Diabetes Is Not Caused by Cassava Toxicity

A study in a Tanzanian community

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OBJECTIVE— To test the hypothesis that consumption of cassava with liberation of cyanide causes diabetes in malnourished individuals.

RESEARCH DESIGN AND METHODS— Glucose tolerance was assessed in two rural communities in Tanzania; in one (Nyambori), the main source of calories was cassava; and in the other (Uswaa), cassava was rarely eaten. Undernutrition was prevalent in both communities. The people of Nyambori were known to have high dietary cyanide exposure for many years from consumption of insufficiently processed cassava. Of the 1435 people in Nyambori ≥15 yr old, 1067 (74%) were surveyed, and 1429 of 1472 (97%) eligible subjects in Uswaa were surveyed. All had 75-g oral glucose tolerance tests and measurement of BMI. Plasma and urine thiocyanate and blood cyanide also were measured in some subjects.

RESULTS— Mean ± SD plasma and urine thiocyanate levels in Nyambori were 296 ± 190 and 497 ± 457 μM (n = 204), respectively, compared with 30 ± 37 and 9 ± 13 μM, respectively, in Uswaa (n = 92) ($P < 0.001$ for all differences). The mean blood cyanide level in Nyambori was elevated (1.4 [range 0.1–30.2] μM; n = 91). The prevalence of diabetes in the cassava village (Nyambori) was 0.5% compared with 0.9% in Uswaa (NS). The prevalence of IGT was similar in the two villages in the 15- to 34- and the 34- to 54-yr-old age-groups; but in those ≥55 yr old, IGT was higher in Nyambori (17.4 vs. 7.2%, P = 0.029). Mean fasting and 2-h blood glucose levels were slightly higher in Nyambori village after adjusting for age, sex, and BMI (4.5 vs. 4.2 and 5.0 vs. 4.4 mM, respectively).

CONCLUSIONS— High dietary cyanide exposure was not found to have had a significant effect on the prevalence of diabetes in an undernourished population in Tanzania. Cassava consumption is thus highly unlikely to be a major etiological factor in so-called MRDM, at least in East Africa.

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BMI, BODY MASS INDEX; IGT, IMPAIRED GLUCOSE TOLERANCE; MRDM, MALNUTRITION-RELATED DIABETES MELLITUS; WHO, WORLD HEALTH ORGANIZATION; NGT, NORMAL GLUCOSE TOLERANCE; ANOVA, ANALYSIS OF VARIANCE; PABA, PARA-AMINOBENZOIC ACID.

MRDM was introduced as a distinct clinical class by WHO in 1985 (1). Two subclasses of MRDM were recognized: fibrocalculous pancreatic diabetes and protein-deficient pancreatic diabetes. There is no doubt about the occurrence of fibrocalculous pancreatic diabetes in specific areas of the tropics (2,3), but the existence of protein-deficient pancreatic diabetes as a distinct entity remains controversial (4). Uncertainty and considerable speculation also surrounds the etiology and pathogenesis of MRDM (4).

A background of chronic protein-calorie malnutrition is considered essential in the development of both types of MRDM (1). It is postulated that chronic undernutrition may lead directly to islet cell damage or increase the vulnerability of pancreatic cells to genetic, immunological, and environmental diabetogenic influences (5).

Toxicity of cyanogenic glucosides derived from the consumption of inadequately processed cassava has been proposed as an important etiological factor, because MRDM is commonly seen in parts of the tropics where cassava is the major staple carbohydrate (1,5).

Although transient hyperglycemia has been shown in rats after exposure to cyanide (6), several studies of glucose tolerance including case-control studies in rural populations in Africa (7), the West Indies (8), South America (9), and Asia (10), where cassava is commonly consumed, have failed to show evidence of increased rates of diabetes. However, evidence of long-term high cyanide exposure was not recorded in these studies. Many varieties of cassava exist and cooking and preparation differ greatly, so that in many cases cyanide will not have been generated. Therefore, we have studied glucose tolerance in a rural population in northwest Tanzania known to have a marginal protein intake and to have been exposed to the toxic effects of insufficiently processed cassava for a prolonged period (11). A similar

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study was conducted in a village in Kilimanjaro region where cassava is eaten infrequently. The prevalence of IGT and diabetes has been compared in the two villages and with previously reported prevalence estimates from six other Tanzanian villages where identical survey methods were used.

RESEARCH DESIGN AND METHODS

Study areas

The study was performed in Nyambori village in Tarime district of Mara region, Tanzania, in those ≥15 yr old. Cassava has been the major staple in this village for many decades. The village was chosen because it had been affected in 1984–1985 by an epidemic of konzo, a newly identified motor neuron disease that, in this village and other parts of Africa, has been associated with high cyanide exposure from consumption of insufficiently processed and subsequently toxic cassava roots (11,13). In Mara region of Tanzania, a very bitter variety of cassava with high content of cyanogenic glucosides was introduced in 1980 because of higher crop yields, and because it was not eaten by wild animals. These roots could be consumed safely only after careful processing. The method used in the area includes crushing the peeled roots into small pieces with a wooden mallet and leaving them to ferment under pressure from stones for up to 6 days. Thereafter, the small pieces are sun dried and pounded into a flour used for preparation of a stiff porridge. A drought in 1984–1985 resulted in food shortage, and the most toxic cassava varieties were the only food crops to produce adequate yields. The processing of cassava was shortened to 1 day because of the food shortage. The resulting high dietary cyanide exposure was verified by reports of frequent acute intoxications after meals and high serum levels of thiocyanate, the main detoxication product of cyanide in the human body. A simultaneous outbreak of spastic paraparesis occurred in Nyambori and surrounding villages. The paralytic disease was identical to that earlier reported from Mozambique and Zaire and had been named konzo. More than 1% of the population in Nyambori have been crippled permanently by konzo, and new cases continue to appear each dry season when the dietary situation is similar to that during the drought. Therefore, we did this study at the end of the dry season. The primary health care workers from the local voluntary agency hospital were used to prepare the villagers for the survey and to obtain a census of the village before the study. All subjects in the village ≥15 yr old were invited to the study—1067 of 1435 (74%) subjects attended.

A parallel study was performed in Uswaa village of Kilimanjaro region following the same protocol. Cassava is consumed infrequently in this region. All residents ≥15 yr old were invited to attend—1429 of 1472 (97%) eligible subjects were seen.

Study protocol

Subjects were requested to report to the village dispensary after an overnight fast. Venous blood samples were obtained fasting and, except for those already known to have diabetes, 2 h after a 75-g oral glucose load. Weight and height were measured, without shoes or coats, with a beam-balance stadiometer. Portions of the fasting and 2-h blood glucose samples were placed in fluoride tubes, and glucose content was analyzed immediately at survey site with a glucose analyzer (YSI, Yellow Springs, OH) powered by a Honda EM650 generator. A portion of every fifth sample was kept frozen at −20°C and later reanalyzed with a hexokinase fluorometric method in a Cobas Bio centrifugal analyzer (Roche, Welwyn Garden City, UK) at the University of Newcastle upon Tyne. The linear correlation coefficient between the survey site and the Newcastle upon Tyne laboratory results was 0.92, and the slope did not differ significantly from unity. The coefficient of variation for measurements on site was 1.8%. From every fasting sample, a portion also was kept frozen at −20°C for analysis of serum cholesterol by an enzymatic method with a Cobas Bio centrifugal analyzer. Hb was measured with a Cyanox digital hemoglobinometer (Buffalo Medical Specialities, Buffalo, NY).

Dietary cyanide exposure was estimated by determination of blood cyanide (14) and plasma and urine thiocyanate (15,16). Specimens for this were collected from 45 subjects verified to have abnormal glucose tolerance during the first part of the study and from 128 age- and sex-matched subjects with NGT. Serum insulin levels also were determined in these subjects (17). Because of limitation of analytical capacity, estimates of blood cyanide were only made in the first 34 and 57 subjects in these two groups, respectively. The women cooking the food in the corresponding households were interviewed in privacy with translation to the local language regarding the frequency of food consumption during the most recent dry period and during the last 24 h.

Plain abdominal X-rays for pancreatic calcification and PABA tests (18) were conducted in 37 subjects found to have glucose intolerance (34 with IGT and 3 with diabetes) and in an age- and sex-matched sample of 45 with NGT. Reliable urinary PABA estimations were not possible, but blood for estimation of serum PABA was taken from all subjects 4 h after ingestion of PABA.

Data analysis

Diabetes was defined according to the 1985 WHO criteria for epidemiological studies, i.e., 2-h blood glucose (venous whole-blood) concn ≥10.0 mM for diabetes and ≥6.7 but <10 mM for IGT. Subjects who already had been diagnosed as having diabetes at the time of study were defined as being diabetic irrespective of current therapy.

Subjects were categorized as either drinkers or nondrinkers according to reported drinking habits. Nondrinkers

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Table 1—*Age and sex distributions of subjects*

	Nyambori		Uswaa	
Age (yr)	*N*	Male (%)	*N*	Male (%)
15–34	623	46.9	608	41.0
35–54	278	37.8	450	40.0
≥55	166	51.2	371	46.1
Total	1067	45.2	1429	42.0

were subjects who, at the time of study, had not been drinking alcohol for at least 6 mo. Subjects were categorized similarly according to their smoking habits.

BMI was defined as weight (kg) divided by the square of height (m^2). Patients with BMI <20 kg/m^2 were regarded as being underweight, those with BMI 20–25 kg/m^2 as being of normal weight, and those with BMI >25 kg/m^2 as being overweight.

Data were analyzed with SPSS/PC$^+$ for the IBM PC/AT microcomputer (19). ANOVA (SPSS procedure means), χ^2 tests (SPSS procedure cross-tabulation), Kruskal-Wallis one-way ANOVA (SPSS procedure *n*par tests), Mann-Whitney test (SPSS procedure *n*par tests), Kendall's tau C correlation coefficient (SPSS procedure cross-tabulation), analysis of covariance (SPSS procedure ANOVA), and multiple regression (SPSS procedure regression) were used as appropriate. The natural logs of fasting and 2-h blood glucose levels and plasma and urine thiocyanates were used if the procedure assumed normally distributed data. The Kilmogorov-Smirnov test (SPSS procedure *n*par tests) was used to test for the normality of distributions. The study was repeated in Uswaa village of Kilimanjaro region after the same protocol but without plain abdominal X-rays, PABA tests, and blood cyanide levels.

RESULTS— Table 1 shows the age and sex distributions of the subjects. For both villages fewer men than women were in the age-groups 25–54 yr, a result, partly, of urban migration of men in search of work.

Table 2 shows the reported frequency at which various foods are normally taken. The main food in Nyambori village was a gruel prepared from cassava flour alone or mixed with sorghum, along with a relish of green leaves and sometimes fish. The diet in Uswaa village was more varied but mainly a mixture of maize and bananas. Protein-containing foods (meat, beans, fish, and milk) were taken more frequently in Uswaa than in Nyambori village. Twenty-four-hour recall gave similar results (data not shown).

BMI was not different for the total population between villages, although women were heavier in Uswaa (Table 3). Serum cholesterol concentrations were slightly higher in Uswaa, whereas hemoglobin levels were also significantly higher, perhaps reflecting better nutritional status in Uswaa. Plasma and urine thiocyanate levels were higher in Nyambori than in Uswaa (Table 4). Mean blood cyanide levels were 1.4 (range 0.1–30.2) μM in Nyambori village. There were no significant differences in plasma and urine thiocyanate by age, smoking, or drinking groups in Nyambori village.

The prevalence of diabetes in Nyambori village was only 0.5% compared with 0.9% in Uswaa (Table 5). The prevalence of IGT did not differ between the two villages in the 15–34 and 35–54 yr age-groups. However, in the ≥55-yr-old age-group, the prevalence of IGT was significantly higher in the Nyambori village community (17.4 vs. 7.2%, $P = 0.029$) (Table 5).

Table 6 shows the prevalence of diabetes and IGT by BMI divided into tertiles for the two villages. In Uswaa village, no significant difference was noted in diabetes prevalence between BMI tertiles, but the IGT figure was significantly greater in the lower (6.8%) compared with the middle (4.0%) and upper (2.8%) tertiles ($P < 0.05$). In Nyambori village, estimates of IGT did not differ between the BMI tertiles, and the difference in diabetes estimates (1.6% in the lower tertile and 0.3% in the upper tertile) were not statistically significant ($P = 0.19$). Figures for six other Tanzanian villages previously surveyed are shown also. The prevalence of diabetes and IGT were closely similar to those of Nyambori village.

However, mean fasting and 2-h blood glucose levels were significantly higher in all age-groups in Nyambori village subjects compared with subjects in Uswaa village (Table 7), although differences were small (0.3–0.5 and 0.5–1.0 mM, respectively). We observed no differences between men and women except in Uswaa where females had higher mean ± SD 2-h blood glucose values (4.6 ± 1.4 vs. 4.0 ± 1.8 mM) and in the >55-yr-old subjects in Nyambori, where again women showed slightly higher values.

No significant differences were observed in plasma or urine thiocyanate levels or in blood cyanide levels between subjects with NGT and those with glucose intolerance in Nyambori village (Table 4).

There was no significant difference in serum PABA concentration between those with glucose intolerance and those with NGT (data not shown). Of the 82 plain abdominal X-rays performed, pancreatic calcification was seen in 1 person who had IGT. Correlations (Kendall tau c test) were sought between blood cyanide and thiocyanate levels, serum insulin, and blood glucose levels for Nyambori village. High plasma thiocya-

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Table 2—*Frequency (%) at which villagers normally consumed various foods*

	Nyambori (N = 156)			Uswaa (N = 39)		
	Never or rarely	Once/wk	Daily	Never or rarely	Once/wk	Daily
Cassava	2	2	96	64	33	3
Maize	96	3	1	5	49	46
Sorghum	61	10	29	74	23	3
Millet	89	3	8	100	0	0
Bananas	100	0	0	67	10	23
Cassava leaves	85	10	5	72	26	3
Beans	91	9	0	85	15	0
Groundnuts	94	4	2	72	28	0
Meat	65	29	6	8	72	21
Fish	33	22	44	3	56	8
Chicken	85	15	1	64	31	5
Other meats	92	3	5	92	8	0
Animal fat	82	7	11	31	26	44
Fruit	72	10	17	15	67	18
Milk	58	12	30	13	28	59

nate levels were associated with high fasting blood glucose levels (r = 0.11, P = 0.013), and higher urine thiocyanate levels were associated with a low fasting serum insulin (r = −0.16, P = 0.04). However, these associations disappeared on multiple regression analysis. For Nyambori village, fasting and 2-h blood glucose levels, age, sex, BMI, drinking and smoking habits, and plasma and urine thiocyanates were all entered into a stepwise multiple regression analysis with the blood glucose levels as dependent variables. For the fasting blood glucose, only age showed a significant association with a multiple R of 3.9%. For the 2-h blood glucose, only age and BMI were significant. Age was entered first with a multiple R of 10.9%. When BMI was added, the multiple R increased to 14.4%. For the two villages, fasting and 2-h blood glucose levels, age, BMI, urine thiocyanate levels, and the villages themselves were entered into a stepwise multiple regression analysis with the blood glucose levels as dependent variables. Again, the villages were associated significantly with both the fasting and 2-h blood glucose levels. Age also was associated with the 2-h blood glucose. No significant association existed with BMI or urine thiocyanate.

CONCLUSIONS— The concept of MRDM developed from the observation that many patients with diabetes in the tropics cannot easily be classified as having either non-insulin-dependent or insulin-dependent diabetes mellitus (1,4). Such patients are often young, with no history of alcohol consumption (20). They present with clinical evidence of malnutrition, a history of childhood malnutrition, and, in some, malabsorption. X-ray of the abdomen may show pancreatic calcification. The diabetes is characterized by insulin resistance, but absence of ketosis. From observations in animals (21–24) and evidence that glucose tolerance may be altered in protein-energy malnutrition in children and adults (15–27), the hypothesis was advanced that protein-calorie malnutrition may be the underlying factor in the development of *tropical* diabetes. In rat studies, fetal or early protein-calorie malnutrition can lead to later abnormal glucose tolerance (21,22). Malnutrition per se could lead to pancreatic β-cell dysfunction or make the cells vulnerable to infection and environmental toxins (5). Dietary cyanide exposure from the consumption of bitter cassava is considered by many to be such an environmental toxin. Epidemiological observations and the fact that cyanide can cause hyperglycemia in animals

Table 3—*Age-adjusted mean ± SD values for BMI, Hb, and serum total cholesterol by sex for Nyambori and Uswaa villages**

	Nyambori (N = 482 men, 600 women)	Uswaa (N = 585 men, 829 women)
Male		
BMI (kg/m^2)	20.5 ± 2.70 (20.3–20.7)	20.2 ± 2.50 (20.0–20.4)
Hb (g/dl)	11.7 ± 1.34 (11.6–11.8)	12.8 ± 1.40 (12.7–12.9)
Serum cholesterol (mM)	3.7 ± 0.91 (3.6–3.8)	3.8 ± 0.97 (3.7–3.9)
Female		
BMI (kg/m^2)	21.0 ± 2.61 (20.8–21.2)	21.6 ± 3.24 (21.4–21.8)
Hb (g/dl)	10.8 ± 1.31 (10.7–10.9)	12.2 ± 1.18 (12.1–12.3)
Serum cholesterol (mM)	3.9 ± 0.94 (3.8–4.0)	4.1 ± 0.88 (4.0–4.2)

Values in parentheses are 95% confidence intervals.
*Differences between villages in total mean values were all statistically significant.

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Table 4—*Mean plasma (μM) and urine (mM) thiocyanate and blood cyanide (mM) levels for Nyambori and Uswaa villages*

	Uswaa	Nyambori		
	All subjects	All subjects	NGT	Abnormal glucose tolerance*
Plasma thiocyanate				
N	90	179	137	42
Mean	28 (0–180)	294 (40–1885)	295 (40–1885)	290 (50–665)
Urine thiocyanate				
N	95	173	128	45
Mean	8 (0–82)	537 (10–2940)	531 (10–2940)	554 (55–2400)
Blood cyanide				
N		91	57	34
Mean		1.4 (0.1–30.2)	1.6 (0.1–30.2)	1.1 (0.1–30.2)

There were no significant differences in mean values between normal and abnormal glucose tolerance categories within Nyambori village (Mann-Whitney *U* test). Ranges given in parentheses.
*Abnormal, diabetes plus IGT.

(6,28) led to the suggestion that cassava consumption may be related causally to MRDM (29). However, there are many exceptions; but despite these, cassava consumption continues to be linked with diabetes, although increasing evidence indicates a lack of association in humans (7–10). Few, if any, studies have been conducted of glucose tolerance in human populations known to have been exposed to high levels of cyanogenic glucosides for prolonged periods, and whose protein intake is marginal. In 1984–1985, the study of an epidemic of spastic paraparesis in a limited area of Mara Region of Tanzania revealed that this paralytic disease was identical to that reported from Mozambique and Zaire (13). This disease, named konzo after a local designation among the first affected population in Zaire, had the same association to cyanide exposure from cassava in Mara region as reported from other affected areas (11,13). Investigations revealed that because of food shortage after drought, villagers had been shortening their traditional cassava detoxication processes. Economic factors, especially the need to see cassava for cash, also had led to a shortening of the detoxication process.

Konzo associated with cassava consumption is thought to occur in individuals with inadequate amounts of sulfur-containing amino acids, which are required for the in vivo detoxication of cyanide (11,13). Detailed inquiry in the affected villages in Mara Region indicated the occurrence of sporadic cases of konzo with onset during dry seasons as far back as the early 1970s, and cases continue to be seen up to the time of the study.

In view of the evidence of persisting dietary cyanide exposure in dry seasons in certain areas of Mara Region, we decided to study glucose tolerance in one village, which was at the center of the epidemic in 1984–1985. The study was performed for the time of the year when food shortage was greatest, i.e., the end of the dry season, and when thiocyanate levels were likely to be high. Table 2 shows the importance of cassava in the diet of Nyambori village subjects. This contrasts markedly with cassava con-

Table 5—*Prevalence (%) of diabetes and IGT by sex and age-group**

	Nyambori			Uswaa			
	Male	Female	Total	Male	Female	Total	*P*†
Diabetes							
Age (yr)							
15–34				0.8	0.6	0.7	0.132
35–54	0.4	0.5	0.5	0.8	0.8	0.8	0.948
≥55	4.0	4.2	4.1	4.6	1.0	2.5	0.745
Total	0.5	0.6	0.5	1.2	0.7	0.9	0.485
IGT							
Age (yr)							
15–34	5.6	4.7	5.1	2.5	3.2	2.9	0.055
35–54	9.9	5.2	7.4	3.9	4.9	4.5	0.125
≥55	14.4	19.9	17.4	5.8	8.2	7.2	0.029
Total	7.9	6.3	7.0	3.3	4.3	3.9	0.001

*Totals are adjusted for age, sex, or age and sex.
†*P* value for the difference between the villages (sex combined).

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Table 6—*Age- and sex-adjusted prevalence (%) of diabetes and IGT by tertiles of BMI*

	Nyambori		Uswaa		Six other villages*	
	IGT	Diabetes	IGT	Diabetes	IGT	Diabetes
BMI (kg/m^2)						
<19.4	8.1	1.6	6.8	1.2	8.3	1.0
19.4–21.4	6.9	0.6	4.0	0.9	7.7	0.6
>21.5	7.2	0.3	2.8	1.4	7.2	1.2
Total	7.0	0.5	3.9	0.9	7.7	0.9
95% CI	5.6–8.7	0.2–1.2	3.0–5.1	0.5–1.6	7.1–8.4	0.7–1.2

*Previously published by McLarty et al. (12)

sumption in the control village in Kilimanjaro Region, where cassava is eaten infrequently. The elevated plasma and urine thiocyanate levels in the cassava-consuming village also reveals that the bitter roots were consumed after insufficient removal of cyanogenic substances. The mean plasma thiocyanate of 296 μM was ~8 times higher than the mean found in a reference population (16).

Blood cyanide levels also were elevated markedly in the study village. This together with the elevated thiocyanate levels suggests greatly increased exposure to cyanide combined with a deficiency of sulfur-containing amino acids in the local diet. The mean urinary thiocyanate level of ~500 μM corresponds to a daily hydrogen cyanide intake of ~13 mg in adults, which is 25% the lethal dose (14). This is one of the highest cyanide exposures recorded in cassava-eating populations. The dietary information suggests that the same exposure has occurred during dry seasons during many previous years.

An exact estimate of protein intake was not made but 33% of the population admitted to rarely or never eating fish. Fish from Lake Victoria is the major source of animal protein in this area. However, the villages in which spastic paraparesis most commonly occurs are some distance from the lake. Few people can afford to eat fish in liberal amounts, and the amount eaten by those who eat fish regularly is generally small. Meat consumption is also very low. Hb levels were significantly lower in the cassava-consuming population.

However, the prevalence of diabetes was not different in the two villages: 0.5% (95% confidence interval 0.2–1.2%) vs. 0.9% (95% confidence interval 0.5–1.6%) ($P = 0.5$) in the cassava-consuming and non–cassava-consuming communities. The prevalence of diabetes in the cassava-consuming village was also closely similar to the prevalence found in six other villages in Tanzania (12). In addition, no differences were found in mean plasma and urine thiocyanate levels and blood cyanide levels between subjects with NGT and abnormal glucose tolerance in the cassava-eating community.

Although no differences were observed in diabetes-prevalence estimates between the two villages, a significantly higher prevalence of IGT was found in people ≥55 yr old in the cassava-consuming village but not in other age-groups. Mean fasting and 2-h blood glucose levels were also slightly but significantly higher in the cassava-consuming population. From previous studies in rural communities in Tanzania, a possible explanation for these differences may lie in the different degrees of western medical acculturation in the two communities. In contrast to the community in Kilimanjaro region, few subjects in the cassava village had ever experienced venepuncture. We have shown that glucose tolerance tests repeated within a few days of the first test yield lower blood glucose values (30). We have suggested that the higher initial values may reflect a stress response, as is seen in the measurement of blood pressure (31). This was found in other villages in Tanzania where IGT rates were identical to those found in Nyambori. On univariate analysis, plasma thiocyanate was associated with the mean fasting blood glucose levels in Nyambori village. However, this effect disappeared on multiple regression analysis and neither plasma nor urine thiocyanate levels were

Table 7—*Mean ± SD fasting and 2-h blood glucose concentrations by sex and age-group**

	Nyambori	Uswaa	P*
Fasting blood glucose (mM)			
Age (yr)			
15–34	4.5 ± 0.7	4.1 ± 0.8	<0.001
35–54	4.5 ± 1.0	4.2 ± 0.9	0.002
≥55	4.7 ± 1.7	4.4 ± 0.9	0.055
Total	4.5 ± 1.0	4.2 ± 0.8	<0.001
2-h Blood glucose (mM)			
Age (yr)			
15–34	4.9 ± 1.0	4.3 ± 1.4	<0.001
35–54	4.9 ± 1.7	4.4 ± 1.7	<0.001
≥55	5.8 ± 3.4	4.8 ± 2.0	0.006
Total	5.0 ± 1.7	4.4 ± 1.6	<0.001

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associated significantly with blood glucose levels.

Nonetheless, it could be argued that the population in Nyambori village had not been exposed to the toxic effects of cyanide for a sufficient length of time for significant β-cell damage to have occurred, that exposure was only intermittent during the year at times of greatest food scarcity, or that the population was insufficiently malnourished for cyanide to have exerted major damage on the β-cell. These possibilities are difficult to prove or refute. We know that the community had been exposed to high dietary cyanide from cassava for at least 6 yr and probably much longer. Many villagers could recall the development of spastic paraparesis in individuals as far back as the early 1970s. In the konzo-affected populations in Mozambique and Zaire, no increase in diabetes prevalence was noted. However, some areas had limited access to medical services. By contrast, Nyambori is situated only 10 km from a missionary hospital and failure to diagnose diabetes or high mortality caused by undertreatment are less likely. However, exposure to increased cyanide levels is intermittent throughout the year, being least after harvest and highest at the end of the dry season and beginning of the long rains. The third possibility was that we may have failed to see increased rates of diabetes because the community was insufficiently malnourished. Undernutrition is common in children <5 yr old in the area, and Hb levels were significantly lower in the cassava-consuming community. The accurate assessment of malnutrition in adults is difficult, and there are no widely accepted criteria by which this can be adequately assessed apart, possibly from BMI and skin-fold thickness. One-third of the population had a BMI <18.9 kg/m^2, suggesting that there was considerable undernutrition at the time of the study. In a study encompassing >7000 subjects in rural Tanzania, we have shown that low BMI of itself is not associated with an increased prevalence of diabetes (32).

Evidence of exocrine pancreatic damage was sought by X-raying the abdomen of 37 subjects with IGT or diabetes and comparing the findings with those in 45 control subjects with NGT. Only 1 person with IGT and none of those with NGT was found to have a calcified pancreas. Therefore, no evidence suggested that high cyanide exposure and undernutrition are associated with pancreatic calcification. PABA tests also were conducted as another index of pancreatic exocrine dysfunction. Unfortunately, urine collections were not obtained in most of the subjects tested, but analysis of PABA levels in blood showed no difference between those with glucose intolerance and those without. Our findings suggest that further hypotheses are required to be tested with respect to the cause of *tropical* diabetes. We suggest that high cyanide exposure from the consumption of bitter cassava is not associated with increased rates of diabetes.

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