Thyroid function in a cassava-eating population affected by epidemic spastic paraparesis

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Abstract. Thyroid function was studied in a rural population in Mozambique that had been affected by an epidemic of spastic paraparesis attributed to dietary cyanide exposure from cassava. Laboratory investigation on a sample of this population demonstrated very high levels of serum and urinary thiocyanate, indicating a heavy exposure to cyanide. The urinary excretion of iodine was within normal limits, indicating an adequate intake of iodine. The serum levels of FT4I were somewhat decreased and serum FT3I, T3/T4 ratio and TSH were somewhat raised. This hormone pattern suggests an adaptation to the antithyroid effect of thiocyanate, but not overt hypothyroidism. A follow-up study on school children was performed, and it also demonstrated high thiocyanate exposure, adequate intake of iodine, and absence of endemic goitre. The results show that if iodine supply is adequate, the thyroid gland is capable of adaptation to a heavy body burden of thiocyanate without development of overt hypothyroidism or goitre.

Cassava is the staple food in many tropical countries, mainly owing to high yields of this plant even on poor soils (Cock 1982). However, cassava roots contain cyanogenic glucosides, sometimes in high amounts. Different methods are used to reduce the cyanide content before consumption. If this processing is inadequately performed, consumers are exposed to a high cyanide intake, which may cause neurological disorders (Wilson 1983). Another harmful effect of cyanide intake is due to its conversion to thiocyanate, which is an antithyroid and goitrogenic compound (Green 1978). A high incidence of goitre in certain areas of Nigeria (Ekpechi et al. 1966) and Zaire (Bourdoux et al. 1978; Vanderpass et al. 1984) thus has been attributed to the combined effect of iodine deficiency and thiocyanate exposure resulting from a high consumption of cassava.

The present study was initiated by an epidemic of spastic paraparesis attributed to cyanide exposure from cassava in a drought-stricken area of Northern Mozambique (Ministry of Health, Mozambique 1984a,b). Owing to shortage of food during the drought, cassava had to be consumed without adequate processing. This resulted in a high cyanide intake as verified by increased serum levels of thiocyanate.

During the recovery after the drought, the Ministry of Health performed an epidemiological and nutritional surveillance in the area affected by the epidemic. The present study was coordinated with this activity and aimed at evaluating the risk of thyroid dysfunction in the cassava-eating population. The serum levels of thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH) thus were determined in a sample of the population. Furthermore, thiocyanate was determined in serum and urine as an indicator of cyanide exposure (Bourdoux 1978), and the urinary iodine excretion was determined as a measure of the dietary iodine intake (Follis 1964).

The laboratory investigations indicated a slight
antithyroid effect of thiocyanate and therefore a follow-up study was performed on school children to determine the goitre rate as well as the urinary excretion of iodine and thiocyanate.

Materials and Methods
The study was carried out in the Memba District, situated in Northern Mozambique and bordering on the Indian Ocean. The district is mainly inhabited by peasants growing cassava, beans, maize, and sorghum. Cassava is the dominating staple food, but it should be noted that dried fish, bartered with fishermen, constitute an important item of the diet. At the end of the dry season the cassava roots are harvested, sun-dried, and stored for later consumption. This procedure will slowly reduce the cyanide content, and the roots are considered suitable for consumption after a drying period of two months. During the drought in 1981, however, the roots were consumed immediately after the harvest owing to a severe food shortage. During the cassava harvests in 1982 and 1983, when this study was performed, the shortage of other foods persisted, and the roots were consumed after only about two and four weeks of sun-drying, respectively.

The laboratory investigations were performed during the cassava harvest in 1982 on 27 subjects aged 5–60 years, with a median age of 28 years (9 male and 9 female adults, and 9 children of more than 4 years of age). They belonged to randomly selected households in the village Acordo de Lusaka located in the centre of the area affected by the epidemic of paraparesis in 1981 (Ministry of Health, Mozambique 1984b).

Serum and urine specimens (the latter collected with 10% thymol in isopropanol as preservative) were frozen within 6 h of collection and then transported to Sweden for analysis. As it was not feasible to perform 24-h urine collections, the urinary excretion of thiocyanate and iodine was related to creatinine, the latter determined with a conventional alkaline picrate method.

Thiocyanate in serum and urine was determined according to Lundquist et al. (1979) using Amberlyst A 21 as adsorbent (Lundquist et al. 1983). Urinary iodine was determined by the catalytic ceric-arsenate method (Sandell et al. 1937) after separation of interfering compounds by ion-exchange on a AG 1-X4 resin according to Sacks (1964).

The serum levels of TSH, T₄ and T₃ were determined by radioimmunoassay methods (Odell 1965; Wide 1983). The free T₄ index (FT₄I) and free T₃ index (FT₃I) were calculated by multiplying the values for T₄ or T₃ by the T₃-uptake values, the latter determined by a commercial reagent kit (Phadebas T₃U Test, Pharmacia, Uppsala, Sweden) using Sephadex as adsorbent. Values for FT₄I and FT₃I were compared with those of a healthy Swedish control group (15 males and 12 females, aged 18–77 with a median age of 28 years). Values for TSH were compared with those of a Swedish control group comprising 212 non-smoking adults (128 males and 84 females, aged 19–85 with a median age of 51 years).

As the laboratory investigation indicated a slight effect of thiocyanate on the thyroid function, the prevalence of goitre was determined in 276 school children from three rural primary schools in the study area. This was carried out during the cassava harvest period of the following year. The thyroid glands were examined as described by Perez et al. (1960) and regarded as enlarged if the volume of the lateral lobes exceeded that of the terminal phalanx of the thumb of the subject examined. Owing to special social circumstances, blood sampling was not feasible during this survey, but urine samples for thiocyanate and iodine determinations could be obtained from 89 children, equally distributed between the three schools.

Results
The levels of thiocyanate in serum and urine were very high, as demonstrated in Fig. 1. As there were no significant differences between children and adults, the results from the two age groups were combined, resulting in a mean serum thiocyanate of 250 ± 24 µmol/l (± SEM) and a mean urinary excretion of 132 ± 28 mmol/mol creatinine. The Swedish reference groups referred to in Fig. 1 had a mean (± SD) serum thiocyanate of 42 ± 34 µmol/l and a urinary thiocyanate of 3.2 ± 1.0 mmol/mol creatinine. The mean values found in the Mozambican study group were, respectively, 6-fold and 30-fold higher.

Fig. 1 also shows the iodine excretion, which could be determined in 21 of the subjects studied. The mean value was 79 ± 7.3 µmol/mol creatinine, and all values, except one slightly raised and one slightly depressed, were within the reference limits of healthy Swedes. All but two had an iodine excretion of more than 50 µg/mg of creatinine, and according to the criterion given by Follis (1964) the distribution of iodine excretion found indicates an adequate iodine intake.

Table 1 shows that as compared with the controls TSH was increased in the cassava-consuming subjects. The FT₄I was reduced, which was mainly explained by low values among the adults. FT₃I,
Fig. 1. Serum thiocyanate and urinary excretion of thiocyanate and iodine in cassava-eating subjects. o children, • adults and —— reference limits of Swedish controls.

on the other hand, was raised mainly owing to high values among the children. The $T_3/T_4$ ratio, finally, was higher in the cassava-consuming group, with similar values in adults and children.

Fig. 2 shows the individual values for TSH, FT$_4$I and FT$_3$I. All subjects had TSH values less than 10 mU/l, indicating that no one had severe hypothyroidism.

The follow-up study aiming at evaluating the goitre rate revealed only 3 subjects with enlarged thyroid glands out of the 276 children studied. This corresponds to a goitre rate of 1.1% with a 99% confidence limit of 0.1%–4.0%, the latter calculated by using the Poisson distribution. When thiocyanate was assayed on urinary samples from school children, a mean (± SEM) value of $83.3 ± 6.3$ mmol/mol creatinine was obtained, demonstrating that their thiocyanate exposure was still high during the cassava harvest two years after the drought. The urinary iodine simultaneously determined was $222 ± 17$ μmol/mol creatinine, indicating that the iodine intake was adequate and in fact higher than in the previous year.

**Discussion**

The serum and urinary levels of thiocyanate found in the present study are in fact higher than the levels reported from cassava-eating populations with endemic goitre attributed to thiocyanate exposure. Bourdoux et al. (1978) thus found that a thiocyanate exposure resulting in a mean (± SEM) serum level of $183 ± 12$ μmol/l was related to a goitre rate of 60–70% in a cassava-eating

**Table 1.**

Serum levels of TSH and thyroid hormones in cassava-eating subjects compared with Swedish adults controls (mean ± SEM).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Controls</th>
<th>Cassava-eating subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N = 27)</td>
<td>Adults (N = 18)</td>
</tr>
<tr>
<td>TSH mU/l</td>
<td>2.1 ± 0.09 (N = 212)</td>
<td>4.3 ± 0.31***</td>
</tr>
<tr>
<td>FT$_4$I arb. u.</td>
<td>95 ± 3.2 (N = 27)</td>
<td>83 ± 4.4*</td>
</tr>
<tr>
<td>FT$_3$I arb. u.</td>
<td>1.9 ± 0.09 (N = 27)</td>
<td>2.3 ± 0.13*</td>
</tr>
<tr>
<td>$T_3/T_4 × 10$</td>
<td>2.0 ± 0.10 (N = 27)</td>
<td>2.9 ± 0.16***</td>
</tr>
</tbody>
</table>

Significant difference with Student's $t$-test compared with controls, $*P < 0.05$ and $***P < 0.01$. 

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population from the Ubangi region in Zaire, whereas the mean serum level in the present study in Mozambique was 250 ± 24 µmol/l. The mean urinary concentration of thiocyanate in Zaire was given as 331 ± 10 µmol/l, and no data on creatinine concentration were presented, but the corresponding value found in the present study, 1137 ± 187 µmol/l, was considerably higher.

Nevertheless, the frequency of goitre in the present study was only 1.1%, which is far below the arbitrary limit for endemic goitre set at 10% (Perez et al. 1960) and corresponds to the sporadic goitre rate of populations with adequate iodine intake in industrialized countries (Thilly et al. 1980). Although it should be kept in mind that seasonal variations of cassava consumption occur in the area studied (Ministry of Health, Mozambique 1984b) and that the exposure to thiocyanate is probably not as high throughout the year, we feel it is unlikely that the low goitre rate is explained by this mechanism.

The explanation probably lies in differences in iodine status between the populations studied in Zaire and Mozambique. The population in Zaire suffered from iodine deficiency, as demonstrated by a low urinary excretion of iodine (Bourdoux 1978), whereas the population in Mozambique had an adequate iodine intake as demonstrated by the present study. This is explained by the fact that the Mozambican population lives close to the ocean and fish is an important item of their diet. It was also found in Sicily that high exposure to thiocyanate from cabbage did not result in goitre in the presence a high iodine intake (Delange et al. 1978). Delange et al. (1983) furthermore reported a goitre rate of only 1.5% in a cassava-eating population in Zaire with raised serum thiocyanate levels but an adequate iodine intake.

These results are easily understood if the mechanism of action of thiocyanate on the thyroid is considered. The main antithyroid effect of thiocyanate is due to its interference with the iodine accumulation of the thyroid gland (Green 1978; Ermans et al. 1980). A low dietary intake of iodine, not sufficiently low to cause goitre and thyroid insufficiency by itself, thus may result in goitre if combined with exposure to thiocyanate. Similarly, a heavy exposure to thiocyanate may be counteracted by a high dietary intake of iodine.

Of interest in this context is the hormone pattern found in the present study showing a decreased FT4I together with a raised FT3I, T3/T4 ratio, and TSH. This is a typical pattern in populations suffering from endemic goitre owing to iodine deficiency (Chopra 1975), but the changes in hormone levels found in the present study were smaller than those reported from endemic goitre areas. Whereas the mean (± SEM) TSH was 31.8 ± 3.2 mU/l in such an area in Zaire (Bourdoux 1978) and 16 ± 2.4 mU/l in an endemic goitre area in New Guinea (Chopra et al. 1975), all values in the present study were below 10 mU/l (Fig. 2).

The results of the present study thus indicate an adaptation of the thyroid function to the heavy thiocyanate exposure in the population studied and, furthermore, that the adequate iodine intake, in addition to this adaptation, has protected against the development of overt hypothyroidism and goitre.

In conclusion, if iodine intake is adequate, the thyroid gland is capable of adaptation to a very heavy body burden of thiocyanate from cassava.

Fig. 2. Serum levels of FT4I, FT3I and TSH in cassava-eating subjects. ○ children, • adults and --- reference limits of Swedish controls.
without development of goitre or hypothyroidism. This has important implications for the assessment of the overall health effects of cassavadominated diets. As cassava constitutes a staple crop with high yields and good resistance against droughts and pests, a reduced cultivation of cassava may in fact impair the health of the millions of poor peasants growing this crop. On the contrary, by raising agricultural productivity, an increased cultivation of cassava can improve health (Okiogbo 1980), provided that efficient processing methods are used to reduce its cyanide content, that protein-rich supplementary foods are available, and that iodine supplementation is given when necessary.

Acknowledgments

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References


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