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Evidence of an Antithyroid Action of Cassava in Man and in Animals[1,2]

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Abstract Previous epidemiological and metabolic studies concerning the etiology of endemic goitre on Idjwi Island (Kivu Lake, Republic of Zaïre) led to the conclusion that iodine deficiency was not the single causal factor. Indeed, goitre prevalence exhibited striking regional variations although the whole island was subjected to a severe and uniform iodine deficiency, and the possible role of a dietary goitrogen was suspected. The present work was undertaken in order to detect an antithyroid activity, in men and in rats, of the foods eaten in this area.

The absorption of cassava in men induces an inhibition of the penetration of iodide into the thyroid as expressed by a considerable drop in radioiodine thyroidal uptake and a rise in urinary excretion of stable and labelled iodide. Inhibition of thyroid uptake is also obtained in rats fed with cassava and this effect is accompanied by a striking rise in the plasma thiocyanate concentration and urinary thiocyanate excretion. These results are similar to those obtained in separate experiments where rats were fed thiocyanate.

These investigations show that cassava grown on Idjwi Island, an endemic goitre area, has an antithyroid action in men and in rats. Cassava could constitute a dietary goitrogen responsible, at least partially, for endemic goitre in this area. The antithyroid action of cassava is due to thiocyanate. Thiocyanate is probably endogenously produced from cyanide, which is released by a cyanogenic glucoside present in large quantities in cassava.

Résumé Des études épidémiologiques et métaboliques antérieures sur l'étiologie du goitre endémique dans l'île d'Idjwi (lac Kivu, République de Zaïre) ont démontré qu'une carence d'iode n'est pas la seule cause de cette maladie. En fait, la fréquence du goitre accuse des variations régionales remarquables, bien que l'île entière souffre d'une carence d'iode sérieuse et uniforme. On soupçonne la présence possible d'un agent causatif du goitre dans le régime alimentaire. La présente étude a été entreprise dans le but de déceler, chez l'homme et le rat, une activité antithyroïdienne attribuable aux aliments mangés dans la région.

L'absorption du manioc chez l'homme empêche l'iode de pénétrer dans la thyroïde, comme l'indiquent une baisse considérable de la captation d'iode radioactif par la thyroïde et une augmentation d'iode stable et marquée dans l'urine. Un régime à base de manioc empêche la captation

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d'iode par la thyroïde chez le rat également. Cet effet est accompagné d'une élévation notable de la teneur en thiocyanate du plasma et de l'élimination de thiocyanate dans l'urine. Ces résultats sont en accord avec ceux d'essais séparés au cours desquels des rats ont été nourris de thiocyanate.

Ces recherches démontrent que le manioc cultivé dans l'île d'Idjwi, région où le goitre est endémique, a une action antithyroïdienne chez l'homme et chez le rat. Il est donc possible que le manioc soit l'aliment responsable, du moins en partie, du goitre endémique dans la région. L'action antithyroïdienne du manioc est due au thiocyanate. Le thiocyanate est probablement produit par réaction endogène à partir du cyanure, qui est lui-même libéré par un glucoside cyanogène présent en grande quantité dans le manioc.

THE role played by cassava in the etiology of endemic goiter has been suspected by several researchers on the basis of observations made in Nigeria (Nwokolo et al. 1961; Ekpechi 1967; Oluwasanmi and Alli 1968; Osuntokun 1971). This hypothesis has been supported by our investigations carried out in Idjwi Island, Kivu Lake, Republic of Zaïre. An epidemiological survey covering the entire population of the island showed very important regional variations of goiter prevalence, which reached 55% in the north of the island and only 5% in the south (Delange et al. 1968). The severity of this endemia is emphasized by the endemic cretinism prevalence, which reaches 1.1% of the population. Several metabolic studies showed that a difference of iodine deficiency cannot account for the epidemiological differences observed between the north and south. Indeed, an extremely severe iodine deficiency has been observed in the goitrous area as well as in the nongoitrous area (Thilly et al. 1972). These observations, and the fact that in other parts of the world subjected to severe iodine deficiency no endemic goiter has been observed (Roche 1959; Choufoer et al. 1963; Riviere et al. 1968), led us to the hypothesis that iodine deficiency is only a permissive factor in the etiology of endemic goiter in man. To explain the epidemiological observations made in Idjwi, we systematically surveyed the differences between the environmental factors in the goitrous and nongoitrous areas of the island. A nutritional survey did not reveal quantitative or qualitative differences between the two regions, except for cassava, the consumption of which is higher in the goitrous area than in the nongoitrous area. Furthermore, the nature of the soil is different in the two regions; in the north, granite, and in the south, basalt (Ermans et al. 1969).

Table 1 shows that the plasma thiocyanate (SCN) concentration observed in the inhabitants of Idjwi is four times higher than in the Belgian controls and that urinary excretion of SCN is higher in the goitrous area than in the nongoitrous one ($P < 0.001$). The presence of abnormal amounts of SCN in blood and urine may be considered evidence of the presence of a goitrogenic factor in the foodstuff (Silink 1964).

TABLE 1. Thiocyanate levels in plasma and urine in Idjwi inhabitants and Belgian controls (number of samples shown in parentheses; data from Ermans et al. 1969).

	Plasma SCN concn (*mg/100 ml* ± SE)	Renal SCN excretion (*mg/24 h* ± SE)
Goitrous area	1.10 ± 0.09 (56)	14.3 ± 1.5 (30)
Nongoitrous area	1.07 ± 0.11 (56)	10.0 ± 0.9 (47)
Belgian controls	0.24 ± 0.03 (30)	–

Metabolic Studies in Man

To detect the antithyroid action of foods consumed in Idjwi, we compared the ingestion of several foods on the thyroidal uptake of radioiodine (Delange et al. 1971). The above-mentioned observations led us to focus our investigation on cassava (*Manihot* spp.). The foods considered were cassava, bananas, peanuts, and pumpkins. They were provided from fields located near the dwellings of the subjects studied and were prepared in the customary manner. One group of subjects was fed rice imported from Europe, used as a goitrogen-free control food. Ten microcuries of ^{131}I were administered orally immediately after ingestion of the meal and thyroidal uptake of ^{131}I was estimated 24 h later. Table 2 shows the results of this investigation. The mean values of thyroidal uptake observed in patients who had eaten bananas, peanuts, and pumpkins are comparable to those of the control group. By contrast, the mean values in patients who had eaten cassava are significantly lower. Additional investigations showed that this effect is accompanied by an increase in

TABLE 2. Influence of the ingestion of different foods on thyroid uptake of radioiodine in the goitrous and nongoitrous areas of Idjwi Island (data from Delange and Ermans 1971).

Foods	No. subjects	Avg amount ingested (*g*)	^{131}I thyroid uptake (*24 h, % dose*)	*t*-test (*P*)[a]
Goitrous area				
Rice (control group)	22	315	86.8 ± 2.4	
Cassava	27	490	71.9 ± 2.4	<0.001
Bananas	10	675	85.4 ± 3.7	>0.5
Peanuts	10	165	92.5 ± 1.7	>0.1
Pumpkins	10	520	79.5 ± 3.5	>0.05
Nongoitrous area				
Rice (control group)	22	505	73.5 ± 2.1	
Cassava	10	475	74.8 ± 2.1	>0.5

[a]Compared with the control group (rice).

urinary excretion of labelled iodine. Similar results are shown in Fig. 1, which concerns an investigation performed on one of the authors (F.D.), and shows the comparison of curves of thyroidal uptake of radioiodine obtained in the same subject after a control meal and after ingestion of a meal of cassava grown in the goitrous area of the island. Urine was completely collected over 24 h following the administration of the tracer. The curve obtained after ingestion of cassava shows a clear slowdown of the thyroidal uptake of ^{131}I compared with the curve obtained after a rice meal. This change is accompanied by an increase in urinary excretion of radioiodine per day, the

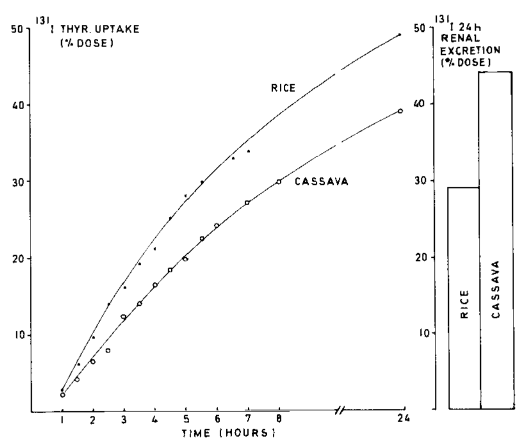

FIG. 1. Comparison of the thyroid uptake and urinary excretion of radioiodine in a Belgian subject after a meal of rice and after a meal of cassava grown in the goitrous area of Idjwi Island.

reduction in thyroid trapping corresponding quantitatively to an increase in its excretion in the urine. This effect is associated with a sharp increase in urinary excretion of stable iodine. These studies show that the absorption of cassava grown in the goitrous area of Idjwi brings about partial inhibition of iodine uptake by the thyroid and an increase of its renal excretion. Similar studies performed in the nongoitrous area of the island showed that, in contrast, the ingestion of cassava grown in that area did not modify thyroid uptake to any appreciable extent (Table 2).

Identification of Antithyroidal Substances

We identified the antithyroidal substance among the foods consumed in Idjwi. The foods most frequently suggested as containing goitrogenic factors belong to the family Cruciferae, *Brassica* species. These plants contain relatively large amounts of thioglucosides, the enzymatic hydrolysis of which releases SCN and allied substances (Van Etten 1969). Enzymatic hydrolysis occurs when the wet, unheated plant is crushed. Among the foods consumed in Idjwi, beans, peanuts, pumpkin seeds, cassava flour, and cassava roots were analyzed for their thioglucoside content but no trace could be detected. It was then necessary to know whether the above-mentioned SCN-like action after cassava ingestion was not related to the endogenous production of SCN. Indeed it is well established that cassava contains cyanogenic

TABLE 3. Cyanide content of cassava from the goitrous area of Idjwi Island.

	Pulp (*mg/kg* ± SE)	Integument (*mg/kg* ± SE)
Flour	30 ± 22	139 ± 145
Variety 1	163 ± 11	227 ± 14
Variety 2	180 ± 3	284 ± 27
Variety 3	454 ± 27	446 ± 23
Variety 4	698 ± 88	963 ± 112

glucosides whose enzymatic hydrolysis releases cyanide. This occurs when plant tissue is traumatized or by intestinal microflora.

After ingestion of cassava, cyanide is absorbed by the gastrointestinal tract and rapidly detoxicated into SCN by an enzymatic reaction involving sulfurtransferase, which is widely distributed in various organs (Montgomery 1969). Among the foods consumed in Idjwi Island, which were analyzed, only cassava contained cyanogenic glucosides. Table 3 shows that the cyanide content of cassava flour is very low (about 30 mg/kg) and frequently nonexistent. Furthermore, in cassava roots the amounts of cyanide are higher in the integument than in the pulp. The varieties of cassava roots analyzed are not identified botanically but they were distinguished by the inhabitants of the island because of their degree of toxicity. No significant difference in cyanide content was observed between cassava roots from the two regions of the island.

These results led us to study the antithyroid action of a single meal of cassava and to compare it with the action produced by acute administration of SCN in iodine-deprived rats. Four groups of rats were administered orally: distilled water, 1 mg SCN, 2 mg SCN, and 5 g cassava roots respectively and immediately injected intraperitoneally with ^{131}I. In each group, rats were killed 2 h and 8 h after the injection. Table 4 shows that,

TABLE 4. Plasma thiocyanate concentration (*mg/100 ml*, ± SE) of rats after a single ingestion of different diets.

Diet	Single ingestion: After 2 h	Single ingestion: After 8 h	No ingestion (*controls*)
Water	0.51 ± 0.02	0.51 ± 0.02	0.54 ± 0.02
SCN (1 mg)	2.30 ± 0.15	1.27 ± 0.02	0.55 ± 0.02
SCN (2 mg)	4.89 ± 0.07	1.65 ± 0.07	0.58 ± 0.02
Cassava	1.51 ± 0.13	1.94 ± 0.08	0.73 ± 0.04

TABLE 5. Thyroid uptake of ^{131}I (*% of dose*) in rats after a single ingestion of different diets.

Diet	After 2 h	After 8 h
Water	25.3 ± 2.6	67.7 ± 3.1
SCN (1 mg)	23.1 ± 1.2	57.1 ± 7.0
SCN (2 mg)	14.1 ± 2.0	51.9 ± 2.6
Cassava	12.9 ± 6.6	40.1 ± 5.7

compared with rats administered distilled water, the plasma SCN concentration of rats fed cassava progressively increased. On the other hand, the administration of SCN rapidly increased the plasma SCN concentration to very high levels (2 h) which then decreased to reach at 8 h values lower than those observed in rats fed cassava. Table 5 shows that thyroid uptake of radioiodine was reduced by administration of cassava and SCN, and was proportional to the dose of SCN administered in the SCN groups (1 and 2 mg). After 8 h, the thyroid uptake of ^{131}I was lower in the cassava group than in the SCN groups. It is noteworthy that the thyroid uptake of radioiodine is closely related to the plasma SCN concentration; the uptake of ^{131}I is inversely proportional to the plasma SCN concentration. Table 6 shows that SCN excretion (8 h) was considerably increased by SCN administration proportionally to the dose of SCN ingested and only slightly increased by cassava ingestion. This is probably due to the progressive production of SCN in rats fed cassava when SCN is already eliminated in SCN-administered rats.

The results obtained in man and in animal are in in agreement with the view that the antithyroid action of cassava is related to the endogenous production of SCN from cyanide released by the cyanogenic glucosides present in cassava. Furthermore, the results suggest that this food in the presence of an iodine deficiency constitutes a goitrogenic factor, the existence of which was

TABLE 6. Thiocyanate excretion 8 h after ingestion of a single meal of different diets.

Diet	SCN (*mg* ± SE)
Water	0.009 ± 0.002
SCN (1 mg)	0.419 ± 0.028
SCN (2 mg)	1.253 ± 0.268
Cassava	0.056 ± 0.013

proposed by Delange and Ermans (1971), and that it can play a role in the etiology of endemic goiter in Idjwi island. However, the results of the food analysis do not allow us to suggest that cassava is the single factor responsible for the difference in goiter prevalence between the north and the south of Idjwi Island.

References

CHOUFOER, J. C., M. VAN RHIJN, A. A. H. KASSENAAR, AND A. QUERIDO. 1963. Endemic goiter in western New Guinea: iodine metabolism in goitrous and nongoitrous subjects. J. Clin. Endocrin. 23: 1203.

DELANGE, F., AND A. M. ERMANS. 1971. Role of a dietary goitrogen in the etiology of endemic goiter on Idjwi Island. Amer. J. Clin. Nutr. 24: 1354.

DELANGE, F., C. THILLY, and A. M. ERMANS. 1968. Iodine deficiency, a permissive condition in the development of endemic goiter. J. Clin. Endocrin. 28: 114.

EKPECHI, O. L. 1967. Pathogenesis of endemic goitre in Eastern Nigeria. Brit. J. Nutr. 21: 537.

ERMANS, A. M., C. THILLY, H. L. VIS, AND F. DELANGE. 1969. Permissive nature of iodine deficiency in the development of endemic goiter, p. 101. *In* J. B. Stanbury [ed.] Endemic goiter. Pan American Health Organization Scientific Publication 193.

ETTEN, C. H. VAN. 1969. Goitrogens, p. 103. *In* I. E. Liener [ed.] Toxic constituents of plant foodstuffs. Academic Press, New York.

MONTGOMERY, R. D. 1969. Cyanogens, p. 143. *In* I. E. Liener [ed.] Toxic constituents of plant foodstuffs. Academic Press, New York.

NWOKOLO, C., O. L. EKPECHI, AND U. NWOKOLO. 1966. New foci of endemic goitre in Eastern Nigeria. Trans. Roy. Soc. Trop. Med. Hyg. 60: 97.

OLUWASANMI, J. O., AND A. F. ALLI. 1968. Goiters in Western Nigeria. Trop. Geogr. Med. 20: 357.

OSUNTOKUN, B. O. 1971. Epidemiology of tropical nutritional neuropathy in Nigerians. Trans. Roy. Soc. Trop. Med. Hyg. 65: 454.

RIVIERE, A., D. COMAR, M. COLONOMOS, J. DESENNE, AND M. ROCHE. 1968. Iodine deficiency without goiter in isolated Yanomama Indians: preliminary note, p. 120. *In* Biochemical challenges presented by the American Indian. Pan American Health Organization Scientific Publication 165.

ROCHE, M. 1959. Elevated thyroidal I^{131} uptake in the absence of goiter in isolated Venezuelan Indians. J. Clin. Endocrin. 19: 1440.

SILINK, K. 1964. Goitrogens in foods and endemic goiter, p. 247. *In* J. Podoba and P. Langer [ed.] Naturally occurring goitrogens and thyroid function. Publishing House of the Slovak Academy of Sciences, Bratislava.

THILLY, C. H., F. DELANGE, AND A. M. ERMANS. 1972. Further investigations of iodine deficiency in the etiology of endemic goiter. Amer. J. Clin. Nutr. 25: 30.