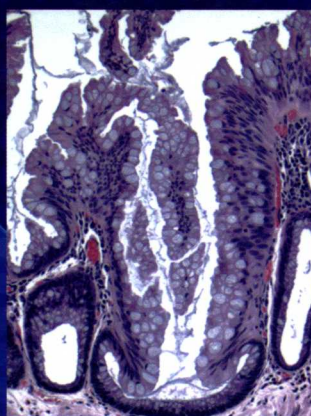
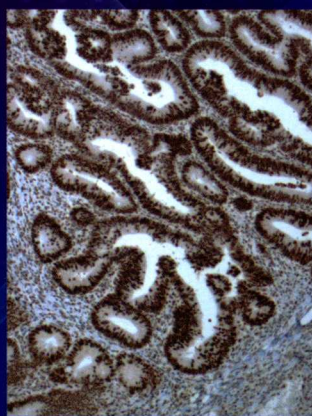


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LEWIN, WEINSTEIN AND RIDDELL'S  
GASTROINTESTINAL  
PATHOLOGY AND ITS  
CLINICAL IMPLICATIONS

SECOND EDITION



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Health

VOLUME 2

Lewin, Weinstein, and Riddell's

# Gastrointestinal Pathology and Its Clinical Implications

SECOND EDITION

VOLUME II

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Lewin, Weinstein, and Riddell's

# Gastrointestinal Pathology and Its Clinical Implications

SECOND EDITION

VOLUME II



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## **Dedication**

### **Robert Riddell**

*To my immortal parents Harry and Joyce.*

*To my wife Hala, who wrote the gastritis chapter, contributed to numerous others and whose constant love, support, and encouragement is greatly appreciated.*

*To Mark, Juliet, and Mike, and grandchildren Alannah, Natalie, Paisley, and Eli, all of whom we are so proud of and who give us more pleasure than they will ever know.*

### **Dhanpat Jain**

*To my teachers who always showed me the right path.*

*To my parents Milap Chand and Biraj who always led me to the right path.*

*To my wife Shilpa without whom nothing would have been possible.*

*To my daughters Nimisha and Anisha for whom it was all worthwhile.*

### **Charles N. Bernstein**

*I dedicate any accolades I receive for the hard work put into this book to Evelyn, Matthew, and Lexie Bernstein. They provide me with the constant entertainment, support, and love that reminds me constantly of what is really important in life.*

### **Sushovan Guha**

*I would like to dedicate this to my wife Sarmistha, to our children Siddarth and Shivani, to my father Sukumar, and to my mother Dolly for their collective wisdom, unflinching support, utmost dedication, and unbridled joy. Also I would like to offer my deepest gratitude to Fred, Klaus, and all the great teachers that I had at UCLA. Finally I would offer my thanks to all the patients that motivated me to be a good doctor.*

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The decision to write a textbook of pathology coupled with clinical implications came primarily because of the increasing interdependence of the pathologist and clinician in the investigation and management of gastrointestinal disorders where modern gastrointestinal pathology plays a dynamic role. In many instances, it is no longer sufficient for the pathologist to simply make a morphological diagnosis. Conversely, we hope that clinicians with gastroenterology interests will view this book as a requisite companion for a general textbook of gastroenterology.

Pathologists can achieve their full potential by understanding the clinical scenarios in which they are playing a part and by appreciating the effect of their decisions in clinical management. We hope that the clinicians who read this book will more readily maximize the information they obtain from gastrointestinal biopsies through an understanding of the indications, by appreciating the need for providing relevant clinical information, which specific questions to ask the pathologist, and also to understand when biopsies are likely to be of limited value.

We have done our best not to perpetuate some of the myths of pathologist uncritically. In areas where issues are controversial, we have tried to state this; we have also frequently offered our own "solutions" to these problems in situations that lack data on which they can satisfactorily be based.

We hope that the greatest criticism that can be leveled against this book is that it assumes that each gastroenterologist, whether medical or surgical, adult or pediatric, has an interested pathologist with whom to work and vice versa. We know that this is frequently not the case. However, by appreciating the necessity of such a working relationship for the best in patient care, we hope that pathologists and clinicians will see the overwhelming benefits of this relationship and will try to foster it.

*Klaus J. Lewin  
Robert H. Riddell  
Wilfred M. Weinstein*

The first edition of this book was published over 20 years ago in 1993. The driving force behind that book came from Klaus Lewin, and was that, to do pathology well, pathologists have to understand the clinical implications of their diagnoses, which explains the title of the book. At the same time clinicians need to understand when to biopsy, where to biopsy, which questions to ask, as well as which cannot be answered by pathology, and what to expect from the pathologist. The book was thus written as a guide for pathologists and clinicians for circumstances that they have to deal with on a day-to-day basis, and also as a resource for any unusual lesion, for difficult diagnoses, and for those issues where good guidelines are lacking. It also explained the unconventional authorship of the book, especially having Wilfred (Fred) Weinstein as both an author and clinical contributor. The book tried to provide answers for such situations and gave rationale for what we did and why, sometimes finding that we did them differently ourselves. Teaching new gastroenterologists where to sample and why and also to teach them how to interpret the pathologist's reports, which are highly variable themselves, is a challenging task. Pathologists can be just as guilty of providing defensive and unhelpful descriptions that are not easily understood and leave the clinician trying to guess how to interpret the findings of the report, especially when told that "clinical correlation is required"—in practice the statement that tends to be a hedge for "I have no idea why you took these biopsies or what I should be looking for."

Most will not be aware that a second edition of this book was well underway in 2000 when it gradually became clear that Klaus was unable to continue. He died a few years later in 2005, and we miss him and his sense of both the important and his sense of the ridiculous, tremendously. However there was

always encouragement from friends, colleagues, and strangers alike to bring forth a new edition. With much encouragement, it began to take shape when Dr. Dhanpat Jain from Yale accepted the Co-Editorship. Fred Weinstein, the third member of the team, decided that the book would not really be the same without Klaus; he did suggest that two of "his boys" Charles N. Bernstein (now in Winnipeg) and Sushovan Guha (at MD Anderson at that time) could fill in his shoes. They agreed to become the "clinical editors" and it has been an absolute pleasure to work with them.

Our goal for the second edition was to keep the philosophy similar to the first edition, the challenge being to incorporate the explosion of knowledge in molecular pathology, cancer biology, and genomics that continues to change our field on a daily basis, and to keep this all relevant for the practicing pathologists and clinician. Since the last edition, images have changed from B&W and "Kodachromes" to digital, so the challenge was to replace these figures and endoscopic photomicrographs. The number of tables and management algorithms has also increased substantially. While adding new material, we were also conscious not to omit important historical details, the challenge being to keep the book to a reasonable size. We have also tried to keep the book relevant on a global level, and international experts helped to write some of the chapters; indeed, it could not have happened without them. We hope that we have been able to fulfill the purpose of the book as a resource not only for practicing and academic pathologists, but also for those in training in pathology and gastroenterology, and our clinical colleagues of all stripes—endoscopists and imagers, gastroenterologists, and surgeons.

**Robert Riddell  
Dhanpat Jain**



So many people have been involved in ensuring that this book becomes a reality that it is difficult to know where to begin. Family and spouses inevitably are first on the list for their huge support and for bearing with our relative absence during this time for the cause.

We thank our clinical editors Drs. Charles N. Bernstein and Sushovan Guha who went through each chapter and were wonderfully responsive in carrying out their roles in a very efficient manner, provided illustrations where needed, and made our lives much easier. They have, in turn, expressed their thanks for the opportunity.

We thank all our authors, who not only contributed their respective chapters but allowed us to “bend” their chapters out of recognition to avoid the stylistic issues that can arise with multiple authors.

We are grateful to our colleagues and friends at each institution for their encouragement, for lending their material to be used, moral support, and valuable advice. We are deeply indebted to our numerous trainees and pathology assistants who took excellent gross photographs, which are an invaluable resource for teaching and worth their weight in gold. We owe a lot of gratitude to our support staff at Photographics division, Yale University, Department of Pathology for their services.

Lastly, we thank the numerous people with Lippincott Williams & Wilkins, but especially Kate Marshall whose unmerciful cajoling helped to get this done as quickly as was possible, and also the expertise of Satheesh Velayutham and his team for their help with the page proofs.

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Lewin, Weinstein, and Riddell's

# Gastrointestinal Pathology and Its Clinical Implications

SECOND EDITION

VOLUME II



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## INTRODUCTION

Over a century ago, two major things put the appendix in the public eye. The first was on the medical front where the appendix was firmly on the map as a cause of disease, culminating in a variety of books written on the appendix, its diseases, and its surgical removal in the decades either side of 1900. The ability to safely remove appendices is attributable to the development of anesthesia and subsequently infection control pioneered by the development of the germ theory by Louis Pasteur, and its subsequent application to surgical sterility by Joseph Lister. Probably the largest treatise on the Appendix was the 800 page book with 400 illustrations by Howard A. Kelly and Elizabeth Hurdon published in 1903, but now available online. This book appears to document the first known recorded case of a disease of the appendix, attributed to Mestivier in 1759 in France, where much of the medical writing was done. The first recorded case of perforated appendix outside of France was attributed to Parkinson in the United Kingdom in 1812. Interestingly, the “big four” infectious causes of appendicitis were attributed to tuberculosis, typhoid, ameba, and actinomycosis.

The social acceptance of appendicitis occurred in 1902 with the delay in the coronation of King Edward VII in England in 1902 because of his appendiceal abscess, after which it became fashionable and very acceptable to have appendicitis!

Appendectomy (appendicectomy) remains one of the most commonly performed operations even though the means of removing it is dynamic and—can be open, laparoscopic, or even transgastric or transvaginal. It has been estimated that more than 280,000 appendectomies are performed in the United States every year, and appendiceal tumors are noted in 0.9% to 1.4% of these.<sup>1,2</sup> However, in practice, pathology that affects subsequent patient management is found in

only about 1% to 2% of appendices.<sup>3,4</sup> Diseases such as endometriosis, sometimes worms, and occasionally intraperitoneal tumors found in resected appendices account for some of the others. Despite the application of laparoscopic appendectomies and early use of imaging in the diagnosis of appendicitis, over the last three decades the rates of perforated appendicitis have stayed similar, in contrast to nonperforated appendices.<sup>1</sup>

Despite the large number of resected appendices, there remains a surprisingly large number of problems regarding the pathology of the appendix and its implication for management and prognosis. Problems still include the causes of acute appendicitis and why it has been so difficult to identify major causes, especially those associated with infection, which, other than obstructive causes, have to be the primary cause of acute appendicitis. Conversely, the frequency with which normal resected appendices can be expected to be found in patients whose appendix is removed for symptoms that might be attributed to the appendix seems to be less of an issue, largely because in many centers, imaging has helped hugely in preoperative diagnosis, so that unexpected appendiceal disease is relatively uncommon.

An infrequent but troublesome issue continues to be that of terminology for appendiceal tumors. A major change since the previous edition is that the proximal margin (base) of the appendix is now usually both identified and sectioned, so that adequacy of resection can be evaluated, if a tumor is identified incidentally. The greatest problem is the finding of a tumor either grossly or incidentally on microscopy, its clinical implications, and how it should be managed.

Problems occur in three major areas

1. mucinous tumors and whether all of them are neoplastic, and the risk of pseudomyxoma if they have perforated;
2. the tumors called *goblet cell carcinoids (microglandular carcinoma)*, whether they are really carcinoids,

carcinomas, or a spectrum that can include both, and how they should be managed, especially in terms of additional surgical treatment; and

3. the circumstances under which serious consideration should be given to right hemicolectomy following appendectomy.

It should also be noted that polyps at the appendiceal orifice cannot be removed by laparoscopic appendectomy as the margin of excision is distal to the polyp. Gastroenterologists sending such patients for surgical excision, and surgeons carrying out appendectomy for appendiceal tumors, need to be aware of this limitation. The appendiceal orifice, and therefore at least a cuff of cecum need to be removed.

## FUNCTION OF THE APPENDIX

This has been questioned, and it is possible that it acts as a reservoir to repopulate the large bowel flora. The presence of an appendix may reduce recurrences of infections such as that of *Clostridium difficile*, although it also seems possible that once *C. difficile* is in the appendix it may act as a reservoir. Lower rates of appendectomy have been found in patients having had *C. difficile* infections.<sup>5-8</sup> Conversely it has also been recognized that ulcerative colitis is often accompanied by appendiceal disease, which may be repopulating the large bowel with inappropriate flora.<sup>9</sup> Some data suggest that appendectomy both prevents ulcerative colitis, or if carried out during the course of the disease, may reduce the severity of recurrences, and the amount of medication required.<sup>10</sup> Indeed trials are underway to determine if appendectomy can be used therapeutically in ulcerative colitis.

It has been suggested that the appendix may be the bursa equivalent governing B-cell regulation; however, patients with appendiceal agenesis have yet to be described with immune deficits or a predisposition to tumors.

## THE NORMAL APPENDIX

### Normal Anatomy, Development, and Gross Appearance

The appendix and cecum are first apparent as an outgrowth from the primitive midgut at the end of the fifth gestational week. The proximal quarter of this outgrowth forms the cecum, and the distal three-quarters is destined to become the appendix, rapidly tapering down in the process. Toward the end of



**Figure 15-1.** Normal appendix, the orifice of which in this patient is elliptical and about 2.5 cm from the ileocecal valve toward the cecal pole (arrow). The remainder of the appendix and mesoappendix can be seen emerging from behind the cecum, to the top left. The ileocecal valve itself has a Y-shaped orifice and modest lipohyperplasia.

intrauterine life the lateral wall of the cecum grows at a greater rate than the medial wall, so that the appendiceal orifice appears to migrate up the medial cecal wall and ultimately comes to lie immediately beneath the ileocecal valve.

The appendix therefore arises from the medial wall of the cecum and averages 6 to 7 cm in length in the adult (Fig. 15-1). In infants it may be as small as 2 cm, but occasionally it reaches 15 cm or more in length. The current record of longest appendix is 26 cm (Guinness Book of Records). In the adult, the average diameter is approximately 0.7 cm. It is easily found by following the taeniae coli of the large bowel, as all three terminate together at the base of the appendix, where they unite to invest the appendix completely with a full longitudinal muscle coat. In the adult the appendiceal orifice is approximately 2.5 cm below the ileocecal valve (Fig. 15-1), and from here its position may vary. Most commonly, it lies posterior to the cecum or ascending colon; the next most frequent site is overhanging the pelvic brim. In this location it may directly impinge on the bladder, with resulting dysuria if inflamed. It may also lie at the side of the cecum, either in front of or behind the terminal ileum, or it may lie directly on the psoas muscle. The appendix may rarely be found in a subhepatic location, primarily because incomplete rotation of the bowel results in failure of descent of the cecum. Both the cecum and the appendix may therefore be in a subhepatic location. In patients with situs inversus the appendix is found in the left iliac fossa.

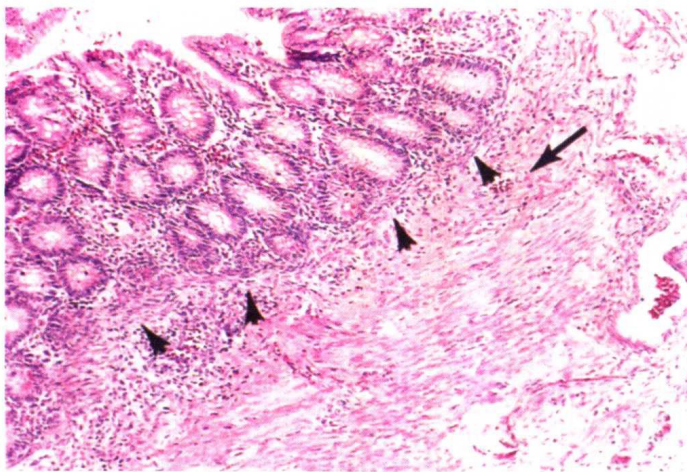
The appendiceal orifice has no uniform shape when viewed from within the cecum; frequently, a small flap of mucosa may partially overhang its orifice (Fig. 15-1). The mesoappendix consists predominantly of fat but contains the appendiceal blood vessels and occasionally small lymph nodes. Its length tends to

govern the mobility of the appendix and therefore, to a certain extent, its final position. The vascular supply of the appendix is from the posterior cecal branch of the ileocolic artery, itself a terminal branch of the superior mesenteric artery. The venous return is into the superior mesenteric vein and then into the portal vein. Occasional lymph nodes may be present in the mesoappendix which then drain to the pericolic and superior mesenteric nodes.

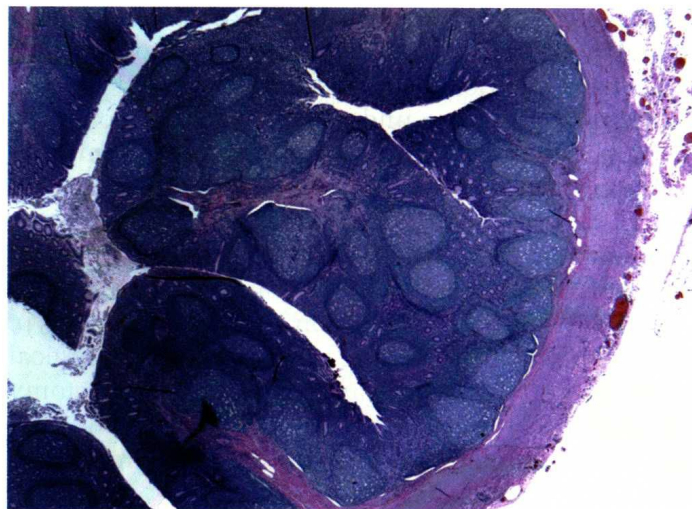
## Histology

The mucosa of the appendix is primarily of the large bowel type, although it has a much heavier lymphoid component. In the neonate, however, there is very little lymphoid tissue and almost no cells in the lamina propria (Fig. 15-2). Within a few months, the amount of lymphoid tissue increases rapidly to form lymphoid nodules with germinal centers, and by puberty these are the dominant features in the appendix (Fig. 15-3). After puberty they gradually regress, and in the elderly they may disappear. It remains questionable as to whether lymphoid tissue can become exuberant enough to cause luminal obstruction with secondary obstructive acute appendicitis, but it seems likely. Interestingly, there are no objective criteria for lymphoid hyperplasia in the appendix (like elsewhere) so it remains a subjective diagnosis. However it is always worth considering infective causes, which in children should include adenovirus infection (see subsequently in this chapter).

The appendiceal epithelium is of the typical large bowel type, consisting primarily of absorptive and goblet cells and occasional endocrine cells, primarily



**Figure 15-2.** Neonatal appendix. There is relatively little lymphoid tissue compared to the usual nodules of lymphoid tissue that develop rapidly. Note also the muscularis mucosae, which are only a few fibers thick immediately beneath the base of the glands (*arrowheads*); the thin, fibrotic submucosa, which lacks the fat seen later in life (*arrow*); and the prominent muscularis propria external to the submucosa.



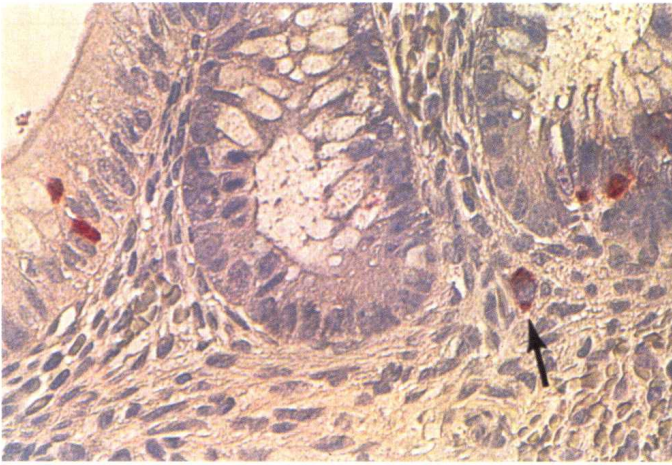
**Figure 15-3.** Typical nodular lymphoid tissue with well-formed germinal centers having a corona of small lymphocytes polarized toward the lumen.

enterochromaffin (EC) cells (Fig. 15-4). Free endocrine cells may also be present in the lamina propria (Fig. 15-5).<sup>11</sup> These lamina propria endocrine cells contain serotonin and are intimately associated with nerves; they appear to be far more frequent in countries with a high incidence of acute appendicitis compared with low-incidence countries,<sup>12</sup> although it is unclear how this situation relates pathogenetically to acute appendicitis. One study suggests that these cells are lost in infants with Hirschsprung's disease along



**Figure 15-4.** Mucosa of normal appendix immunostained with chromogranin A to show the endocrine cells, most of which are enterochromaffin cells.



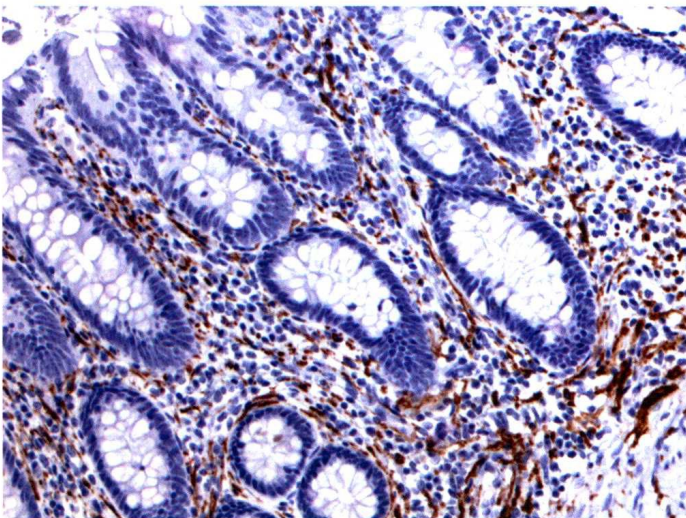


**Figure 15-5.** Individual free endocrine cell in the lamina propria, as demonstrated by chromogranin A immunoreactivity (arrow).

with the nerves that are usually intimately associated with them.<sup>13</sup> Surprisingly, Paneth cells are rare in the appendix even though they are not uncommon in the cecum. The epithelial cells immediately over the lymphoid follicles often have fewer goblet cells and enlarged nuclei, and are reminiscent of the microfold cells in the small intestine.

The lamina propria in the adult contains a predominance of immunoglobulin A–producing plasma cells. A smattering of other cells are present, including histiocytes, which tend to be relatively superficial, occasional eosinophils. Numerous nerves are also present in the lamina propria (Fig. 15-6), and these include calretinin immunoreactive nerves (Fig. 15-7B).

The muscularis mucosae may be broken regularly by the lymphoid follicles and may virtually disappear in these areas. The submucosa is without fat in the neonate; submucosal fibrosis uniting the muscularis mucosae and propria is therefore normal in children



**Figure 15-6.** Nerves in the lamina propria of the appendix demonstrated with calretinin.

and should not be interpreted as evidence of previous appendicitis (Fig. 15-2).

The muscularis propria contains a complete circular and longitudinal muscle coat. As the latter is formed from fusion of all three taeniae coli, unlike the remainder of the large bowel, it is of uniform thickness throughout.

The muscularis propria of the appendix is richly innervated (Fig. 15-7A). The myenteric plexus is unusual in the appendix, and although standard sources indicate it is as elsewhere in the bowel, that is not our experience. The myenteric plexus is sometimes identifiable, but more usually it is rudimentary, with ganglion cells being scattered almost randomly and sometimes diffusely in both the internal circular and longitudinal muscle, rarely being almost in the subserosa (Fig. 15-7A). Many of the neurons and nerves are calretinin immunoreactive (Fig. 15-7B). Further, interstitial cells of Cajal (ICCs) are also diffusely distributed throughout both muscle layers (Fig. 15-7C).<sup>14,15</sup> In right hemicolectomies, especially those carried out for complex masses involving the appendix, the issue may be whether sections come from the large bowel or the adjacent appendix. The distribution of ganglion cells and the myenteric plexus (or lack of it) is an easy way of telling them apart. Individual ganglion cells as well as clusters may be seen elsewhere in the appendix.<sup>16</sup> This becomes important in a patient with potential long-segment Hirschsprung's disease in whom the appendix is removed to see if ganglion cells are present. The atypical location of ganglion cells and lack of plexus may lead to a panicked consideration of conditions such as intestinal neuronal dysplasia and give a false impression of an abnormality in the distribution of ganglion cells rather than recognizing that this is normal. In the neonate, if ganglion cells are being sought as evidence for lack of Hirschsprung's disease, particularly on frozen section, nucleoli may be difficult to see and cytoplasm may not be well developed. Distinction from prominent endothelium depends on the orientation of the latter toward the lumen and the larger size of the ganglion cell (Fig. 15-8).

## ROUTINE PATHOLOGIC EXAMINATION OF THE APPENDIX

Examination of the appendix is primarily aimed at the diagnosis of acute appendicitis and identification of tumors (incidental or otherwise). Extreme care in sectioning of the appendix is needed when the appendix appears distended and a mucinous neoplasm is suspected. Standard practice is to bisect the tip longitudinally for a distance of about 2 cm and then