

Tropical enteropathy in Rhodesia

G. THOMAS, D. J. CLAIN, AND A. C. B. WICKS

From the Department of Medicine, University of Rhodesia, Salisbury, Rhodesia

SUMMARY Tropical enteropathy, which may be related to tropical sprue, has been described in many developing countries including parts of Africa. The jejunal changes of enteropathy are seen in Rhodesians of all social and racial categories. Xylose excretion, however, is related to socioeconomic status, but not race. Upper socioeconomic Africans and Europeans excrete significantly more xylose than lower socioeconomic Africans. Vitamin B12 and fat absorption are normal, suggesting predominant involvement of the proximal small intestine. Tropical enteropathy in Rhodesia is similar to that seen in Nigeria but is associated with less malabsorption than is found in the Caribbean, the Indian subcontinent, and South East Asia. The possible aetiological factors are discussed. It is postulated that the lighter exposure of upper class Africans and Europeans to repeated gastrointestinal infections may account for their superior xylose absorption compared with Africans of low socioeconomic circumstances. It is further suggested that the milder enteropathy seen in Africa may be explained by a lower prevalence of acute gastroenteritis than is experienced elsewhere in the tropics.

Tropical enteropathy is characterised by asymptomatic jejunal abnormalities and xylose malabsorption in apparently healthy people. A minority have malabsorption of two unrelated substances and some have recurrent diarrhoea (Lindenbaum *et al.*, 1966a; Lindenbaum *et al.*, 1966b; Klipstein *et al.*, 1972; Baker and Mathan, 1972). It is recognised throughout the developing world, particularly in the tropics. Detailed reports have come from the Indian subcontinent (Lindenbaum *et al.*, 1966a; Baker and Mathan, 1972), South East Asia (Sprinz *et al.*, 1962; Colwell *et al.*, 1968), the Caribbean (Klipstein *et al.*, 1968; Klipstein *et al.*, 1972), Mexico (Garcia, 1968), the Middle East (Parkins *et al.*, 1966; Halsted *et al.*, 1969), and parts of Africa (Banwell *et al.*, 1964; Cook *et al.*, 1969; Falaiye, 1971; Rhodes *et al.*, 1971; Lindenbaum *et al.*, 1972; Cook *et al.*, 1973).

The association between subclinical enteropathy and overt tropical sprue is controversial. The difficulty in separating the two by objective criteria and the improvement of subclinical malabsorption with conventional treatment for tropical sprue, suggest a close relationship (Klipstein *et al.*, 1968). Baker and Mathan (1972) favour the existence of two distinct entities, and in support of this make the following points: the occurrence of subclinical

enteropathy in Africa where the presence of tropical sprue has been in doubt; the frequency of enteropathy in children in whom tropical sprue is rare; and the regular recovery of tropical enteropathy on moving to a temperate climate, whereas tropical sprue may present for the first time after the patient has left the tropics.

This study was undertaken to establish whether tropical enteropathy occurs in Rhodesia, and to provide the background data for the investigation of tropical sprue.

Methods

PATIENTS

The population of Rhodesia is both African and European. The African population can be broadly divided into lower and upper socioeconomic groups. Those in the higher social classes tend to live in towns in circumstances comparable with those of Europeans. We have, therefore, studied the following groups for comparison: upper socioeconomic Africans consisting of doctors, nurses, medical students, and technicians; lower socioeconomic Africans, consisting of urban hospital cleaners, ward patients without evidence of gastrointestinal disease, and rural hospital workers; and European medical students. Informed consent was obtained from each volunteer.

INVESTIGATIONS

The following investigations were performed: jejunal biopsies were obtained just distal to the ligament of Treitz, using the Crosby capsule (Crosby and Kugler, 1957), which was positioned by the rapid method of Wicks and Clain (1972), under an image intensifier. The specimens were examined immediately under a dissecting microscope (Holmes *et al.*, 1961), and then fixed in 10% formalin for histology. Dissecting microscope appearance was graded from 1 to 6 according to the predominant villous pattern: grade 1—fingers; 2—leaves; 3—joined leaves and short ridges; 4—long ridges; 5—convolutions; 6—flat.

The criteria suggested by Schenk and Klipstein (1972) were used to grade histological sections for villous abnormalities and cellular infiltrations. For villous appearance, grade 0 is normal, grades 1-3 show progressive broadening and flattening of villi, and grade 4 is flat. For cellular infiltration grade 0 is normal, grade 1 shows a mild increase, grade 2 a moderate increase, and grade 3 a marked increase. Histological sections were also measured using a calibrated micrometer eye piece (Shiner and Doniach, 1960). Villous height was taken from the base to the apex and width at the widest part of the villus. Mucosal thickness was assessed from the muscularis mucosa to the base of the villi and epithelial cell height was measured half way up the villus. At least 10 readings were recorded from each specimen, and measurements and grades are compared with 50 British controls (Stewart *et al.*, 1967).

Xylose excretion was determined after a 25 g dose and five hour urine collection (Roe and Rice, 1948). Faecal fat excretion was estimated on a diet supplemented to contain 80-100 g fat, and expressed as the mean of a five day collection (van de Kamer *et al.*, 1949). Vitamin B12 absorption was measured using the plasma uptake method (Booth and Mollin, 1956; Doscherholmen and Hagen, 1957) and calculated as a percentage of the administered dose per litre of plasma. In this study CO57-labelled vitamin B12 was used. The range of normal values in the following series using CO57 was 0.22% to 2.9% (Nelp *et al.*, 1963; Workman and Rusche, 1966; Armstrong and Woodliff, 1970; Donaldson, 1970; Coiner and Walsh, 1971).

Results

JEJUNAL BIOPSIES

Jejunal biopsies were obtained from 17 Africans of upper socioeconomic status, 26 Africans of lower socioeconomic status, and 16 Europeans. Dissecting microscopy and histological grades, mean histological measurements, and grades of cellular infiltra-

Table 1 *Jejunal microscopy and histological grades*

	<i>Jejunal dissecting microscopy grades</i>						
	No.	1	2	3	4	5	6
Africans (socioeconomic)							
Upper	17	0	8	9			
Lower	26	3	18	4	1		
Europeans	16	1	10	5			
British controls (Stewart <i>et al.</i> , 1967)	50	28	22				
	<i>Jejunal histological grades</i>						
	No.	0	1	2	3	4	
Africans (socioeconomic)							
Upper	17	1	8	8			
Lower	26		14	12			
Europeans	16	1	9	6			

Table 2 *Mean histological measurements of jejunal biopsies*

	No.	Villous height (μ)	Villous width (μ)	Cell height (μ)	Mucosal thickness (μ)
Africans (socioeconomic)					
Upper	17	293	140	31.76	143
Lower	26	302	146	31.33	159
Europeans	16	311	143	31.28	150
British controls (Stewart <i>et al.</i> , 1967)	50	489	146	32.7	109

Table 3 *Jejunal biopsy cellular infiltration*

	<i>Jejunal biopsy infiltration grades</i>				
	No.	0	1	2	3
Africans (socioeconomic)					
Upper	17		5	10	2
Lower	26		15	8	3
Europeans	16		10	6	

tion are represented in Tables 1, 2, and 3 respectively. All three groups revealed predominantly leaves and joined leaves under the dissecting microscope and very few had a majority of fingers, in contrast with the British controls. Only two biopsies were normal histologically, with the rest evenly spread over grades 1 and 2 in all three groups. Figure 1 shows a biopsy with predominant leaves, grade 2 under the dissecting microscope, photographed with the scanning electron microscope; and Fig. 2 is a grade 2 histological section from a European medical student. Statistical analysis of these results reveals no difference between racial and social groups in Rhodesia, with the exception of mucosal thickness which is significantly greater in the lower socioeconomic Africans ($P < 0.01$) (analysis of variance for measurements; χ^2 for grades). However compared with 50 British controls (Stewart *et al.*, 1967), except for villous width, all histological measure-

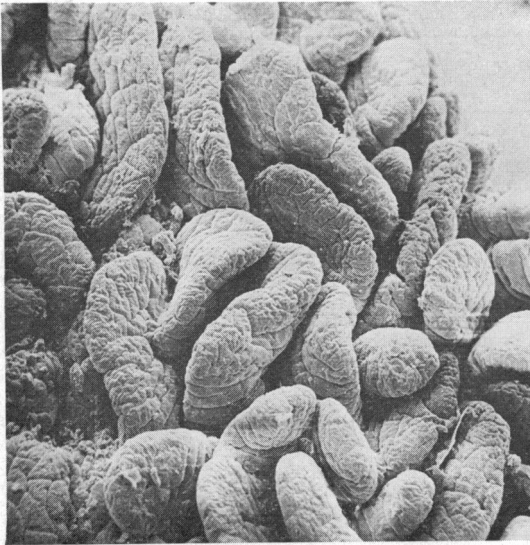


Fig. 1 *Grade 2 dissecting microscopy of jejunal biopsy, with predominant leaves, photographed with scanning electron microscope.*

ments and dissecting microscopy grades in the Rhodesian groups are inferior (Student's *t* test $P < 0.001$).

XYLOSE EXCRETION

Figure 3 shows the xylose excretion of 28 Africans of upper socioeconomic status and 51 Africans of lower socioeconomic status. The results of the upper socioeconomic group ranged from 3.6 g-16.5 g with a mean of 7.3 g and only two (7%) were less than 5 g. This is not statistically different from 10 Europeans, range 5.3 g-8.3 g, mean 7.2 g. In contrast, the 51 Africans of lower socioeconomic status ranged from 1.2 g-13.2 g, mean 5.4 g with 20 (39%) less than 5 g. Within this group were 31 rural Africans, range 1.6 g-13.2 g, mean 5.4 g and 20 urban Africans, range 1.2 g-10.4 g, mean 5.5 g. The xylose excretion of Africans from upper socioeconomic circumstances is significantly greater than Africans from lower socioeconomic circumstances (analysis of variance $P < 0.001$). There is, however, no difference between urban and rural Africans of lower socioeconomic status.

FAECAL FAT EXCRETION

Twenty ward patients without evidence of gastrointestinal disease had an average 24 hour faecal fat excretion ranging from 1.2 g to 4.9 g with a mean of 2.5 g.

VITAMIN B12 ABSORPTION

The range of vitamin B12 absorption in 42 Africans



Fig. 2 *Grade 2 histological section of jejunal biopsy from a European medical student.*

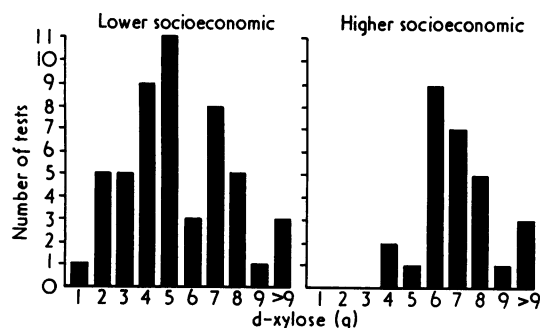


Fig. 3 Xylose excretion of 51 lower socioeconomic Africans and 28 upper socioeconomic Africans.

of lower socioeconomic status was 0.86% to 2.8% with a mean of 1.35%. Ten upper socioeconomic Africans had a range of 0.51% to 1.56% and a mean of 1.17%. These figures are within the normal range, 0.22% to 2.9%, found by other workers also using CO^{57} labelled vitamin B12 as described in the methods section. There is no significant difference between Africans of upper or lower socioeconomic circumstances (analysis of variance).

Discussion

Table 4 gives the results of seven comprehensive investigations of small intestinal structure and function, in asymptomatic people in the tropics outside Africa. The subjects of these studies were apparently healthy people selected at random or as representative of the age and sex distribution within the populations studied. Non-specific changes consisting of broadening and shortening of villi and infiltration with chronic inflammatory cells are present in the great majority of jejunal biopsies. Xylose malabsorption is common but variable and steatorrhoea unusual. Vitamin B12 malabsorption, indicat-

ing more distal involvement, is more prevalent in the Caribbean than in the Indian subcontinent and South East Asia, with the exception of Bangladesh. These differences suggest a geographical variation in the severity of tropical enteropathy.

The present study confirms the presence of tropical enteropathy in Rhodesia. Jejunal abnormalities, with few exceptions, are present irrespective of race or socioeconomic circumstances. Xylose malabsorption, however, is related to socioeconomic but not racial categories. Africans and Europeans of upper socioeconomic status have similar xylose excretion which is significantly greater than Africans of lower socioeconomic status. There is no difference between rural and urban Africans from low socioeconomic circumstances. Vitamin B12 and fat malabsorption are not seen, which suggests that the proximal small intestine is predominantly involved. In other series, only Jeejeebhoy *et al.* (1966) in India and Falaiye (1971) in Nigeria report complete absence of steatorrhoea and vitamin B12 absorption and of steatorrhoea respectively. Our findings are more akin to those from India and Thailand, where vitamin B12 malabsorption is unusual, than the Caribbean where it is more prevalent (Table 4).

Falaiye (1971) in Nigeria reports the only previous comprehensive survey from Africa. All of his 50 subjects had jejunal abnormalities, 24% had xylose malabsorption, 35% had folic acid malabsorption, but none had steatorrhoea, and vitamin B12 absorption studies were not done. Other series from Africa are less detailed. Banwell *et al.* (1964) and Cook *et al.* (1969) confirm the presence of jejunal abnormalities in Ugandan Africans. They mention xylose malabsorption, but give no specific details. Cook *et al.* (1973) comment that jejunal biopsies of Zambian Africans are similar to those observed in Uganda. In Liberia xylose malabsorption is seen in 28.6% of schoolchildren (Rhodes *et al.*, 1971) and in 32% of rural adults (Lindenbaum *et al.*, 1972).

Table 4 Geographical distribution of tropical enteropathy

Country	Subjects studied (no.)	Absorption			Structural changes
		Xylose	Fat	Vit. B12	
% Abnormal					
India (Jeejeebhoy <i>et al.</i> , 1966)	32* (U)	—	0	0	92
India (Baker and Mathan, 1972)	71 (U)	19	10	1.5	92
	308 (R)	51	1.6	2.2	—
Bangladesh (Lindenbaum <i>et al.</i> , 1966a)	106† (U)	40	7	20	100
Thailand (Troncale <i>et al.</i> , 1967)	40 (R)	38	6	3	100
Puerto Rico (Klipstein <i>et al.</i> , 1972)	96 (R)	25	4	29	82
Dominican Republic (Klipstein <i>et al.</i> , 1973)	42 (R)	45	2	26	94
Haiti (Klipstein, 1971)	29 (R)	72	—	58	100

*Intestinal morphology examined in 13, and vitamin B12 absorption in 12.

†Intestinal morphology examined in 12 subjects, fat absorption in 14, and vitamin B12 absorption in 30.

U: urban. R: rural.

The aetiology of tropical enteropathy is uncertain but present evidence favours an environmental cause. Jejunal biopsies from stillborn fetuses in the tropics have mainly finger villi (Chacko *et al.*, 1969; Stanfield *et al.*, 1965) but soon after birth the intestines of infants change to predominantly leaves and joined leaves (Chacko *et al.*, 1969; Cook *et al.*, 1969). This is presumably an environmental response similar to that of expatriates who develop tropical enteropathy after arriving in the tropics from temperate climates (Lindenbaum *et al.*, 1966b; Sheehy, 1968). Furthermore, these same expatriates recover when they return to their home countries (Lindenbaum, 1971).

The occurrence of intestinal malabsorption, which may persist for months, after acute gastroenteritis (King and Joske, 1960; Lindenbaum, 1965; Jones *et al.*, 1972) has led to the suggestion that repeated gastrointestinal infections may be a factor responsible for tropical enteropathy. There is some experimental support for this hypothesis. The introduction of bacteria into the intestines of germ-free animals causes villous abnormalities and decreased xylose absorption (Sprinz *et al.*, 1961; Heneghan, 1963; Kenworthy, 1967), and isolated loops of rat jejunum are protected from the morphological changes that develop in the intestine still receiving food (Chacko *et al.*, 1968; Gleeson *et al.*, 1969).

The influence of poor nutrition is uncertain. Expatriates with tropical enteropathy are well nourished (Lindenbaum *et al.*, 1968; Sheehy, 1968; Keusch *et al.*, 1970). On the other hand, in the Caribbean the incidence of abnormalities increases with the poverty of the diet. Haiti has the worst diet and the most abnormalities, Puerto Rico the best diet and least abnormalities, and the Dominican Republic falls in between on both counts (Table 4). Socio-economic circumstances must govern the diets of these people and factors such as sanitation are likely to be proportionately bad. This could lead to an increase in acute intestinal infection and therefore may be equally or more important. Mayoral *et al.* (1967) and Tandon *et al.* (1968) report small intestinal morphological changes in adults due to diet-induced hypoproteinaemia. Both these studies were in areas endemic for tropical sprue, which was not entirely excluded as the cause of hypoproteinaemia. Further, in temperate regions protein deficiency secondary to diet (Gough *et al.*, 1963), the nephrotic syndrome (Jensen *et al.*, 1966), and liver disease (Marin *et al.*, 1969) is associated with normal jejunal biopsies.

Intestinal parasites are unlikely to play an important role in the aetiology of tropical enteropathy as most investigators have found no difference in affected or unaffected people with regard to parasite infestations (Banwell *et al.*, 1964; Lindenbaum *et al.*,

1966b; Russel *et al.*, 1966; Troncale *et al.*, 1967; Cook *et al.*, 1969; Halsted *et al.*, 1969; Klipstein *et al.*, 1972). Parasites were not looked for in this study but *Giardia lamblia*, *Schistosoma mansoni*, and hookworm play no part in symptomatic malabsorption in Rhodesia (Thomas and Clain, 1976) and are unlikely to influence subclinical changes.

A correlation between xylose malabsorption and jejunal changes has been found by Kent and Lindenbaum (1967) in Bangladesh, Klipstein (1971) in Haiti, and Falaiye (1971) in Nigeria. In contrast, however, Russell *et al.* (1966) in Pakistan, Troncale *et al.* (1967) in Thailand, and Baker and Mathan (1972) in India emphasise the lack of such a correlation. Jejunal abnormalities of equal severity are common to all Rhodesians, but xylose malabsorption occurs only in lower socioeconomic Africans. This indicates that similar histological changes do not necessarily lead to similar xylose absorption.

A possible relationship between xylose absorption and social class has previously been hinted (Robins *et al.*, 1967; Klipstein *et al.*, 1968) but no statistical evidence produced. Baker and Mathan (1972), in contrast with ourselves, have found a difference between village and urban Indians. They comment that village sanitation was negligible and the water supply was faecally contaminated. It would be interesting to know if there was a contrast in socio-economic circumstances between their groups, which seems likely.

Lindenbaum *et al.* (1966b) describe a difference in xylose absorption between American Peace Corps volunteers, living with the local population, and 'protected' Americans who maintained their sophisticated way of life, in Pakistan. The mean value for the Peace Corps workers was 5.3 g with 39.5% less than 5 g. The 'protected' Americans in contrast, had a mean of 7.1 g with 3.3% less than 5 g. There is a remarkable parallel in our study. The lower socioeconomic group of Africans had a mean of 5.4 g with 39% less than 5 g and the upper socioeconomic group a mean of 7.3 g with 7% less than 5 g. Lindenbaum did not biopsy his 'protected' group and so we do not know if there were jejunal changes. It is an attractive postulate that our upper class Africans and Europeans represent another protected group. In common with the Americans, and by virtue of good living conditions, they are certainly protected from attacks of gastroenteritis, parasites, and malnutrition, which may be implicated in tropical enteropathy.

Tropical enteropathy in Rhodesian Africans from poorer circumstances is associated with less severe malabsorption than in many other tropical regions (Table 4), but appears similar to that seen in Nigeria (Falaiye, 1971). Cook (1974) has drawn attention to the lower prevalence of acute gastrointestinal

infections in Africa, compared with India and South East Asia. If, as has been suggested, repeated attacks of gastroenteritis have a causative relationship with tropical enteropathy, this lighter exposure could account for the milder form seen in Africa. Diet and sanitation are poor for the majority of the inhabitants of the African continent and seem unlikely to account for this difference.

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