

Fine Structure of the Small Bowel in Dermatitis herpetiformis

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Summary. In seven patients with dermatitis herpetiformis, the intestinal structure was studied by means of the electron microscope. In 5 patients the absorptive epithelial cells showed variable modifications consisting of a dilatation of the rough endoplasmic reticulum and an overdevelopment of the smooth endoplasmic reticulum. The striated border microvilli were abnormal and presented edema and fusion with occasional disappearance, leaving clear areas on the intestinal surface. In two patients the ultrastructural study showed no modifications of the epithelial cells.

In all the cases examined the only constant finding consisted of a marked lymphocytic infiltration of the epithelium. The lymphocytes traversed through the basement membrane and were located in the intercellular space. The latter was frequently widened. The widening of the intercellular space was interpreted as secondary to the passage of the leukocytes through the epithelium.

On the basis of this study it was suggested that the lymphocytic infiltration could impair the absorptive ability of the intestinal epithelium, and that the electron microscopic study supports the opinion that some relationship exists between the intestinal changes in dermatitis herpetiformis and those present in non tropical sprue.

Since a few years ago it is known that patients with dermatitis herpetiformis may show variable degrees of villous atrophy of the small bowel (Shuster and Marks, 1965; Marks *et al.*, 1966; Fry *et al.*, 1967; Marks *et al.*, 1968). The association between the skin and intestinal alterations is fairly frequent and appears to be present in 70% of the patients (Van Tongeren *et al.*, 1967).

The macroscopic and histological modifications of the intestinal mucosa are similar to that found in idiopathic steatorrhea and in most of the cases the small bowel atrophy is reversed after a gluten-free diet (Fry *et al.*, 1968). These facts suggest that some similarity exist between the intestinal pathology of dermatitis herpetiformis and that of non tropical sprue.

As to our knowledge no description exists on the fine structure of the intestine in dermatitis herpetiformis, a brief description of our findings seemed therefore warranted.

Materials and Methods

Intestinal biopsies of seven patients with dermatitis herpetiformis were obtained by means of a Crosby capsule from the 4th duodenal segment or from the first portion of the jejunum. Immediately after extraction the tissue was positioned by placing its non villous surface on a piece of filter paper and was divided in two halves. One of them, was fixed in 4% neutral formaldehyde for routine histologic study. The remaining half was diced into small



Fig. 1. Low-power view of jejunal biopsy of case 4. Severe villous atrophy and marked leukocyte infiltration of the mucosa can be observed. $\times 150$

cubes that were fixed for 2 hours in cold 1% Osmium tetroxide in phosphate buffer, and embedded in Araldite. Thin sections were stained with lead citrate, or potassium permanganate, and examined with a Philips 300 electron microscope operated at 60 kv.

For the light microscope study $5\ \mu$ sections were stained with hematoxylin eosin and periodic acid-Schiff. All the patients were studied radiologically by barium meal examination. The clinical findings of the patients are summarized in the table. The fecal fat excretion was determined by the van de Kamer method (van de Kamer *et al.*, 1949) on stools collected on a 3-day period.

Table

Case No.	Age	Sex	Duration of D/H. (years)	Treatment	Faecal fat excretion (g/day)	Jejunal biopsy	Clinical comment
1	52	♀	10	Dapsone	7.37	SVA	Diarrhoea
2	38	♂	8	Dapsone	13.22	PVA	Meteorism
3	74	♂	3	none	5.62	PVA	Diarrhoea
4	43	♀	8	Dapsone	3.60	SVA	—
5	47	♂	0.5	none	1.67	PVA	—
6	78	♂	1	Dapsone	2.78	normal	—
7	57	♀	2	Dapsone	1.81	normal	—

SVA = severe villous atrophy. PVA = partial villous atrophy

Results

Light Microscopy. The histological classification used was the accepted one of normal mucosa, partial villous atrophy and subtotal villous atrophy. In 2 patients the size and aspect of the intestinal villi were normal according to currently accepted morphologic criteria. In the remaining 5 variable degrees of villous atrophy were found (Fig. 1). The result of the histologic study is summarized in

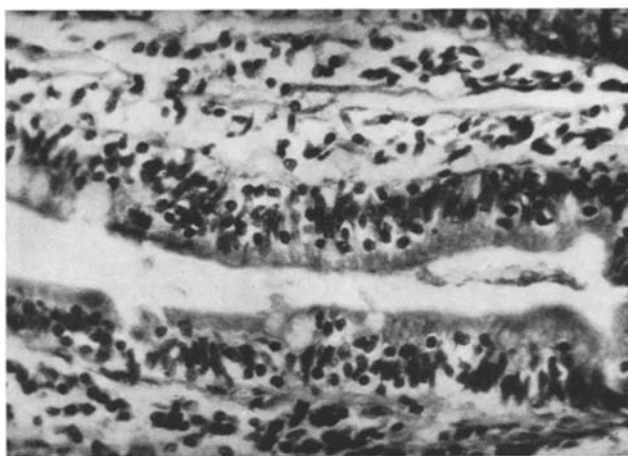


Fig. 2. Light microscope view of two adjacent villi. The marked lymphocytic infiltration of the epithelium can be observed. $\times 450$

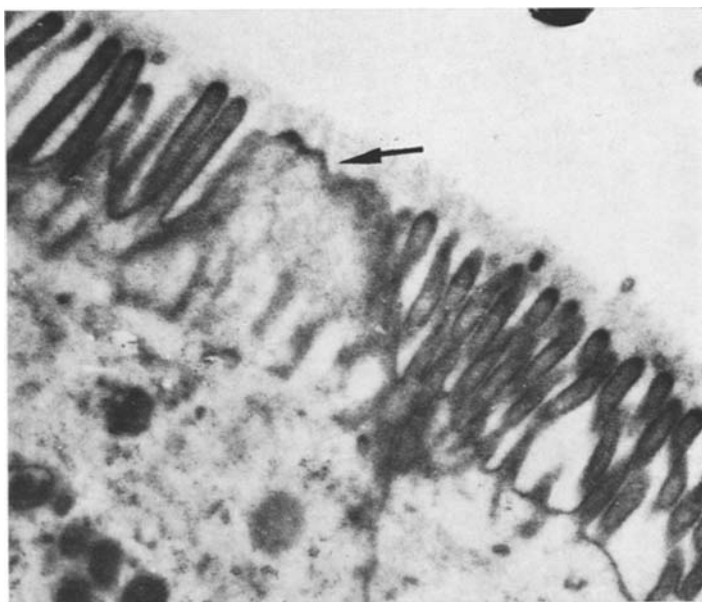


Fig. 3. Fusion and edema of the apical microvilli. The "fuzz" (arrow) is present on the edematous area. $\times 27000$

the table. In all the cases, even in those with normal-appearing villi, a marked lymphocytic infiltration of the epithelium was found (Fig. 2). Another characteristic and constant finding consisted in the appearance of clear areas in the lower part of the epithelium, with a displacement of the epithelial cell nuclei toward the intestinal surface.

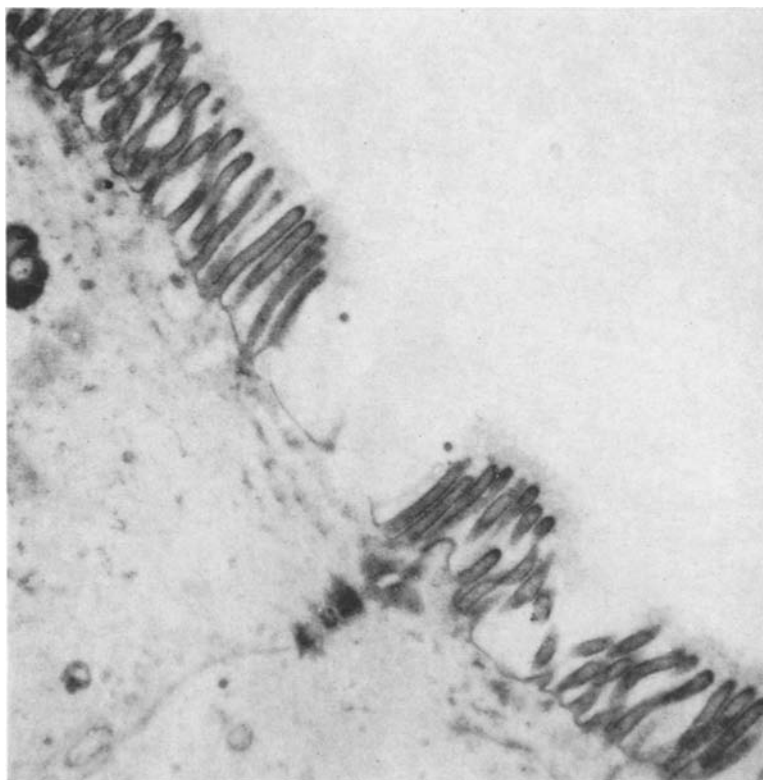


Fig. 4. Partial atrophy of the apical microvilli with appearance of clear areas in the striated border. $\times 18000$

Electron Microscopy. The ultrastructural study was performed in the columnar epithelial cells of the tip of the villi and at the luminal surface (zone 3 of Padykula *et al.*, 1961) except in those cases with a severe subtotal villous atrophy, with a flat intestinal surface.

In the cases with partial and subtotal villous atrophy the absorptive epithelial cells showed variable modifications. The apical microvilli were scarce and short. Fusion and edema of microvilli were frequently observed (Fig. 3). The inner fibrillar or microtubular system was present and ended in a partially disrupted terminal web. At places the microvilli were absent and the striated border showed clear areas dispersed among the microvilli (Fig. 4). In the two cases with normal appearing mucosa the apical microvilli showed no modifications.

The cytoplasmic organelles presented variable alterations. In the deeply altered cells the mitochondria appeared swollen with a matrix of low electron density and few cristae. The smooth-surfaced endoplasmic reticulum appeared composed of dilated sacs located in the upper half of the cell (Fig. 5). Occasionally a marked development of the smooth surfaced endoplasmic reticulum was found, which appeared as closely packed vesicles of small size. The Golgi complex and

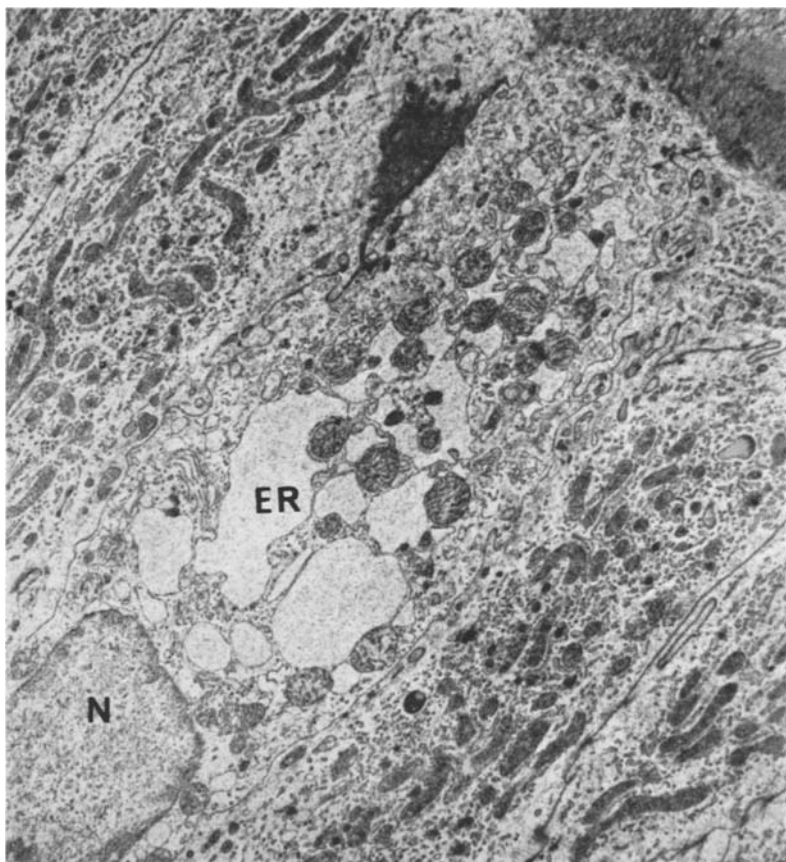


Fig. 5. Hypertrophy and dilatation of the rough-surfaced endoplasmic reticulum (*ER*) of the supranuclear zone. The endoplasmic reticulum appears as dilated sacs which contain a granular material of low electron density. $\times 6000$

the nuclei showed no modifications. In no case lipid droplets were observed within the endoplasmic reticulum or in the intercellular space.

A peculiar and constant finding in all the cases examined consisted of a marked leukocytic infiltration of the epithelium. The cells appeared to be lymphocytes and were especially numerous in the basal half of the epithelium. In some places a continuous layer of lymphocytes was present separating the epithelial cells from the basement membrane. The lymphocytes were located in the intercellular space among the epithelial cells (Fig. 6). Frequently the intercellular space was dilated, appearing as large areas of low electron density with no structures within it. This wide areas resembled in size and shape the space occupied by the lymphocytes and were considered as remnants of their passage through the epithelium (Fig. 7).

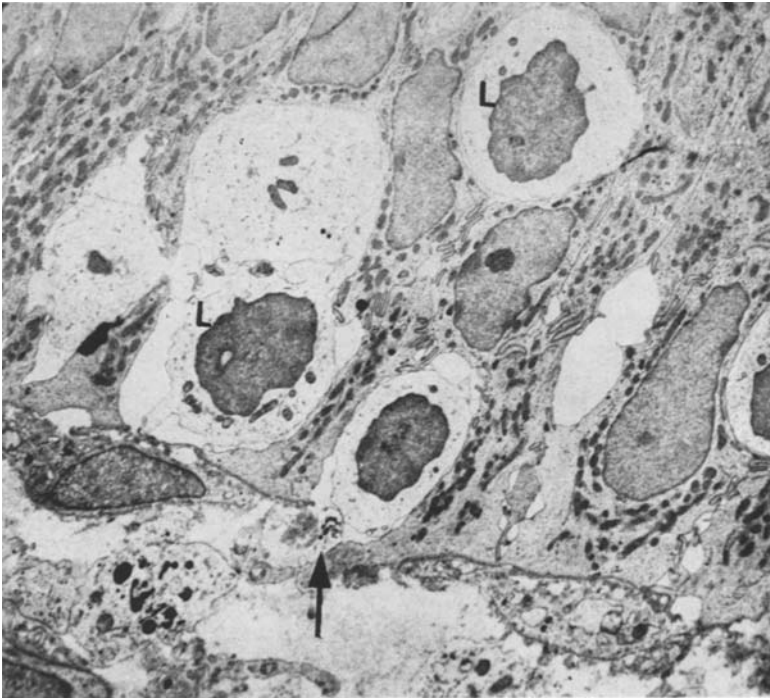


Fig. 6. Lymphocytic infiltration of the intestinal epithelium. The lymphocytes (*L*) are located in the intercellular space. The arrow points to a wide gap of the basement membrane. $\times 2500$

The basement membrane separating the epithelium from the underlying stroma was partially disrupted. This was especially evident at the places with leukocyte infiltration (Fig. 8). Lymphocytes traversing the stroma to the epithelium were frequently to be seen. At times areas of disrupted basement membrane were seen under the epithelial cells. In the places where the basement membrane was absent a fuzzy material of moderate electron density was present. In the cases with subtotal villous atrophy the ultrastructural modifications were more marked than in those with an almost normal histologic appearance.

Discussion

Although less severe, the electron microscope findings in the small bowel of the patients with dermatitis herpetiformis are similar to those reported in adult and children celiac disease (Hartman *et al.*, 1960; Zetterqvist and Hendrix, 1960; Padykula *et al.*, 1961; Shiner and Birbeck, 1961; Ashworth *et al.*, 1961; Rubin *et al.*, 1962; Shearman *et al.*, 1962; Rubin *et al.*, 1966; Biempica *et al.*, 1968).

Apparently a close relationship existed between the light and electron microscope pictures. In those cases with a severe villous atrophy the ultrastructural modifications were especially advanced. On the contrary, in those with an

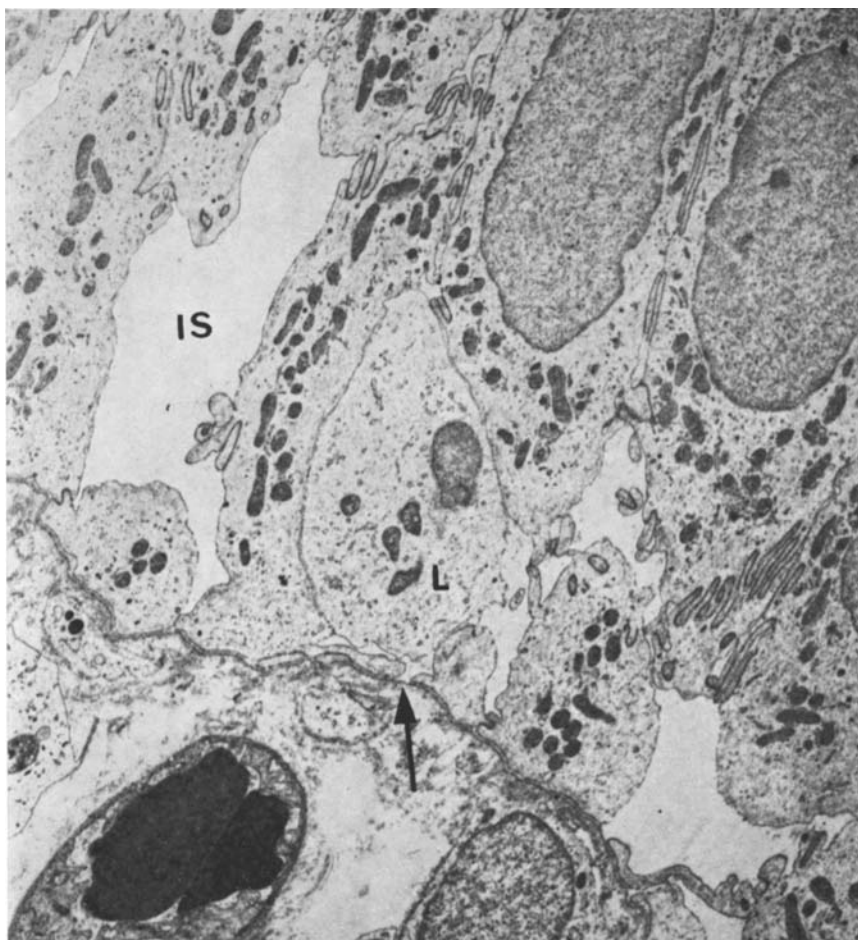


Fig. 7. Marked dilatation of the intercellular space (*IS*) in the lower half of the epithelium. The clear intercellular areas are similar to the space occupied by a lymphocyte (*L*). The arrow points to the well-defined basement membrane. $\times 6000$

almost normal intestinal mucosa the epithelial cells showed minor modifications.

As expected, no close relationship was found between the intestinal structure and the clinical and laboratory data, especially as respects to the daily fat excretion. The only constant finding in all the cases examined consisted of the marked lymphocytic infiltration of the intestinal epithelium. The leukocytes migrating through the epithelium provoked the appearance of a widened intercellular space. The dilatation of the intercellular space can also be observed in the normal intestinal epithelium (Dobbins, 1966). However, it never attains the marked dilatation seen in dermatitis herpetiformis. At the light microscope level cells of probable lymphoid origin are commonly found in the normal intestinal

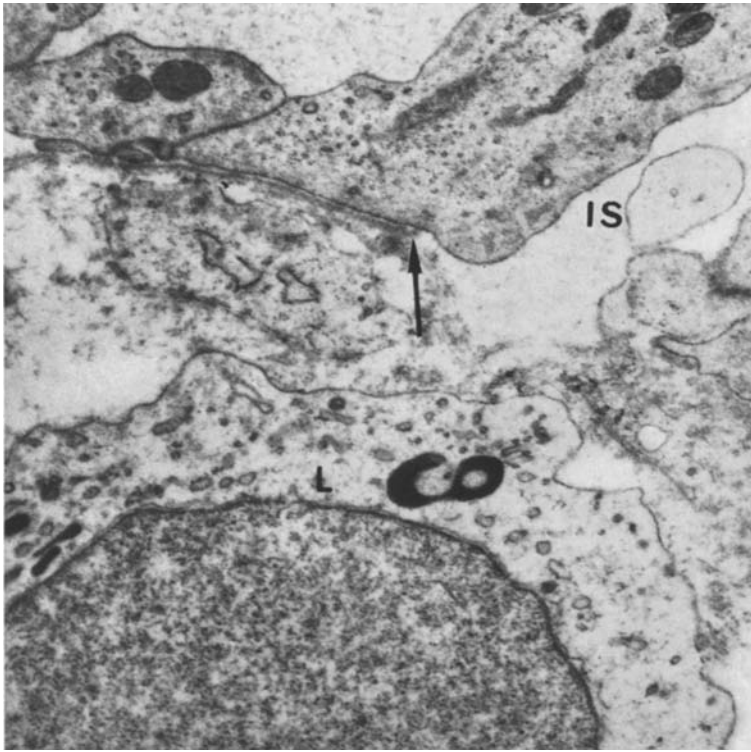


Fig. 8. The arrow points to an interruption of the basement membrane. The intercellular space (*IS*) is continuous with the lamina propria, where a lymphocyte (*L*) may be seen. $\times 18000$

epithelium (Toner, 1968). In a recent report Shields *et al.* (1969) found 75 ± 6 small lymphocytes per each one thousand mucosal cells. The considerable increase in the number of intraepithelial lymphocytes in all the cases examined can be considered as a pathological finding.

Although no definitive proof exists it appears to us that the lymphocyte infiltration of the epithelium could impair its absorptive ability. This is especially evident in those cases with a continuous lymphocyte layer between the epithelial cells and the basement membrane. The pathogenesis and significance of the intestinal changes associated with dermatitis herpetiformis are not clear. The different possibilities existent for the relationship between the skin and gut abnormalities have been pointed out by Marks *et al.* (1968). The fact that a gluten-free diet improves the clinical state and the structure and function of the small intestine in some patients with dermatitis herpetiformis suggests that a close similarity exists between the intestinal abnormalities in this disease and those present in non tropical sprue.

The electron microscopy study also supports this view showing a marked similarity in the ultrastructural modifications of both diseases.

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