

CONTEMPORARY ISSUES IN  
SURGICAL PATHOLOGY

PATHOLOGY  
OF THE COLON,  
SMALL INTESTINE,  
AND ANUS

---

SECOND EDITION

Edited by  
H. Thomas Norris

CHURCHILL LIVINGSTONE

# **PATHOLOGY OF THE COLON, SMALL INTESTINE, AND ANUS**

## **SECOND EDITION**

*Edited by*

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SMALL INTESTINE, AND ANUS**

**SECOND EDITION**

# CONTEMPORARY ISSUES IN SURGICAL PATHOLOGY VOLUME 17

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# Foreword

Since the first volume in the *Contemporary Issues in Surgical Pathology* was published in 1983, eighteen volumes have appeared, and the series has been established as an authoritative source for current information that fully covers the latest developments in the field. The volumes published have been organized by specific anatomic site or organ system. The quality of the volumes is a direct result of the efforts of the editors of the individual volumes and their contributors. The response by its readership has been heartening. I would like to thank the many colleagues who have contributed time from their busy schedules in support of this project.

One of the most successful volumes has been *Pathology of the Colon, Small Intestine, and Anus*, edited by Dr. H. Thomas Norris, Professor and Chairman of the Department of Pathology and Laboratory Medicine at East Carolina University School of Medicine. With the publication of this volume, the series has reached a milestone. The first edition of this volume was completely sold out within a relatively short time. The second edition, the first revised edition in the series, brings this popular volume up to date. In this volume, Dr. Norris has again assembled a group of authorities in their subject, who provide a volume that should be of great practical value for the practicing pathologist. I would like to personally thank Dr. Norris for a job well done.

In the future we will continue publishing volumes on subjects not yet covered in the series, as well as adding timely second editions of selected books in the series. Comments and suggestions from the readership of the series will be greatly appreciated.

*Lawrence M. Roth, M.D.*  
*Series Editor*



# Preface

Since this book's initial publication in 1983, there has been an extraordinary increase in knowledge about the subjects covered in this text. The criteria for diagnosis of these lesions has also been refined. Greater insight into the progression of a lesion to a malignancy has been the result of discoveries using contemporary techniques of molecular biology. In addition, a much greater understanding of the pathogenesis of these lesions has developed.

Once again, we review in eleven chapters the latest knowledge on subjects of current interest. All of the authors have extensively reviewed and rewritten their chapters to incorporate this new information. Each author is widely recognized for his expertise in gastrointestinal pathology. Each chapter is designed to give concise but comprehensive coverage of each of its topics, with emphasis on recent advances in knowledge, areas of rapid change, and new techniques.

The general organization of the book is identical to the first edition. The initial chapters deal with various aspects of inflammatory bowel disease. The first chapter deals with the diagnosis of and comparison between ulcerative colitis and Crohn's disease. The second chapter deals with the differential diagnosis of inflammatory bowel disease. This is followed by a chapter on the experimental pathology of inflammatory bowel disease, including immune-mediated aspects of the disease process. A chapter on dysplasia associated with inflammatory bowel disease concludes the chapters on inflammatory bowel disease. The book then changes direction with a re-examination of the spectrum of ischemic bowel disease. The next chapter deals with small bowel biopsy processing and interpretation, with emphasis on malabsorption syndromes. The final five chapters deal with neoplasia of the lower gastrointestinal tract. The relationship between polyps and cancer is extensively reviewed, with emphasis on recent discoveries involved in the development of cancer. The next chapter presents an extensive review of cancer of the colon, focusing on the early stages of development. Neoplasms of the appendix are then reviewed extensively. Neoplastic lesions of the endocrine cells of the gut are discussed in depth. The book ends with a chapter on neoplasms of the anus.

This second edition, the first second edition in Churchill Livingstone's series, *Contemporary Issues in Surgical Pathology*, is a direct response to you, the reader. The first edition was dedicated to informing the reader of specific areas of gastrointestinal pathology in which advances had been particularly dramatic or pivotal in understanding the disease process. This dedication continues in the second edition. It is the expectation of the contributors that the second edition will continue to help refine current practices in gastrointestinal pathology.

A note of special thanks is appropriate to all of the authors who have found time in their hectic schedules to complete their contributions. Once again, their cooperation and contributions have been outstanding.

*H. Thomas Norris, M.D.*

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# Diagnosis and Comparison of Ulcerative Colitis and Crohn's Disease Involving the Colon

*Stanley R. Hamilton*

Ulcerative colitis (UC) and Crohn's disease (CD) are the two recognized forms of idiopathic inflammatory bowel disease (IBD). Clinically significant involvement of the colon occurs in about one-third of patients with CD. As a result, the distinction between UC and colonic Crohn's disease (CCD) poses a frequent problem for gastroenterologists and surgeons. Because of the widespread use of endoscopy, pathologists are often asked to interpret biopsy specimens taken in an attempt to make this distinction. In some patients, the diagnosis is not clear prior to the time of a resection, and UC and CCD must be distinguished in the surgical specimen.

In the past, distinguishing UC from CCD was largely an intellectual exercise because the medical and surgical therapy for the two diseases were similar. With recent advances, however, this situation has changed. Medical therapy for UC and CD sometimes utilizes different drugs. Of even greater immediate importance to the patient, surgical techniques for continent ileostomy or ileoanal anastomosis with pouch reservoir offer the potential to avoid an ileostomy appliance following colectomy. These newer surgical procedures are, however, usually contraindicated in patients with CD.<sup>1</sup> In addition, the risk of colorectal cancer as a complication of idiopathic IBD is higher in patients with UC than in those with CCD. Colonoscopic surveillance for dysplasia, the precursor lesion to carcinoma, is currently recommended for patients with UC, but the approach to patients with CCD is less standardized.<sup>2</sup> As a consequence of these

various considerations, pathologists are under greater pressure than was the case of a few years ago to distinguish UC and CCD in biopsy and resection specimens. This chapter presents pathologic findings that can be helpful in this differential diagnosis.

## DEFINITION OF IDIOPATHIC INFLAMMATORY BOWEL DISEASE

Inflammatory diseases of the bowel, with the term used in a generic sense, include a large group of diseases of the small and large intestine in which inflammation has a pathogenetic role. The etiologies of inflammatory diseases of the bowel thus include infectious agents, ischemia, irradiation, toxic materials, and a variety of other causes,<sup>3</sup> as discussed in Chapter 2. Idiopathic IBD refers to UC and CD. The first principle in the diagnosis of UC and CCD is that inflammatory diseases of the bowel that are not idiopathic IBD must be excluded. Clinical history, physical findings, laboratory results, and radiographic features, as well as pathologic findings, are considered in patient diagnosis. Recognition that UC and CD are largely diagnoses of exclusion is essential so that patients with inflammatory diseases of the bowel for which specific therapy is available are treated appropriately. Treatment of some forms of inflammatory diseases of the bowel, such as infectious colitis, with the nonspecific anti-inflammatory drugs

used for idiopathic IBD can have disastrous consequences for the patient. Therefore, consideration of inflammatory diseases of the bowel other than idiopathic IBD is the important first step in evaluating biopsy and resection specimens.

## **ULCERATIVE COLITIS AND COLONIC CROHN'S DISEASE IN RESECTION SPECIMENS**

### **LABORATORY PROCEDURES FOR RESECTION SPECIMENS**

Accurate diagnosis of UC and CD in resection specimens often depends on accurate documentation of the anatomic distribution of the pathologic findings. As a result, a standardized procedure for examining resection specimens is strongly recommended for surgical pathology laboratories. A number of such procedures have been described.<sup>4,5</sup> In our laboratory, the resection specimen is brought for processing as soon as possible after removal from the patient. The specimen is then oriented in anatomic position for opening. If the surgeon does not mark the splenic and hepatic flexures, these landmarks can sometimes be identified at either end of the omental attachment to the transverse colon or by the curvature of the colon produced by the mesocolon. The colon is opened along the anterior free taenia, and any small bowel is opened along the anterior aspect of the mesenteric border. The specimen is then stretched slightly and pinned out flat in anatomic position on a 24 × 20 × 2-inch sheet of Styrofoam. The Styrofoam is inverted and floated in a 25 × 21 × 15-inch flat pan (Belart, Pequannock, NJ) containing neutral buffered formalin for overnight fixation of the specimen. Although this fixation procedure is complicated by regulatory requirements to reduce exposure of laboratory personnel to formalin fumes, it remains an important first step for evaluation of resection specimens.

After overnight fixation, the specimen is rinsed thoroughly in running water and photographed. A low-power view of the entire specimen as well as close-up photographs of areas of particular interest are included. Such photographs are often essential for documentation of findings. Photographs of fresh specimens are generally avoided because of light reflection and drying under flood lights as well as rolling of and leakage of blood from unfixed cut edges.

Gross description complements the gross specimen photographs. The anatomic structures in the specimen are noted and measured. Abnormal mucosa, bowel wall, and serosa or pericolon and perirectal soft tissue are described, and their anatomic locations are noted. Tissue for histopathologic sections is then removed from the resection margins, anatomic landmarks, areas of abnormality, random sites at 10- to 20-cm intervals throughout the length of the specimen, and representative lymph nodes. Each tissue block is labelled with a designation and described as to its source in the gross description. In addition, the site of each block is drawn on extra copies of the specimen photographs, which are retained in the laboratory records. The salient histopathologic findings in the various areas are briefly noted in a paragraph of description included in the surgical pathology report.

The goal of systematic specimen processing is to allow accurate reconstruction of the findings for diagnosis. Documentation of the anatomic distribution of histopathologic findings is often critical for correct diagnosis of difficult cases, as is discussed below.

The surgical pathology report includes the organs and structures in the resection specimen, the type of operation, the classification of the idiopathic IBD, the site of predominant involvement, and any complicating features. A representative report would be: "Terminal ileum, cecum, appendix, colon, rectum, and anus (total proctocolectomy with ileostomy): Active ulcerative colitis predominantly involving the left and transverse colon. Negative for tumor and dysplasia."

**Table 1-1. Comparison of Ulcerative Colitis and Crohn's Disease Involving the Colon: Gross Pathology in Resection Specimens**

Features	Ulcerative Colitis	Colonic Crohn's Disease
Distribution of gross abnormalities		
Continuous involvement	+++	-/+
Distal predominance	+++	-/+
Rectal involvement	+++	+
Total colonic involvement	+	-/+
Discontinuous, segmental involvement ("skip lesions")	-/+	+++
Right colonic predominance	-/+	+
Relative rectal sparing	-/+	+
Terminal ileal involvement	-/+	+
Anal involvement	-/+	+
Character of colonic mucosal abnormalities		
Loss of mucosal folds	+++	+
Diffuse granularity	+++	+
Prominent vascularity	+++	-/+
Numerous inflammatory polyps	+	-/+
Discrete ulcers	-/+	+++
Serpiginous ulcers	-/+	+
Linear, longitudinal ulcers	-/+	+
Fissuring ulcers	-/+	+
"Cobblestone" appearance	-/+	+
Aphthoid ulcers	-/+	+
Prominent edema	-/+	+
Character of bowel wall abnormalities		
Shortening of colonic length	+++	+
Thickening	-/+	+++
Stricture	-/+	+
Serositis and adhesions	-/+	+
Fistula	-/+	+

+++ = usually present; + = sometimes present; -/+ = usually absent

#### GROSS PATHOLOGY OF ULCERATIVE COLITIS AND CROHN'S DISEASE INVOLVING THE COLON

The pathologic findings in patients with UC and CCD are dynamic. The findings are influenced by a variety of factors, including severity of activity, duration of disease, and therapy prior to resection. As a result, the pathologic findings of UC or CCD show striking variability among individual patients. In addition, the type of resection determines the type of specimen available for examination: obviously, pathologic findings in the rectum and anus cannot be assessed in an abdominal colectomy specimen, whereas

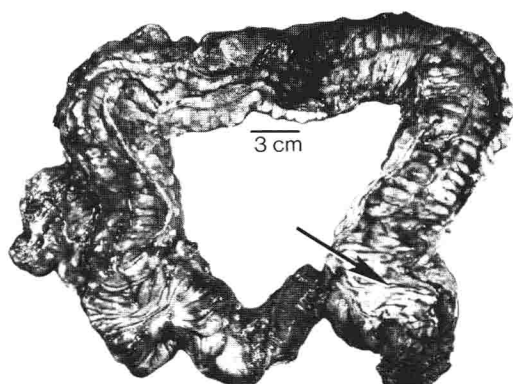
a total proctocolectomy specimen allows pathologic evaluation of the entire large bowel.

The gross pathology<sup>4, 6-8</sup> of *typical* UC and CCD is summarized and compared in Table 1-1. Problem areas are addressed in the later section entitled "Colitis of Indeterminate Type."

UC is characterized by the continuous nature of the gross abnormalities (Fig. 1-1), although sometimes with variability in the severity. Distal predominance of the abnormalities with involvement of the rectum (proctitis) is a usual feature, although there may be exceptional cases with relative sparing of the rectum.<sup>9</sup> In some specimens, involvement of the entire colorectum is



**Fig. 1-1.** Long-standing ulcerative colitis in a specimen from a total abdominal colectomy with rectal mucosal stripping and ileoanal pull-through procedure. The entire left and transverse colon show smooth featureless mucosa without folds. The right colon is less involved, as some mucosal folds remain. A nodular area of high-grade dysplasia is present in the proximal transverse colon (see Ch. 4).

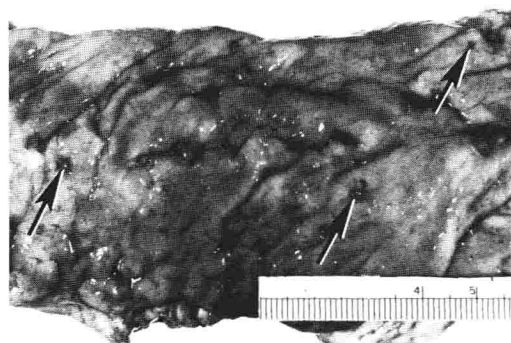


**Fig. 1-2.** Crohn's disease involving the colon in a specimen from a total proctocolectomy. The distal ascending, transverse, and proximal left colon show linear longitudinally oriented ulcers. The cecum and rectum (arrow) are relatively spared.

evident, whereas in other cases the proximal colon is uninvolved. The terminal ileum is normal in the majority of UC resection specimens. Abnormality of the terminal ileum, when present, is usually associated with a rigidly dilated and incompetent ileocecal valve. The incompetence appears to allow colonic contents to backflow a short distance into the terminal ileum, leading to "backwash ileitis." Appendiceal involvement occurs commonly in UC, often in the absence of proximal colonic involvement.<sup>10</sup> Anal abnormalities occur in a minority of specimens and, when present, usually consist of excoriation and acute fissures.

In contrast to UC, the distribution of gross abnormalities in CCD is typically discontinuous or segmental, with "skip lesions" separated by uninvolved colon. The right colon is sometimes the site of predominant involvement, and the rectum is spared in a sizeable proportion of specimens (Fig. 1-2). The terminal ileum is involved in some specimens, often with long lengths affected. The appendix is often abnormal. The anal region is sometimes the site of multiple fistulas, ulcers, chronic fissures, and edematous skin tags. Anal involvement, however, seems less common in the United States than in Great Britain.

In addition to the differences in distribution



**Fig. 1-3.** Discrete ulcers in Crohn's disease involving the colon. The central portion of the figure shows an area of irregular ulceration. Aphthoid ulcers surrounded by relatively uninvolved mucosa are also present (arrows).

of gross abnormalities, the character of the lesions also differs in UC and CCD. The colonic mucosa grossly involved by UC usually shows loss of folds associated with generalized granularity, producing "featureless mucosa" (Fig. 1-1). With activity, vascularity is prominent and the mucosa is friable. Ulceration, when present, is within otherwise abnormal mucosa. Numerous inflammatory polyps are present in some specimens.

The characteristic mucosal features of CCD are discrete ulcers surrounded by otherwise grossly uninvolved mucosa (Fig. 1-3). The configuration of the ulcers varies greatly. Ulcers in CCD may be serpiginous, or may be linear and longitudinally oriented, described as "rake" or "railroad track" ulcers (Fig. 1-2). The ulcers may produce sharp crevices into the bowel wall, termed fissuring. Interconnecting ulcers surrounding edematous areas of mucosa result in a "cobblestone" mucosa. Tiny, punched-out ulcers in otherwise grossly normal mucosa (Fig. 1-3) are referred to as "aphthoid" ulcers, because of their similarity to oral aphthous ulcers. Striking mucosal and submucosal edema is sometimes seen in CCD.

In typical UC, the colonic length is reduced, but the bowel wall itself is usually of normal thickness. In contrast, thickening of the bowel wall is the rule in CCD, and the colonic length is not usually reduced. Strictures, serosal inflammation sometimes associated with adhesions, and fistulas to other areas of bowel or to other structures such as skin or urinary bladder are seen in typical CCD.

#### HISTOPATHOLOGY OF ULCERATIVE COLITIS AND CROHN'S DISEASE INVOLVING THE COLON

As described in the preceding discussion of laboratory procedures, the anatomic distribution of pathologic findings is often extremely helpful for accurate diagnosis. The distribution of histopathologic abnormalities generally corresponds to that of the gross abnormalities summarized in Table 1-1. The character of the histopatho-

logic abnormalities in UC and CCD is summarized and compared in Table 1-2.

The granular mucosa devoid of folds in UC typically shows atrophy. Destruction of crypt architecture with shortening and distortion of those crypts that remain is characteristic of UC (Fig. 1-4A). Villous transformation of the mucosal architecture is sometimes present. The lamina propria usually shows increased numbers of chronic inflammatory cells, including plasma cells, eosinophils,<sup>11</sup> and lymphocytes. Active UC is characterized by crypt epithelial infiltration by neutrophils. Destruction of crypt epithelium with accumulation of fibrinoinflammatory exudate in the crypt lumen produces the crypt abscess. Dilated congested blood vessels are prominent with active inflammation, and the epithelium typically shows reduced numbers of goblet cells and reduced quantity of mucin in the remaining goblet cells. Chronic inflammation of the lamina propria is greater with active than inactive disease. Paneth cell metaplasia of the epithelium and thickening of the muscularis mucosae are sometimes seen. Erosions and ulcers, when present, arise within abnormal mucosa. Multinucleated giant cells, usually representing foreign body reaction in areas of ulceration or erosion, may be seen occasionally.

A striking increase in the number and size of lymphoid nodules with prominent germinal centers occurs in the rectum of some specimens. This lymphoid proliferation is referred to as *follicular proctitis* and leads to distortion of remaining crypts (Fig. 1-5). Inflammatory polyps are common in UC and are characterized by proliferation of distorted glands and inflamed granulation tissue, frequently on a stalk of mucosa and submucosa. The proportion of epithelial and stromal structures is highly variable, as some inflammatory polyps are composed only of granulation tissue while others have numerous glands. Finger-like "filiform" inflammatory polyps occur in some cases; the normality of the mucosal architecture in this form of inflammatory polyp is striking. The grossly normal mucosa of the proximal colon in resection specimens of UC without apparent total colonic involvement is commonly abnormal on histopa-

Table 1-2. Comparison of Ulcerative Colitis and Crohn’s Disease Involving the Colon: Histopathology in Resection Specimens

Features	Ulcerative Colitis	Colonic Crohn’s Disease
Distribution of histopathologic abnormalities See Table 1-1		
Character of mucosal abnormalities		
Atrophy with prominent crypt loss and distortion	+++	+
Diffuse chronic inflammation	+++	+
Prominent vascularity	+++	-/+
Crypt abscesses	+++	+
Depleted epithelial mucin	+	-/+
Paneth cell metaplasia	+	-/+
Thickened muscularis mucosae	+	-/+
“Follicular proctitis”	+	-/+
Numerous inflammatory polyps	+	-/+
Noncaseating epithelioid cell granulomas	-/+	+
Granulomatous inflammation	-/+	+
Fissuring ulcers	-/+	+
Aphthoid erosions or ulcers	-/+	+
Focal active inflammation	-/+	+
Clusters of lymphocytes	-/+	+
Character of bowel wall abnormalities		
Widened, edematous submucosa	-/+	+++
Lymphangiectasia	-/+	+++
Submucosal inflammation and lymphoid aggregates	+	+++
Submucosal fibrosis	-/+	+
Muscularis propria and pericolonc inflammation with lymphoid aggregates (“transmural”)	-/+	+++
Noncaseating epithelioid cell granulomas in bowel wall and lymph nodes	-/+	+
Fibrous stricture	-/+	+
Fistula with granulation tissue	-/+	+
Neural hyperplasia	-/+	+
Vasculitis	-/+	+

+++ = usually present; + = sometimes present; -/+ = usually absent

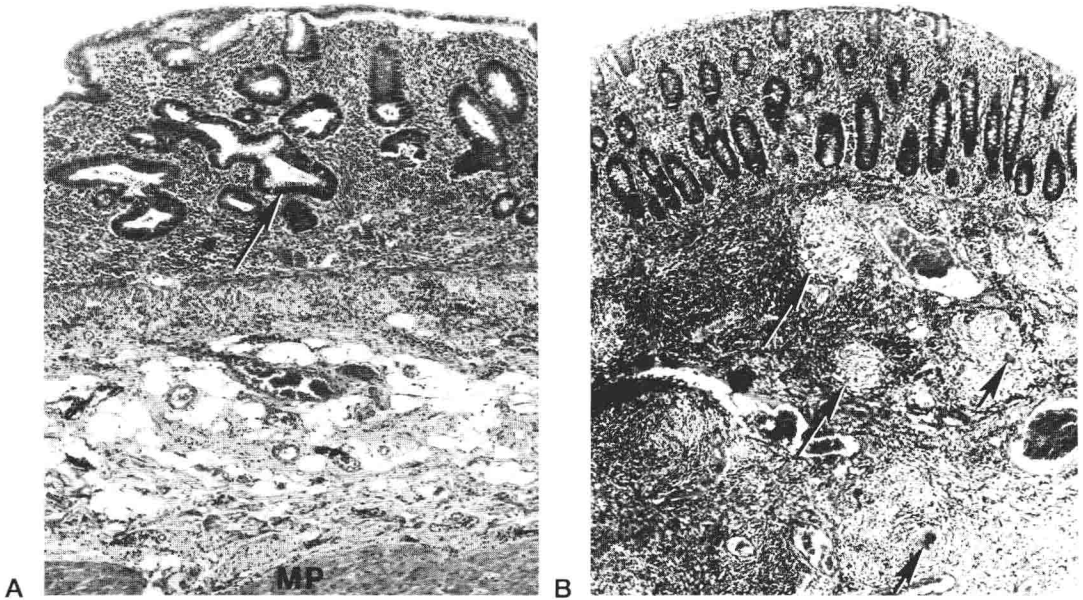
thologic examination: chronic inflammation of the lamina propria and increased epithelial mitotic figures are usually present.

In CCD, the noncaseating epithelioid cell granuloma is the characteristic finding (Fig. 1-4B). Granulomas are found in a majority of cases when a diligent search is carried out. Well-formed granulomas have a demarcated aggregate of epithelioid cells with abundant pink cytoplasm. Multinucleated giant cells formed by fusion of the epithelioid cells are often present in the aggregate. A cuff of chronic inflammatory cells frequently surrounds the accumulation of epithelioid cells. Necrotizing or confluent granu-

lomas are very uncommon and should raise the question of tuberculosis and yersiniosis. Granulomatous inflammation or “microgranulomas” composed of ill-defined collections of chronic inflammatory cells with a heavy admixture of epithelioid cells can also be seen commonly with CCD.

The histopathologic features of the ulcers in CCD are sometimes distinctive. Fissuring ulcers show cleft- or crack-like penetration of the mucosa. The aphthoid erosion or ulcer typically occurs over a pre-existing lymphoid nodule and is surrounded by uninfamed mucosa. Crypt abscesses are common in CCD, but crypt architec-

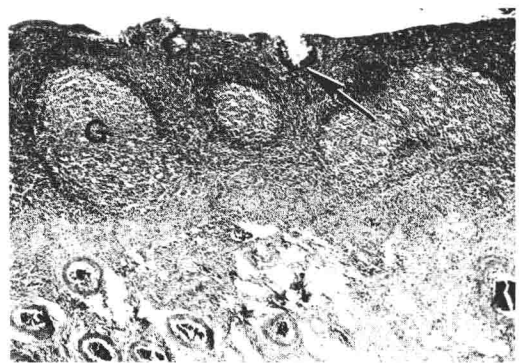




**Fig. 1-4.** Comparison of histopathology of ulcerative colitis and Crohn's disease involving the colon. (A) The mucosa in this specimen of low-grade active ulcerative colitis shows loss of crypts with bizarre configuration (arrow) of those remaining. Epithelial mucin is markedly reduced. The lamina propria shows diffuse chronic inflammation that extends into the superficial submucosa. The deep submucosa and muscularis propria (MP) are uninvolved. (B) The mucosa in this specimen of active Crohn's disease shows preservation of crypt architecture and epithelial mucin. The lamina propria shows diffuse chronic inflammation that extends into the deep submucosa. Multiple noncaseating epithelioid cell granulomas (long arrows), some with multinucleated giant cells (short arrows), are present. (H&E,  $\times 50$ .)

ture and epithelial mucin content are frequently maintained (Fig. 1-4B). In addition, crypt abscesses may show contiguous granulomatous inflammation (Fig. 1-6) or granulomas. Diffuse or patchy chronic inflammation may occur in the lamina propria. Focal active inflammation of rectal mucosa with crypt epithelial infiltration by neutrophils, surrounded by a cuff of inflammatory cells amid otherwise uninfamed mucosa, is characteristic of CCD. Clusters of lymphocytes, particularly near the bases of crypts, are sometimes seen but should not be confused with lymphoid nodules.

Histopathologic findings in the bowel wall are particularly helpful in the differential diagnosis of UC and CCD. The submucosa in UC may show inflammation and lymphoid aggre-



**Fig. 1-5.** "Follicular proctitis" in ulcerative colitis. The lamina propria of the rectum contains confluent hyperplastic lymphoid nodules with enlarged germinal centers (G). Crypts (arrow) are compressed and distorted. (H&E,  $\times 40$ .)