the cropping area to the farmer's residence or processing point.

Yield

For the reasons stated above, cassava yield is very low (6.4 tons/ha) and is gradually decreasing in Africa.

Overcoming the Constraints

Control of Diseases, Insect Pests, Nematodes, and Weeds

Vegetative propagation of cassava has ensured the maintenance of diseases and insect pests. Because cassava is a low-income crop, generally grown by smallholders with low annual incomes, chemical control of diseases and pests is uneconomical and may not be acceptable to the farmers. In view of the present farming systems and social factors in Africa, replacement with disease- and insect-free planting material is difficult. The most severe diseases and insect pests are already widely spread, the vector populations are high, and methods of eradicating certain diseases and insects are complicated. For these reasons, effective control of diseases and insect pests will have to be achieved primarily through the use of resistant varieties and partly through biological control of certain insect pests.

The populations of soil-borne pathogens and nematodes can be reduced or eliminated by rotating cassava with other crops or by fallowing.

Control of Insect Pests

The most economical method of controlling grasshoppers with insecticides is by spraying the nymphs soon after they hatch, because the first instars hatched from the oviposition site exhibit a strong gregarious behaviour (COPR 1975). Several hundred cassava clones have been screened for resistance to grasshoppers. Some clones have indicated a certain amount of tolerance in that the shoots and stems were not damaged by grasshoppers.

Low cyanide cassava varieties are most severely damaged by grasshoppers (Terry et al. 1977). The older the leaves of the plant, the lower the cyanide content and the greater the damage inflicted by grasshoppers. Similar information has been presented by Bernays et al. (1977).

Cassava clones resistant to both CMB and CGM have been identified. A factor responsible for their resistance to the pests appears to be a pubescent covering on the surface of upper young leaves.

Figures 1 and 2 show the relationships between CMB and CGM resistance ratings and hair density on the leaf upper surface. The hair density on the leaf upper surface is highly correlated with that on the leaf under surface,

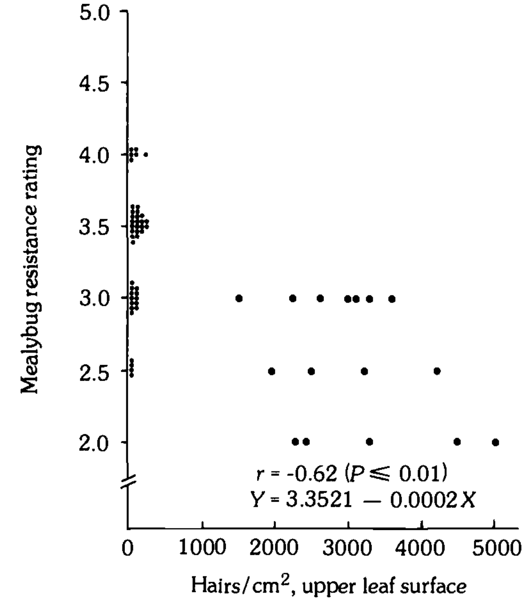

*Fig. 1. Relationship between number of hairs/cm² on upper surface of fully expanded cassava leaf and cassava mealybug (*Phenacoccus manihoti*) damage ratings (rating 0, no damage; rating 5, severe damage). (Slope of line significant at $P \leq 0.01$.)*

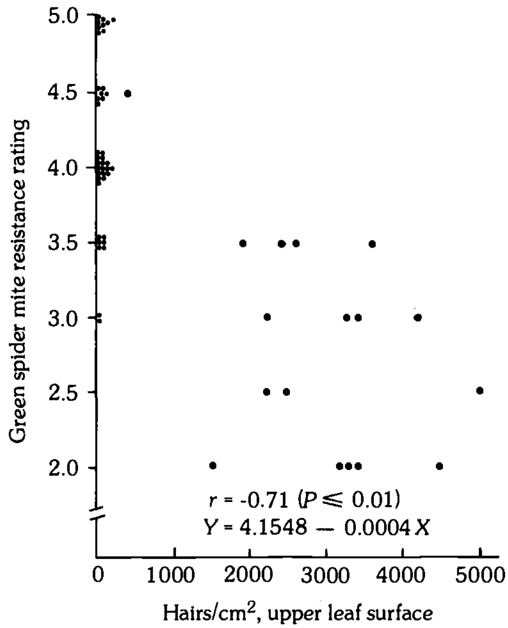

*Fig. 2. Relationship between number of hairs/cm² on upper surface of fully expanded cassava leaf and green spider mite (*Mononychellus tanajoa*) damage ratings (rating 0, no damage; rating 5, severe damage). (Slope of line significant at $P \leq 0.01$.)*

petiole, and young stem. Preliminary results indicate that another mechanism of resistance to CMB exists in addition to pubescence. Genetic sources for higher levels of resistance to CMB are being sought.

The most promising clones at present, in terms of resistance to the pests and diseases and combined with adequate yield and consumer acceptance, are TMS 4(2)1425, 60142, 42025, and 61324 (Hahn et al. 1981).These are being rapidly multiplied and distributed to farmers in Nigeria, and their hybrid seeds are being used in national programs on selection of resistant cassava varieties. The meristem tip of the resistant clones will also be used in national programs after disease indexing.

Many natural enemies of CMB, collected by the Commonwealth Institute of Biological Control (CIBC), have been introduced into Nigeria with the approval of the Nigeria quarantine authorities. One predator (*Scymnus* spp.) and one parasitoid (*Apoanagyrus lopezi*) have been raised and released in the field at the International Institute of Tropical Agriculture (IITA). They have successfully established themselves in the field (Herren and Lema 1981).

They are now being distributed to several countries in Africa for release and testing. The complementary effect of host plant resistance to disease and the presence of natural enemies of the pests will allow the problems to be maintained below economic damage thresholds. It was found that planting early during the rainy season also reduced the damage caused by CMB and CGM.

Control of Diseases

Significant progress has been made in producing improved cassava varieties and populations that are resistant to diseases (especially to CMD and CBB). The improved varieties are high yielding (20–30 tons/ha), have desirable root characteristics, are resistant to lodging, meet consumer quality standards, and are low in cyanide content.

Cassava that is resistant to CMD in Nigeria maintains its resistance when planted in the cassava-growing countries in West Africa, Central Africa, East Africa, and Asia (India). The high level of resistance to CBB also holds true in countries of West Africa and Central Africa, where the disease is present. Seeds from the improved varieties and populations resistant to CMD and CBB and that possess other desirable agronomic characteristics have been supplied to many countries in Africa and Asia (India).

Improved varieties originally resulting from IITA breeding programs have been produced and released in Sierra Leone, Guinea, Liberia, Benin, Nigeria, Gabon, Zaire, Tanzania, Rwanda, and Seychelles. They are continuously in great demand by farmers in these countries.

Control of Root-Knot Nematodes

Several hundred cassava germ-plasm accessions have been tested for resistance to root-knot nematodes but none with a high level of resistance has been identified. Efforts are being directed toward finding a source with high levels of resistance from both cultivated and related *Manihot* species.

Rotation of crops and fallow systems, which reduce root-knot nematode populations, seem to be the best method of minimizing nematode damage. Suggested rotation crops for West Africa are groundnut (*Arachis hypogaea*), centro (*Centrosema pubescens*), giant star grass (*Cynodon nlemfuensis* cv IB-8), and stylo (*Stylosanthes gracilis* L) (F.E. Caveness, personal communication).

Weed Control

Promising weed control methods include improved timing of hoe-weeding, chemical weed

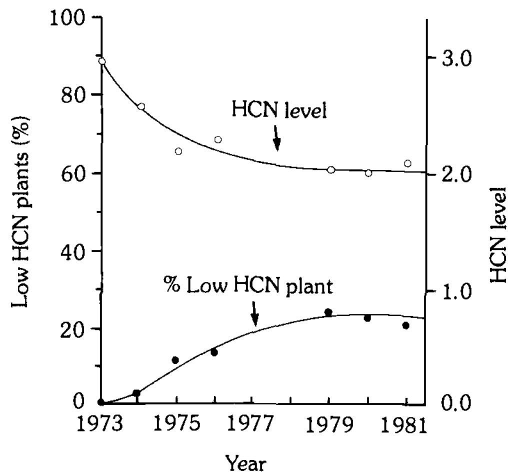

Fig. 3. Improvement of cassava for low cyanide in terms of frequency of low cyanide plants and cyanide levels over 9 years, since 1973, through continuous recombinations and selections based on picrate leaf-test.

control, and integrated weed control methods. Hoe-weeding at 3 and 8 weeks after planting resulted in good weed control and crop yield. Excellent weed control has been obtained with pre-emergence application of fluometuron (2.0–3.0 kg/ha), diuron (2.0 kg/ha), and a formulated mixture of atrazine plus netolachlor, provided that the rate of atrazine in the mixture does not exceed 1.0 kg/ha. Repeated application of paraquat with a proper sprayer has also been effective. In the improved disease resistant cassava varieties with good canopy, yield reduction due to weeds is kept at a minimum either by hoe-weeding at 3 and 5 weeks after planting or using a selective pre-emergence herbicide (Hahn et al. 1979).

Improvement of Cultural Practices

Intercropping characterizes traditional cropping systems in Africa. Cassava is commonly intercropped with vegetables, plantains, yams, sweet potato, melon, maize, rice, and legumes; however, intercropping with shorter duration (2–5 month) crops is most profitable.

Okigbo (1977) reported that the highest yield of component crops in maize–cassava intercropping, which is commonly practiced in Africa, is obtained when the cassava is planted at the same time as the maize or not more than 2 months later. Mulching with chipped cassava stems, rice straw, or maize stover improves soil temperature and moisture regimes, increases or sustains soil fertility and organic matter content, suppresses weeds, reduces erosion, and reduces damage by mealybug and green spider mite, which collectively results in higher yields (IITA 1975).

Improvement of Cassava for Low Cyanide Content

Cassava contains a large amount of cyanide both in the tuberous roots (5–40 mg/100 g of fresh weight) and in the leaves (100–400 mg/100 g of fresh weight). At IITA, the breeding of cassava for low cyanide has been ongoing since 1973, when Sadik et al. (1974) evaluated 88510 cassava seedlings using the picrate leaf-test method and selected 92 (0.1%) seedlings as being low in cyanide. The results of cassava improvement for low cyanide at IITA, using the picrate leaf-test method, over the past 9 years are shown in Fig. 3. The population for low cyanide has been significantly improved

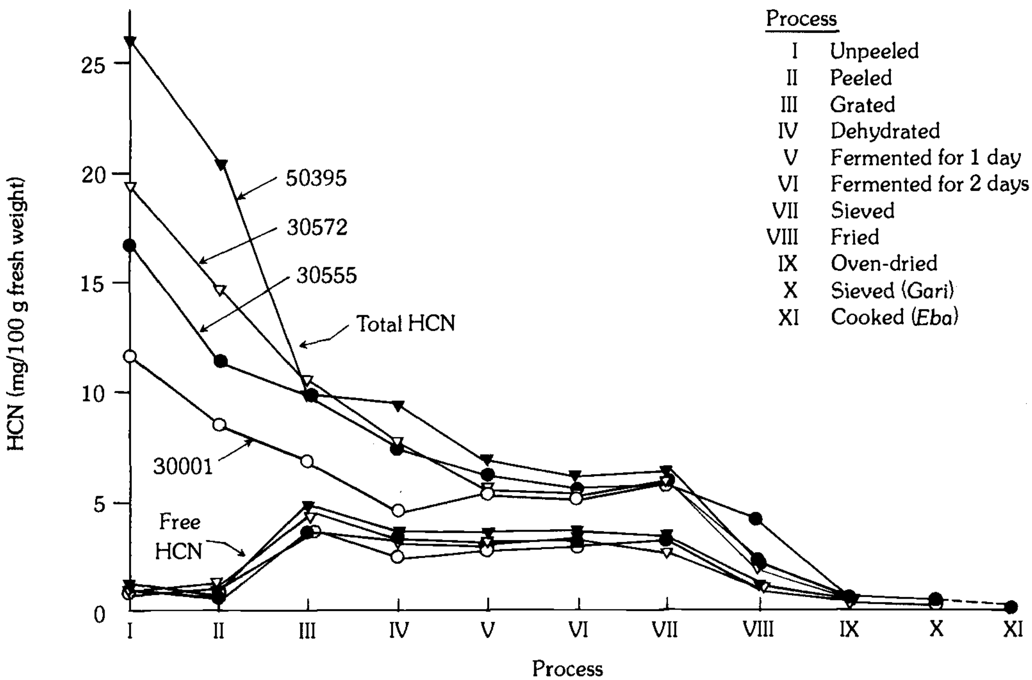

Fig. 4. Effect of traditional processing of four varieties of cassava tuberous roots, in the preparation of gari, *on total and free cyanide content at each respective stage of processing.*

through continuous recombination and selection but remained at a frequency of about 25% low cyanide seedlings within the population after 5–6 years of selection. No further progress in increasing the frequency of low cyanide seedlings in the populations is likely to be made with the picrate leaf-test method and the resources available at IITA. This may be due to (1) inaccurate screening methods, (2) genetic reasons (close linkage between the genes controlling the enzymes involved), or (3) a narrow genetic basis. The plants found to have low, medium, or high cyanide by the picrate leaf-test method had average cyanide levels of <80, 80–200, or >200 mg/100 g of fresh leaf weight respectively. Cooke et al. (1978), using an enzymatic assay method, determined quantitatively the cyanide content of the peeled tuberous roots of 108 cassava clones selected as being low in cyanide by the picrate leaf-test method and compared them with picrate leaf-test ratings. The correlation coefficient between the cyanide content in the tuberous roots (dry-weight basis) and leaf-test ratings was $r = 0.36$ ($P \leqslant 0.01$). This served as the basis of screening cassava-breeding material for low cyanide at IITA; screening large numbers of seedlings and clones at an early stage of breeding followed by rescreening them using the more reliable quantitative enzymatic method at a later stage of breeding.

An automated analysis for cyanide has been developed adopting Cooke's enzymatic manual method; the automated method enabling analysis of 300 samples per day (40 samples/hour) compared with 40 samples per day by Cooke's method (Rao and Hahn 1981).

Realized heritability for low cyanide has been estimated as 43%, using data obtained by picrate leaf-testing of seedlings (IITA 1974). Broad sense heritability has been estimated as 66%, using total cyanide data obtained by the enzymatic method from a field trial in a randomized complete block design with four replications each for seven clones.

Relatively high yielding (15–25 tons/ha), low cyanide (5.0–10.0 mg/100 g fresh tuberous root

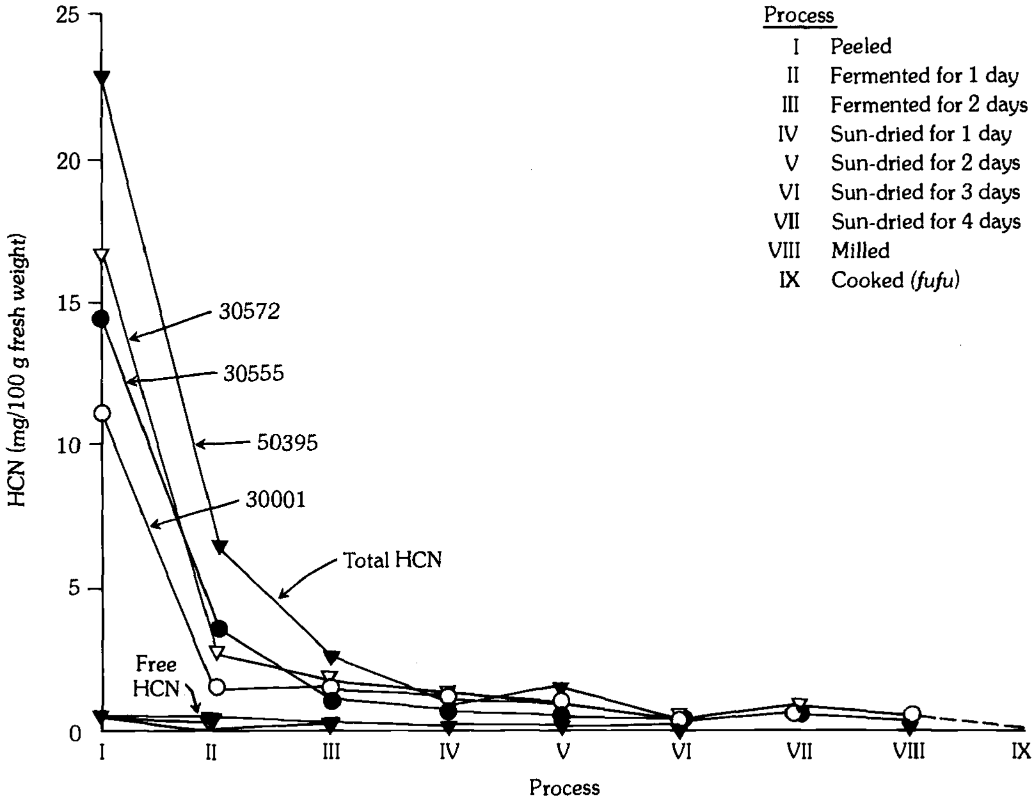

Fig. 5. Effect of traditional processing of four varieties of cassava tuberous roots, in the preparation of fufu, *on total and free cyanide content at each respective stage of processing.*

weight) varieties and resistant to CMD and CBB have been produced.

Low and high cyanide seedlings within 20 families were compared for plant height and stem diameter. Low cyanide seedlings were shorter in plant height and smaller in stem diameter than the high cyanide seedlings (Table 1). This may indicate that low cyanide cassava does not grow as well as cassava with a higher cyanide content. This may also explain, in general, the poorer performance of low cyanide varieties compared with high cyanide varieties.

Effect of Cassava Mosaic Disease on Cyanide in Leaves

Both free and total cyanide content in leaves decreased as CMD ratings increased ($r = -0.74$ ($P \leqslant 0.01$), $y = 76.62 - 6.74x$). The leaves with more chlorotic spots due to CMD were lower in cyanide content (Mahungu and Hahn 1981a). This may be one reason why most of the people in Africa who consume cassava leaves as a vegetable prefer leaves affected by CMD.

Table 1. Comparison of average plant height and stem diameter between low and high cyanide cassava seedlings from 20 families.

Cyanide level	Plants observed	Plant height (cm)	Stem diameter (cm)
Low	45	92.2	1.09
High	368	152.0	1.70
Difference		59.8 ($P \leqslant 0.01$)	0.61 ($P \leqslant 0.01$)

Effect of Traditional Processing Methods on Cyanide

Traditional processing of cassava tuberous

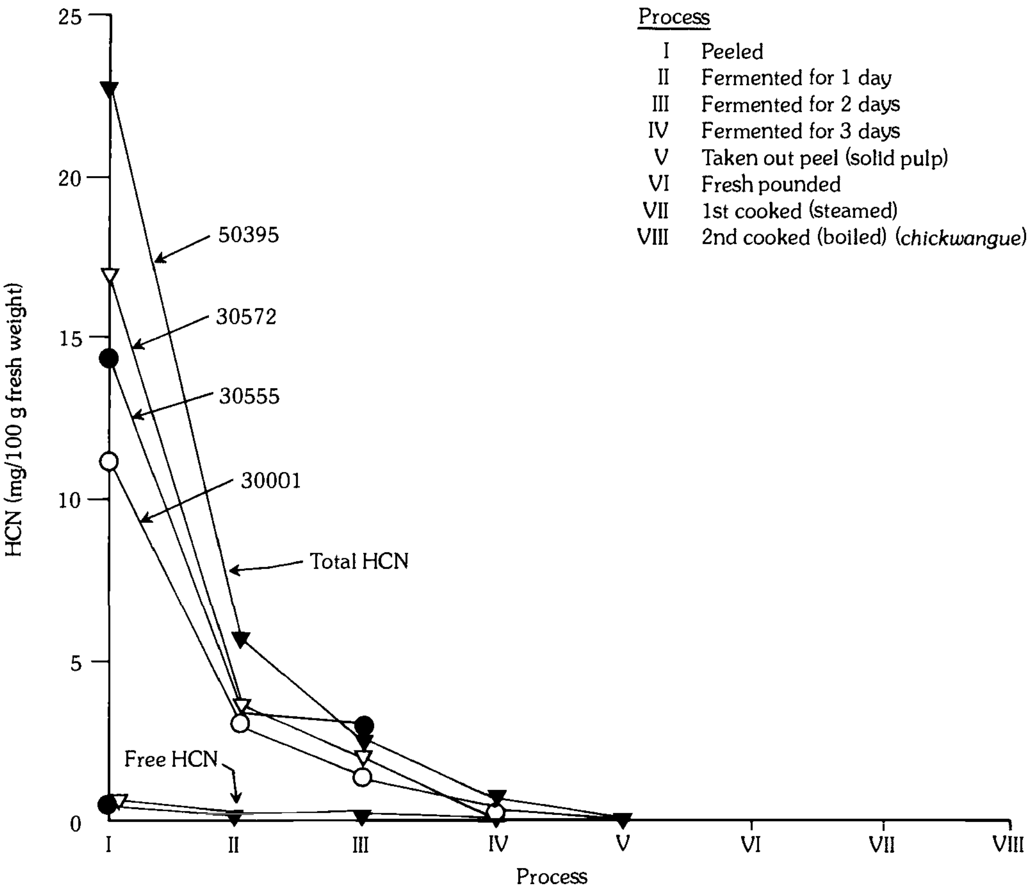

Fig. 6. *Effect of traditional processing of four varieties of cassava tuberous roots, in the preparation of* chickwangue, *on total and free cyanide content at each respective stage of processing.*

roots in Africa includes such procedures as removing peels, grating, fermentation (in water or in a sack), boiling, frying, sun-drying, and pounding, depending on the products being made (*gari*, *fufu*, *chickwangue*). Cassava leaves are first soaked in hot water (60°C) for 2-5 min, pounded, and dehydrated before cooking.

Tuberous roots from six varieties were fermented in water and the effect of fermentation on cyanide content was studied. Total cyanide contents in the peeled fresh tuberous roots, ranging from 4.45–17.75 mg/100g of fresh weight, were reduced to a range of 0.13–0.60 mg/100 g of the fermented tuberous roots on the 3rd day of fermentation and after removing the chaffs. Nearly 95% of the original

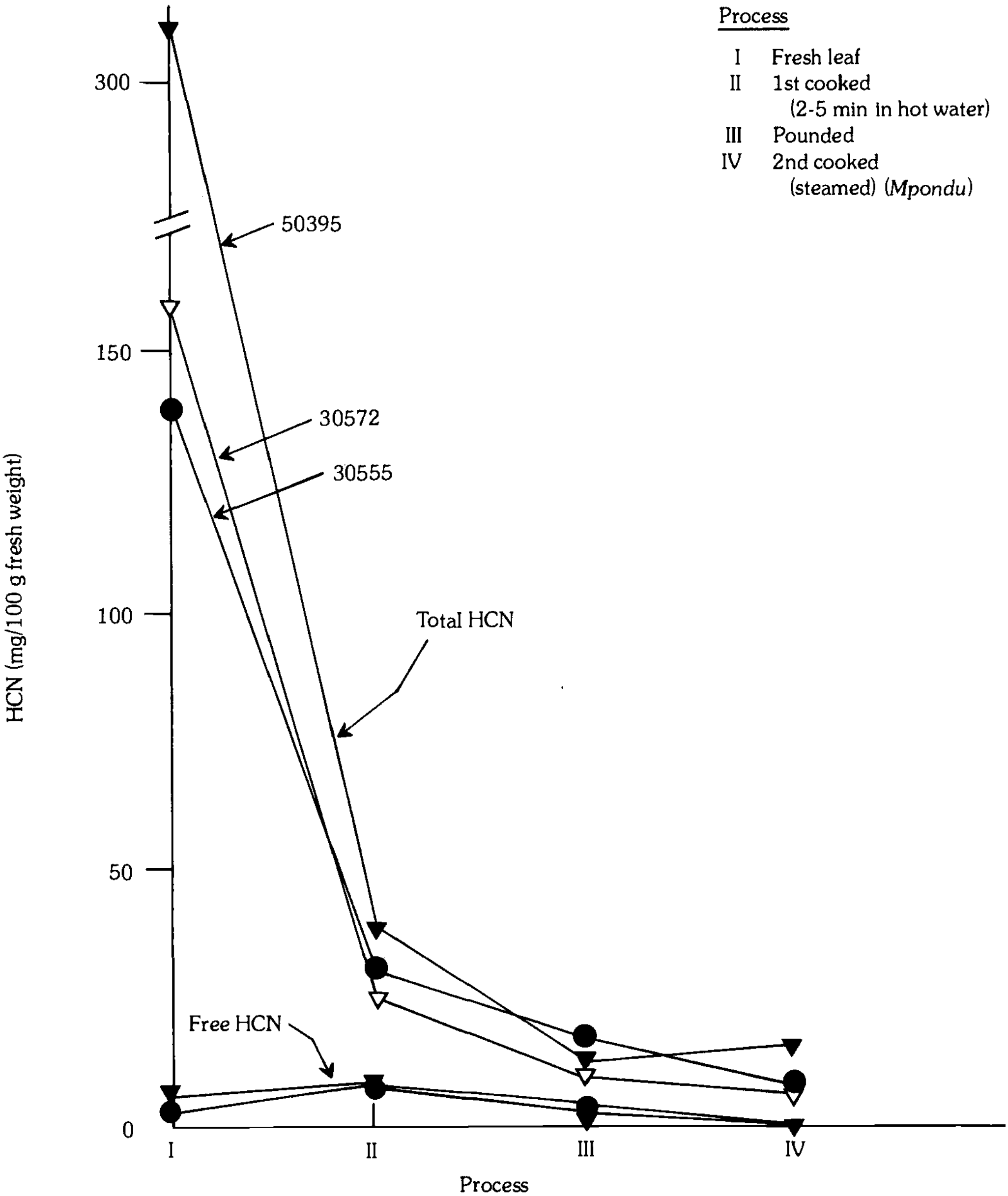

Fig. 7. Effect of traditional processing of three varieties of cassava leaves, in the preparation of mpondu *or* sakasaka, *on total and free cyanide content at each respective stage of processing.*

total cyanide in the fresh tuberous roots was hydrolized or diffused into the water. However, the free cyanide content increased on the 1st and 2nd day of fermentation. It decreased, however, to a range of 0.1–0.3 mg/100 g on the 3rd day of fermentation (Mahungu and Hahn 1981b).

To process cassava to make *gari*, the fresh tuberous roots from four varieties with different cyanide levels were peeled, grated, dehydrated, fermented for 2 days, and fried. Cyanide contents were assessed at each of the successive steps to observe any changes in cyanide content as the procedures progressed. The results are shown in Fig. 4.

Throughout the processing procedures, all of the cassava varieties, even the high cyanide varieties, showed drastic decreases in cyanide content. Similar trends were also observed during the processing of tuberous roots to prepare *fufu* and *chickwangue* (Figs. 5, 6). Processing of cassava to prepare *fufu* and *chickwangue* is more successful in reducing cyanide than processing cassava to prepare *gari* (Yamaguchi et al. 1981).

A total of 202 *gari* samples from major cassava-growing areas in Nigeria were assessed for cyanide content (Table 2). The mean cyanide content of *gari* was 0.6 mg/100 g of *gari*, with a standard deviation of 0.50.

When cassava leaves from three varieties were processed by traditional methods into *mpondu* or *sakasaka*, which are the most popular dishes made from cassava leaves in Africa, cyanide was reduced by 90%, but it still remained relatively high at about 20 mg/100 g of processed leaves (Fig. 7) (Yamaguchi et al. 1981).

Sample Size for Cyanide Assay

Standard errors of means were estimated for a varying number of plants, using the data from

Table 2. Frequency distribution of cyanide content in *gari* for 202 samples from major cassava-growing areas in Nigeria.

Cyanide content (mg/100g)	Frequency
0.0–0.4	69
0.4–0.8	86
0.8–1.2	17
1.2–1.6	21
1.6–2.0	5
2.0–2.4	2
2.4–2.8	0
2.8–3.2	2

Table 3. Frequency distribution of total protein content in cassava leaves for 150 clones.

Classes (% protein)	Frequency (%)
20.0–22.0	2.65
22.0–24.0	10.60
24.0–26.0	31.76
26.0–28.0	33.78
28.0–30.0	16.56
30.0–32.0	0.66

leaf cyanide level ratings by the picrate leaf-test method (which uses a rating of 1 for low, 2 for medium, and 3 for high cyanide). The results showed that one observation each for 4–5 plants per clone may be statistically appropriate for the leaf cyanide assay using the picrate leaf-test method.

Standard errors of means were also estimated using the tuberous root cyanide data obtained with the enzymatic method from a trial in a randomized complete block design with four replications for seven clones with varying levels of cyanide. Two plants from each plot were observed. The results showed that 2–3 plant observations per plot for 2–3 replications (blocks) appeared to be statistically appropriate for the root cyanide assay using the enzymatic method to confirm cyanide levels quantitatively, subsequent to a qualitative picrate leaf-test.

Leaf Protein

A total of 151 clones were evaluated for total leaf protein content. The total leaf protein content ranged from 20.0–30.0% with a mean of 26.1% on a dry-weight basis (Table 3). The broad sense heritability for total protein content was estimated to be 32%. Significant correlation (r = 0.56 ($P \leq 0.01$)) between protein content in leaves and CBB was observed but not with fresh tuberous root yield, dry-matter percentage, or CMD ratings (Mahungu et al. 1981).

Bernays, E.A., Chapman, R.F., Leather, E.M., McCaffery, A.R., and Modder, W.W.D. 1977. The relationship of *Zonocerus varigatus* (L) with cassava (*Manihot esculenta*). Bulletin of Entomological Research, 67, 391–404.

Center for Overseas Pest Research (COPR). 1975. Control of *Zonocerus varigatas* L. in Nigeria. Second Interim Report, 1973–1974, London, England, 57 p.

Cooke, R.D., Howland, A.K., and Hahn, S.K. 1978. Screening cassava for low cyanide using an enzymatic assay. Experimental Agriculture, 14, 367–372.

Food and Agriculture Organization of the United Nations (FAO). 1980. 1979 production yearbook. Rome, Italy.

Hahn, S.K. and Williams, L. 1973. Investigations on cassava in the Republic of Zaire. Report au Commissaire d'État a l'Agriculture, Republic of Zaire, 1-12.

Hahn, S.K., Terry, E.R., Leuschner, K., Akobundu, I.O., Okali, C., and Lal, R. 1979. Cassava improvement in Africa. Field Crop Research, 2.

Hahn, S.K., Ng, S., and Chukwuma, E. 1981. Pubescence in cassava and resistance to both cassava mealybug and green spider mite. In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

Herren, H.R. and Lema, K.M. 1981. Biological control of cassava mealybug (*Phenacoccus manihoti*). In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

International Institute of Tropical Agriculture. 1974. 1974 IITA annual report. Ibadan, Nigeria, 127 p.

1975. 1975 IITA annual report. Ibadan, Nigeria, 37-46.

Jones, W.O. and Akinrele, I.A. 1976. Improvement of cassava processing and marketing. International Institute for Tropical Agriculture, Ibadan, Nigeria, 1-53 (mimeo).

Mahungu, N.M. and Hahn, S.K. 1981a. Effect of cassava mosaic disease on cyanide in leaves. In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

1981b. Effect of fermentation on cyanide content in cassava storage roots. In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

Mahungu, N.M., Yamaguchi, Y., and Hahn, S.K. 1981. Screening cassava leaves for protein content. In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

Nyiira, Z.M. 1972. Report of investigation on cassava mite *Mononychellus tanajoa* Bondar. Kwanda Research Station, Kampala, Uganda, 14 p.

1975. Advances in research on the economic significance of the green cassava mite (*Mononychellus tanajoa*) in Uganda. In Terry, E. and MacIntyre, R., ed., The International Exchange and Testing of Cassava Germ Plasm in Africa: Proceedings of an Interdisciplinary Workshop held at IITA, Ibadan, Nigeria, 17-21 November 1975. International Development Research Centre, Ottawa, Canada, IDRC-063e, 27-29.

Okigbo, B.N. 1977. Preliminary cassava interplanting trials. Paper presented at the 1st National Cassava Workshop of the National Accelerated Food Production Program (NAFPP), Umudike, Nigeria, 20 p.

Rao, P. and Hahn, S.K. 1981. An automated enzymatic assay for determining the cyanide content of cassava (*Manihot esculenta* Crantz) and cassava products. In 1981 IITA Annual Report. International Institute of Tropical Agriculture, Ibadan, Nigeria (in press).

Sadik, S., Okereke, O.U., and Hahn, S.K. 1974. Screening for acyanogenesis in cassava. International Institute of Tropical Agriculture, Ibadan, Nigeria, IITA Technical Bulletin No. 4, 4 p.

Terry, E.R., Schaefers, G.A., and Garber, M.J. 1977. Preferential feeding and damage to cultivars of Nigerian cassava by the variegated grasshopper (*Zonocerus varigatus*). Annals of Applied Biology, 85, 167-173.

Yamaguchi, Y., Mahungu, N.M., and Hahn, S.K. 1981. Effect of processing of cassava storage roots on cyanide content (in preparation).

Agricultural Research on Cassava in Asia and Australia

Gerard H. de Bruijn[1]

Until recently, research on predominantly noncommercially produced food crops, such as cassava, has been very limited. Since the late 1960s, a change in attitude toward food production has taken place throughout the world, particularly within developing countries. This, along with the increased commercial importance of cassava, has had a strong influence on stimulating new research activities on this crop. These were initiated at recently founded international research centres, such as Centro Internacional de Agricultura Tropical (CIAT) in Colombia and the International Institute of Tropical Agriculture (IITA) in Nigeria. As well, some national programs were started or enlarged. An important area of support in this field was the initiative taken by the Canadian government to support the development of an international cassava research network. The resulting activities were mainly canalized through the International Development Research Centre (IDRC) (Nestel and Cock 1976). Apart from IDRC's support of the cassava program at CIAT, a variety of cassava development projects were started all over the tropics (Nestel and Cock 1976). Different Asian institutions were supported by this program. IDRC's support for Asian root crop studies, primarily cassava, has surpassed CDN$2.5 million during the period between 1971 and 1980 (P. Stinson, personal communication).

This paper deals with the recent development of cassava research activities in Asia and Australia. Information on recent and present programs was obtained, in part, through direct contact with research workers from a number of the main research centres. In order to get a more complete picture of recent developments, the author conducted a survey to determine the availability of literature on cassava since 1970. For this purpose, *Abstracts on cassava* (CIAT Cassava Information Center (Vols. I-VI)) was screened for publications from Asia and Australia. Considering the thorough approach of CIAT's documentation service of world cassava literature, it was assumed that the selected abstracts would provide a sufficient representative picture of the research activities of the countries studied. These research activities are compared with the relative importance of cassava within the different countries and some conclusions and suggestions are put forward.

Production Versus Research

In Table 1, the area devoted to cassava production and the resulting yields within some Asian countries are compared with similar data from other parts of the world for the years 1969–1971, 1975, and 1980 (FAO 1975, 1980). An increase in production from 1970 to 1980 occurs all over the world, except in South America, where the area devoted to cassava production increased but yield decreased. In Asia, some countries show a tremendous increase in area and production, particularly in Thailand. The present production level of Thailand equals that of Indonesia, the leading cassava producer in Asia for a long time.

Tables 2 and 3 are based on the number of publications cited in *Abstracts on cassava* (CIAT Cassava Information Center). Table 2 groups the number of publications cited according to year and country. From 1970–1978, the total number of these papers has more than doubled. In Thailand, there is a fivefold increase, but in Malaysia the number of papers is relatively stable over the same period. There is also a significant increase in India. In Indonesia, the Philippines, China/Taiwan, and Australia, very little pertaining to cassava was

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Table 1. Area devoted to cassava production and resulting yields in some Asian countries compared with total area under production and total quantities produced in other continents.

	Area (1000 ha)			Production (1000 metric tonnes)		
	1969–1971	1975	1980	1969–1971	1975	1980
Indonesia	1424	1500	1420	10695	12920	13300
Thailand	211	429	1015	3208	6358	13500
India	352	384	370	4993	6328	6500
Vietnam	133	160	480	950	1180	4000
China	161	25?	243	1938	392?	3174
Philippines	82	90	185	436	485	1900
Sri Lanka	65	186?	55	376	727?	530
Malaysia	30	23	40	271	351	410
Other Asian countries	12	14	33	76	73	245
Asia (total)	2470	2811	3841	22943	28814	43559
Africa	5789	6057	7294	38406	43972	46773
South America	2483	2547	2610	34445	31432	30556
North and Central America	125	116	160	780	769	1024
Oceania	17	20	20	187	221	222
World (total)	10884	11551	13925	96761	105208	122134

Sources: FAO (1975, 1980).

Table 2. Number of publications cited in *Abstracts on cassava* (Vols. I-VI) from some countries in Asia and Australia.

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total
Indonesia	—	1	—	—	2	3	4	3	3	10	26
Thailand	10	4	5	8	17	14	21	29	50	10	168
India	17	6	16	23	19	17	28	33	27	3	189
Vietnam	—	—	—	—	—	—	—	—	—	—	—
China/Taiwan	—	—	—	—	3	5	3	2	3	1	17
Philippines	—	2	—	1	2	5	2	3	5	5	25
Sri Lanka	—	—	—	2	4	2	2	—	—	—	10
Malaysia	11	8	12	9	12	8	12	10	10	5	97
Others	3	2	3	1	—	3	2	3	2	2	21
Australia	—	—	1	1	2	4	3	1	11	5	28
Total	41	23	37	45	61	61	77	84	111	41	581

Table 3. Number of publications cited in *Abstracts on cassava* (Vols. I–VI), according to research subject, from some countries in Asia and Australia. (A "research intensity factor" is also calculated.)

	Indonesia	Thailand	India	China/ Taiwan	Philippines	Sri Lanka	Malaysia	Others	Australia	Total
Cultural practices	14	41	35	1	3	1	14	6	4	119
Fertilizers	3	37	21	—	1	—	9	—	10	81
Selection + breeding	1	31	22	9	2	—	3	1	—	69
Pests and diseases	3	1	39	5	4	—	5	2	1	60
Physiology/morphology	—	2	20	1	1	—	3	—	1	28
Toxicity	—	3	14	—	1	6	2	—	—	26
Processing/storage	—	15	13	—	7	1	18	2	5	61
Animal nutrition	1	24	10	—	2	1	33	5	1	77
Economics/marketing	2	9	10	—	3	1	6	2	5	38
Others	2	5	5	1	1	—	4	3	1	22
Research intensity factor	2	22	32	9	27	18	282	—	Very high	

published in 1970 but some information on cassava research activities in these countries has been published since that time.

Table 3 gives an indication of the emphasis placed upon different research subjects within the various countries. There are large differences in research emphasis between countries. India's research activities are the most balanced. Thailand's research is reasonably balanced but the limited attention given to pests and diseases is striking.

Dramatic differences among countries become clear if the national cassava production figures are compared with the number of papers cited. A "research intensity factor" for each of the countries has been calculated by dividing the total number of publications cited by the production level per year in millions of tonnes (the average of 1969-1971, 1975, and 1980) (Table 3). Accordingly, Australia has a very high cassava research intensity, followed by Malaysia. "Normal" values are obtained in India, Thailand, the Philippines, and Sri Lanka. Very low values are found in Indonesia and China/Taiwan. For Vietnam, the factor approaches zero, unless relevant work is not entering the international documentation systems. The same could also be said for China.

Country Discussions

Indonesia

Although Indonesia has led Asia in cassava production for many years, it has now been equaled by Thailand. Research activities in Indonesia are very limited. So far, most of the research has been oriented toward rice. About half of the work cited is related to research on the Mukibat system. In this system, *M. glaziovii* is grafted onto *M. esculenta*, which can lead to an increase in yield (de Bruijn and Dharmaputra 1974). Research on the Mukibat system has been carried out, since 1973, by a team at Brawijaya University in Malang, East Java, with support from IDRC. Another IDRC project on intercropping with cassava started in 1981 at the same university. Recently, the Indonesian government has indicated that Malang will be the national centre for cassava research (H. Soetono, personal communication). It is clear that there is a strong need for further extension of cassava research in view of the national importance of the crop as a local food for export.

Thailand

Thailand is the main cassava exporting country in the world, with 95% of the cassava produced being exported and the rest being used as animal feed, flour, etc. (Sophon Sinthuprama 1979).

There has been a tremendous increase in cassava production during the last 10 years (Table 1) and it seems that research activities have followed this trend, as would be expected. The Field Crop Division of the Ministry of Agriculture is devoting a lot of attention to cassava. Also, projects such as the IDRC-supported work at Khon Kaen University made an important research contribution, in this case in the field of animal nutrition. Published work indicates that quite a lot of attention is given to studying fertilizer use, cropping systems, selection, and processing. Nevertheless, farmers rarely use fertilizers; monoculture and sole cropping are the normal systems used; and none of the cultivars that have been introduced has outyielded the popular local selection Rayong No. 1 (Sophon Sinthuprama 1979). In order to safeguard continuity of cassava production in Thailand, appropriate systems of fertilization and crop rotation should be employed. A first priority of any such system would be to restore soil fertility or at least maintain it. This concern may play a central role in future research efforts in Thailand, and local researchers are, apparently, aware of it (Sophon Sinthuprama 1979).

India

During the last 10 years, India has led the rest of Asia in conducting research on cassava (Table 2) (although Thailand may be the leading country now). Most research in India is carried out at the Central Tuber Crops Research Institute (CTCRI) in Trivandrum, Kerala. This institute, established in 1963 (Hrishi 1975), is probably the largest local research institute on tuber crops in the tropics. It has a comprehensive research program, with cassava receiving high priority. The CTCRI was responsible for establishing the Indian Society for Root Crops, which has been publishing the *Journal of Root Crops* since 1975.

As discussed earlier, the cited publications (Table 3) indicate that, of the Asian countries, India has the most balanced research program in terms of the attention given to various research topics.

China/Taiwan

As in Indonesia, very little research on cassava has been conducted in China (Table 3), compared with its level of production. Almost all of the cited references are from Taiwan, which began research on cassava around 1975. Later, some work was published in Taiwan on cassava diseases.

Philippines

The Philippines has published very little on cassava (Table 3). Due to a relatively low production level, however, the research intensity factor is not very different from that of India or Thailand. According to Food and Agriculture Organization of the United Nations (FAO) statistics, there has been a large increase in cassava production in recent years, from 0.5 million tonnes in 1975 to about 2 million tonnes per year at present (Table 1).

The Philippine Root Crop Research and Training Center is currently carrying out a comprehensive research program (F.G. Villamayor, Jr., personal communication). Until recently, attention was focused on selection and breeding, cultural management, postharvest technology, and development of tools. In the near future, the research emphasis will be on processing and utilization, tool development, and cropping systems. At present, 13 studies have been completed and 55 are ongoing (F.G. Villamayor, Jr., personal communication).

Sri Lanka

Cassava research in Sri Lanka is very limited. In 1974, a project was conducted on cyanogenic glucosides, but no additional work has been cited in recent years. The geographical location of the country, however, presents an opportunity to import the technology developed at the CTCRI in Trivandrum, India. At present, IDRC is supporting a root crops program, including cassava, at the Central Agricultural Research Institute, Peradeniya (P. Stinson, personal communication).

Malaysia

Of the Asian countries, Malaysia shows the highest cassava research intensity (Table 3). The starch industry utilizes about 90% of all cassava produced. Chip production, for animal-feed mills, accounts for the remaining 10% (Tan Swee Lian et al. 1981). Only a very small fraction of local production is used directly for human consumption. The Malaysian Agricultural Research and Development Institute (MARDI) at Serdang is the major centre for root crop research, but regional centres are selected for adaptability trials. In recent years, a cassava research team has been built up at MARDI and has made a promising start. Attention has been focused on various relevant subjects such as breeding, agronomy, fertility, crop physiology, and crop protection (MARDI 1981). In addition to MARDI, the University of Malaysia is studying cassava, mainly from the point of view of improved utilization (Nestel and Cock 1976). The research program, however, is imbalanced somewhat (Table 3) and a high proportion of the work published has been on animal nutrition and processing and storage.

Australia

Although cassava production in Australia is still very limited, a series of research activities has been undertaken during the last 10 years and is being enlarged upon. This is not surprising, considering that in Queensland the estimated suitable cassava production area amounts to 500 000 ha (University of Queensland 1981). This means that Australia may become an important cassava producing country in the future. Research programs are carried out by the University of Queensland (D.G. Edwards, personal communication), Australian Cassava Products Pty. Ltd. (N.V. Harris, personal communication), and the Department of Primary Industries (G. Hammer, personal communication). Initially, the Department of Agriculture, University of Queensland, concentrated its research on plant nutrition. Now, subjects such as cultural practices and crop physiology are important components of the program. Development of a proper crop rotation system and adequate fertilizer application, to maintain high productivity, is seen as a major goal (University of Queensland 1981).

The main objective of the Australian Cassava Products Pty. Ltd. research program, on potential cassava production areas, is to develop relevant production systems for starch, animal feed, and fuel alcohol (N.V. Harris, personal communication).

The Department of Primary Industries is also investigating the potential of cassava. In this regard, cooperative work on nutrition and physiology is being conducted with the University of Queensland. This may be extended to a program for evaluating cassava roots and tops as a component in stock feed rations (G. Hammer, personal communication).

Discussion

Although many new programs have been

initiated during the last 10 years, it is clear that cassava research activities in most Asian countries are not proportionate to the local importance of the crop, especially in Vietnam, China, and Indonesia. Moreover, there are some imbalances in the research orientation of national programs. Some of these biases may be accentuated by external support for specific research programs. There appears to be a need for a number of Asian countries to evaluate research priorities, depending upon local demands and prospects for the crop, but also in relation to farmers' needs and means.

With regard to research priorities, it seems that in most countries there is a need for further development of ecologically acceptable and productive cropping and crop rotation systems for cassava. These systems should be adequate to maintain or improve soil fertility, thus safeguarding the possibility of long-term cassava production without soil exhaustion. This problem now receives high priority in Thailand, where soil depletion because of continuous cassava cultivation may be the most serious in Asia. Similarly, further investigations on plant nutrition are necessary to maintain fertility levels and to raise present relatively low yield levels.

National, international, and regional cooperation will be required to optimize output from present research efforts and to initiate new activities. This could be achieved through further strengthening of the international cassava research network (Nestel and Cock 1976). Regular contact between cassava research workers from Asian countries and discussion of the setup and progress of programs, directly or through the services of external coordinators, could be valuable.

Currently, in addition to IDRC-supported projects, other activities are taking place. CIAT has stationed a specialist in the Philippines to assist in developing and introducing new cassava production technology in Asian countries (CIAT 1980b). In 1980, the first CIAT cassava course in Asia, in which 24 trainees from five Asian countries participated, took place in the Philippines, with support from IDRC (CIAT 1981). As well, cassava researchers from Asian countries have been trained at CIAT. In addition, CIAT and IITA are providing germ plasm to interested institutions.

In view of the present, and still increasing, importance of cassava in Asian countries, continued support would be most welcome, especially for countries where research efforts are still very limited.

Centro Internacional de Agricultura Tropical (CIAT). 1975. Abstracts on cassava. Vol. I. Cali, Colombia.
1976. Abstracts on cassava. Vol. II. Cali, Colombia.
1977. Abstracts on cassava. Vol. III. Cali, Colombia.
1978. Abstracts on cassava. Vol. IV. Cali, Colombia.
1979. Abstracts on cassava. Vol. V. Cali, Colombia.
1980a. Abstracts on cassava. Vol. VI. Cali, Colombia.
1980b. CIAT report 1980. Cali, Colombia.
1981. Informe CIAT. Cali, Colombia.

De Bruijn, G.H. and Dharmaputra, T.S. 1974. The Mukibat system, a high-yielding method of cassava production in Indonesia. Netherlands Journal of Agricultural Science, 22, 89-100.

Food and Agriculture Organization of the United Nations (FAO). 1975. Production yearbook. Vol. 29. Rome, Italy.
1980. Production yearbook. Vol. 34. Rome, Italy.

Hrishi, N. 1975. Tapioca production technology, introduction. Short specialized training course on tapioca production technology. September 1975. Central Tuber Crops Research Institute, Trivandrum, India.

Malaysian Agricultural Research and Development Institute (MARDI). 1981. Field crops research programme 1981-1985. Information Paper No. 1. Serdang, Malaysia.

Nestel, B. and Cock, J. 1976. Cassava: The development of an international research network. International Development Research Centre, Ottawa, Canada, IDRC-059e, 69 p.

Sophon Sinthuprama. 1979. Cassava and cassava-based intercrop systems in Thailand. In Weber, E., Nestel, B., and Campbell, M., ed., Intercropping with Cassava: Proceedings of an International Workshop held at Trivandrum, India, 27 Nov.-1 Dec. 1978. International Development Research Centre, Ottawa, Canada, IDRC-142e, 57-65.

Tan Swee Lian, Chan Seak Khen, Chew Wee Yong, and Geh Swee Lan. 1981. The cultivation of cassava. Malaysian Agricultural Research and Development Institute, Serdang, Malaysia, 19 p.

University of Queensland. 1981. Cassava research program. Department of Agriculture, University of Queensland, St. Lucia, Queensland, Australia, 99 p.

Discussion: Overview of Production and Utilization of Cassava and Agricultural Research on Cassava

The discussion centred on three themes: future production practices of cassava, future markets for cassava, and the relationship between HCN and production.

Future production practices: It was suggested that traditional production practices have persisted because farmers have lacked a secure market for cassava, or because available research recommendations have not been applicable at the producer level. However, experiences in Colombia, Nigeria, and Thailand indicate that, once farmers consider cassava to be a cash crop or consider research recommendations to be applicable, they adopt improved production practices. Thus, the acceptance of new production techniques may depend upon the development of new markets.

Future markets: It was suggested that both the fuel-alcohol and animal-feed markets may develop for cassava. In the first case, however, the market is justifiable only if the country has excess food supplies or agricultural capacity. Even if these conditions are met, the country must determine if the conversion of cassava is economically and socially beneficial, and establish the necessary infrastructure and policy framework implied by the development of a cassava-alcohol system. The animal-feed market potentially exists in every producing country. A major barrier to its development is that the feed-compounding industry is often underdeveloped and depends upon formulae from developed countries, which, unfortunately, exclude feedstocks available in cassava-producing countries. A second barrier is that, in many instances, the supply and price of cassava is inconsistent. Therefore, the development of this market may require the removal of barriers by means of government intervention.

Relationship between HCN and production: It was pointed out that HCN content is a function of both the genetic composition of cassava and production conditions. Therefore, the development of a cassava variety with a consistently low HCN content may not be possible, owing to difficulties in ensuring constant production conditions. Furthermore, some of the research conducted in Africa indicates a positive association between insect resistance and HCN content of the plant. This association has not yet been found in other parts of the world, and there is no clear association between HCN content and disease resistance. Until the role of HCN in the production of cassava is better understood, it is not possible to suggest that genetically reducing or removing the HCN content in cassava is the most important area of research.

Cassava, Cyanide, and Animal Nutrition

Guillermo Gomez[1]

Cassava is the principal root crop and a major calorie staple in the rural lowland tropics. Cassava roots are peeled and used for human consumption either as a fresh vegetable or in the form of processed products. In some tropical regions, cassava leaves are also consumed as human food or animal feed. Whole cassava roots are often used in either fresh or processed form (dried, ensiled) as animal feed (Gomez 1979).

Cassava varieties, or cultivars, are classified as "sweet" or "bitter" according to the low- or high-cyanide content of their roots; however, the cyanide concentrations in the roots exhibit a wide range of values among the different varieties studied (Joachim and Pandittesekere 1944; de Bruijn 1973; Muthuswamy et al. 1973; Cooke et al. 1978b; Gomez et al. 1980). In addition to varietal differences, the cyanide content in cassava tissues appears to be affected by several factors such as the age of the plant and the part of the plant, as well as by environmental factors such as soil and temperature conditions (Bolhuis 1954; de Bruijn 1973).

The cyanide in cassava roots and tissues is mainly found in a bound form as a cyanogenic glucoside (linamarin), which accounts for approximately 90% of the total cyanide content (Nartey 1978); the remainder being present as free cyanide. Processing of cassava roots leads to the rapid conversion of bound cyanide to free cyanide, which is then released. The cyanide content of the processed products, therefore, is considerably lower than that of the fresh roots.

The purpose of this paper is to briefly review some of the factors, such as variety and age of plants, that affect the cyanide content in the roots, the effects of drying whole-root chips on cyanide elimination, and the results of animal-feeding trials using cassava meals produced from roots of low- or high-cyanide content varieties.

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Effect of Variety and Age of Plants on the Cyanide Content in Cassava Roots

Cassava varieties grown under practically identical edaphoclimatic conditions differ, at a given age, in the cyanide content of their root tissues (Gomez et al. 1980). One-year-old plants of variety MCol 1684 produced roots with the highest cyanide concentration (825 mg/kg, dry-matter basis) in the parenchymal tissue or pulp; the roots of nine other varieties studied contained cyanide levels ranging from 49–221 mg/kg (Table 1). With the exception of variety CM 305-38, the local varieties exhibited the lowest cyanide concentrations in the root parenchyma.

The root cortex, or peel, contains higher cyanide concentrations than the parenchyma (Table 1). For the 10 varieties studied, the total cyanide levels in the root cortex ranged from 2–48 times the levels found in the root parenchyma. Varieties such as MCol 22, Llanera, and CM 305-38, having relatively low cyanide con-

Table 1. Total cyanide content (mg/kg, dry-matter basis) in root tissues (parenchyma and cortex) of 10 cassava varieties (harvested at 12 months).

Variety	Total cyanide: Parenchyma	Total cyanide: Peel	Total cyanide content ratio (peel/parenchyma)
Llanera (local)	73	3210	44
Valluna (local)	52	407	8
MCol 22	88	4229	48
MVen 218	120	2987	25
MCol 1684	825	1450	2
CM 305-38	49	1962	40
CM 321-188	147	3879	26
CM 323-375	221	2876	13
CM 326-407	100	2373	24
CM 342-55	106	1942	18

Source: Gomez et al. (1980).

tents in the parenchyma (49–88 mg/kg), had cyanide levels in the root cortex ranging from 1962–4229 mg/kg. In both the root cortex and parenchymal tissues, the proportion of free cyanide ranged from 5–17% (Gomez et al. 1980) of the total cyanide content, confirming that most of the cyanide occurs as cyanogenic glucoside (Nartey 1978).

Recent studies on the effect of plant age (9–12 months) on the cyanide content of roots indicate that the cyanide concentration in the parenchyma appears to be the most stable parameter and is almost unaffected by plant age. A comparison of results from two varieties, one high- and one low-cyanide content cultivar, showed that the cyanide content of the root parenchyma of variety CMC-84 was approximately three times that of variety CMC-40 (623 ± 25 vs 234 ± 10 mg/kg, dry-matter basis) (CIAT 1981) throughout the period from the 9th to the 12th month of age of the plants. Plant age affected the cyanide concentration in the root cortex of both varieties, decreasing progressively from the 9th to the 12th month of age, with the decline being more pronounced in the roots of variety CMC-40. Variety CMC-40, considered a low-cyanide content cultivar, had very high levels of cyanide in the root cortex (~5000 mg/kg), notably in the roots of 9-month-old plants.

The cyanide levels in fresh chips decreased progressively from the 9th to the 12th month of age of plants in a manner similar to the trend observed with respect to the cyanide content of the root cortex. At 12 months, the total cyanide levels in fresh chips were 61 and 66% of those found at 9 months of age for the varieties CMC-40 and CMC-84 respectively (Table 2) (CIAT 1981).

The aforementioned results indicate that the root parenchymal cyanide level is characteristic of a given variety and that roots from local varieties, normally used for human consumption, are low in cyanide content. Plant age does not appear to affect the cyanide content of the parenchyma but has some effect on the cyanide level of the root cortex.

Effect of Drying Whole-Root Cassava Chips on Cyanide Elimination

Drying whole-root chips is very effective in reducing the cyanide content of cassava roots considerably. Sun-drying on concrete floors (Thanh et al. 1979) is the most practical method of drying cassava; however, on a small scale, wood-framed trays allow for a faster drying process (Best 1979).

The sun-drying process is dependent upon climatic factors such as ambient temperature, intensity of solar radiation, relative humidity, and wind velocity. In addition, the size and form of the chips and the loading rate (amount of fresh chips per surface drying area) also affect the length of the drying period.

A comparison of sun-drying whole-root chips on a concrete floor at two loading rates (10 and 12 kg/m^2) and on inclined trays at three loading rates (10, 15, and 20 kg/m^2) was made (CIAT 1981). Roots of varieties CMC-40 and CMC-84 from 15-month-old plants were used in the experiment. At the loading rates studied, floor-drying was more efficient in reducing cyanide content than tray-drying (Fig. 1). Increasing the loading rate of chips on trays up to 20 kg/m^2 resulted in higher cyanide losses than with lower loading rates, especially with the high-cyanide content variety CMC-84. The proportion of free cyanide in the dried chips appeared to increase progressively as the loading rates on the trays increased. Even with relatively high loading rates, floor- and tray-drying of chips of the low-cyanide content variety CMC-40 produced dried chips containing cyanide levels below 100 mg/kg on a dry-matter basis (standard set at the European market for imported cassava); however, this low cyanide content level could not be reached with the chips of the high-cyanide

Table 2. Effect of plant age on cyanide content of fresh whole-root chips of varieties CM-40 and CMC-84.

	CMC-40		CMC-84	
Age of plant (months)	Total cyanide (mg/kg, dry matter)	Free cyanide (% of total)	Total cyanide (mg/kg, dry matter)	Free cyanide (% of total)
9[a]	584	32	980	18
10	459	24	750	23
11	379	35	723	24
12	355	42	646	20

[a]Mean values of 14 (CMC-40) and 17 (CMC-84) samples; all other values are means of 18 samples.

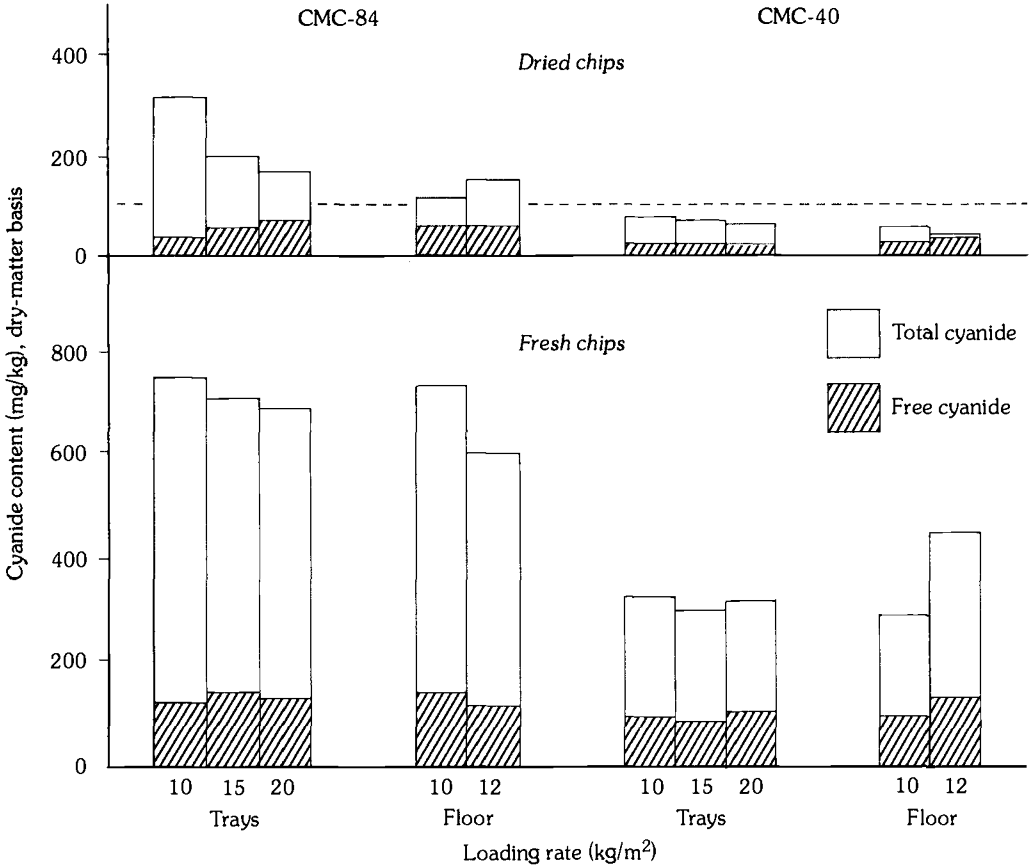

Fig. 1. Effect of loading rate on cyanide reduction in chips dried on trays and on a concrete floor.

content variety.

A sufficient number of 14-month-old plants of each variety was harvested, the roots were processed through a chipping machine, and the cyanide content of the fresh chips was determined. Almost 900 mg/kg of total cyanide were found in the fresh chips of variety MCol 1684, whereas the two local varieties had the lowest cyanide values (137–173 mg/kg) (Table 3). The free cyanide in the fresh chips of all of the varieties was considerably higher than that found within either the parenchyma or the root cortex; free cyanide levels ranged between 24 and 48% of the total cyanide.

The fresh chips of these varieties were either sun-dried on inclined trays or oven-dried in a forced-air oven at 60°C throughout a 24-hour period (Gomez et al., unpublished data). The loading rate for both types of drying was 10 kg/m^2. Oven-drying at 60°C produced dried chips with a final cyanide content lower than that of the corresponding sun-dried chips; the oven-dried chips of variety MCol 1684 were the

Table 3. Dry-matter and cyanide (total and free) contents in fresh whole-root chips of 10 cassava varieties (harvested at 14 months).

Variety	Dry matter (%)	Total cyanide (mg/kg, dry-matter basis)	Free cyanide (%)
Llanera (local)	31.4	173	24
Valluna (local)	23.9	137	28
MCol 22	36.8	267	27
MVen 218	35.8	281	26
MCol 1684	30.2	884	48
CM 305-38	34.1	227	34
CM 321-188	36.1	306	40
CM 323-375	37.3	573	35
CM 326-407	37.4	403	29
CM 342-55	31.7	381	36

Source: Gomez et al., unpublished data.

only ones containing more than 100 mg/kg. Residual cyanide values (total cyanide in dried chips/total cyanide in fresh chips × 100) in oven-dried chips ranged from 13–21%, compared with 20–30% for sun-dried chips of the same varieties. Approximately 60–80% of the total cyanide in the dried chips, obtained by either process, was present as free cyanide.

The available data on cassava drying indicates that sun-drying on a concrete floor; oven-drying at 60°C; and, to a lesser extent, drying on inclined trays led to a reduction in the total cyanide content of the dried chips of the order of 10–30% of the initial cyanide content in the fresh chips. In addition, about 60–80% of the cyanide in the dried chips occurred as free cyanide.

Animal-Feeding Trials Using Cassava Meal from Low- and High-Cyanide Content Varieties

A considerable amount of information has been obtained on the use of cassava in animal feed (Nestel and Graham 1977) and on different aspects of cassava toxicity (Nestel and MacIntyre 1973). Despite this data, very little has been reported on the actual effects of the cyanide content of the cassava products used, although some inferior experimental results have been attributed to the cyanide content of cassava. One of the reasons for this absence of information has been partially due to the lack of an adequate methodology for cyanide analysis; however, the development of an enzymatic method (Cooke 1978; Cooke et al. 1978a) has permitted a more accurate and reproducible cyanide estimation than other methodologies used previously.

In order to ascertain the effect of cassava cyanide on animal performance, several feeding trials using cassava meals, produced from either low- or high-cyanide content varieties, have been carried out on growing rats, pigs, and chickens.

Balanced diets supplying 20% crude protein and consisting of cassava meal (40–42%), soybean meal (37–39%), cellulose (5%), corn oil (10%), and mineral-vitamin premixes (5%) were fed to growing rats throughout a 28-day experimental period. The results are summarized in Table 4. The cassava meals used were based on MCol 1684 and Valluna (MCol 113) varieties. Data on body growth and feed consumption were similar for both varieties tested, as well as for the two drying systems (solar and artificial)

Table 4. Effect of sun-drying and oven-drying whole-root chips of low- and high-cyanide content varieties on the nutritive value of cassava meal for growing rats.

Cassava variety	Cassava meal: Total cyanide (mg/kg, dry matter)	Cassava meal: Free cyanide (%)	Rat results[a]: Total weight gain (g)	Rat results[a]: Total feed consumed (g)	Rat results[a]: Feed/gain
MCol 113					
SD[b]	30	60	156	446	2.86
OD[c]	16	72	144	404	2.81
MCol 1684					
SD	182	77	148	403	2.72
OD	122	72	158	415	2.63

Source: Gomez et al., in preparation.
[a]Means of 8 rats/group; average initial body weight = 43.7 g; duration of experimental period = 28 days.
[b]SD = sun-drying process.
[b]OD = oven-drying process.

Table 5. Effect of cassava meal, obtained from varieties with low- and high-cyanide content, in broiler diets.[a]

Percentage of cassava meal in diet	MCol 113: Final weight gain (g)	MCol 113: Feed intake (g)	MCol 113: Feed/gain	MCol 1684: Final weight gain (g)	MCol 1684: Feed intake (g)	MCol 1684: Feed/gain
0[b]	1977	4346	2.2	—	—	—
10	1714	3982	2.3	1655	4018	2.4
20	1804	4264	2.4	1796	4213	2.3

Source: Santos, J. et al., unpublished data.
[a]Each value is the mean of 140 chickens/group, throughout an 8-week period.
[b]Commercial diet without cassava meal.

used. The difference in the cyanide levels observed did not significantly affect rat performance during the 28-day experimental period.

Results of feeding trials with broilers have clearly shown that least-cost diets, with levels of 10 and 20% cassava meal from either low- or high-cyanide content varieties, produced similar results (Table 5). Actually, the diets with 20% cassava meal produced better results than those with 10% cassava meal, suggesting that there is no apparent toxic effect at these levels (Santos, J. et al., unpublished data).

Experimental results with growing pigs (17–50 kg) have shown that a diet based on cassava meal (74%) produced from a high-cyanide content variety was consumed less than a diet based on cassava meal produced from a low-cyanide content variety (Job 1975); the difference in feed intake was reflected in a significant difference in average daily weight gain. Recent experimental evidence suggests that the consumption patterns of pigs for diets containing 30% cassava meal from either high- or low-cyanide content varieties differ according to the initial body weight of the animals; heavier pigs (~21 kg) consumed more of the high-cyanide content cassava meal diet than the low-cyanide content diet, whereas the reverse was observed for the groups of lighter pigs (~17 kg) (Gomez et al., unpublished data). Further studies are required to elucidate the effect of residual cyanide in cassava meal on feed palatability for pigs.

Available information on cassava as animal feed suggests that the normal drying processes considerably reduce the cyanide content of the roots to a relatively low level in cassava meal, which is apparently not toxic when incorporated into balanced diets for growing animals.

Best, R. 1979. Cassava drying. Centro Internacional de Agricultura Tropical, Cali, Colombia, Series 05EC-4, 24 p.

Bolhuis, G.G. 1954. The toxicity of cassava roots. Netherlands Journal of Agricultural Science, 2, 176–185.

Centro Internacional de Agricultura Tropical (CIAT). 1981. Annual report. Cali, Colombia.

Cooke, R.D. 1978. An enzymatic assay for the total cyanide content of cassava (*Manihot esculenta* Crantz). Journal of the Science of Food and Agriculture, 29, 345–352.

Cooke, R.D., Blake, G.G., and Battershill, J.M. 1978a. Purification of cassava linamarase. Phytochemistry, 17, 381–383.

Cooke, R.D., Howland, A.K., and Hahn, S.K. 1978b. Screening cassava for low cyanide using an enzymatic assay. Experimental Agriculture, 14, 367–372.

de Bruijn, G.H. 1973. The cyanogenic character of cassava (*Manihot esculenta*). In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29–30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 43–48.

Gomez, G. 1979. Cassava as a swine feed. World Animal Review, 29, 13–20.

Gomez, G., de la Cuesta, D., Valdivieso, M., and Kawano, K. 1980. Contenido de cianuro total y libre en parénquima y cáscara de raíces de diez variedades promisorias de yuca.Turrialba, 30, 361–365.

Joachim, A.W.R. and Pandittesekere, D.G. 1944. Investigations of the hydrocyanic acid content of manioc (*Manihot utilissima*). Tropical Agriculturist, 100, 150–163.

Job, T.A. 1975. Utilization and protein supplementation of cassava for animal feeding and the effects of sulphur sources on cyanide detoxification. PhD thesis, Department of Animal Science, University of Ibadan, Ibadan, Nigeria, 519 p.

Muthuswamy, P., Krishnamoorthy, K.K., and Raju, G.S.N. 1973. Investigations on the hydrocyanic acid content of tapioca (*Manihot esculenta* Crantz) tubers. Madras Agricultural Journal, 60, 1009–1010.

Nartey, F. 1978. *Manihot esculenta* (cassava). Cyanogenesis, ultrastructure and seed germination. Munksgoard, Copenhagen, Denmark, 262 p.

Nestel, B. and Graham, M., ed. 1977. Cassava as animal feed: Proceedings of a workshop held at the University of Guelph, 18–20 April 1977. International Development Research Centre, Ottawa, Canada, IDRC-095e, 147 p.

Nestel, B. and MacIntyre, R., ed. 1973. Chronic cassava toxicity: Proceedings of an interdisciplinary workshop, London, England, 29–30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 162 p.

Thanh, N.C., Muttumara, S., Lohani, B.N., Rao, B.V.P.C., and Burintratikul, S. 1979. Optimization of drying and pelleting techniques for tapioca roots. Asian Institute of Technology, Bangkok, Thailand, Final Report No. III, 119 p.

Thyroid Cassava Toxicity in Animals

Olumide O. Tewe[1]

The cyanogenic glucosides contained in cassava have been implicated in neurological and endocrinological anomalies observed in humans (Osuntokun and Monekosso 1969; Ekpechi et al. 1966; Delange 1974). Maner and Gomez (1973) have also indicated their effects on livestock. Increased thiocyanate levels have been reported in most of these studies, indicating the significance of this goitrogenic substance in the metabolism and the subsequent effects on the performance of livestock fed on continuous, long-term diets of cassava.

Studies at the University of Ibadan and Centro Internacional de Agricultura Tropical (CIAT) have attempted to quantify the hydrocyanic acid (HCN) levels of Nigerian cassava varieties and their implications with respect to thiocyanate production, iodine metabolism, and thyroid histology during the growth and reproductive phases of life. The effect of iodine and protein deficiency on these parameters has also been evaluated.

Hydrocyanic Acid Content of Nigerian Cassava Varieties

The cassava used for animal feed ranges from fresh whole tubers and peels to dried peel and pulp. The bitter cassava varieties prevail in southern Nigeria, whereas in northern Nigeria the sweet cassava cultivars are predominant. As shown in Table 1, the bitter varieties invariably contain higher hydrocyanic acid levels, with the peels showing the highest HCN levels in each of the forms that cassava is consumed. Oven-drying produces cassava with higher HCN content than sun-drying. Studies conducted on the cyanide content of cassava consumed in the Ubangi area of Zaire, where endemic goitre and cretinism are highly manifested, have been reported by Simons-Gérard et al. (1980). Whole roots of bitter cultivars averaged 74.5 ppm HCN, whereas whole roots of sweet cultivars averaged 32.9 ppm HCN. The remarkably high levels of cyanide in the Nigerian cassava varieties that are used for animal feed and human consumption appear significant enough to necessitate an elucidation of their role in livestock performance and pathophysiology.

Thyroid Cassava Toxicity During the Growth Phase

Cassava Diets and Thiocyanate Production in Different Animals

The results of a 3-week trial carried out with African giant rats, a rodent recently domesticated at the University of Ibadan by Ajayi (1974), are presented in Table 2.

Another study carried out on albino rats, using fresh and dried cassava-based diets, showed that serum thiocyanate concentration and rhodanese activity were consistently higher in growing rats than in weanling rats (Tewe and Maner 1978). A third trial involving growing pigs, which were fed cassava peel rations, showed that the diet produced pathological changes that were evident in the colloid and secretory cells of the thyroid gland (Tewe 1982).

Increased serum thiocyanate concentrations, associated with cassava-based diets, have been reported in rats and humans by Ermans et al. (1980). These authors also documented that, at high levels of thiocyanate concentration, a renal adaptive mechanism occurs in rats that prevents the serum thiocyanate concentration from increasing beyond a critical level. Studies at the University of Ibadan, involving giant rats, confirm the relationship between increased thiocyanate excretion and high HCN content cassava diets. This adaptive mechanism appears

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Table 1. Hydrocyanic acid content (ppm) of Nigerian cassava varieties.

	Fresh			Sun-dried			Oven-dried		
	Whole root	Pulp	Peel	Whole root	Pulp	Peel	Whole root	Pulp	Peel
Sweet cultivars	88.3 ± 13.7	34.3 ± 4.3	364.2 ± 16.3	23.1 ± 3.2	17.3 ± 2.1	264.3 ± 14.3	51.7 ± 12.3	23.7 ± 4.1	666.8 ± 23.2
Bitter cultivars	416.3 ± 21.3	201.3 ± 15.2	814.7 ± 18.6	41.6 ± 3.9	26.7 ± 7.4	321.5 ± 15.9	63.7 ± 19.6	31.3 ± 11.3	1250.0 ± 41.3

NOTE: Values are the average of two sweet cultivars and six bitter cultivars respectively.

Table 2. Serum, organ, and urine thiocyanate concentrations in African giant rats fed on cassava-based rations.

	Corn (0 ppm HCN)	Oven-dried cassava Peel (597.3 ppm HCN)	Tuber (150.4 ppm HCN)	Flour (109.6 ppm HCN)
Serum (mg/100 mL)	1.3 ± 0.02[b]	3.75 ± 0.03[a]	3.42 ± 0.03[a]	3.01 ± 0.06[a]
Organs (mg/g)				
Liver	0.31 ± 0.06[b]	1.81 ± 0.11[a]	1.17 ± 0.13[a]	1.28 ± 0.15[a]
Kidney	0.26 ± 0.06[b]	1.31 ± 0.13[a]	0.78 ± 0.06[a]	1.33 ± 1.13[a]
Spleen	0.43 ± 0.03[b]	2.01 ± 0.11[a]	0.33 ± 0.02[b]	1.06 ± 0.18[a]
Urine (mg/100 g of feed intake)				
Week 1	2.10 ± 0.26[c]	10.16 ± 1.3[a]	5.32 ± 0.76[b]	3.71 ± 0.53[b]
Week 2	2.37 ± 0.72[c]	12.33 ± 2.0[a]	7.61 ± 1.16[b]	5.31 ± 0.71[b]
Week 3	2.21 ± 0.31[c]	18.74 ± 3.28[a]	7.34 ± 1.04[b]	4.38 ± 1.00[b]

NOTE: Means followed by different superscripts, in horizontal rows, are significantly different ($P<0.05$).

to improve with time, as noted by the progressive increase in thiocyanate excretion per gram of feed taken up to the 2nd week of a 3-week period. The higher serum thiocyanate concentrations observed in growing albino rats, in comparison with lower serum thiocyanate concentrations in weanling rats, is probably due to increased feed intake during the growth phase as opposed to during lactation when the pups depend more upon their dam's milk. Indeed, studies conducted by Tewe and Maner (1981c) have demonstrated that, although serum thiocyanate is significantly increased by cassava diets in lactating rats and their offspring during lactation and the postweaning growth phase, no carry-over effect was noticed. The fact that concentrations of thiocyanate were found in different organs in giant rats indicates the possibility of increased thiocyanate intake in consumers of meat from animals raised on cassava-based diets. In this context, the effect of heat on the thiocyanate content needs to be investigated because meat is usually cooked before being consumed.

Pathological lesions observed in the thyroid of pigs fed on diets of cassava peel confirm the role of this root staple in observed goitre and endemic cretinism in humans. The implications of long-term feeding of cassava-based diets to livestock are also obvious.

Nutritional Factors in Iodine Metabolism and Thyroid Histology in Animals

The interaction of cyanide, protein, and iodine in thiocyanate production and iodine metabolism were investigated in two trials involving weanling rats and pigs respectively. The results of a factorial analysis of some of the parameters measured are presented in Table 3. Pathological changes in the thyroid gland of pigs were pronounced when the pigs received iodine deficient rations, whereas protein deficiency essentially caused the thyroid gland to atrophy. Dietary cyanide plus iodine deficiency caused hyperplastic goitre, but the presence of dietary cyanide alone resulted in only an increase in thyroid weight but no thyroid lesions after a 56-day feeding trial.

The results clearly indicate that thyroid cassava toxicity in animals can be aggravated by consuming cassava diets that are not nutritionally balanced. Specifically, iodine deficiency enhances low serum iodide levels and thyroid lesions. Protein deficiency can also play an important role in iodine metabolism because it is involved in the production of the tyrosyl derivatives of the thyroid hormone. The role of some essential amino acids, notably tyrosine, in the production of goitrous symptoms in human

Table 3. Factorial analysis of some metabolites and thyroid weight[a] in pigs and rats fed varying levels of cyanide, protein, and iodine.

	Dietary factors													
	Cyanide (A)		Protein (B)		Iodine (C)		AB		BC		AC		ABC	
Parameters	Rats	Pigs	Rats	Pigs	Rats	Pigs	R	P	R	P	R	P	R	P
Urinary SCN^-		**												
Urinary I		*		**		**						*		**
Serum SCN^-	**	**	**	**			**	**	*		*			
Serum PBI				**	**	**								
Serum protein			**	**										**
Thyroid weight[b]				**		**								

Source: Tewe and Maner (1980, 1981b).
NOTE: * = ($P<0.05$); ** = ($P<0.01$).
[a]Thyroid weight was expressed in g/kg of body weight before the factorial analysis.
[b]Urinary I and thyroid weight were not determined in rats.

and animal populations on cassava diets needs to be investigated. Ermans et al. (1980) have demonstrated alterations in the long-term distribution of ^{125}I among thyroidal iodo-amino acids in iodine-deficient rats fed increasing doses of SCN^-. In studies at the University of Ibadan and CIAT, observations that protein deficiency does not change serum protein bound iodine (PBI) in rats but reduces that of pigs show variations in iodine metabolism in different animal species exposed to nutritionally deficient diets. It should be noted, however, that protein deficiency in rats also caused considerable reduction in the volume of urine excreted. This might have contributed to the reduced loss of iodine from the circulatory system in rats.

Thyroid Cassava Toxicity During the Reproductive Phase

Two studies were conducted on rats and pigs to monitor the effect of cassava diets on placental thiocyanate transfer, iodine metabolism, thyroid weight, and histology in gestating animals. The concentrations of iodine and thiocyanate in the milk of lactating sows were also determined. The results, which are reported by Tewe et al. (1977) and Tewe and Maner (1981c), show that:

(1) In rats, a fresh cassava diet containing 173 ppm HCN caused marked changes in the thiocyanate concentrations of urine and serum from gestating rats. Amniotic fluid thiocyanate was also significantly increased by the fresh cassava diets ($P<0.01$), but fetal thiocyanate was not significantly different when compared with that from rats on corn starch diets (Tewe et al. 1977).

(2) In pigs fed on diets of fresh cassava containing 0, 250, and 500 ppm cyanide per kg of fresh cassava, serum thiocyanate was slightly ($P>0.05$) increased in the gilts receiving the 500 ppm CN^- diet, whereas serum protein bound iodine decreased during gestation in all groups. Fetal serum thiocyanate was significantly ($P<0.05$) higher in the group receiving 500 ppm CN^-. A small increase in maternal thyroid weight with increasing levels of cyanide was observed. Pathological changes were observed in the thyroid of the 500 ppm CN^- group. The values of some metabolites are summarized in Table 4.

Although the consumption of a cassava diet during gestation did not affect performance during lactation, milk thiocyanate and colostrum iodine concentrations were significantly ($P<0.05$) higher in the group fed cassava containing 500 ppm added CN^-. The size of the litters and weight of the young produced from pregnant rats and pigs fed on the cassava diets were practically normal. This has also been reported by Delange et al. (1980).

In a subsequent trial (Tewe and Maner 1978), an increase in fetal thiocyanate concentration in rats was not detected even though they were fed a cassava diet that included 1000 ppm CN^-. This is not in consonance with the investigations reviewed by Delange et al. (1980) that indicate that the rat placenta allows antithyroid drugs and iodine to pass through it freely.

Delange et al. (1980) have reported that thyroid hyperplasia was more marked (three to four times) in pups at weaning than at birth. In studies at the University of Ibadan and CIAT, observations that the pig secretes large amounts of thiocyanate in its milk also support the observation that the lactation period is critical for animals fed on goitrogenic substances.

Investigations on the effect of cassava diets during the reproductive phase need to be carried

Table 4. Influence of cassava-based rations, fed during gestation, on metabolites and thyroid weights in gilts, fetuses, and suckling pigs.

	Dietary HCN level (ppm)		
	0	250	500
Gestating gilts			
Serum thiocyanate (mg/100 mL)	2.01	2.15	2.29
Serum protein bound iodine (mg/100 mL)	3.1	3.2	3.1
Amniotic fluid thiocyanate (mg/100 mL)	0.90	0.45	1.18
Thyroid (g/100 g body weight)	5.52	7.44	7.98
Fetuses			
Thyroid (g/kg body weight)	0.54[a]	0.36[b]	0.52[a]
Serum thiocyanate	0.85[b]	0.87[ab]	1.02[a]
Lactating sows			
Serum thiocyanate (mg/100 mL)	0.74[ab]	0.58[b]	0.78[a]
Serum protein bound iodine (mg/100 mL)	3.2	3.6	3.7
Colostrum thiocyanate (mg/100 mL)	1.32	1.19	1.41
Milk thiocyanate (mg/100 mL)	1.15[b]	1.15[b]	1.35[a]
Colostrum iodine (mg/100 mL)	4.9[b]	6.0[b]	15.2[a]
Milk iodine (mg/100 mL)	0.7	1.0	0.07
Suckling pigs			
Serum thiocyanate (mg/100 mL)	0.63	0.50	0.78
Serum protein (g/100 mL)	6.61	6.38	5.86
Serum protein bound iodine (mg/100 mL)	4.7	4.9	4.9

Source: Tewe and Maner (1981a).
NOTE: Means followed by different superscripts, in horizontal rows, are significantly different ($P<0.05$).

out to determine the possible interactions of iodine, protein, and essential amino acid deficiencies and their effect on fetal and infantile development in humans and animals. Pathophysiological evidence from studies conducted at the University of Ibadan and CIAT indicate that cassava diets might have deleterious effects on the overall productivity of animals when consumed over long periods of time.

Ajayi, S.S. 1974. The biology and domestication of the African giant rat (*Cricetomys Gambianus* Waterhouse). PhD thesis, Department of Forest Resources Management, University of Ibadan, Ibadan, Nigeria, 243 p.

Delange, F. 1974. Endemic goitre and thyroid function in Central Africa. Monographs in paediatrics. Vol. 2. S. Karger, Basel, Switzerland.

Delange, F., Van Minh, N., Vanderlinden, L., Dohler, K.D., Hesch, R.D., Bastenie, P.A., and Ermans, A.M. 1980. Influence of goitrogens in pregnant and lactating rats on thyroid function in the pups. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 127–134.

Ekpechi, O.L., Dimitriadou, A., and Fraser, R. 1966. Goitrogenic activity of cassava (a staple Nigerian food). Nature, 210, 1137.

Ermans, A.M., Kinthaert, J., Van der Velden, M., and Bourdoux, P. 1980. Studies on the antithyroid effects of cassava and of thiocyanate in rats. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 93–110.

Maner, J.H. and Gomez, G. 1973. Implications of cyanide toxicity in animal feeding studies using high cassava rations. In Nestle, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 113–120.

Osuntokun, B.O. and Monekosso, G.L. 1969. Degenerative tropical neuropathy and diet. British Medical Journal, 3, 178–179.

Simons-Gérard, E., Bourdoux, P., Hanson, A., Mafuta, M., Lagasse, R., Ramioul, L., and Delange, F. 1980. Food consumed and endemic goitre in the Ubangi. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 69–80.

Tewe, O.O. 1982. Effect of cassava peel based rations on the performance, metabolism and pathology of pigs. To be presented at the International Pig Veterinary Society Symposium, Ciudad Jardin, Mexico, 26-31 July.

Tewe, O.O. and Maner, J.H. 1978. Influence of the cyanogenic glucoside fraction of cassava on performance, thiocyanate concentration and rhodanese activity of rats during growth and reproduction. Nigerian Journal of Animal Production, 5(2), in press.

1980. Cyanide, protein and iodine interaction in the performance, metabolism and pathology of pigs. Research in Veterinary Science, 29, 271-276.

1981a. Performance and pathophysiological changes in pregnant pigs fed cassava diets containing different levels of cyanide. Research in Veterinary Science, 30, 147-151.

1981b. Cyanide, protein and iodine interaction in the performance and metabolism of rats. Journal of Environmental Pathology and Toxicology, in press.

1981c. Long term and carry over effect of dietary inorganic cyanide (KCN) in the life cycle performance and metabolism of rats. Toxicology and Applied Pharmacology, 58, 1-7.

Tewe, O.O., Maner, J.H., and Gomez, G. 1977. Influence of cassava diets on placental thiocyanate transfer, tissue rhodanese activity and performance of rats during gestation. Journal of the Science of Food and Agriculture, 28, 750-756.

Toward Lower Levels of Cyanogenesis in Cassava

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Throughout history, the capacity of cassava to produce acute cyanide poisoning in humans and animals, unless adequate precautions are taken, has drawn special attention. Knowledge about its toxic nature has probably contributed significantly to the wide variety of methods used to prepare cassava for human consumption (Gietema-Groenendijk 1970). Despite its toxicity, cassava has become a major food crop and is an important dietary staple for 300–500 million people in tropical areas (Nestel and Cock 1976).

The amount of HCN produced by cassava roots varies considerably among varieties due to genetic factors, but ecological factors also play an important role (Bolhuis 1954; de Bruijn 1971). Based upon potential daily cassava consumption and the amount of HCN a person can ingest without danger, cassava varieties producing less than 50 mg HCN per kg of fresh peeled roots are considered "innocuous" (Koch 1933; Bolhuis 1954). Thus, if one avoids consuming dangerous amounts of HCN, this should be sufficient. In recent years, however, it has been found that under specific local conditions, notably low iodine levels, chronic consumption of low quantities of HCN can cause serious health problems, such as goitre and cretinism, due to the action of thiocyanate, which is produced during the detoxification of cyanide (Ermans et al. 1980; Delange et al. 1982). This means that chronic cassava consumption can, locally, become a greater problem than the danger of acute poisoning. One of the major implications of these findings is the necessity to reduce the amount of dietary HCN for populations within problem areas (Ermans et al. 1980). This could be accomplished by altering food preparation methods, growing low cyanide content cassava varieties, or a combination of the two.

This paper deals with the possibility of cultivating cassava with low, or possibly zero, cyanide levels. After dealing with the genetic aspects and ecological factors, prospects and practical implications are discussed.

Factors Influencing Glucoside Content

Genetic Aspects

There is sufficient evidence to confirm the presence of genetic variation in the cyanogenesis of cassava; so that in the past a bitter species (*M. utilissima*) and a sweet species (*M. aipi*) have been distinguished within the genus *Manihot* (Pohl 1827). After it had become clear that there was a wide range of levels of cyanogenesis between very low cyanide content cultivars and very high cyanide content cultivars the distinction between the two different species was abandoned and the original name, *M. esculenta* Crantz, was reinstated.

Although the genetic background of some cyanogenic plants is well understood (Butler et al. 1973), very little is known about the genetic background of cassava. Bolhuis (1954) concluded that cyanogenesis is not based on a small number of genes. The continuous range of root HCN levels, from about 10 mg/kg to more than 600 mg/kg, gives evidence that the genetic control is multigenic. So far, a cyanide-free cassava clone has not been found, although Bolhuis (personal communication), during his breeding work in Indonesia before World War II, found a type with cyanide-free roots — unfortunately, this type was subsequently lost. Very low HCN levels in fresh roots have been reported by Koch (1933), who found varieties

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in Indonesia producing only 6 mg/kg, and by Bourdoux et al. (1982), who found varieties in Zaire with levels as low as 2 mg/kg.

At Centro Internacional de Agricultura Tropical (CIAT), the germ-plasm bank was screened for zero-cyanide clones in 1973; however, none was found (CIAT 1974). Normanha (1969) also reported that in Brazil an HCN-free variety had not been found. Following a study of wild *Manihot* species in Brazil, Nassar and Fichtner (1978) were unable to find a zero-HCN type, although in one of the species (*M. oligantha* subsp. nesteli) the HCN content of fresh peeled roots was not more than 62 mg/kg.

At the International Institute of Tropical Agriculture (IITA), Sadik et al. (1974) screened the leaves of 88 510 plants, none of which was cyanide free. More than 99% of the plants had a high degree of cyanogenesis and only 92 of the screened plants (0.1%) had a low cyanide level. Most low HCN content plants were offspring of two cultivars. Selection for low HCN content plants at IITA has, nevertheless, provided some promising results. The percentage of low HCN content plants within the population tested was 12% in 1975, compared with 2% in 1974 and only 0.1% in 1973 (IITA 1976). The heritability of cyanogenesis in the IITA population was estimated to be 43%, quite a high value. According to Magoon (1970), cyanogenesis of cassava has a low heritability.

Total root HCN content of nine low-cyanide clones at IITA varied from 33–92 mg HCN/kg (IITA 1981). Assuming that the peel weight is 15% of the total root weight, and the peel HCN content is eight times that of peeled roots, the HCN content of the peeled roots of the IITA clones must have varied from 16–45 mg/kg.

In comparing HCN levels of different cultivars, the HCN distribution should be taken into account. In a study of this (de Bruijn 1971), it was concluded that the variation in glucoside content among different clones is much more pronounced in peeled roots than in leaves or the peel of the roots. It was also found that the ratio between HCN content of root peel and that of the inner part of the root was 2.6 (840 mg/kg: 330 mg/kg), on average, for eight very toxic clones and 9.5 (690 mg/kg : 73 mg/kg), on average, for eight less toxic clones. At IITA (1981), this ratio for low cyanide content clones ranged from 5–12. It was concluded (de Bruijn 1971) that clones with low-cyanide levels in the peeled roots have a characteristically high ratio of peel HCN to inner root HCN levels compared with similar ratios from clones with high-cyanide levels in the peeled roots. The same is true for the ratios of the HCN content of leaves and those of peeled roots.

It has been suggested that there is a positive relationship between cyanide level and root yield. Bolhuis (1954) pointed out that the literature is conflicting on this point. Up to now, there is no clear evidence in favour of this relationship. A comparison of 67 cultivars (de Bruijn 1971) revealed a weak positive correlation ($r = 0.20$; $P < 0.10$) between root yield and HCN content of peeled roots on a dry-matter basis. Cooke et al. (1978) reported a similar correlation that was statistically significant on a fresh-weight basis but not a dry-weight basis. At CIAT (1975), no evidence was found indicating that high cyanide content types have higher root yields. At IITA (1981), a number of low-cyanide clones gave relatively high root yields. It appears that, even if a weak positive correlation between HCN levels and root yield exists, the combination of high root yield and low-cyanide content is possible, and would be a desirable goal for breeders.

Apart from the genetic variation in glucoside content, there are also indications of genetically based differences in the activity of the enzyme linamarase, which is involved in the breakdown of glucosides. The distribution of this enzyme activity in different parts of the plant, as well as in different varieties, has been studied (de Bruijn 1971). Very high values were found in the leaves and root peel, whereas very low values were found in peeled roots. There were also differences among varieties. The highest values in the peeled roots were about four times the lowest values. The enzyme activity in the root peel showed similar differences between the highest and lowest varieties.

Ecological and Physiological Factors

Although efforts to obtain cyanide-free cassava will be oriented toward breeding and selection initially, knowledge on the influence of ecological and physiological factors is important as long as cyanide-producing cassava is grown.

It is generally agreed that nitrogen fertilization increases glucoside concentration (Van de Goor 1941; Vijayan and Aiyer 1969; de Bruijn 1971; Obigbesan 1973; Nugroho and Dharmaputra 1979).

A number of authors refer to the increasing effect of potassium deficiency on cyanogenesis (Darjanto 1952; de Bruijn 1971; Obigbesan 1973; Pushpadas and Aiyer 1976).

The application of organic matter is reported to decrease glucoside levels (de Bruijn 1971; Nugroho and Dharmaputra 1979). Severe drought has been reported as increasing glucoside levels (Darjanto 1952; Didier de St. Amand 1960; de Bruijn 1971). Turnock (1937) mentions that glucoside content is higher during the rainy season than during the dry season. De Bruijn (1971) reported an increase in glucoside content at the beginning of the rainy season in Ivory Coast.

Although a relationship between glucoside levels and plant age has been reported, de Bruijn (1971) could not trace such an influence and suggests that fluctuations in glucoside content during growth are mainly due to changes in ecological conditions.

Other factors have also been reported as influencing glucoside content. Lorenzi et al. (1978) found that pruning the aerial part of the plant before harvesting the roots reduced the root HCN content from 67 to 35 mg/kg in 14 days, the major decrease taking place in the first 3 days. Shanmugam and Shanmughavelu (1974) reported that ethrel application could increase root yield and decrease HCN content. Bambang and Soetono (1979) found that root HCN content decreased with increasing plant population. Use of the Mukibat system, in which *M. glaziovii* is grafted onto *M. esculenta* (de Bruijn and Dharmaputra 1974), causes an increase in the glucoside content of the roots in comparison to the traditional system (Rajendran et al. 1976; Bambang and Soetono 1979).

It is generally accepted that the glucoside content of the roots can vary greatly due to differences in soil and climatic conditions. It is difficult to trace the exact origin of this variation, but variations in soil fertility and rainfall pattern probably play an important role.

The influence of different ecological conditions on glucoside content is not yet well understood. With regard to the influences of nitrogen and potassium fertilization, the suggestion has been made (de Bruijn 1971) that the supposition that glucoside concentration is positively correlated with the availability of the precursor amino acids, valine and isoleucine, in the plant may explain the role of these elements, as manuring with nitrogen increases, and that with potassium decreases, the concentration of these amino acids in the leaves of various plants.

Discussion

Without doubt, the first possibility of decreasing cyanide levels in cassava roots lies in breeding and selecting low or zero cyanide content cultivars. In fact, the desirability of screening for clones incapable of producing cyanide and clones with low cyanide levels in existing collections, and of noncultivated types, was put forward at an earlier workshop on chronic cassava toxicity (Nestel and MacIntyre 1973). In view of recent findings about the danger of chronic cassava toxicity in some regions, the need for more intensive efforts to reach acceptably low cyanide levels has become even more urgent. Even though screening for zero-cyanide levels has been unsuccessful so far, the fact that some varieties with almost negligible root HCN content have been found, together with the reported, but lost, zero cyanide content cultivar in Indonesia (G.G. Bolhuis, personal communication), provides hope that zero-cyanide clones will be found in the future. Even if HCN-free cassava becomes available, however, all of the problems will not be solved immediately, because it will not be easy to introduce new varieties to local populations. Changing the existing food preparation methods so that a safe product is obtained from toxic cultivars will also be difficult. Thus, the short-term solution of Ermans et al. (1980), i.e., iodine supplementation, seems to be most relevant.

It should not be forgotten that the problem of chronic cassava toxicity, according to current information, only exists in some specific areas, especially where iodine is deficient. In most places where cassava is an important food crop, consumption of low cyanide content cultivars, or well processed high cyanide content cultivars, does not seem to cause problems, apart from the danger of acute poisoning in cases of improper preparation. Problems can also arise when presumed low cyanide content cassava actually has a much higher toxicity level because of unfavourable ecological conditions.

Nevertheless, a solution for areas suffering from chronic cassava toxicity is needed, and the cooperation of specialists from different disciplines is necessary. In this regard, the first task will be to direct the activities of agricultural scientists toward obtaining zero or low levels of cyanogenesis in cassava.

Bambang, G. and Soetono, H. 1979. Comparison between yields of Mukibat and ordinary cassava at five densities. Agrivita, 2(6), 1-11.

Bolhuis, G.G. 1954. The toxicity of cassava roots. Netherlands Journal of Agricultural Science, 2, 176-185.

Butler, G.W., Reay, P.F., and Tapper, B.A. 1973. Physiological and genetic aspects of cyanogenesis in cassava and other plants. In Nestel, B.L. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 65-71.

Centro Internacional de Agricultura Tropical (CIAT). 1974. Annual report, 1973. Cali, Colombia.

1975. Annual report, 1974. Cali, Colombia.

Cooke, R.D., Howland, A.K., and Hahn, S.K. 1978. Screening cassava for low cyanide using an enzymatic assay. Experimental Agriculture, 14, 367-372.

Darjanto, R.M. 1952. Ratjun assam hydrocyan (The toxic HCN). Pusat Djawatan Pertanian Rakjat. Bagian publikasi & propaganda, Djakarta, Indonesia , 8 p.

De Bruijn, G.H. 1971. Étude du caractère cyanogénétique du manioc (*Manihot escuelenta* Crantz). Mededelingen Landbouwhogeschool Wageningen, 71-13, 140 p.

De Bruijn, G.H. and Dharmaputra, T.S. 1974. The Mukibat system, a high yielding method of cassava production in Indonesia. Netherlands Journal of Agricultural Science, 22, 89-100.

Delange, F., Iteke, F.B., and Ermans, A.M., ed. 1982. Nutritional factors involved in the goitrogenic action of cassava. International Development Research Centre, Ottawa, Canada, IDRC-184e, 100 p.

Didier de St. Amand, J. 1960. Étude de la teneur en hétéroside cyanogénétique des variétés de manioc cultivées sur les Hauts-Plateaux de Madagascar. Rapport Office de la Recherche Scientifique et Technique Outre-Mer, Paris, France, 59 p.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Gietema-Groenendijk, E. 1970. Bereiding van cassave (Preparation of cassava). Agromisa, Wageningen, The Netherlands, 108 p.

International Institute of Tropical Agriculture (IITA). 1976. Annual report, 1975. Ibadan, Nigeria.

1981. Annual report, 1980. Ibadan, Nigeria.

Koch, L. 1933. Cassaveselectie (Cassava breeding). Thesis. Landbouwhogeschool, Wageningen, The Netherlands, 86 p.

Lorenzi, J.O., Gutierrez, L.E., Normanha, E.S., and Cione, J. 1978. Variação de carboidratos e ácido cianidrico em raizes de mandioca, após a poda da parte aérea (Variation in carbohydrate and HCN content in cassava roots after pruning the aerial part). Bragantia, 37(16), 139-144.

Magoon, M.L. 1970. Problems and prospects in the genetic improvement of cassava in India. In Tropical Root and Tuber Crops Tomorrow. Vol. I. Proceedings of the Second International Symposium on Tropical Root and Tuber Crops. August 1970. University of Hawaii, Honolulu, HI, USA, 58-61.

Nassar, N.M.A. and Fichtner, S.S. 1978. Hydrocyanic acid content in some wild *Manihot* (cassava) species. Canadian Journal of Plant Science, 58, 577-578.

Nestel, B. and Cock, J., ed. 1976. Cassava: The development of an international research network. International Development Research Centre, Ottawa, Canada, IDRC-059e, 69 p.

Nestel, B.L. and MacIntyre, R., ed. 1973. Chronic cassava toxicity: Proceedings of an interdisciplinary workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 162 p.

Normanha, E.S. 1969. Tóda mandioca tem venemo (All cassava is toxic). Coopercotica, 26(234), 24-25.

Nugroho, J.H. and Dharmaputra, T.S. 1979. The effect of nitrogen fertilizer and organic matter on the yield of Mukibat cassava. Agrivita, 2(6), 21-27.

Obigbesan, G.O. 1973. The influence of potassium nutrition on yield and chemical composition of some tropical root and tuber crops. In International Potash Institute Colloquium, 10th, Abidjan, Ivory Coast, 439-451.

Pohl, J.E. 1827. Plantarum Brasiliensis, icones et descriptiones 1:32. (Cited by Rogers, D.J. 1963. Studies of *Manihot esculenta* Crantz and related species. Bulletin of the Torrey Botanical Club, 90, 43-54.)

Pushpadas, M.V. and Aiyer, R.S. 1976. Nutritional studies on cassava (*Manihot esculenta* Crantz). II. Effect of potassium and calcium on yield and quality of tubers. Journal of Root Crops, 2, 42-71.

Rajendran, P.G., Kamalan, P., and Mani, S.B. 1976. Quality aspects of Mukibat tubers. Journal of Root Crops, 2, 64-66.

Sadik, S., Okereke, O.U., and Hahn, S.K. 1974. Screening for acyanogenesis in cassava. International Institute of Tropical Agriculture, Ibadan, Nigeria, Technical Bulletin No. 4, 4 p.

Shanmugam, A. and Shanmughavelu, K.G. 1974. Influence of ethrel on growth and yield of tapioca. Indian Journal of Plant Physiology, 17, 44-46.

Turnock, B.J.W. 1937. An investigation of the poisonous constituents of sweet cassava (*Manihot utilissima*) and the occurrence of hydrocyanic acid in foods prepared from cassava. Journal of Tropical Medicine and Hygiene, 40, 65-66.

Van de Goor, G.A.W. 1941. Gegevens over de betekenis van groenbemesting bij sawahrijst. Vergelijking met kunstmeststoffen. Landbouw (Buitenzorg), 17, 871-872.

Vijayan, M.R. and Aiyer, R.S. 1969. Effect of nitrogen and phosphorus on the yield and quality of cassava. Agricultural Research Journal of Kerala, 7(2), 84-90.

Discussion: Animal and Genetic Research Trends in Cassava

Ermans: Considering that linamarin is easily synthesized in plants, would you consider the question of free cyanide a classical observation or an artifact?

Gomez: The amount of free cyanide in fresh cassava tissue is very low, as reported by Nartey. About 90% of it is mainly linamarin and about 10% free cyanide, but as soon as it is processed, hydrolysis proceeds very fast, releasing free cyanide. Dr Cooke is going to discuss the effect of different processing techniques on the free cyanide in cassava. The amount of free cyanide that I quoted in my paper was determined in the dry cassava product, so it is a stable free cyanide. We usually process cassava roots and sample fresh chips very fast to avoid hydrolysis of the linamarin to free cyanide, because this increases with the length of time of sampling after processing. By the time we complete the drying process, the result is a reduction to about 20–25% of the initial total cyanide present in the product, and the proportion of free cyanide is usually between 50 and 80% of the total cyanide, depending upon the conditions of drying. Thus, I do not believe that the question of free cyanide is an artifact; it is, in fact, real.

Ermans: Regardless of whether the cyanide is free or bound, it is still present in the cassava product and, therefore, does not change the toxicity.

Gomez: It may change the toxicity. Sampling of dry cassava meal at regular intervals will help to determine the rate of decrease of the cyanide content with time, due mainly to a possible release of free cyanide at temperatures between 26 and 30°C. Therefore, the actual amount of total cyanide in dry cassava meal may decrease with time due to the fact that most of the cyanide is free.

De Bruijn: Free cyanide is a relative value, i.e., if you start with a certain amount of linamarin, during processing this is hydrolyzed to give a continuous source of free cyanide, which becomes very high because the amount of the bound form (linamarin) is decreasing. I think it is worthwhile to look at the absolute amount of free cyanide in relation to the amount of linamarin originally present. I think you might find that the decrease in linamarin content is responsible for the high free cyanide figure, making it a relative value.

Cock: If dried cassava is to be used for human consumption, the free cyanide will be driven off when it is cooked. Therefore, the actual levels of cyanide in the dried material, which is later cooked and eaten, will be much lower than they would be if the cyanide was in the bound form.

De Bruijn: I have noticed that, even when fresh cassava is cooked, a lot of the free cyanide can be blocked by the tissue. Thus, the free cyanide is still available for consumption even after the enzyme has been destroyed by cooking and the starch is gelatinized. This can be toxic, even though the linamarin itself is not toxic as far as I know.

Bourdoux: We have only limited information about the toxicity of linamarin itself.

Cooke: Yes indeed, in rats, based upon studies at the University of Guelph, there is no doubt that linamarin is hydrolyzed when there is no linamarase present in the diet. I think one of the conclusions that is very clear from the work of Ermans and associates is that in humans as well, hydrolysis of the linamarin contained in processed products takes place during digestion (not necessarily by acids). Until about 10 years ago, the medical profession felt that glucosides were not toxic in the absence of the hydrolytic enzymes that produce free cyanide. In contrast, it is now obvious that heat-processed products in which linamarase has been destroyed still contain linamarin that is converted to thiocyanate in the organism. Therefore, at some stage during digestion, we must be hydrolyzing the glucosides.

De Bruijn: My recollection of these studies is that if you use very high levels of linamarin then you will run into problems of toxicity. It seems that some hydrolysis can take place without the enzyme (linamarase) but the rate is very low compared with what happens in the presence of the enzyme. The result is that you need about 20 times the toxic level before the effect is felt and under normal conditions I think it is not very serious.

Cooke: The proof, or rather the relevant data, must surely be the human system, typified by the studies reported from Zaire, in which the foodstuffs must have contained little or no linamarase, yet the thiocyanate levels in the urine kept elevating. An appreciable amount of hydrolysis, therefore, must be taking place. I agree that the extent is uncertain, but to say that it is unimportant is perhaps being a little optimistic.

De Bruijn: If people consume cassava leaves every day or from time to time, they must be consuming the enzyme all the time as well.

Cooke: The problem is that they boil the leaves or process them in various ways and these treatments are going to remove the linamarase activity.

Bourdoux: Again, I insist that there is very little experimental information on the toxicity of linamarin itself. As far as humans are concerned, our data do not fully support the statement by Cooke on the direct role of linamarin. As a matter of fact, what we measure in feedstuffs is cyanide. We do not know whether the feedstuffs contain glycosides or cyanide. However, the direct role of cyanogenic glucosides in humans has been reported from the limited states where the administration of laetrile, another cyanogenic glucoside, to patients, resulted in toxicity and, occasionally, in death.

Oke: We must be very careful about jumping to any conclusions relating laetrile and cyanide toxicity because this is a controversial subject. Just as some deaths have occurred as a result of using laetrile, many other people with cancer have been given high doses of laetrile without experiencing any toxic effects. It probably depends upon the presence of hydrolyzing enzymes in the gut, i.e., if the activity is high then toxicity results and if it is low or absent then large doses can be taken without any toxicity. We have done some work in this area and have found that you can give as much as 45 mg linamarin/kg body weight to rats without any ill effects and yet we have also found that a toxic dose of cyanide is only about 13 mg/kg body weight.

Bourdoux: We have found that even gut bacteria can cause hydrolysis of the glucoside without any enzyme.

Phillips: There are two problems that bother me with respect to the use of large quantities of cassava in animal feed: (1) What is the quality of the meat from animals fed large quantities of cassava? This may be of less concern in

Latin America, but I understand that you get a whiter meat and a whiter fat when you have a high percentage of cassava, as opposed to maize, for example, in the feed. (2) How do you carry out the ensiling of cassava and what about considering the ensiling of the aerial part of cassava?

Gomez: We have done some work on evaluating the carcasses of pigs fed large quantities of cassava-based meals and there seems to be no problem with the quality of the meat. This has also been confirmed by workers in Thailand. In fact, some people claim that the lard is harder compared with that of pigs fed maize or sorghum and is preferred for this reason. Even then, we never use very large quantities of cassava-based meals in commercial rations because we are dealing with a computerized least-cost formulation. Cassava meal is usually bought at 80% of the price of sorghum; therefore, the normal amount used for pig rations would be around 30–40%, which is not near the maximum possible. For poultry, one would use about 20–30%, judging from the current prices of feedstuffs in Colombia. At higher levels, broilers may end up with a lack of skin pigmentation. However, people in Thailand have used cassava leaves at a level of 1–2% to obtain the right pigmentation.

With respect to the silage process, this was carried out in airtight silos for about 6 months, during which samples were taken at regular intervals for cyanide determination. The silage was then fed to pigs after the addition of protein, mineral, and vitamin supplements. We have found no significant difference between this and fresh cassava roots.

As for ensiling the whole plant, work is in progress in Brazil in this area, but we believe that in most of the developing countries in Latin America the demand is for dried cassava meal as a source of energy as opposed to the use of leaves and other aerial parts. We can see a great future in using cassava leaves as a protein supplement because they dry faster in the sun than the roots and have a high protein content; however, our attention is not focused on this aspect yet.

Tewe: I would like to add that we have found that cassava peels (waste from the *gari* industry) can supplement the diet in the presence of large quantities of palm oil (due to lower energy) to produce a fatty carcass, which meets with our own consumer preference, although this may not necessarily be so in temperate countries. There are reports that the level of cassava used in European Economic Community markets for pigs is not allowed to exceed 40% due to the production of a fatty carcass.

Cooke: I notice that ensiling of cassava reduced the total cyanide content to about one-third or 40%, all of which was free cyanide. Did you then treat this silage before feeding it to animals because otherwise it would seem to be a fairly toxic mixture?

Gomez: No, as soon as you open the silo most of the free cyanide escapes.

Cooke: In your Tribolium data, the live weight decreased with cassava containing over 100 ppm cyanide. What percentage of cassava was incorporated into the growth media?

Gomez: I do not know the exact composition but I assume that the cassava used was incorporated at a level of at least 50% of the diet. We have carried out similar experiments with rats using higher levels of cyanide (150–200 ppm) and have not found any differences as far as weight gained and feed consumption are concerned, but with Tribolium we have observed differences. This shows that there may be differences in the susceptibility and sensitivity among animal species to different levels of cyanide.

Ermans: There seems to be a progressive weight gain in chicks fed high and low cyanide content cassava diets. How do you account for this?

Gomez: What we are doing, in effect, is comparing two levels of total cyanide; we prepared cassava meals from either a high cyanide variety containing 100 ppm total cyanide, of which 60% was free cyanide, or from a low cyanide variety containing 30 ppm total cyanide, of which 60–70% was free cyanide. Broilers fed diets containing either one of these meals yielded similar results, indicating that with adequate processing cassava meal from bitter varieties can be safely used in animal feeding.

Gaitan: A minor point about the measurement of PBI in rats, which I understand was done due to a lack of facilities for T_4 determination. Rats have very low levels of thyroid-binding proteins. Your rats were in the 3 μg level, which would overshadow any minor changes in the thyroxine concentrations in the rats. Although you were able to detect changes at that level in pigs, I think it would be better to measure the free thyroxine and, if possible, to contrast the values with concomitant TSH measurements. I think the PBI could give rise to artifacts.

Tewe: I agree. We are now trying to measure T_4 and TSH.

Ermans: Were your rats subjected to an iodine-deficient diet, and what was the influence on the transfer of thiocyanate?

Tewe: The rats used in the gestation trials were fed diets containing adequate amounts of iodine. However, placental thiocyanate transfer differed between rats and pigs. No placental transfer was observed in rats at levels of up to 1000 ppm cyanide in the diet. For pigs, a diet containing 500 ppm cyanide gave elevated fetal serum thiocyanate. This species difference shows the importance of not extrapolating the results directly to humans. Rats tend to eat slowly, whereas pigs eat very fast, and this affects the cyanide intake per unit time and hence the toxicity.

Ermans: Your work is very important because, apart from the problem of the thyroid gland, it is clear that the main problem with cassava is the induction of chronic cyanide intoxication, an area in which information is still very limited. It is, therefore, very important to look not only at the thyroid gland but also at other tissues and other functions. From our work in Zaire, we have observed that patients have an excess of about 7 mg thiocyanate per day in their urine and this can only be caused by ingestion of about 3–4 mg of cyanide, which is about one-tenth of the lethal dose in humans. Thus, a very important aspect is to check the influence of chronic administration of cyanide in animals.

Tewe: This confirms the multifactorial effect of cassava toxicity because the toxic dose varies depending upon whether one takes it by mouth all at once, as glucoside in cassava, through drinking water, etc. This is why it is easier to use animal models in this type of work.

Cooke: Everyone has been asking: What level of cyanide is permissible? According to the data collected by Dr Delange's group in Ubangi, Zaire, the amount of thiocyanate excreted per day is 10.75 mg, whereas in Brussels it is 5.37 mg. The difference of 5 mg should come from about 2.5 mg of cyanide, if we assume 100% conversion of linamarin to cyanide and of cyanide to thiocyanate during digestion. This is a worst-case assumption because both percentages are likely to be less than 100, and further work is required to study these conversions. Cassava consumption patterns are quite seasonal, but if 500 g is taken as a daily intake, this 2.5 mg of cyanide would be attained if the cassava product contains 5 ppm cyanide.

Bourdoux: We are assuming 100% conversion of cyanide to thiocyanate and that the only process of detoxification is by rhodanase. There is also vitamin B_{12} and other pathways that can detoxify cyanide and so the problem is more complicated. On the whole, we do not have enough data to be able to carry out the calculation of what level of cyanide is permissible even though there are 200 million goitrous patients in the world.

Matta: Before salt iodation in villages in the highlands of Guatemala, where cassava is not eaten, the incidence of goitre was as high as 60%. Thus, there are factors other than cyanide in cassava that cause goitre. I would like to recommend that we should carry out a long-term study on endemic goitre by comparing a place where cassava is consumed with a place where it is not consumed. This seems to be the only way of determining the role of other factors, as there seems to be many. For instance, one of the first things that happens to children in the tropics is that they get an overgrowth of bacteria in the small bowel and I wonder what these bacteria would do to the absorption of iodine? On the other hand, we have documented that children in the first year of life in the tropics are sick with diarrhea for 2–3 months, and for 2 months in the second year of life, suffering from 7–8 episodes of diarrhea per year, some becoming chronic and continuing for months. What happens to the absorption of micronutrients, particularly iodine, during these periods? Another observation has been that wherever there is endemic goitre there is always malnutrition. What happens to the absorption of iodine during the course of the malnutrition? How are these factors related to each other? There is also the problem that wherever you find these two nutritional problems, you always find bacteria in the water, e.g., high coliform counts in water. I think this factor should also be examined in an epidemiological study, which, although expensive to carry out, would contribute to our knowledge on goitre etiology.

Cock: There is a possibility of getting acyanogenic cassava. If it exists, it may well be controlled by recessive genes and will not normally be detected unless massive inbreeding programs are developed. This could be very costly. The developing of anther culture techniques to produce haploids could make exposure of acyanogenesis easier. In addition, the combination of anther culture with mutation breeding should prove promising because mutation breeding is particularly useful when deletion rather than addition of a character is required.

De Bruijn: I agree that we should continue to look for acyanogenic cassava and I have a feeling that one day we will succeed. However, I do not have much confidence in mutation breeding for this characteristic because it is like gambling, you may be lucky but I doubt if there is much chance. Perhaps, we should try the wild species of cassava because, so far, it is not found in cultivated cassava species.

Cock: We should be guided by the story of Opaque-2 maize, which contains high lysine, is more nutritious than the ordinary variety of maize, is excellent for feeding to pigs, and is very high yielding, but you cannot convince any farmer to grow it. Will we not get into the same problem if we breed a zero cyanide cassava?

Ermans: Do you have any information on the influence of fertilizer on the linamarin content of cassava?

De Bruijn: Yes, nitrogen fertilizer increases yield, as does low soil potassium, but phosphorus, magnesium, and calcium produce conflicting results and are not as important. A poor soil will be low in potassium and, therefore, will increase the cyanide content of cassava.

Phillips: Even if it is economical to use fertilizer, there is still the question of whether or not farmers will use it. I can tell you a story about farmers in Thailand who were given free fertilizer for their cassava. During harvesting, it was discovered that there was no increase in cassava yield; however, there was a significant increase in the yield of the pepper plants. Apparently, all of the fertilizer was applied to the pepper plots. Because we are dealing with a problem that requires new technology to meet the food needs of a population, there is hope that it may be accepted.

Cock: Although it is difficult to achieve a minimum cyanide intake, it would be nice to know what amount of iodine would be needed to counteract the effect of some of the cyanide ingested from cassava. What would be useful would be a range of values relating the iodine intake required with cyanide levels in cassava.

Gaitan: The question of genetics might be very important, especially when considering an area in which 60% of the population has goitre, but in the rest of the population this condition is absent. This may be due to genetic effects. As far as I know, there are no comprehensive genetic studies on endemic goitre.

Processing and Detoxification of Cassava

O.L. Oke[1]

Cassava is the name given to the farinaceous root of a plant that belongs to the natural order Euphorbiacene, namely *Manihot esculenta* Crantz. The plant, originally a native of Brazil, was imported by the Portuguese to West Africa to feed their slaves and is now grown in almost every part of the tropics, where it has become the staple food. It is now estimated that cassava is the staple food of about 200-300 million people around the world; contributing about 8-10% of their daily quota of energy. However, unlike other well-known sources of energy (maize, wheat, rice, potato), virtually all (about 97%) cassava is grown in the tropics; accounting for the lack of research, in the past, on cassava relative to research on other crops. With the assistance of the International Development Research Centre (IDRC), however, cassava research is now being conducted, and the importance of cassava as a food crop is finally being recognized.

Processing

Because cassava consists mainly of starch and contains cyanogenic glucosides, the whole idea of processing is to make it palatable and remove the toxicity. Consequently, cassava is never eaten raw. Soaking (fermentation) and the action of heat play prominent roles in the processing of cassava.

The sweet variety of cassava is usually boiled directly to make it soft, fried to gelatinize the starch, or roasted. Because cassava does not keep, it has to be used up within 24 hours after harvest. After about 3 days, it becomes stale and discolouration of the flesh begins to take place, which continues inward toward the centre.

Traditionally, cassava is processed into various dried products using simple techniques, such as those followed to produce *gari*, which is the product that has received the greatest attention. To make *gari*, cassava is harvested; washed; decorticated, with a loss of about 13-20% of its substance; and shredded. It is then disintegrated by washing and fermented for about 4 days in sacks under heavy stones to eliminate excess moisture. The extruded juice, which contains most of the cyanogenetic glycoside, is discarded. The contents are dried and fried in iron pans at about 80-85°C to make white *gari*, or fried in a pan with a small amount of oil to make yellow *gari*. The product is granular, free flowing, and has a faint sour odour. To make high quality *gari* (*Olowonyo*), the product is sieved to produce very fine particles. This has a high swelling capacity, e.g., it can hold over three times its own dry volume in hot water and hold the moisture.

Collard and Levi (1959) found that fermentation takes place in two stages. *Corynebacterium manihoc* breaks down the starch to produce organic acids that decrease the pH and result in the hydrolysis of linamarin, yielding gaseous hydrocyanic acid. This stage is accomplished within 24 hours. The production of the organic acid stimulates the growth of a fungus (*Geotricum candida*), which produces the aldehydes and esters responsible for the characteristic flavour of *gari*. The *gari* can be made into a thick paste with hot water and eaten with vegetable soup and meat, or dispersed in cold water, with or without sugar and milk, and eaten with bean balls or coconut.

Meuser and Smolnik (1979) have developed a process for mechanizing the production of *gari* based on laboratory and industrial pilot plant experiments (Fig. 1). The process is similar to the traditional method and pays particular attention to sanitary and nutritional requirements. The roots are peeled mechanically and ground to a mash, which is fermented anaerobically at 37°C, with the sugars being decomposed to lactic acid, acetic acid, and a small amount of ethanol. At the end of fermentation (usually

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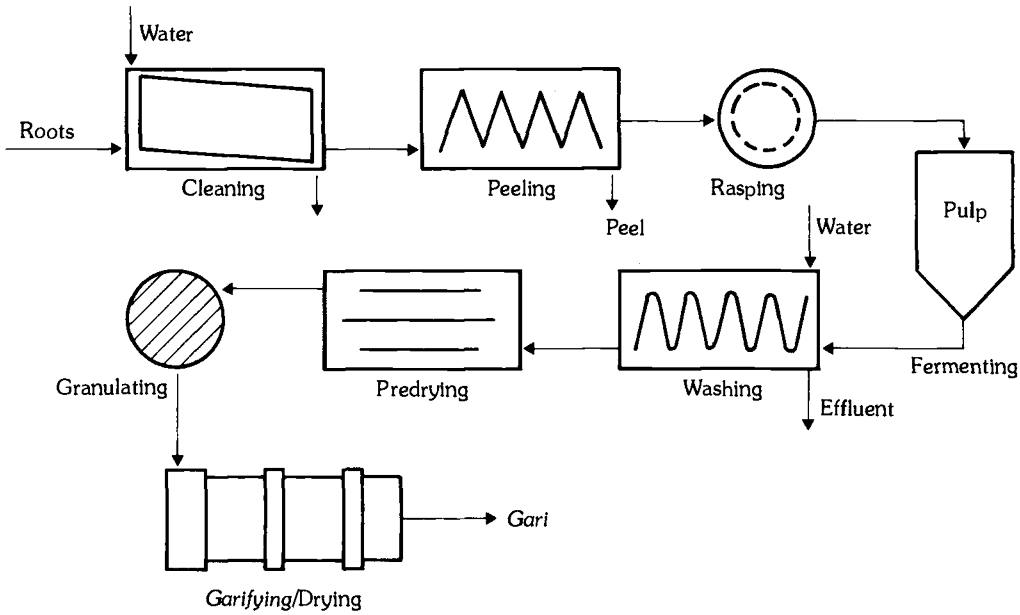


Fig. 1. Simplified flow diagram for gari *production.*

5 days, or 3 days if seeded with liquor), the fruit water is pressed out after washing and the mash is washed to remove the bound cyanide and other soluble substances. It is then drained mechanically and converted to a crumbly product by heating directly in pans to gelatinize some of the starch granules, in order to obtain particles of desired structure and ensure good digestibility. The product is then ground into flour of any granular size, which has a high starch, low mineral, and low protein content (Table 1). The residual cyanide is very low (less than 10 ppm) and the product can be stored without any change in taste for more than 1 year, with a water content of less than 12%. The washing of the mash causes a loss of about 50% of the protein and 40–70% of the minerals. The product keeps a fresh taste for a long time.

Table 1. Effect of washing fermented pulp on hydrocyanic acid content of cassava products.

Constituent	*Gari Berlin* Sample I[a]	Sample II[b]	*Farinha Amazonia*
Lactate (% ds)	0.6	0.4	0.4
Acetate (% ds)	0.15	0.05	0.05
Protein (% ds)	1.4	0.7	0.8
Minerals (% ds)	1.2	0.7	0.7
HCN (ppm)	76.7	ND	2.5

NOTE: % ds = percentage dissolved solids.
[a]Without washing.
[b]With washing.

A foodstuff similar to *gari* is known as *fufu.* In this case, the peeled cassava is soaked in water to ferment for about 2 days. The soft flesh is sieved and allowed to settle and the residue discarded. It is then transferred to a bag to allow excess moisture to drain off. The product is stored in a vessel with a small amount of clean water put on top to keep it fresh, the water being changed daily. For the preparation of *fufu* meal, the required quantity is mixed with cold water in an iron pot until it becomes a pulp. It is then warmed over a wood fire and stirred continuously with a wooden stirring device until a sticky dough, or *fufu*, is formed. Like *gari*, it is eaten with vegetable soup.

The residue from *fufu* is usually fried in iron pots and spread in the sun to dry. It is known as *kpokpogari*, and can be eaten with fish, groundnut, or meat.

Simons-Gérard et al. (1980) provided a detailed description of several of the cassava products (from the bitter cassava variety) eaten in Zaire. In the preparation of *fuku*, the peeled root is cut into pieces that are dried in the sun for 1–2 days. The pieces are then bruised in a mortar with corn, which has been fermented for 12–24 hours. Further fermentation of the corn is stopped by grilling the resulting flour on a plank. This is then made into a gruel with boiling water and eaten in this form.

Unlike *fuku*, the preparation of *chickwangue* involves soaking the cassava in water for 2–6 days before mashing it into a puree that is simmered to form a paste of firm and elastic consistency. The paste is then enveloped in palm or banana leaf.

Ntuka is prepared by soaking the cassava roots for 3-5 days, followed by peeling and steaming in a pot.

In the case of *moteke*, the cassava roots are soaked in stagnant water for 1–2 days and then worked into a paste. The paste is divided into pieces and dried in the sun before grinding into flour. The gruel is made by mixing the flour with boiling water.

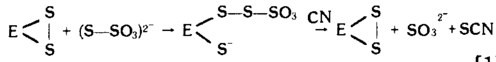
About 95% of the food eaten in Ubangi (Zaire) is made from cassava and about 80% of this consists of *fuku*, which is eaten twice daily on the average.

In Sri Lanka, cassava roots are peeled, washed, cut into pieces, and boiled in water. The water is drained off and the pieces are eaten with curry. Alternatively, it can be cut into chunks and cooked in spices as a vegetable. Recently, there have been attempts to use cassava as a substitute for flour, both for making bread and for use in traditional breakfast preparations such as *pittu*, *hoppers*, and *string hoppers* (Wijeratne 1974).

In some parts of the tropics, cassava roots are fermented to make beer and also used in the production of alcohol. In Brazil, the alcohol produced is blended with gasoline at a ratio of 20:80 to form gasohols for fuel. In North America and Europe, cassava is made into gel and used as a thickener in convenience foods. It is also made into commercial starch. It is a good substrate for producing single-cell proteins. Research is under way toward making composite flour, baby foods, and other new products with cassava. In the early 1950s, bread baked in Brazil and Madagascar contained about 10–13% cassava flour by law.

Detoxification

When cassava is processed into foodstuffs, not all of the cyanogenic glucosides are eliminated; some remain and are ingested. In the absence of B-glucosidase, most of the glucoside is excreted, unchanged, in the urine and very little in the faeces (Adewusi 1981). However, if taken together with leaf components or other ingredients that may contain B-glucosidase (in addition to residual linamarase and cyanogenic glucoside, which will react upon rehydration), hydrolysis takes place and hydrocyanic acid (cyanide) is liberated. If the amount of cyanide released is minimal, the body has a very efficient system of detoxification to thiocyanate (SCN) through the enzyme rhodanese (reaction 1) (Oke 1969):



[1]

The toleration for hydrocyanic acid in foodstuffs and animal feeds, and methods of reducing it in fresh roots to within suitable limits, are major problems related to the use of cassava products. It is difficult to remove the last traces without making the food unsuitable for consumption. Even when the sweet variety is boiled or dried, or when the bitter variety is fermented, there is still the possibility of some residual cyanide, and the range may be very wide, 10–120 ppm, depending upon the cyanide content of the fresh root.

Because peeled cassava root contains about 61% water and a soluble toxic cyanogenic glucoside, the first stage in the detoxification process is the removal of at least part of the water, which will carry the toxin with it. This is accomplished in several ways, e.g., putting the cassava in a sack and weighing it down with stones; centrifuging, as is done commercially; use of a mechanical press; manual squeezing; etc. Most of the residual glucoside (and water) is then eliminated by some form of heating. In some cases, there is an initial step that involves soaking the root for a number of days, during which time the microflora in the cassava cause fermentation to occur, which is now known to be complementary to the activity of the endogenous linamarase, which effectively carries out the degradation. Maduagwu 1981 found that inhibition of linamarase activity by 1,5-gluconolactone (a potent inhibitor of B-glucosidase activity) resulted in a significant reduction in the degradation of linamarin — about 35% in 24 hours and 65% in 72 hours.

When glucose is included in the above medium, on the other hand, degradation of linamarin is enhanced by about 10%, especially after 36 hours. This is due, presumably, to an increase in microbial population in situ. Because various cassava species contain different amounts of sugars, this may become an important factor in the relative rates of fermentation. When fermentation was inhibited by sterilization or the addition of sodium iodoacetate, the rate of disappearance of bound cyanide from the medium was similar to that from the control, especially within the first 48 hours, indicating that it is the endogenous linamarase that effectively causes the breakdown of the linamarin.

In some cases, detoxification is carried out by heating only. This seems to be effective in some cases but not in others, because the heat may result in the breakdown of the enzyme linamarase without affecting the glucoside. Thus, cooking destroys the enzyme linamarase at about 72°C, while leaving about 90% of the glucoside intact. In a similar manner, simple drying of sliced or rasped roots is capable of removing about 90% of the glucoside at 60°C but is less effective if heating is carried out at 100°C due to denaturing of the enzyme. On the contrary, Paula and Rangel (1939) reported that cassava containing 39 ppm cyanide was reduced to 17 ppm cyanide by sun-drying and 6 ppm cyanide by oven-drying. Joachim and Pandittesekere (1944) reported that boiling a variety of cassava roots containing 103–232 ppm cyanide could reduce the cyanide content to 27–87 ppm regardless of the initial content of cyanide in the roots. Those roots that did not become soft and floury upon boiling were least affected. Raymond et al. (1941) were able to reduce the cyanide content from 332 ppm to 10 ppm by boiling, whereas Paula and Rangel (1939) removed all of the cyanide in their roots by boiling. Steeping in warm water for short periods before drying can reduce the cyanide content to a considerable degree, especially if the root is grated as well. Thus, Razafimaherry (1953) reported that the Madagascar food product *bournoka*, which is prepared by steaming, is free of cyanide.

From the traditional processing of cassava, the glucoside is eliminated at the soaking (fermentation) stage, during the heating stage (especially with palm oil), or both. In Nigeria, the effect of cyanide toxicity is counteracted by using palm oil in the preparation of cassava foods. It is interesting that *gari* prepared by frying the fermented cassava pulp with palm oil usually does not contain any cyanide, compared with 5–20 ppm cyanide in *gari* fried without palm oil (unpublished data). The effect of palm oil on cyanide toxicity is currently under investigation (Formunyan, in preparation).

Because *gari* is the cassava product that has been studied most extensively, most of the mechanisms of detoxification will be inferred from it. The bark of cassava contains most of the enzyme, whereas the inner part contains little. During peeling and grating, the enzyme comes into contact with the glucoside and hydrolysis takes place, liberating cyanide. The rate at which the cyanide is liberated depends upon the length of time that the enzyme is in contact with the glucoside. This is probably the reason for allowing fermentation to proceed for days. This could be accelerated, however, if the whole root is grated, because the activity of the enzyme in the bark (and leaves) is so great that hydrolysis is complete within a very short period of time (1 hour). A lot of work has been carried out in this regard by Meuser and Smolnik (1979). As is well known, the first stage in the breakdown of linamarin is hydrolysis to glucose and cyanohydrin, with the cyanohydrin breaking down further to acetone and hydrocyanic acid. Thus, the cyanide in cassava can occur as free hydrocyanic acid or as bound cyanide (glucoside or cyanohydrin) (reaction 2).

$$\text{glu—O—}\underset{\displaystyle CH_3}{\overset{\displaystyle CN}{C}}\text{—}CH_3 + H_2O \xrightarrow{\text{Linamarase}} \text{glucose} + \text{HO—}\underset{\displaystyle CH_3}{\overset{\displaystyle CN}{C}}\text{—}CH_3 \qquad [2]$$

Because of the high instability of cyanohydrin at pH values greater than 5.0 (the pH of the pulp is usually about 6.0), the equilibrium reaction is usually to the right, i.e., the release of cyanide (reaction 3) (Cooke 1978).

$$\text{HO—}\underset{\displaystyle CH_3}{\overset{\displaystyle CN}{C}}\text{—}CH_3 \underset{pH<5.0}{\overset{pH>5.0}{\rightleftharpoons}} HCN + O = \underset{\displaystyle CH_3}{C}\text{—}CH_3 \qquad [3]$$

Therefore, Meuser and Smolnik (1979) devised a means of removing the fruit water in *gari* preparations to limit the cyanide content to less than 10 ppm. The next problem is removal of the residual cyanide by heating. Using different drying techniques, Meuser and Smolnik (1979) showed that freeze-drying or flash-drying eliminates only the free cyanide, which accounts for only 50% of the total cyanide present, whereas roller-drying or drum-drying of the fresh pulp at a pH of 5.5–5.8 removes the cyanide almost completely. In this case, thermal decomposition of the glucoside probably takes place and the equilibrium reaction to the right (i.e., cyanide release) is favoured (reaction 3). On the other hand, roller-drying of fermented and dewatered pulp results in high residual cyanide, due to a lowering of the pH to 3.8, which favours the equilibrium to the left, i.e., high stability of cyanohydrin (reaction 3). Under this condition, there is no further release of cyanide and the equilibrium between bound and free cyanide is stabilized in favour of the bound cyanide in the form of cyanohydrin. The optimum condition, therefore, was chosen for drying the chips, i.e., in a warm stream of air.

Another way of eliminating the cyanide is by allowing fermentation to proceed for a longer period of time (5 days) to allow the water binding capacity of the mash to be sufficiently changed so that the fruit water can be pressed out to a reasonable degree, carrying with it the toxic cyanide. The bound cyanide can also be eliminated from unfermented pulp by diluting the fruit water. About 50% of the fruit water can be separated as a relatively concentrated solution. This is extremely useful for eliminating the acidic and toxic fruit waters. Using this newly developed process, the cyanide content of the *gari* prepared by Meuser and Smolnik (1979) can be eliminated almost entirely (Table 1) so that no health risks should arise.

Conclusions

In most of the methods used to process cassava into foodstuffs, there is usually residual cyanide, which can vary from traces to high amounts. Amongst populations that consume a lot of cassava products, a high incidence of thyroid malfunction has been reported, which has been correlated with the ingestion of the cassava products. It is necessary, therefore, to study more closely the traditional methods of processing cassava to remove cyanide. More accurate analytical techniques are needed to enable following the principles involved in the detoxification processes and improving upon them.

Finally, there is a need to study cases of acute toxicity resulting from cassava and cassava products more carefully to determine the factors involved in the toxicity, i.e., whether it is the cyanogenic glucosides or other constituents that have not yet been isolated. This might answer the question of whether or not there are goitrogens present in cassava or the diets of people in the endemic goitre areas reported by Ekpechi (1964) and Delange et al. (1973). Can it be due to their diathesis? It is known that not all forms of nutrients have equal activity and that, for unknown reasons, some individuals have greatly increased nutrient requirements, whereas others are susceptible to toxicity from excess. Have these people lost the ability to dispose of the thiocyanate being formed or are they metabolizing the glucoside at such an unusual rate that there is enough thiocyanate to compete with iodine, or is the problem simply one of iodine or protein deficiency? These problems are posed so that none of the salient points will be overlooked in subsequent interpretations of data in an effort to determine the exact causes of goitre.

Adewusi, S.R.A. 1981. Cyanide metabolism in plants and animals. PhD thesis, Chemistry Department, University of Ife, Ile-Ife, Nigeria, in preparation.

Collard, P. and Levi, S. 1959. A two-stage fermentation of cassava. Nature, 183, 620.

Cooke, R.D. 1978. An enzymatic assay for total cyanide content of cassava. Journal of the Science of Food and Agriculture, 29, 345.

Delange, F., van der Velden, M., and Ermans, A.M. 1973. Evidence of an antithyroid action of cassava in man and in animals. In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29–30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 147–151.

Ekpechi, O.L. 1964. Pathogenesis of endemic goitre in eastern Nigeria. British Journal of Nutrition, 21, 537.

Formunyan, R. 1982. Effect of palm oil in the detoxification of cyanide from cassava. PhD thesis, Animal Science Department, University of Ife, Ile-Ife, Nigeria, in preparation.

Joachim, A.W.R. and Pandittesekere, D.G. 1944. Investigations on the hydroorganic acid content of manioc. Tropical Agriculture, 100, 150.

Maduagwu, E.N. 1981. Differential effects on cyanogenic glycosides in fermenting cassava root pulp by B-glucosidase and microbial activities. Proceedings of a National Conference on the Green Revolution in Nigeria. Port Harcourt, University of Science and Technology, Port Harcourt, Nigeria.

Meuser, F. and Smolnik, H.D. 1979. Processing of cassava to gari and other foodstuffs. Starch/Starke, 32, 116.

Oke, O.L. 1969. The role of hydrocyanic acid in nutrition. Cassava as food in Nigeria. World Review of Nutrition and Dietetics, 11, 170.

Paula, R.D.G. and Rangel, J. 1939. HCN or the poison of bitter or sweet manioc. Revista Alimentar (Rio de Janeiro), 3, 215.

Raymond, W.D., Jojo, W., and Nicodemus, Z. 1941. The nutritive value of some Tanganyika foods. II. Cassava. East African Agricultural Journal, 6, 154.

Razafimaherry, R. 1953. Glucosides cyanogénétiques Pois du Cap Manioc et Bononoka. Bulletin Academie Malgache (Ser Nouvelle), 31.

Simons-Gérard, E., Bourdoux, P., Hanson, A., Mafuta, M., Lagasse, R., Ramioul, L., and Delange, F. 1980. Foods consumed and endemic goitre in the Ubangi. In Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R., ed., Role of Cassava in the Etiology of Endemic Goitre and Cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 69–80.

Wijeratne, W.R. 1974. Cultivation, processing, and utilization of cassava in Sri Lanka. In Araullo, E.V., Nestel, B., and Campbell, M., ed., Cassava Processing and Storage: Proceedings of an Interdisciplinary Workshop, Pattaya, Thailand, 17–19 April 1974. International Development Research Centre, Ottawa, Canada, IDRC-031e, 73–75.

Traditional Cassava Detoxification Processes and Nutrition Education in Zaire[1]

P. Bourdoux, P. Seghers, M. Mafuta, J. Vanderpas, M. Vanderpas-Rivera, F. Delange, and A.M. Ermans[2]

In spite of its well-recognized toxic properties, cassava is eaten by millions of people throughout the world. This paper discusses some of the aspects of detoxification processes associated with the consumption of cassava in Zaire.

Earlier studies (Delange et al. 1982) have shown an increase in serum and urinary thiocyanate concentrations from Bas Zaire to Ubangi. These variations might result from either differences in the amount of cassava consumed or differences in the cyanide (HCN) content of the food ingested. The former hypothesis was ruled out on the basis of nutrition surveys conducted in three study areas in Zaire. The latter hypothesis was investigated in terms of the HCN content of cassava tubers and cassava-based foods. In a second step, a laboratory analysis was carried out on some currently used cassava detoxification processes. Finally, on the basis of the results obtained, a trial of nutrition education was attempted with one family in a small community of Ubangi.

HCN Content of Fresh Tubers

It is generally agreed that the amount of HCN in cassava tubers varies greatly due to a number of factors, including the variety of the cassava and environmental conditions under which it is grown.

[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.

[2]Centre Scientifique et Médical de l'Université Libre de Bruxelles pour ses Activités de Coopération (CEMUBAC), Belgium, and Institut de Recherche Scientifique (IRS), Zaire, Goitre Program; Departments of Radioisotopes and Pediatrics, University of Brussels, Belgium.

Although the tubers from Bas Zaire, Kivu, and Ubangi belonged to the same botanical species (*Manihot esculenta*), morphological differences were evident for plants and tubers from Kivu when compared with those from Ubangi and Bas Zaire, which appeared to be nearly identical. Because of the differing geographical location of the three study areas, the respective environmental conditions were also different, with equatorial forest in Ubangi, savanna in Bas Zaire, and highlands in Kivu.

The tubers in these regions showed an extremely wide variation in HCN content, ranging from 5–142 mg HCN/kg in Bas Zaire to 12–205 mg HCN/kg in Kivu and 2–309 mg HCN/kg in Ubangi (Bourdoux et al. 1982). Within each of the three areas, this variation was probably a result of varietal differences among the fresh tubers studied and the different environmental conditions.

A relative comparison of the tubers from the three areas was made based on the arbitrary categories originally proposed by Bolhuis (1954). The percentage of tubers containing less than 50 mg HCN/kg increased from 45% in Ubangi to 80% in Bas Zaire, whereas the percentage of tubers with greater than 100 mg HCN/kg was similar in Ubangi and Kivu (24 and 21% respectively) but significantly lower in Bas Zaire (4%). Between areas, it was not possible to account for the difference in HCN content between the tubers. In summary, the HCN content of the tubers analyzed increases from Bas Zaire to Kivu to Ubangi.

HCN Content of Cassava Products

Cassava is subjected to various processes in an attempt to reduce the HCN content. A wide variety of traditional detoxification processes are used in different countries but all of them tend to bring the substrate (linamarin) and the enzyme (linamarase) into contact to liberate HCN.

In the three areas studied, the main food items consumed and the associated detoxification processes used by the inhabitants are as follows:

Area	Cassava product	Detoxification process
Ubangi	Paste (*fuku*)	Sun-drying + cooking
	Leaves (*mpondu*)	Washing + cooking
Kivu	Paste (*bugali*)	Fermentation + cooking
Bas Zaire	Paste (*fufu*)	Soaking + sun-drying + cooking
	Chickwangue	Soaking + sun-drying + cooking

Source: Bourdoux et al. (1982).

The typical food items in Ubangi are *fuku* and *mpondu*, which were found to have the highest mean HCN contents (17.3 and 8.2 mg HCN/kg respectively). A residual level of 6.3 mg HCN/kg was found in *bugali* from the Kivu district. Because *bugali* is prepared from cassava and sorghum grain, which is notorious for its cyanogenic content (dhurrin), the total HCN content cannot be related entirely to linamarin. The HCN content of food items from Bas Zaire, prepared through a process of soaking for several days, drying, and then cooking, is much less than in food items from either of the two other study areas.

These results suggest the presence of significant amounts of HCN in some cassava products prepared by traditional processes. It is also apparent that the efficiency of detoxification increases from Ubangi to Bas Zaire, where soaking is used widely. To determine whether or not the detoxification processes used by the inhabitants of these areas can lead to well-detoxified cassava products, the various steps in each of these processes were analyzed.

Detoxification Processes

Tubers and leaves were sampled at random at the local market and food items were prepared following the same procedures as those used by the local inhabitants (Bourdoux et al. 1982, Table 18). Extra care was taken during the test in an attempt to decrease the HCN content as much as possible.

The final HCN content, about 1.5 mg HCN/kg, of the foods prepared in the laboratory reflects the efficiency of the detoxification processes. For comparison, a series of *mpondu* samples prepared by workers of the IRS centre were examined and revealed an HCN content ranging from <1.0–25 mg HCN/kg. This demonstrates that well-detoxified foodstuffs can be obtained if the detoxification process is conducted with care.

Effect of Drying and Temperature

The most disturbing finding obtained during the preparation of *fuku* was an increase in the HCN content after sun-drying. Repeatedly, an increase in HCN content was observed in other similar experiments. The extent of the increase, however, varied from one experiment to another. This increase may have been due to the removal of water from the tubers. The variability observed might be accounted for by the time interval between the harvesting and processing of the tubers.

In a subsequent experiment, the tubers were dried for 1–8 days and the percentage of water removed from the tubers was determined (Bourdoux et al. 1982, Table 20). From the results, it is evident that the longer the drying period, the greater the amount of water removed from the tubers (e.g., 14.1% after 1 day, 70.0% after 8 days). This indicates that the main effect of sun-drying is the removal of water from the tubers, with a subsequent increase in HCN content.

Effects of Heating

The effects of heating were investigated further by dividing the tubers into four identical parts (longitudinal section) and oven-drying them at 60, 105, and 165°C to constant weight (Bourdoux et al. 1982, Table 21). These temperatures were chosen because they exceed sun-drying conditions and the decomposition temperatures reported for linamarase (72°C) (Joachim and Pandittesekere 1944) and linamarin (150°C) (Cerighelli 1955). Such temperatures, however, are never achieved by the local inhabitants while preparing their meals.

Slight heating (60°C) produced a further loss of water and a concomitant increase in the HCN content. In contrast, increasing the temperature of drying beyond 60°C causes the HCN content to decrease.

Effects of Soaking on HCN Content

Prolonged soaking of the tubers (1–5 days) resulted in lowering their HCN content, e.g., soaking for 1 day removed 45% of the HCN, whereas soaking for 5 days resulted in the removal of 97% of the initial HCN content (Bourdoux et al. 1982, Table 22).

When the HCN content is determined by autolysis, it is necessary to stress that the values obtained might be minimum values because if, for any reason, the linamarase was destroyed, HCN would not be produced from persisting linamarin.

This hypothesis, i.e., the destruction or elimination of linamarase by soaking, was evaluated by adding fresh cassava tubers with extremely low HCN content, which supposedly contained the enzyme, to bitter tubers after 6 days of soaking. Inasmuch as the sweet cassava contained excess linamarase, it was observed that the low HCN content in the bitter tubers after 6 days of soaking was actually due to the release of the linamarin originally present and not a result of the deactivation or release of the enzyme.

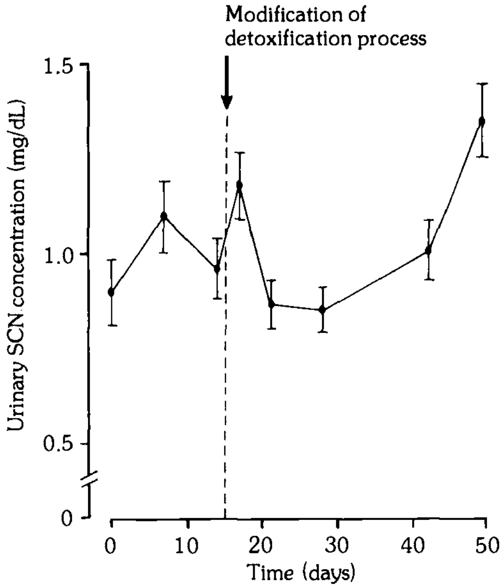


Fig. 1. Changes with time in urinary SCN concentrations (mean±SEM) in 29 persons in the village of Bokuda (Ubangi) during a trial of nutrition education.

Nutrition Education in Ubangi

Based upon the encouraging results obtained from the laboratory experiments, which indicated that improved detoxification of cassava foodstuffs is possible, a family of 29 persons was asked to modify the preparation of their main food item (*fuku*) by adding a 3-day period of soaking, a 1-day drying period for the soaked tubers, and cooking the flour for 30 min. The aim of these modifications was to reduce the thiocyanate (SCN) overload previously noted for this population. The reason for the changes were explained extensively and the consent of the whole family was obtained. The effect of this dietary manipulation was monitored by determining the concentration of urinary thiocyanate in samples collected on days 0, 7, 14, 21, 28, 42, and 49 (Fig. 1).

Before the introduction of the modifications, urinary SCN levels were fairly constant and close to 1 mg/dL. The urinary SCN concentration decreased slightly, but not significantly, on days 21 and 28 and then increased to similar or even higher levels than the initial values. A similar trend was observed in all of the people tested.

The results were shown to the villagers and, upon questioning, they explained that they had followed the modified procedures for only 3 days, after which time they decided to sell the well-detoxified cassava (i.e., *chickwangue*) at the market of Gemena to make some money. This unsuccessful trial indicates that, even with appropriately informed and apparently motivated people, changing the nutritional habits of a rural population is quite difficult.

Summary and Conclusions

The results of this study indicate that:

(1) The HCN content of tubers increases from Bas Zaire to Kivu to Ubangi.

(2) The HCN content of cassava products also increases from Bas Zaire to Kivu to Ubangi and is closely linked to traditional cassava processing methods. In this context, soaking may be regarded as the most efficient detoxification process.

(3) Well-detoxified food items can be prepared if the detoxification process is carried out carefully. Even in Ubangi, well-detoxified foodstuffs can be prepared with only slight modification of traditional cassava processing procedures.

(4) Modifying the food habits of rural populations in Africa is difficult.

The differences in the SCN levels observed in the inhabitants of the three areas investigated can be accounted for by the differences in the HCN content of fresh tubers or, more likely, due to differences in the HCN content of the food items ingested.

Evidence indicates that if, for any reason, the efficiency of cassava detoxification decreased, thiocyanate overload and concomitant thyroid problems would occur in persons that would otherwise be unaffected by such problems. Taking into account the relative role of iodine and SCN intake, similar problems would occur as a result of an increase in the dietary supply of cassava in areas with moderate or low iodine intake.

Bolhuis, G.G. 1954. The toxicity of cassava roots. Netherlands Journal of Agricultural Science, 2, 176–185.

Bourdoux, P., Seghers, P., Mafuta, M., Vanderpas, J., Vanderpas-Rivera, M., Delange, F., and Ermans, A.M. 1982. Cassava products: HCN content and detoxification processes. In Delange, F., Iteke, F.B., and Ermans, A.M., ed., Nutritional Factors Involved in the Goitrogenic Action of Cassava. International Development Research Centre, Ottawa, Canada, IDRC-184e, 51–58.

Cerighelli, R. 1955. Plantes vivrières. In Cultures Tropicales. Librairie Baillière et Fils, Paris, France, 289–378.

Delange, F., Iteke, F.B., and Ermans, A.M. 1982. Nutritional factors involved in the goitrogenic action of cassava. International Development Research Centre, IDRC-184e, 100 p.

Joachim, A.W.R. and Pandittesekere, D.G. 1944. Investigation of the hydrocyanic acid content of manioc (*Manihot utilissima*). Tropical Agricultural Magazine of the Ceylon Agricultural Society, 100, 150–163.

Effects of Cassava Processing on Residual Cyanide

Rodney D. Cooke[1]

Significance of Residual Bound and Free Cyanide

Cassava is one of the few human food crops in which the content of cyanide can cause nutritional problems. This is due to the fact that cassava contains the cyanogenic glucosides linamarin and lotaustralin, which, upon tissue damage, are hydrolyzed to hydrogen cyanide by the endogenous enzyme linamarase (Conn 1969; Nartey 1978).

Cyanide toxicity in humans and animals on cassava diets is a well-recognized problem (Oke 1968; Coursey 1973; Ermans et al. 1980; Osuntokun et al. 1969), but understanding its extent has been difficult, because little of the published data permits one to relate the effect of cyanide intake to health parameters. Monitoring the cyanide intake in differing diets has posed some problem and the majority of studies only detail the cassava content in the diets. This is due partly to some limitations in traditional assay methods for determining the total (potential) cyanide content of cassava and its products (Cooke 1978, 1979).

Another problem is that the relative toxicities of free cyanide (nonglycosidic) and bound cyanide (cyanogenic glucosides) are uncertain (Montgomery 1969). This is an important factor because these two forms of cyanide respond very differently to cassava processing. The toxicity of cassava and cassava products was, until recently, assumed to be associated with free cyanide, 50-60 mg of which constitutes a lethal dose for an adult human. The cyanogenic glucosides were, at first, thought to be of little consequence to mammals if cassava hydrolytic enzymes were inactivated. The possibility of hydrolysis during digestion has latterly been considered and oral doses of pure linamarin have been shown to produce physiological and biochemical changes in rats without the simultaneous presence in the food of linamarase activity (Philbrick et al. 1977; Barrett et al. 1978).

A difficulty with human, as opposed to animal, data is that the populations studied were in a poor nutritional state, which complicates attempts to differentiate the effects of cassava ingestion. Furthermore, chronic toxicity aspects are characterized by a number of strong interactions with other nutritional problems. Cyanide detoxification mechanisms (Westley 1981) increase the requirement for sulfur containing essential amino acids. Moreover, thiocyanate, one of the detoxification products, inhibits iodine absorption and promotes goitre (Ermans et al. 1980).

In summary, gauging the extent of cyanide toxicity in animals has been difficult because of the problem of measuring cyanide intake. In human studies, this is complicated further by the constraints involved in measuring the effects of cyanide toxicity on human health. At the Tropical Products Institute, we have simplified the first of these problems by developing an enzymatic assay for the cyanide content of cassava and cassava products that readily permits measurement of the free and bound cyanide ratio.

Analytical Difficulties Relating to Cassava Cyanide Assay

Current Assay Methods

Traditional autolytic or chemical assay methods for cassava cyanogenic glucosides depend on three stages: (1) hydrolysis of the cyanogenic glucosides; (2) isolation of cyanide

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released from the mixture (steam distillation or aspiration); and (3) determination of the cyanide.

During the first two stages, there may be problems of incomplete reaction, artifacts, and side reactions (Wood 1966; Zitnak 1973.) This may explain the many conflicting reports (Coursey 1973) describing the effects of different agronomic practices and different storage and processing conditions on the cyanide content of cassava. The enzymatic assay achieves a rapid and quantitative hydrolysis of the cyanogenic glucosides and obviates the need for steam distillation or aspiration (Cooke 1978, 1979). Minor variations in the assay procedure permit measurement of total cyanide, nonglycosidic (free) cyanide, and HCN (Cooke 1978; Cooke and De La Cruz 1982b).

Cassava Sampling Problems

Many reports discuss the effects of differing agronomic practices on the cyanide content of cassava, but few describe the sampling methods used in the various studies (Zitnak 1973). A study of three cultivars (de Bruijn 1971) indicated both longitudinal and radial gradients in the peeled roots. This has been confirmed by an analysis of eight cultivars (Cooke 1978) showing that the radial gradient is especially marked. The outer parenchyma (near the peel), in some cases, has over 10 times the cyanide concentration of the central portions. The longitudinal gradient is shallower, but sampling that ignores these two gradients can produce very misleading results.

Analysis of 43 roots, from nine plants of two clones grown under the same conditions (Cooke et al. 1978), indicated that there is also a considerable interroot variation. Representative sampling of roots and plants, therefore, is essential in any agronomic study.

Effects of Processing on the Cyanide Content of Cassava: Simple Processing Procedures Applied to Cassava Pieces

Cassava roots are traditionally processed by a wide range of methods to reduce their toxicity, improve their palatability, and convert the perishable fresh roots into stable products. These methods comprise combinations of drying, soaking, boiling, and fermentation of the roots. All of these processes decrease the total cyanide content of the cassava. The data reported in many earlier studies that employed these techniques (reviewed by Coursey (1973) and Nartey (1978)) were based on traditional assay methods.

Dehydration

Drying chips of peeled cassava roots in a forced-air dryer showed that about 25–30% of the bound cyanide was removed at 47 and 60°C (Fig. 1). The marginally greater loss at 47°C reflects the longer time spent in the intermediate moisture content range, under which conditions the enzyme is active. Faster drying, at 80 or 100°C, resulted in only a 10–15% decrease in bound cyanide (Cooke and Maduagwu 1978). The corresponding losses of free cyanide were 80% at 47°C and 85% at 60°C (Fig. 1) and over 95% at higher temperatures. The rate of loss of free cyanide is complex (Fig. 1) because it is a function of three processes: (1) loss of the volatile hydrogen cyanide; (2) loss and degradation of the less volatile cyanohydrins; and (3) production by endogenous linamarase of cyanohydrins during the initial stages of drying.

The nonglycosidic fraction of the total cyanide present in both fresh roots and chipped roots that have been stored for several hours is usually

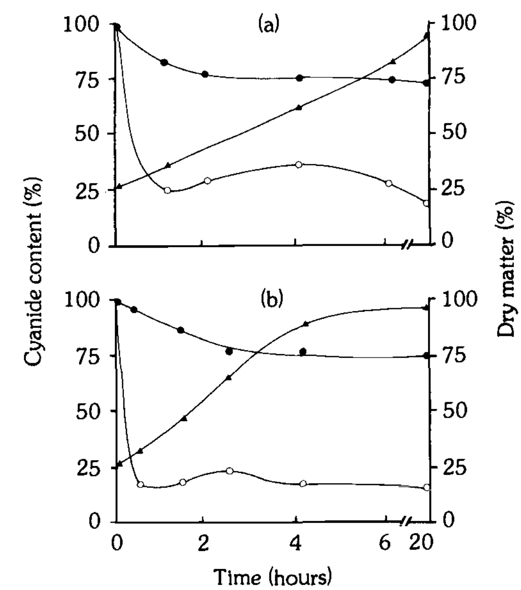

Fig. 1. Effect of drying cassava chips at (a) 46.5°C and (b) 60°C on the cyanide concentrations in the chips (dry weight basis). Free (nonglycosidic) cyanide (0), percentage of initial concentration in the chips; bound cyanide (•); dry matter content (▲).

10% or less (Cooke 1978). Consequently, the decrease in total cyanide content through air-drying is small. The slower drying rates achieved through sun-drying produce greater losses of bound cyanide, consistent with the inverse relationship between drying rate and cyanide loss observed in air-drying experiments (Cooke and Maduagwu 1978).

Losses of cyanide during dehydration, when evaluated using the enzymatic assay method, are generally smaller than those reported in earlier studies, e.g., Paula and Rangel (1939) reported an 85% loss of cyanide through oven-drying; 90% losses were quoted by Charavanapavan (1944); and Tewe et al. (1978) reported cyanide losses of 43 and 94% after oven-drying sweet and bitter grated cassava samples.

Boiling in Water

The free cyanide content of fresh chips is rapidly removed in boiling water (over 90% is removed within 15 min). The bound cyanide decreases at a much slower rate; 55% of the bound cyanide had been removed when the chips were thoroughly cooked, i.e., after 25 min (Cooke and Maduagwu 1978). Earlier reports of cyanide losses through boiling are quite variable, e.g., losses of 90–100% (Raymond et al. 1941; Paula and Rangel 1939), 50–80% (Joachim and Pandittesekere 1944; Pieris et al. 1974), and 10% (de Bruijn 1971) have been reported.

Soaking (Leaching) in Water

Rapid stirring in cold water produced a negligible decrease in bound cyanide after 4 hours, but 90% of the free cyanide was removed and most of this could be accounted for in the water. Stirring the chips overnight (18 hours) at tropical ambient temperatures caused a marked decrease in bound cyanide accompanied by a drop in pH and a sour smell, indicating the onset of fermentation (Akinrele 1964). The free cyanide content had increased, perhaps due to endogenous linamarase activity following cell disintegration or microbial glucosidase activity.

These studies of simple processing of cassava pieces (the chips used in the studies were small, with mean dimensions of 40 mm × 8.2 mm × 6.8 mm) indicate that the residual bound cyanide (cyanogenic glucoside) concentrations are greater than earlier studies had suggested. Many traditional cassava preparation methods are based on cassava pieces and the need to investigate the chronic toxicity implications of the residual bound cyanide is emphasized. Other traditional cassava preparation methods are based on disintegrated or homogenized tissues in which the bound cyanide is rapidly converted to nonglucosidic cyanide. The differences in the rate of cyanide loss when processing homogenates are described in the following sections.

Cassava Starch Extraction

Cassava starch is traditionally extracted on a small scale in many tropical countries. The process consists of wet-milling the washed roots, washing the starch from this milled pulp on vibrating trays or in mixing tanks, sedimenting the starch in wooden canals or concrete tanks, and sun-drying the product. The cassava used is usually harvested when the plant is between 8 and 20 months of age, but the root cyanide concentration is similar in this age range (Cooke and De La Cruz 1982a). Representative cyanide behaviour during the process is shown in Table 1.

A large percentage of the cyanogenic glucosides is rapidly hydrolyzed to free cyanide following tissue disintegration during milling. The greatest proportion of the cassava cyanide

Table 1. Cyanide concentrations at the different stages of starch extraction.

Stage	Moisture content (%)	Dry matter (kg)	Cyanide concentration (mg/100 g, dry basis)	Proportion of cyanide in free form (%)	Quantity of cyanide (g)
Fresh roots	61.0	100	40.9	14	40.9 (100)[a]
Milled roots	72.8	100	35.4	81	35.4 (86.6)
Residue	85.3	28.4	13.2	87	3.74 (9.1)
Wash water	93.8	11.9	229.4	100	27.30 (66.7)
Green starch	44.7	73.9	1.4	96	1.04 (2.5)
Dry starch	8.6	71.7	0.4	59	0.29 (0.7)

Source: Arguedas and Cooke (1982).
[a]Values in parentheses are the quantities of cyanide at each stage as a percentage of that in the raw material.

appears in the wash water (40–70%). The freshly sedimenting starch contains about 8–14% of the cyanide present in the raw material and this is reduced after 1–3 days of sedimentation to less than 4%. Slow sun-drying further reduces the cyanide content of the product to less than 1% of that initially present in the raw cassava. A key step in obtaining these very low residual cyanide concentrations is the conversion of most of the cyanogenic glucosides to free cyanide in the initial processing stage. Free cyanide is much easier to remove than bound cyanide (as described earlier) and the extended mixing in water; soaking in water, with associated fermentation; and slow sun-drying constitute an efficient process for removing this residual cyanide.

Importance of Cyanohydrin Decomposition in Determining Total Cyanide Loss During Cassava Processing

The preceding portions of this paper underline the importance of cyanogenic glucoside hydrolysis to free cyanide in determining the rate of cyanide removal during processing. The free cyanide produced is a mixture of cyanohydrin, resulting from linamarase action on the glucoside (Conn 1969), and HCN, resulting from chemical or enzymatic (E.E. Conn, personal communication) hydrolysis of the cyanohydrin. A recent study (Cooke and De La Cruz 1982b) of disintegrated cassava tissues in water and buffer solutions at different temperatures has indicated that the autolytic conversion of cyanogenic glucosides to free cyanide is rapid at pHs near 6. The subsequent slower conversion of the nonvolatile cyanohydrin component to HCN is a key factor in the loss of total cyanide from the tissue homogenates. This can only be said of homogenates; in tissue pieces, chips, etc., in which the proportion of damaged tissue is small, the hydrolysis of bound cyanide determines total cyanide loss. The importance of cyanohydrin decomposition to cyanide loss is consistent with the similar rates of total cyanide loss from parenchymal, cortex, leaf, and whole root homogenates despite their different linamarase activities.

The rate of cyanohydrin decomposition to HCN is very pH dependent (Cooke 1978). Those traditional processing methods that involve extensively disintegrated tissues usually undergo lactic acid fermentation (Okafor 1977), with a consequent decrease in pH to less than 4.0. This hinders total cyanide loss and perhaps explains why such traditional products retain considerable residual cyanide. Cassava starch has very low residual cyanide levels (Arguedas and Cooke 1982) because the root homogenates are thoroughly eluted with water to wash out the starch. This elution also removes most of the cyanide.

The foregoing review provides support for the utilization of the enzymatic assay method, on the basis of which residual cyanide levels appear to be higher than those reported in earlier literature. It also emphasizes the need to investigate chronic toxicity implications, especially of bound cyanide in cassava-based foods.

Akinrele, I.A. 1964. Fermentation of cassava. Journal of the Science of Food and Agriculture, 15(10), 589–594.

Arguedas, P. and Cooke, R.D. 1982. Residual cyanide concentrations during the extraction of cassava starch. Journal of Food Technology, 17, 251–262.

Barrett, M.D.P., Alexander, J.C., and Hill, D.C. 1978. The effect of linamarin and thiocyanate production on the thyroid activity of rats. Journal of Toxicology and Environmental Health, 4, 735–740.

Charavanapavan, C. 1944. Studies in manioc and lima beans with special reference to their utilization as harmless food. Tropical Agriculturist, 100(3), 164–168.

Conn, E.E. 1969. Cyanogenic glycosides. Journal of Agricultural and Food Chemistry, 17(3), 519–526.

Cooke, R.D. 1978. An enzymatic assay for the total cyanide content of cassava. Journal of the Science of Food and Agriculture, 29, 345–352.

1979. Enzymatic assay for determining the cyanide content of cassava and cassava products. Cassava Information Centre, Centro Internacional de Agricultura Tropical, Cali, Colombia, 05EC-6, 14 p.

Cooke, R.D. and De La Cruz, E.M. 1982a. The changes in cyanide content of cassava tissues during plant development. Journal of the Science of Food and Agriculture, 33, 269–275.

1982b. Evaluation of enzymatic and autolytic assays for cassava cyanide. Journal of the Science of Food and Agriculture, in press.

Cooke, R.D. and Maduagwu, E.N. 1978. The effects of simple processing on the cyanide content of cassava chips. Journal of Food Technology, 13, 299–306.

Cooke, R.D., Howland, A.K., and Hahn, S.K. 1978. Screening cassava for low cyanide using an enzymatic assay. Experimental Agriculture, 14(4), 367–372.

Coursey, D.G. 1973. Cassava as food: toxicity and technology. In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 27-36.

De Bruijn, G.H. 1971. Étude du caractère cyanogénétique du manioc (*Manihot esculenta* Crantz). Mededelingen Landbouwhogeschool (Wageningen), 71, 1-140.

Ermans, A.M., Mbulamoko, N.M., Delange, F., and Ahluwalia, R. 1980. Role of cassava in the etiology of endemic goitre and cretinism. International Development Research Centre, Ottawa, Canada, IDRC-136e, 182 p.

Joachim, A.W.R. and Pandittesekere, D.G. 1944. Investigation of the hydrocyanic acid content of manioc (*Manihot utilissima*). Tropical Agriculturist, 100, 150-163.

Montgomery, R.D. 1969. Cyanogens. In Liener, I.E., ed., Toxic Constituents of Plant Foodstuffs. Academic Press, New York, NY, USA, 143-157.

Narty, F. 1978. Cassava-cyanogenesis, ultrastructure and seed germination. Munksgaard, Copenhagen, Denmark, 262 p.

Okafor, N. 1977. Microorganisms associated with cassava fermentation for gari production. Journal of Applied Bacteriology, 42, 279-284.

Oke, O.L. 1968. Cassava as a food in Nigeria. World Review of Nutrition and Dietetics, 9, 227-250.

Osuntokun, B.O., Monekosso, G.L., and Wilson, J. 1969. Relationship of a degenerative tropical neuropathy to diet. Report of a field survey. British Medical Journal, 1, 547-550.

Paula, R.D.G. and Rangel, J. 1939. HCN or the poison of bitter or sweet manioc. Revista Alimentar (Rio de Janeiro), 3, 215.

Philbrick, D.J., Hill, D.C., and Alexander, J.C. 1977. Physiological and biochemical changes associated with linamarin administration to rats. Toxicology and Applied Pharmacology, 42, 539-551.

Pieris, N., Jansz, E.R., and Kandage, R. 1974. Cyanogenic glucoside content of manioc. 1. Enzymic method of determination applied to processed manioc. Journal of the National Science Council of Sri Lanka, 2(1), 67-76.

Raymond, W.D., Jojo, W., and Nicodemus, Z. 1941. The nutritive value of some Tanganyika foods. II. Cassava. East African Agricultural Journal, 6, 154-159.

Tewe, O.O., Maner, J.H., and Gomez, G.G. 1977. Influence of cassava diets on placental thiocyanate transfer, tissue rhodanase activity and performance of rats during gestation. Journal of the Science of Food and Agriculture, 28, 750-756.

Westley, J. 1981. Cyanide and sulfur. In Vennesland, B., Conn, E.E., Knowles, C.J., Westley, J., and Wissing, F., ed., Cyanide in Biology. Academic Press, New York, NY, USA, 61-76.

Wood, T. 1966. The isolation, properties and enzymic breakdown of linamarin from cassava. Journal of the Science of Food and Agriculture, 171, 85-90.

Zitnak, A. 1973. Assay methods for hydrocyanic acid in plant tissues and their application in studies of cyanogenic glycosides in *Manihot esculenta*. In Nestel, B. and MacIntyre, R., ed., Chronic Cassava Toxicity: Proceedings of an Interdisciplinary Workshop, London, England, 29-30 January 1973. International Development Research Centre, Ottawa, Canada, IDRC-010e, 89-96.

Additional Reading List

Cardenas, O.S. and de Buckle, T.S. 1980. Sow cassava starch production: a preliminary study. Journal of Food Science, 45, 1509-1512.

Cooke, R.D., Blake, G.G., and Battershill, J.M. 1978. Purification of cassava linamarase. Phytochemistry, 17, 381-383.

Harris, J.R., Merson, G.H.J., Hardy, M.J., and Curtis, D.J. 1980. Determination of cyanide in animal feeding stuffs. Analyst, 105, 974-980.

Maduagwu, E.N. 1979. Cyanide content of gari. Toxicology Letter, 3, 21-24.

Maduagwu, E.N. and Fafunso, M. 1980. Particle size distribution of HCN in gari, a cassava-based product. Toxicology Letter, 7, 171-174.

Meuser, F. and Smolnik, H.D. 1980. Processing of cassava to gari and other foodstuffs. Stärke, 32, 116-122.

Meuser, F., Smolnik, H.D., Rajani, Ch., and Giesemann, H.G. 1978. Comparison of starch extraction from tapioca chips, pellets and roots. Stärke, 30, 299-306.

Ngaba, P.R. and Lee, J.S. 1979. Research note: Fermentation of cassava. Journal of Food Science, 44, 1570-1571.

Discussion: Cassava Processing and Nutrition Education

The discussions during this session reflected the need for clarification of several issues related to domestic and commercial processing of cassava.

Is the quantity of the enzyme linamarase a limiting factor in the efficiency of processing cassava? It was pointed out that in cassava pieces, or disintegrated tissues, the limitation of the cyanide loss is the conversion of glucosides through linamarase.

Does cooking cassava in oil play an important role in the elimination of cyanide? What are the possible mechanisms of action? Apparently, the addition of palm oil results in much higher cooking temperatures, which, in turn, lead to decomposition of some of the glucosides and release of cyanide. In Nigeria, for example, cassava is often consumed as *gari*, which is cooked in palm oil. Palm oil has also been used, traditionally, by local populations as an antidote to cyanide toxicity caused by the consumption of cassava. This information, however, is not based on documented studies.

What is the relative efficiency, and mechanism involved, in the preparation of cassava leaves by fermentation or the addition of bicarbonate? Both of these processes are used in Zaire. It was felt that with the bicarbonate treatment the residual cyanide levels are probably as low and maybe lower than after fermentation. Depending upon the amount, the addition of bicarbonate would result in a high pH and low acidity, with subsequent breakdown of cyanohydrin. This, in turn, would facilitate the reduction of residual cyanide.

Are the different cyanide levels reported in cassava roots in various studies real or related to the method of determination used? It was apparent that there was a lack of standardization in this area. In some studies, the concentration of cyanide content was expressed on the basis of the fresh weight. There may also be differences in drying conditions and original water content of the tubers. It is also probable that newly developed analytical methods, such as the enzyme assay technique, would result in different values. The measurement of free versus bound cyanide was also discussed.

Means of improving traditional methods of detoxification and promoting the adoption of these techniques by local populations were discussed. For example, it was suggested that tissues be soaked in water for an additional 3 days, as compared with the traditional drying of cassava pieces in the sun in Zaire. An initial attempt to modify the people's nutritional practices had not proved successful. It was pointed out that the suggested change was quite significant in the face of food shortages and implications for increased manpower resources to monitor soaked cassava. A suggestion was also made to increase the use of multiple washing of cassava. Because both bound and free cyanide are soluble in water, multiple washing of cassava, and changing the water each time, can remove most of the cyanide, even in the absence of fermentation. Caution was advised in the use of this process because it also leads to the removal of starch and reduces the nutritional value of the raw material.

Further discussion of Dr Cooke's enzyme assay methods was recommended, with some concern being expressed about its utility in laboratories in developing countries. The method is more rapid than the traditional one but is also more complex.

It was obvious that more attention needs to be paid to the field of nutrition education as it relates to consumption of cassava and endemic goitre.

Conclusions and Recommendations

There was general agreement that research on endemic goitre and cretinism has produced fruitful results. In particular, the causal relationship between chronic consumption of cassava and the occurrence of endemic goitre and cretinism has been definitively established. As well, successful preventive and therapeutic measures have been proposed.

It can be estimated that about 1 billion people are at risk of being goitrous, with a large proportion of this population in the tropics having intakes of iodine of around 50 μg/day or less. There are probably 500 million of these people who eat enough cassava to potentially aggravate the problem of lack of iodine and who could develop goitre rapidly if their cassava intake increased.

It was stressed, therefore, that continued research is required. In this regard, recommendations along five lines were presented as guidelines for future efforts.

(1) *Further evaluation of the multifactorial etiology of endemic goitre*: Although iodine deficiency is recognized as the main etiological factor of endemic goitre, other factors have been identified. Some of them, such as cassava, play an additional role; others, such as water pollution, can play a decisive etiological role, even in the absence of iodine deficiency.

It has been recommended that a few additional detailed studies be conducted in areas of the world with a high prevalence of goitre and high cassava consumption to further evaluate the conclusions of the work conducted in Zaire.

Additional variables should be studied in these areas to further define acceptable cyanide levels in human foods. These variables include, for example, the content of essential sulfur amino acids in food, the intake of vitamin B_{12}, the role of water supply and sources, and the role of seasonal variations in the intake of cassava. Because of the possible shortage of technical facilities in all of the areas under investigation and to facilitate comparison of the results obtained, some reference laboratories could be responsible for the achievement of some of the crucial analytical procedures.

In the long term, it has been recommended that the following be investigated: (i) other animal models more closely related to humans regarding thyroid physiopathology, such as pigs and monkeys; (ii) the subclinical effects of endemic goitre on human development, such as the impairment of intellectual development and minimal brain damage in individuals of endemic areas who do not present all of the dramatic features of endemic cretinism; and (iii) the implementation of goitre prophylaxis programs in different contexts based on iodination of salt, bread, and water, and the real impact of these programs on the health of the populations.

(2) *Evaluation of environmental factors involved in chronic cassava toxicity of organs other than the thyroid*, such as the nervous system (ataxic neuropathy) and the pancreas (calcifying pancreatitis).

(3) *Food sciences technology and processing*: (i) Evaluate simplified methods for estimating cyanide content of plants and food products, in particular for

agricultural screening for low cyanide varieties (enzymatic methods look particularly promising). (ii) Extend studies on the effects of processing on residual cyanide levels in human foods. (iii) Recommend an acceptable level of cyanide in food. (iv) Set up and appreciate the efficiency of nutritional education trials of modified processing methods of cassava and appreciate the resulting decreasing degree of thiocyanate overload in humans.

(4) *Agriculture*: Continue agricultural studies to select low cyanide cassava varieties, bearing in mind the possible effects of a low cyanide content on resistance to diseases and pests and on production yield.

Assess possible toxicity for humans of milk or meat from animals fed on cassava-based diets.

(5) *Information*: Continue efforts to disseminate the information presently available on cassava toxicity and future research plans as widely as possible to appropriate scientific groups in various parts of the world through organizations such as the International Development Research Centre (IDRC), Centro Internacional de Agricultura Tropical (CIAT), Food and Agriculture Organization of the United Nations (FAO), and World Health Organization (WHO).

In parallel, disseminate information on improved technology in processing of cassava or utilization of low cyanide varieties in populations affected or at risk and appreciate the acceptability and effects of this sanitary education on the physical and mental health of these populations.

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