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Edited by James Cock, Reginald MacIntyre, and Michael Graham

The International Society for Tropical Root Crops in collaboration with Centro Internacional de Agricultura Tropical
International Development Research Centre
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The Toxic Effect of Cassava on Human Thyroid

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Previous investigations on the goitre endemia of Idjwi Island (Eastern Zaïre) had suggested that cassava could play a role in the etiology of endemic goitre. The suggested mechanism was a loss of iodide in the urine due to the antithyroid action of thiocyanate resulting from the endogenous conversion of linamarin contained in cassava. This hypothesis was further tested in 677 inhabitants of another extremely severe goitre endemia situated in the Ubangi area (Northwestern Zaïre) where cassava is also a staple food.

Very low renal excretion of iodide (11.3 μg/day) and high thiocyanate content in serum (0.83 mg/100 ml) and urine (11.3 mg/day) indicate that this population is subjected to an extremely severe iodine deficiency and to the consumption of a goitrogenic foodstuff. Cassava consumption is followed by a sharp increase in urinary excretion of stable iodine and in the level of serum and urinary thiocyanate. The highest urinary concentrations of thiocyanate are observed in the subjects presenting the largest goitres.

The data confirm the hypothesis that consumption of cassava increases serum thiocyanate concentration which has an antithyroid action and causes a loss of iodide in the urine. In view of the iodine deficiency already prevailing in the diet, this mechanism could play a critical role in goitre development.

The prime function of the thyroid gland is to secrete a sufficient quantity of hormones to regulate oxidative processes in the tissues (Degroot and Stanbury 1975). Since iodine is a major constituent in these hormones, the activity of the thyroid is critically dependent on the amount of iodine contained in our food. Normal iodine intake is at least 100 μg/day. If the iodine intake is distinctly inadequate, the thyroid gland is stimulated by a regulatory process involving increased secretion of thyrotrophic hormone by the pituitary. This stimulation ensures the maintenance of normal thyroid function. It also causes hyperplasia of the gland and goitre (Delange 1974).

A number of natural substances contained in our food have the property of preventing iodine from penetrating the thyroid. The consequences are identical to those of iodine deficiency, the main one being goitre development. These substances are therefore referred to as natural goitrogens (Yamada et al. 1974).

By definition, we speak of endemic goitre in man when goitre development is present in more than 10% of a population (Querido et al. 1974).

Goitre Programme in Zaïre of CEMUBAC (Centre d'Etudes Médicales de l'Université de Bruxelles dans les Actions de Coopération, Belgium) — IRS (Institut pour la Recherche Scientifique, Zaïre) (1), Departments of Pediatrics (2) and of Radioisotopes (3), University of Brussels, Belgium.

(Kelly and Snedden 1960). The main cause of endemic goitre is iodine deficiency, but the additional role of natural goitrogens has been demonstrated in several regions of the world. In particular, results from Nigeria (Nwokolo et al. 1966; Ekpechi 1967; Oluwasanmi and Alli 1968; Ekpechi 1973) and from Zaïre (Delange and Ermans 1971; Ermans et al. 1973; van der Velden et al. 1973) suggest that cassava is one of the goitrogens which may play a role in the etiology of endemic goitre. We have established that: (1) one meal of cassava causes an increase in urinary excretion of stable iodine in man (Delange and Ermans 1971); and (2) a constant cassava-based diet administered to rats causes goitre development and modifies the biochemical parameters of thyroid function in a manner characteristic of severe iodine deficiency (Ermans et al. 1972).

The following mechanism has been proposed for explaining the goitrogenic action of cassava (Ermans et al. 1972, 1973): cassava contains large amounts of a cyanogenic glucoside, linamarin. After ingestion of cassava, linamarin is hydrolyzed into cyanide by means of a specific glucoside, linamarase, also contained in cassava. Cyanide is transformed into thiocyanate under the influence of a specific enzyme called rhodanase. Thiocyanate is released in the circulation and excreted in the urine.

Thiocyanate is a goitrogenic substance because it competes directly with the iodide trapping process of the thyroid (Vanderlaan and Vanderlaan 1947) and, at higher concen-
Fig. 1. Comparison of the patterns of thyroidal uptake of radioiodine and urinary excretion of stable iodine in the control group (rice meal) and the cassava group.

concentration with the intrathyroidal processing of iodine (Raben 1949; Wollman 1962; Scranton 1969). This two-fold action reduces the quantity of iodine available for hormone synthesis and increases iodine excretion through the urine. This situation could induce or aggravate a state of iodine deficiency and thus provoke goitre.

If this pattern is correct, it may be expected that cassava consumption by man will be followed by: (1) an increase in urinary excretion of stable iodine; (2) an increase in the level of blood thiocyanate; and (3) an increase in the level of urinary thiocyanate.

Finally, there should be some relationship between the volume of the thyroid and the concentration of blood and urinary thiocyanate.

The aim of our work was to ascertain whether this was indeed the case in endemic goitre.

Patients and Methods

The study was conducted in the goitre endemia of Ubangi, in northwestern Zaïre. This is an exceptionally severe endemia where goitre affects 70% of the total population and the prevalence of cretinism varies between 1 and 7% (Thilly et al. 1974). It is about 1500 km from the Kivu endemia (Delange 1974), and has a totally different biotope, consisting essentially of tropical forest. The population lives almost entirely off locally grown food. Cassava is a staple food.

We studied a sample of 677 randomly selected inhabitants, of both sexes, between 1 and 80 years of age, and all clinically euthyroid. Results were compared with corresponding results obtained in a similar study of 71 inhabitants of Idjwi Island in Kivu (Eastern Zaïre), and those of 116 normal Belgian subjects used as controls.

Urinary iodine was determined by the Riley and Gochman (1964) method, using a Technicon Autoanalyzer. The Aldridge (1945) method was used for thiocyanate assays.

Investigations and Results

The first stage consisted of assessing the effect of a cassava meal on iodine metabolism. Thyroidal uptake of radioiodine and daily urinary excretion of iodide were compared in two groups of 22 patients each, matched for their radioiodine uptake values after fasting. One group received a diet based solely on cassava for 24 h; the other was fed rice, regarded as non-goitrogenic, and served as the control group. Fig. 1 shows that the uptake values in the cassava group are consistently lower than those of the control group but the difference is not significant until the 24th hour (p < 0.05). However, during this period, urinary excretion of stable iodine rises to 18.1 ± 1.6 μg/day in the cassava group, compared with 9.3 ± 1.1 μg/day in the control group. The difference is highly significant (p < 0.001).

In a second investigation we studied the influence of cassava consumption on the serum level of thiocyanate. This level was determined in a group of 10 subjects before and after consumption of substantial quantities of cassava over a period of 3 days. Corresponding assays were performed in a control group fed with rice. The serum level of thiocyanate did not vary in the control group, but increased in 8 out of 10 patients in the cassava group. The average level rose from 0.32 to 0.47 mg/100 ml, which is a highly significant increase (p < 0.005). During the same period, urinary concentrations of thiocyanate remained stationary in the rice group, but rose from 0.68 to 0.82 mg/100 ml in the cassava group. This differ-
ence is slightly significant ($p < 0.05$).

A third investigation concerned the action of chronic cassava consumption on the level of urinary thiocyanate. This was accomplished by the Zairean chemist on the team (M.M.) on himself. Urinary samples were collected at the end of a 5-month stay in Brussels where the subject ate no cassava, and after his return to Ubangi where he went back to his traditional diet. Thiocyanate concentration varied considerably from day to day. However, the average concentration after 4–7 weeks in Zaire (0.5 mg/100 ml) was still the same as in Brussels, whereas in the 3rd month after the return to Zaire it increased to twice its Brussels level and in the fifth month rose to five times the original value.

The next stage consisted in looking for biochemical signs of iodine deficiency and goitrogen consumption in the Ubangi population. We therefore determined daily urinary excretion of iodide and thiocyanate together with the blood level of thiocyanate in our Ubangi sample (Silink and Marsikova 1951).

In the Belgian controls, daily renal excretion of iodide is $51.2 \pm 5.8 \mu g/day$, that of thiocyanate $6.7 \pm 1.3 \, mg/day$ and the blood concentration of thiocyanate $0.22 \pm 0.02 \, mg/100 \, ml$. In contrast, in the two African populations the values for urinary excretion of iodide were greatly reduced (12.6 and 11.3 $\mu g/day$ respectively), while urinary excretion of thiocyanate (14.3 and 11.3 $mg/day$) and blood concentration of thiocyanate (1.10 and 0.83 $mg/100 \, ml$) were substantially above normal.

The next stage consisted of determining whether there was any relationship between urinary and serum concentration of thiocyanate in the Ubangi population. The two parameters were determined in 138 randomly selected Ubangi inhabitants (Fig. 2). The line represents the theoretical relationship which we should expect to find between the two parameters if the variations in one triggered identical variations in the other. However, the observed situation is such that the points follow a curve of the power function type and not a straight line. This suggests that, above a critical blood

![Fig. 2. Relationship between serum and urinary thiocyanate concentration in 138 endemic goitre patients.](image-url)
threshold, further intakes of thiocyanate increase the urinary concentration of the ion without perceptibly modifying blood concentration. Blood thiocyanate levels are extremely variable and exceed 1.5 mg/100 ml in 20% of the cases.

During separate investigations in Belgium we established that above this critical level thiocyanate acts directly on the thyroid by inhibiting intrathyroidal penetration of iodide.

In the last stage of our study we looked for a possible relationship between thyroid volume and urinary excretion of thiocyanate. Urinary concentration of thiocyanate was determined in 416 inhabitants of three separate villages. Iodide concentration was determined in the samples of two of the same villages. Urinary iodine concentration was 2–3 μg/100 ml in all the patients investigated and did not vary appreciably in accordance with thyroid volume. In contrast, urinary concentration of thiocyanate varied substantially between the three villages and within each village, increasing steadily in proportion to thyroid volume and attaining its highest levels in subjects presenting large goitres.

Figure 3 shows the evolution, for the same patients, of urinary thiocyanate concentration as a function of age in both sexes. The values are identical for both sexes up to puberty. In male subjects average urinary thiocyanate declines after age 15 until adulthood. In women, however, it continues increasing, up to a maximum level at age 30–40, and then decreases. This pattern of development in relation to age and sex closely resembles the frequency distribution curve for visible goitres in relation to age and sex in goitreous African populations (Delange 1974).

**Discussion**

The Ubangi population is subjected to an ex-
tremely severe iodine deficiency. The high levels of serum and urinary thiocyanate repre-
sent a biochemical indicator of the consump-
tion of a goitrogenic foodstuff by that popula-
tion (Silink and Marsikova 1951).

It is difficult to distinguish the respective
roles of thiocyanate and iodine deficien-
cy in the etiology of endemic goitre be-
cause the effects of thiocyanate are the same
as those of iodine deficiency. Nevertheless,
this work has provided strong evidence in
favour of the hypothesis that cassava consump-
tion and the resulting production of thiocyana-
te have an antithyroidal effect in man. All
four points on which the proof of the hypo-
thesis rested have been effectively confirmed. Cas-
sava consumption is followed by: (1) an
increase in urinary excretion of stable iodine.
In this respect all the findings made in Idjwi
(Delange 1974; Delange and Ermans 1971)
and Ubangi are consistent. The result is that
the iodine deficiency is aggravated; (2) an in-
crease in the level of serum thiocyanate; (3)
an increase in the level of urinary thiocyanate.
This effect is moderate in the case of acute cas-
sava intake but extremely marked after a
period of chronic consumption; (4) finally the
concentration in urinary thiocyanate is in pro-
portion to thyroid volume. This relationship
does not allow any conclusion as to whether
the increased thiocyanate is the cause or con-
sequence of the goitre. But, even in the latter
case, the increase in thiocyanate could play a
role in goitre development by triggering a
vicious process in which the goitrous gland
became less and less capable of metabolizing
increasing quantities of thiocyanate.

The mechanism whereby cassava affects
iodine metabolism in man is shown in Fig. 4:
acute consumption of cassava causes increased
concentration of serum thiocyanate which,
one it has exceeded a critical level, may result
in the inhibition of intrathyroidal penetration
and/or organification of iodine and cause an
increase in urinary excretion of stable iodine.
In these acute conditions little or no changes
are observed in urinary thiocyanate, perhaps
because of the very long half-life of this ion in
the plasma (Ermans et al. 1972). By contrast,
chronic cassava consumption results in a very
marked increase in concentration. Urinary
concentration of thiocyanate constitutes a
more reliable indicator of the degree of thio-
cyanate impregnation than serum concentra-
tion.

In the conditions encountered in Zaïre it is
conceivable that acute and chronic conditions
alternate or overlap depending on the type and
frequency of food intake. Probably, the re-
currence of such situations causes substantial
iodine losses which, in view of the iodine de-
iciency already prevailing in the diet, plays a
critical role in goitre development.

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Utilization of Cassava as a Carbohydrate Source for Pigs

V. F. Hew and R. I. Hutagalung

Cassava is shown to serve as an inexpensive source of valuable energy for pigs. The correct choice of cassava with low cyanogenic glucosides and the use of high quality proteins to make up for nutrient deficiencies in amino acids and vitamins makes the replacement of grains by cassava possible. The use of cassava would substantially reduce the cost of feed.

When 30 Landrace pigs were assigned to diets containing 0, 15, 30, 45, and 60% cassava as the energy source in their diets, no significant difference in performance nor carcass characteristics was observed. The increase in cassava levels was accompanied by an increase in fishmeal, a high quality and locally available protein source. The inclusion of fishmeal rather than other proteins of plant origin in high cassava diets is comparable to the supplementation in the cassava diets of methionine or other synthetic amino acids.

\footnote{Animal Improvement Division, Malaysian Agricultural Research and Development Institute, Serdang, Selangor, Malaysia, and Faculty of Agriculture, University of Malaya, Kuala Lumpur 22-11, Malaysia, respectively.}