Colitis caused by *Escherichia coli* 0157:H7: A study of six cases

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ABSTRACT: The clinical and pathologic features of six patients with proven verotoxin-producing *Escherichia coli* colitis are described. Clinical data, 25 biopsy specimens and two autopsies from these patients are reviewed. All presented with crampy abdominal pain and bloody diarrhea. Colonoscopic findings included edema, erythema, pseudomembranes and hemorrhage. On biopsy, two patients had ischemic colitis, one had pseudomembranous colitis and three had a combination of concurrent ischemic and pseudomembranous colitis. Four cases showed fibrin-platelet thrombi in mucosal capillaries and submucosal arterioles. The classical pattern of infectious colitis was not seen in these cases. Other nonspecific changes included patchy mucosal edema, congestion, focally prominent interstitial hemorrhage and mild, patchy increase of the lymphoplasmocytic component of the lamina. Ischemic necrosis was present in 10 of 25 biopsies (40%), pseudomembranes in seven of 25 biopsies (28%), and four of 25 biopsies (16%) showed both. Colon from one autopsy revealed edema, pseudomembranes and intramural infarction. Concurrent thrombotic thrombocytopenic purpura was clinically documented in three of six patients. It is concluded that, in the context of hemorrhagic colitis, the following observations are indicative of *E coli* 0157:H7: the combination of pseudomembranous and ischemic colitis; ischemic colitis in a young patient; or pseudomembranous colitis with *Clostridium difficile*-negative culture and toxin. Multiple biopsies are required to demonstrate the full-blown features. *E coli* 0157:H7 colitis should be added to the differential diagnosis of submucosal edema. **Can J Gastroenterol 1990;4(4):141-146** *(pour résumé, voir page 142)*

Key Words: E coli *0157:H7, Ischemic colitis, Pseudomembranous colitis, Verotoxin*

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VEROTOXIN-PRODUCING *ESCHERICHIA coli* 0157:H7 is an important cause of hemorrhagic colitis which is being diagnosed with increasing frequency (1). The complications are potentially life threatening: hemolytic-uremic syndrome is well documented, and, more recently, thrombotic thrombocytopenic purpura has been observed (2-4).

The identification of diagnostic pathological lesions that suggest verotoxin-producing *E coli* infection is important because clinical markers of the disease may be negative or inapparent. For instance, in the adult age group, bacteria are shed in the stool only for a few days to a week after onset of symptoms (4,5). The assay for verotoxin is positive for only a few additional days, and is not available in many tertiary care hospitals. Thus, delay by the patient in seeking medical attention, or by clinicians in obtaining stool for culture, reduces the likelihood of isolating the organism. Thrombotic thrombocytopenic purpura may dominate the clinical picture to the extent that colitis is overlooked altogether (4).

The authors previously reported two

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RESUME: L'étude décrit les manifestations cliniques et pathologiques de six patients atteints de colite à *Escherichia coli* produisant des vérotoxines. Les données cliniques, 25 prélèvements biopsiques et deux autopsies sont passés en revue. Tous les sujets présentaient des douleurs abdominales à type de crampes et des diarrhées sanglantes. La côlonoscopie a révélé de l'oedème, de l'érythème, des pseudomembranes et des hémorragies intestinales. D'après les biopsies, deux patients souffraient de colite ischémique; un, de colite pseudomembraneuse; et trois, d'une combinaison de colite ischémique et pseudomembraneuse. Quatre cas montraient des thrombi fibrinoplaquettaires dans les capillaires de la muqueuse et les artérioles de la sousmuqueuse. Aucun des cas ne présentait la morphologie classique de la colite infectieuse. Parmi les autres changements non spécifiques figurent l'oedème disséminé de la muqueuse, la congestion, l'hémorragie interstitielle en foyers, et l'infiltration modérée et en aires de la lamina par des plasmocytes et des lymphocytes. Une nécrose ischémique était présente dans dix des 25 biopsies (40%); des pseudomembranes, dans sept cas sur 25 (28%); et les deux phénomènes étaient manifestes dans quatre des 25 biopsies (16%). Le côlon d'un sujet autopsié a révélé un oedème, des pseudomembranes et une infection intramurale. Un purpura thrombocytopénique thrombotique a été cliniquement confirmé chez trois patients sur six. On conclut que, dans le contexte de la colite hémorragique, les observations suivantes indiquent la présence d'*E coli* 0157:H7: une colite pseudomembraneuse et ischémique combinée; une colite ischémique chez un jeune patient; ou une colite pseudomembraneuse accompagnée d'une culture négative de *Clostridium difficile* et de toxine. De multiples biopsies sont nécessaires pour révéler toutes les caractéristiques de cette affection. *E coli* 0157:H7 devrait figurer au diagnostic différentiel de l'oedème de la sousmuqueuse.

cases of *E coli* 0157:H7 colitis complicated by thrombotic thrombocytopenic purpura and briefly described the unusual finding of simultaneous ischemic and pseudomembranous colitis (3). In the present report, several pathological alterations are described, which, in combination, strongly suggest the diagnosis of verotoxin-producing *E coli*.

PATIENTS AND METHODS

Sixteen patients with positive stool cultures for *E coli* 0157:H7 were identified from the records of the microbiology laboratories of two teaching hospitals over a period of one-and-a-half years. Six of these patients had a total of 25 colonic biopsies. Two of the six patients died and the autopsy material was reviewed. The biopsies were serially sectioned and stained with hematoxylin and eosin. Clinical features, abdominal x-rays, and endoscopic findings of these six patients were reviewed.

RESULTS

Clinical features: All six patients presented with a one to five day history of crampy abdominal pain, bloody diarrhea, nausea and vomiting. There was no history of travel outside of Canada. Two patients received a few doses of erythromycin. Four of the cases were sporadic. In the other two cases, a milder, self-limited form of diarrhea developed in other family members and social contacts. Three patients developed thrombotic thrombocytopenic purpura (as defined by the presence of thrombocytopenia, microangiopathic hemolytic anemia, fever, normal prothrombin and partial thromboplastin times, normal fibrinogen levels, and declining neurological and renal functions). Dilated, edematous small and large bowel (with occasional thumbprinting) were seen on standard abdominal x-rays (Figure 1). Colonoscopy showed erythema, edema and hemorrhage in all six patients and pseudomembranes in two (Figure 2). There was pancolitis in one patient with predominance on the right side. Only the left colon was visualized in the remaining five patients. However, bleeding above the level of the colonoscope was reported in two of these five patients.

Pathological findings: The histopathological findings are shown in Figure 3. Pseudomembranous colitis was diagnosed when the type 2 lesion described by Price and Davies (6) was identified (Figure 3b). This as well as the other histological types 1 and 3 were noted in four patients. Mucosal biopsies in five patients revealed ischemic colitis defined as variable depth of coagulative necrosis, with or without type 3 pseudomembranes (Figure 3c). In three patients pseudomembranous colitis was seen concurrently with ischemic colitis. Pseudomembranous colitis and ischemic colitis were present in seven of 25 (28%) and 10 of 25 (40%) biopsies, respectively. The two processes occurred contiguously in four of 25 (16%) biopsies.

Platelet-fibrin thrombi were visualized in the biopsies of four patients. Patchy, sometimes prominent, interstitial hemorrhage and edema of the lamina was present in all patients.

Neutrophilic infiltration of gland and lamina was not a feature of the biopsies, and only the rare microfocus could be identified. The lymphoplasmocytic component of the lamina was only focally and mildly increased. Submucosa was included in two biopsies from the same patient and was markedly edematous.

Two patients died; both were elderly and both cases were complicated by thrombotic thrombocytopenic purpura. At autopsy, the colon of one patient showed only edema and petechial hemorrhages. The second patient died following central nervous system complications of thrombotic thrombocytopenic purpura. In this case, the colon showed extensive ischemic necrosis with focal pseudomembrane formation (Figure 4).

DISCUSSION

The salient pathologic changes seen in these six cases of *E coli* 0157:H7 infection were ischemic colitis and all three morphological types of pseudomembranous colitis. Half of the patients had the unusual finding of simultaneous pseudomembranous and ischemic colitis. None of the biopsies showed the features of infectious colitis.

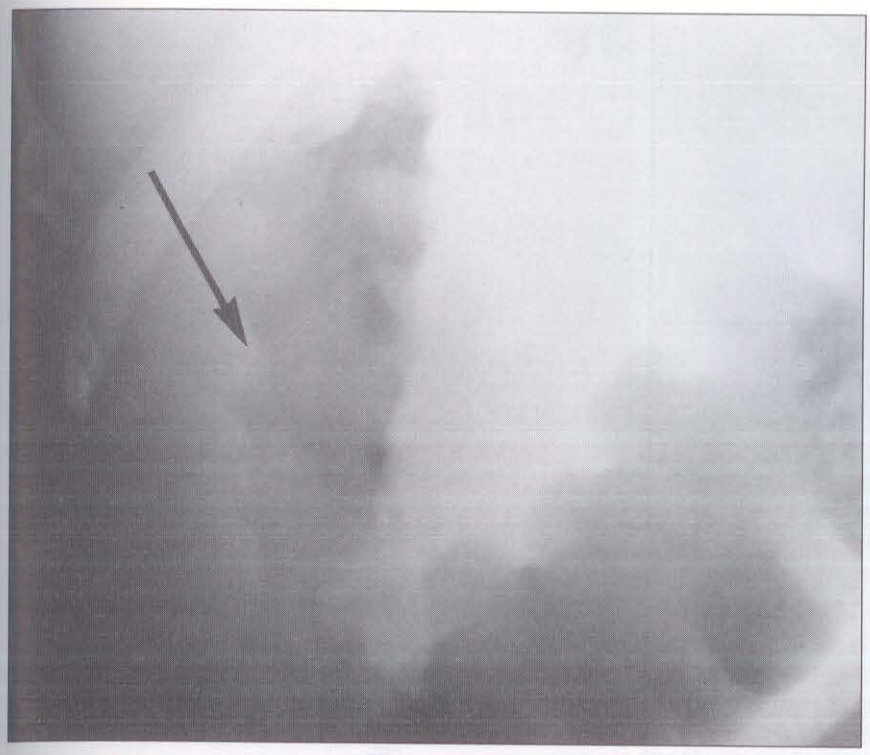


Figure 1) *Abdominal x-ray showing thumbprinting (arrow) in the ascending colon*

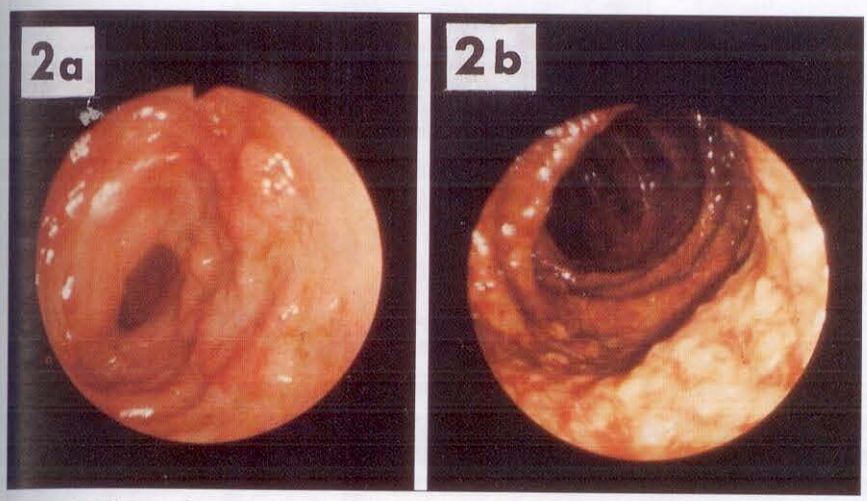


Figure 2) *Colonic endoscopy showing submucosal edema* (**2a**) *and pseudomembranes, erythema and hemorrhage* (**2b**)

Since ischemic colitis was identified in only 10 of 25 biopsies and pseudomembranous colitis in only seven of 25, it is evident that multiple samples are necessary for demonstration of the lesions and for adequate evaluation of the colonic mucosa.

Concurrent bowel infarction and pseudomembrane formation have been described in a subset of ischemic bowel disease under diagnostic terms such as nonocclusive intestinal ischemia and pseudomembranous enterocolitis. They occur as complications of various conditions such as shock, postoperative states and heart failure (6-9). In contrast with *E coli* 0157:H7 colitis, small bowel involvement is common and the prognosis is poor. On occasion, pseudomembranes can also be seen associated with ischemic colitis in mesenteric artery occlusion. Usually only type 3 pseudomembranes, and not the full spectrum of types 1 to 3, are present in occlusive ischemic colitis (8). In contrast, mucosal hemorrhagic necrosis of the type seen in ischemic bowel disease, as well as intramural and transmural infarction, are not a feature of antibiotic-associated pseudomembranous colitis. Thus, in the context of hemorrhagic colitis, the simultaneous occurrence of pseudomembranous colitis and ischemic colitis seems to be a distinctive finding of *E coli* 0157:H7 colitis.

The clinical presentation in many previously reported cases of *E coli* 0157:H7, as well as in the present study, suggested ischemic rather than infectious colitis (1,3,4). Three of the present six patients were under 50 years of age, and mucosal ischemia was a component of the histopathology in five cases. Ischemic colitis is unusual in young patients. Thus, its presence in young patients would also suggest a diagnosis of *E coli* 0157:H7. Conversely, the possibility of an infectious etiology may be overlooked in the elderly patient presenting clinically with ischemic colitis.

A biopsy showing pseudomembranous or pseudomembranous and ischemic colitis may be the only clue to *E coli* 0157:H7 colitis. The diagnosis of *E coli* 0157:H7 is suggested in any patient with biopsies showing pseudomembranous colitis but negative *Clostridium difficile* cultures or toxin.

Other pathological findings seen radiologically and/or endoscopically may also be helpful in pointing to the diagnosis of *E coli* 0157:H7. The differential diagnosis of submucosal edema of the colon is essentially limited to inflammatory bowel disease (particularly Crohn's disease), ischemic colitis, and pseudomembranous colitis. Since the basic pathology of *E coli* 0157:H7 colitis was that of ischemic, pseudomembranous, or pseudomembranous and ischemic colitis, it is not surprising that submucosal edema was also present. Other colonic lesions associated with ischemic colitis were also found in the present study: focal interstitial hemorrhage (six cases) and small vessel fibrin-platelet thrombi (four cases). The rare section showed capillary thrombi in otherwise normal mucosa.

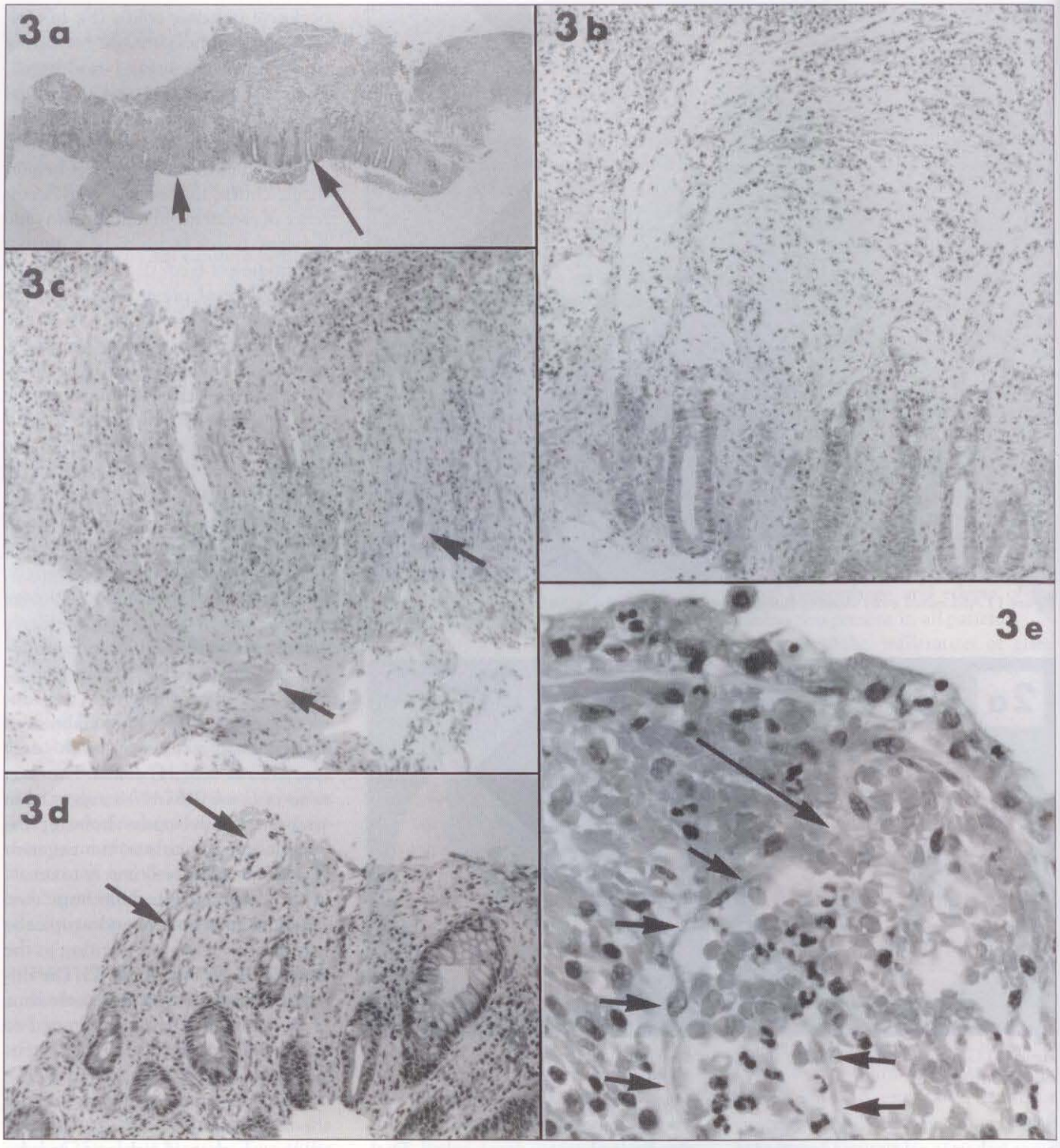
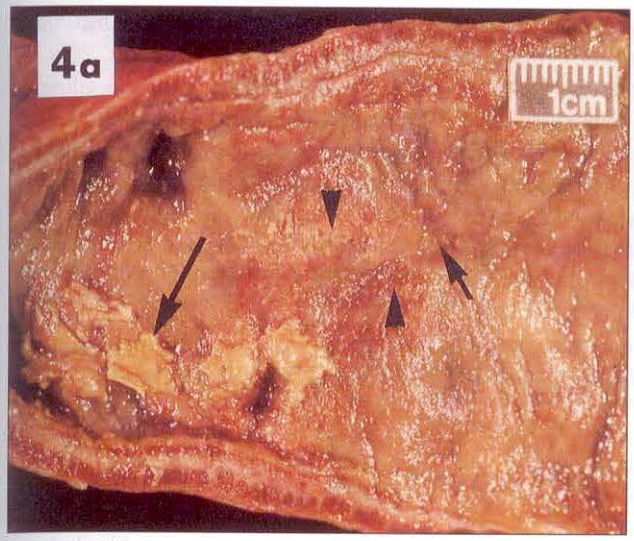


Figure 3) *Colonic biopsies.* **3a** *Segment of colonic mucosa where pseudomembranous colitis (long arrow) is continuous with ischemic colitis (short arrow).* **3b** *On higher magnification, the pseudomembranous component is formed of the typical 'fire cracker' lesions and streaming exudate.* **3c** *There is full thickness infarction of the mucosa in the ischemic portion of the biopsy with thrombi in submucosal vessels and mucosal capillaries (arrows).* **3d** *Several biopsies show a lesser degree of ischemia identified only by attenuation of the superficial portion of a few glands (arrows).* **3e** *Microfoci of superficial hemorrhages are common and result from rupture of large, dilated mucosal capillaries (short arrows outline capillary, long arrow the disruption)*

The colonic pathology observed here has been reported to a limited extent in the literature. One case reported by Morrison et al (2) was associated with pseudomembranes identified histologically but not recognized on endoscopy. Richardson et al (10) described three cases of *E coli* 0157:H7 colitis complicated by hemolytic-uremic syndrome in the pediatric age group. Pseudomembrane formation was present in one case, (again seen only on microscopic examination) and ischemic necrosis (personal communication) in two cases (10). None of these



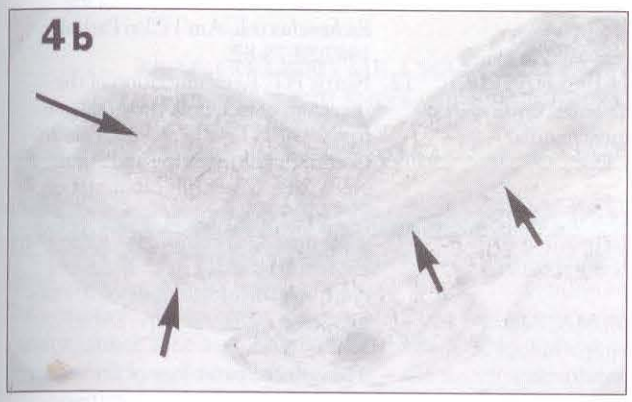


Figure 4) *Colon removed at autopsy.* **4a** *Variegated pattern of mucosal infarction (arrow heads), ulceration (short arrow) and adherent exudate forming pseudomembranes (long arrow).* **4b** *Section taken at the level of the pseudomembrane. There is extensive transmural hemorrhage (long arrow) and intramural infarction extending into the muscularis propria (short arrow).* **4c** *Ischemic necrosis (arrow) and hemorrhage of muscularis propria*

TABLE 1
Algorithm for diagnosis of *Escherichia coli* 0157:H7 infection

Diagnosis of *E coli* 0157:H7 is suggested by biopsies showing:
Ischemic colitis in a young patient
Simultaneous ischemic and pseudomembranous colitis
Pseudomembranous colitis with negative *Clostridium difficile* culture/toxin
Pseudomembranous colitis in elderly with clinical picture of ischemic colitis
Diagnosis of *E coli* 0157:H7 should be included in the differential diagnosis if:
Minimal findings on biopsy with radiologically or endoscopically proven submucosal edema or hemorrhage
Biopsy-proven ischemic colitis in an elderly patient

reported cases showed pseudomembranous and ischemic colitis. In all other reported cases, the pathological alterations in mucosal biopsies showed a spectrum, including: no alterations; nonspecific changes including interstitial hemorrhage, mild increase of the lymphoplasmocytic component of the lamina propria and edema; neutrophilic infiltrates of the lamina propria and glands in the fashion of infectious colitis; and apoptosis of surface epithelium (1,4,5,11). It is surprising that only four of all of the reported cases showed ischemic colitis or pseudomembranous colitis, and that pseudomembranous and ischemic colitis was not seen in any report of *E coli* 0157:H7 infection; other associated features such as submucosal edema and hemorrhage were prominent findings in most cases. Possible explanations for this discrepancy include mucosal sampling limited to the distal colon (with the more severe proximal disease not visualized endoscopically) and a patient population with a milder form of colitis than observed in the present study. Indeed, three of the six cases were complicated by thrombotic thrombocytopenic purpura and two of the six patients died, a far higher percentage of complications than in other series.

The relationship between pseudomembranous colitis and ischemic colitis has been extensively debated. Some authors consider pseudomembranous colitis as part of the spectrum of ischemic colitis, whereas others regard pseudomembranous colitis and ischemic colitis as distinct and separate entities. The findings

described in the present six cases suggest that pseudomembranous colitis and ischemic colitis are indeed on a continuum of the same disease. The mechanism by which the pseudomembrane forms has been suggested by Norris in his review of the spectrum of ischemic bowel disease (12). Whereas total cessation of bloodflow to bowel results in coagulative necrosis, an acute inflammatory infiltrate develops in bowel mucosa when colonic bloodflow ceases and is then re-established. Norris suggests that this process evolves to pseudomembrane formation.

The authors have demonstrated in these cases of *E coli* 0157:H7 colitis, disruption and/or thrombosis of mucosal capillaries and, to a lesser extent, thrombosis of small submucosal arterioles. Lysis of these thrombi or collateral blood supply from the rich mucosal plexus to the ischemic mucosa may result in reflow of blood, acute inflammatory infiltrate and subsequent pseudomembrane formation.

Finally, in light of the preceding discussion, the authors have found the algorithm presented in Table 1 useful in the diagnosis of *E coli* 0157:H7 colitis.

APPENDIX: While this work was in preparation, two papers showing pathological findings somewhat similar to those above were presented at the International Academy of Pathology, San Francisco California, March 1989 (13,14).

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