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THE JEJUNAL MUCOSA IN KWASHIORKOR*

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The 'tissue paper' intestine of patients with severe kwashiorkor is well known to tropical pathologists and it is usually considered to involve all coats of the intestinal wall. However, histological study of the small gut mucosa in man has been very difficult until the advent of peroral biopsy (Shiner, 1956). This paper reports a series of 17 infants with kwashiorkor whose jejunal mucosa was studied after peroral biopsy.

Material and Methods

The patients studied were all in the Children's Ward of King George VI Hospital, Nairobi, in February and March 1963. They were all under the age of 3 years and all presented with the clinical picture of kwashiorkor as described by Trowell, Davies, and Dean (1954a). They all had marked wasting, oedema, dyspigmentation of the hair, and the typical dermatosis.

Jejunal biopsies were performed by a technique already described (Burman, 1963) using an adult Crosby capsule (Crosby and Kugler, 1957). The specimens were examined with the dissecting microscope before sections were cut. The sections were stained with haematoxylin and eosin and by the periodic acid-Schiff (PAS) technique.

All haematological investigations were carried out on venous samples using sequestrene as the anticoagulant. The haemoglobin content was measured by the cyanmethaemoglobin method and the packed cell volume by the Hawksley microhaematocrit.

The serum folate was measured as *L. casei* activity using the technique of Baker, Herbert, Frank, Pasher, Hutner, Wasserman, and Sobotka (1959) as modified by Chanarin and Berry (1964). The total serum proteins and the serum globulin were estimated with an auto-analyser using the methods of Stevens (1959) and Glenn (1965), respectively. The sera for these estimations were separated as soon as possible and kept in a deep freeze, or in CO_2 snow, until the estimations were performed at St. Mary's Hospital.

Results

Studies were carried out on 17 patients. Their ages, sex, weight, serum proteins, haematological

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TABL

DETAILS OF 17 PATIENT

Case No.	Sex	Age (mth.)	Weight (kg.)	Serum Proteins (g./100 ml.)		Haemo-globin (g./100 ml.)	PCV (%)	MCHC (%)	Bone-marrow	Serum Folate (mμg./ml.)	Associated Conditions
				Total	Albumin						
1	M	36	9·5	4·3	1·7	7·0	24·5	28·6	NB	25·0	
2	F	24	6·4	3·7	1·6	8·0	32	25	NB	6·0	Dysentery
3	F	12	4·08	5·6	2·8	8·0	29·5	27·1	NB	2·5	Malaria
4	F	18	6·8	4·1	2·2	9·4	33	28·5	NB	8·0	
5	M	12	5·89	4·7	2·7	5·3	18	29·4	MB	13·5	Dysentery
6	M	18	6·8	7·8	3·8	7·6	29·5	25·8	MB	12·5	
7	M	30	8·6	6·4	2·0	9·7	32·5	29·8	NB	7·5	Malaria
8	F	30	6·8	3·8	1·5	9·5	33·5	28·4	NB	6·5	
9	M	12	7·7	3·2	1·6	10·3	36·5	28·2	NB	4·0	
10	F	13	6·8	5·4	3·0	6·4	22·5	28·4	NB	10·0	
11	F	18	7·7	6·2	3·6	10·5	38·0	27·6	—	14·5	
12	M	24	10·9	3·7	1·9	11·0	40·0	27·5	NB	6·0	
13	M	18	6·4	4·7	2·6	9·7	33·0	29·4	—	7·5	
14	F	13	5·9	4·6	2·7	10·3	34	30·3	NB	6·0	Malaria
15	F	18	7·3	5·5	3·1	3·0	13	22·1	—	14·5	Malaria
16	F	12	6·8	5·7	3·4	8·0	30	26·7	—	7·5	
17	M	14	6·4	2·8	1·0	7·5	27	27	NB	30·0	

NB, normoblastic; MB, megaloblasti

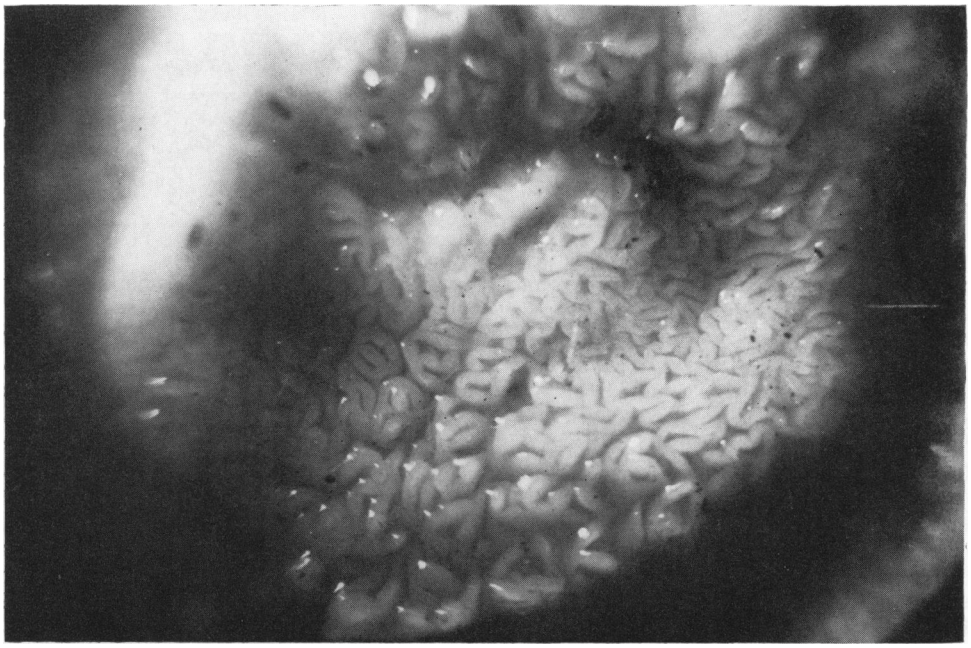

FIG. 1.—The dissecting microscope appearances of Case 3 showing ridges. (× 13.)

findings, and findings in the jejunal mucosa are given in Table 1. The dissecting microscope appearances are classified by a system whereby ++++ are distributed between ridges, leaves, and fingers after inspection of the whole specimen. Fingers are defined as projections where the cross-section is roughly circular. Ridges are projections where the largest cross-sectional diameter is at least 10 times the smallest (Baker, Mathan, and Cherian, 1963), and leaves lie between these two. The method is only semi-quantitative and Fig. 1 shows the dissecting microscope appearances of Case 3. The same technique was applied to 15 specimens obtained from infants aged 1 to 3 years who were investigated for a variety of gastro-intestinal symptoms in England. None of these infants had coeliac disease, fibrocystic disease of the pancreas, dysentery, or other disease of the small gut, and, for the purpose of this paper, they

ITH KWASHIORKOR

Jejunal Mucosa							Comment
Dissecting Microscope			Histology				
Ridges	Leaves	Fingers	Villi	Cellular Infiltration of Substantia Propria	Brush Border	Epithelial Cells	
++++			B	+++	N	I	
	++++		N	+++	N	N	
++++			N	+++	N	I	
++	++		N	+++	N	I	
++++			N	+++	N	I	
++++			N	++	N	N	Lymphoid follicle
++	+	+	B	+++	N	N	Some villi tongue shaped
	++++		B	++++	N	I	
++	+	+	B	+++	N	I	
++++			B	++++	N	I	
++	++		N	+++	N	I	
++++			N	+++	N	I	Lymphoid follicle
	++++		B	++++	N	I	
	++++		B	+++	N	I	
++++			N	+++	N	N	
	++++		B	+++	N	I	
++++			N	++++	N	I	

broad; N, normal; I, irregular.

TABLE 2

DISSECTING MICROSCOPE APPEARANCES OF JEJUNAL MUCOSA IN PATIENTS WITH KWASHIORKOR COMPARED WITH NORMAL CHILDREN

	No. of Patients	Villous Type (%)		
		Ridges	Leaves	Fingers
Normal	15	5	48	47
Kwashiorkor ..	17	59	38	3

TABLE 3

CELLULAR INFILTRATION OF SUBSTANTIA PROPRIA OF JEJUNAL MUCOSA IN PATIENTS WITH KWASHIORKOR COMPARED WITH NORMAL CHILDREN

	Degree of Cellular Infiltration				Total
	+	++	+++	++++	
No. normal	5	14	1		20
No. with kwashiorkor ..		1	12	4	17

are considered to be normal. Table 2 compares the dissecting microscope appearances of these two groups of children, and it can be seen that leaves are common in both groups, but fingers are found in most 'normal' children and are very uncommon in infants with kwashiorkor. Ridges are the predominant villous type in kwashiorkor but are distinctly rare in the English children.

In the sections of the mucosa, the villi were either tall and slender, similar to those normally found, or were broader than usual (Fig. 2). The characteristic type of villus seen in each section is tabulated in Table 1. Broad villi were predominant in 8 specimens but there was no correlation with the dissecting microscope appearances. The width of the villi in section presumably depends upon whether the majority of the leaf or ridge-shaped villi were cut transversely or longitudinally.

The cellular infiltration of the substantia propria was assessed by a semi-quantitative method from + to ++++. The sections were assessed at the same time as 20 English infants of the same age who were considered normal. Each section was assessed on at least two occasions with consistent results. The two groups of children are compared in Table 3 and it can be seen that the children with kwashiorkor have a greater cellular infiltrate than the normal group. The cells of the substantia propria are lymphocytes, plasma cells, eosinophils, and polymorphs. There was no relation between the degree of cellular infiltration and the presence of dysentery.

The superficial epithelial cells appeared normal in

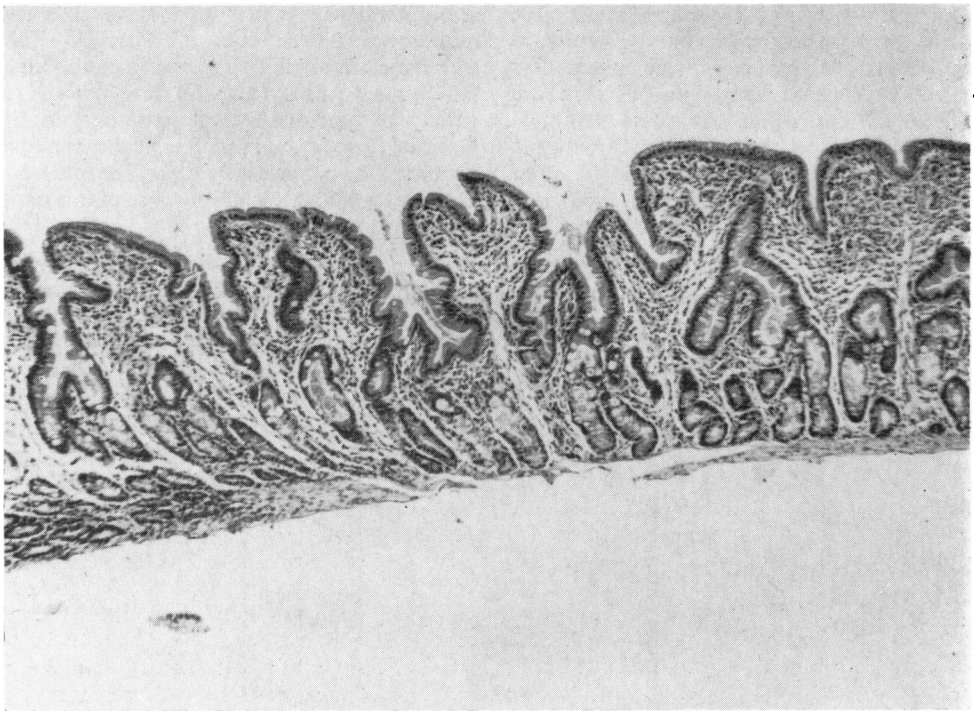

FIG. 2.—Section of jejunal mucosa from Case 7 showing broad villi but normal epithelium. (H and E × 96.)

4 patients, but in the other 13 they were abnormal. They were shorter than usual with an average height about three-quarters of that of cells at the tip of a normal villus. Their nuclei, instead of being basal and arranged in neat rows with regular size, shape, and staining properties, were irregular in all these respects and the epithelium was infiltrated with lymphocytes (Fig. 3). The goblet cells, which vary considerably in normal patients, appeared normal in size and number. The Paneth cells in the crypts also appeared normal with normal granules.

The brush border was studied in sections stained with both the H and E and the PAS techniques and in all cases the brush border was normal (Fig. 4).

Discussion

The typical jejunal mucosa in patients with kwashiorkor consists of villi in the shape of ridges and leaves with an increased cellular infiltrate of the substantia propria. The superficial epithelial cells show some shortening with irregular nuclei but a normal brush border. There is an increased lymphocytic infiltration in the epithelium. These changes are very similar to those found by Sprinz, Sribhibhadh, Gangarosa, Benyajati, Kundel, and Halstead (1962) in a third of Thai people from a low socio-economic group. That the abnormality of the epithelium is typical of patients with kwashiorkor is supported by the fact that 2 of the 4 specimens with normal epithelium were from 2 of the 4 patients whose serum albumin was over 3 g./100 ml. One of these, Case 15, had a very low haemoglobin (3·0 g./100 ml.) and presumably this was the cause of the oedema in this child. Of the 4 with a normal epithelium, 2 had malaria, another had dysentery, and the fourth had a megaloblastic bone-marrow. One of them, Case 6, was the only one in the whole series where the cellular infiltration of the substantia propria was assessed as only ++. The patients with a normal epithelium thus appear to differ from the majority of patients studied in one or more respects, though all were diagnosed clinically as kwashiorkor.

The brush border of the normal epithelial cell has been shown under the electron microscope to consist of large numbers of microvilli which increase the absorptive area of the gut by a factor of approximately 20 (Spencer, 1961). In kwashiorkor, the brush border appears normal, but obviously electron microscopic studies are urgently needed to confirm this. The normality of the Paneth cells reported

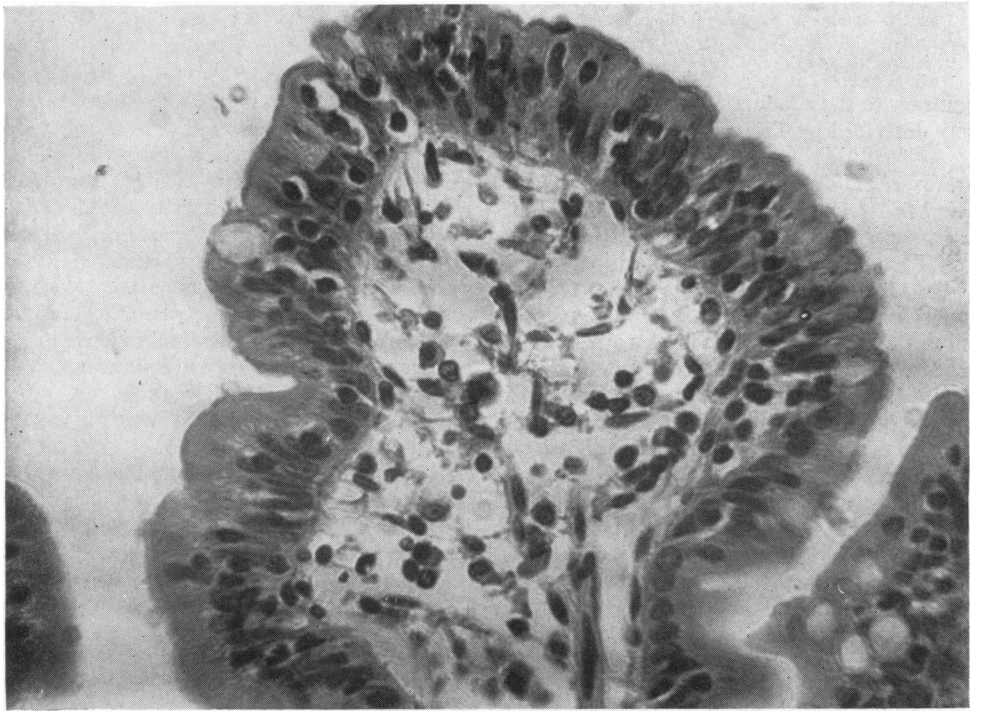

FIG. 3.—A high power view of villous epithelium from Case 1 showing irregular nuclei with lymphocytic infiltration. (H and E × 720.)

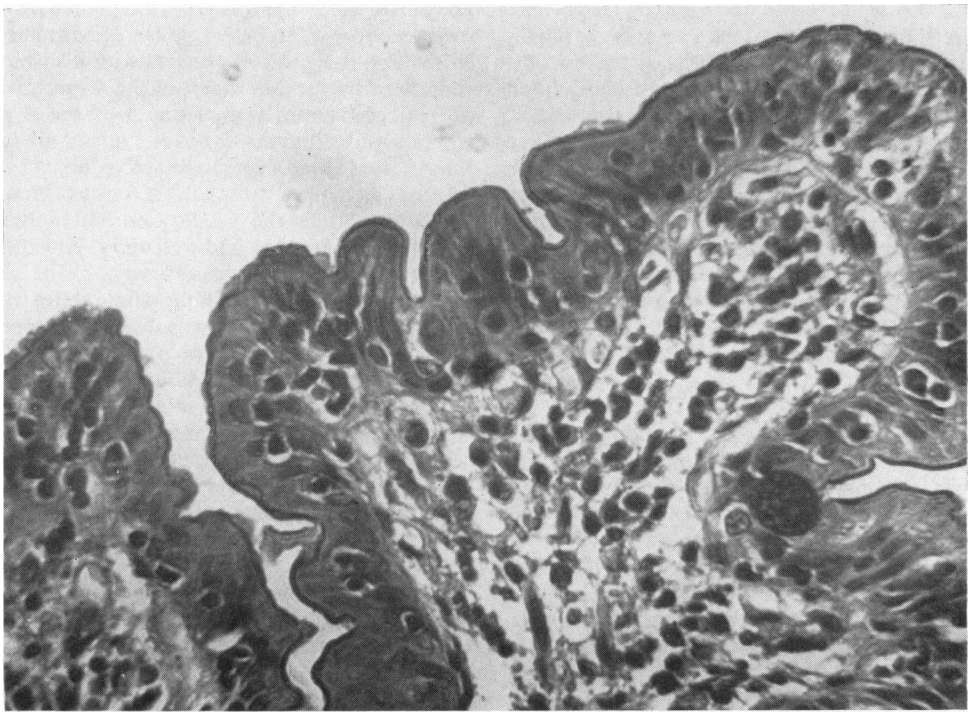

FIG. 4.—A high power view of villous epithelium from Case 1, showing a normal brush border. (PAS. × 720.)

here is contrary to their reduction in size and lack of granularity described by Trowell, Davies, and Dean (1954b).

The group of children available as controls were English or West Indian children living in London, and clearly specimens of jejunal mucosa from African children who have not got kwashiorkor are needed. This is particularly so in the case of the dissecting microscope appearances. A similar picture was seen in 21 older patients with hookworm disease in Mombasa, Kenya (Burman, 1965), and J. P. Stanfield (1964, personal communication) has found the changes to persist 5 months after the treatment of kwashiorkor was started. Baker, Ignatius, Mathan, Vaish, and Chacko (1962) have been unable to find any correlation between xylose and fat excretion and villous architecture. They also found that the villi of normal Southern Indians were entirely leaves, ridges, and convolutions, though stillborn foetuses from the same population had only finger-shaped villi. A similar difference between the villous architecture in the foetus and the adult has been noted in rats (Baker *et al.*, 1963) and in long-nosed bandicoots (van Lennep, 1962). The presence of ridge-shaped villi in the jejunal mucosa of patients with kwashiorkor cannot be considered specific and, in two cases in the present series, only ridges were seen with the dissecting microscope when the histology was quite normal. Ridges and leaves may well be present in the majority of Africans, though Booth (1962) described finger-shaped villi in a small group of African controls in Kampala, unless they were malnourished, had pancreatic steatorrhoea, or suffered from severe hookworm infestation.

The changes in the intestinal mucosa in kwashiorkor are thus relatively minor and cannot be described as complete atrophy. They are not sufficient to account for the steatorrhoea which is usually found (Gillman and Gillman, 1951). These biopsies were taken from the upper jejunum, and Passmore (1947) points out that the intestinal atrophy is most marked in the terminal ileum. It is thus possible that major changes lower down the small gut may have been missed.

The haematological findings in this series of patients were very similar to those found by Kondi, MacDougall, Foy, Mehta, and Mbaya (1963) in patients with kwashiorkor and marasmus on admission to the same ward in Nairobi. The two series are compared in Table 4. The serum folate

TABLE 4
HAEMATOLOGICAL FINDINGS IN PRESENT SERIES COMPARED WITH THOSE FOUND BY KONDI *ET AL.* (1963)

	No. of Patients	Haemoglobin (g./100 ml.)		PCV (%)		MCHC (%)		Megaloblastic Bone-marrow
		Mean	Range	Mean	Range	Mean	Range	
Present series	17	8·3	3·0–11·0	29·9	13–40	27·6	22–30	2 = 12%
Kondi and others ..	47	9·0	4·2–12·0	30·0	15–37	30·0	24–37	5 = 11%

levels recorded here differ from those found by Kondi and her colleagues. In 6 of her 7 cases, the serum folate was low and in one it was abnormally high. In the present paper, 9 had a level below 8 mμg./ml. which was the lowest figure recorded by Chanarin and Berry (1964) in 28 normal English adults. Of the 8 patients with a normal serum folate, 6 were the only 6 with haemoglobins below 6 g./100 ml., and 2 were the only 2 with megaloblastic bone-marrows. From these data, it seems unlikely that folic acid deficiency is the main cause of either the severe anaemia or the megaloblastic erythropoieses present on admission in patients with kwashiorkor. The dissecting microscope appearances of the jejunal mucosa in patients with a low and normal serum folate are compared in Table 5. Those

TABLE 5
DISSECTING MICROSCOPE APPEARANCES OF JEJUNAL MUCOSA IN PATIENTS WITH KWASHIORKOR RELATED TO SERUM FOLATE LEVELS

Serum Folate	No. of Patients	Villous Type (%)		
		Ridges	Leaves	Fingers
Normal	8	88	12	0
Low	9	33	61	6

with a normal serum folate have virtually all ridge-shaped villi, whereas this type of villus accounts for only one-third of the total when the serum folate is low. If the ridged mucosa is a more severe stage of abnormality than leaves (Booth, Stewart, Holmes, and Brackenbury, 1962), then the abnormal dissecting microscope appearances in kwashiorkor cannot be due to folic acid deficiency. Of the 4 specimens which showed normal epithelial cells, only 2 had a low serum folate, so that this finding also does not appear to be related to folic acid.

Summary

Jejunal biopsies were carried out on 17 patients with kwashiorkor. The specimens had ridge or leaf-shaped villi with increased cellularity of the substantia propria. The epithelial cells are short with irregular nuclei. This change does not appear to be related to folic acid deficiency.

I am very grateful to Dr. J. R. Harries for permission to study patients under his care. Dr. Henry Foy provided facilities at the Wellcome Trust Research Laboratories, Nairobi, and was extremely helpful in arranging this visit as well as providing excellent advice on all aspects of the investigation. Dr. I. Chanarin kindly performed the estimations of serum *L. casei* activity and Dr. B. Houghton the serum protein estimations.

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