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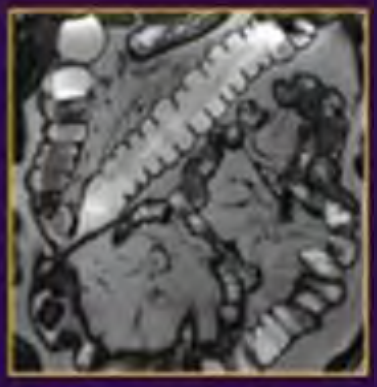
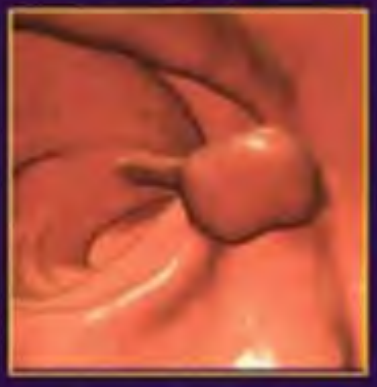
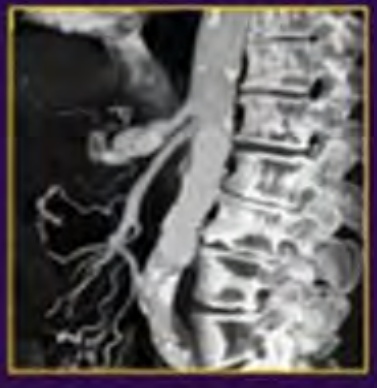
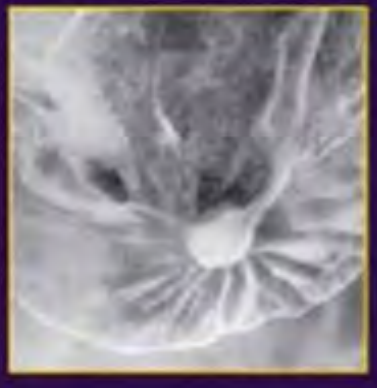
FOURTH EDITION

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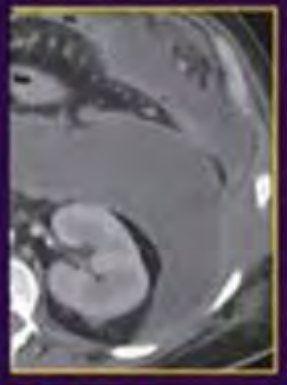
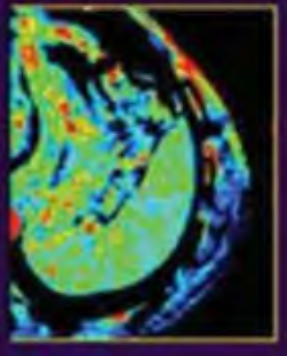

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2-Volume Set

Textbook of Gastrointestinal Radiology

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Textbook of Gastrointestinal Radiology

Fourth Edition

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To Margaret and our children,
Diana, Elizabeth, and George
RICHARD M. GORE

To Deborah, my beautiful and amazing wife
and better half for 37 years and counting …
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PREFACE

In the 20 years since the publication of the first edition of *Textbook of Gastrointestinal Radiology*, much has changed in our discipline. Technologic advances have dramatically improved the capabilities of computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, fluoroscopy, angiography, and interventional radiology for abdominal and pelvic imaging and therapy. The extraordinary anatomic resolution achieved with modern imaging techniques has been complemented by the introduction and maturation of metabolic, functional, and molecular imaging, which provide new opportunities for staging and follow-up and monitoring tumor response to therapy in the oncology patient.

To keep pace with these amazing technologic, imaging, and therapeutic advances, every chapter of the fourth edition has been updated and revised. Several new chapters on molecular and functional imaging have also been included. Moreover, new authors have been recruited for nearly one third of the chapters to provide these chapters with fresh insight and perspective.

In this new edition, we have taken great care to maintain the objective of the first three editions—namely, to provide complete and up-to-date coverage on the state of the art of gastrointestinal radiology in a practical and usable form.

As in the first three editions, our basic organizing principle is the integration of rapidly changing information, common sense, and good judgment for the development of a rational and useful approach for radiologic diagnosis and treatment. To this end, the text contains sections on general radiologic principles for evaluating the hollow viscera and solid organs and for performing and applying specific imaging and therapeutic techniques. Other sections present the clinical, radiologic, and pathologic aspects of disease in the various gastrointestinal organs. The chapters in these sections are designed to illustrate and integrate the spectrum of abnormalities seen with all diagnostic modalities available to the radiologist, including conventional radiography, barium studies, cholangiography, multidetector CT (MDCT), ultrasonography, MRI, positron emission tomography/computed tomography (PET/CT), positron emission tomography/magnetic resonance (PET/MR), angiography, diffusion-weighted MRI, and CT and MR perfusion imaging.

Once again, we have been able to assemble an outstanding group of internationally recognized authors for the fourth edition. Their time, effort, and expertise are truly appreciated. As editors, we have tried to strike a balance between uniformity of style and author individuality so that each contributor is able to speak in his or her own unique voice.

We trust that the collective efforts of the authors of the 127 chapters in this text, as well as our own, have enabled us to accomplish our goal of providing students and practitioners of gastrointestinal radiology a valuable educational resource that is clear, interesting, and enjoyable to read.

Richard M. Gore

Marc S. Levine

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I

General Radiologic Principles

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1 Imaging Contrast Agents and Pharmacoradiology

JOVITAS SKUCAS

CHAPTER OUTLINE

Only a basic introduction and overview about contrast agent use in medical imaging are presented in this introductory chapter. These agents can be subdivided into intravascular contrast agents for computed tomography (CT) and angiography, intraluminal gastrointestinal (GI) tract agents, cholangiographic agents and a unique group of agents useful in magnetic resonance imaging (MRI). The currently active research field of contrast agent–assisted, image-guided therapy will be discussed briefly. In addition, there is a section on pharmacologic agents useful in GI radiology.

Intravascular Contrast Agents

IODINATED WATER-SOLUBLE AGENTS

Basic Properties

With the exception of MRI, all current intravascular contrast agents use iodine for x-ray absorption. Theoretically, sodium iodide is ideal, but its toxicity and iodism preclude its use. The complex delivery molecules developed over the years represent an attempt to deliver the greatest iodine concentration with the least toxicity. From a simplistic viewpoint, the intravascular contrast agents can be viewed merely as vehicles for delivering iodine to a blood vessel or structure. These water-soluble intravascular contrast agents can be subdivided into the following categories: (1) ionic, high osmolality, roughly five times the osmolality of blood; (2) nonionic, low osmolality, roughly twice or slightly more than the osmolality of blood; and (3) isotonic agents—nonionic dimers. The basic structures and physicochemical characteristics of available contrast agents are not covered here; these topics are discussed in appropriate specialized publications.[1]

At the x-ray energies used in CT, the mass attenuation coefficient for iodine is considerably greater than that of surrounding soft tissues and blood. After the intravascular injection of iodinated contrast, initial CT images reveal aortic and major arterial enhancement, followed by a capillary or parenchymal "blush" and eventual venous opacification. The rate of contrast injection and timing of subsequent CT scans determine the structures enhanced on any one image. Compared with earlier scanners, multidetector CT (MDCT) scanners require shorter injection rates because of the short scanning times; as a result, faster injection rates of more concentrated contrast agents are necessary, and a contrast's viscosity has a dominant role. Various techniques of intravascular contrast agent administration are discussed elsewhere in this text.

A number of drugs, especially more acidic ones, are incompatible to mixing with contrast agents, an incompatibility less evident with nonionic agents. Nevertheless, as a general safety precaution, a drug probably should not be mixed with a contrast agent, and a catheter should be flushed if used for both drug and contrast injection.

Ionic Agents

Acetylation of aminotriiodobenzoic acid and further structural changes led to the development of ionic contrast agents. These agents are formulated as salts and consist of a cation and anion. Two commonly used cations are sodium and meglumine. The anion portion of the molecule consists of a benzene ring containing iodine substituted at positions 2, 4, and 6, plus a number of other side chains. These side chains determine water solubility and indirectly affect resultant toxicity. The benzene ring can be viewed as a scaffold for attaching iodine and side chains. When the molecule dissociates, three iodine atoms are available for every two particles in solution, or a ratio of 1.5:1.

Further refinements of ionic contrast media consist of the attachment of two monomer triiodinated benzene rings at one of the side groups. Such a dimer, containing two benzene rings, with each having three iodine atoms and only one cation particle, has six iodine atoms per two particles, or a ratio of 3:1.

Ionic contrast agents are hypertonic at the concentrations used for vascular opacification; considerable effort has been spent in an attempt to decrease their osmolality. In general, the viscosity of a sodium salt is less than that of a corresponding meglumine salt, but the sodium salt tends to be more toxic. Toxicity and viscosity limitations during intra-arterial injections are not as relevant for the intravenous (IV) injections used with CT.

Nonionic Agents

If the carboxyl group in position 1 on the benzene ring is replaced with a stable side group, the molecule no longer dissociates when in solution, and each particle in solution has three iodine atoms, or a ratio of 3:1. A dimer structure can also be achieved by linking two triiodobenzoic acid molecules (ioxaglic acid), formulated as a meglumine sodium salt, another contrast agent with a ratio of 3:1. A contrast agent with a ratio of 6:1 has also been developed (iodixanol) and is often referred to as being iso-osmolar.

Various manufacturers have taken different approaches to the type of side chains used with ionic and nonionic contrast agents. As a result, these compounds differ in their viscosities and other properties. The interaction with other molecules also differs between ionic and nonionic agents and is affected by the type of side branches present. Within limits, however, for each group of contrast agents, viscosity varies directly with iodine concentration.

Commercial contrast agents also contain chelating agents, usually calcium edetate disodium, to chelate impurities and buffering agents to achieve an acceptable pH. Their action is more important during contrast agent manufacture than during clinical use.

The American College of Radiology (ACR) has published criteria for situations in which nonionic agents are preferred,[2] although in many practices this is a nonissue because nonionic agents are used almost exclusively. The nonionic agents are associated with less patient discomfort and thus result in less motion artifacts; this is an evident advantage, especially with complex examinations such as three-dimensional (3D) reconstruction.

Pharmacokinetics

After a bolus intravascular injection, the initial plasma iodine concentration is determined by contrast agent iodine concentration and injected volume. Ionic and nonionic contrast agents are eventually distributed throughout the extravascular, extracellular space, with intravascular and extravascular equilibrium achieved within 10 minutes after intravascular injection. They are excreted mostly by renal glomerular filtration.

After injection, the relative plasma iodine concentration in a particular vessel depends on dilution by blood, extravascular diffusion, and renal excretion; the first factor is most important during arterial and venous phase imaging, with extravascular diffusion playing a larger role during the parenchymal phase. In theory, a contrast agent can be designed to have fast or slow extravascular diffusion and rapid or slow renal clearance; an ideal blood pool agent should have slow extravascular diffusion. In practice, with an equivalent iodine dose, nonionic agents achieve greater initial peak vascular enhancement than ionic agents, but subsequent blood iodine concentrations and parenchymal opacification are similar for the two types of agents (except renal visualization). Ionic and nonionic agents have similar extravascular diffusion rates. Extensive literature is available on relative time-dependent blood iodine concentrations and renal excretion of various contrast agents.

Dynamic CT scanning after a single bolus injection relies on the enhancement of vascular structures above baseline. Correct arterial phase timing is obtained by injecting an initial test dose or using automatic bolus tracking. One mg iodine per gram of tissue corresponds roughly to an increase of 30 Hounsfield units (HU), which is about the limit for detection. In general, it is desirable to have sufficient iodine concentration in the vascular structures of interest to elevate them above baseline by up to 100 HU. With this degree of enhancement, major vessel thrombi are detected and vascular fistulas and related conditions evaluated. Whether early dynamic scanning (arterial phase) is superior to portal venous phase or even delayed scanning after contrast equilibration depends on the organ in question and information sought. For the liver, these arterial and portal phase time window are roughly 20 to 30 seconds. These short time intervals are readily achieved with MDCT.

A typical CT examination consists of a precontrast scan, followed by scanning after the initial bolus reaches the structure of interest. A relatively large-caliber venous catheter and power injector provide reproducible injection rates, keeping in mind that prediction of bolus arrival is somewhat empiric because, among other factors, decreased cardiac output can prolong vascular flow times.

Intravascular contrast agents cross the placenta, are excreted in breast milk, and affect fetal and infant thyroid function. If feasible, alternate studies should be considered during pregnancy. Breast-feeding should be stopped for 1 to 2 days after contrast injection.

Acute Adverse Reactions

Only a brief summary of contrast reactions and their therapy are provided here. More detailed information is available from ACR[2] and European Society of Urogenital Radiology (ESUR)[3] publications.

The nonionic contrast agents have a considerably lower osmolality than the ionic agents; adverse reactions caused by hyperosmolality are therefore reduced with the nonionic agents. Hyperosmolality is also related to vasodilation of the involved capillaries. Nonionic contrast agents induce less hypotension than ionic agents.

Risk factors for acute renal failure include diabetes mellitus with decreased renal function, renal insufficiency, dehydration, and use of a high dose. Atopy confers an increased risk to contrast reactions, but allergies to shellfish appear not to increase the risk of reaction.[4] Iodinated contrast agents are contraindicated in patients with obvious hyperthyroidism. Also, these agents should be avoided for 2 months prior to thyroid isotope imaging or radioactive thyroid therapy.[4]

Types of Reactions. Acute reactions vary from minor effects to severe and life-threatening. Sensations of warmth, nausea, and vomiting appear to be a direct side effect to contrast. Reactions such as mild changes in blood pressure or mild wheezing are often self-limiting or may progress to more severe reactions. An arbitrary but useful grading of contrast reactions is mild, moderate, severe, and fatal. Compilations of reactions to ionic contrast agents in the 1970s and 1980s revealed a risk of severe

reaction to be 1 in 1000 to 4000 studies. Types of reactions are similar with ionic and nonionic agents. In general, the risk of adverse reactions varies with contrast osmolality, so fewer reactions occur with nonionic agents than with ionic agents. In particular, the risk of severe adverse reactions is lower with nonionic contrast agents.[5] Deaths have occurred with both ionic and nonionic agents.

At times, urticaria and even more severe reactions do not represent a classic antigen-antibody reaction but are secondary to histamine or serotonin release induced directly by the contrast agent. However, histamine release is probably not the only factor involved in serious contrast reactions. Among other effects, contrast agents activate the complement system, which acts as a host defense, and is related to coagulation abnormalities and bradykinin release. Overall, only a minority of unpredictable reactions mimics immunoglobulin E (IgE) hypersensitivity, probably secondary to an antigen-antibody reaction. How to classify the rare bowel wall edema is not clear.[6] Iodide mumps is a rare delayed reaction to iodine-containing contrast media.

Some reactions are disease specific. IV contrast agents in the presence of a pheochromocytoma can lead to catecholamine release and acute hypertension. In this setting, the onset of such hypertension should suggest a pheochromocytoma.

Over the years, many radiologists have avoided the use of intravascular contrast agents in patients with sickle cell disease, although the prevalence of adverse reactions has not been established. Over an extended period, bottled hyperosmolar contrast agents can leach allergens from rubber stoppers. As a rule, contrast-containing vials and bottles should be stored in an upright position.

Premedication. The specific allergen responsible for iodinated contrast sensitization is unknown. It is difficult to prove that iodine is responsible for hypersensitive contrast reactions, a common assumption. A myosin protein rather than iodine is believed to be the allergen responsible in shellfish. Rather than ask a patient about iodine allergies, a more appropriate question appears to be whether drug allergies are present. On a practical level, the cause of an adverse reaction is often not sought, and the reaction is simply labeled as allergic, hypersensitive, or anaphylactic.

No reliable blood test detects patients who are allergic to contrast media. Risk factors associated with a contrast reaction include asthma and a history of prior reaction to contrast. However, even these are unpredictable, and a patient manifesting a severe reaction may have had prior intravascular contrast with no adverse reaction. Although patients with urticaria-like reactions have increased plasma levels of prekallikrein and α_2-macroglobulin and lower levels of C1-esterase inhibitor, their predictive value is limited because of normal variation.[7] Pretesting with a small dose of contrast was once popular but has been abandoned as having little or no value. Acute reactions have developed after less than 1 mL of administered contrast.

In a multi-institutional study involving ionic contrast agents, pretreatment with methylprednisolone, 32 mg, 12 hours and 2 hours before contrast injection, significantly reduced the risk of reactions.[8] With this two-dose regimen, the number of reactions in patients receiving ionic contrast agents approximated those seen with nonionic agents and no pretreatment. Premedication is often considered for patients who have had a previous reaction to a contrast agent. Regimens that have been proposed range from 3 days to immediately before a scan. At the University of Rochester, we recommend that patients who have had a significant prior reaction to IV contrast agents be pretreated with 50 mg of prednisone orally every 12 hours, for a total of three doses, with the last dose given approximately 1 hour before the examination, and 25 to 50 mg of diphenhydramine hydrochloride (Benadryl) orally, 2 hours before the examination.

The prevalence of seizures after IV contrast injection is increased in patients with brain metastases. Capillaries in brain metastases do not exhibit normal blood-brain barrier integrity and are permeable to a contrast agent. To decrease the risk of seizures, it has been suggested that these patients be premedicated with diazepam, 5 mg IV, before contrast administration.[9]

Treatment of Reactions. Any physician injecting a contrast agent intravascularly can expect to encounter a broad spectrum of reactions, from mild to severe, and must be prepared to deal with them. In general, mild reactions such as flushing or mild urticaria require no treatment, and most reactions resolve spontaneously. Similarly, nausea and vomiting require general support and observation only. If symptoms occur before all the contrast agent has been administered, the rate of injection should be slowed or the injection postponed until symptoms clear.

Early IV access should be established. The catheter used for contrast injection should be kept in place, ensuring intravascular access until the possibility of a reaction has passed. With progressive hypotension, it becomes increasingly difficult to cannulate a peripheral vein.

Moderate urticaria developing in the absence of other significant symptoms can be treated with diphenhydramine, 25 to 50 mg, orally or injected. With more severe urticaria, one should also consider an H2 blocking agent such as cimetidine (Tagamet), 300 mg injected slowly (diluted) IV. For severe urticaria, epinephrine, 0.1 to 0.3 mL (1:1000) should be given subcutaneously unless contraindicated. If needed, the dose can be repeated in 15 minutes. Epinephrine should be used with caution in older patients who have underlying cardiovascular disease; electrocardiographic monitoring should be considered for these patients.

Severe reactions, such as severe bronchospasm, convulsions, or significant cardiopulmonary reactions, require prompt and vigorous therapy. Bronchospasm and laryngeal edema generally respond to subcutaneous epinephrine. If needed, the epinephrine dose can be repeated. Diphenhydramine and corticosteroids, such as hydrocortisone, 100 to 300 mg IV, are also often used. Oxygen should be administered by mask or nasal cannula. Beta agonist inhalers alone may be beneficial for mild bronchospasm or can be used in conjunction with aminophylline therapy. With refractory bronchospasm, aminophylline, 250 to 400 mg diluted in dextrose and water, can be administered IV over a 10- to 20-minute period. Aminophylline should be used with caution because it could exacerbate coexisting hypotension. Tracheal intubation should be considered early in the course of these symptoms; later, severe laryngeal edema may make intubation difficult if not impossible.

Because the treatment of hypotension in the settings of tachycardia and bradycardia is different, the pulse rate should

be monitored. A pulse may not be palpable in a hypotensive patient; cardiac auscultation or electrocardiographic monitoring may be necessary.

Hypotension in the absence of other major signs of an anaphylactic reaction should initially be treated with oxygen, leg elevation, and rapid administration of IV fluids. Epinephrine should be considered, keeping in mind that fluid therapy alone may be sufficient therapy. Although subcutaneous epinephrine injections are adequate for a mild to moderate reaction, IV administration is needed for moderate to severe hypotension. For IV administration, epinephrine should be diluted to 1:10,000 and 1.0 to 3.0 mL administered slowly. The dose can be repeated in 15 minutes, and the rate of injection can be titrated to achieve the desired result. A vasopressor agent such as dopamine, 2 to 5 μg/kg/min, can be added to sustain blood pressure. For unresponsive hypotension, other agents are available for treatment of underlying shock. An H2 blocker such as cimetidine can be added, 300 mg in dextrose and water, infused slowly. Similarly, diphenhydramine, 25 to 50 mg, can be injected IV. Corticosteroids are also often used, with a typical dose of hydrocortisone being 500 mg IV. Steroids probably have no immediate effect on a reaction; their main use is to decrease delayed reactions.

At times, hypotension can be corrected with vigorous hydration alone, keeping in mind that overhydration of patients with possible underlying cardiovascular and/or renal disease also carries a risk. Thus, the initiation of therapy by adequate hydration is reasonable, but appropriate pharmacologic therapy should be instituted without undue delay.

Hypotension in the presence of bradycardia suggests a vasovagal reaction. Some patients respond to being placed in a Trendelenburg position. Hypotension in these patients should be treated with rapid IV infusion of isotonic saline. Oxygen should be administered. Bradycardia can be treated with atropine (0.5 to 1.0 mg IV), with the dose repeated every 5 minutes, to a maximal total dose of 3.0 mg.

Some patients receive long-term therapy with a beta blocker such as propranolol. A contrast reaction in these patients can be confusing because, even in the setting of anaphylactic shock, a beta blocker–induced bradycardia can persist. IV glucagon, 1.0 mg or more, may be useful for bradycardia. Dopamine is also effective. Doses of epinephrine that are usually administered may not be effective in reversing this hypotension.

Emergency cardiopulmonary resuscitation is necessary for cardiovascular collapse. Refractory seizures are treated with IV diazepam (Valium) and/or phenobarbital.

Contrast extravasation is treated by extremity elevation, warm or cold compresses and, if extensive, a plastic surgery consultation. Hyaluronidase, an enzyme that breaks down interstitial barriers, has been injected into the extravasation site by some investigators, but its impact on tissue healing is still not clear.

This discussion is only meant to be a guide. The treatment of all reactions should be individualized.

Contrast-Induced Nephropathy. The pathogenesis of contrast-induced nephrotoxicity is incompletely understood, but it is believed that a number of intrinsic renal events lead to renal medullary ischemia, usually augmented by a reduced intravascular volume.[10] Direct cytotoxicity, oxidative tissue damage, and apoptosis are contributing factors. This nephrotoxicity is manifested by a significant rise in the serum creatinine level. Various authors use different definitions of significant, with the ESUR guidelines using a creatinine level increase of more than 25%, or 44 μmol/L (0.5 mg/dL), within 3 days.[3] A transient nonoliguric decrease in renal function lasting up to 3 weeks is more common than the more ominous oliguric manifestation, which may require hemodialysis.

Risk factors for nephrotoxicity appear to be multifactorial and include preexisting renal insufficiency, diabetes, dehydration, cardiovascular disease, advanced age, myeloma, hypertension, hyperuricemia, and possibly contrast osmolality and dose. Patients at the greatest risk for acute renal failure are diabetics with preexisting renal insufficiency. Precaution is also necessary with treatment by agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, cyclosporin, or even sulfonamides; underlying nephrotoxicity is a common pathway.

In diabetics with underlying cardiovascular or renal insufficiency, metformin, a biguanide antihyperglycemic agent, is associated with lactic acidosis and resultant increased mortality. This association appears to be indirect and probably involves underlying renal insufficiency. However, enough patients taking metformin and receiving IV contrast have developed lactic acidosis to prompt the U. S. Food and Drug Administration (FDA) to issue a warning—metformin should be discontinued before or at the time of contrast use for 48 hours after the procedure and reinstated only if renal function remains normal. However, substantial inconsistencies exist in the guidelines.[11] Adequate hydration should be maintained.

Because iodinated contrast agents are not protein-bound (except for cholangiographic agents), they can be dialyzed. In patients on hemodialysis, additional hemodialysis sessions are generally not necessary.

The most important preventive measure is to ensure that the patient is well hydrated. If IV hydration is necessary, some evidence suggests that the IV use of sodium bicarbonate hydration is superior to sodium chloride.[12,13] Other guidelines include the use of low-osmolar contrast, discontinuing nephrotoxic drugs for at least 24 hours, and consideration of alternate imaging in high-risk patients. The osmotic diuretic mannitol does not provide any benefit; this loop diuretic furosemide exacerbates renal dysfunction.[2] Currently, it is probably safe to assume that diuretics do not offer any protective effect, and anecdotal evidence even suggests that diuretics should be stopped prior to a contrast study.[14]

N-acetylcysteine, an antioxidant, appears to diminish contrast-induced renal toxicity,[15,16] although some have questioned its renal benefit.[17] Many of these studies have involved coronary angiography and differ in methodology from contrast CT. The role for theophylline is less well established.

Hemodialysis after contrast use in preexisting renal failure patients is not thought to be warranted. Hemofiltration in chronic renal failure patients, on the other hand, has caused less creatinine level increase than in controls.[18] The complexity of this procedure and the cost of hemofiltration limit its use to select patients.

IODINATED OIL

Intra-arterial iodized poppy seed oil (Ethiodol or Lipiodol) is used for several indications:

1. As a CT diagnostic agent for liver tumor detection, especially hepatocellular carcinoma.

Often used as a gold standard, it detects more tumors than other imaging modalities. Nevertheless, a study of explanted livers revealed that pretransplantation iodized oil CT tumor sensitivity is still rather low. Also, one should keep in mind that iodized oil is retained by some benign tumors, even hemangiomas.

2. Ethiodol is often included as a chemoembolization ingredient when injecting into a tumor feeding artery.

   This acts as a chemotherapeutic agent carrier and, because of its high viscosity, is a temporary embolizing material that prolongs chemotherapeutic agent contact with a tumor. Ethiodol remains within tumor neovascularity much longer than in normal liver parenchyma and thus acts as a marker.

3. Occasionally, ethiodol is injected during percutaneous radiofrequency ablation of hepatocellular carcinomas.[19]

   This aids in the CT delineation of extent of coagulation necrosis.

For a number of reasons, intra-arterial iodized oil is considerably more popular in the Far East than in the West.

OTHER AGENTS

Several reports have described the use of gadolinium (Gd)-based contrast agents for CT imaging in patients with renal insufficiency or prior severe reaction to an iodinated agent. One should keep in mind, however, that the pharmacokinetic properties of gadopentetate dimeglumine (Gd-DTPA), with only one gadolinium ion, are similar to iodinated agents containing three to six iodine atoms. Also, the toxicity of gadolinium agents, at doses achieving equivalent x-ray stopping power, is greater than that of nonionic iodinated agents. This is in distinction to the use of approved lower gadolinium MRI doses, which are insufficient for useful x-ray contrast, but have negligible nephrotoxicity.[3] The ESUR position is that gadolinium-based contrast agents are more nephrotoxic than iodinated contrast agents in equivalent x-ray attenuation doses.[3]

Carbon dioxide is a viable angiographic contrast agent for certain digital vascular indications in the abdomen. It has been used as a guide for vascular interventional procedures. It displaces blood, forms a gaseous column, and is cleared by the lungs.

Apart from MR, viable abdominal reticuloendothelial contrast agents have eluded clinical development. The first such agent, thorium dioxide (Thorotrast), used until the 1950s, has left a painful and sorry legacy. Iodinated oily emulsions accumulate in the liver, spleen, bone marrow and, to a lesser extent, in other organs, long enough to permit CT imaging, but high toxicity and low specificity led to their abandonment. Colloidal iodine or emulsified perfluorooctyl bromide particles are also incorporated in reticuloendothelial cells. Most studies of emulsified perfluorooctyl bromide took place in the 1980s, and its use has lost favor since then.

Liposomes are taken up by the reticuloendothelial system, and considerable effort has been expended to encapsulate water-soluble iodinated contrast agents inside liposomes. Research activity peaked during the 1990s but, in spite of occasional more recent papers, pronounced adverse reactions limit the use of liposomal CT contrast agents in humans. Most current reticuloendothelial contrast research revolves around MRI agents.

Gastrointestinal Contrast Agents

BARIUM SULFATE

Barium sulfate is a white crystalline powder having a molecular weight of 233. Because of its specific gravity of 4.5, patients tend to comment that a cup of barium suspension is "heavy." The terms *thick* and *thin* should only be used when referring to viscosity. They should not be used to signify radiodensity, which has many other causative factors.

Although barium sulfate itself is inert and does not support bacterial growth, some additives in commercial preparations are organic. When a container is opened or reconstituted with tap water, the suspension should be refrigerated if it is to be kept overnight. Although many commercial formulations contain preservatives, bacterial contamination can and does occur.

Certain commercial formulations are advertised as being applicable throughout the GI tract. Invariably, these represent a compromise. The GI tract varies in pH, in composition of mucus, and in type of mucosa, and optimal coating in one part does not mean that a similar coating can be expected in another. Coating the mucosa with barium or simply opacifying the lumen requires different barium formulations.[20] The large-particle, high-density barium suspensions designed for double-contrast use should not be simply diluted and used for single-contrast studies. Ingesting such a diluted suspension causes rapid barium particle sedimentation, with the nondependent lumen containing little barium; lesions on the nondependent wall can therefore be missed. Products designed primarily for single-contrast examinations, on the other hand, can be diluted considerably before any settling occurs, mainly because they contain relatively small barium particles.

Ingestion of a barium sulfate suspension tends to be constipating. Currently, commercial barium products have additives that minimize this effect, and the formation of a bariolith is rare.

PHARYNGOGRAPHIC AGENTS

Pharyngeal radiography was already established in the 1960s, when cineradiography became popular to evaluate dysphagia. Although conventional or digital radiography produces high anatomic resolution, dynamic swallowing is best evaluated with video fluoroscopy or cineradiography. This pharyngogram, commonly called a modified barium swallow, evaluates oropharynx anatomy and function using contrast agents of varying consistencies.

After a stroke, appropriate patient feeding without inducing aspiration can be determined by using barium suspensions of different viscosities and barium-coated food. Contrast consistencies used range from barium-coated crackers to a viscosity approaching that of water. To improve patient acceptance, some investigators have developed their own contrast agents such as barium pudding or barium honey. Anatomic detail is best studied with high-density barium products such as the 250% w/v suspensions designed for gastric double-contrast examinations. Fistulas are also best studied with this type of contrast agent. A barium paste can also be used to study anatomy, but the high paste viscosity limits its application in fistula detection. The volume of barium used should be individualized. Thus, with suspected aspiration, a several-milliliter bolus is swallowed

initially; if no aspiration is detected, the bolus is gradually increased in volume.

The oropharynx handles high- and low-viscosity liquids differently, so pharyngeal function should be studied with high- and low-viscosity barium suspensions. The low-viscosity suspension should have a viscosity approaching that of water, whereas the high-viscosity suspension should be similar to a thick milkshake. It should be emphasized that some high-density double-contrast barium products are relatively fluid and are not applicable as high-viscosity preparations.

A tracheoesophageal fistula is easier to detect fluoroscopically with the patient in the lateral position. With the patient in a frontal position, it may not be possible to determine whether barium in the trachea was aspirated or flowed through a fistula.

UPPER GASTROINTESTINAL TRACT STUDIES

Studies of the esophagus consist of single-contrast, double-contrast, and mucosal relief views, together with fluoroscopic evaluation of motility. Normal esophageal tonicity leads to lumen collapse when a primary peristaltic wave has passed. Therefore, regardless of which method is used, the study must be performed reasonably quickly.

Some patient symptoms are reproduced by using a cold contrast suspension or acidic contrast. Although some have found acidified contrast useful, it is not commonly used.

Sufficient air is introduced into the esophagus for a double-contrast study in some patients with poor esophageal motility or those with gastroesophageal reflux. In most patients, however, an additional negative contrast agent is necessary to obtain double-contrast views. Solid gas-producing tablets, powder, or liquid effervescent agents are used. These contain sodium bicarbonate and an acid, such as tartaric acid or citric acid, which, in the presence of a liquid, produce carbon dioxide. About 400 to 500 mL of gas is necessary for adequate esophageal and gastric distention. One technique is to have the patient drink, in quick succession, first one and then another liquid effervescent solution, followed immediately by 60 to 120 mL of a barium suspension. The two effervescent agents distend the esophagus by releasing carbon dioxide, and barium then coats the esophageal mucosa.

The high-density, low-viscosity barium products designed for the stomach and duodenum also coat the esophagus wall. Visualization of the esophagus is impaired if barium is ingested before effervescent agents. On the other hand, the quality of the gastric mucosal coating is improved if the barium suspension is given first. The sequence of ingestion can be tailored to the patient's symptoms—if esophageal disease is suspected, the effervescent agents are given first; if gastroduodenal disease is suggested, the barium suspension is given first.

Esophageal varices tend to be more prominent and their detection easier if the esophageal lumen is collapsed. Although high-density, low-viscosity barium products detect larger esophageal varices, commercially available barium pastes are recommended. Some of these pastes are too viscous and tend to flow in a bolus; these should be diluted with water so the paste viscosity is similar to that of honey.

In a patient with acute dysphagia, an esophagram can be therapeutic. With the patient upright, the weight of a barium column can dislodge a foreign body into the stomach. Liquid effervescent agents increase the intraluminal esophageal pressure and may also push a foreign body into the stomach. This technique should be performed with care to avoid perforation. Glucagon has also been proposed to help relieve spasm, although it is not clear whether pharmacoradiology has a significant role in acute dysphagia.

Commercial barium sulfate tablets with a diameter of 12 mm are available and are useful to evaluate subtle esophageal strictures. For results to be meaningful, the patient should be at least in a 45-degree upright position and at least 60 mL of water should be ingested with the tablet. Tablet transit time through the esophagus normally is less than 20 seconds. These tablets contain 650 mg of barium sulfate plus additives. The tablets dissolve in the esophagus or stomach (Fig. 1-1). Relatively fresh tablets should be used because older tablets take longer to dissolve.

It has been proposed that barium tablets be administered routinely during chest radiography because tablet retention in the esophagus is associated with the presence of structural or functional esophageal abnormalities, but this technique is not widely used.

In patients with suspected esophageal perforation, study of the esophagus with a water-soluble agent may not detect a subtle leak. Thus, administration of higher density barium sulfate enables detection of leaks that might otherwise be missed.[21] For this part of the examination, barium suspensions varying from 35% to 80% w/v are used. Residual barium in the mediastinum does not result in clinically detectable

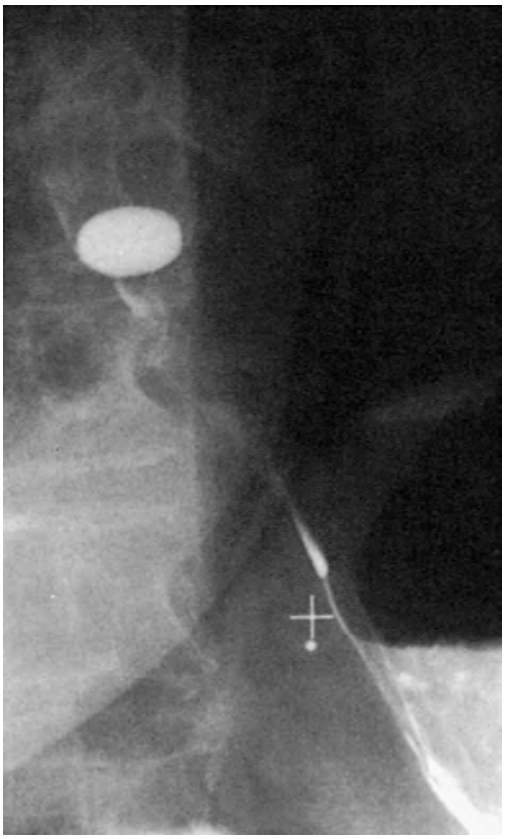

Figure 1-1 Barium sulfate tablet proximal to a stricture. A previous esophagram suggested narrowing at this site, and the tablet confirms this finding. *(From Schabel SI, Skucas J: Esophageal obstruction following administration of "aged" barium sulfate tablets—a warning. Radiology 122:835–836, 1977.)*

mediastinitis and does not interfere with subsequent radiographic evaluation.

High-density, low-viscosity barium preparations specifically designed for the upper GI tract produce best double-contrast results. A volume of 60 to 120 mL of a 250% w/v suspension is generally sufficient. A good barium formulation should result in routine identification of the areae gastricae. Small cancers, ulcers, gastritis. and duodenitis are readily detected during a high-quality examination.

When appropriate double-contrast gastric views have been obtained, a lower density barium suspension is ingested for subsequent single-contrast evaluation. For this part of the examination, barium suspensions varying from 35% to 80% w/v are used. Various external compression paddles are available and are helpful in obtaining mucosal relief views.

SMALL BOWEL STUDIES

A number of techniques have been developed to study the small bowel, such as conventional antegrade study, enteroclysis, retrograde ileography, peroral pneumocolon, and CT and MR enterography. The type of examination performed varies with clinical indication. Specific contrast agents have been developed for each type of study.

An antegrade examination is the simplest and most traditional way of studying the small bowel. Serial small bowel radiographs are obtained after the patient ingests a barium suspension. The primary contrast agent requirement is that it does not flocculate or precipitate during transit. The barium does not coat the mucosa; visualization is obtained primarily by filling the bowel lumen with the barium suspension. A 40% to 60% w/v suspension is typical. Many radiologists prefer a volume of 500 to 800 mL.

Contraindications to an antegrade barium study are suspected colonic obstruction or bowel perforation. A number of clinicians hesitate to request a barium study in the setting of small bowel obstruction and prefer to wait until the obstruction clears. Such an approach is analogous to obtaining a chest radiograph only after a pneumonia clears. Small bowel obstruction is not a contraindication. Barium proximal to a small bowel obstruction continues to stay in suspension, and barium inspissation does not occur. With a small bowel obstruction, an antegrade study with barium is safe and not only can detect the site of obstruction but also suggest a cause.

In enteroclysis (small bowel enema), contrast is injected through a steerable catheter directly into the small bowel, so the flow-limiting function of the pylorus is bypassed. The barium suspension can be infused by gravity, hand-held syringes, or an infusion pump. Typical infusion rates are 75 to 100 mL/min, although the flow rate should be individualized. If the rate is too slow, excessive peristalsis results in a study similar to a conventional antegrade small bowel examination. With a flow rate that is too high, overdistention leads to bowel atonia and lack of progression.

It is debatable whether single-contrast or double-contrast enteroclysis yields better results. For the double-contrast portion, many U.S. investigators use a solution of methylcellulose in water (≥0.5%). Methylcellulose helps propel a barium suspension ahead of it. Water can be used as the second contrast agent, although water tends to wash off barium adhering to the mucosa. The total volume of the two contrast agents is tailored for each examination; in some patients, up to 2 L are required. The contrast agents are instilled until a lesion is detected or contrast reaches the right colon. If needed, glucagon is administered to induce hypotonia.

Air as a second enteroclysis contrast agent, used more commonly in Japan and Europe, results in considerably more radiographic contrast than obtained with methylcellulose. Air does not propel the barium ahead of it as quickly as methylcellulose; it tends to percolate through barium-filled loops of bowel. Nevertheless, with overlapping bowel loops, as is common in the pelvis, infusion of air is often helpful. Air bubbles can be confusing, although some think that better diagnostic results can be achieved with air, even in patients with inflammatory bowel disease.

Several tubeless enteroclysis techniques have been described. One simple method is to initially perform a conventional small bowel study, but when barium approaches the cecum, the patient swallows additional effervescent agents, turns prone, and the table is turned into a 20- to 40-degree Trendelenburg position. Efflux of gas results in a double-contrast small bowel study. A tubeless double-contrast small bowel technique consists of effervescent granules coated with an acid-resistant lacquer. Gas is released directly into the small bowel lumen.

Barium formulations specifically designed for enteroclysis provide the best results and are commercially available. For a single-contrast study, a barium suspension having a specific gravity of about 1.25 (equivalent to ≈35% w/v) is typical. For a double-contrast study, the barium suspension should be in the range of 50% to 95% w/v.

Retrograde ileography consists initially of a single-contrast barium enema, but infusion of barium is then continued retrograde into the ileum. Because flow is controlled by the examiner, the ileum can be readily studied without overlapping loops from the more proximal small bowel. Barium is instilled until the region in question is reached. Premedication with glucagon increases patient comfort and also relaxes the ileocecal valve. If a redundant sigmoid colon obscures part of the small bowel, the barium enema can be followed by a saline enema; such a solution pushes barium ahead of it and results in a see-through effect. A 20% to 25% w/v barium suspension is typical for such a study.

It is not unusual to achieve a double-contrast study of the terminal ileum during a double-contrast barium enema, especially if glucagon is used. This type of study is useful in suspected ileal Crohn's disease or gynecologic malignancies involving the ileum.

A peroral pneumocolon, consisting of antegrade and retrograde components, is designed to evaluate the distal ileum or right colon. Initially, a conventional antegrade small bowel examination is performed. When barium outlines the terminal ileum, air is instilled through the rectum to obtain double-contrast views of the distal small bowel or proximal colon. This study can also be combined with enteroclysis. Routine use of a hypotonic agent is helpful.

BARIUM ENEMA

Single-contrast and double-contrast techniques are well established methods of evaluating the colon. Numerous studies have compared the relative accuracy of a single-contrast versus double-contrast barium enema. Some radiologists prefer a single-contrast study in older or debilitated patients.

Dry and liquid barium formulations are commercially available. If dry barium-prefilled enema bags are used, the amount of water added and degree of subsequent shaking to achieve wettability should be standardized. The level marking on the enema bag should not be used to gauge the amount of water needed; resultant dilutions tend to be erratic. Liquid barium-filled enema bags should be kept on their sides because considerable settling can occur if bags are stored before use.

A 12% to 25% w/v barium suspension is commonly used for single-contrast barium enemas. The main requirement of the barium suspension is that it neither flocculates nor settles during the examination. Because the sedimentation rate depends, in part, on the amount and type of additives present, some products that are well suspended at higher concentrations settle readily when diluted. If there is doubt about a commercial product's sedimentation rate, a radiograph obtained with a horizontal x-ray beam should reveal any settling tendencies.

Double-contrast barium enema suspensions should consist of relatively high barium concentrations but should still be sufficiently fluid to flow readily through enema tubing. Their viscosity is greater than that of the lower concentration barium formulations designed for single-contrast studies. The resultant mucosal coating should be uniform, without undue artifacts. The suspension should not dry out while an examination is in progress. These barium formulations are generally in the range of 60% to 120% w/v, with 85% being typical.

Even when all conditions are standardized, the subsequent mucosal coating can vary among practices because of variations in local water hardness and type of water used (distilled water or cold or hot tap water). Premixed liquid formulations are available to avoid these variations. The barium suspension is simply poured into an enema bag without further dilution.

Some radiologists perform colonic lavage before a barium enema. This lavage invariably results in water retention and subsequent dilution of the barium suspension. Barium manufacturers recognize this difference and market two different preparations; the one designed to be used after colonic lavage has a barium suspension with a slightly greater specific gravity.

Tumors can be difficult to detect in a segment involved by severe diverticulosis. This segment can be further studied if the double-contrast barium enema is followed by a methylcellulose enema.

WATER-SOLUBLE CONTRAST AGENTS

Indications

Water-soluble organic iodine compounds designed for the GI tract were introduced in the 1950s. Ever since, controversy has surrounded the relative merit and role of these agents. These compounds do not coat the GI mucosa; rather, they provide bowel visualization simply by passive filling of the intestinal lumen.

For most bowel examinations, experienced radiologists prefer barium suspensions. Some surgeons, however, are still being taught about the purported dangers of barium and insist on the use of water-soluble agents. Stimulation of peristalsis in postoperative patients and lack of radiographically visible sequelae of spill from the GI tract are reasons cited by some surgeons for their preference for water-soluble agents.

Water-soluble agents are indicated if an acute perforation is suspected. The examination generally confirms or excludes a perforation, with the realization that small perforations can be missed. Similarly, walled-off perforations or a perforation in an area of spasm can be difficult to detect, and it may be necessary to complete the examination with barium.

With a chronic or loculated perforation, the higher radiographic visibility of barium often yields more information than that obtained with water-soluble contrast agents. Thus, a chronic abscess or other cavity in continuity with the bowel lumen can be safely studied with barium. If there is a possible communication with the peritoneal cavity, however, water-soluble agents are preferred.

Meconium ileus and meconium plug syndrome can be treated with an iodinated contrast enema. The patient should be well-hydrated.

Some surgeons treat postoperative adynamic ileus with oral, full-strength, ionic contrast agents, but studies on these types of agents have been limited. Also, a hypertonic fluid proximal to a mechanical obstruction results in further distention.

Contrast Agents

In general, to achieve adequate radiographic opacification of most GI structures, at least a 60% solution of an ionic contrast agent is needed. The resultant iodine concentration is 282 to 292 mg/mL for the more commonly used commercial products, with a resultant osmolality of about 1500 mOsm/kg, or approximately five times that of serum. Because of this hyperosmolarity, fluid is drawn into the bowel lumen, and diarrhea is common after their use. These agents stimulate intestinal peristalsis, so faster visualization of the distal small bowel can be achieved than with barium sulfate. The need for a faster examination should be balanced against decreased radiographic contrast obtained with these agents. In general, intraluminal dilution leads to poor visualization of the small bowel.

Some commercial ionic contrast agents designed for oral use, such as the diatrizoate meglumine preparations Gastrografin and oral Hypaque, contain flavoring agents. These are preferred to the nonflavored products, which are designed primarily for IV use.

Nonionic contrast agents with an iodine concentration of approximately 300 mg/mL have an osmolality of 600 to 710 mOsm/kg, which is less than 50% of that of ionic agents. At this concentration, however, they are still hyperosmolar compared with serum.

Ideally, one of the nonionic agents should be used whenever a water-soluble agent is indicated for evaluation of the GI tract; for certain examinations, some radiologists use nonionic agents. If a perforation into the pleural or peritoneal cavity is suspected in an adult and aspiration is not a consideration, nonionic agents probably do not offer any major advantage over their ionic counterparts. Nevertheless, some leaks are better defined with barium than water-soluble agents. In studies of the GI tract in infants and children, in whom perforation is not an issue, barium rather than a water-soluble is the preferred contrast agent.

NEGATIVE CONTRAST AGENTS

When performing double-contrast GI studies, the cheapest second contrast agent is air. Excellent double-contrast esophageal views can be obtained if the patient swallows air together with the barium preparation.

One commercial preparation incorporated carbon dioxide directly in the barium suspension; when the patient drank this "bubbly barium," carbon dioxide was released into the esophagus and stomach. The effect was similar to that of drinking a bottle of club soda, and this product did not achieve ready acceptance.

Effervescent tablets, granules, and powders are commercially available. They produce carbon dioxide on contact with water and most are satisfactory in achieving adequate gastric and duodenal distention. There is, however, considerable variation in their dissolution time. Most commercial effervescent powders and granules come in single-dose packages. In clinical use, the patient places the effervescent agent in the mouth and uses small amounts of water to wash it down. This is immediately followed by a barium suspension. The swallowed gas is used for double-contrast views of the stomach and duodenum.

Liquid effervescent agents, consisting of separate acid and base solutions, can be prepared locally by a hospital pharmacy. The acid portion consists of citric and tartaric acids and the base portion is sodium bicarbonate. A dose of 12 to 15 mL is satisfactory for most patients.

Carbon dioxide is used by some in place of air for double-contrast barium enemas and CT colonography. Carbon dioxide is absorbed faster than air. Whether a gas or air is used probably does not influence examination quality although, with all other factors remaining constant, colonic distention is less with carbon dioxide compared with air.

Some double-contrast preparations result in excessive gas bubbles. An antifoam agent should be added empirically if these occur on a regular basis. Although many commercial barium preparations already include such an agent, in some areas the amount is not sufficient. A commonly used antifoam agent is dimethyl polysiloxane (simethicone); the addition of 1.5 mL of simethicone (equivalent to 100 mg) is often sufficient to eliminate bubbles.

GASTROINTESTINAL COMPUTED TOMOGRAPHY AGENTS

The term *double-contrast abdominal CT* is used by some to signify the use of IV and oral contrast. However, this is a misuse of the traditional connotation of double contrast and is best avoided to prevent confusion.

Full-strength barium preparations should not be diluted to the low concentrations needed for CT. The barium particles settle out after ingestion of such a dilute solution, leading to inhomogeneous bowel lumen opacification. The uppermost part of a loop of bowel may not contain enough barium for visualization, and excess barium in the dependent portion results in streak artifacts.

Stable but low-concentration barium formulations specifically designed for CT are commercially available, with most of these brand names ending in *-cat*. Most CT barium products contain small particles that resist settling. Additives selected also prevent barium sedimentation. At the low barium concentrations used, barium particles do not coat the mucosa but simply provide lumen opacification.

An esophagus marked with a contrast agent aids in evaluating the mediastinum during chest CT. The low-concentration CT agents used in the rest of the GI tract do not opacify the esophagus long enough, although one option is to have the patient drink small sips of a conventional CT contrast agent before each scan. More convenient is a high-viscosity, low-concentration barium paste, which provides prolonged esophageal coating.[22] Mucosal adherence by such a paste is long enough to allow a typical CT examination to be completed. Ingested water is often a useful and satisfactory contrast agent for evaluation of the GI tract during helical CT.

The traditional method of opacifying the stomach and small bowel is to have the patient drink approximately 500 mL of a dilute CT contrast agent several hours before the examination, with a similar amount ingested immediately before scanning. Ideally, such an agent should differentiate bowel from surrounding structures without introducing artifacts. Use of a dilute iodine solution or a barium suspension is generally a personal preference. A 1% to 3% w/v barium sulfate suspension or a 2% to 5% solution of Gastrografin or similar iodinated agent is typical. One refinement (granted, little practiced) is to use a 2.0% barium concentration for jejunal opacification and a slightly lower concentration for pelvic structures. With slower CT units, an iodine solution produces fewer streak artifacts than barium, a problem of little consequence with multislice CT. Commercial barium suspensions tend to taste better than iodine solutions, a factor when examining children and nausea-prone cancer patients.

The iodine taste can be masked by adding sugar and various fruit extracts; although essentially sugar-free iodine contrast is available, barium products, in general, contain less sugar than corresponding iodine contrasts. At the dilutions used, the iodinated solutions are hypoosmolar, but some patients still develop diarrhea. The poor taste and hence poor acceptance of iodinated agents by patients can be partly overcome by the empiric addition of a flavored juice such as Kool-Aid.[23] At the dilutions used in CT, nonionic contrast agents do not have any real advantage over ionic agents.

With suspected pelvic disease, a contrast agent can be ingested the evening before the examination. Even if full-strength Gastrografin is ingested, overnight dilution in the bowel is sufficient to eliminate most streak artifacts. Better rectosigmoid opacification is obtained after ingestion of such a full-strength contrast agent than dilute barium, probably because hyperperistalsis is induced by the iodinated agent. Nevertheless, identifying the large bowel is less of a problem than identifying fluid-filled loops of small bowel on abdominal CT.

Both CT and MR enterography can detect Crohn's disease with somewhat similar accuracy.[24] Adequate CT bowel opacification can be achieved by using a 2% flavored barium suspension.

CT enteroclysis consists of bowel intubation and instillation of an iodinated contrast agent, dilute barium suspension, or methylcellulose suspension. Whether a positive or water-density agent is superior is not clear; an IV contrast agent to opacify bowel mucosa aids in lesion detection. Negative oral contrast agents designed specifically for CT enteroclysis have also become available. Also, with MDCT and coronal reconstruction now more readily available, retained bowel fluid often provides a sufficient marker, especially in dilated bowel loops.

If the imaging study is performed to evaluate a rectal lesion, a high-viscosity, low-volume barium paste may suffice; approximately 100 mL of a 3.6% w/v carboxymethylcellulose and 2% w/v barium sulfate paste mixture has been proposed in this clinical setting.[25]

A basic question when protocoling an examination on multidetector CT is whether intraluminal water-density or

fat-density contrast, or even a gas, is superior to a positive contrast agent. Positive bowel contrast creates artifacts, especially with maximal intensity projection images of vascular structures. Also, bowel wall enhancement by IV contrast is useful for detecting bowel wall thickening, and a positive intraluminal contrast can obscure subtle lesions. As a result, MDCT studies can be performed with oral water-density or even negative contrast agents. Although adequate for gastric and duodenal distention because of its absorption from the bowel, ingested water does not readily distend the distal small bowel; use of a carboxymethylcellulose or polyethylene glycol solution inhibits absorption and improves distention (compared to water). A preliminary study of simethicone-coated cellulose (SonoRx, Bracco Diagnostics, Monroe Township, NJ), developed for oral use in upper abdominal ultrasonography, found no significant advantage over oral water in abdominal CT.[26]

In the past, a number of fat density products, such as mineral oil, corn oil, and milk, and even a paraffin emulsion, were proposed for CT use, but these have had limited application. Residual bowel gas often serves as a marker, especially in the colon. If a nasogastric tube is in place, air can be injected into the stomach and small bowel. If excessive amounts of gas are present, imaging with window settings slightly wider than usual is helpful. 2D colonography and 3D virtual colonoscopy require colonic distention with a contrast agent; typically, air is used, and carbon dioxide is used less often.

ADVERSE REACTIONS

Barium Sulfate

Barium sulfate is poorly soluble in water. The constipating tendency of barium products is well known to most radiologists. Through the judicious use of additives, this side effect is minimized in most current formulations, although barium impaction in the colon is still occasionally encountered.

Aspiration of small amounts of commercial barium formulations is of little clinical significance. After barium aspiration, most is cleared from major bronchi and trachea within hours, although some is retained in the interstitium and in macrophages. This residue is generally not visualized on radiographs. Alveolarization of barium, however, can result in prolonged retention. If aspiration is suspected clinically, nonionic, sterile, iso-osmolar iodinated contrast can be used rather than barium.

Hypersensitivity reactions during GI examinations are rare, although they have been known to occur. Although barium sulfate is inert, commercial formulations contain numerous known proprietary additives.[27] These include stabilizing, flavoring, coating, and viscosity-varying agents and range from natural flavors and gums, such as lemon, pectin, and guar, to synthetic products, such as various methylcelluloses. Some radiologists may still be familiar with chocolate-flavored barium products, which are no longer used because of common allergies to chocolate. Anaphylaxis can be caused by carboxymethyl. The role of effervescent agents in these reactions is speculative. Methylparaben and similar compounds, used as preservatives, can induce hypersensitivity reactions, but barium manufacturers have replaced them with more innocuous preservatives in most commercial barium products.

Reactions appear to be more common during double-contrast than single-contrast studies. Most reactions are mild and consist of urticaria or pruritus, although erythema multiforme, respiratory complications, anaphylaxis, GI angioedema, and even death have occurred. Patients with asthma and severe food allergies appear to be at a slightly increased risk for these reactions, but the average radiologist will probably not encounter a hypersensitivity reaction to a barium product in a lifetime of practice.

The cause of hypersensitivity reactions during most barium studies is not known. In general, the incriminating agent is not sought and no testing performed in most patients who develop a reaction.

Esophageal perforation and spillage of barium into the mediastinum result in an inflammatory reaction, with barium persisting in the mediastinum for a prolonged period. Such prior extravasation can often be recognized radiographically as dense linear radiopacities, but no strong evidence exists that these sequelae have any clinical significance for the patient.

Most perforations associated with a barium enema occur in the rectum and are not immediately detected by fluoroscopy. Rectal perforations tend to result from injudicious insufflation of an enema balloon. A British survey over a 3-year period between 1992 and 1994 revealed a complication rate of 1 in 9000 and a death rate of 1 in 57,000.[28] Although 10% of patients with a bowel perforation died (3 of 30), the mortality was 56% (9 of 16) in patients developing a cardiac arrhythmia.

Spillage of barium into the peritoneal cavity can be secondary to a preprocedure perforation, such as in patients with ulcers. Some perforations, however, are associated with a barium study and can occur during an upper GI examination or barium enema, and even during enteroclysis. Initially, leukocytes are drawn into the peritoneal cavity, together with an inpouring of fluid. Profound hypovolemia develops if massive inpouring of fluid into the peritoneal cavity is untreated. Bacterial contamination during a perforation can result in overwhelming sepsis and shock within hours.

Immediate management of barium peritonitis includes infusion of large volumes of IV fluid. Antibiotics are administered because of associated bacterial contamination. Most patients undergo surgery, with an attempt made to evacuate barium from the peritoneal cavity. Invariably, barium crystals embedded on the peritoneal surface resist dislodgment. Attempts to remove barium particles with a wet sponge simply induces diffuse peritoneal bleeding.

Barium crystals incite an inflammatory reaction; eventually, these crystals become coated by a fibrin membrane, and extensive fibrosis and granulomatous tissue develop. Dense fibrosis can involve adjacent structures and, depending on location, subsequent ureteral obstruction or bowel deformity and stenosis develop. Perirectal fibrosis can narrow the rectosigmoid lumen and even mimic a carcinoma. Residual barium is identified with conventional radiography or CT. No evidence suggests that barium in soft tissues is a carcinogen (Fig. 1-2).

The barium intravasation can involve systemic veins and the portal venous system.[29,30] Some patients have no predisposing factors to account for intravasation. Overall, barium intravasation is associated with a mortality rate of more than 50%.

Water-Soluble Agents

The risk of sensitivity reactions to oral iodinated contrast agents is considerably less than with intravascular injection. In young children and adults with hypovolemia, however, the introduction of large volumes of a hypertonic agent into the GI tract

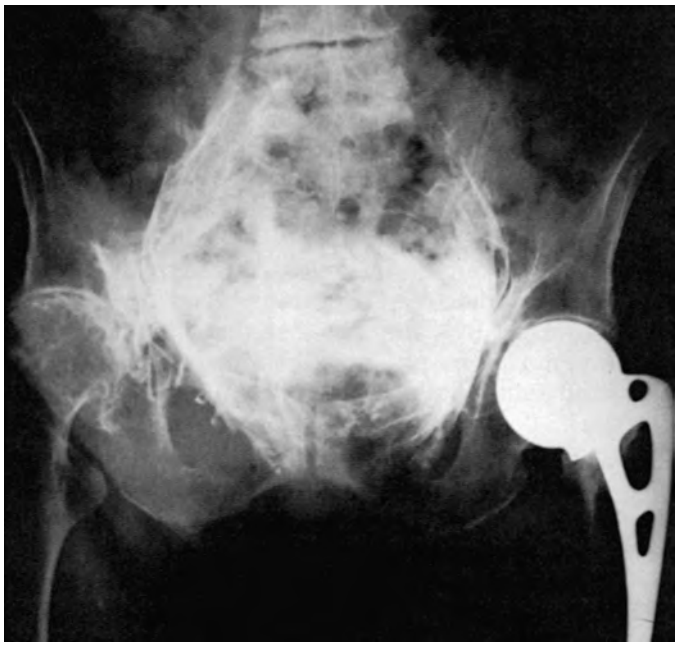

Figure 1-2 Prior colonic perforation during a barium enema. Barium crystals are encased by dense adhesions that also involve bowel. *(From Miller RE, Skucas J: Radiographic Contrast Agents. Baltimore, University Park Press, 1977, p 137.)*

can result in hypovolemia, shock, and possibly death. In such a setting, adequate intravascular fluid replacement and the use of a nonionic contrast agent should be considered.

If aspiration or a tracheoesophageal fistula is suspected, hyperosmolar ionic contrast agents are contraindicated because they can induce pneumonia, pulmonary edema, or death. The nonionic agents are reasonable substitutes. In most adults, however, barium sulfate is the preferred contrast of choice.

Other Contrast Agents

Some reactions occur even before a contrast agent is instilled. Latex, used in some enema balloons, has been implicated in some reactions. The offending antigen in latex is believed to be a water-soluble, heat-stable protein. It is found on the surface of cured latex and probably is a contaminant of natural latex when it is obtained from the *Hevea brasiliensis* tree. In sensitive individuals, contact with skin leads to urticaria; contact with mucous membranes can result in more severe anaphylactic reactions. Currently, nonlatex and synthetic latex products are available.

Cholangiographic Contrast Agents

With normal renal function, only about 1% of an ionic or nonionic contrast agent dose undergoes hepatic excretion, which is insufficient for CT bile duct visualization. In the setting of renal failure, however, it is not unusual to detect gallbladder opacification, even with conventional radiography.

Cholecystography using oral cholecystographic agents has been supplanted by other imaging modalities and currently is rarely performed. Several commercial cholecystographic agents are available. To ensure oral absorption, they have hydrophilic and lipophilic properties; in blood, they are bound to albumin and, theoretically, should have high toxicity, but in actual practice, adverse reactions are uncommon. They undergo enterohepatic circulation and occasionally delayed reactions are encountered.

IV cholangiographic agents undergo hepatocyte uptake and biliary excretion by active transport. They are excreted unchanged or after conjugation with glucuronic acid. These hepatocyte-specific liver contrast agents consist of triiodobenzene compounds which, by means of benzene ring substitutions, have had their hydrophilicity decreased to the point that they can now pass through membranes. Iodipamide meglumine (Cholografin) is the only agent available in the United States. Most of the injected contrast is bound to albumin; biliary visualization is generally evident about 15 minutes after the start of IV injection. One might assume that because cholangiographic agents undergo hepatocyte uptake, they would make useful CT liver contrast agents; in actual practice, however, hepatocyte uptake is too slow and excretion too fast for them to serve this function.

Toxicity and allergic reactions are more severe with iodipamide than with more typical intravascular contrast agents. Nephrotoxicity is dose dependent. In part because of this toxicity, cholangiography has been supplanted by other imaging, including MRI and direct cholangiopancreatography. The latter is achieved by percutaneous transhepatic cholangiography, an endoscopic retrograde approach, or injection through a surgically placed tube.

Direct cholangiography is generally performed with full-strength contrast concentrations (≈300 mg iodine/mL). In particular, when searching for subtle leaks, a high iodine concentration is advantageous. Also, when injecting proximal to an obstruction, a high iodine concentration allows for dilution by residual bile. When searching for stones, however, dilution of contrast with an equal volume of water appears useful; subtle stones can be missed in markedly opacified bile ducts. Contrast overinjection during direct cholangiography should be avoided. In the United States, syringe injection is common, but in Europe, a drip infusion technique is more popular. The study should be terminated if the pancreatic duct begins to opacify—acute pancreatitis is a complication of this study. Earlier studies suggested that meglumine salts of ionic contrast agents resulted in less bile duct epithelial damage than corresponding sodium salts; the use of nonionic contrast makes this point moot.

Indications for CT cholangiography have been evolving. CT cholecystography is performed 10 to 12 hours after oral administration of a cholecystographic contrast agent (iopanoic acid). Another approach is slow infusion of a cholangiographic contrast agent, resulting in biliary images superior to those obtained with conventional IV cholangiography. Major intrahepatic ducts are visualized in most individuals. Preliminary evidence has suggested that CT cholangiography is somewhat superior to MR cholangiopancreatography (MRCP) in visualizing small biliary stones. It is not useful in jaundiced patients because insufficient contrast is excreted into bile ducts.

MRCP is a noninvasive imaging technique for visualizing biliary and pancreatic ducts. It has evolved as an alternative to diagnostic endoscopic retrograde cholangiopancreatography (ERCP) and diagnostic percutaneous cholangiography. Two approaches are feasible—an IV contrast-assisted technique and a technique without contrast using heavily T2-weighted images to make nonflowing fluid hyperintense. The former uses primarily hepatobiliary MR agents (see later); contrast-containing

bile is hyperintense on T1-weighted sequences. A limitation of this procedure is that reasonable hepatocyte function is required to accumulate enough biliary contrast to be imaged. The contrast-less technique, often simply called MRCP, has none of these limitations and has become the primary imaging study for visualizing bile ducts.

Magnetic Resonance Imaging Contrast Agents

INTRAVASCULAR AGENTS

The term *contrast agent* has a different meaning in MRI than usually applied to barium sulfate or iodinated agents. MRI contrast agents are not visualized directly; rather, their primary function is to alter water proton relaxation times. These agents have considerable variation in diffusion and renal clearance, thus leading to the use of a specific contrast agent for a specific application. Although MRI contrast agents are more complex and serve a more varied function than CT contrast agents, they are used for the same primary purpose—to improve lesion detection and characterization by increasing contrast tissue signal intensity differences because of different effects on tissue proton relaxation. These differences vary with time and depend on the degree of lesion vascularity. Much current MRI contrast agent research has focused on improving their specificity.

MRI contrast agents are often classified by their metal component. A more useful classification is based on their distribution, with the realization that many agents overlap between categories; many are initially blood pool agents but subsequent distribution depends on their molecular configuration:

1. Conventional gadolinium chelates (extracellular agents)
2. Macrophage-monocytic phagocytic (reticuloendothelial) agents
3. Primarily hepatobiliary agents (intracellular agents)
4. Primarily blood pool agents

All currently available MRI contrast agents shorten tissue T1 and T2 relaxation times. The paramagnetic gadolinium and manganese contrast agents primarily shorten T1 and thus increase signal intensity (enhancement) of normal parenchyma on T1-weighted images. The superparamagnetic iron oxides primarily shorten T2, thus decreasing signal intensity on T2-weighted images and, depending on the sequence used, increase the T1 signal. These metal ions are chelated to other structures, such as DTPA, to reduce their toxicity.

Gadolinium Chelates

The most often used vascular MRI contrast agents are gadolinium chelates. These mostly hydrophilic compounds are chelated to "mask" the toxic gadolinium ion. Their biodistribution and perfusion-related issues are similar to iodine-containing contrast agents. To take full advantage of these MRI contrast agents, dynamic imaging must be performed shortly after contrast injection (arterial to portal venous phases); later, these agents equilibrate with the extracellular space, and lesions become isointense to parenchyma. Liver tumor detection with these agents relies on differences in blood flow between tumor and normal tissue. A more recent application of these agents is in MR angiography (MRA) as a substitute for abdominal digital subtraction angiography (DSA). Image processing allows for the separation of arteries and veins.

At recommended doses, gadolinium chelates have a lower adverse reaction rate than iodinated contrast agents, but anaphylactic reactions and even cardiopulmonary arrest, including fatal ones, do occur. Risk factors for reactions are not well defined but appear to be similar to those for iodine contrast. Unlike iodine-related reactions, gadolinium-related reactions tend to be delayed, at times occurring even 1 hour or more later. These agents are excreted by glomerular filtration and, in the usual doses, nephrotoxicity is uncommon, although nephrogenic systemic fibrosis has been reported in some patients with renal disease.[31]

In patients on hemodialysis, about 80% of gadolinium is dialyzed after the first and essentially all after the fourth dialysis. A normal dose has been used in hemodialysis patients.

Gadolinium agents exhibit poor water relaxivity at higher magnetic fields (>4 T). Undoubtedly, new MRI agents will be developed for use with high field strength magnets.

Reticuloendothelial Agents

Larger superparamagnetic iron oxide (SPIO) particles are taken up by the reticuloendothelial system (RES) and, among other effects, result in decreased liver and spleen parenchymal enhancement on T2-weighted images. Uptake is also present in lymph nodes and bone marrow. Ferumoxides (Endorem, Guerbet, Villepinte, France) is an SPIO agent consisting of a colloidal mixture of ferrous and ferric oxide. Tissues lacking reticuloendothelial (RES) cells, such as metastases, have little or no signal loss and thus appear hyperintense to the resultant hypointense, normal RES-containing liver or spleen parenchyma. Not only are known tumors better identified but, compared with unenhanced MRI sequences, more tumors are detected. This differentiation is not absolute, however, because some well-differentiated neoplasms contain RES cells and thus take up iron oxide particles. These SPIO-induced changes differ among various tumors, potentially providing tissue characterization of different tumors. SPIO enhancement is impaired in diffuse liver disease. Nevertheless, imaging interpretations with these compounds is complex; some of the particles are ultrasmall, and T1-weighted gradient-echo sequences result in imaging patterns similar to those with Gd chelates and ultrasmall SPIO particles.

These agents have a longer intravascular half-life than gadolinium chelates. A prolonged scanning window is available once these particles are within the RES; eventually, free iron is used in normal iron metabolism. Their role in clinical imaging has not yet been clearly defined. Disadvantages include prolonged scanning times and an increased false-positive rate.

Hepatobiliary Agents (Intracellular Agents)

Several hepatobiliary-specific paramagnetic contrast agents, such as Gd-EOB-DTPA (Eovist, Bayer Imaging, Whippany, NJ) and Gd-BOPTA (MultiHance, Bracco Diagnostics) are initially extracellular and then undergo hepatocyte uptake. Early dynamic perfusion imaging is similar to that with conventional gadolinium chelates, but this can be followed by delayed hepatic imaging; each phase yields different information. Image interpretation differs from conventional gadolinium scans; thus, with Gd-BOPTA, a hepatocellular carcinoma shows early peripheral enhancement, but parenchymal phase images reveal an isointense or even hypointense tumor.[32]

These agents are eliminated by biliary and renal pathways. Eovist achieves greater liver enhancement than MultiHance, has

a biliary excretion rate of about 50% of the injected dose, and a delayed biliary phase is evident. Gd-BOPTA exhibits a T1 relaxivity roughly double that of conventional gadolinium agents, probably secondary to its binding to albumin, which decreases extravascular leakage. Although only a small percentage is taken up by hepatocytes, this has a prolonged effect on liver signal intensity.

Mn-DPDP (Teslascan, GE Healthcare AS, Buckinghamshire, England) dissociates partly in plasma, with free Mn^{2+} taken up by hepatocytes and other tissues, including the pancreas. Nondissociated Mn-DPDP is eventually eliminated by the kidneys. It is often considered to be a hepatobiliary-specific paramagnetic contrast agent, having an effect lasting for several hours, thus permitting delayed imaging. It is injected by slow IV infusion, so dynamic imaging is not feasible. On T1-weighted images, this agent selectively enhances normal liver parenchyma and hepatocyte-containing tumors such as focal nodular hyperplasia, regenerative nodules, and hepatocellular adenomas and carcinomas, but shows little or no enhancement of metastases, cysts, and hemangiomas. This agent differentiates hepatocellular carcinomas from metastases, with metastases of nonhepatocyte origin becoming more conspicuous because of an increased signal from surrounding normal liver parenchyma. An exception is metastatic neuroendocrine tumors; occasionally, these tumors enhance with Mn-DPDP. A possible use is during MRI-guided thermal tumor ablation when prolonged tumor visualization is beneficial[33]; Mn-DPDP identifies more focal tumors in cirrhotic and noncirrhotic livers than detected on precontrast images. It appears useful in defining intrahepatic biliary anatomic variants, such as in pretransplantation liver lobe donors. Because it does not differentiate between benign and malignant primary liver neoplasms, its diagnostic impact is not clear.

Manganese is excreted in bile, but excretion is inhibited in biliary stasis. It is contraindicated in severe liver failure. Mn-DPDP's overall safety appears to be similar to that of the other hepatocyte gadolinium products.

Blood Pool Agents

Ultrasmall superparamagnetic iron oxide (USPIO) particles, unlike most MRI contrast agents, shorten T1 and T2 relaxation times, with a few exceptions. Initially conceived as MRI lymphographic agents, their current role has evolved mostly into blood pool agents. They have a blood half-life measured in hours. One disadvantage is the superimposition of arteries and veins, although image processing techniques such as subtraction and phase contrast can differentiate these structures. These iron oxide contrast agents appear useful in differentiating highly vascular lesions, such as hemangiomas, from solid neoplasms. Also, their prolonged reduction of intravascular T1 values makes them useful for MR angiographic interventional procedures without need for repeat contrast injection. Their relaxivity increases at lower field strengths, and they are therefore suitable for use in open magnets.

Iron oxide particles smaller than 10 nm pass through capillaries and are eventually cleared by liver, spleen, bone marrow, and lymph node reticuloendothelial cells, resulting in homogeneous signal loss in these structures. These agents therefore can potentially identify lymph node metastasis independently of node size; normal nodes lose signal intensity but nodes (or regions of nodes) containing metastases do not take up these particles.[34]

A potential use for iron oxide agents is to label them with a target-specific drug, such as cholecystokinin, with receptors in the pancreas. Development of such agents is still in its infancy.

A separate group of blood pool contrast agents consists of gadolinium-based products bound to albumin, dextran, or another similarly large molecule (also called macromolecular MRI contrast agents); imaging using Gd-BOPTA has already been discussed (see earlier). Biodegradable polymeric MRI contrast agents have been reported.[35] Tight albumin binding prolongs blood pool time. The clinical role of these agents presumably will be similar to that of USPIO agents.

Carbon dioxide is a blood pool MRI contrast agent. An intravascular column of carbon dioxide leads to signal loss and results in a black blood MR angiography technique.

More complex applications of MRI contrast agents involve combining two agents (sometimes called double-contrast MR imaging). For example, more information is obtained about a focal tumor by combining perfusion data of a gadolinium chelate with its RES status obtained with a SPIO agent than is possible with a single agent alone. Such combined contrast agent use is mostly experimental.

Another research approach involves excitation-based, frequency-labeled, exchange transfer imaging to separate tissue magnetization transfer contrast components by using a paramagnetic chemical exchange saturation transfer agent.[36] MRA of hepatic vessels appears comparable to DSA and superior to portal vein images for evaluating liver arteries.

GASTROINTESTINAL AGENTS

An oral MRI bowel contrast agent identifies the bowel lumen and differentiates the normal bowel wall from an abnormal process. Bowel distention can be obtained by injecting contrast via a nasojejunal catheter (enteroclysis) or having the patient drink a large quantity of fluid (enterography). An oral contrast agent aids in identifying a soft tissue tumor in the bowel wall and in adjacent organs.

Oral MRI contrast agents are subdivided into positive contrast agents, which predominantly shorten T1 and increase MRI signal intensity on T1-weighted images, and negative contrast agents, which shorten T2 and decrease signal intensity or simply lack hydrogen protons and water-density contrast. Positive contrast agents consist of various iron, manganese, and gadolinium paramagnetic compounds; they are useful in detecting sinus tracts. On the other hand, they mask intraluminal content and make bowel wall visualization difficult.

A distinction between positive and negative contrast agents is not absolute, and some agents change properties with dilution and the MRI sequence used. Gadolinium is a positive contrast agent that shortens T1 in the small bowel but, when concentrated in the colon, it acts as a negative contrast agent. Ferric ammonium citrate is hyperintense on T1- and T2-weighted images at concentrations lower than 45 mg/mL; at higher concentrations, and at 10 to 20 mg/mL, bowel loops become hypointense on T2-weighted images. A more relevant issue is whether such contrast improves lesion detection; current results are not clear.

A dilute barium sulfate suspension is a useful negative agent. Perfluorocarbons lack hydrogen protons and do not produce an MRI signal on T1- or T2-weighted images, but their role as oral agents is not established. Methylcellulose, polyethylene glycol, and dilute magnesium sulfate[37] have been evaluated. Air and

water are also MR contrast agents. Nonabsorbable water-density agents are similar to those used for CT (see earlier).

Positive contrast agents accentuate motion artifacts. However, contrast artifacts are more pronounced with negative agents, but bowel wall abnormalities are better evaluated with negative agents. Antiperistaltic pharmacologic agents have been used; they reduce motion artifacts, even with a high field strength unit.

MR colonography is performed using water, a gadolinium solution, or a barium suspension as a luminal contrast agent. Evaluation can include surface-rendered, virtual endoscopic endoluminal views, orthogonal sections in three planes, and water-sensitive images.[38] A preliminary report has suggested that MR proctography is inferior to barium proctography for detecting pelvic floor abnormalities.[39]

Pharmacoradiology

Pharmacologic agents useful in GI radiology will be discussed in this section. Included are those having an intravascular effect (vasoconstrictors and vasodilators), those modifying gut motility, and those affecting bile flow. Excluded are experimental agents, agents designed for molecular imaging, and therapeutic materials.

From a radiologist's viewpoint, most gut motility agents can be divided into those that increase GI tonicity and motility and those that decrease these functions. Some agents have different effects on different parts of the GI tract; they are discussed separately in the section on mixed action agents.

Bowel tonicity is not the same as peristalsis. In general, however, pharmacologic agents that increase bowel tonicity also result in increased peristalsis. For example, agents inducing gastric hypertonia tend to result in faster gastric emptying and hypertonic small bowel agents result in faster small bowel transit. Hypotonic agents have an opposite effect.

One exception to this classification is famotidine, which suppresses gastric secretions. A preliminary report suggested that famotidine may be useful prior to an upper GI examination; the decreased gastric secretion improved the quality of the examination.[40]

VASOCONSTRICTORS

The primary use of vasoactive drugs in abdominal imaging is to alter blood flow in a way designed to increase diagnostic accuracy. Some drugs aid delivery of chemotherapeutic agents to neoplasms. All side effects must be acceptable. Vasoconstrictors aid primarily in detecting and characterizing neoplasms; they constrict normal blood vessels but have little if any effect on malignant vessels.

Epinephrine, an adrenergic hormone, stimulates α and β receptors and, depending on specific innervation, results in vasoconstriction or dilation. Initially used in renal arteriography, epinephrine decreases contrast opacification of normal renal parenchyma, thus accentuating renal cell carcinoma vasculature. Limitations for the use of epinephrine include a variable dose response and the ability of some inflammatory tissue neovascularity to respond similarly to neoplastic neovascularity. Hepatic and splenic arterial injection results in spasm of these vessels but little constriction of normal hepatic, gastric, duodenal, and pancreatic small vessels. Also, normal mesenteric vessels do not respond appreciably to epinephrine.

Propranolol blocks β-adrenergic vasodilation and, when used in conjunction with epinephrine, results in mesenteric vessel vasoconstriction.

Norepinephrine has α receptor stimulation similar to that of epinephrine but lacks β receptor stimulation. It has been less well studied for imaging use than epinephrine.

Patients with a pheochromocytoma have increased epinephrine or norepinephrine levels after contrast injection; it thus appears prudent to premedicate these patients with α- and β-adrenoceptor antagonists to control symptoms and prevent an adrenergic crisis, although this may not be necessary when using some nonionic contrast agents.

Angiotensin, a hormone family with vasoconstrictive activity, is a potent vasoconstrictor acting on normal vessel smooth muscle. Similar to epinephrine, it tends to enhance visualization of malignant neoplasms by a selective increase in tumor blood flow.

Vasopressin in pharmacologic doses has a pressor effect and constricts normal splanchnic small vessels (including capillaries), thus decreasing portal blood flow. It has little effect on hepatic artery flow. Transcatheter vasopressin infusion controls some GI hemorrhage, keeping in mind that intra-arterial administration may cause mesenteric infarction or small bowel necrosis.

Bombesin, a gut peptide, releases endogenous gastrin, which activates gastric mucosal sensory neurons, which in turn increase gastric mucosal blood flow and thus protect the mucosa against damage. Somatostatin negates this bombesin-induced gastroprotection. Although bombesin is not used in radiology, the somatostatin analogue, octreotide, has been used for therapy of esophageal and gastric variceal bleeding. Gut neuroendocrine tumors also contain somatostatin receptors, and octreotide is useful for diagnosis and palliation of these tumors. It suppresses carcinoid tumor symptoms.

VASODILATORS

Vasodilators increase blood flow in a selective vascular bed. Their effects differ in normal and neoplastic vessels, but vasodilators are less suitable than vasoconstrictors for outlining small neoplasms; increased normal vascularity tends to obscure a small tumor. Occasionally helpful is a high-calorie meal, which accentuates superior mesenteric artery and portal vein blood flow.

Tolazoline, an adrenergic alpha receptor blocking agent and synthetic vasodilator, aids in the angiographic visualization of small vessels. Direct mesenteric artery injection leads to improved venous visualization. Its effect on neoplasm visualization is mixed. Whether tolazoline has a role in intra-arterial provocative mesenteric angiography to identify GI bleeding is not clear. Infusion therapy with tolazoline and heparin has been used to treat nonocclusive mesenteric ischemia.[41] Intra-arterial verapamil and tolazoline appear to be comparable in their vasodilatory efficacy.[42]

Bradykinin is a nonapeptide, produced from decapeptide kallidin, normally present in blood in an inactive form. Bradykinin is a plasma kinin, potent vasodilator, and one of the mediators of anaphylaxis released from cytotropic antibody-coated mast cells. Radiographically, bradykinin injected into the superior mesenteric artery improves portal vein visualization.

Acetylcholine, a parasympathetic hormone, is a vasodilator previously used mostly to evaluate renal artery stenosis.

Dopamine, a potent renal artery dilator, is similar to acetylcholine; it has also been studied mostly in renal vessels. Preliminary work has suggested that dopamine decreases contrast-induced nephrotoxicity, but further studies found that it may have a deleterious effect.[43]

Prostaglandins have variable vascular effects, depending on their chemical composition and specific use. Prostaglandin therapy is used in neonates with cyanotic congenital heart disease. Prostaglandin E1 (PGE1) has a similar effect on splanchnic vasculature as acetylcholine and tolazoline, resulting in increased portal vein blood flow. Thus, superior mesenteric artery injection of PGE1 during CT hepatic arteriography results in increased conspicuity between hepatocellular carcinoma nodules and surrounding parenchyma.[44] Also, the use of PGE1 during CT hepatic arteriography helps reduces the number of pseudolesions around the gallbladder bed.[45] Preliminary work has suggested that it may reduce contrast-induced nephropathy, but this is associated with a number of side effects, and its role is not clear. PGF2α dilates normal colonic vessels but vasoconstricts inflammatory and neoplastic colon vessels.

Persistent, usually asymptomatic, gastric distention, detected on radiographs, is a complication of prostaglandin therapy. Distention usually resolves after cessation of therapy. Superficially, this condition resembles pyloric stenosis, although imaging shows gastric mucosal thickening and distal antral and pyloric elongation, but no muscular wall thickening.

Papaverine is a vasodilator of large and small vessels. Similar to other vasodilators, it improves portal vein visualization during mesenteric angiography. It is not degraded in a single pass through the liver, and repeated injections can lead to systemic hypotension.

Secretin increases pancreatic blood flow. At times, selective venous sampling after intra-arterial secretin injection aids in detecting gastrinomas. IV secretin, however, does not appear reliable enough for detecting chronic pancreatitis or a pancreatic adenocarcinoma.

GASTROINTESTINAL AGENTS THAT PRODUCE HYPOTONIA

Bowel hypotonia is helpful in a number of settings. For example, a spasmolytic agent dilates a segment of spastic colon that otherwise might mimic a benign stricture or malignancy. Similarly, polyps and diverticula in the small bowel can be detected more readily if the bowel is dilated and atonic. Spasmolytic pharmacologic agents can be divided into hormonal agents (e.g., glucagon) and anticholinergic agents. Agents evaluated for use in the GI tract include morphine, propantheline bromide (ProBanthine), atropine, and related compounds. With some agents, after initial enthusiasm, recognition of toxicity and undesirable side effects led to their abandonment.

Glucagon

Human glucagon is a single-chain polypeptide containing 29 amino acid residues, with a molecular weight of 3483. It is generated by α cells in the islets of Langerhans. In some species, glucagon is also produced in the stomach; whether any gastric glucagon is produced in humans is controversial. The glucagon amino acid sequence in animals ranges from one similar to that in humans to completely different sequences. Identical amino acid sequences are found in humans, pigs, and cattle; this was once significant, when glucagon was obtained from animal pancreatic tissue, but became a moot issue when a synthetic product was developed. Injectable glucagon is produced by the expression of recombinant DNA. The chemical structure of this synthetic glucagon is identical to that of human glucagon.

Glucagon is a hormone that has significant metabolic influence on a number of organs. It binds at specific receptor cell membranes in target organs. In the liver, it stimulates glucose output and hepatic ketogenesis. It lyses adipose tissue and leads to a reduction of circulating cholesterol and triglyceride levels. It stimulates insulin release and appears to be involved in liver regeneration, but its full role in the liver is not clear. Glucagon increases blood flow to the kidneys. Specific effects are also present in the adrenal glands and heart. It is metabolized in the liver and kidney. Glucagon is degraded by gastric secretions and therefore is ineffective when given orally.

In smooth muscle, glucagon is a relatively potent spasmolytic agent, and it is this spasmolytic action that accounts for its use in radiology. Pharmacologic doses are used. Smooth muscle in different GI tract segments varies in sensitivity to glucagon (Table 1-1). For example, 0.1 mg IV is sufficient to induce gastroduodenal hypotonia in most adults, but such a small dose is inadequate for colonic hypotonia, for which a dose several times greater is needed.

Intravascular glucagon is also a vasodilator. It improves portal vein visualization during mesenteric arteriography, although it has been replaced by other vasodilators because of its propensity to induce nausea and vomiting at the doses required for vasodilation.

Gastrointestinal Tract. Acute esophageal obstruction caused by food impaction is often related to an underlying stricture or spasm. Spasmolytic drugs have been recommended if spasm is suspected, but in a multicenter, double-blind study of glucagon and diazepam, no significant difference in disimpaction was evident between spasmolytic agents and placebo.[47] Effervescent agents have also been used to treat esophageal food impaction, with varying success.

The main advantage of glucagon over anticholinergic agents in inducing upper GI tract hypotonicity is its lack of side effects. In the United States, glucagon is generally used to induce hypotonia; in some countries, the anticholinergic agent scopolamine butylbromide (Buscopan) is used more often. One reason for using an anticholinergic agent is the higher cost of glucagon, although the price ratio of glucagon to Buscopan fluctuates considerably worldwide.

Glucagon decreases intragastric and intraduodenal mean pressures. Some studies suggest that barium mucosal coating in

TABLE 1-1 Spasmolytic Effect of Intravenous Glucagon: Average Duration of Atonicity (min)

Location and Response	GLUCAGON DOSE (mg)			
	0.25	0.5	1	2
Stomach	4.9	8.7	10.1	15.1
Duodenal bulb	7.5	10.1	12.5	16.7
Duodenum	7.8	10.1	12.5	16.1
Proximal small bowel	8.3	9.4	13.7	19.7
Distal small bowel	8.6	9.4	14.0	19.7

From Miller RE, Chernish SM, Brunelle RL, et al: Double-blind radiographic study of dose response to intravenous glucagon for hypotonic duodenography. Radiology 127:55–59, 1978.

the stomach and duodenum is improved more with anticholinergic agents than with glucacon, the rationale being that anticholinergics also decrease gastric secretions, whereas glucagon has no such effect. In actual practice, Buscopan and glucagon produce essentially equal distention and barium coating of the stomach and duodenum. A more basic question is whether induced gastric and duodenal hypotonia improves the ability to detect lesions. The diagnostic quality with and without glucagon does not appear to differ significantly. Radiologists in the United States tend not use a hypotonic agent during upper GI studies.

In enteroclysis, barium is instilled until a lesion or obstruction is reached, or the terminal ileum is filled. Glucagon is helpful if it is deemed desirable to slow down barium progression, such as when a suspicious region is identified. In general, 0.25 mg IV is sufficient to induce hypotonia, permitting a leisurely study of the region in question.

During a barium enema, glucagon relaxes the ileocecal valve and allows easier barium reflux into the distal small bowel. Thus, if retrograde ileography is being performed for suspected distal ileal disease, it appears reasonable to administer glucagon. Anticholinergics have little effect on the ileocecal valve.

In select patients, a peroral pneumocolon examination allows double-contrast study of the terminal ileum and right colon. Barium is introduced via a conventional oral examination or enteroclysis approach, and air is added through an enema tip. Because glucagon relaxes the ileocecal valve, it may increase the success rate of this examination.

Colon hypotonia is achieved by injecting 2 mg of glucagon intramuscularly. Hypotonia begins within several minutes and lasts about 15 minutes. Hypotonia can also be achieved with 0.25 to 0.5 mg of glucagon IV, although in some patients up to 1.0 mg may be necessary; the onset of hypotonia with an IV injection is almost immediate and lasts approximately 10 minutes. In general, the smaller IV dose is used because of cost considerations. In infants and children, an IV dose of 0.8 to 1.25 μg/kg has been recommended.[48]

Few studies have evaluated whether the use of glucagon results in a more accurate diagnosis, and whether glucagon is injected during a barium enema varies considerably among radiologists. It is more commonly used in hospitalized, older, and ill patients. In some practices, it is injected routinely for double-contrast barium enemas but individualized with single-contrast studies. In an outpatient setting, many radiologists use glucagon when a patient has painful spasm or spasm interfering with the examination, is unable to retain the enema, or has suspected colitis or diverticulitis. Glucagon decreases the extent and severity of colonic spasm during a barium enema and makes patients more comfortable.

Occasionally, colonic spasm persists despite administration of glucagon. It has been my empiric observation that patients with long-standing diabetes have more glucagon-resistant colonic spasm than nondiabetic patients, but the reason for this decreased response in diabetics is not known. Many diabetics already have high blood glucagon levels, although these levels are in the physiologic rather than pharmacologic range. The presence of autonomic neuropathy in some diabetics may be a factor. At times, refilling the colon several minutes later results in a marked decrease of spasm.

Reduction of Intussusception. Because of its spasmolytic effect and tendency to relax the ileocecal valve, it was thought that glucagon might have a role in ileocolic intussusception reduction. A number of reports described intussusception reduction after the administration of glucagon, but such empiric use does not imply that any eventual reduction can be attributed to glucagon; even a second or third attempt at reduction improves the overall success rate. Controlled studies have found similar success rates for intussusception reduction with and without glucagon.

Current controversy centers not on whether glucagon is useful in intussusception reduction, but whether the contrast agent should be barium, a saline solution, or air, and whether fluoroscopy or sonography is the preferred imaging modality.

Preferred Imaging Modality with Glucagon

In Computed Tomography. In spite of glucagon's diverse effects in the liver, it does not appear to influence hepatic CT enhancement. With older scanners, glucagon and somatostatin were used to decrease motion artifacts. There is little need to induce bowel hypotonia with multidetector scanners, but the ability to maintain bowel distention with a hypotonic agent aids gastric and bowel wall evaluation. Although some studies suggest that glucagon prior to CT colonography does not improve colonic distention,[49] others find an antispasmodic agent useful in maintaining hypotonia during air insufflation and scanning. Spasm developing during the study can be decreased by the judicious use of glucagon.

In Ultrasonography. Occasionally, bowel atonia is helpful in abdominal ultrasonography. An acoustic window to the biliary tract can sometimes be obtained by filling the stomach with fluid and inducing hypotonia of the surrounding GI structures.

In Magnetic Resonance Imaging. Currently, glucagon is used infrequently in MRI, although it may have a role if oral MRI contrasts agents and bowel distention are used. When evaluating mural and serosal disease, IV glucagon allows better visualization of normal bowel loops and bowel wall thickening.[50] Glucagon also helps eliminate ghost images of positive contrast-opacified bowel.

Contraindications and Side Effects

A myth persists that glucagon should not be given to diabetic patients. It should be pointed out that glucagon is used to treat hypoglycemic reactions in diabetics. On the other hand, in the setting of hyperglycemia and ketoacidosis, temporary additional glucose level elevation induced by glucagon is of limited importance. The diabetic patient can safely receive glucagon whenever clinically indicated prior to an imaging study.

Side effects of glucagon are less than those with atropine or propantheline. In one study, the side effects with glucagon were similar to those seen with a placebo. The prevalence of nausea and vomiting after injection of glucagon is dose dependent.[51] When given IV, glucagon slowly decreases these reactions.

Because commercially available glucagon has an amino acid residue similar to human glucagon, allergic reactions should not occur, although rare ones have been reported. In these patients, an allergy to the preservative used, rather than to glucagon, should be considered. Glucagon is a naturally occurring polypeptide and, in pure form, should not result in hypersensitivity reactions. Previously, commercial glucagon contained bovine or porcine insulins, protoinsulins, other nonglucagon

protein contaminants, and preservatives, and any of these may be associated with a hypersensitivity reaction. A rash, periorbital edema, erythema multiforme, respiratory distress, and hypotension have been reported. Currently used genetically engineered glucagon should be associated with few anaphylactic reactions.

Contraindications to glucagon include prior sensitivity, suspected pheochromocytoma, or insulinoma. Glucagon can release catecholamines from a pheochromocytoma and result in the sudden onset of life-threatening hypertension. Such hypertension can be countered with the α-adrenergic blocking agent phentolamine mesylate (Regitine). In adults, a dose of 5 mg IV appears useful, although considerable variability exists in treatment requirements. Glucagon can also stimulate insulin release from an insulinoma, resulting in severe hypoglycemia; this condition is treated with glucose.

Anticholinergic Agents

Anticholinergic agents as a group are effective in tissues with receptors supplied by cholinergic postganglionic autonomic nerves. They block the effect of acetylcholine liberated from nerve endings. They reduce GI tract motility, decrease tonicity in the urinary tract, and may also have a hypotonic effect on the bile ducts. These agents also decrease salivary and bronchial secretions, dilate pupils, and increase heart rate, with the duration of action and specific effect on various target organs dependent on the specific compound and dose. Their action on tonicity and motility is similar to glucagon, but, unlike glucagon, they also reduce secretions. Current evidence suggests that the latter effect is insignificant in imaging studies.

Some of these agents have been used in peptic ulcer disease therapy in conjunction with antacids and H2 receptor antagonists, although these applications have been inconclusive and controversial. They also play a role in the treatment of irritable bowel syndrome and have been used as supplemental therapy in treating biliary and ureteral colic to relax smooth muscle spasm; results here also are inconsistent.

Useful Agents. The most widely known anticholinergic agent is atropine sulfate. It is available in tablets and as a parenteral injectable liquid. Radiologists in North America may still remember the anticholinergic agent propantheline bromide, in vogue in the 1960s and early 1970s as a GI hypotonic agent. Currently, atropine and propantheline have been supplanted by other agents.

In many countries, the short-acting anticholinergic agent scopolamine butylbromide is used, but it is not available in the United States. It is administered IV; the usual dose is 20 mg before an upper GI examination. Its hypotonic effect lasts for 15 to 20 minutes. It does not induce gastroesophageal reflux, nor does it have any significant effect on the visualization of a hiatal hernia. It may be useful with CT and MRI in evaluating suspected gastric cancers.[52] One study found that it improves colonic distention during CT colonography (compared with controls), and the authors recommended its use.[53]

Pirenzepine, an antimuscarinic drug, shows promise as a hypotonic agent without the adverse effects of scopolamine.

Although other anticholinergic agents are available, their side effects and longer duration of action limit their application in radiology. For example, scopolamine hydrobromide is available but is not used in radiologic examinations because of its adverse side effects.

Oral hyoscyamine sulfate is a potential hypotonic agent, having actions and contraindications similar to those of atropine and other anticholinergic agents. It appears to provide no benefit when used as pain premedication during a barium enema, although it aids in achieving distention during CT colonography.

Complications. In patients predisposed to glaucoma, increased intraocular pressure induced by anticholinergic drugs may precipitate an acute attack. Although most patients with a history of glaucoma have chronic glaucoma, a patient may have acute angle-closure glaucoma and not be aware of it. Acute glaucoma should be suspected if eye pain or loss of vision develops after administration of an anticholinergic agent. Buscopan use can result in blurred vision.

The effect on the autonomic nervous system can lead to urinary retention. This complication is exacerbated in patients with prostatic hypertrophy or other predisposition to urine retention. Allergic reactions to anticholinergic agents are uncommon.

GASTROINTESTINAL AGENTS THAT INCREASE BOWEL MOTILITY

In some patients, the rate of gastric emptying is increased if the barium volume used is increased. A cold suspension is not only better tolerated but also leads to faster gastric emptying. Faster small bowel transit can be achieved by adding a hyperosmolar product to a barium suspension; a small amount of diatrizoate meglumine (Gastrografin) can be added to an oral barium suspension.

High-osmolality sorbitol added to oral CT contrast will accelerate bowel opacification. Some manufacturers add sorbitol to their barium sulfate products.

Metoclopramide

Metoclopramide is an antiemetic agent and is also useful in treating diabetic gastroparesis. Its primary effects in the GI tract are an increase in gastric peristalsis, pyloric relaxation, and increase in small bowel peristalsis. It has no major effect on the colon. Metoclopramide appears to decrease gastric secretions but has little effect on mucosal barium coating. A typical dose is 10 to 20 mg parenterally or orally. It is a relatively safe drug, although extrapyramidal side effects, such as acute dystonia and tardive dyskinesia, develop occasionally.

Oral metoclopramide reduces small bowel transit time. It can be given shortly before a small bowel study or up to 90 minutes before the procedure. Administered orally before a CT scan, metoclopramide improves opacification of the ileum, right colon, and transverse colon but not the more proximal bowel. Longitudinal contractions and foreshortening of ileal loops tend to elevate the ileum out of the pelvis. Metoclopramide also appears to improve visualization of the pancreas in abdominal sonography, with its primary benefit being decreased gastric and duodenal gas artifacts.

Domperidone

Domperidone, a potent dopamine antagonist, increases gastric emptying and accelerates small bowel transit. Although it decreases small bowel transit time, its effect on the small bowel appears to be less than that with metoclopramide.[54] It has been used for the treatment of diabetic gastroparesis. Domperidone

may increase serum levels of prolactin in patients with a pituitary prolactin-releasing tumor. It has also been associated with sudden cardiac death.[55]

Cisapride

Cisapride is a prokinetic substance that induces antral contractility, enhances gastric emptying, and promotes small bowel peristalsis. It also enhances lower esophageal sphincter tone and is a relatively potent esophageal motor stimulator. It has been proposed for the treatment of diabetic patients with gastroparesis and as an antigastroesophageal reflux agent. It has had limited application in radiology. Its use has been discontinued in the United States because of associated cardiac arrhythmias and deaths.[56]

Neostigmine

Neostigmine methyl sulfate is a cholinesterase inhibitor that promotes gastric and small bowel peristalsis and leads to faster gastric emptying and shorter small bowel transit time. It promotes peristalsis when activity is depressed by cholinergic stimulation. It is useful in treating colonic pseudo-obstruction (Ogilvie's syndrome),[57] but is contraindicated with mechanical bowel obstruction and in some settings of adynamic ileus.[58] It has led to colon perforation.

Erythromycin

Erythromycin, primarily an antibiotic, improves gastric motility and promotes gastric emptying. It is used as an aid in postoperative gastroparesis and for the treatment of diabetic gastroparesis, but has had little application in radiology.

MIXED ACTION AGENTS

Morphine

Some radiologists may undoubtedly remember using morphine sulfate for hypotonic duodenography, a procedure relegated to history. Currently, morphine has a role in nuclear medicine and a possible role in MRCP (see later).

Cholecystokinin

Cholecystokinin, a peptide hormone, has myriad functions; it induces gallbladder contraction and increases bowel peristalsis, resulting in faster small bowel transit. It also regulates pancreatic enzyme secretion, inhibits gastric acid secretion, affects satiety signaling, and acts as a neurotransmitter. It stimulates aldosterone secretion from human adrenocortical cells. From a radiologic viewpoint, cholecystokinin induces simultaneous contraction of the sphincter of Oddi and gallbladder; thus, most of the bile from the gallbladder refluxes into the intrahepatic bile ducts and reenters the gallbladder after hormone infusion stops.

Secretion of cholecystokinin is impaired in celiac disease and bulimia nervosa. Untreated celiacs have low postprandial cholecystokinin levels. It is overexpressed in certain neuroendocrine tumors and in medullary thyroid carcinomas.

Generally, only the COOH-terminal octapeptide of cholecystokinin is used. This fragment is more potent than the entire molecule.

Ceruletide

Ceruletide is a synthetic compound similar to cholecystokinin in its pharmacologic effects—namely, it delays gastric emptying and induces gallbladder contraction, duodenal hypoperistalsis, and hyperperistalsis of the jejunum, ileum, and colon. It reverses bowel aperistalsis induced by drugs acting on enteric neural or smooth muscle.

In the early 1980s, ceruletide appeared to be a promising agent to increase small bowel peristalsis and thus shorten the duration of a small bowel examination, but radiologists lost interest in this agent; given IV, ceruletide induces nausea, vomiting, and abdominal cramps. For accelerating small bowel transit, a usual dose of 0.25 to 0.3 μg/kg is administered. Whether the shorter small bowel transit time leads to a better small bowel study is debatable; pronounced contractions tend to obscure anatomic detail, particularly in the distal ileum.

Because ceruletide induces gastric hypotonia, it should not be administered prior to significant amounts of barium reaching the jejunum. Such gastric stasis can be overcome by also administering metoclopramide.

DRUGS AFFECTING THE BILIARY TRACT AND PANCREAS

Bile flow into the duodenum is regulated by bile production in the liver and gallbladder tonicity. Agents affecting only the latter are considered in this section.

Inhibition of gallbladder contractions can be achieved by glucagon, atropine, and other cholinergic drugs, somatostatin, some calcium channel antagonists, and several other less studied drugs, keeping in mind that contractions are also inhibited in obesity, diabetes mellitus, celiac disease, and autonomic neuropathy.

Gallbladder contraction is stimulated by cholecystokinin, ceruletide, motilin, prostigmine, erythromycin, and possibly by cisapride and cholestyramine.

Glucagon relaxes the gallbladder. Glucagon also decreases papilla of Vater mean pressures. Currently, little clinical use has been made of these findings. Glucagon is of limited use in percutaneous transhepatic cholangiography or various biliary drainage procedures. In an occasional patient with persistent distal common bile duct narrowing, in the sphincter of Oddi region, glucagon aids in differentiating a tumor, impacted stone, and spasm. In most patients, however, judicious use of fluoroscopy is sufficient.

Glucagon improves bile duct visualization during MRCP.[59] Because incomplete duct visualization may lead to a repeat study or even an invasive procedure such as ERCP, glucagon is routinely used at some centers. Although earlier studies suggested that glucagon improves the quality of operative cholangiography, a double-blind prospective study found no improvement.[60] Use of fentanyl during surgery is associated with sphincter of Oddi spasm and, in these patients, glucagon may have a role.

Hypotonic agents are commonly used during ERCP to induce duodenal hypotonia, inhibit contractions of the sphincter of Oddi, and aid ampullary cannulation. In the United States, glucagon is used almost exclusively for this purpose; in other countries, an anticholinergic drug such as scopolamine is used more often.

Neostigmine, together with morphine, has been proposed as a provocative test in hepatobiliary scintigraphy for evaluation of sphincter of Oddi dyskinesia in postcholecystectomy patients.[61]

Morphine may have a role in MR cholangiography; IV morphine constricts the sphincter of Oddi, thus distending the biliary and pancreatic ducts.[62] It may also improve duct visualization in primary sclerosing cholangitis. An interval of 10 to 20 minutes between morphine injection and imaging appears useful.

Cholecystokinin's effect on the gallbladder has been used to increase radiographic contrast during oral cholecystography; it also aids in evaluating gallbladder function. The gallbladder ejection fraction is typically determined with hepatobiliary scintigraphy but less often with ultrasonography; MR cholangiography uses an infusion of cholecystokinin as an alternate method.

A provocative test using a cholecystokinin derivative (Sincalide) to identify acalculous cholecystitis patients likely to benefit from cholecystectomy has not achieved general clinical acceptance. Cholecystokinin relaxes the sphincter of Oddi and appears to assist in the passage of bile duct stones. On the other hand, a cholecystokinin receptor antagonist provides pain relief in patients with biliary colic.[63] Interestingly, cholecystokinin does not induce its usual sphincter of Oddi inhibitory effect after a cholecystectomy. Cholecystokinin is also useful as a diagnostic test of pancreatic function.

Ceruletide has an effect on the gallbladder similar to that of cholecystokinin or a fatty meal.[64] In patients with recurrent symptoms after cholecystectomy, an ultrasonographically detected increase in extrahepatic bile duct dilation following ceruletide injection suggests sphincter of Oddi dysfunction.

The cholecystokinin-secretin pancreatic exocrine function test is used to detect pancreatic exocrine insufficiency but does not differentiate between chronic pancreatitis and pancreatic carcinoma. MRI can also evaluate pancreatic exocrine function by measuring duodenal filling after stimulation with secretin.[65] Secretin improves pancreatic duct visualization and aids in detecting abnormalities during MR pancreatography.[66] Pancreas divisum and other abnormalities are more readily detected after secretin, potentially obviating the need for ERCP. MR pancreatography is best performed within 5 minutes after secretin injection.[67] Secretin-augmented MR pancreatography and MRI perfusion are useful for detecting graft dysfunction after pancreatic transplantation.[68]

Analysis of duodenal aspirations of pancreatic juice after cholecystokinin-octapeptide stimulation can detect pancreatic insufficiency in patients with chronic pancreatitis. However, the analogous secretin test is more commonly used.

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2

Barium Studies: Single and Double Contrast

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CHAPTER OUTLINE

Since the 1980s, advances in cross-sectional imaging and endoscopy have led to a gradual but steady decline in the number of barium studies performed in the United States.[1,2] Although barium studies no longer reign supreme in the diagnosis of gastrointestinal (GI) disease, single- and double-contrast examinations continue to have a role in modern radiology practice. In general terms, barium studies can demonstrate GI abnormalities in three ways:

1. Mucosal relief views of the collapsed or partially collapsed lumen obtained with a small volume of barium. These views enable visualization of the folds in various portions of the GI tract (Fig. 2-1A). Because the folds contain a submucosal core, these views are particularly useful for showing abnormalities involving the submucosa, such as esophageal varices.
2. Single-contrast views of the filled lumen obtained with a large volume of low-density barium (Fig. 2-1B). These views enable visualization of contour abnormalities, strictures, and large polypoid defects.
3. Double-contrast views obtained after the mucosal surface has been coated with a thin layer of high-density barium and the lumen has been distended with gas (Fig. 2-1C). These views enable visualization of subtle mucosal lesions, such as the early changes of inflammatory bowel disease and early neoplastic lesions.

Although these three types of views are incorporated to varying degrees in both single- and double-contrast examinations, single-contrast studies rely more heavily on diagnostic fluoroscopy, mucosal relief, and barium filling,[3] whereas double-contrast studies emphasize the interpretation of double-contrast images supplemented by barium filling and mucosal relief.

In the past, there was considerable controversy about the relative virtues of single-contrast and double-contrast techniques.[4,5] Currently, however, most authors believe that double-contrast techniques provide superior mucosal detail and allow earlier detection of subtle lesions than single-contrast techniques. As a result, it is generally recommended that double-contrast studies be performed on patients who are young enough and healthy enough to undergo this type of examination. In contrast, single-contrast barium studies are most appropriate in older or debilitated patients who are unable to cooperate for a double-contrast examination.[6,7]

This chapter discusses the principles for performing and interpreting single- and double-contrast barium studies.[8] These principles are illustrated with examples drawn from throughout the GI tract.

Single-Contrast Studies

DIAGNOSTIC PRINCIPLES

Depending on the organ examined, single-contrast techniques may include observation of function (e.g., pharyngeal and esophageal motility), compression imaging, full-column distention, mucosal relief views, and limited air-contrast images.[9-11] The use of compression during fluoroscopy is a critical component of the single-contrast examination. Small lesions (e.g., small ulcers, polypoid neoplasms) are often visible only when the barium pool is adequately thinned or displaced by manual compression. The barium suspension must also be adequately diluted if lesions (especially small lesions) are to be detected in the thinned-out barium pool.

Full-column distention of the lumen is ideal for showing strictures, large neoplasms, and lesions projecting tangentially, such as ulcers or diverticula. Full-column views of barium-filled structures in various projections enable depiction of large ulcers and tumors. However, small lesions may be visible on full-column views only when viewed in profile. In such cases, mucosal techniques are required to supplement the barium-filled views.

EQUIPMENT

Fluoroscopic equipment has evolved dramatically with the transition from analogue cassette-based radiography to digital imaging and viewing on picture archiving and communications system (PACS) workstations.[12-15] Regardless of the imaging technology, single-contrast examinations can be performed with conventional or remote control fluoroscopic units.[12] The ability to obtain optimal compression views is a major prerequisite of any well-designed fluoroscope. Compression can be performed manually or with a variety of hand-held devices on

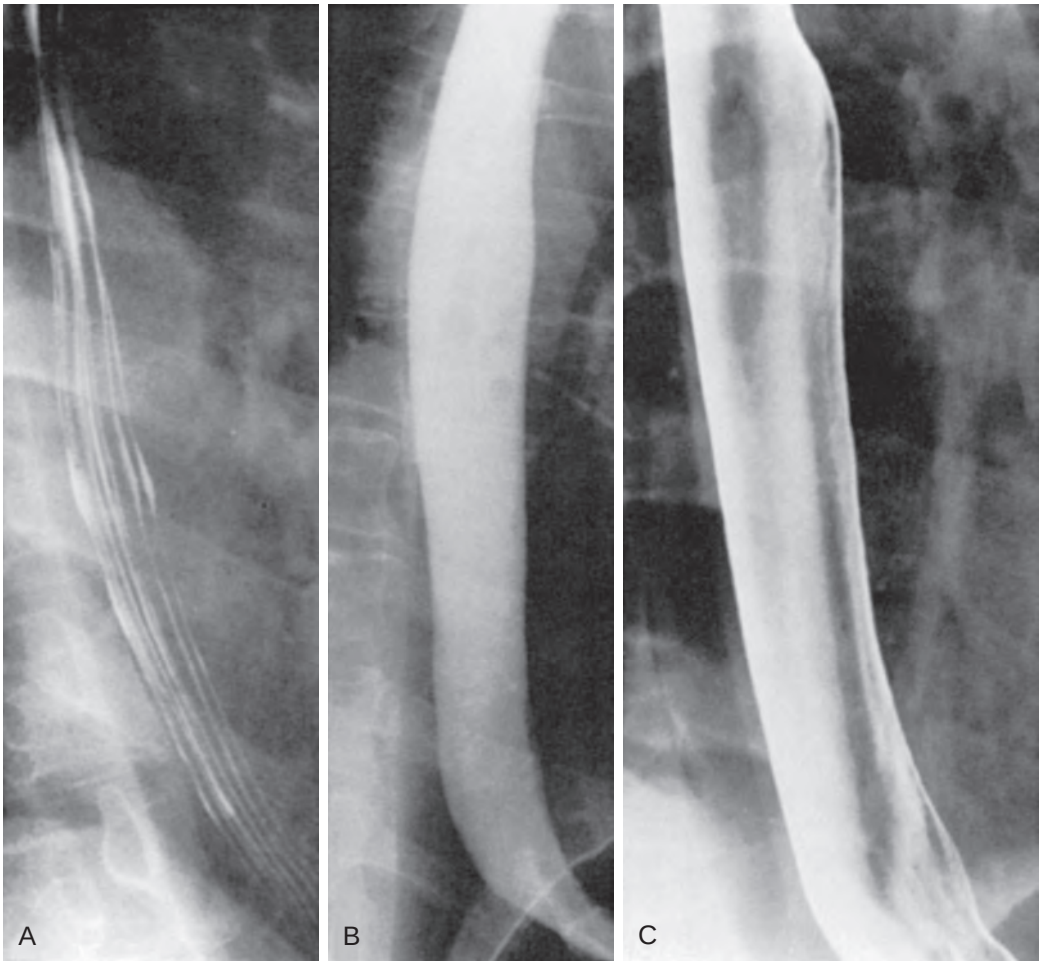

Figure 2-1 Three types of views for visualizing the gastrointestinal tract, as illustrated in the esophagus. **A.** Mucosal relief view. With the esophagus collapsed and coated, the normal longitudinal folds are seen. **B.** Single-contrast view. With the patient continuously drinking barium in the prone position, the barium-filled esophagus is demonstrated. **C.** Double-contrast view. With the patient in the upright position, the smooth, featureless surface of the esophagus is seen.

a conventional unit; alternatively, the plastic cone on the spot image device of the fluoroscope can be used for applying compression.

On remote control equipment, compression is easily performed with a vertical movable device incorporated into the machine, facilitated by the ability to angle the x-ray tube. Remote control units often contain a compression device that allows graded compression and tube angulation with compression. Nevertheless, many radiologists prefer standard fluoroscopic units rather than remote control units because it is generally easier to move, turn, and compress the patient when the fluoroscopist performing the procedure is at the tableside.

BARIUM SUSPENSIONS

Numerous barium products are available commercially; a number are formulated for specific purposes, whereas others can be used for a variety of examinations.[16,17] Barium suspensions for single-contrast studies should be of moderate density (50%-100% w/v) when not diluted. The optimal barium suspension for a particular study depends on the structure being examined and the type of examination being performed. For example, an esophagogram requires a moderately dense barium suspension that provides full-column and mucosal relief imaging; a high-density barium suspension or paste may also be needed for optimal mucosal coating. A similar barium suspension can be used for an upper GI series, in which compression views, mucosal relief views, and limited double-contrast views are required. A standard peroral small bowel follow-through study can be performed with the same barium suspension used for the upper GI series. A single-contrast enteroclysis study requires a 15% to 20% w/v barium suspension, although somewhat denser solutions have been recommended.[18,19] Finally, a 15% to 20% w/v barium suspension is used for a single-contrast barium enema, because this is the optimal suspension for obtaining compression views of the colon.

QUALITY CONTROLS

Quality control for single-contrast examinations requires balancing the barium density, kilovoltage, and width of the barium column to achieve adequate translucency of the barium-filled bowel. This permits radiographic penetration of the barium suspension to visualize lesions that might otherwise be obscured by barium in the lumen.[6,10,11] The visibility of skeletal shadows through the barium column indicates that small filling defects are more likely to be seen, which is particularly important for the detection of colonic polyps.

Another quality control consideration, especially during the barium enema and small bowel follow-through, is the ability to see through overlapping loops of bowel.[6,20] On barium enemas, a tortuous sigmoid colon may have overlapping loops, even with appropriate compression. Similarly, on small bowel

follow-throughs, overlapping small bowel loops in the pelvis may compromise the fluoroscopist's ability to detect abnormalities in the distal ileum. In such cases, pelvic loops can be better visualized by placing the patient in a prone position while he or she lies on a bolster or inflated balloon to lift these loops superiorly from the pelvis.[21]

ESOPHAGOGRAPHY

Routine single-contrast esophagography includes fluoroscopic observation of the esophagus supplemented by motion recordings, full-column views, and mucosal relief views.[22,23] Full-column (barium-filled views) and mucosal relief views constitute the single-contrast phase of the examination. Motion recordings can be used to document pharyngeal function and esophageal motility using analog or digital recordings or rapid sequence solid-state recordings built into modern digital fluoroscopes.[12-15]

Depending on the imaging options of the fluoroscopic equipment, full-column technique is performed by obtaining partial or full-length views of the esophagus distended with barium. These views allow detection of esophageal carcinoma (Fig. 2-2) and other abnormalities at the gastroesophageal junction such as hiatal hernias, peptic strictures, and lower esophageal rings.[22] Lower esophageal rings are best visualized on prone views of the barium-filled lower esophagus, sometimes supplemented with a solid bolus such as a marshmallow or barium tablet.[22-24]

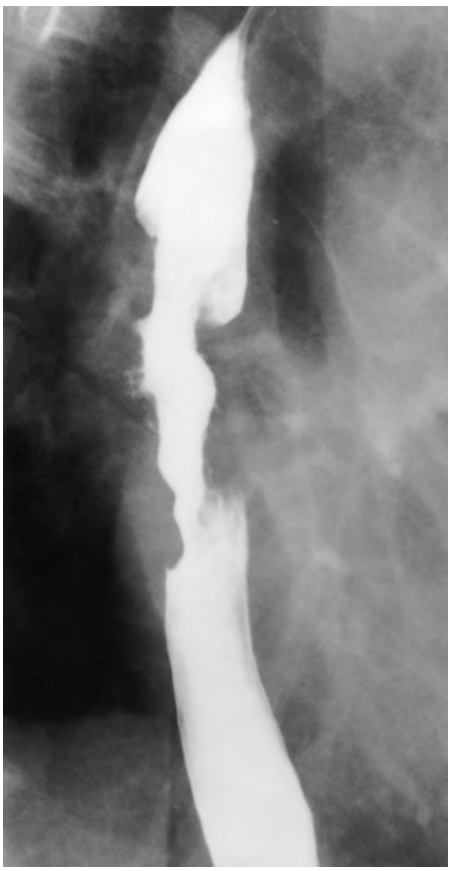

Figure 2-2 Annular carcinoma of the midesophagus. The lesion is well shown on the full-column portion of the barium esophagogram.

Full-column images of the esophagus are usually obtained with the patient on the fluoroscopic table in the prone, right anterior oblique position; a bolster may be used to increase intra-abdominal pressure. Esophageal peristalsis is inhibited by rapid swallowing of barium, allowing the esophagus to distend fully. Multiple images of the esophagus should be obtained at all levels; these images may be full-length views of the esophagus or coned-down views at different levels, depending on the imaging options of the fluoroscopic equipment.

Maximal distention of the esophagogastric region is required for optimal detection of hiatal hernias and lower esophageal rings (Fig. 2-3).[22,24] Rapid ingestion of the barium suspension followed by deep inspiration (or a Valsalva maneuver) promotes distention of the gastroesophageal junction. Careful fluoroscopic observation is required to visualize lesions only seen when this region is optimally distended.

Full-column views are complemented by mucosal relief views of the collapsed esophagus, with coating of the longitudinal folds by the barium suspension.[23] A high-density barium suspension (e.g., that used for a double-contrast upper GI series) is ideal for this purpose. The patient takes one or several swallows of high-density barium to coat the esophageal folds with barium. These mucosal relief views may reveal thickened, irregular folds, small esophageal neoplasms, and reflux or infectious esophagitis (Fig. 2-4). Nevertheless, double-contrast views are better for showing the plaques of *Candida* esophagitis, the small ulcers of herpes esophagitis, and the giant ulcers of cytomegalovirus (CMV) or human immunodeficiency virus (HIV) esophagitis.[25]

Single-contrast mucosal relief views are also best for detecting esophageal varices.[23,26] The patient takes several swallows of the barium suspension, which coats the lower esophagus, and is then asked not to swallow to inhibit peristalsis. Intermittent fluoroscopic observation is performed for several minutes to visualize the varices optimally as they become more distended.

Fluoroscopic observation is an integral part of the radiographic evaluation of the esophagus and is usually adequate to assess esophageal function.[9,23] Motion recording methods greatly aid in evaluating oropharyngeal swallowing disorders because of the rapid events that occur with deglutition, and may also be used to assess esophageal motility. Motion recordings should be obtained while the patient takes multiple discrete swallows of barium, because rapid swallowing causes reflex inhibition of esophageal peristalsis. With the use of single swallows, the single-contrast esophagogram is an excellent technique for evaluating esophageal motility.[9]

UPPER GASTROINTESTINAL SERIES

The single-contrast upper GI series is a complex examination requiring fluoroscopic observation, abdominal compression, and the use of multiple techniques for examining the esophagus, stomach, and duodenum.[11,27] The study can be performed quickly and is tolerated even by patients who are immobile or unable to cooperate fully.

The examination starts with the table upright. After the patient ingests several swallows of barium, the stomach is compressed with a compression paddle or the cone on the fluoroscope to demonstrate the rugal folds, assess the pliability of the gastric wall, and detect focal areas of rigidity secondary to

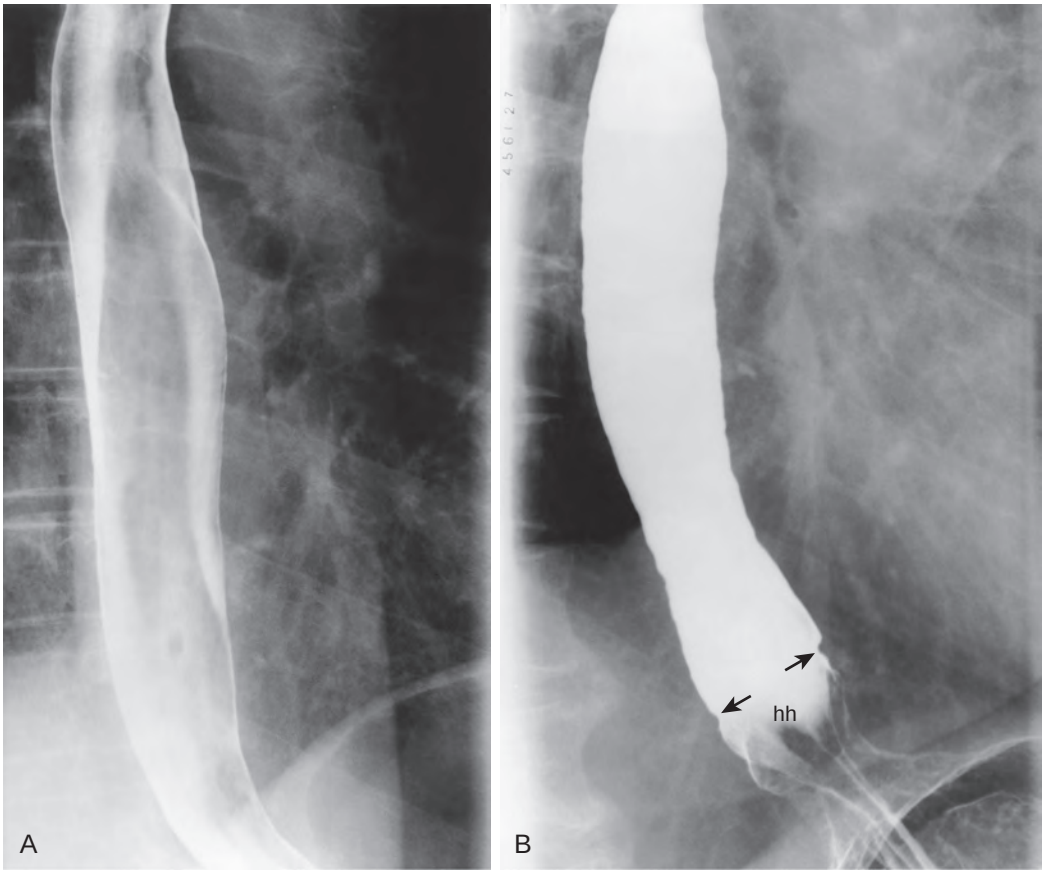

Figure 2-3 Hiatal hernia and lower esophageal ring seen only on prone single-contrast esophagogram. A. Upright double-contrast view of the esophagus shows no abnormalities. **B.** Prone full-column view of the esophagogastric region in the same patient shows a hiatal hernia (hh) and a widely patent lower esophageal mucosal ring (*arrows*).

tumor or scarring. If the stomach empties, the barium-filled duodenal bulb can also be examined by compression in the upright position.

The table is then lowered to the horizontal position, and mucosal relief views of the stomach are obtained, first with the patient in a supine position and then after the patient turns into a prone position. These views supplement the upright compression views and can sometimes show small polyps, erosions, or ulcers that are later obscured in the barium-filled stomach (Fig. 2-5).[4,28,29]

With the patient in the prone, right anterior oblique position, the esophagus is then examined using the same techniques described previously (see earlier, "Esophagography"). The gastric antrum and duodenal bulb usually fill with barium in this position, so prone compression views of the antrum and duodenal bulb should be obtained using an inflatable balloon placed beneath the patient to thin out the barium pool, enabling detection of anterior wall lesions in the antrum and duodenal bulb (Fig. 2-6).[27]

With the patient in the supine, left posterior oblique position, air in the stomach rises into the gastric antrum and duodenal bulb, so limited double-contrast images of these areas can be obtained (Fig. 2-7). Compression can be used to displace the barium suspension, separate antroduodenal structures, and improve distention with air. The fluoroscopic portion of the examination is completed at this time. Some radiologists may then choose to obtain a standard set of overhead radiographs of the stomach and duodenum with the patient in prone, supine, right anterior oblique, and right lateral positions.

SMALL BOWEL

The small bowel can be examined by single-contrast technique with a small bowel follow-through, enteroclysis, or retrograde study via an ostomy or reflux from the colon.[18,19,21] A peroral small bowel follow-through may be performed after a single-contrast upper GI series or as a separate study. A large volume (≥500 mL) of barium is recommended to promote gastric emptying, accelerate small bowel transit, and optimally distend small bowel loops. Fluoroscopic imaging and compression of all small bowel loops is a critical component of the examination because focal lesions are easily obscured by overlapping loops of small bowel unless compression is applied to separate these loops and ensure an adequate examination.

A small bowel follow-through typically requires a minimum of 500 mL of orally ingested barium, which can be the same product used for a single-contrast upper GI series. Prone overhead or low-magnification digital images of the small intestine are taken at timed intervals (e.g., every 30 minutes) until barium fills the right side of the colon. Depending on the barium product used, transit time through the small bowel is typically 60 to 90 minutes. Fluoroscopic spot imaging with manual compression should be performed at regular intervals during the examination. Compression of all loops and appropriate imaging of the entire small bowel is required to optimize detection of abnormalities (Fig. 2-8). When the barium suspension has reached the colon, compression views of the terminal ileum are obtained (typically with the patient in a supine or left posterior oblique position) for optimal visualization of this region.

Clear delineation of pelvic loops of small bowel, which often overlap, is not always possible, but several maneuvers may be performed to improve visualization of these loops.[21] First, the patient should be told not to void during the examination because a full bladder elevates pelvic small bowel loops, enabling them to be separated with manual compression. A similar effect may be achieved by instilling air into the rectum. The patient can also be placed in a prone Trendelenburg position with an inflated balloon beneath the lower abdomen and pelvis to displace pelvic small bowel loops superiorly for better visualization of these loops. If a remote control unit is available, the tube can be angulated to further separate these loops (Fig. 2-9).

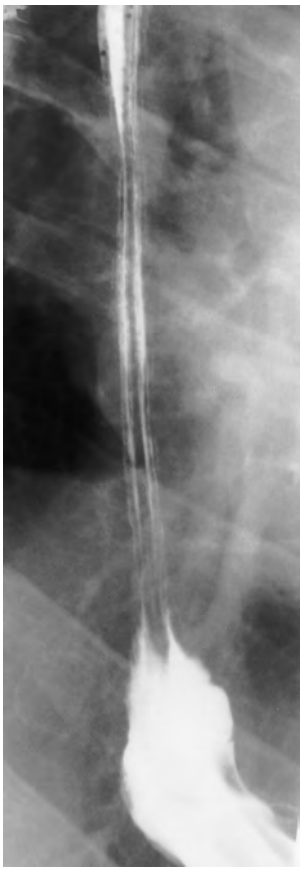

Figure 2-4 Reflux esophagitis on mucosal relief view of the esophagus. Mucosal relief view from single-contrast esophagogram shows crenulated, irregular folds in the distal esophagus, suggesting esophagitis. Reflux esophagitis was confirmed at endoscopy.

Enteroclysis

An intubation small bowel study (enteroclysis) may be performed via a tube placed in the duodenum or jejunum.[19,21,30] Several enteroclysis catheters are available commercially. The patient can be intubated via the mouth or the nose, with each approach having advantages and drawbacks. When single-contrast enteroclysis is performed, jejunal intubation is preferred to prevent duodenogastric reflux and emesis of barium.

Approximately 800 mL of a 15% to 20% w/v barium suspension is placed in an enema bag, which is hung on an adjustable vertical stand or IV pole. A water-soluble contrast agent may be added to stimulate intestinal peristalsis and shorten the length of the examination.[16,17,21] The barium suspension is allowed to flow through the tube by gravity, and the rate of flow is regulated by adjusting the height of the enema bag. If the barium suspension flows too slowly, adequate distention is not achieved. Conversely, rapid flow rates may cause reflex paralysis of the small intestine, with slow transit and excessive duodenogastric reflux. Initially, the enema bag is placed about 2 feet above the table; the bag can be raised or lowered during the examination to adjust the flow rate for optimal distention of small bowel loops (Fig. 2-10).

The examination is performed under fluoroscopic guidance with the patient in a supine position. Careful compression spot images of all loops of small intestine are obtained under fluoroscopic guidance as bowel segments become fully distended to depict even subtle abnormalities (Fig. 2-11). When the entire small intestine has been opacified, overhead radiographs or low-magnification digital images of the small bowel are obtained; the patient can then be placed in a prone position to aid in separating small bowel loops in the pelvis.

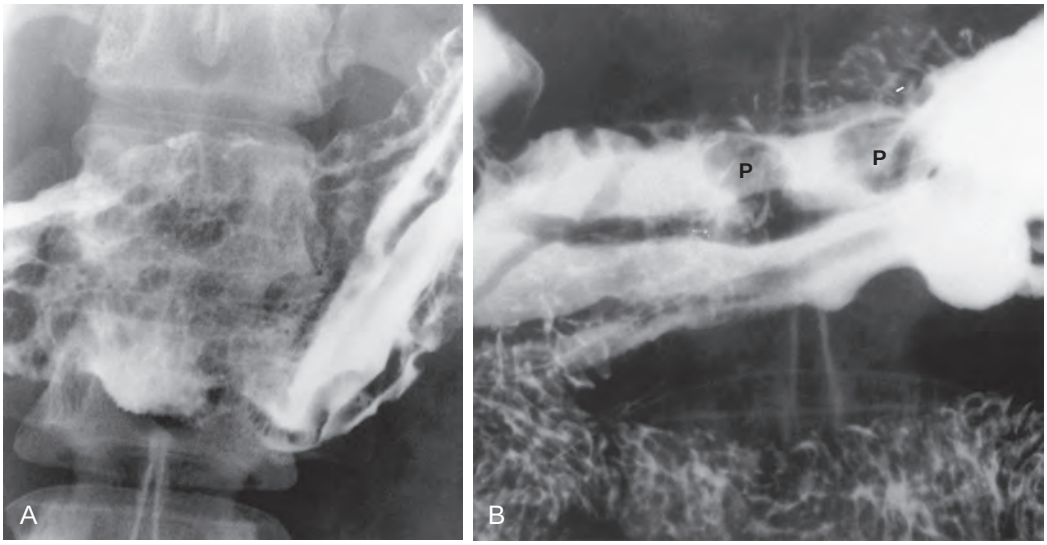

Figure 2-5 Recumbent compression views for detecting lesions in the stomach. A. Compression view of the gastric antrum shows antral erosions as multiple tiny nodules containing punctate collections of barium. **B.** In another patient, compression view of the antrum shows several small polyps (P) as filling defects in the barium pool. The findings in **A** and **B** were not well shown on double-contrast views but were confirmed at endoscopy.

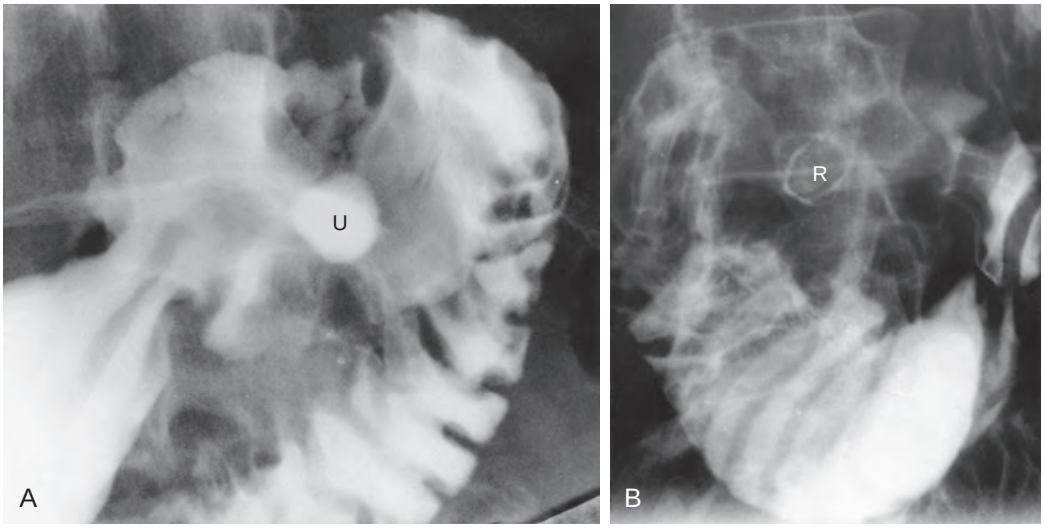

Figure 2-6 Prone compression view of the duodenal bulb showing an anterior wall ulcer. **A.** Prone view of the duodenal bulb (a balloon paddle compression device was used) shows an anterior wall ulcer (U) with surrounding edema. **B.** Supine oblique air-contrast view of the duodenal bulb in the same patient shows a ring shadow (R) because of barium coating the rim of the unfilled anterior wall ulcer crater.

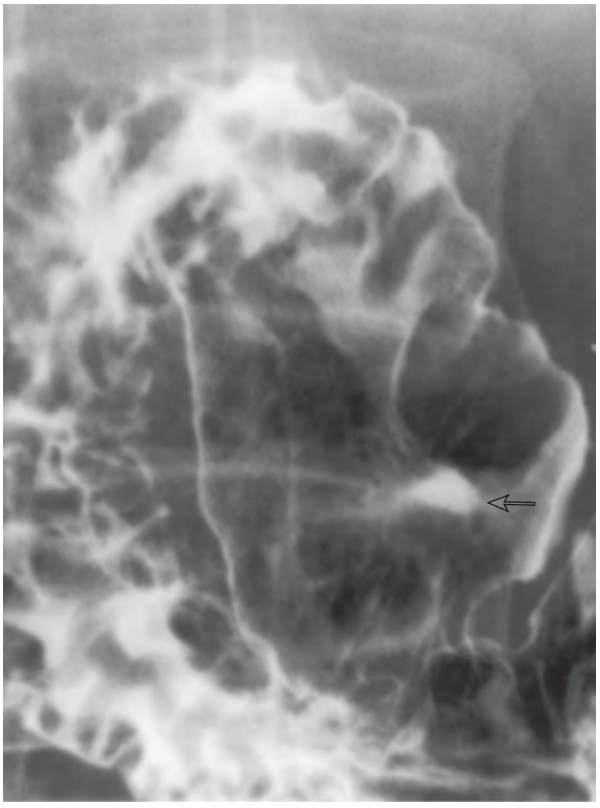

Figure 2-7 Posterior wall duodenal ulcer on air-contrast view of the bulb. Supine oblique air-contrast view of the duodenal bulb with compression shows a small posterior wall ulcer (*arrow*), emphasizing the importance of obtaining limited double-contrast views as part of a thorough single-contrast upper gastrointestinal examination.

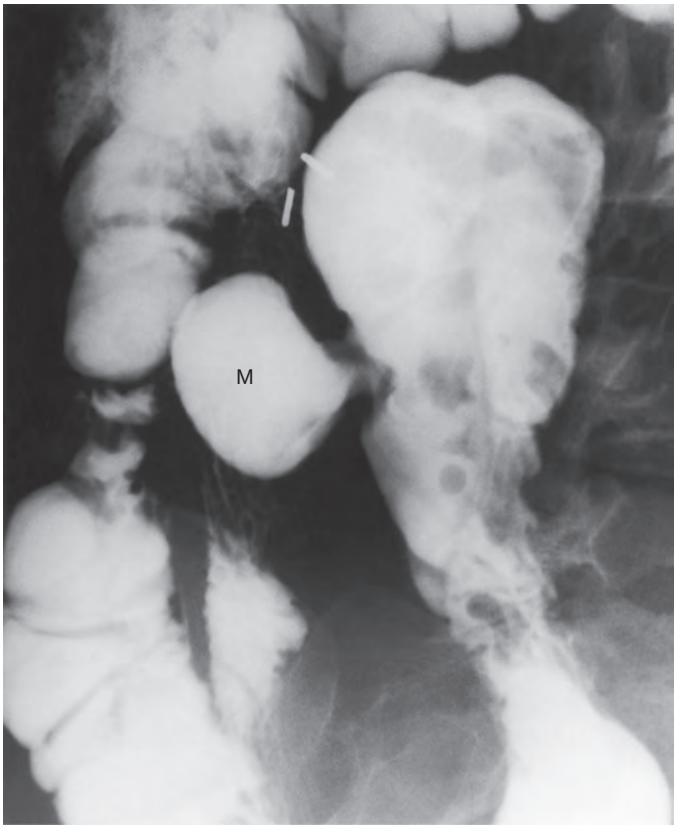

Figure 2-8 Compression spot image of the small bowel showing a Meckel's diverticulum. A peroral small bowel follow-through study was performed in a patient with gastrointestinal bleeding. Compression spot image of the right lower quadrant shows a Meckel's diverticulum (M) as the cause of the patient's bleeding. The diverticulum was removed at surgery.

BARIUM ENEMA

Fluoroscopic observation, careful imaging with graded compression, and knowledge of appropriate technical factors enables detection of a variety of lesions in the barium-filled colon on single-contrast examinations.[20,31] Although single-contrast barium enemas are less sensitive than double-contrast examinations for detecting small polypoid lesions and for evaluation of inflammatory bowel disease,[6,20,32] the single-contrast barium enema can be performed quickly and is usually a better choice for patients who are immobile, older, or incontinent.[6,7]

Preparation of the large bowel is the most important prerequisite for an accurate single- or double-contrast barium enema.[4,27] The diagnosis of neoplasms, including small polyps,

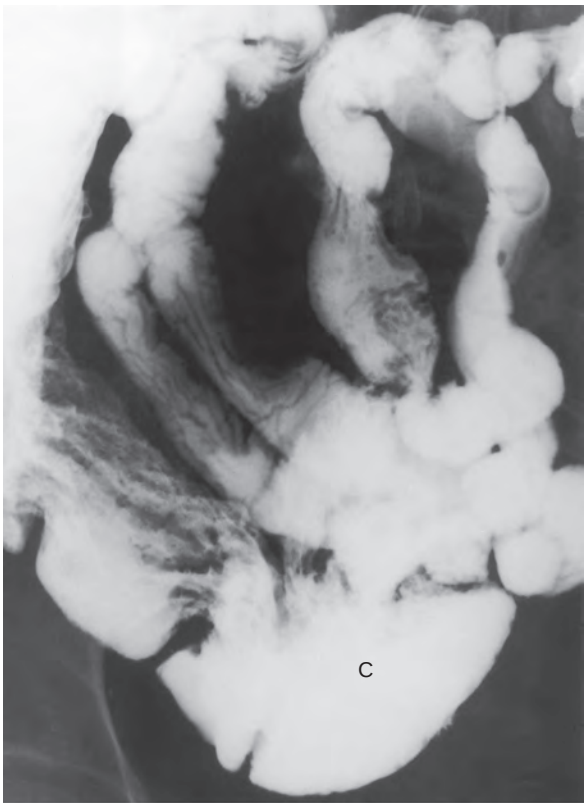

Figure 2-9 Peroral small bowel follow-through study in a posthysterectomy patient with pelvic small bowel loops lying deep within the pelvis. A prone image of the pelvis with a bolster placed beneath the patient and x-ray tube angulation clearly shows the cecum (C) and ileocecal junction. Note how pelvic loops of ileum are well separated and visualized.

Figure 2-10 Single-contrast enteroclysis. Normal small bowel loops are well distended, with the folds in a parallel arrangement. The use of a dilute barium suspension permits a see-through effect for visualization of overlapping loops of small bowel.

is easier and more reliable in a well-cleansed colon. Conversely, the presence of stool invariably limits the detection of polyps and is the most common cause of errors when interpreting the images.[4,31]

A variety of colon-cleansing protocols can be used to obtain a thoroughly clean colon in the vast majority of patients.[31,33] One recommended bowel preparation regimen includes the following:

1. A 24-hour clear liquid diet
2. One glass of water hourly the day before the examination
3. A saline cathartic such as magnesium citrate at 4:00 PM the day before the examination
4. 60 mL of a flavored castor oil or other irritant cathartic at 8:00 PM the day before the examination
5. An optional 1500-mL tap water cleansing enema the morning of the barium enema examination, although the need for a water enema is controversial[34]

If a tap water enema is administered, the patient needs to wait at least 30 minutes before the single-contrast barium enema is performed to avoid excess fluid in the colon, which might further dilute the barium suspension and degrade the quality of the study.[31,33,35]

A thorough examination protocol must be followed to ensure that an adequate single-contrast barium enema is obtained.[6,20,31] All portions of the colon must be adequately visualized and imaged without overlapping segments to increase the fluoroscopist's confidence that suspected lesions are real

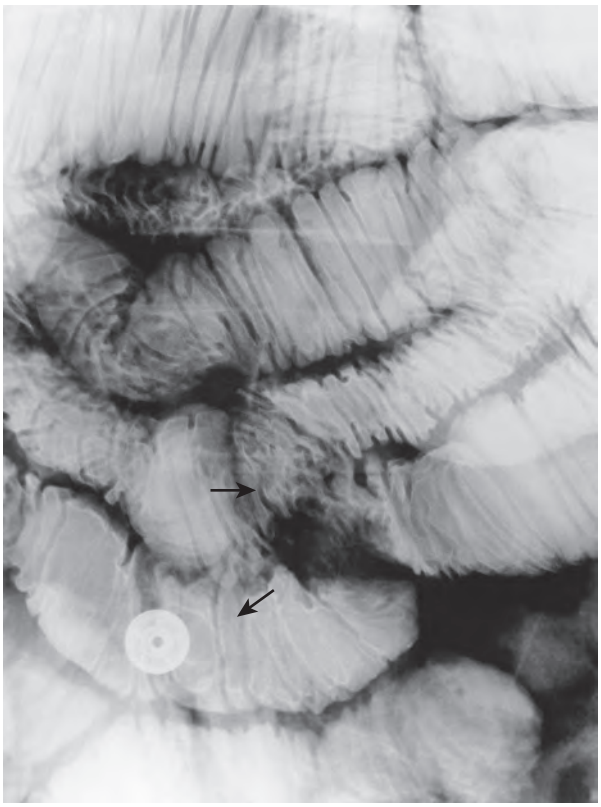

Figure 2-11 Nonobstructing adhesions on single-contrast enteroclysis with compression. Compression view of the mid small bowel shows focal nonobstructing adhesions (*arrows*) with angulation of the affected bowel and an inability to separate adjacent loops.

(Fig. 2-12). As in the small bowel follow-through, manual compression of the colon is a critical component of the examination because polyps and polypoid cancers protruding into the lumen may only be visualized with adequate thinning of the barium column (Fig. 2-13).[20,31] Overhead radiographs may be obtained at the end of the examination, followed by a postevacuation radiograph.

The following technique can be used for performing a thorough single-contrast barium enema.[31] After insertion of the rectal tip, the patient is placed in the left posterior oblique position, the flow of the barium suspension is started slowly, and a spot image of the rectosigmoid region is obtained while distention is minimal. Because the rectum cannot be compressed, this early image allows smaller lesions to be detected more easily. The rectosigmoid region is again imaged when fully distended. An appropriate number of views are obtained to demonstrate the sigmoid colon without overlapping loops. The entire colon is then opacified to the cecum, avoiding ileal reflux, if possible. Compression spot images of the remaining segments of colon are then obtained. After the fluoroscopic examination has been completed, overhead radiographs may be obtained. When using a remote control unit, the overheads may be taken during the fluoroscopic portion of the examination. A reasonable sequence of overheads includes a left lateral view of the rectum, prone and supine views of the colon, supine left and right anterior oblique views of the colon, and a prone angled view of the rectosigmoid.

A postevacuation radiograph is generally obtained at the end of the study to document colonic emptying and rule out gross colonic dysmotility. The postevacuation radiograph may also show that a filling defect seen on earlier barium-filled views persists or disappears, thereby indicating whether this finding was caused by a true polyp or residual stool (Fig. 2-14).

Double-Contrast Studies

PERFORMANCE

The yield of diagnostic information from double-contrast studies can be maximized only with meticulous attention to the technical aspects of the examination. The major principles of performance include mucosal coating, distention, and projection.

Mucosal Coating

The diagnostic quality of double-contrast studies depends on the quality of mucosal coating. In the absence of good coating, lesions can be missed or patchy coating can be mistaken for a lesion. Good mucosal coating requires optimal interaction between the barium suspension and mucosal surface. An appropriate barium suspension must be chosen; it must be prepared properly,[36] and the mucosal surface must be clean enough to enable adequate coating. Even when the mucosal coating is only slightly impaired, major abnormalities can be missed (Fig. 2-15).

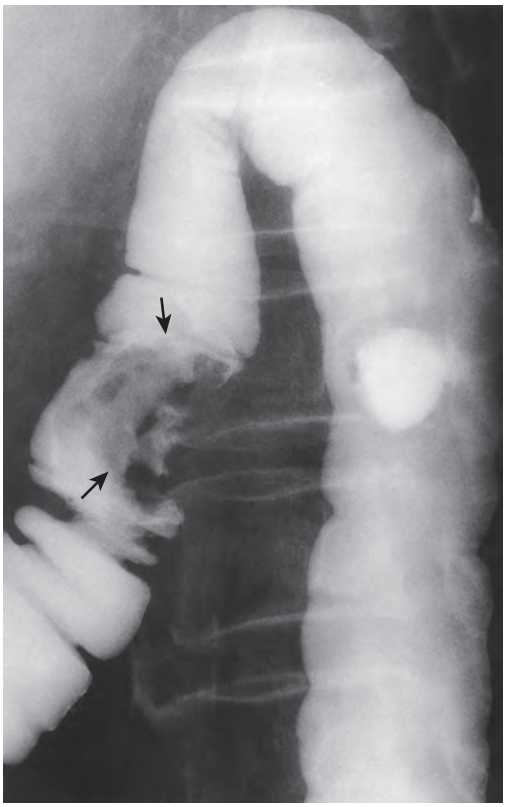

Figure 2-12 Colonic carcinoma on single-contrast barium enema. This oblique compression spot image of the splenic flexure shows a polypoid, ulcerated carcinoma (*arrows*) of the distal transverse colon. Careful patient positioning and the use of compression are critical components of this examination.

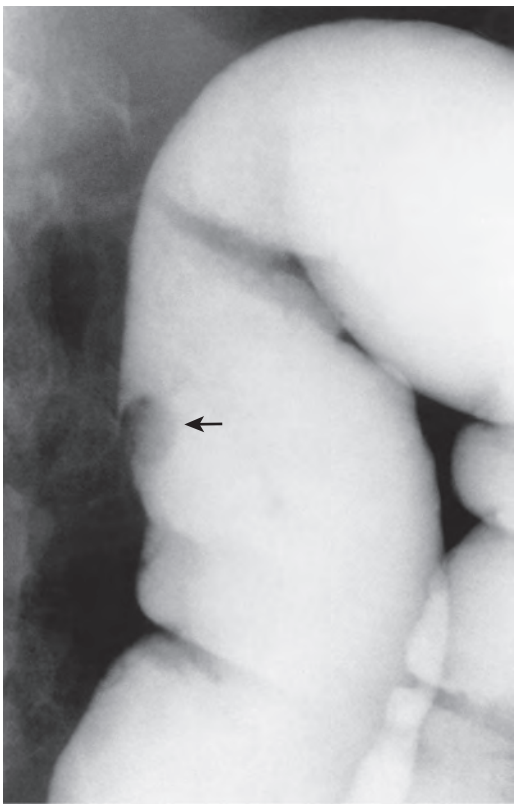

Figure 2-13 Small colonic polyp on compression spot image from a single-contrast barium enema. Oblique compression spot image of the splenic flexure shows an 8-mm colonic polyp (*arrow*). This small polyp was not seen on other images of the same area when compression was not applied.

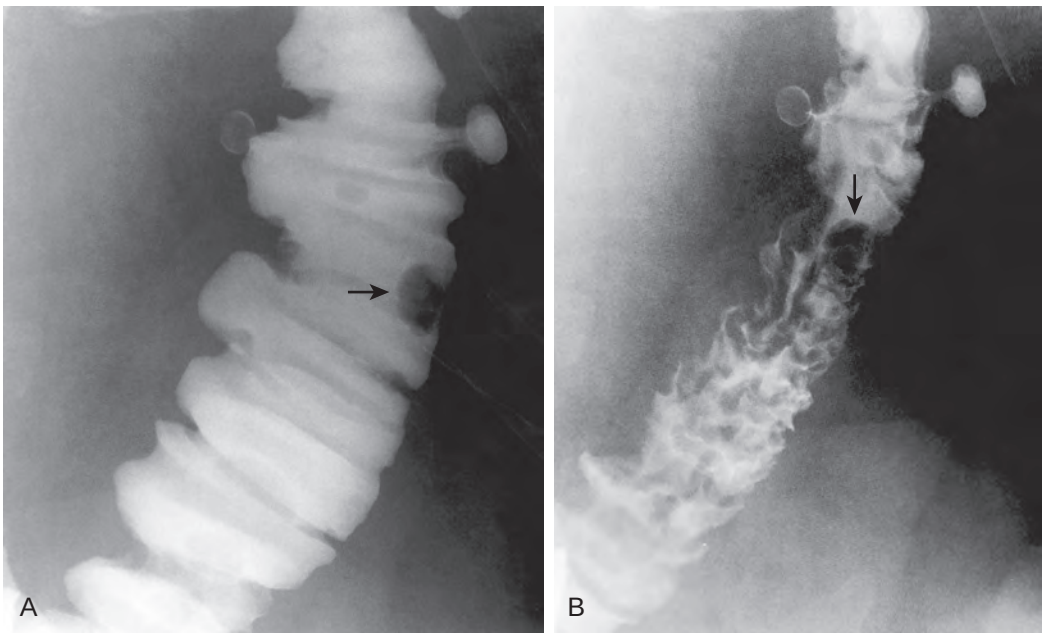

Figure 2-14 Value of postevacuation radiographs for detecting colonic polyps. **A.** Compression spot image shows a small (<1 cm) filling defect (*arrow*) in the descending colon on a single-contrast barium enema. Diverticula are also present in this region. The filling defect was not clearly present on other views. **B.** Postevacuation compression spot image of the descending colon (note the location of the previously seen diverticula) again shows this small filling defect (*arrow*), indicating that it is a true polyp. A small adenoma was removed at colonoscopy.

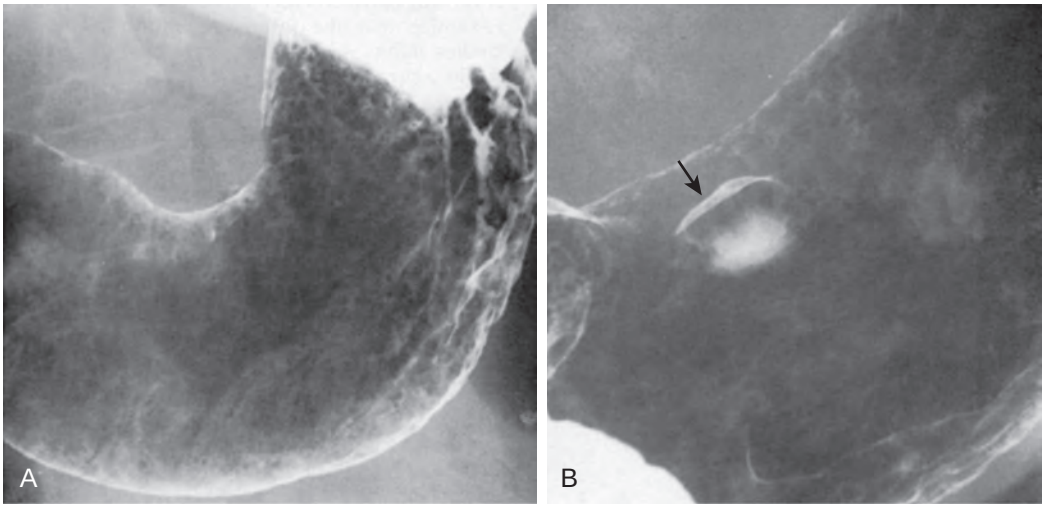

Figure 2-15 Risk of suboptimal coating. A. On the initial radiograph, an ulcer crater is barely recognizable along the lesser curvature of the stomach. **B.** With additional rotation and improved coating, the large ulcer crater (*arrow*) is clearly seen.

Distention

Normal folds are soft and pliable and are therefore effaced with moderate distention. The optimal degree of distention is that which just effaces the normal folds. Inadequate distention may conceal lesions, but overdistention can also obscure lesions such as shallow ulcers. Varying degrees of distention may therefore be required for optimal visualization of complex or subtle lesions. Overdistention may accentuate areas of rigidity, whereas partial collapse may accentuate abnormalities of the folds. The final diagnosis represents a synthesis of the information obtained with these various views (Fig. 2-16).

Projection

An adequate number of views should be obtained, so each loop of bowel is projected free of overlapping loops. Ideally, each segment of bowel should also be demonstrated in profile. In practice, however, these goals cannot always be achieved. It is therefore important to assess overlapping loops of bowel and be able to recognize abnormalities that are viewed en face as well as in profile. This is particularly important for recognition of short, annular lesions in the colon because it may be difficult to demonstrate every colonic bend in profile (Fig. 2-17).

INTERPRETATION

After every effort is made to obtain excellent images, it is important to extract all of the diagnostic information available on these images. The interpretation of double-contrast studies also differs substantially from the interpretation of single-contrast studies.

Dependent and Nondependent Surfaces

The distinction between the dependent and nondependent surfaces must be understood. The nondependent surface has a thin coating of barium because all the free barium falls onto the