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Ultrastructural Study of M Cells from Colonic Lymphoid Nodules Obtained by Colonoscopic Biopsy

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The present study was undertaken to investigate ultrastructurally the epithelium covering lymphoid nodules obtained from colonoscopic biopsies of the human colon and rectum. Colonoscopy using the dye spraying contrast method was performed in nine patients who showed x-ray evidence of lymphonodular hyperplasia. Fifty-two colonoscopical biopsy specimens of lymphoid nodules were obtained from the ascending, transverse, and descending colon and rectosigmoid region. All specimens were observed by light and electron microscopy. Light microscopy disclosed large lymphoid follicles protruding into the lumen with a "dome-type" configuration. These extended to the lamina propria of the mucosa and were associated with a massive lymphoid aggregation extending as far as the muscularis mucosa from the submucosa. The epithelium covering these nodules contained a few goblet cells and many lymphocytes. Observation of the elevated surface at the apex by scanning electron microscopy revealed M cells with sparse microvilli in the dome epithelium surrounded by crypts. Transmission electron microscopy disclosed M cells enfolding many immature or mature lymphocytes and plasmocytes. The M cells had cytoplasmic microvilli (so-called "microfolds") on their surfaces, well-developed tubulovesicular systems, and vacuoles in the cytoplasm. The basic structure of the M cells as observed by scanning and transmission electron microscopy was the same as that of M cells in the Peyer's patches of humans and mice. The apical surface of the colonic lymphoid follicles in Crohn's disease patients was associated with erosions observed by scanning electron microscopy. The erosions proved to be the naked surface of the dome after removal of the epithelium, and many holes from 2.0 to 6.0 μm in diameter were observed on the naked surface. At high magnification, lymphocytes were seen projecting from holes (18%) on the naked surface of the dome. These ultrastructural findings indicate that human colonic lymphoid follicles are very similar to those seen in other species.

KEY WORDS: M cells; lymphoid follicles; large intestine; human.

Lymphoid follicles increase in number from the duodenum to the terminal ileum in the mammalian intestine and aggregate as Peyer's patches. Microfold (1) or membranous (2) epithelial (M) cells are found in the epithelium covering gut-associated lymphoid tissue such as Peyer's patches and solitary lymphoid follicles in the small intestine. These M cells are specialized epithelial cells that transport antigens, including viruses (3, 4) and bacteria (5–13) from the gut lumen to the extracellular space, allowing them to encounter many types of cells,

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TABLE 1. CLINICAL DIAGNOSIS AND SITE AND NUMBER OF FOLLICLES OBTAINED BY COLONOSCOPIC BIOPSY

				*Site and number of dome-type follicles and flat-type ( ) follicles**					
Cases	*Age*	*Sex*	*Clinical diagnosis*	*A*	*T*	*D*	*S*	*R*	*Total*
1	42	F	Radiation proctitis	2 (1)	2 (1)				4 (2)
2	35	M	Lower GI tract bleeding	1	2	3 (1)		1	7 (1)
3	58	F	Lower GI tract bleeding					6 (2)	6 (2)
		M	Submucosal tumor of					3 (1)	3 (1)
4	51		the rectum						
5	18	F	Crohn's disease	3			2 (1)		5 (1)
6	39	F	Lower GI tract bleeding					4	4
7	60	F	Ascending colon cancer	2 (1)	(1)				2 (2)
8	25	M	Crohn's disease	2	2 (1)		3		7 (1)
9	20	F	Lower GI tract bleeding					4	4
			Total	10 (2)	6 (3)	3 (1)	5 (1)	18 (3)	42 (10)

*A: ascending colon; T: transverse colon; D: descending colon; S: sigmoid colon; R: rectum.

e.g., lymphocytes, macrophages, and plasma cells. However, there are only a few reports (14, 15) describing the ultrastructure of M cells in the human large intestine, with the exception of the appendix (16, 17).

In 1973, Hoshi and Mori (18) reported the existence of cecal patches in chickens; these organs are sometimes called the cecal tonsils. Owen and Nemanic (16) found M cells on the surface of cecal patches in mice and rats and showed that these patches had a lobulated pitted surface similar to that of Peyer's patches. Similar structures called lymphoglandular complexes have been described in other animals such as the dog and the echidna (19). In the dog, these organs are restricted to the cecum and adjacent colon and do not aggregate in one patch.

Recently, ultrastructural studies of lymphoid tissue in the large intestine have been performed in rodents. In 1986, Bland and Britton (20) reported the presence of M cells in the epithelium covering colonic lymphoid patches of rats and their uptake of ferritin–India ink and bacteria. In 1990, Owen et al (21) demonstrated the uptake of reovirus type 1 in M cells on the follicular epithelium of lymphoid nodules in the rectum and colon of mice. Lymphoid-glandular complexes in the human colon have been described by Kealy (22), but their functional significance is largely unknown despite the importance of the large bowel in inflammatory and neoplastic diseases. The present study was undertaken to investigate ultrastructurally the epithelium covering areas of lymphoid nodules obtained by colonoscopic biopsy in the human colon and rectum.

MATERIALS AND METHODS

Patients. Biopsies of colonic lymphoid tissues were taken during colonoscopic examination. Colonoscopy was performed on nine patients (three men and six women) who showed x-ray evidence of lymphonodular hyperplasia. The clinical diagnoses were radiation proctitis (one patient), submucosal rectal tumor (one patient), cancer of the ascending colon (one patient), Crohn's disease (two patients), and lower gastrointestinal tract bleeding (four patients) (Table 1). All patients gave informed consent.

Colonoscopic Biopsies. After the usual premedication, the colonoscopic examination was performed by means of a fiberoptic colonoscope (Olympus CF type-PCF10) and a video colonoscope (Olympus CF type-V10I). After 0.2% indigo carmine solution was directly sprayed on the mucosal surface of the colon through a Teflon tube inserted through the colonoscope, colonoscopical biopsies were performed under direct vision in all patients (23). A total of 52 colonoscopic biopsy specimens of lymphoid nodules were obtained from the ascending, transverse, and descending colon and the rectosigmoid region (Table 1). The biopsy was done using standard type forceps (Olympus), and the size of the specimens obtained was 3 mm. All biopsy specimens were divided into two groups for light and electron microscopy after rinsing with physiological saline solution.

Processing for Light and Electron Microscopy. All biopsy specimens were fixed in 2.5% glutaraldehyde at 4° C for 2 hr. Light and electron microscopic observations were preceded by examination using a dissecting microscope. Transmission electron microscopic samples were fixed for 2 hr in 1% osmium tetroxide, dehydrated through an ethanol series, transferred to propylene oxide, and embedded in epoxy resin. Ultrathin sections were cut using glass knives and a Porter-Blum MT2-B ultramicrotome. These sections were stained with uranyl acetate and lead citrate and viewed using a Hitachi H-500 electron microscope. Materials for scanning electron microscopic observation were fixed in 1% osmium tetroxide and dehydrated

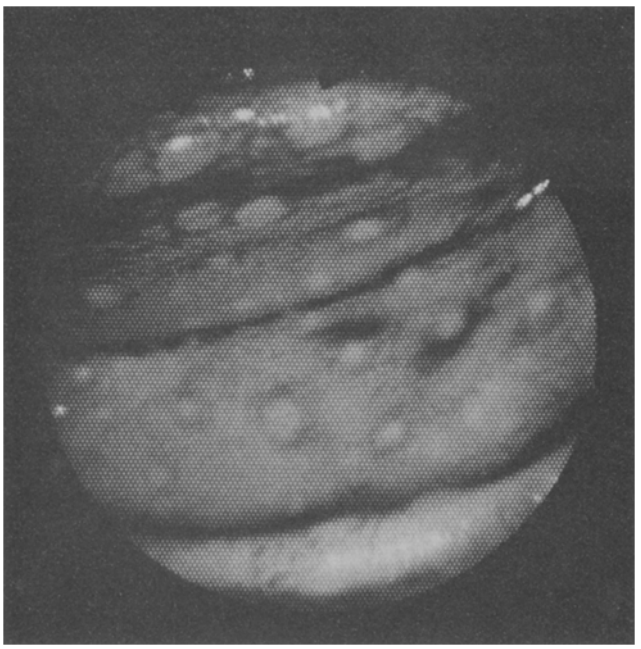

Fig 1. A colonoscopic photograph showing scattered white elevated nodules revealed by the dye spraying contrast method.

through an ethanol series. After being transferred to isoamyl acetate, they underwent critical-point drying and evaporation-coating with gold–palladium and were observed using a Hitachi S-570 electron microscope.

RESULTS

Colonoscopy and Histological Examination. Colonoscopy showed the colonic mucosa to be studded with multiple small 1- to 4-mm elevated white nodules (Figure 1). These were located diffusely throughout the colon in five cases and only in the rectosigmoid region in four cases. After observation of serial sections of specimens obtained by biopsy, we found that large lymphoid follicles of more than 2 mm in size protruded into the gut lumen and showed a dome-type configuration (Figure 2). These extended as far as the lamina propria of the mucosa and were associated with massive lymphoid aggregations spreading beyond the muscularis mucosa from the submucosa (Figure 2). The epithelium covering these follicles, which was associated with a few goblet cells and many migrating lymphocytes, was specialized, differing from the surrounding mucosa distinctly (Figure 3). Dome-type follicles were found in all portions of the colon and rectum. However, the surfaces of these small lymphoid follicles located in the submucosa and lamina propria of the mucosa were not elevated (non-dome type or flat type), and the epithelium covering them was similar to that of the surrounding mucosa, which had more goblet cells and was associated with a few migrating lymphocytes. The proportion of dome-type follicles to flat-type was 42:10 (Table 1).

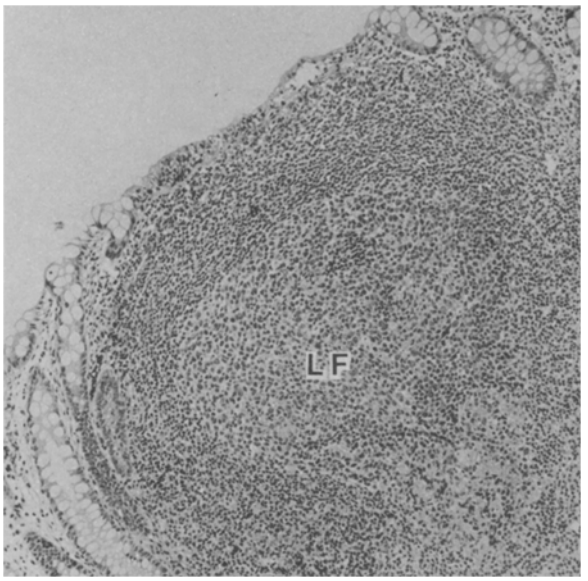

Fig 2. A light photomicrograph of a lymphoid follicle (LF) from the rectum (H&E, ×100).

Electron Microscopy of Epithelium Covering Lymphoid Nodules. Scanning electron microscopy

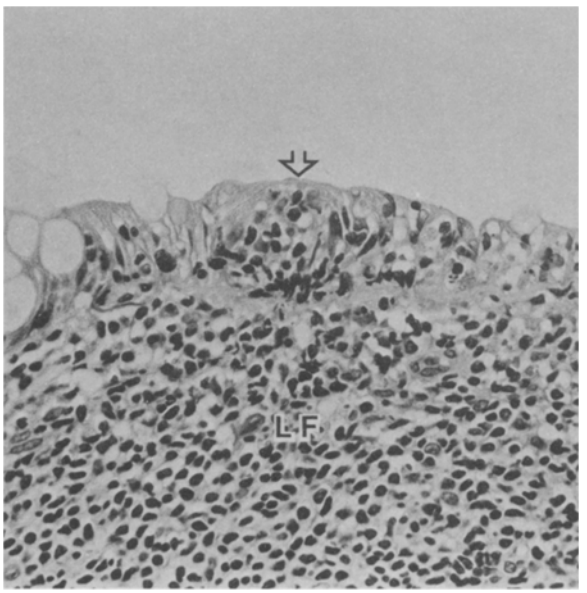

Fig 3. Enlargement of Figure 2 showing the epithelium covering the lymphoid follicle (LF). An epithelial cell associated with many lymphocytes can be recognized (open arrow) (H&E, ×400).

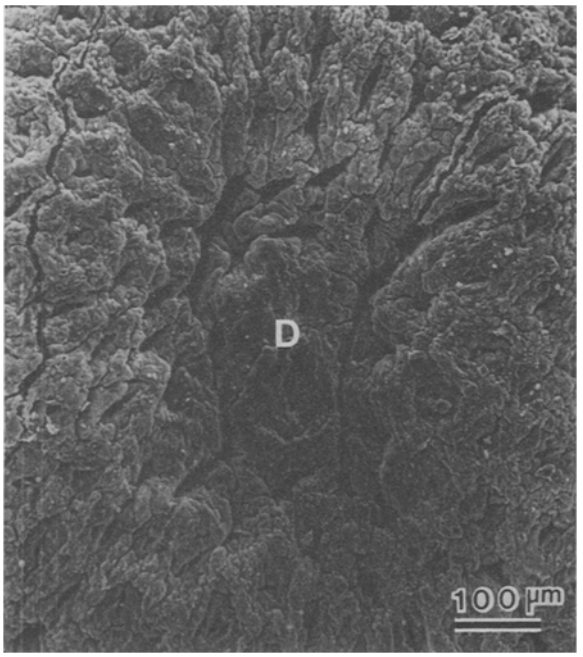

Fig 4. A scanning electron micrograph of a lymphoid nodule of the rectum is shown. The surface at the apex of the lymphoid nodule is surrounded by many crypts and an elevated dome configuration (D).

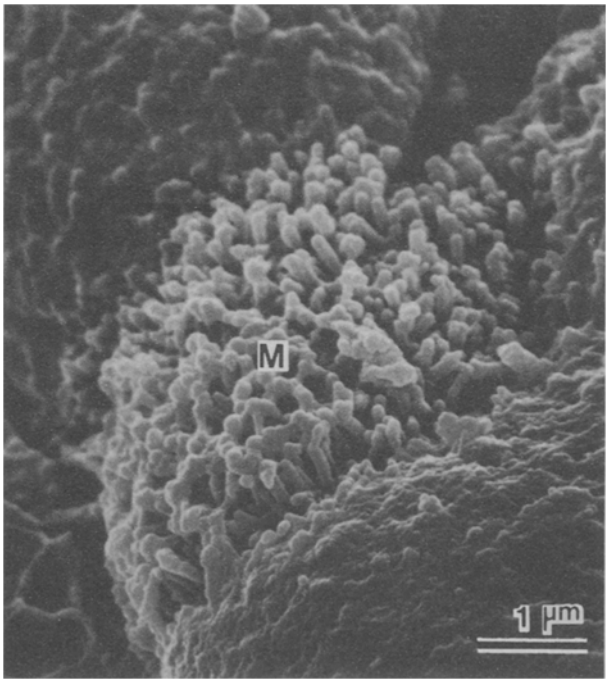

Fig 5. A scanning electron micrograph of an M cell in the dome epithelium of Figure 4. The M cell has sparse microvilli associated with few glycocalyx. M cell, M.

showed the regions of colonic lymphoid nodules to be generally elevated. More careful observation of the elevated surface at the apex of a lymphoid follicle revealed a dome-like configuration surrounded by many crypts (Figure 4). High magnification of the dome by scanning electron microscopy disclosed the existence of M cells with few glycocalyx, and columnar cells adjacent to them so thick as to prevent delineation of the underlying microvilli (Figure 5).

Transmission electron microscopy showed M cells enfolding many immature or mature lymphocytes and plasmocytes (Figure 6). Lymphocytes were observed crossing through discontinuities of the basal lamina in the vicinity of M cells in lymphoid follicles of the transverse colon (Figure 6). Cytoplasmic microvilli (so-called microfolds) were seen on the surfaces of the M cells, and well-developed tubulovesicular systems and vacuoles were found in the cytoplasm (Figure 7). M cells and adjacent columnar cells made contact with each other through desmosomes and junctional complexes in the same manner as adjacent columnar cells normally do (Figure 7). Lymphoid cells enfolded within the M cell sent out complex cytoplasmic projections, and the projections of the M cell extended into the lymphoid cells (Figure 7).

The basic structure of the epithelial cells as observed by scanning and transmission electron microscopy was the same as that of M cells in Peyer's patches in humans and mice. M cells were identified in all nine patients, but they could be found only on the epithelium covering dome-type lymphoid follicles. Although a few lymphocytes were observed in the epithelium of flat type follicles, no M cells were found in them.

In humans, the authors have confirmed ultrastructurally that M cells are present in the large intestine.

Scanning Electron Microscopy of Erosions of Colonic Lymphoid Nodules in Patients with Crohn's Disease. The apical surface of the colonic lymphoid nodules had occasional erosions in Crohn's disease. A scanning electron micrograph of the surface of a dome-type lymphoid follicle of the ascending colon associated with erosions is shown in Figure 8A. The erosion revealed the naked surface of the dome beneath the epithelium. Many holes of 2.0–6.0 μm in diameter were observed on the naked surface of the dome (Figure 8B). At high magnification, parts of lymphocytes were seen in

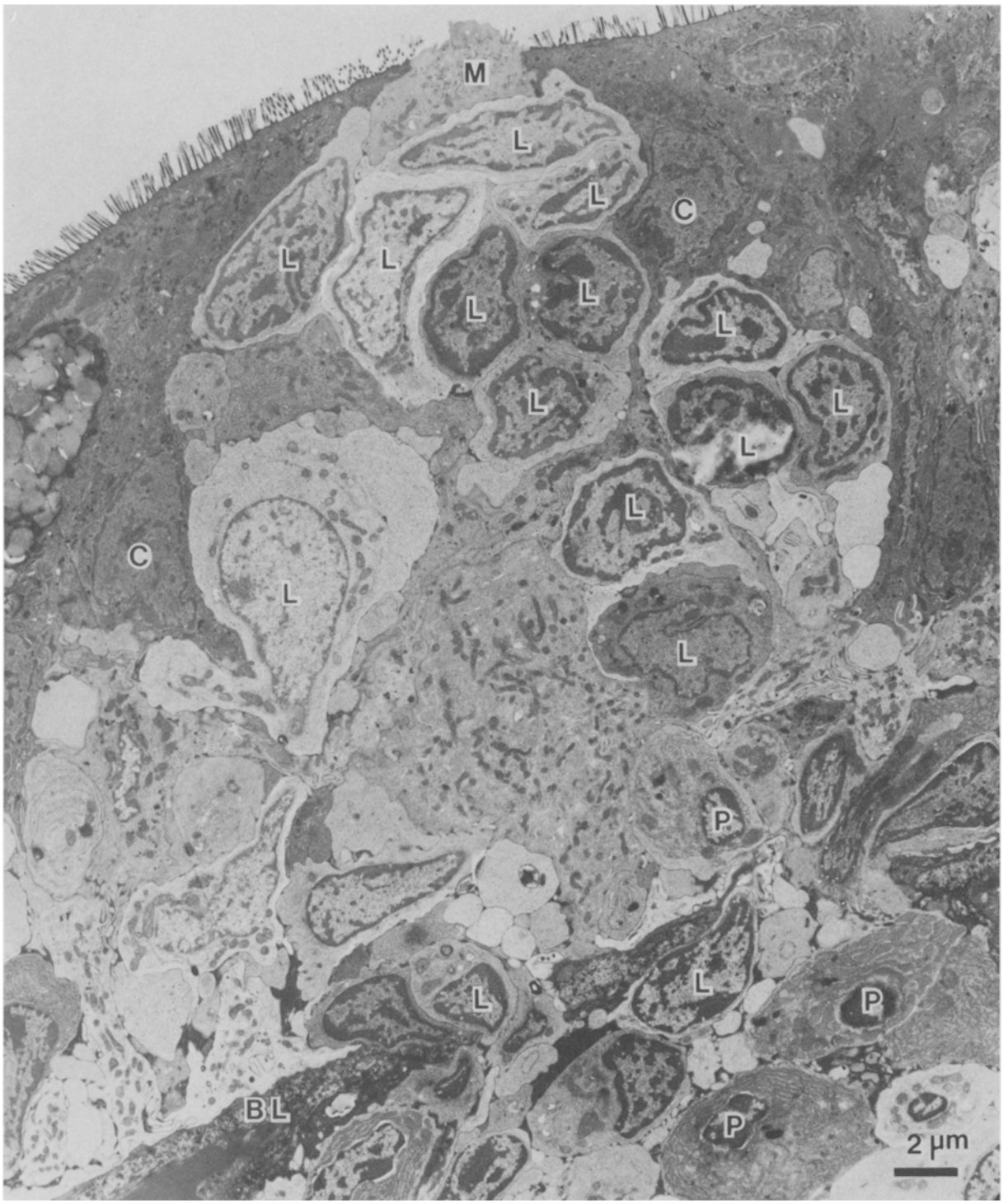

Fig 6. A transmission electron micrograph shows an M cell that has enfolded many immature and mature lymphocytes (L) and plasmocytes (P) in a lymphoid follicle of the transverse colon. Lymphocytes (L) are observed crossing through a discontinuous part of the basal lamina (BL) at this site. Columnar cells, C; M cell, M.

28/152 holes (18%) on the naked surface of the dome (Figure 8C), and the tentaclelike cytoplasmic projections of some lymphocytes were also seen in holes (Figure 8D). These ultrastructural

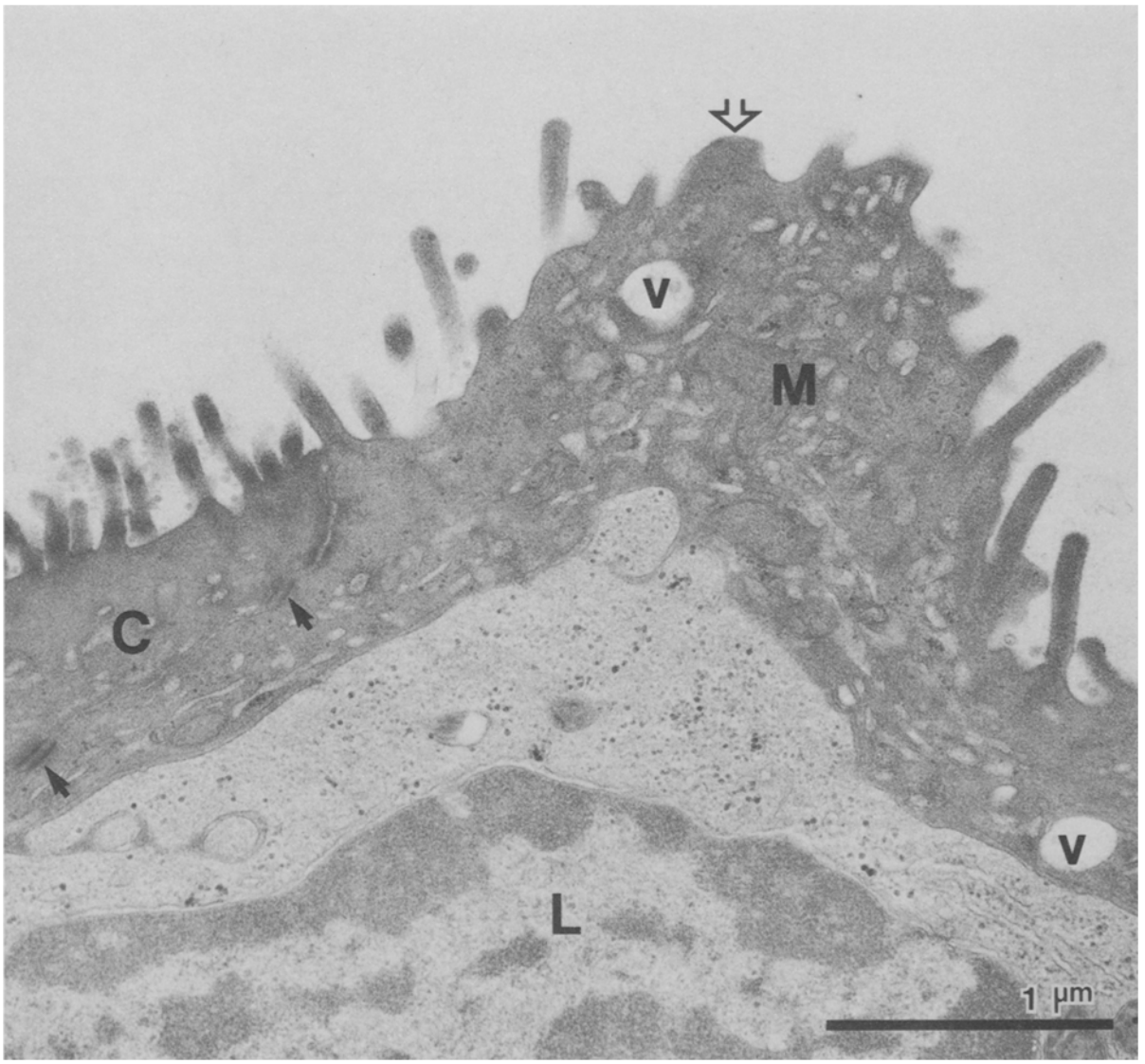

Fig 7. A transmission electron micrograph of the epithelium covering a lymphoid follicle, showing a parallel section of the apex of the same M cell seen in Figure 6. Note the cytoplasmic microvilli (open arrow) and vacuoles (V) in the cytoplasm of the M cell and the desmosome (solid arrow) formed with adjacent columnar cells (C).

findings suggest that such porosity may facilitate bidirectional passage of lymphocytes.

DISCUSSION

Colonic lymphoid nodules are occasionally recognized in patients with inflammatory bowel disease (24), sarcoidosis (25), lower gastrointestinal tract bleeding (26), familial polyposis (27), dys- and hypogammaglobulinemia (28, 29), and colonic carcinoma (30). However, these have been considered to be a normal variant because of the absence of other histological abnormalities (31). Some workers have described a peculiar radiological appearance, so-called lymphonodular hyperplasia of the colon (32, 33). Laufer and deSa (34) suggested that in the pediatric colon, however, the term lymphoid hyperplasia should be reserved for nodules of more than 2 mm in diameter, whereas the term lymphoid follicular pattern is more appropriate for normal-sized nodules of 2 mm or less that are evident radiographically. Lymphoid nodular hyperplasia has also been noted more frequently in children (32) than in adults (33), but its clinical significance and nature have been questioned. Peyer's patches in humans are known to increase in size and number

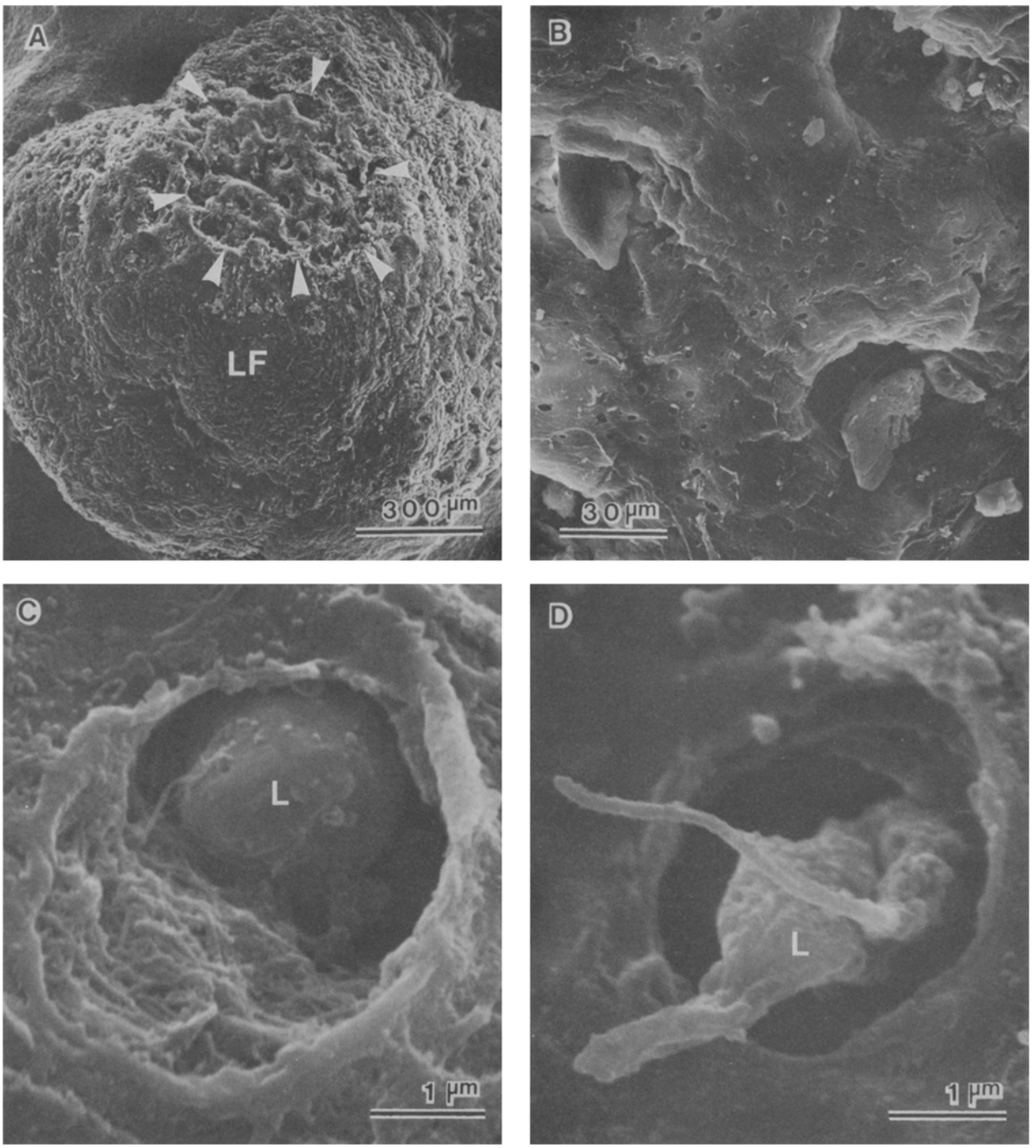

Fig 8. A scanning electron micrograph (A) of a lymphoid nodule with an erosion (arrows) in the ascending colon of a patient with Crohn's disease (case 5). The erosion reveals the naked basal lamina of the dome after removal of the epithelium, and many holes of 2.0–6.0 μm in diameter can be observed in the surface (B). At high magnification, a part of a lymphocyte (L) can be seen in one of the holes on the naked surface of the dome (C). The tentaclelike cytoplasmic projections of a lymphocyte (L) can also be seen in one of these holes (D).

during at least the first 10 years after birth (35). In the adult colon, Dukes and Bussey (36) found that the occurrence of lymphoid follicles was 3–3.5/cm^2 on the average with a range of 1–7/cm^2. They also found that they increased in number from the cecum down towards the rectum. However, Kenney et al

(33) and Kelvin et al (37) reported that follicles were seen most often in the hepatic flexure and that a rectosigmoid location was infrequent on air-contrast barium-enema examination. In 1986, Langman and Rowland (38) reported that the average density of follicles was 18.4/cm^2 in the cecum, 15.0/cm^2 in the colon and 24.5/cm^2 in the adult rectum.

The rectal mucosa has been probably the major portal of entry for the human immunodeficiency virus (HIV) among homosexual men (39, 40), and the virus can infect several types of cells found in the mucosa. Traumatic disruption of the epithelial barrier has been postulated as facilitating removal of microorganisms into rectal tissue, but no uptake of viruses has actually been documented. In 1990, Owen et al (21) demonstrated that M cells in the follicle epithelium of lymphoid nodules in the rectum and colon of mice take up and transport reovirus type 1, which is replicated within M cells and then spreads to remote sites.

O'Leary and Sweeney (14) investigated the lymphoglandular complexes (LGC) of the human colon and described two morphological types of LGC, a classical pattern, so-called non-dome type, and a dome type. They briefly reported on epithelial cells with similar ultrastructural characteristics, which they also designated as M cells. We also demonstrated that M cells existed in the covering epithelium of colonic lymphoid nodules obtained by colonoscopic biopsy and in rectum as well as in Peyer's patches. The ultrastructural characteristics of human M cells include sparse microvilli or microfolds, poorly developed terminal webs, and the enfolding of many lymphocytes by the cytoplasm. In contrast, in the rat colon, M cells have no microfolds on the surface (20). The structure of the M cells that we observed in the human large intestine was similar to that of M cells that have been demonstrated to transport particles across the epithelium in the Peyer's patches of other species (2–13) and have been suggested to have an antigen sampling function.

There are at least two hypotheses for the derivation of M cells. The first suggests that they derive from mature enterocytes overlying the Peyer's patches (41, 42), while the second hypothesis suggests that they derive directly from undifferentiated crypt cells (43–45). It is not known whether the development of M cells is independent of or under the influence of the immune system. Jacob et al (15) reported that when the lymphocyte is near the center of the enterocyte there is usually little change in enterocyte morphology, but when the lymphocyte is near the apical surface of the enterocyte, the latter closely resembles the microfolds of typical M cells. This finding may support the hypothesis that M cells derive from mature enterocytes.

In rats and mice, colonic lymphoid patches, certain markers (20), colonic bacteria, and viruses (21) are preferentially transported through this follicle-associated epithelium, indicating its role in antigen uptake. Our data and these findings support the possibility that the early "aphthoid" ulcers detected in the colon of Crohn's disease are typically located over preexisting lymphoid cell aggregates (46) and perhaps represent ports of entry for potentially pathogenic agents.

Mammalian lymphoid organs are divided into primary and secondary categories. In 1989, Crouse et al (47) demonstrated that germinal centers were not prominent in the proximal colonic lymphoid tissue of the rat and that this tissue was extremely sensitive to the action of steroids in a manner very similar to lymphocytes of the thymus and to the bursa of Fabricius in birds. Furthermore, they showed that these lymphoid nodules developed in grafts of fetal colon transplanted to an ectopic site under the kidney capsule, where the exogenous antigens normally present in the gastrointestinal lumen are presumably absent. Both of these observations support the hypothesis that these proximal colonic lymphoid nodules are largely populated by immature lymphocytes and resemble primary lymphoid tissue. However, in 1990, Owen et al (48) reported that the cytochemical components of colonic lymphoid follicles and Peyer's patch follicles in mice were remarkably similar. In our study, we found that humans also had dome-type lymphoid follicles associated with germinal centers, and those were very similar to Peyer's patches. This seems to be secondary lymphoid tissue that expands as a consequence of antigen stimulation, much as is the case with Peyer's patches.

The porosity of the basement membrane in Peyer's patches was reported by Shimazui (49) and McClugage et al (50). After removal of the epithelium covering dome-type colonic lymphoid follicles, scattered holes were seen in the basal lamina of the dome, and parts of lymphocytes were seen in these holes. These structures were thought to represent the pathway of lymphocyte migration through the basal lamina of the colonic epithelium and may be a morphological adaptation of the lymphoid follicles. Intraepithelial lymphocytes also have been shown

to have the potential to modulate the expression of I region associated antigens (Ia) on the surface of murine intestinal epithelial cells (51). In the human small intestine and large intestine, the lamina propria shows positive human leukocyte antigen DR (HLA-DR) reactivity in capillary walls, macrophages, and some lymphocytes, while epithelial cells are consistently positive only in the small intestine and are negative or weakly positive in the colon and rectum (52, 53). However, under inflammatory conditions, the colonic epithelium clearly expresses HLA-DR antigens (54). These observations suggest that important mechanisms of immune regulation act on mucosal surfaces.

In humans, the proximal colon is the primary site of development of carcinomas in the familial cancer syndrome designated as Lynch variant I (55). Bland and Britton (56) reported that 80% of dimethylhydrazine dihydrochloride-induced colon tumors in Sprague-Dawley rats arose from the epithelium overlying lymphoid follicles. Nauss et al (57) found a highly significant association between sessile adenocarcinomas and lymphoid aggregates. Oohara et al (58) found that 55% of microscopic adenomas originated in the basal cells adjacent to the lymphoid follicles on the muscularis mucosa. The relation between these findings and M cells is unclear, indicating the need for further studies of colonic lymphoid tissue.

Further investigations are also required to find a more direct approach for functional evaluation of lymphoid follicles of the large intestine and characterization of the immune cells comprising these follicles.

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