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Hamster (*Mesocricetus auratus*) Enteritis Caused by Epithelial Cell-Invasive *Escherichia coli*

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When inoculated orally, *Escherichia coli* strain 1056 caused acute enteritis in 7 of 22 weanling hamsters. *E. coli* strain 1056 was isolated from the ileum of a hamster with proliferative ileitis. It was lactose negative, nonmotile, and anaerogenic. By electron microscopy and indirect fluorescent-antibody techniques, *E. coli* strain 1056 was detected in absorptive epithelial cells, resembling invasive *E. coli* and shigella infections of other species. Ileitis did not progress to epithelial cell hyperplasia, which is characteristic of proliferative ileitis of hamsters. A control group of 10 hamsters, inoculated with nonenteropathogenic *E. coli* isolated from a normal hamster, did not develop signs or lesions.

Escherichia coli has been implicated in the pathogenesis of acute enteritis and proliferative ileitis in hamsters (1, 2, 8–10, 23, 27, 28). *E. coli* isolated from hamsters with proliferative ileitis has been shown to produce diarrhea and enteritis by oral inoculation (2). *E. coli* has also been observed within the cytoplasm of absorptive ileal epithelium by electron microscopy and indirect fluorescent-antibody techniques shortly after oral inoculation of ground proliferative ileum (8). The proliferative ileal lesions, however, are associated with a small, curved bacteria which is different from *E. coli* (8, 14).

This study was undertaken to determine the pathogenesis of the lesions produced by oral inoculation of pure cultures of *E. coli*. *E. coli* utilized in this study was isolated from a hamster with proliferative ileitis. The enteropathogenicity of this organism has been demonstrated previously by use of an ileal loop technique (10).

MATERIALS AND METHODS

Inoculation procedures. *E. coli* strain 1056, serotype O:105 (P. J. Glantz, Pennsylvania State University, University Park), was isolated from a ground ileal suspension from a hamster with proliferative ileitis. An untyped *E. coli* strain 1940 was isolated from the ileum of a normal hamster.

Pure cultures of *E. coli* were grown for 18 to 24 h in 25 ml of Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.). The cultures were centrifuged (1,700 × *g* for 30 min), and the broth was decanted. Remaining bacteria were suspended in 10 ml of sterile phosphate-buffered saline (PBS) at pH 7.3, and 1.0 ml was given by gavage to hamsters. Bacterial suspensions were enumerated by plate counts of serial dilutions.

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Hamsters (*Mesocricetus auratus*) were housed in groups of 3 to 5 in polycarbonate cages with pine shavings. They were given food (Lab Blox, Wayne, Allied Mills, Chicago, Ill.) and water ad libitum. A total of 22 hamsters received *E. coli* strain 1056, and 10 hamsters received *E. coli* strain 1940. Animals were of both sexes and 3 to 4 weeks old when inoculated.

Hamsters were killed by chloroform inhalation when they became moribund or 25 days after inoculation. Each animal was necropsied, and ileal contents were cultured for aerobic bacteria. Tissue samples were collected for examination by light and electron microscopy. Portions of ilea were immediately frozen for indirect fluorescent-antibody studies.

Light and electron microscope procedures. Representative tissue samples were fixed in buffered neutral 10% Formalin. They included ileum, jejunum, duodenum, stomach, cecum, colon, mesenteric lymph node, spleen, pancreas, liver, kidney, and lung. They were embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin.

A small sample of ileum was collected and diced into 1-mm-square blocks. Tissue was fixed at 4°C in 3% glutaraldehyde in 0.1 M Sorensen phosphate buffer. After fixation, the tissue was washed again in buffer, dehydrated with a series of acetone dilutions, and embedded in Spurr resin.

Thick (2 μm) and ultrathin sections were cut with glass knives on an ultramicrotome (LKB Instruments Inc., Rockville, Md.). Thick sections were stained with alkaline toluidine blue (3). Ultrathin sections were stained with 1% uranyl acetate and Reynolds lead citrate for examination with the electron microscope (RCA EMU-3G).

Bacteriological procedures. Ileal contents were cultured on MacConkey agar. After 24 to 48 h of incubation at 37°C, suspect *E. coli* colonies were placed on triple sugar iron slants and lysine iron decarboxylase agar slants (BBL Microbiology Systems). Isolates were identified by slide agglutination with specific antisera which was prepared in rabbits.

Antigen was prepared by growing *E. coli* strain 1056

for 18 h in 200 ml of Trypticase soy broth. The culture was centrifuged (400 × *g* for 20 min), and the broth was decanted. Sedimented bacteria were washed twice in PBS, resuspended in 35 ml of 0.5% formalinized PBS, and autoclaved at 121°C at 15 lb/in^2 for 2 h.

Rabbits that had negative *E. coli* strain 1056 titers were inoculated intravenously in the marginal ear veins at 4-day intervals with 5 successive inoculations of 0.5, 1.0, 2.0, 4.0, and 4.0 ml of antigen. At 7 days after the last inoculation, rabbits were bled by intracardiac puncture. Serum antibody titers to *E. coli* were determined, using original antigen in a tube agglutination test.

Fluorescent-antibody procedures. Specimens of intestine for study by the indirect fluorescent-antibody (IFA) technique were stored at −70°C. The intestine was washed with PBS, filled with OCT compound (Lab-Tek Products, Div. of Miles Laboratories, Naperville, Ill.) and immediately frozen. Frozen sections were cut at 8 μm with a cryostat (CTD-International-Harris-Cryostat, International Equipment Co., Div. of Damon Corp., Needham Heights, Mass.). Tissue sections were fixed in cold acetone overnight.

Slides were immersed in distilled water for 2 min and then air dried. Drops of anti-*E. coli* strain 1056 antiserum were placed on the sections. Slides were incubated at 37°C in a moist chamber for 20 min. Controls were overlaid with preinoculation serum collected from rabbits before hyperimmunization or absorbed anti-*E. coli* strain 1056 antiserum. The method utilized for absorption of the anti-*E. coli* antiserum has been previously described (6).

After incubation, slides were washed in 2 changes of PBS (pH 7.6) for 15 min. Slides were rinsed for 15 s in distilled water and allowed to air dry.

Drops of diluted fluorescein isothiocyanate-conjugated anti-rabbit globulin (Microbiological Associates, Walkersville, Md.) were placed on tissue sections. Slides were incubated in a moist chamber at 37°C for 20 min, washed, and air dried. Tissue sections were examined with a microscope (Leitz Ortholux; Leitz/Opto-Metric Div. of E. Leitz Inc., Rockleigh, N.J.) equipped with a Blau BG 38 barrier filter and a Blau BG exciter filter.

RESULTS

Inoculations. A summary of the necropsy results from the inoculation of weanling hamsters with two different *E. coli* strains are presented in Table 1. Neither gross nor microscopic lesions of intestine or abdominal viscera were observed at 25 days postinoculation in the 10 hamsters that received 6 × 10^8 *E. coli* strain 1940 cells.

Acute enteritis occurred in 7 of 22 (32%) hamsters inoculated with 7 × 10^8 *E. coli* strain 1056 cells. Of the 7, 2 died and 5 were killed by chloroform inhalation. The mean number of days postinoculation at which the 7 hamsters died or were killed was 6.1 days, with a range from 3 to 13 days.

Gross lesions. Gross lesions of acute enteritis in hamsters that received *E. coli* strain 1056 were similar to one another. The small intestine contained yellow or dark red fluid and was hyperemic.

Light-microscopic lesions. Sections of intestine with acute enteritis were characterized by villi that were shorter and blunter than normal villi (Fig. 1). Fusion of adjacent villi was commonly observed. Necrosis of villi was characterized by pyknosis of epithelial cells and ulceration of epithelium. Villar epithelium was flattened from columnar to cuboidal. Acute inflammation was characterized by polymorphonuclear inflammatory cells in crypts and within the ileal lumen. Infiltration of the lamina propria with polymorphonuclear inflammatory cells was observed commonly. In some cases, mucosa was covered by a pseudomembrane, appearing as an eosinophilic matrix which contained nuclear debris.

Acute suppurative adenitis of mesenteric lymph nodes was observed in 2 of 7 hamsters with acute enteritis. Lymphadenitis was characterized by focal areas of necrosis in the cortex and diffuse infiltration of polymorphonuclear inflammatory cells in the cortex and medulla. Mesenteric lymph node hyperplasia was observed in 3 of 7 hamsters with acute enteritis. It was characterized by enlargement of the entire lymph node and germinal centers which were

TABLE 1. *Necropsy results from the oral inoculation of weanling hamsters with E. coli*

Group	Necropsy diagnosis (no. with diagnosis/total inoculated)	Intracellular *E. coli* observed by EM[a] (positive/total observed)	Reisolation of inoculated *E. coli* (positive/total cultured)	Intracellular *E. coli* strain 1056 by IFA[b] technique (positive/total observed)
E. coli strain 1056	Acute enteritis (7/22)	4/5	7/7	3/4
	No disease (15/22)		10/15	0/3
E. coli strain 1940	Acute enteritis (0/10)			
	No disease (10/10)	0/4	0/10	

[a] EM, Electron microscopy.
[b] IFA, Indirect fluorescent antibody.

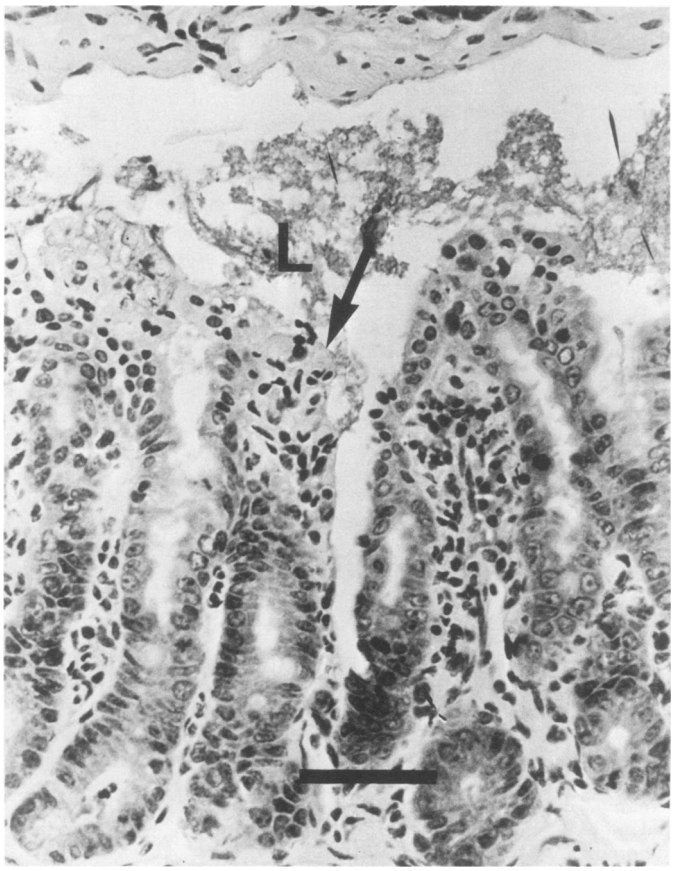

FIG. 1. *Blunted and fused ileal villi in a hamster with acute enteritis. There are necrosis and sloughing of epithelium at villar tips (arrow). Debris is observed in the lumen (L). The tissue was taken from a hamster at 6 days postinoculation with E. coli strain 1056. Hematoxylin and eosin stains were used. Bar = 50 μm.*

prominent and had wide perifollicular zones of lymphocytes. Cells were commonly seen in mitosis.

Focal areas of coagulative necrosis were observed in the livers of 3 of 7 affected hamsters. Lesions were randomly scattered and irregular in shape. Areas of necrosis were accompanied by polymorphonuclear inflammatory cell infiltration. Of the 15 hamsters in the group that received *E. coli* strain 1056 that did not have acute enteritis, 3 had mononuclear inflammatory cell infiltrates in several hepatic portal triads.

Ulceration of the glandular portion of the stomach was detected grossly or microscopically or both in 2 of 7 hamsters with acute enteritis. Colitis occurred in 5 of 7 affected hamsters and was evidenced by infiltration of the lamina propria with polymorphonuclear inflammatory cells, sloughing of epithelium, and cellular debris in crypts. Colonic intussusceptions occurred in 3 of the 5 hamsters with colitis. Intussusceptions occurred at the same place in all 3 hamsters, at the flexure between the transverse and descending colon. Cecal lesions, similar to colonic lesions, occurred in 2 of 7 hamsters with acute enteritis.

Lesions were not observed in the pancreas, spleen, kidney, or lung of any inoculated hamster.

Electron-microscopic lesions. Electron microscopy of the small intestine was done on 4 hamsters which received *E. coli* strain 1940. Ultrastructural changes were not observed within absorptive epithelial cells. Intracellular organisms were not observed.

Electron microscopy was done on the small intestine of 5 hamsters, inoculated with *E. coli* strain 1056, that had acute enteritis. These hamsters were killed by chloroform inhalation at 3, 4, 6, 6, and 13 days postinoculation. Intracellular bacterial organisms were observed in 4 of the 5 hamsters (Table 1). Organisms were not found

in the hamster necropsied at 13 days postinoculation.

Bacterial organisms were observed in the cytoplasm of absorptive epithelial cells, with similar ones in the ileal lumen. Only a few absorptive epithelial cells on a villus contained bacteria, and organisms were not observed in crypt epithelial cells. Organisms were rod shaped and measured 0.62 to 1.00 μm wide and up to 2.2 μm long (Fig. 2). They had a double-layered membranous cell wall. Beneath the cell wall was a narrow electron-translucent space. The central portion of the organism contained an electron-dense granular material with an electron-translucent central region which contained electron-dense strands. Organisms divided by binary fission.

Organisms appeared to enter epithelial cells by a process similar to phagocytosis (Fig. 3). Some organisms, which were near the cell surface, were enclosed within a membrane. Most organisms were not membrane bound but surrounded by a clear electron-translucent zone.

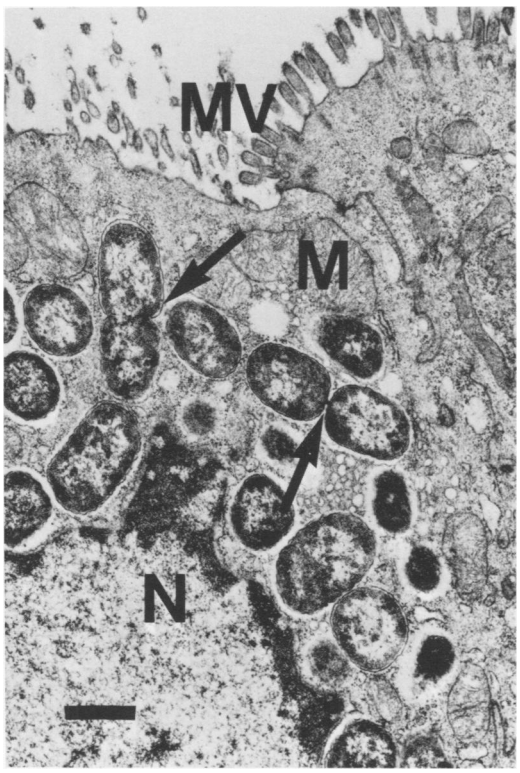

FIG. 2. *Portion of an ileal epithelial cell which contains numerous bacterial organisms. Several organisms are dividing (arrows). Indicated portions are mitochondria (M), nucleus (N), and microvilli (MV). The tissue was taken from a hamster with acute enteritis at 6 days postinoculation with E. coli strain 1056. Bar = 1 μm.*

There was distention and vacuolation of mitochondria in most cells that contained organisms. Microvilli of some affected cells were sparse and irregular. A few cells that contained organisms were degenerative (Fig. 4). Compared to unaffected cells, these cells were electron translucent, had a more granular cytoplasm, distended mitochondria, and sparse irregular microvilli.

Microbiology. *E. coli* strain 1940 was lactose positive on MacConkey agar, had an acid slant and acid butt with gas on triple sugar iron slants, and was lysine iron decarboxylase agar slant positive. *E. coli* strain 1940 was not reisolated from the ileum of any hamster which received it (Table 1).

E. coli strain 1056 was lactose negative on MacConkey agar, had an alkaline slant and acid butt with no gas on triple sugar iron slants, and was lysine iron decarboxylase agar slant negative. *E. coli* strain 1056 was recovered from the ilea of all 7 hamsters with acute enteritis, and *E. coli* strain 1056 was recovered from 5 of the 6 cultured livers. The one liver from which *E. coli* strain 1056 was not recovered contained an unrelated *E. coli* strain. A colonic culture of the hamster necropsied at 13 days postinoculation revealed *E. coli* strain 1056. From the 15 hamsters without ileal lesions, *E. coli* strain 1056 was isolated from the ilea of 10 of them (Table 1).

The indirect fluorescent-antibody technique for detection of *E. coli* strain 1056 was done on ilea from hamsters inoculated with *E. coli* strain 1056. Of the 7 ilea examined, 4 had acute enteritis and 3 had normal ilea (Table 1).

Three of the 4 ilea with acute enteritis had strong fluorescence in the lumen and on the surface of villi. Many intracellular, fluorescent bacteria were observed within absorptive epithelial cells. Ileal sections of a hamster with acute enteritis necropsied at 13 days postinoculation did not have fluorescence. Two of 3 ilea from hamsters without ileal lesions contained a few fluorescent bacteria within the lumen; however, bacteria were not observed intracellularly. Control sections prepared by using preinoculation rabbit sera or absorbed anti-*E. coli* strain 1056 sera placed on duplicate sections were uniformly negative.

DISCUSSION

After weanling hamsters were inoculated orally with *E. coli* strain 1056, 32% developed acute enteritis. *E. coli* strain 1056 was cultured from the ilea of all hamsters which developed

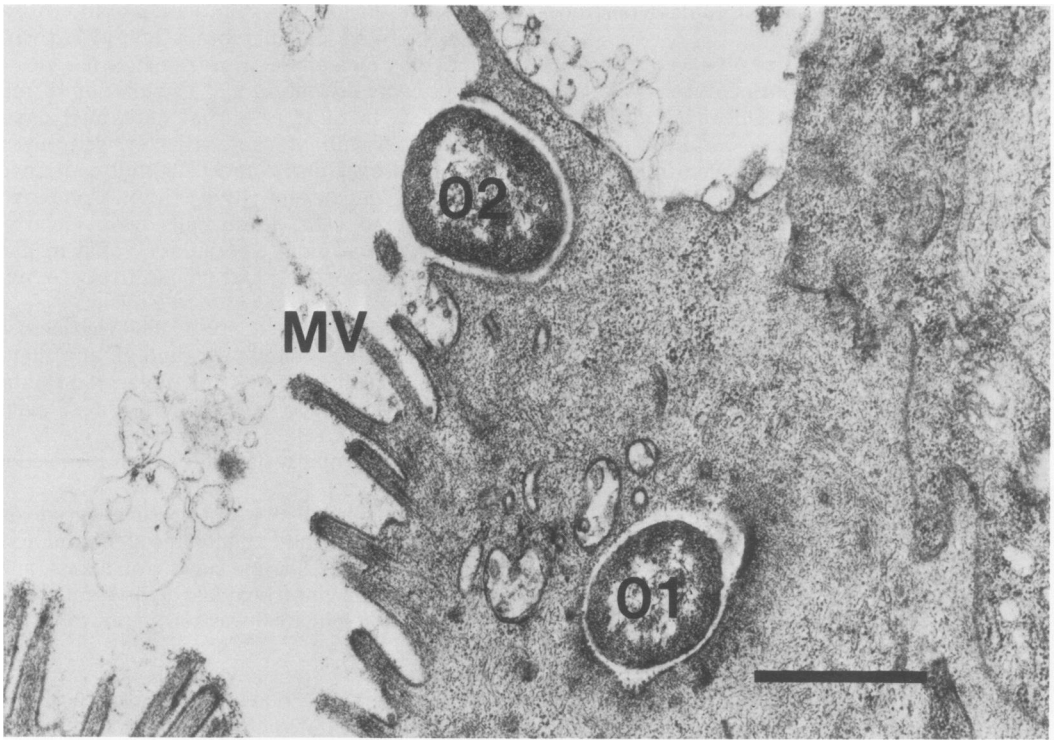

FIG. 3. *An ileal epithelial cell containing a bacterial organism (01) which is membrane bound. A second organism (02) is partially surrounded by cell cytoplasm. Microvilli (MV) of the affected cell are irregular. This section of ileum was taken from a hamster at 6 days postinoculation with E. coli strain 1056. Bar = 1 μm.*

acute enteritis. From the hamsters without acute enteritis, *E. coli* strain 1056 was isolated from 67%, demonstrating that exposed hamsters could act as carriers without having lesions. The indirect fluorescent-antibody technique showed that *E. coli* strain 1056 was within absorptive epithelial cells in ilea affected with acute enteritis. Organisms were also demonstrated on the surface of the mucosa in animals with acute enteritis and carrier animals which did not have lesions. Rabbits infected with enteropathogenic *E. coli* also had organisms on the surface of the intestinal mucosa; however, intracellular organisms were not observed (4). The absence of clinical signs and lesions in hamsters inoculated orally with *E. coli* strain 1940 demonstrated that not all *E. coli* organisms could cause inflammation of the intestine. Ileal cultures from these hamsters were negative for *E. coli* strain 1040; thus, the organisms were unable to colonize the intestine.

Data regarding the pathogenesis of acute enteritis produced by *E. coli* strain 1056 were obtained by electron microscopy of absorptive epithelial cells. Electron micrographs showed that individual organisms were taken into epithelial cells by a process much like phagocytosis. In a similar phagocytic manner, shigella organisms were shown to be engulfed by cells in monolayers (21). A similar process has been described in *Salmonella typhimurium* infections of the small intestine; however, several salmonellae are usually taken into the cell at the same time (25). *E. coli* strain 1056 organisms were found to be membrane bound in the apical cytoplasm, presumably shortly after they were engulfed. The membrane was later lost, because cell membranes were not observed around most organisms found deep in the cytoplasm. In shigella infections, organisms can be observed with or without cellular membranes; however, the majority of organisms are membrane bound (26). The electron-translucent space surrounding many organisms was believed to be an artifact. Cell penetration and replication of the organism were reported as important in the pathogenesis of shigellosis (16). Our electron micrographs demonstrated that after *E. coli* strain 1056 had penetrated the cell it could replicate by binary fission.

Epithelial cells which contained *E. coli* strain 1056 were near the tips of villi rather than within

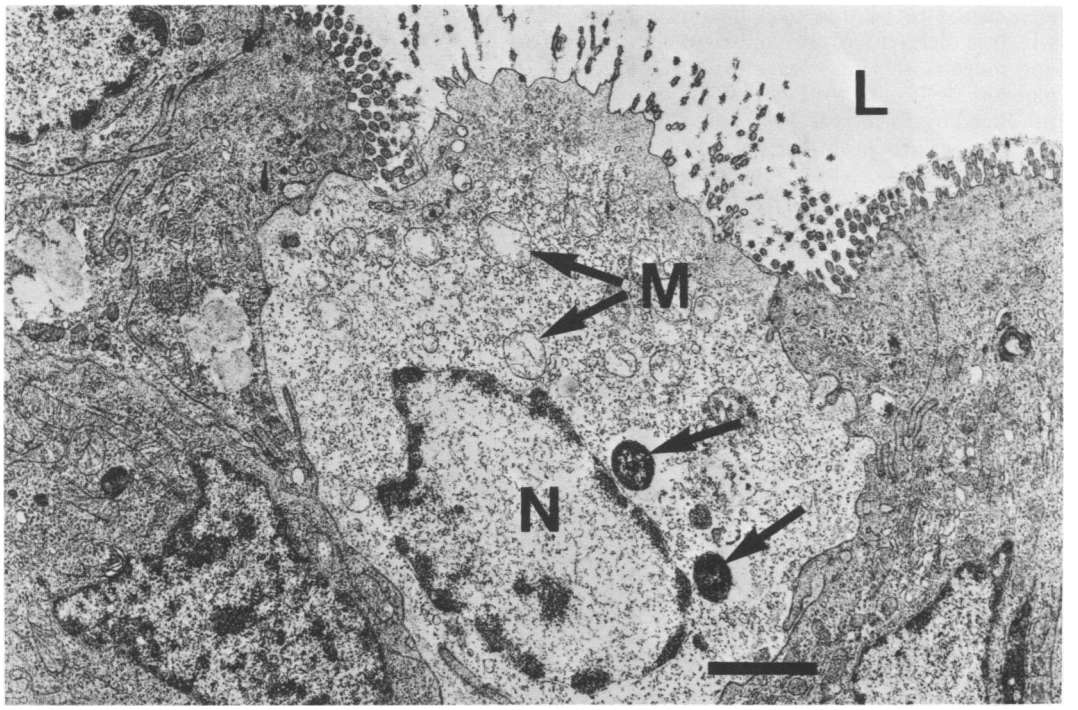

FIG. 4. *An ileal epithelial cell containing bacterial organisms (arrows) in a state of degeneration. Adjacent cells appear to be structurally normal. Indicated portions are nucleus (N), mitochondria (M), and lumen (L). This section of ileum was taken from a hamster at 6 days postinoculation with E. coli strain 1056. Bar = 2 μm.*

crypts. Some affected cells showed degenerative changes which included shortening of villi, distention and vacuolation of mitochondria, and decreased density of cytoplasm. Intracellular *E. coli* that was observed after hamsters were inoculated with ground proliferative ilea similarly affected villar epithelial cells and caused degenerative changes (8). Similar findings have been reported in shigellosis of rhesus monkeys in that most affected epithelial cells were near villar tips (26).

Intussusceptions occurred shortly after inoculation of *E. coli* strain 1056. Similar to the results with hamsters inoculated with salmonella, intussusceptions always occurred at the flexure between the transverse and descending colon (22). Acute suppurative necrotic hepatitis was observed early after inoculation. *E. coli* strain 1056 was cultured from the liver of 5 hamsters that died. These hepatic lesions and bacterial isolations from livers indicate that hamsters developed a bacteremia probably secondary to the intestinal lesions. This is similar to the Ekiri syndrome of children, where shigella, which is normally only within absorptive epithelium, becomes systemic, causing fatal bacteremia (7). Suppurative lymphadenitis and lymph node hyperplasia of mesenteric lymph nodes were believed to develop secondary to intestinal lesions. Gastric ulceration was believed to be a nonspecific lesion associated with stress similar to the development of stomach ulcers in rats (17).

Based on lesions observed in our studies with light and electron microscopy and fluorescent-antibody techniques, we found that acute enteritis produced in hamsters by *E. coli* strain 1056 closely resembles shigellosis and invasive *E. coli* infections of other species (5, 15, 20, 24, 26). Also, *E. coli* strain 1056 caused colitis in 5 of 22 inoculated hamsters. It has been reported that *E. coli* which caused syndromes similar to shigellosis was usually anaerogenic, nonmotile, unable to ferment lactose, and many times cross reacted with shigella antisera (11). Although *E. coli* strain 1056 reacted with *E. coli* serotype O: 105 antisera and not shigella antisera, the organism was anaerogenic, nonmotile, and lactose negative. *E. coli* strain 4165, which was also isolated from a hamster with proliferative ileitis, was biochemically similar to *E. coli* strain 1056 and has been reported to react with *Shigella boydii* type 11 and type 12 antisera (28).

Hyperplasia of the ileum in proliferative ileitis

is believed to be due to a bacterial organism which is ultrastructurally different from *E. coli* and more closely resembles *Campylobacter* organisms (8, 12–14, 28). Lesions of acute enteritis produced by *E. coli* strain 1056 in this study did not progress to proliferation. The gross, light-microscopic, and electron-microscopic lesions produced did not differ from the acute enteritis lesions observed in hamsters inoculated with suspensions of proliferative ilea (1, 8). It may be that an organism such as an enteropathogenic *E. coli* must first cause ileitis before proliferation of the ileal epithelium can occur. This hypothesis of pathogenesis would involve microbial synergism similar to other reported infectious diseases (18, 19). Others, however, have reported that acute enteritis and intracellular *E. coli* were not observed after inoculation with proliferative ilea (12–14). In considering data from these reports, it is possible that acute enteritis produced by *E. coli* is a separate syndrome and not associated with hyperplasia.

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