Jejunal mucosal morphology in healthy north Indian subjects

MK BENNETT,* GK SACHDEV,† DP JEWELL,* BS ANAND†

*From the Departments of Gastroenterology, *John Radcliffe Hospital, Headington, Oxford, and †GB Pant Hospital, New Delhi*

SUMMARY Morphometric measurements have been performed on small intestinal biopsy specimens obtained from 18 healthy adult Indian volunteers. The measurements were made using a computer aided measuring system, and results were similar to those previously reported for an adult Caucasian population.

Histological abnormalities of the jejunal mucosa have been noted in a high proportion of apparently healthy asymptomatic subjects living in developing countries, especially in the tropics.¹ These findings are often accompanied by malabsorption of two or more unrelated substances; this syndrome is known as subclinical tropical enteropathy (STE). The mucosal abnormalities seen in STE are qualitatively similar to those seen in tropical sprue but of a milder degree,^{2,3} which suggests a possible relation between these two conditions.⁴ In India, tropical sprue runs a milder course in the north compared with the southern part of the country,⁵ where the disease is not only more severe but also has an epidemic form.⁶ Over 90% of the healthy subjects in southern India have morphological abnormalities of the jejunal mucosa,⁷ and it is possible that the severity of tropical sprue is related to the high prevalence rate of mucosal changes in the normal population. To examine this jejunal mucosal biopsy specimens were obtained from asymptomatic volunteers in New Delhi (north India) and the results were compared with a similar western population.

Subjects and methods

Eighteen healthy volunteers consisting of medical students, resident doctors, and nurses were included in the study. The group was chosen since it had similar standards and conditions of hygiene to a western population, enabling comparison with morphological studies from western and Indian countries. There were 14 men and four women in the age range of 18 to 28 years (mean (SD) = 24.33 (2.39)). Informed consent was obtained from each volunteer.

After an overnight fast, a Crosby capsule was introduced and a biopsy specimen was obtained from a point just beyond the duodenojejunal junction; the position of the capsule was checked under fluoroscopy. The biopsy specimens were properly orientated over a filter paper using a dissecting microscope and then fixed in 10% formol-saline.

Further processing was carried out in Oxford, where the tissue was routinely processed to wax and multiple sections taken perpendicular to the lumen. Serial sections of 4 μ m were stained by haematoxylin and eosin and alcian blue/periodic acid Schiff; an average of 29 levels were examined. No obvious parasitic infestation was noted in any of the specimens. The following features were assessed: areas of the mucosa, lamina propria, and epithelium. Villous height and crypt depth in correctly orientated areas were recorded and all values were related to unit lengths of muscularis mucosae. The absolute values were obtained by calibrating the readings against a standard stage graticule measuring 2 mm in 0.1 mm divisions. Sections were viewed through a 10 $\times$ objective and an image was projected on to a magnetised graphic table using a camera lucida. The image was then traced manually using a cursor with cross hairs. The resolution of the table was 0.1 mm. The cursor was connected to a MOP videoplan (Reichert-Jung UK), which is a semiautomated image analyser system, for the evaluation of these measurements and basic statistics. By means of a Leitz projecting microscope and a 40 $\times$ objective lens, an image of the mucosa was cast on to a flat surface and the epithelial cell height was measured. This was calibrated by projecting the image of a stage micrometer slide, with 0.1 mm divisions, measured at the beginning and end of each measuring session. The number of intraepithelial lympho-

cytes within the mucosa was calculated by a differential count of at least 600 cell nuclei; the results were expressed as intraepithelial lymphocytes per 100 enterocytes.

Results

The results were tabulated after exclusion of three biopsies from the assessment because of inadequacies of the specimens. The villous to crypt ratio was calculated from measurements of the height of the villous (from the tip of the villous to the base of the crypt) and the depth of the crypt (from the mouth to the base of the crypt). The values directly measured were within the expected range reported for adult Caucasians, (Table). Those values which were derived—that is, the volume of mucosal lamina propria and epithelium—showed differences from the values calculated by Slavin *et al.*⁸ The ratio of epithelial volume to mucosal volume and lamina propria volume showed a greater proportion of lamina propria in this study group; the significance of this finding is unclear.

Discussion

Subclinical tropical enteropathy has been recognised in a number of underdeveloped countries. Detailed reports are available from the Indian subcontinent,⁹⁻¹¹ Africa,¹²⁻¹⁴ the Caribbean,^{15,16} Middle East,¹⁷⁻¹⁸ and south east Asia.¹⁹⁻²⁰ In most studies histological abnormalities of the jejunal mucosa were seen in the majority of healthy subjects examined, from 83% to 100%. In sharp contrast to the above studies, the present study found abnormal mucosa in none of the normal asymptomatic volunteers examined.

The cause of STE is uncertain, but a number of possibilities exist. Since STE is found only in the underdeveloped part of the world, nutritional deficiency may play an important part. For example, in

the Caribbean, histological abnormalities are most severe in residents of Haiti, who have a poor diet compared with those of Puerto Rico, whose diet is far superior and the mucosal abnormalities milder.¹⁵⁻¹⁶ Protein deficiency by itself, however, is not associated with histological abnormalities.²¹⁻²³ Moreover, the presence of mucosal abnormalities in American peace corp workers in Pakistan, despite excellent protein intake,²⁴ and in Europeans and Americans living in the tropics^{24,25,30} points away from nutritional deficiency having an important aetiological role. Recurrent intestinal parasitic infestations and food toxins are other possibilities, but most workers have found no association between these and the severity of mucosal abnormalities.^{10,12,18,26,28}

Thus the most likely possibility is an environmental factor. Visitors from temperate countries develop tropical enteropathy after arriving in the tropics.²⁹ In a recent study from Angola³⁰ abnormal jejunal mucosa was seen in all the 19 Europeans examined, and the severity of the histological damage was similar to that seen in the native Africans. Moreover, the histological abnormalities are known to recover when the visitors return to their home countries.³¹

Similarly, the mucosal damage of STE has been shown to subside in Indian and Pakistani immigrants in America.^{14,27} The precise aetiological factor in the environment remains conjectural, but recurrent intestinal infection has to be considered. A study from south India reported jejunal bacterial overgrowth in eight of 12 asymptomatic subjects,³² but another study from the eastern part of the country (West Bengal) found normal bacterial flora in all 11 control subjects.³³ Several workers have argued in favour of recurrent subclinical enteric infections as being responsible for the jejunal mucosal abnormalities.²⁷

The striking difference in the jejunal morphology between residents of Delhi and those of Bombay⁹ (western India) and Vellore (south India), where abnormalities were noted in 92% subjects each, is difficult to explain. In terms of socio-economic

Morphometric measurements of jejunal mucosa in Indian volunteers and reported normal Caucasian values

	Mean	SD	Range	Reported values	Reference
Villous to crypt ratio	3.7:1			4:1	
Villous height (μm)	523	(±61)	(432-649)	386-525	37
Crypt depth (μm)	138	(±23)	(111-185)	132	39
Volume/mm ² of muscularis mucosae					
Mucosa	0.397	(±0.09)	(0.234-0.556)	0.405	8
Lamina propria	0.248	(±0.06)	(0.158-0.382)	0.181	8
Epithelium	0.152	(±0.046)	(0.057-0.217)	0.224	8
Intraepithelial lymphocytes/100 enterocytes	24	(±7)	(13-37)	34	40
Epithelial cell height (μm)	34	(±4.67)	(26.3-40.2)	30-40	42

status, the volunteers tested by us were similar to those of Jeejeebhoy *et al*⁶: in both, the studies were carried out on doctors and nurses. Nutritional deficiency is therefore unlikely to explain the morphological differences noted between the two studies. The aetiological agent thus appears to be a factor in the environment and in this respect enteric pathogens are the strongest possibility.

The association between STE and tropical sprue is uncertain. The similarity of the mucosal abnormalities and the epidemiological distribution of the two conditions suggests a close relation. There are arguments, however, to suggest that the two are distinct entities: in Africa, STE is common but tropical sprue is rare. Similarly, STE is often seen in children, but tropical sprue is not very common.⁷ In India, the prevalence of abnormal jejunal morphology in patients with tropical sprue varies from as high as 100% in Vellore³⁴ to between 44% and 66% in Delhi (north India).^{35, 36} In this context, the observation that the jejunal mucosa of healthy control subjects is normal in north India is interesting and suggests that the milder form of tropical sprue seen here is related to a better preserved jejunal mucosa.

We conclude that STE is not as widespread and universal in the tropics as we generally believed; certainly in a north Indian city its prevalence is negligible. The aetiology of STE is almost certainly related to an environmental factor and repeated enteric infections appear to be the most likely possibility. Finally, it is tempting to ascribe the milder form of tropical sprue seen in the north to the presence of a normal jejunal mucosa in the general population.

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Requests for reprints to: Dr MK Bennett, Department of Histopathology, Freeman Road Hospital, High Heaton, Newcastle Upon Tyne, England.