# PATHOGENESIS OF JEJUNAL MUCOSAL ALTERATIONS: SYNECHIA FORMATION

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Structural alterations in the jejunal mucosa have been described in association with a number of diseases.[1-8] These changes have been defined by the examination of the whole biopsy specimen with the dissecting microscope and by the use of histologic sections. The mucosal lesions seen range in increasing severity from leaf-shaped villi, to villus ridges and convolutions, to a completely flat surface.[4,5] The purpose of the present communication is to present evidence relevant to the pathogenic mechanisms which lead to these changes.

## MATERIAL AND METHODS

Over 500 jejunal biopsy specimens from 139 patients have been examined. The types of disorders which these patients had are listed in Table I. Detailed clinical features of many of the patients and the morphologic characteristics of their jejunal tissues have been presented previously.[6-10] The method of obtaining biopsy specimens and their subsequent preparation for morphologic analysis have been described.[6,7]

TABLE I

| | No. of patients |
|---|---|
| Celiac disease | 19 |
| Tropical sprue | 24 |
| Protein malnutrition | 3 |
| Anemia | 7 |
| Regional enteritis | 5 |
| Post-gastrectomy | 4 |
| Agammaglobulinemia | 3 |
| Other gastrointestinal disorders including diarrhea | 69 |
| Normal | 5 |

## RESULTS

Most biopsy specimens, except those which were flat or convoluted, revealed a mixed pattern when examined with the dissecting microscope.

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Thus, leaf-shaped villi were usually found admixed with normal finger-shaped villi, and villus ridges often occurred in the presence of leaf-shaped villi. For uniformity in designation, the specimens have been grouped under the most severe change seen. All of the tissues obtained from patients with untreated celiac disease had a flat or almost flat mucosa. Those from patients with tropical sprue showed considerable variation in the degree of villus abnormality. Four had a normal villus pattern, 10 showed villus ridges, 6 were convoluted and 5 were completely flat. Of the biopsy samples from patients with diagnoses other than celiac disease or tropical sprue, 22 were normal, 16 had leaf-shaped villi, 47 had ridges, and 9 had a convoluted pattern. Two specimens, one from a patient with an iron deficiency anemia and one from a patient with protein malnutrition, were completely flat.

Specimens which demonstrated a normal villus pattern, leaves, ridges or convolutions were in most cases serially sectioned. Two of the normal tissues, 7 with the leaf-shaped pattern, and 13 of those ridged showed microscopic evidence of what we have interpreted as villus fusion or synechia formation. This process occurred most frequently near the tips of the villi (Figs. 1 to 3), but was also seen at any level along the villus wall (Figs. 3 and 4). An inflammatory cell infiltrate in the lamina propria and in the surface epithelium was invariably present (Figs. 1 to 5). In some of the synechiae, only surface epithelial cells of adjacent villi and inflammatory cells were in focal contact with each other (Figs. 4 and 5). In others, bridging connective tissue elements were obvious (Figs. 3 and 6). The sizes of the synechiae were variable. Some consisted of from no more than 2 or 3 adjacent epithelial cells while others included a major portion of two adjacent villi.

Connective tissue stains of finger-shaped villi demonstrated a central core consisting of the lacteal of the villus, smooth muscle cells and an arteriole, all of which were surrounded and enveloped by a reticulin stroma (Figs. 4 and 5). A network of reticulin extended laterally from the central core, and at the sides of the villus united with the basement membrane under the surface epithelium (Fig. 5). Sections through the long diameter of leaf-shaped villi and villus ridges frequently revealed the connective tissue elements of two or more villi (Figs. 6 and 7). The lateral reticulin networks arising from the central cores located in the inner portion of the ridges communicated haphazardly with each other rather than with the lateral basement membrane (Figs. 6 and 7).

## Discussion

Alterations in the jejunal villus architecture with the formation of leaf-shaped villi, villus ridges and convolutions, and complete absence

of villi have been explained by two mechanisms. Doniach and Shiner [11] and Creamer [12] proposed that variations in epithelial cell turnover determined the size and shape of villi. On the basis of the finding that the villus shape correlated with the population of adult surface epithelial cells in the mucosa, these authors concluded that when sufficient cells were available, finger-shaped villi were present, whereas with few adult cells leaves and ridges were formed. The hypothesis was proposed that adult cells may be decreased because of (a) maturation arrest of the crypt cells, (b) shortened adult cell survival with concomitant crypt cell hyperplasia, and (c) crypt cell hypoplasia. Studies of crypt cell activity have been based principally on estimations of mitotic rates—a procedure which should theoretically provide direct evidence for the proposed hypothesis. Unfortunately, these studies have thus far led to controversial findings.[13–15]

The second mechanism of jejunal villus alteration, proposed by Reid and Brunser [16] is that there is progressive distention of villi, from base to tip, due to increased numbers of inflammatory cells in the lamina propria. The best evidence in support of this concept is found in the observations of the effect of gluten instillation into the the small bowel of patients with gluten sensitive enteropathy.[17] Histologic changes 6 to 10 hours after gluten administration consist of edema and inflammatory cell infiltration of the lamina propria with blunting and then almost complete loss of the villous pattern. The dissecting microscope appearance of the small bowel mucosa during this process exhibits no leaves, ridges or convolutions.

It is difficult to conceptualize how either crypt cell hypo- or hyperplasia or progressive distention of the lamina propria by inflammatory cells could lead to villus leaves and ridges. In either of these two situations an alteration in the size and shape of the individual villi would be expected. However, their relationship to each other should not change. The end result of an alteration in crypt cell proliferation would be a change in the ratio of crypt to surface epithelium, while that of lamina propria infiltration by inflammatory cells would be a uniform concentric broadening of the villi.

The present study demonstrates that villus synechiae are commonly encountered in jejunal biopsy specimens which show minimal other abnormalities. A perusal of photomicrographs published previously suggests that similar changes have been observed by others.[11,16,18] The frequency with which these changes are found leads us to propose that the formation of synechiae results in the development of leaf-shaped villi, and to ridges and convolutions when a number of adjacent villi are involved. The presence of the central mesenchymal core of a num-

ber of villi within leaves and ridges provides support for this proposal. Inflammatory cells within the surface epithelium as well as in the lamina propria of all specimens showing synechiae, suggests that inflammation may be an important factor in the formation of intervillus adhesions. Fibrin deposition and erosions, mechanisms whereby inflammation usually results in adhesion formation, however, have thus far not been identified. Although degenerative changes of the surface epithelial cells characterized by variable cytoplasmic staining, loss of nuclear polarity, and a variable decrease in the staining reaction of enzymes, have been seen in some specimens,[8] these changes have not been found consistently in tissues exhibiting synechiae.

Our findings, like those of Creamer's,[12] indicate that most abnormal intestinal biopsy specimens do have a decrease in the crypt/surface epithelial cell ratio.[19] It is, therefore, possible that abnormalities in the development and maturation of epithelial cells may be a contributing factor to synechia formation.

Although intervillus adhesions are easily distinguished from goblet cell mucus which frequently bridges adjacent villi in both normal and abnormal tissues (Fig. 5), the possibility that such mucus secretion plays a role in adhesion formation must also be entertained. While the staining characteristics of goblet cell acid and neutral mucopolysaccharides in these specimens are apparently no different from those of the normal controls,[7] alterations in viscosity may be involved.

The formation of ridges, which in most instances are arranged in a parallel fashion, suggests that mechanical factors may also be of importance. Although it is not possible to orientate peroral biopsy specimens according to their positions *in situ,* Creamer's study of the postmortem appearance of the small bowel has shown that the crests of the mucosal folds are more severely involved than the troughs, and that the long axes of the villus ridges on the crests were always directed parallel to the flow of lumen contents.[20] It is reasonable to suggest that inflammatory adhesions would most likely occur between villi on margins which may be in apposition as a result of the flow of intestinal content.

The evidence presented and reviewed suggests that the formation of synechiae between adjacent villi is a mechanism for the development of villus leaves, ridges and convolutions. Adhesions between parallel ridges or distention of the ridges by an inflammatory cell infiltrate could subsequently lead to a flat mucosa. It has also been suggested that a flat mucosa may develop as a result of edema and inflammatory cell infiltration within the lamina propria of the villi. This process may occur without the prior formation of leaves, ridges or convolutions.[17]

## Summary

Jejunal mucosal abnormalities characterized by the formation of leaf-shaped villi, ridges and convolutions, most likely occur as a result of inflammatory adhesions between villi. Complete loss of a villous pattern with a flat mucosa may result from (a) further adhesions between adjacent ridges, or (b) an inflammatory cell infiltration and edema within the lamina propria of the villi.

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## LEGENDS FOR FIGURES

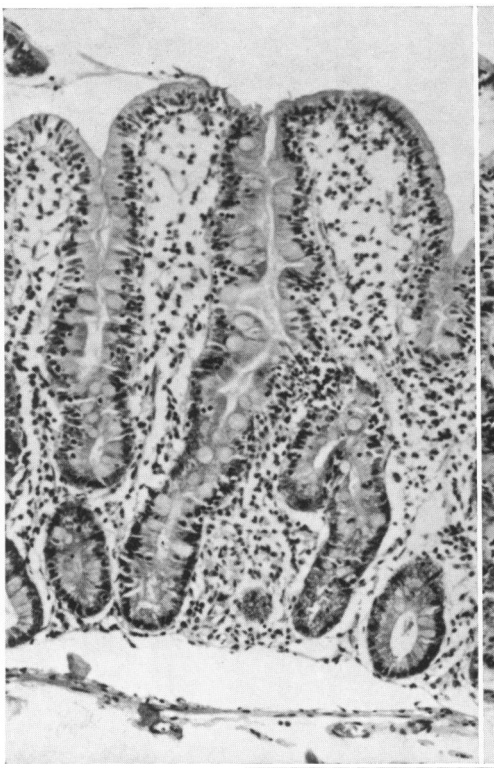
Unless otherwise stated, sections have been stained for reticulin by the Wilder stain.

Figures 1 to 3 are serial sections of a biopsy specimen which showed villus leaves and ridges with the dissecting microscope. Hematoxylin and eosin stain. × 40.

FIG. 1. Slightly broadened finger-shaped villi are present. There is a moderate inflammatory cell infiltrate in the lamina propria and between the surface endothelial cells.

FIG. 2. Fusion of two adjacent villi involves the epithelial cells near their tips.

FIG. 3. Stromal elements of the lamina propria appear in the synechia at the tips of the villi.



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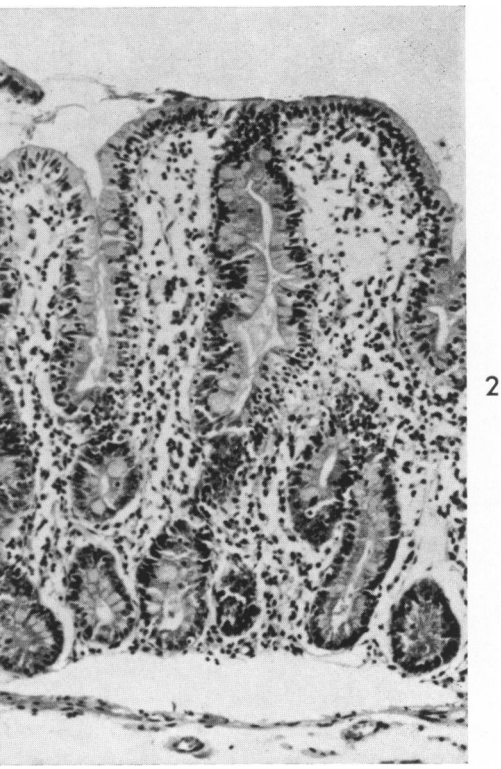

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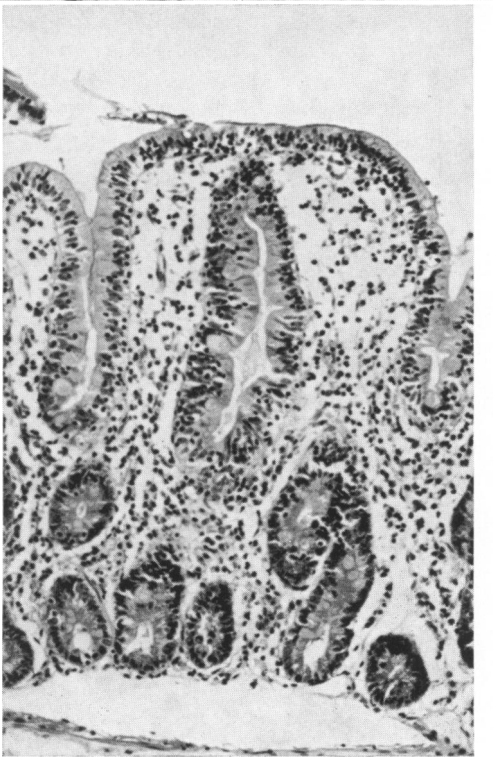

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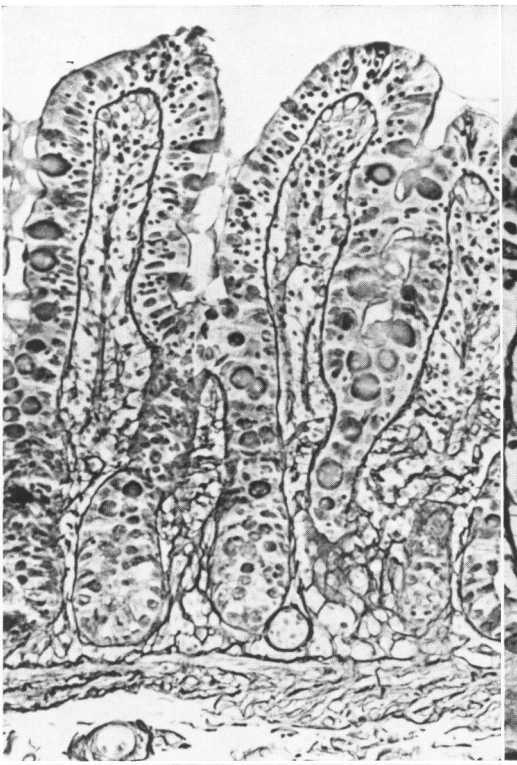
FIG. 4. A jejunal biopsy specimen which showed villus leaves with the dissecting microscope. Villi are slightly shortened and broadened. A moderately extensive inflammatory cell infiltrate appears in the lamina propria and surface epithelium. A number of synechiae between adjacent villi are apparent. × 40.

FIG. 5. A high-power view of the section shown in Figure 5. Each villus contains a single central reticulin core. The inflammatory cell infiltrate in the surface epithelium is composed mainly of lymphocytes, although a few neutrophils and eosinophils are present. Goblet cell mucus secretions form bridges between adjacent surface epithelial cells; a well developed synechia is present between adjacent surface cells. × 100.

FIG. 6. Jejunal specimen which showed villus ridges with the dissecting microscope. The stromal elements in the core of the lamina propria suggest that two adjacent villi have fused. Connective tissue elements bridge the two fused villi. × 100.

FIG. 7. Villus ridges and convolutions were demonstrated with dissecting microscopic examination. The stromal elements in the core of at least 4 villi are evident within the mucosal ridge. There is prominent thickening of the basement membrane beneath the epithelium at the upper lumen surface in both this section and the one depicted in Figure 6. × 100.



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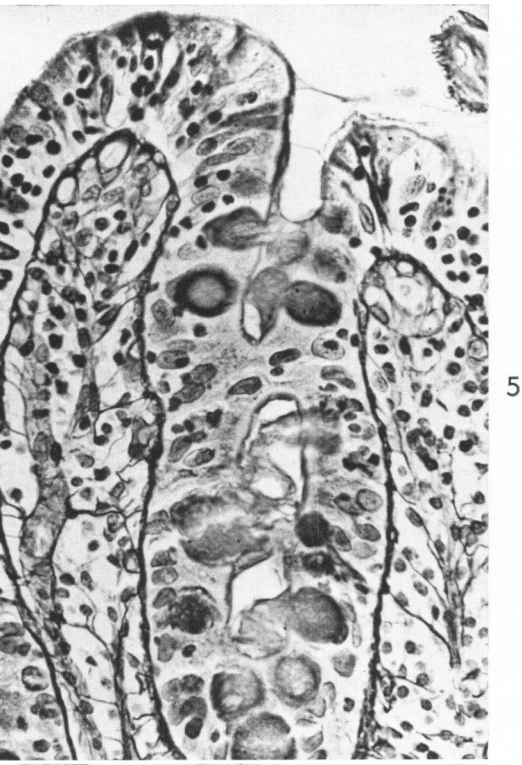

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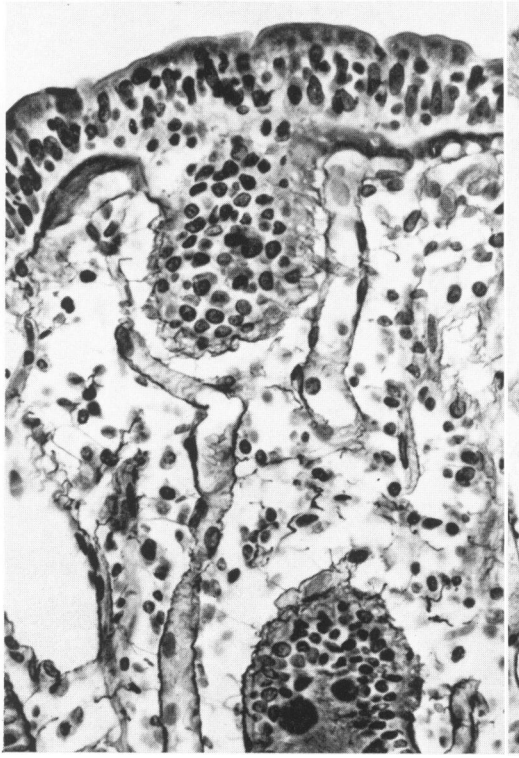

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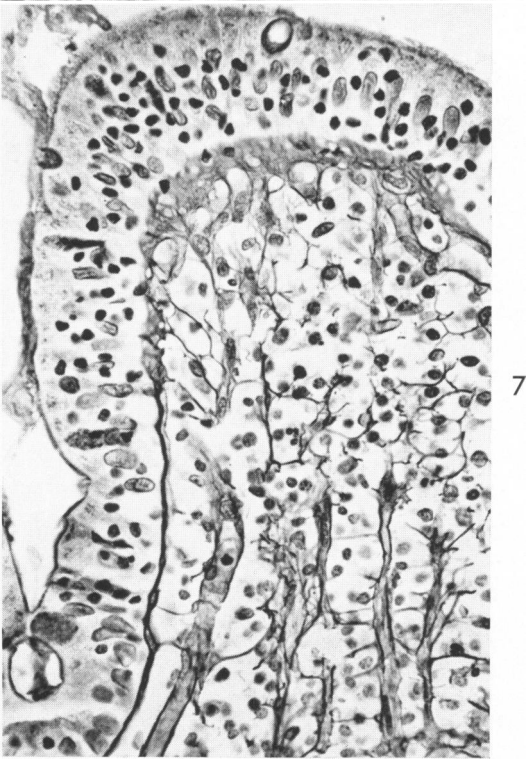

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