Radiology of Iatrogenic Disorders

Morton A. Meyers
Gary G. Ghahremani

Iatrogenic Gastrointestinal Complications

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Morton A. Meyers, M.D.
Professor and Chairman
Department of Radiology
School of Medicine
State University of New York at Stony Brook

Gary G. Ghahremani, M.D.
Professor and Chairman
Department of Diagnostic Radiology
Evanston Hospital-Northwestern University

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Series Editor

Morton A. Meyers, M.D.
Professor and Chairman
Department of Radiology
School of Medicine
State University of New York at Stony Brook
Long Island, New York 11794 U.S.A.

Volume Editors

Morton A. Meyers, M.D.

Gary G. Ghahremani, M.D.
Professor and Chairman
Department of Diagnostic Radiology
Evanston Hospital-Northwestern University
Evanston, Illinois 60611 U.S.A.

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Series Editor:
Morton A. Meyers, M.D.

Also in this series

Iatrogenic Thoracic Complications
Iatrogenic Pediatric Complications
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Dedicated to our wives
Bea and Zohreh
for their love, patience, and encouragement,
and to our children
Richard and Amy Meyers
Lilly and Susan Ghahremani

Series Editor's Foreword

The purpose of this series of volumes is to present a comprehensive view of the complications that result from the use of acceptable diagnostic and therapeutic procedures. Individual volumes will deal with iatrogenic complications involving (1) the alimentary system, (2) the urinary system, (3) the respiratory and cardiac systems, (4) the skeletal system and (5) the pediatric patient.

The term *iatrogenic*, derived from two Greek words, means physician-induced. Originally, it applied only to psychiatric disorders generated in the patient by autosuggestion, based on misinterpretation of the doctor's attitude and comments. As clinically used, it now pertains to the inadvertent side-effects and complications created in the course of diagnosis and treatment. The classic categories of disease have included: (1) congenital and developmental, (2) traumatic, (3) infectious and inflammatory, (4) metabolic, (5) neoplastic, and (6) degenerative. To these must be added, however, iatrogenic disorders—a major, although generally unacknowledged, source of illness. While great advances in medical care in both diagnosis and therapy have been accomplished in the past few decades, many are at times associated with certain side-effects and risks which may result in distress equal to or greater than the basic condition. Iatrogenic complications, which may be referred to as "diseases of medical progress," have become a new dimension in the causation of human disease.

A highly accurate index of the overall incidence of iatrogenic illnesses is difficult to establish, but there is little doubt that it approaches epidemic proportions in certain instances. The literature indicates that paramount causes include drugs and hospital-associated risks:

- Every year in the United States, up to one and a half million people—between 3 and 5 percent of all hospital admissions—are admitted primarily because of drug reactions. Once in the hospital, between 18 and 30 percent of all patients have a drug reaction. The length of their stay is about doubled as a result[1–3].
- In one study of a general medical unit over a twelve-month period, one-quarter of the 67 deaths in the unit were due to adverse drug reactions[3]. In acutely ill hospitalized patients, the drug-related death rate has been recently reported to be nearly one per thousand[4].
- Hospital-acquired infections occur in about one in 20 patients and there is approximately 25 percent excess mortality among patients with nosocomial bloodstream infections. About one-third of all infections seen in hospital practice are nosocomial in origin[5]. The incidence of postoperative wound infections is about 7.4 percent[6].
- It has been reported that one out of every five patients admitted to the medical service of a typical university teaching hospital suffers an iatrogenic episode, which is classified as moderate or severe in 40 percent. Over one-fourth of the episodes result from diagnostic and therapeutic procedures[7].
- Of all patients admitted to a multidisciplinary intensive care unit in one recent study[8], over 12 percent were admitted because of iatrogenic disease. Potentially avoidable therapeutic and technical errors accounted for half of these; the remaining adverse reactions that were determined to be unpreventable represent the risk-benefit ratio of a treatment compared with the natural history of the illness. Furthermore, once in a medical-surgical intensive care unit, patients are subject to often harmful adverse occurrences[9].
- Ten percent of hospital deaths are associated with a diagnostic or therapeutic

procedure which is considered a contributing, precipitating or primary cause of obitus[10].

This series is not intended to support or encourage any concept of diagnostic or therapeutic nihilism. Rather, it is intended to assess and detail the broad spectrum of the mechanisms and effects of complications experienced in order to further refine clinical practice. Undue conservatism would effectively prohibit the meaningful application of any diagnostic or therapeutic method, virtually any of which carries a potential risk to the patient. Many inherent complications of medical and surgical techniques can be controlled only to an irreducible minimum, despite the exercise of utmost care and skill. In this series, areas of practical clinical concern are addressed rather than topics of pure academic interest. Radiologic documentation is often critical to uncover or confirm the presence and to evaluate the extent of many iatrogenic complications. The large number of illustrations used in each volume attest to the aim of fully employing the power of visual instruction.

Oscar Wilde's wry statement that "experience is the name men give to their mistakes" is beneficial only if physicians continue to be open-minded and to learn from each other. It is a medical axiom that advances introduce new problems which, in turn, generate solutions and further advances. Lewis Thomas[11] affirms that "Mistakes are at the very base of human thought . . . What is needed, for progress to be made, is the move based on the error." This series is designed in the hope that iatrogenic illnesses may be minimized, or appropriately anticipated and promptly recognized and managed, so that the prime injunction of clinical medicine can be further fulfilled: "Physician, do no harm."

Morton A. Meyers, M.D.

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Preface

Nearly four thousand years ago Hammurabi's code of practice not only made the payment for medical care dependent upon successful recovery of the patient, but worse yet, it imposed harsh reprisals for operative mishaps. This law of retribution for failure to cure fortunately was not enforced beyond a brief period in Babylonian history. Advancements in medicine have been based upon triumphs and oversights, both of which have contributed toward strengthening the foundation of our current knowledge. Just as D. H. Lawrence stated that the greatest secret of Victorian England was sex—in the sense that many more people were participating in it than openly discussing it—so it might be said that the understated effects of many advances in the diagnosis and treatment of digestive disorders are iatrogenic complications.

In this context, the present volume is aimed to review the broad spectrum of clinical gastrointestinal disorders caused by application of modern diagnostic and therapeutic methods. The purpose is not to emphasize dangers but rather to provide a perspective of the underlying mechanisms and clinical presentations of iatrogenic gastrointestinal complications. Guidelines and characteristic features are established which help in their anticipation, prompt recognition, and management. Every physician will do well by looking ahead for such often inevitable problems, and using the past experiences for guidance in their solution.

The first chapter includes a comprehensive review of drug-induced gastrointestinal disorders, probably the most common iatrogenic problem in medicine today. Voltaire had once stated that "A physician is one who pours drugs of which he knows little into a body of which he knows less." The text and references listed in the first chapter challenge that widely quoted opinion, clearly reflecting the depth of current medical knowledge on this subject.

Gastrointestinal endoscopy and intubation have become particularly valuable methods in the diagnosis and management of digestive disorders. Their widespread use has led to an increasing frequency of the complications described in Chapters 2 and 3. The iatrogenic problems associated with the performance of radiologic procedures are reviewed in detail in Chapter 4.

By far the largest portion of this book, Chapters 5 through 11, is devoted to the complications of surgery. The coverage of this subject, which carries significant morbidity and mortality, has been made relatively extensive for two reasons: to permit a review of postoperative anatomy which is a prerequisite for accurate diagnosis of abnormalities superimposed on the distorted gastrointestinal landmarks; and to detail a wide range of surgical complications even though some perhaps elude a clear definition in terms of being iatrogenic versus inherent risk of operation.

The final section in this volume, Chapter 12, deals with gastrointestinal sequelae of radiation therapy. Awareness of their pathophysiology and manifestations should become even more important in the future considering the apparent increase in the incidence of cancer and the number of patients treated with this modality.

Both the text and the accompanying illustrations emphasize the critical role of diagnostic imaging in the evaluation of iatrogenic gastrointestinal disorders. Their correct diagnosis and management depend upon close consultation between the clinician and radiologist.

Morton A. Meyers, M.D.
Gary G. Ghahremani, M.D.

Contributors

Morton A. Meyers, M.D., F.A.C.R.
Professor and Chairman, Department of Radiology, State University of New York School of Medicine, Stony Brook, New York, U.S.A.
Chapters 2, 9, 10, 11

Gary G. Ghahremani, M.D., F.A.C.R.
Professor and Chairman, Department of Diagnostic Radiology, Evanston Hospital—Northwestern University, Evanston, Illinois, U.S.A.
Chapters 2, 3, 9, 10, 11

William H. Brewer, M.D.
Assistant Professor, Department of Radiology, Medical College of Virginia, Richmond, Virginia, U.S.A.
Chapter 9

H. Joachim Burhenne, M.D., F.R.C.P. (C)
Professor and Head, Department of Diagnostic Radiology, University of British Columbia, Vancouver, British Columbia, Canada
Chapter 7

Morton Burrell, M.D.
Professor, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.
Chapters 1, 6

Leonid Calenoff, M.D.
Professor, Department of Radiology, Northwestern University Medical School, Chicago, Illinois, U.S.A.
Chapter 5

James L. Clements, Jr., M.D.
Professor, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
Chapter 8

Peter Cooperberg, M.D., F.R.C.P. (C)
Associate Professor, Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada
Chapter 7

David W. Gelfand, M.D.
Professor, Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina, U.S.A.
Chapter 4

Burton M. Gold, M.D.
Assistant Professor, Department of Radiology, School of Medicine, State University of New York at Stony Brook, Long Island, New York, U.S.A.
Chapter 10

Sven-Ola Hietala, M.D.
Assistant Professor, Department of Radiology, Medical College of Virginia, Richmond, Virginia, U.S.A.
Chapter 9

Thomas H. Hunt, M.D.
Assistant Professor, Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina, U.S.A.
Chapter 4

Eric A. Hyson, M.D.
Attending Radiologist, Waterbury Hospital, Waterbury, Connecticut, U.S.A.
Chapter 1

Bernard S. Jay, M.D.
Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.
Chapter 6

David J. Ott, M.D.
Assistant Professor, Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina, U.S.A.
Chapter 4

James V. Rogers, Jr., M.D.
Professor, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
Chapter 8

Lee F. Rogers, M.D.
Professor and Chairman, Department of Radiology, Northwestern University Medical School, Chicago, Illinois, U.S.A.
Chapters 5, 12

Robert Toffler, M.D.
Clinical Associate Professor, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.
Chapter 1

William E. Torres, M.D.
Assistant Professor, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
Chapter 8

Contents

1 Drug-Induced Gastrointestinal Disorders

Eric A. Hyson, Morton Burrell, and Robert Toffler

Gastrointestinal disorder related to drug administration is a common phenomenon (1–6). In one study, drug reactions occurred in 16% of all hospital inpatients, with gastrointestinal reactions accounting for 26.9% of the total (1). Although frequently the reaction may be minor, such as mild nausea, vomiting, or diarrhea, serious drug-induced disease is often encountered as well. Outpatient illness serious enough to warrant medical service admission included 2.9% drug-induced cases in one series, excluding suicide attempts and drug abuse (5). Gastrointestinal reactions, usually hemorrhage, were the second most common manifestation (18.5%) after cardiovascular (22.2%).

The radiologist is often in a unique position to assist in making the diagnosis of drug-induced gastrointestinal disease. Radiographic changes may result from ulceration, vascular disease, motility disturbances, alteration of gastrointestinal tract flora, allergic phenomena, and other drug effects (7,8). Although the diagnosis may be suggested by radiographic studies, the clinical history of drug administration is usually essential.

Following is a list of drugs and their associated gastrointestinal complications.

Gastrointestinal Erosions and Ulcerations
- Salicylates
- Corticosteroids
- Other antiarthritics (indomethacin, phenylbutazone, oxyphenbutazone, ibuprofen, naproxen, tolmetin, fenoprofen)
- Miscellaneous (reserpine, spironolactone, iron)
- Potassium supplements (enteric-coated, potassium gluconate, slow-release)

Hypomotility disorders
- Ganglionic blockers (hexamethonium, mecamylamine, pentolinium)
- Psychoactive drugs (antiparkinsonian anticholinergics, phenothiazines, tricyclic antidepressants)
- Narcotics
- Miscellaneous (clonidine, vincristine, dantrolene, ^{131}I-induced myxedema)

Bleeding disorders
- Heparin
- Oral anticoagulants

Ischemic-thrombotic disease
- Oral contraceptives
- Digitalis
- Ergot derivatives

Cathartic colon
- Castor oil
- Phenolphthalein
- Bisacodyl
- Senna
- Danthron
- Cascara sagrada

Retroperitoneal fibrosis
- Methysergide
- Miscellaneous (ergotamine, dihydroergotamine, LSD, ? others)

Liver tumors
- Estrogens
- Androgens

Esophageal moniliasis
- Corticosteroids
- Immunosuppressives
- Antibiotics

Enterocolitis
- Pseudomembranous enterocolitis
  - Antibiotics (tetracycline, chloramphenicol, penicillin, ampicillin, cephalexin, neomycin, erythromycin, sulfamethoxazole-trimethoprim, lincomycin, clindamycin)
- Acute, transient antibiotic colitis (penicillin, ampicillin, amoxicillin)
- Gold enterocolitis
- Gastrointestinal urticaria (penicillin)

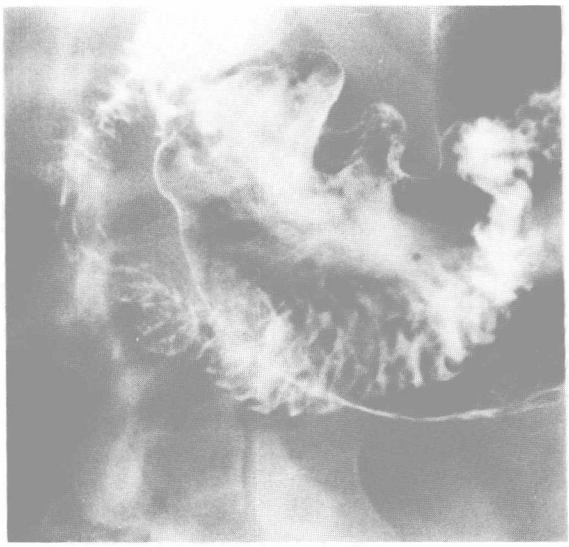
Miscellaneous
- Obstruction (Drug masses: aluminum hydroxide, cholestyramine, bulk laxative, tablets)
- Pancreatitis (corticosteroids, estrogens, diuretics, salicylazosulfapyridine, antineoplastic agents, indomethacin, anticoagulants, phenformin)
- Gallstones (estrogens, clofibrate)
- Fibrotic peritonitis (practolol)
- Enzyme esophagitis (papain)

Ulceration

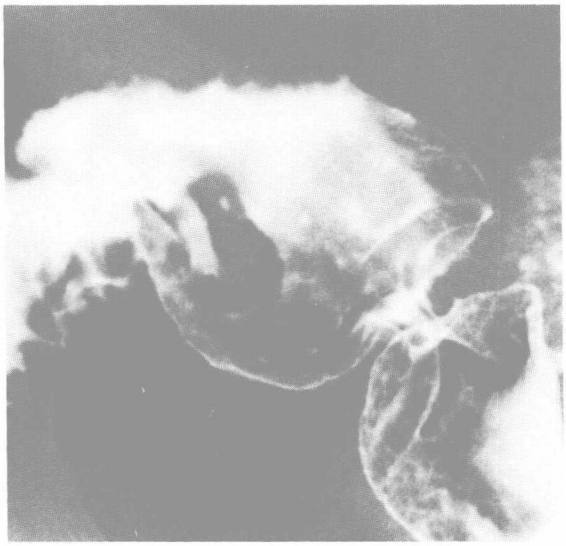
Salicylates

Many drugs have been reported as possibly related to gastric ulceration, but the most convincing evidence relates to aspirin (9,10). Superficial gastric erosions following aspirin ingestion have been well documented by endoscopy (11–13), and even the cellular mechanism of gastric mucosal injury by aspirin has been established (11). In the acid environment of the gastric lumen, aspirin remains in its nonionized form and hence readily crosses into the cells of the gastric mucosa. However, once inside the mucosal cell in a more alkaline medium, aspirin (acetylsalicylic acid, a weak acid) ionizes, leading to cellular injury, sloughing of gastric mucosa, and superficial erosion. Other salicylates may be less damaging to the stomach, but the evidence is less clear (13,14).

In the past, radiographic demonstration of gastritis and superficial erosions, such as those caused by aspirin, was difficult with the conventional upper gastrointestinal barium contrast studies. Even with erosions documented by endoscopy, the upper gastrointestinal tract series might show merely slightly enlarged gastric mucosal folds in only a minority of cases (14). However, with the newer double-contrast methods for examination of the stomach, superficial gastric erosions are more readily seen (15,16) (Fig. 1-1) although endoscopy is still more sensitive (12). Patients with "aspirin gastritis"



a



b

Fig. 1-1, a and b. Multiple superficial gastric erosions. Evident in the antrum (**a**) and duodenum (**b**), these probably do not extend below the muscularis mucosae and thus are too superficial to be called ulcers. They are shown to best advantage in double-contrast examinations. This patient had epigastric pain, guaiac-positive stools, and a history of repeated aspirin ingestion.

typically have gastrointestinal bleeding, either gross or occult (11).

Evidence has accumulated that use of aspirin is also related to chronic gastric ulcer. The earliest evidence came from Australia where a high incidence of gastric ulcer was discovered in middle-aged females who regularly ingested analgesics (17–20). More recent studies in the United States have also shown significant association between heavy aspirin intake and chronic gastric ulcer; considering the widespread use of aspirin in this country, the risk of gastric ulcer in any one individual aspirin user is probably small (21,22). No significant relationship between salicylates and duodenal ulcer or gastric carcinoma has been demonstrated (17,18,20,21).

Aspirin-associated gastric ulcer usually has no radiologic features to distinguish it from idiopathic ulcer. However, some evidence indicates that "aspirin ulcer" is relatively more common in the gastric antrum (22). One report noted a high frequency of hourglass stomach in gastric ulcer patients with a history of prolonged aspirin use (23).

Corticosteroids

While early reports stressed that corticosteroids are associated with peptic ulcer disease, particularly gastric ulcer (24–27), others have found no significant relationship (28–30). The controversy has been rekindled by Conn and Blitzer who, on the basis of a statistical review of the literature, concluded that there is an insignificant difference in the incidence of peptic ulcer disease in patients treated with steroids and in those not treated with steroids (31). The arguments continue (32,33), but the ulcerogenic properties of corticosteroids have been neither completely established nor refuted (10). Much of the controversy centers around patients with rheumatoid arthritis who seem to have a higher incidence of peptic ulcer disease even without steroid therapy (28–30).

The radiographic description of "steroid ulcers" varies. Peptic ulcers in corticosteroid-treated patients tend to be predominantly gastric (usually antral) rather than duodenal, the reverse of the control population (25,34). Descriptions of the individual ulcers, however, range from large and deep (34), to shallow (25), to indistinguishable from idiopathic ulcers (35). There has been general agreement that peptic ulcers in patients taking steroids show less surrounding edema, spasm, and scarring, a situation that is perhaps related to the anti-inflammatory effect of the corticosteroids (25,36,37). Some reports have emphasized the relatively silent nature of peptic ulcer disease in patients receiving corticosteroids and an associated high complication rate from bleeding and perforation (25,34,36).

The possibility of a relation between colonic perforation and corticosteroid use has also been raised, both in a diseased colon involved with diverticulitis or ulcerative colitis and in an otherwise normal colon with punched-out ulcerations (29,38,39). A causal relationship has not been established, but steroid therapy does tend to make clinical recognition of perforation more difficult since the patient's symptoms and physical findings are often of mild degree.

Other Antiarthritics

Gastritis and chronic gastric ulcer have also been associated with some of the newer antiinflammatory medications (40). The association has been strongest for indomethacin, phenylbutazone, and oxyphenbutazone (41–47). Preliminary reports suggest that there is less gastric mucosal injury with the most recently introduced antiarthritics, ibuprofen, naproxen, tolmetin, and fenoprofen (11,48–52). Occasionally more distal gastrointestinal tract ulcerations and perforations in the small bowel and colon have been linked to ingestion of certain of these new "super aspirins" (53–56).

Miscellaneous

Reserpine and other Rauwolfia alkaloids, now used principally for treatment of hypertension, increase gastric acid secretion when given in large oral doses, and there is some evidence for association with peptic ulcer disease (57–60). However, in routine oral doses, the increase in acid secretion is probably insignificant and ulcerogenic potential minimal (59). Sporadic cases of gastric ulceration associated with spironolactone have been reported (61). In children ingestion of toxic amounts of iron preparations has resulted in several cases of ulcerative gastric stricture and one case of mesenteric infarction due to caustic effects (62–67). Esophageal ulceration has been

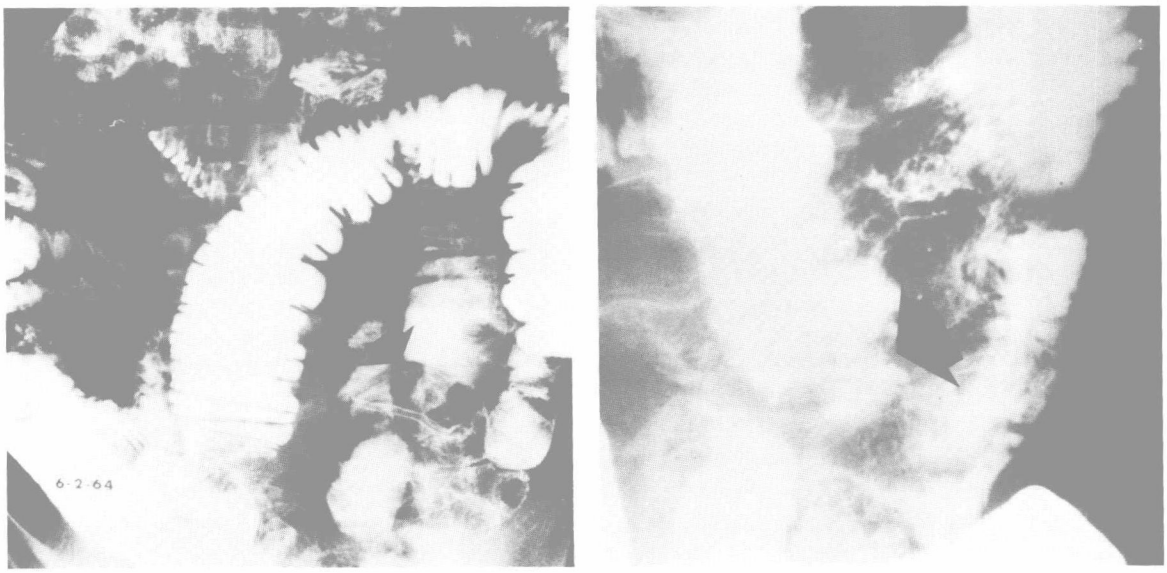
noted in three patients who took tetracycline just before going to bed, raising the possibility of stasis of the pills in the esophageal lumen as a contributing factor (68).

Potassium Supplements

As potassium-wasting diuretics have come into widespread use for hypertension and cardiac failure in recent years, a need for a simple means of potassium replacement has arisen. To avoid gastric irritation from orally ingested potassium chloride, an enteric-coated form was developed to dissolve in the more alkaline environment of the small bowel. However, as use of enteric-coated potassium chloride tablets increased in the early 1960s, it became clear that they were occasionally ulcerogenic in the small intestinal mucosa (69–73). Most affected patients had increasing postprandial crampy abdominal pain of days' to months' duration, suggesting partial small bowel obstruction. Barium contrast studies typically show a transition in small bowel caliber due to the partial obstruction (Fig. 1-2a) and occasionally define the cause, a short segmental ulcerated stricture with proximal bowel dilatation (70,74) (Fig. 1-2b). Although the short circumferential ulceration is seen grossly in the resected small bowel specimen (Figs 1-3, 1-4) the lesion usually appears radiographically as a short stricture without an ulcer niche (Fig. 1-5). The ulcer-strictures occur usually in the midjejunum and are uncommonly multiple. Surgical resection of the involved segment of bowel has been the treatment of choice (72). Less common manifestations of enteric-coated potassium chloride ulcerations include free small intestinal perforation and hemorrhage (69,72) (Fig. 1-6).

Potassium chloride injury to the small bowel probably results when accumulation of a locally high concentration of ionized potassium bathes the mucosa in the immediate vicinity of a tablet (71). It has been suggested that the high potassium level causes local vascular damage followed by circumferential hemorrhagic infarction and mucosal slough (75). At this point the lesion may perforate or bleed, but usually healing simply leads to a stricture.

Enteric-coated potassium chloride tablets have been withdrawn from the market in the United States but are still in use in other countries. Other forms of oral potassium supplements still in use in this country, however, have occasionally been associated with gastrointestinal tract ulceration. Potassium gluconate liquid and the new slow-release potassium chloride tablets



a b

Fig. 1-2, a and **b. Partial small bowel obstruction associated with ingestion of enteric-coated potassium chloride tablets. a Arrow** indicates level of obstruction. **b** Close-up of area of obstruction demonstrates short, segmental ulcerated stricture. (Courtesy of S. Schwartz, MD, New Haven, Connecticut)