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A New Concept of the Pathogenesis of Ulcerative Colitis[1]

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Although much has been written of the pathologic changes in the large bowel of patients with ulcerative colitis, little evidence of the specificity of the lesion has been presented to date. The purpose of this paper is to describe certain distinct changes in the connective tissue of the colon which appear to be of fundamental importance in the pathogenesis of the disease. We suspect that ulcerative colitis falls into that group referred to as collagen disease.

Biopsy material taken during proctoscopic examination from a series of patients, both normal and with ulcerative lesions of the bowel, were frozen, dried, and mounted according to the method described by Gersh and Catchpole (*1*). The tissue was then treated with leukofuchsin after exposure to periodic acid, as described by Hotchkiss (*2*), except that care was taken to adjust the periodate leukofuchsin and wash solutions to a pH of 3.5, a modification suggested by Johnson and Permutt (*3*). Other frozen dried sections were viewed with the phase contrast microscope, thereby eliminating reagents which might alter the morphology. Similar sections were treated with aqueous 0.05% toluidine blue (National Aniline).

Biopsy specimens also were fixed in 10% formalin for hematoxylin eosin and reticulum stains.

The sections of biopsy material from patients with ulcerative colitis revealed a virtual absence of the homogeneous ground substance of the basement membrane of the epithelial cells. The reticulum of the basement membrane was present but was frequently fragmented.

The epithelial cells of the mucosa were morphologically intact, as was the intercellular cement substance, but in many areas the mucosa had separated from the underlying connective tissue. In the intervening space a homogeneous, Hotchkiss-positive, metachromatic material was observed. Such areas were often free of inflammatory response. Intracellular epithelial polysaccharide in the diseased tissue was dispersed rather than polar. In the lamina propria and submucosa there was an accumulation of homogeneous, Hotchkiss-positive, metachromatic ground substance which proved to be water-soluble.

With phase microscopy (done by Solbert Permutt) the basement membranes are seen as bright areas and are considerably thicker than in those sections treated with reagents (Fig. 1). In the ulcerative colitis epithelium these areas are absent.

The question arises as to whether the changes are merely the result of an inflammatory process regardless of etiology. Gersh and Catchpole (*1*) have described the disappearance of the basement membrane in rabbitskin after the subcutaneous injection of turpentine. Examination of the bowel of one patient with active amebiasis, in which there was profound inflammation with considerable necrosis, indicated that the basement membranes of the epithelium were intact (Fig. 1, *D*). A similar finding was noted in a patient with lymphopathia venerium with concomitant colitis. Further studies were made during experimental traumatization of the bowel of a dog with an electrocautery, biopsy specimens being taken during the height of the inflammatory process. The basement membranes remained intact even in areas where the epithelial cells were necrotic.

Last, the examination of a series of sections from ulcerative colitis patients who were responding well to ACTH therapy disclosed areas where the ground substance of basement membrane had returned, although surrounding regions remained free of this structure. The basement membrane was observed in areas where the inflammatory process as indicated by mononuclear infiltration was still quite evident.

The above-described changes in the ground substance of connective tissue of the bowel appear to be of primary importance in the pathogenesis of ulcerative colitis. As alterations in the basement membrane occur, the epithelium sloughs away from the submucosal connective tissue and secondary bacterial invasion results. Warren and Sommers (*4*), in a detailed study of the pathology of ulcerative colitis, have described two types, one primarily a vasculitis resembling periarteritis nodosum or thromboangitis obliterans, the second and most common variety the crypt abscess type. All our cases fall into this latter group. The crypt abscess form is described as primarily a surface phenomenon, with abscess formation occurring in the lumina of mucosal crypts rupturing through the epithelium into the submucosa. We believe the abscess formation can occur by virtue of the rupturing of the epithelium first, as a result of the changes described in the basement membrane, the epithelium thereby losing its property of barrier.

We suspect that the basement membrane plays a far greater role than maintaining the continuity of

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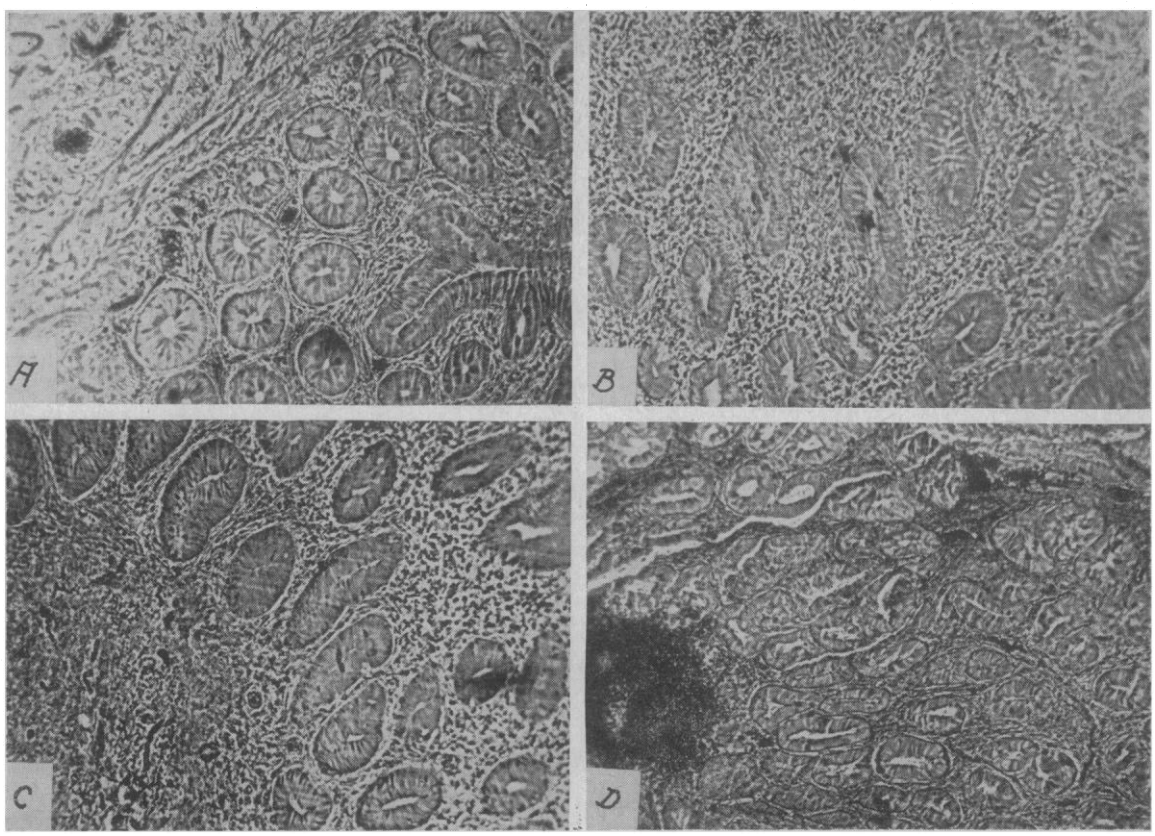

FIG. 1. Sections of human biopsy material. Large bowel under phase contrast microscopy, ×100. Frozen dried material. *A*, Normal. Note clear areas at base of epithelium, representing homogeneous ground substance of the basement membrane. *B*, Ulcerative colitis. Note complete absence of the basement membrane. *C*, Ulcerative colitis treated with ACTH. Note areas of returning basement membrane, although inflammatory process is still evident. *D*, Amebiasis. Note intact basement membrane in spite of marked inflammation and necrosis.

the epithelium and submucosal connective tissue. Gersh and Catchpole (*1*) have so clearly pointed out the dynamic state of this structure and the ground substance generally. This laboratory is now engaged in studies designed to elucidate some of the properties of this structure in the gastrointestinal tract.

The mechanism of the connective tissue changes described is not yet clear. Changes in basement membrane and ground substance of connective tissue generally are thought to be associated with the hypersensitive state. The fact that localized periarteritis (*4*) is frequently seen in ulcerative colitis is highly suggestive. Many of the so-called complications of ulcerative colitis—i.e., arthritis, erythema nodosum, and glomerulitis—are compatible with the concept of ulcerative colitis falling into the collagen disease group, as is the response of the disease to ACTH (*5, 6*). Further studies in this direction are in progress.

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