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THE EFFECTS OF VASCULITIS ON THE GASTROINTESTINAL TRACT AND LIVER

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The multisystem effects of vasculitis frequently involve the liver and other organs of the digestive system. The frequency of involvement and most common manifestations vary considerably depending on the type of vasculitis. Disorders of the gastrointestinal tract may be the first manifestations of the disease, particularly in common forms of vasculitis, such as Henoch-Schönlein purpura (HSP), systemic lupus erythematosus (SLE), and Sjögren's syndrome vasculitis. The severity of the injury varies from life-threatening mesenteric ischemia or pancreatitis to nonspecific motility disorders of the esophagus. Furthermore, medications used to treat vasculitis also commonly affect the gastrointestinal tract. The consultant in gastroenterology or hepatology must be keenly aware of these manifestations, their varied clinical presentations, and the potential for gastrointestinal side effects of treatment.

When considering the gastrointestinal manifestations of vasculitides, it is valuable to consider the size of the vessel typically involved in a given disease.[73] The size of the vessel often influences the sites of ischemic injury and subsequent severity of organ damage. Involvement of small vessels, such as intramural arteries and vasa recta in the bowel wall, leads to patchy, focal ischemia and mucosal ulceration. Involvement of large or medium-sized vessels may cause more ischemia, leading

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to intestinal infarction, gangrene, and perforation. Aneurysmal dilation and rupture may occur in medium-sized vessel disease leading to hemorrhage within the bowel wall and into the bowel lumen. In contrast to atherosclerotic disease in the gastrointestinal tract (discussed in the articles by Dr. Cappell), the patchy involvement of many of these vasculitic processes tend to cause ischemia in a focal, short segment distribution.[10]

Because of the importance of type of vessel wall affected on the form and severity of clinical manifestations, vasculitides are most frequently categorized by the size of the vessel wall involved. The categories of vasculitis followed in this article are listed in Table 1. The Chapel Hill International Consensus Conference in 1994 devised a nomenclature system for selected categories of vasculitis.[73, 74] Large vessel vasculitides, such as giant cell arteritis and Takayasu's arteritis, involve the aorta and major arterial branches. Medium-sized vessel vasculitis, such as polyarteritis nodosa (PAN) and Kawasaki's disease, involves the major

Table 1. CATEGORIES OF VASCULITIS

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ANCA = Antineutrophil cytoplasmic autobodies.
From Jennette JC, Falk RJ: Small vessel vasculitis. N Engl J Med 337:1513, 1997; with permission.

visceral arteries and their branches. Small vessel vasculitis affects arterioles, venules, and capillaries, although occasionally it can also involve larger vessels such as arteries. The section on small vessel vasculitides affecting the gastrointestinal system discusses Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangitis, HSP, and Behçet's disease.

POLYARTERITIS NODOSA

PAN is a necrotizing, focal segmental vasculitis of medium-sized and small arteries involving many different organ systems. The pathophysiology of PAN involves antigen-antibody complex deposition in vessel walls. This deposition leads to inflammation, edema, and eventual necrosis of the tunica intima and media.[86] The compromised vessel can then easily fragment and subsequently stenose or thrombose. The vessel wall can also undergo aneurysmal dilation.

Common, nongastrointestinal manifestations of PAN include malaise, fatigue, weight loss, skin involvement with ulcerations and palpable purpura, renal involvement with segmental necrotizing glomerulonephritis and hypertension, polyarthralgias, arthritis, and mononeuritis multiplex.[10] PAN occurs in approximately 6 in 100,000 patients with a male-to-female ratio of 2:1. The peak incidence is found between the ages of 40 and 60 years.[86]

Abdominal symptoms occur in 35% to 50% of patients with PAN.[10, 86] Most often the patient complains of abdominal pain, which is nonspecific and vague. The pain is thought to be secondary to bowel ischemia. The diagnosis is based on the clinical picture and mesenteric arteriography. Typically the arteriogram shows narrowed, tapered arteries as well as small aneurysms often at the branching points of these vessels. Mesenteric visceral arteriographies are abnormal in up to 80% of PAN patients.[10] Tissue biopsy provides the best mechanism to confirm the diagnosis.

Ulcerations may be found throughout the gut in approximately 6% of PAN. They occur most commonly in the jejunum and frequently bleed.[74] Significant gastrointestinal or interabdominal bleeding may occur if there is an aneurysmal rupture. Vasculitis involving the full thickness of the bowel wall can lead to bleeding related to mucosal ischemia, perforation, and infarction. Perforation occurs in roughly 5% of PAN patients and bowel infarction in 1.4%. Survival after bowel infarction is rare in PAN patients, often requiring extensive resection and treatment with high-dose steroids and other immunosuppressive therapies.[38] Other gastrointestinal manifestations of PAN have been reported. Acalculous cholecystitis is found in 17% of patients.[43] Appendicitis, pancreatitis, biliary strictures, and a chronic wasting syndrome have all been reported.[9, 15, 43, 103] Hepatomegaly and elevated liver enzymes are found commonly because of hepatic vasculature involvement.[10] Treatment of

PAN with steroids and cyclophosphamide or azathioprine has improved survival greatly.

A subgroup of PAN patients has been found to have hepatitis B infections.[55, 57, 59] The disease is clinically similar to classic PAN. These patients are thought to develop PAN shortly after infection secondary to hepatitis B surface antigen–associated immune complexes.[57] Limited data show a possible role for the use of α-interferon in the treatment of these patients.[57, 59]

SMALL VESSEL VASCULITIDES ASSOCIATED WITH ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODIES

Churg-Strauss syndrome was first described in 1951 in a group of 13 patients who had asthma, eosinophilia, necrotizing glomerulonephritis, and necrotizing vasculitis with granulomatous inflammation.[73, 74] Churg-Strauss syndrome, Wegener's granulomatosis, and microscopic polyangiitis are classified as small vessel vasculitides associated with antineutrophil cytoplasmic autoantibodies (ANCA).[73, 74]

Churg-Strauss syndrome clinically starts as asthma or rhinitis, progresses to an eosinophilic infiltrating pneumonia or gastroenteritis, and within typically 3 years becomes a systemic small vessel vasculitis. The necrotizing vasculitis may affect medium-sized vessels as well. Pulmonary vasculitis is more common in this syndrome than in PAN, whereas glomerulonephritis is less common than in PAN and the other ANCA-associated small vessel vasculitides.[26] Gastrointestinal involvement occurs in about 50% of patients.[26] Gastrointestinal findings include eosinophilic infiltration of the stomach leading to gastroenteritis and ischemic ulcerations in the stomach and small and large bowel, leading to abdominal pain and bleeding and less often perforation, infarction, and cholecystitis.[55, 56, 96] Visceral arteriogram findings are similar to those found in PAN, although aneurysms are less common in Churg-Strauss syndrome.

The clinical picture along with ANCA staining patterns and specific immunochemical assays can help distinguish Churg-Strauss syndrome from the other ANCA-associated small vessel vasculitides. In Churg-Strauss syndrome, the presence of asthma, eosinophilia, and necrotizing granulomatous inflammation helps to distinguish it from Wegener's granulomatosis, which has necrotizing granulomatous inflammation without asthma. Wegener's granulomatosis has a cytoplasmic ANCA (c-ANCA) staining pattern on indirect immunofluorescence microscopy. Microscopic polyangiitis has neither asthma nor granulomatous inflammation, although 90% of these patients show a similar perinuclear ANCA (p-ANCA) staining pattern to that found in 70% of Churg-Strauss syndrome patients.[76, 96] Gastrointestinal manifestations in Wegener's granulomatosis are less common.[66, 95] Cholecystitis, inflammatory ileocolitis, and hemorrhage and bowel infarction have all been seen in Wege-

ner's granulomatosis.[44, 63, 104] Microscopic polyangiitis is similar to Wegener's granulomatosis in its spectrum of clinical manifestations.[96]

In patients with generalized ANCA-associated small vessel disease, recognition and identification of a specific diagnosis and quick initiation of therapy are important because often serious organ damage can be decreased or prevented. High-dose corticosteroid treatment alone is often effective in Churg-Strauss syndrome, although occasionally a cytotoxic drug may be needed.[96] In Wegener's granulomatosis, cyclophosphamide combined with corticosteroids is effective, inducing improvement in greater than 90% of patients and remission in 75%.[44, 66] Treatment in microscopic polyangiitis is similar to that in Wegener's granulomatosis.[96]

HENOCH-SCHÖNLEIN PURPURA

HSP is a systemic vasculitis with IgA-dominant immune complex deposits affecting small vessels (capillaries, venules, or arterioles) typically in the skin, gastrointestinal tract, joints, and kidneys.[73, 74] HSP is the most common systemic vasculitis in children, although it can develop at any age. Most patients are between the ages of 4 and 7 with the peak incidence at 5 years of age.[110, 133] The incidence is approximately 13.5 per 100,000 children per year.[152] The disease often is preceded by an upper respiratory tract infection. Throat swabs for group A, β-hemolytic streptococcus may be positive in up to 75% of patients.[133] Most cases of HSP last 4 weeks or less, and symptoms may recur several times over a period of weeks to months.[133] The most common complaints are a purpuric rash in the dependent areas of the body, especially the buttocks and lower extremities; arthralgias, especially in the knees and ankles; and abdominal pain.[26, 133] Glomerulonephritis with hematuria and proteinuria occurs in about 50% of patients, although renal insufficiency is found in only 10% to 25% of patients, and renal failure is rare.[3, 26]

Gastrointestinal involvement occurs in up to 75% of patients with HSP.[133] The most common presenting symptom is abdominal pain, which is often dull in quality and periumbilical.[133] Nausea and vomiting are common as well. Abdominal pain is thought to be due to extravasation of blood and fluid into the bowel wall, which can lead to ulceration of the bowel mucosa and eventual bleeding into the lumen. Fifty percent of patients may have melena, and 15% may develop hematemesis.[3] Upper gastrointestinal endoscopy should be considered in patients with melena or hematemesis. Such studies may reveal hemorrhagic, erosive duodenitis or more commonly redness, petechiae, and ulcerations and erosions of the mucosa, especially in the second part of the duodenum.[78] Petechial colonic lesions in the descending colon are common findings on colonoscopy.[29] Computed tomography (CT) scan features, such as multifocal bowel wall thickening with skipped areas, mesenteric edema, and vascular engorgement, provides radiographic evidence to support a diagnosis of HSP.[75]

Severe, life-threatening gastrointestinal complications of HSP are rare, with intussusception being the most common occurring in 1% to 5% of patients.[133] Often a submucosal hematoma is the cause of these ileoileal or ileocolic intussusceptions.[133] Colicky abdominal pain that has suddenly increased in intensity and the passage of red currant jelly–like stools point to intussusception. On abdominal examination, a palpable sausage-shaped mass may be found. Abdominal ultrasonography is the imaging method of choice to diagnose an intussusception. A barium enema may lead to bowel perforation in this setting and is usually not successful in reducing an HSP-associated intussusception.[75] Furthermore, barium enema may not show an ileoileal intussusception.[68] Other gastrointestinal complications found in HSP patients include protein-losing enteropathy with weight loss and edema,[130] esophageal and ileal strictures,[97, 162] gastric and small bowel perforations,[101, 149] bowel infarction,[101] pancreatitis,[128] appendicitis,[98] and cholecystitis.[88]

The prognosis for HSP is generally good with the exception of those few patients who go on to end-stage renal disease. Treatment for HSP with gastrointestinal complications, including intussusception, bowel perforation or infarction, and severe bleeding, is surgical with laparotomies being performed in 5% to 12% of HSP patients.[101] Corticosteroids are used in the treatment of HSP. Immunosuppressive drugs, such as azathioprine, may be beneficial as well, especially in patients with evidence of severe glomerulonephritis.[12]

BEHÇET'S DISEASE

Behçet's disease is a chronic, recurring multisystem disorder that has been characterized by the classic triad of aphthous ulcers, uveitis, and genital ulcers. International criteria for classification of Behçet's disease have helped clarify the diagnosis of Behçet's disease, which remains clinical.[72, 115] Although these criteria focus on the mucocutaneous manifestations of the disease, additional findings, such as synovitis, aseptic meningitis, and recurring phlebitis, occur. Large vessel arteritis, which was previously underappreciated clinically, occurs in 10% to 25% of patients.[115] Gastrointestinal arteritis or venulitis may involve the esophagus, ileum, colon, or rectum. Esophageal involvement may manifest as ulcers, varices, and less often perforations.[7, 170] Segmental mucosal ulcerations in the ileocecal area that bleed and perforate are common intestinal manifestations.[54, 92] When evaluating these patients, Crohn's disease should be the main differential diagnosis because of the many similarities it has with the intestinal ulcers found Behçet's disease.[158] A small number of cases have reported involvement of the superior mesenteric artery in Behçet's disease, including aneurysm formation and intimal thickening leading to infarction and perforation of the small bowel.[25]

Although direct involvement of the liver is not a known manifestation of Behçet's disease, among 30 Turkish patients with Budd-Chiari

syndrome, those with Behçet's disease accounted for 40% of these patients.[137] Acute pancreatitis is a rare manifestation of Behçet's disease.[70] The effects of treatment for mucosal lesions in Behçet's disease are inconsistent and transient. Corticosteroids are often the first-line therapy, but their benefit remains controversial. Cytotoxic therapies, including alkylating agents such as cyclophosphamide and chlorambucil, are used for severe involvement of large veins and arteries.[115]

GASTROINTESTINAL MANIFESTATIONS OF IMMUNE COMPLEX SMALL VESSEL VASCULITIS

Systemic Lupus Erythematosus

SLE is a multisystemic autoimmune disorder with protean clinical presentations as a result of widespread inflammation and immune complex deposition. Although an unusual initial presentation, gastrointestinal symptoms in SLE occur commonly, affecting approximately 50% of patients.[35, 65, 127]

Dubois and Tuffanelli's review[35] of more than 500 cases of SLE indicate that the three most common gastrointestinal symptoms are nausea and vomiting (53%), anorexia (49%), and abdominal pain (19%). Other, less common symptoms include diarrhea, dysphagia, heartburn, and hemorrhage. These symptoms reflect the underlying pathophysiology of SLE. Virtually any gastrointestinal tissue can be involved, most often as a result of SLE vasculopathy (Table 2).

Since the initial reports of Harvey et al[61] of gastrointestinal arteritis spanning from the esophagus to the large intestine, numerous other reports have followed.[18, 46, 90, 173] *Lupus enteritis* refers to the alimentary

Table 2. GASTROINTESTINAL AND LIVER MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Oral	Hepatic
Painless ulcerations	Hepatomegaly
Esophagus	Steatosis
Dysmotility	Abnormal LFTs
Stomach	CAH
Gastritis	Granulomatous disease
Pancreas	Cirrhosis
Pancreatitis	Other
Large and Small Bowel	Serositis
Ischemia, hemorrhage, perforation	Ascites
Pseudo-obstruction	
Pneumatosis intestinalis	
Malabsorption	
Inflammatory bowel disease (UC)	
Protein-losing enteropathy	

UC = ulcerative colitis; LFTs = liver function tests; CAH = chronic active hepatitis.

tract lesions in SLE[65] and encompasses several lesions, including gastritis and ulcerations,[112] pseudo-obstruction,[20] hemorrhage,[90] intussusception, infarction, and perforation.[65]

The most common symptoms of intestinal vasculitis are abdominal pain, nausea, vomiting, and tenderness.[65, 173, 126] In some cases, the involvement is so severe that the patient may appear to have an "acute surgical condition of the abdomen."[126] Distention, guarding, rebound, and diarrhea have also been reported to a lesser extent. Diarrhea may herald the onset of vasculitis-induced ischemia or may simply be due to mesenteric inflammation–induced motility changes. Cases of protein-losing enteropathy,[35] malabsorption,[11] and ulcerative colitis[35, 89] have been described, although none of these entities commonly accompanies SLE.

Small vessel inflammation leading to ischemia underlies SLE vasculopathy.[73, 74] Because decreased blood flow affects the mucosa first, sloughing and ulceration with some blood loss occur. Life-threatening hemorrhage is exceedingly rare.[90] Compromised mucosal integrity may further predispose SLE patients to pneumatosis cystoides intestinalis.[83, 90] Further vascular compromise causes more severe anoxic injury, at which point the muscular layers and myenteric plexi become involved, leading to ileus and even obstruction secondary to severe bowel edema.[18] Ultimately the entire bowel wall may be compromised, resulting in infarction and perforation.[46, 65, 173]

As the pathophysiology suggests, some of these lesions may progress along a continuum, depending on the extent of blood vessel inflammation, and clearly some overlap exists. Moreover, it can be difficult to attribute a particular finding to one cause alone. Gastrointestinal hemorrhage in SLE, for example, has many causes, including ischemic bowel disease secondary to vasculitis as well as peptic ulcer disease and gastritis resulting from any combination of vasculitis, steroid therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress-related mucosal disease. All of these can be exacerbated by the presence of the uremia prevalent in SLE patients with severe renal involvement.[65]

Clinically evident intestinal vasculitis occurs in only approximately 2% of patients with SLE.[112] The associated morbidity and mortality in those with abdominal emergencies are extremely high, with mortality exceeding 50%.[173] Moreover, patients with SLE often depend on corticosteroids, which not only mask abdominal symptoms, but also predispose those with diverticula to perforate.[173] Lactic acidosis, hyperamylasemia, an increase in lactic dehydrogenase, and leukocytosis are nonspecific and often late signs of mesenteric ischemia. Laboratory evidence of a lupus exacerbation in the presence of abdominal pain should always raise concern for the diagnosis of mesenteric ischemia. Radiographic abnormalities consistent with bowel ischemia include thumbprinting, separated loops of distended bowel loops suggesting edema, and nonspecific changes of impaired motility (*ileus*). The absence of such roentgenographic evidence, however, does not exclude the diagnosis.[65]

The results of the study of Zizic et al[173] suggest that a higher index of suspicion for intra-abdominal vasculitis should exist in SLE patients

with peripheral vasculitis, nervous system involvement, circulating rheumatoid factor, thrombocytopenia, and ischemic necrosis of bone, all of which may be reflective of widespread and severe disease. The milder cases have a better prognosis because improvement of vasculitis generally can be expected with steroid therapy.[65, 173]

Since the initial descriptions of Pollack et al,[126] it has generally been accepted that the diffuse vasculitis of SLE can affect the retroperitoneal structures, primarily the pancreas. Pancreatitis is an uncommon initial presentation of SLE.[36, 131] The pancreatitis of SLE almost always presents acutely, although two cases of chronic pancreatitis have been reported.[17] In contrast to lupus enteritis, lupus pancreatitis even in patients on steroid therapy is usually symptomatic, with abdominal pain radiating to the back associated with nausea, vomiting, and hyperamylasemia.[131]

Lupus pancreatitis may result from SLE and most commonly occurs in patients whose flareup involves multiple organs.[131] Previous literature suggested that it occurs more commonly as a complication of corticosteroid treatment of the disease, as less than 20% of all SLE-related pancreatitis cases occur in patients who are not on steroid therapy. This viewpoint may lead to withholding steroid therapy, with a potential for life-threatening results. In their review of this entity, Reynolds et al[131] argue that SLE may itself contribute to pancreatitis in patients taking steroids, explaining a greater incidence of pancreatic inflammation in SLE patients than in other steroid-treated disorders.

Ascites occurs in approximately 10% of SLE patients, perhaps as a result of peritoneal inflammation of SLE vasculitis.[35, 65] It is often difficult to ascertain the exact cause of ascites in SLE patients because these patients may have nephrotic syndrome or constrictive pericarditis (or both) in addition to serositis.[14, 35] Dubois and Tuffanelli[35] suggested that abdominal pain with ascites connotes vasculitis, whereas the absence of pain indicates either nephrosis or cardiac involvement. Other authors contend that polyserositis rarely manifests as ascites.[14, 65]

Massive ascites develops rarely in SLE and does not respond well to traditional steroid therapy.[14, 114, 140] The ascitic fluid in SLE patients may contain autoantibodies[90] and low complement levels.[14] Care should be taken to avoid attributing all ascites in SLE patients to vasculitis alone. These patients may develop spontaneous bacterial peritonitis in preexisting ascites. Malignancies should also be considered in the diagnosis.

SLE also manifests in the form of motor dysfunction. Esophageal dysmotility has been reported to occur in up to one third of SLE patients.[60, 65, 129, 151] Stevens et al[151] found aperistalsis in 4 of 16 patients with SLE. Most motility disorders in SLE patients are mild and nonspecific.[60] Aperistalsis, however, has been reported in 10% to 25% of patients.[60, 151] Its presence should raise concern for a mixed connective tissue disorder with sclerodermatous features. In fact, controversy remains as to whether the presence of significant esophageal dysfunction in lupus always reflects concomitant systemic sclerosis or mixed connective tissue disease or is a manifestation of SLE itself.[65] Proximal esophageal motility disor-

ders are also common in SLE. Ramirez-Mata et al[129] found esophageal manometric abnormalities in 16 of 50 patients with SLE, almost half of which occurred in the upper third of the esophagus. Again, whether this reflects a spectrum of overlap with polymyositis or a variant of SLE alone is a matter of further investigation and definition.

Although conflicting literature exists regarding liver disease associated with SLE, overall, there seems to be an historical tendency to minimize hepatic involvement in SLE. Many liver function abnormalities have been attributed to aspirin or azathioprine used in the treatment of SLE because the elevated values often tend to normalize with cessation of pharmacotherapy.[143] Initial reports of autoimmune or *lupoid* hepatitis, many cases of which meet current SLE diagnostic criteria, might retrospectively be attributable to viral causes.[161]

Twenty percent to 30% of patients with SLE demonstrate elevated transaminases.[161] In Dubois and Tuffanelli's analysis[35] of 520 cases of SLE, hepatomegaly occurred in 23% and jaundice in 4%. Runyon et al[136] retrospectively discovered biochemical liver abnormalities in more than half of 238 patients with SLE, and almost one fifth had liver disease either by biopsy or by a twofold increase in at least two biochemical parameters on four separate occasions. Steatosis was the most common finding, but other abnormalities included cirrhosis, chronic active hepatitis, granulomatous hepatitis, cholestasis, centrilobular necrosis, microabscesses, primary biliary cirrhosis, and hemochromatosis. Although SLE may not account for all of these, the authors could not find an alternative cause in the 14 most severe cases.[136]

Clearly, difficulty arises in attempting to categorize a given hepatic abnormality as strictly related to SLE, medications, concomitant viral illness, or autoimmune hepatitis. Further, an overlap syndrome involving chronic active hepatitis and SLE hepatitis may exist.[161] Nevertheless, it seems that hepatic involvement in SLE can occur for any number of reasons and should be followed carefully.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (AAS) is a disorder manifested by both arterial and venous thromboses in association with laboratory findings of the lupus anticoagulant or high titers of IgG, IgM, and IgA anticardiolipin antibodies. The exact cause for the formation of these antibodies remains unknown, but hypotheses focus on infection and genetic predisposition. Often but not always associated with SLE or other autoimmune disorders, this disease has been linked to a number of gastrointestinal manifestations.[21, 23]

The gastrointestinal manifestations of AAS can be attributed to its underlying vasculopathy and resulting tissue ischemia. Arterial occlusion was the underlying mechanism for case reports of intestinal and omental ischemia and infarction, pancreatitis mucosal ulcerations, and one case report of esophageal necrosis with perforation.[21, 23, 77, 165] Hepato-

megaly and abnormal liver function and injury tests may indicate portal venous occlusion with resultant Budd-Chiari syndrome and development of esophageal varices.[23] Despite the dual blood supply to the liver, hepatic infarction is also documented, presumably as a result of widespread vascular occlusions.[23]

Treatment of gastrointestinal problems related to AAS depends on the exact manifestation but does not significantly differ from treatment of similar lesions regardless of their cause and includes procedures such as shunting, sclerotherapy, and surgery. Pharmacologic management, including anticoagulants, steroids, and other immunosuppressive agents, may be required for life-threatening coagulopathy.

Rheumatoid Arthritis

The preponderance of literature regarding gastrointestinal involvement in rheumatoid arthritis (RA) has to do with the effects of medications, mostly NSAIDs, used to treat RA. Previous speculation that patients with RA have a higher incidence of peptic ulcer disease (PUD) as a result of RA itself has not been supported. In fact, evidence indicates that PUD develops with equal frequency in patients with osteoarthritis.[77, 165] These observations suggest that PUD in RA is probably a result of pharmacologic therapy. Further, Sun et al[154] found a 27.8% incidence of PUD in RA patients, with a notable absence of such findings in those patients receiving neither NSAIDs nor steroid treatment for their disease. These pharmacologic effects are discussed in more detail in a separate section.

RA is a systemic disease and as such can encompass the gastrointestinal tract (Table 3). More than 50% of patients with RA may complain of pain and crepitus while chewing[47] as a result of temporomandibular joint involvement. In addition, there seems to be a direct relationship

Table 3. GASTROINTESTINAL AND LIVER MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Oral	Small and large bowel
Temporomandibular joint involvement	Ulceration
Stomach	Hemorrhage
Gastritis (NSAID-induced)	Infarction
Chronic atrophic gastritis	Perforation
Esophagus	Collagenous colitis
Diminished distal peristalsis	Rectum
Decreased LES tone ± hiatus hernia	Vasculitis
Varices (Felty's syndrome)	Other
Hepatic	IBD
Biochemical abnormalities	Splenomegaly (Felty's)
Nodular regenerative hyperplasia (Felty's)	Amyloidosis
Portal fibrosis (Felty's)	

NSAID = Nonsteroidal anti-inflammatory drug; LES = lower esophageal sphincter; IBD = inflammatory bowel disease.

between the severity of RA as a whole and the presence of temporomandibular joint arthritis.[47, 147]

Similar to many collagen vascular disorders, underlying vasculitic lesions produce most of the extra-articular involvement in RA. *Clinical rheumatoid vasculitis* refers to the occurrence of extra-articular vasculitis that can involve the skin, nervous system, and viscera.[19, 142] Although its exact incidence remains unquantified, this entity presents in a small percentage of patients with RA, more often in those with positive rheumatoid factor and subcutaneous nodules.[142]

Of those with this vasculitic syndrome, the gastrointestinal tract becomes involved in up to 10% of patients,[142] often with catastrophic results, such as visceral ischemia,[19, 46, 142] ulceration,[19, 46] hemorrhage, infarction,[142] and perforation.[46] Although inflammatory bowel disease is rare, both ulcerative colitis[19] and Crohn's disease[159] have been described.

To explore further the extent of gastrointestinal involvement, Marcolongo et al[100] obtained gastric, colonic, and rectal biopsy specimens in patients with RA. Gastric biopsy specimens in patients with RA showed a statistically significant incidence of chronic atrophic gastritis compared with normal controls. Furthermore, more than 90% of patients with RA had histologic evidence of inflammatory cellular infiltrate in the lamina propria and interstitium of the colon and rectum as well as significant vasculitis affecting these regions. Scott et al[142] also found rectal vasculitis in 34% of patients biopsied. Moreover, the presence of such seemed to correlate with more severe disease.

The intense gastrointestinal immunologic component of RA demonstrated by Marcolongo et al may be related to the increased levels of antigliadin and antireticulin antibodies noted in patients with RA, while overt celiac sprue is uncommon. When intense colonic inflammation occurs in RA, it may be accompanied by a subepithelial collagen band, and the histologic picture is one of collagenous colitis.[169] Proposed causes for this entity include infection and immune complex deposition as well as a variant of inflammatory bowel disease.[169]

Pathophysiologically the thick collagen-containing colonic wall cannot allow adequate water resorption, resulting in a typical presentation of profuse diarrhea possibly associated with pain, flatulence, and weight loss.[169] Endoscopy in this setting most often proves normal but may show mild hyperemia, congestion, or both.[169]

Secondary amyloidosis also occurs with RA, with prevalence estimates between 5% and 20%.[31] In their study of this entity in RA, Kobayashi et al[84] employed gastroduodenal biopsy to demonstrate an incidence of 13.4%. Moreover, the same study found that those patients with amyloid deposits more frequently had gastrointestinal symptoms, including diarrhea and nausea. The worrisome long-term complications of secondary amyloidosis include pseudo-obstruction, malabsorption, protein-losing enteropathy, and gastrointestinal hemorrhage.

Although many extra-articular symptoms are overshadowed by intense joint discomfort, patients with RA sometimes experience heartburn, dysphagia, or both. Sun et al[154] found decreased peristalsis in the

distal two thirds of the esophagus as well as reduced lower esophageal sphincter tone and hiatal hernia in many patients. Of note, none of the patients in the study had evidence of scleroderma.

Hepatic manifestations of RA consist of abnormal liver function and injury tests.[2, 166] In one study, γ-glutamyltransferase and alkaline phosphatase of liver origin were elevated in 47% and 24%, perhaps as acute phase reactants. The same study showed some hepatocellular damage as well, although salicylate-induced or ethanol-induced damage by factors unrelated to RA could not be excluded. The clinical significance of these data remains uncertain, but medications such as steroids and chloroquine tend to normalize these abnormalities.[2]

Less than 1% of patients with RA have leukopenia and splenomegaly. This triad, which often occurs patients who have had a more severe form of arthritis, defines a condition known as *Felty's syndrome.* The splenomegaly ranges from only radiologically detectable to massive without relation to the degree of neutropenia.[135] Concomitant hepatomegaly and abnormal liver biopsy specimens occur in up to two thirds of patients with Felty's syndrome, whereas abnormal liver function tests may be present in only one third.[135]

The hepatic histopathologic lesions identified in Felty's syndrome include nodular regenerative hyperplasia in up to 70%, portal fibrosis, sinusoidal lymphocytosis, and abnormal lobular architecture.[135, 157] These abnormalities carry significant clinical ramifications. Portal hypertension with bleeding esophageal varices represents the most devastating outcome of nodular hyperplasia.[135, 157] Immune complex mediated or platelet occlusion of small hepatic portal vessels coupled with increased splanchnic blood flow constitutes the presumed insult.[135]

Sjögren's Syndrome

Sjögren's syndrome, a chronic autoimmune disorder, primarily manifests as dry eyes and mouth. *Primary Sjögren's syndrome* refers to the presence of keratoconjunctivitis sicca and xerostomia, whereas *secondary Sjögren's syndrome* describes the former two in association with another autoimmune disease, usually RA.

The lymphocytic infiltration and destruction of exocrine glands usually accompanied by one or more of several serologic autoantibodies leads to the major subjective gastrointestinal manifestations of primary Sjögren's syndrome (Table 4). These subjective manifestations include dry mouth, dysphagia,[28, 121, 146] dyspepsia,[121, 125, 146] nausea, and epigastric pain.[28, 125, 146]

By definition, xerostomia affects all patients with Sjögren's syndrome. The lymphocyte infiltration causes enlargement of parotid or submandibular glands and destruction of acinar glandular cells, with resultant dryness and difficulty chewing, swallowing, and speaking. The absence of saliva not only causes difficult passage of food boluses, but also contributes to the high prevalence of dental caries in this popula-

Table 4. GASTROINTESTINAL AND LIVER MANIFESTATIONS OF SJÖGREN'S SYNDROME

Oral	Pancreatic
Xerostomia	Pancreatitis
Dental caries	Hepatic
Parotid/submandibular enlargement	CAH
Esophageal	PBC
Dysphagia	Cryptogenic cirrhosis
Webs	
Motor dysfunction	
Gastric	
Superficial gastritis	
Chronic atrophic gastritis	
Ulceration	

CAH = Chronic active hepatitis; PBC = primary biliary cirrhosis.

tion.[28, 125] Therapy focuses on providing patient comfort and prophylactic dental care.[125]

Whether dysphagia, a hallmark symptom, represents a motility versus glandular abnormality remains uncertain. Some authors[82] suggest that dry mouth is most likely the primary reason for dysphagia in Sjögren's syndrome patients. After observing a 10% incidence of upper esophageal webs as well as minor esophageal manometric abnormalities in Sjögren's syndrome patients, Kjellen et al[82] suggested that neither of these was responsible for the common complaint of dysphagia (73%) in their study. Further, Palma et al[121] found slight increases in lower esophageal sphincter pressure in one third of Sjögren's syndrome patients, yet these findings did not correlate with the symptom of dysphagia.

Other authors assert that xerostomia is not the only or even the major contributor to dysphagia.[6, 28, 160] Anselmino et al[6] argue that patients with primary Sjögren's syndrome may have dysphagia as a result of esophageal dysmotility. Using esophageal manometry, the same authors demonstrated defective peristalsis in almost one third of patients with primary Sjögren's syndrome and severe dysphagia, results that coincided with previous studies.[160] The same study showed no differences in salivary outflow between Sjögren's syndrome patients with and without dysphagia as measured by Saxon's test, suggesting that xerostomia alone is an inadequate explanation for dysphagia in these patients.[6]

In all likelihood, both xerostomia and dysmotility contribute to dysphagia in patients with Sjögren's syndrome. The presence of esophageal atrophy suggests that inflammatory infiltrate of the esophageal exocrine glands may at times affect the musculature with resultant impairment of motor coordination.[28]

The common complaints of epigastric pain, dyspepsia, and nausea may result from the common occurrence of chronic atrophic gastritis in patients with both primary and secondary Sjögren's syndrome.[28, 102, 125, 146] In their study of 16 patients with primary and secondary Sjögren's

syndrome, Maury et al[102] found an 81% incidence of chronic atrophic gastritis compared to 35% in the control group matched for age, gender, medication, and rheumatic disease other than Sjögren's syndrome.

Pathologically, all types of atrophic gastritis occur in patients with primary Sjögren's syndrome. The location of inflammatory involvement seems to be age related, with young patients having both antral and corpus lesions, middle-aged patients having antral lesions, and elderly patients having corpus lesions.[125]

Histologically, Sjögren's syndrome patients display similarities between the gastric mucosa of chronic atrophic gastritis and the salivary glands,[122] indicating that chronic atrophic gastritis may be a manifestation of a diffuse destructive exocrine process. It has also been suggested that patients with Sjögren's syndrome may be at risk for gastric mucosal compromise as a result of the loss of the protective effects of salivary-produced epidermal growth factor.[28, 146] Serologic evaluation reveals that many of these patients have hypochlorhydria or achlorhydria, hypergastrinemia, hypopepsinogenemia, and sometimes antibodies to parietal cells.[28, 102, 125]

Superficial gastritis has also been reported in association with Sjögren's syndrome. In their study of 20 Italian patients with Sjögren's syndrome, Ostuni et al[117] endoscopically demonstrated superficial gastritis in 85% of patients. In light of the continuum of gastritis, these varied findings may merely reflect the stage of disease, with superficial gastritis occurring early and chronic atrophic gastritis representing a later manifestation of the disease process. Although much less common, some authors postulate that chronic gastric inflammation may eventually lead to pernicious anemia.[122]

Pancreatitis, usually chronic, has been observed with variable frequency in the Sjögren's syndrome population.[146] Several studies[34, 45, 52] have illustrated impaired pancreatic response to pharmacologic challenges. Further, a rare entity consisting of chronic pancreatitis, sclerosing cholangitis, and Sjögren's syndrome has also been reported.[111] Intestinal involvement in Sjögren's syndrome develops rarely, and only case reports of sigmoiditis, inflammatory bowel disease, malabsorption, and celiac sprue have been described.[28, 146]

The exact mechanism by which Sjögren's syndrome affects other organs is yet to be elucidated. The affected regions share the presence of glandular cells. A plausible explanation could evoke antibodies to ductal epithelial cells. Kino-Ohsaki et al[81] discovered such an antibody to both pancreatic ductal and salivary glandular tissues. This antibody also cross-reacted with human carbonic anhydrase (CA) II, an enzyme that catalyzes the conversion of bicarbonate and hydrogen ions to water and carbon dioxide. The same authors further found high CA II antibody titers in patients with Sjögren's syndrome and thus postulate an autoimmune cause for the chronic pancreatitis seen in these patients.

Sjögren's syndrome can also involve the liver and biliary tree. In their study of 63 patients with liver disease, Golding et al[53] found the combination of keratoconjunctivitis sicca and xerostomia in 51% of pa-

tients with liver diseases, including primary biliary cirrhosis, chronic active hepatitis, and cryptogenic cirrhosis.

Skopouli et al[148] studied 300 patients with primary Sjögren's syndrome and found biochemical evidence of liver disease, including elevated alkaline phosphatase and transaminases, in only 5.6%. Only 2% had clinical manifestations of such involvement, including pruritus, palmar erythema, and jaundice. Significantly, 92% of the patients with positive antimitochondrial antibody titers had histologic evidence of early primary biliary cirrhosis, suggesting that this is a sensitive marker for the development of primary biliary cirrhosis in these patients. In this large study, there was a paucity of both chronic active hepatitis and cirrhosis.

In Skopouli's study,[148] abnormal biopsy results in the three patients with histologic or serologic abnormalities suggestive of viral cause were attributed to the viral agent alone. Literature regarding hepatic involvement in Sjögren's syndrome attempts to implicate a causal role for hepatitis C virus (HCV) in the pathogenesis of Sjögren's syndrome. One study found a 13% incidence of HCV in these patients, with histologic evidence of chronic active hepatitis in those who underwent biopsy.[49] It has been suggested that the coexistence of HCV and Sjögren's syndrome explains the previously reported higher incidences of cirrhosis and chronic active hepatitis in these patients. Alternatively the prevalence of HCV in the patients studied may contribute to the pathogenesis of Sjögren's syndrome.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are perhaps the two most studied entities that fall under the rubric of *idiopathic inflammatory myopathies.* They are extremely rare disorders, with new diagnoses limited to 5 to 10 cases per year in the United States.[125] Proximal limb muscle weakness and tenderness, sometimes accompanied by pain, characterize early disease, with ultimate culmination over time into muscular atrophy and fibrosis.[134] Despite the predominant involvement of the proximal skeletal musculature, the disorders have several systemic effects, including the gastrointestinal tract.

The gastrointestinal manifestations of the idiopathic inflammatory myopathies include motor abnormalities, such as uncoordinated swallowing and nasal regurgitation, uncoordinated esophageal and gastrointestinal peristalsis, and reduced gastrointestinal motility.[29, 67, 134] Patients with these disorders have also been found to have hiatal hernia with reflux and stricture formation,[29] gastrointestinal ischemic necrosis,[134] inflammatory bowel disease,[26, 87] and malignancy[134] (Table 5).

Impaired deglutition is a manifestation of cricopharyngeal striated muscle involvement in these diseases. These patients can have nasal regurgitation of food and may even develop aspiration pneumonia.[134]

Table 5. GASTROINTESTINAL AND LIVER MANIFESTATIONS OF POLYMYOSITIS AND DERMATOMYOSITIS

Oral	Other
Oropharyngeal dysphagia	IBD
Esophageal	Malignancy
Dysmotility	Widespread mucosal ulceration, perforation (children)
Gastroesophageal reflux	
Stricture	
Gastric	
Dysmotility	

IBD = Inflammatory bowel disease.

This preesophageal involvement tends to improve with pharmacotherapy.[29]

Polymyositis and dermatomyositis have been shown to affect the distal esophagus and gastrum as well, causing symptoms of dysphagia and heartburn. In their study of 13 patients with either polymyositis or dermatomyositis, DeMerieux et al[29] used scintigraphic techniques to demonstrate significant delays in both esophageal and gastric emptying in 8 patients, underscoring the fact that these disorders do not exclusively affect skeletal muscle. The same study showed a direct relationship between the extent of skeletal muscle weakness and the degree of delayed emptying.

Using cineradiography, DeMerieux et al[29] also provided evidence for distal esophageal involvement, such as impaired motility, hiatal hernia, dilation, and stricture formation in all of the 60% of patients who reported dysphagia. Furthermore, the degree of distal esophageal involvement seemed to correlate with the duration of myositis.

The number of case reports regarding the association of the inflammatory myopathies with inflammatory bowel disease continues to grow and suggests a pathophysiologic connection between these two entities. To this end, Leibowitz et al[93] postulate a causal role for bowel inflammation, stating that this leads to antigen release into the circulation, which, in turn, causes the formation of immune complexes that may deposit within muscle. This postulation serves to explain only those patients with polymyositis or dermatomyositis who have bowel inflammation, suggesting that those without such have contracted the disease by one of the numerous other postulated mechanisms.[125]

In general, associations of Crohn's disease with myositis predominate. In early case reports, patients with known Crohn's disease had histologic evidence of myositis.[105] In later instances, the diagnosis of myositis preceded the development of inflammatory bowel disease.[87] Because subclinical inflammatory bowel disease was not excluded in these patients, the apparent onset of myositis presenting may reflect the spectrum of the progression of inflammatory bowel disease, and patients with polymyositis or dermatomyositis may actually have subclinical

bowel inflammation, as in other autoimmune disorders, particularly the seronegative spondyloarthropathies.[107–109]

The vasculitis of dermatomyositis, in particular, can cause mucosal ulceration and even intestinal perforation.[50] This type of presentation occurs more commonly, although not exclusively, in children. Banker and Victor[8] described ulceration, perforation, and vascular changes spanning from the esophagus to the large intestine in seven of eight children studied. The resulting gastrointestinal catastrophes contributed to the death of all seven children.

Patients with either polymyositis or dermatomyositis have a higher incidence of malignancy. Those with dermatomyositis, in particular, have a 10% incidence of malignancy within the first year after diagnosis.[124] Therefore a diagnosis of either should prompt a thorough investigation, including evaluation of the gastrointestinal tract.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is an autosomal recessive relapsing disorder that primarily affects Sephardic Jews, who once inhabited the Mediterranean coast. The presentation typically reflects the effect of serositis involving the peritoneum, pleura, and synovial membranes associated with fever, rash, and hematuria.

Langevitz et al[91] found that peritoneal involvement in FMF occurred in 95% of patients and was the first presentation of the disease in 55%. The type of abdominal pain that results from peritoneal FMF may be quite severe, often accompanied by distention, rigidity, rebound, hypoactive or absent bowel sounds, nausea, vomiting, and leukocytosis, clinically mimicking an acute surgical abdomen.[91, 150] Even radiologic evidence of bowel obstruction has been shown.[150] Despite the impressive clinical picture, these symptoms completely resolve after 24 to 48 hours without intervention.[150] Many of these patients have undergone laparotomy.[57] Intraoperative findings of hyperemia consistent with inflammation as well as scant culture negative ascites have been described.[150] The latter may organize into fibrous tissue, causing adhesions with resultant possible obstruction, volvulus, and strangulation.[150]

Amyloidosis, a frequent complication of FMF, develops in more than one fourth of patients.[91] The primary site of involvement is the kidneys, but extensive involvement can lead to varying degrees of splenomegaly, although Langevitz et al[91] suggest that this results from inflammation rather than amyloid deposition. Amyloid-induced intestinal malabsorption may occur, although diarrhea in FMF often follows colchicine prophylaxis.[91]

FMF has been linked to both Henoch-Schönlein syndrome and PAN.[41, 51, 119] In these instances, gastrointestinal manifestations may result from the underlying vasculitis. In their study of eight patients with FMF and Henoch-Schönlein syndrome, Flatau et al[41] found that three had bloody diarrhea, three had guaiac positivity, and one had hematemesis.

Ozdogan et al[119] also suggested that vasculitis is common in FMF. They found occult blood in the stools of 47% of patients with FMF after an acute abdominal attack.

Prophylactic colchicine therapy results in complete remission of abdominal pain in almost two thirds of patients, and another one fourth have reduced frequency and severity of attacks.[33, 91] Additionally, colchicine may prevent or reduce already present amyloidosis.[91]

Seronegative Spondyloarthropathies

The term *seronegative spondyloarthropathies* refers to a group of rheumatologic disorders that lack rheumatoid factor and have strong associations with both HLA-B27 positivity and gut inflammation, the latter of which may often be subclinical.[30, 73, 106–109] They include reactive arthritis, Reiter's syndrome, ankylosing spondylitis, psoriatic spondylitis, and *undifferentiated* conditions.[42] In some instances, it appears that the primary insult involves the gastrointestinal tract.

Reactive Arthritis

Reactive arthritis describes joint inflammation that usually affects the lower extremities, occurring secondary to primary infection elsewhere in the body, often in the gastrointestinal tract. Both bacterial and parasitic organisms have been implicated in the development of joint inflammation. They include *Salmonella, Shigella, Campylobacter, Yersinia, Clostridium difficile, Hafnia alvei, Strongyloides stercoralis, Taenia saginata, Giardia lamblia, Ascaris lumbricoides, Filaria,* and *Cryptosporidium.* Because this type of arthritis is by definition a reactive one, no organisms have ever been cultured from a joint aspirate, although microbial antigenic material has been identified.

The exact mechanism by which joint inflammation evolves from such infections remains speculative. Both acute and chronic inflammatory gut lesions unattributable to NSAID therapy have been found in approximately two thirds of patients with reactive arthritis,[30, 107] and case reports of patients with both uroarthritis and enteroarthritis who have subsequently developed Crohn's disease exist.[109] Additionally, some patients with reactive arthritis can progress to ankylosing spondylitis, and the presence of gut inflammation itself may contribute to such a progression.[109]

Intestinal inflammation produces increased intestinal permeability, facilitating absorption and translocation and circulation of organisms to the rest of the body. The immune complexes produced by antigen-antibody reaction may deposit in joints resulting in inflammation.[168] Others suggest that the immune response incited by bacterial antigens has cross-reacted with joint components.[37]

Others, underscoring the high degree of HLA-B27 positivity among these patients, purport that antigenic material from the infecting organ-

ism binds to a portion of the antigen presenting cell encoded for by the B component of the major histocompatibility complex. The antigen presenting cell then elicits a response from CD8 T cells, and a cascade of inflammatory events ensues.[42]

Segal[144] asserts a neurologic association between gut and joint involvement and attempts to explain the predominantly lower extremity distribution of arthritis in reactive arthritis (as well as the axial distribution in ankylosing spondylitis) by proposing that the inflammatory mediator–producing peptidergic nerves supplying these joints originate from the same vertebral level as those supplying the gastrointestinal tract.[144]

As in RA, the intense intestinal inflammation accompanying enteropathic arthritis has been reported in association with collagenous colitis, in which patients have profuse watery diarrhea and a histologic picture in the colon likened to that of celiac sprue of the small bowel.[80]

Ankylosing Spondylitis

Ankylosing spondylitis, another seronegative spondyloarthropathy, primarily affects young men, who often initially present with insidious low back pain and stiffness. Inflammation then progresses to fibrosis at the insertions of ligaments and tendons in the iliosacral region.[167] The largely axial distribution of rheumatologic symptoms should not distract from the truly systemic nature of the disease, including its effects on the gastrointestinal tract.

It is estimated that 2% to 18% of patients with ankylosing spondylitis have inflammatory bowel disease, although Mielants et al[108] have shown endoscopic evidence of lesions resembling Crohn's disease in up to 61% of patients with ankylosing spondylitis, thereby underscoring subclinical gastrointestinal involvement in this entity. In that study, approximately 13% of those patients with ankylosing spondylitis went on to develop inflammatory bowel disease. Identified risk factors for the development of inflammatory bowel disease in these patients included the presence of chronic inflammatory gut lesions, high erythrocyte sedimentation rate and C-reactive protein, and HLA B27 negativity,[108] in contrast to previous suggestions of the strong association between ankylosing spondylitis and inflammatory bowel disease.[142]

Just as in ankylosing spondylitis alone, the spondylitic arthritis in patients with inflammatory bowel disease is characteristically symmetric with a predominantly axial distribution, worse in the morning and exacerbated by prolonged immobility. Exacerbations of ankylosing spondylitis do not correlate with bowel symptoms. Neither surgical nor pharmacologic treatment of the inflammatory bowel disease seems to affect the rheumatic symptoms of ankylosing spondylitis, for which physical therapy, NSAIDs, steroids, and radiation have all been employed.[42]

Ankylosing spondylitis associated with inflammatory bowel disease is distinguishable from *colitic arthritis*. The latter is asymmetric, affecting

few peripheral joints (mainly knees and ankles), and occurs in close temporal relationship to colitis. Moreover, colitic arthritis usually responds to pharmacologic or surgical treatment of inflammatory bowel disease, whereas the arthritis of ankylosing spondylitis–related inflammatory bowel disease does not.

The pathophysiologic relationship between inflammatory bowel disease and ankylosing spondylitis remains obscure, with the leading theories citing infectious or immunologic origins. Some[37] advocate an infectious cause, as one study showed an association between *Klebsiella pneumoniae* in feces with active inflammatory disease. Stodell et al[153] found a high incidence of IgG-containing cells in the rectal lamina propria of patients with ankylosing spondylitis, which had previously been reported in both Crohn's disease and ulcerative colitis, underscoring an immunologic cause for these diseases.

Psoriatic Arthritis

Psoriatic arthritis also falls under the rubric of *seronegative spondyloarthropathy.* In general, this inflammatory arthritic condition affects 5% to 42% of persons with psoriasis, and the distribution of involvement may vary.[141] Of those who develop the disease, approximately one half have asymmetric inflammatory arthritis, whereas spondylitic psoriasis and symmetric arthritis affect one quarter each.[141]

A few reports of inflammatory bowel disease occurring in patients with psoriatic arthritis exist. Perhaps the relative paucity of literature dissecting the relationship between these two entities stems from both the relatively low incidence of psoriatic arthritis in general as well as the conflicting methods of classification of the disorder.

Nevertheless, in their endoscopic study of 64 patients with psoriatic arthritis, Schatteman et al[138] found macroscopic inflammatory lesions in 11% and microscopic lesions in an additional 5%. The same study showed that these acute and chronic lesions occurred only in those patients with either axial arthritis or oligoarthritis but not in those with polyarthritis. Moreover, those patients with inflammatory lesions were frequently HLA-B27 and HLA-Bw62 positive.

Theoretically the gastrointestinal tract could serve as a portal of entry for antigens that might be implicated in the development of psoriatic arthritis. It may be difficult to place sole responsibility on the increased permeability of the gastrointestinal tract because these patients have skin lesions as well.

LARGE CELL VASCULITIDES

Takayasu Arteritis

Takayasu arteritis, a large vessel arteritis of undetermined cause, typically afflicts young women of Asian descent. Pathologically, infiltra-

tion of arterial walls with inflammatory cells produces vessel wall thickening and variable degrees of stenosis.[138] These stenotic regions are at further risk for complete occlusion secondary to thrombosis. Although the inflammation of Takayasu arteritis typically involves the proximal aorta and its primary branches, any portion of the aorta may be involved. The involvement of the descending abdominal aorta and its branches gives rise to gastrointestinal symptoms of temporal arteritis, including abdominal pain, nausea, diarrhea, and hemorrhage. In their study of 84 cases of radiographically or clinically diagnosed temporal arteritis, Nakao et al[113] found that of the 54 patients who underwent aortography, 5 had mesenteric and 1 had hepatic arterial involvement. Six patients in the study had localized abdominal pain, which may have been attributable to vasculitis. Both stenotic[64, 171] and saccular[118, 145, 171] aneurysmal lesions of the intra-abdominal arteries are reported, with the latter presumably occurring as vessels weaken from extensive inflammation.

There are some reports of inflammatory bowel disease, both Crohn's disease and ulcerative colitis, occurring in association with Takayasu arteritis.[64, 118, 145, 171] The underlying pathophysiology relating these two entities remains speculative. In the cases that the authors reviewed, the diagnosis of inflammatory bowel disease preceded that of Takayasu arteritis, supportive of one proposed theory that invokes a causal role for inflammatory bowel disease, with bowel inflammation allowing absorption of immune complexes into the circulation. These complexes can then be deposited within blood vessels, causing vasculitis. Supportive evidence that the bowel inflammation proceeds from ischemia and vascular insufficiency is lacking because the specific vessels involved do not necessarily correlate with the anatomic region of inflammation.[64] Antibodies to both colonic mucosa and aorta have been detected in the sera of some of these patients, suggesting that the underlying common pathway has an immunologic basis.[118, 145]

Giant Cell Arteritis

Inflammatory large vessel arteritis involving the cranial and, in particular, the temporal arteries constitutes giant cell arteritis. Involvement of the facial arteries and resultant masseter muscular ischemia leads to the frequent complaint of pain with chewing known as *jaw claudication.*

Aortitis, selective for white greater than 50 years of age, afflicts approximately one tenth of patients with giant cell arteritis.[138] In his study of this entity, Ostberg[116] described two cases of *gangraena intestini* and one case of *pancreatitis acuta.*[116] The paucity of additional literature on alimentary tract involvement in giant cell arteritis attests to its rarity.

Hepatic involvement as evidenced by abnormal liver function and injury tests occurs in approximately 20% of patients and can rarely be the primary manifestation of the disease.[71] The typical picture is cholesta-

sis, with elevations of alkaline phosphatase and γ-glutamyltransferase, although many patients had mild transaminase elevations. Hyperbilirubinemia is rare.[71]

Liver biopsy specimens are usually unrevealing, showing either normal or nonspecific changes, yet granulomas, lymphocytic infiltration, dilated bile canaliculi, and even hepatocellular necrosis with dropout have been reported.[32, 71]

Although the pathophysiology for hepatic involvement in giant cell arteritis has not been defined, it has minimal clinical significance. The abnormal laboratory values typically resolve with steroid treatment.

ADVERSE GASTROINTESTINAL EFFECTS OF DRUGS USED FOR COLLAGEN VASCULAR DISEASES

Although the previous discussion has made it clear that gastrointestinal involvement is common in many different types of vasculitis, side effects of the medications used to treat these disorders are an equally important cause of gastrointestinal complaints. Specialists with an interest in gastroenterology and hepatology must be able to recognize this potential and recommend ways to avoid the side effects. The most common cause of these side effects is the NSAIDs, but other agents that affect the gut less frequently may cause severe injury. This section focuses on the nonimmunosuppressive effects of these medications.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are an important part of the medical armamentarium for the treatment of rheumatologic diseases. These drugs are commonly used for short courses for acute self-limited diseases and are also used as long-term therapy for chronic disorders. Their use is associated with gastrointestinal injury that typically presents as ulcer disease of the stomach or duodenum; however, similar injury is less commonly noted in the small intestine and colon.

The mechanism of injury that leads to ulcer in the stomach and duodenum has been attributed to the inhibition of mucosal prostaglandin synthesis, which thereby diminishes its cytoprotective effect. Cytoprotection is the defense mechanism of the gastroduodenal mucosa that offers protection from injury in the acidic environment of the upper gastrointestinal tract.[132] Once an irritant (e.g., alcohol) injures the surface epithelium, there is back-diffusion of acid from the lumen into the epithelium resulting in injury and inflammation, which eventually leads to erosion and ulceration. Prostaglandin acts through several mechanisms to protect against this process. Interference with these mechanisms leaves unchecked the injurious factors and favors the development of

ulcers. Prostaglandins reduce injury to the mucosa by increasing mucosal mucus and bicarbonate secretion, by increasing mucosal blood flow, and by promoting cellular proliferation of the epithelial cells. A mucus gel layer lies above the gastroduodenal epithelium and maintains a microenvironment of bicarbonate-rich fluid just above the epithelial cells, thereby reducing the surface cell's exposure to acid. Mucosal blood flow transports bicarbonate from the base of the glands, where it is secreted into the bicarbonate layer above the epithelial surface, where it contributes to the gradient between the epithelial cell and the acidic milieu of the luminal gastric contents. These mechanisms help to establish a barrier to damage by acid; epithelial cell proliferation in the crypts of the glands and their migration to the surface are important to repopulate the surface of the mucosa after injury.

These three mechanisms help to prevent injury to the mucosa and the subsequent formation of an ulcer. NSAIDs lead to mucosal injury through reduction of prostaglandin synthesis by inhibiting cyclooxygenase activity, which is the rate-limiting step in the local production of prostaglandins from membrane bound arachidonic acid. There are two cyclooxygenase (COX) enzymes. COX 1 is active in the normal constitutive physiologic mechanisms just described. COX 2 is induced in inflammatory processes. Most currently available NSAIDs are nonselective inhibitors and affect both pathways. Inhibition of COX 1 pathway produces the unwanted effect of decreasing protective prostaglandin production and predisposes to ulcer formation. Drugs that are given as prodrugs or as enteric-coated formulations for the purpose of minimizing exposure of the gastroduodenal mucosa to the drug are equally injurious because cyclooxygenase inhibition is a systemic effect and not related to topical exposure.

Although mucosal injury occurs in many patients, only a minority develop clinically significant disease.[48] There is no correlation of symptoms (e.g., dyspepsia with mucosal injury, i.e., ulcer). Thus, it is not helpful for the clinician to use symptoms to identify patients who are at risk of NSAID-induced complications. Many patients complain of dyspepsia but do not have ulcer disease. Epidemiologic studies have identified a group of patients who are at an increased risk of complications from NSAIDs. This group includes patients who are older than 65 years and those who have had prior ulcer disease. The risk is also greater in patients who are concomitantly receiving corticosteroids.[48] There is also an increased risk of ulcer complications, such as perforation and bleeding, in patients who receive large doses of NSAIDs. All NSAIDs carry an increased risk of ulcer disease, although that risk appears to be greater with certain drugs, such as indomethacin. Many ulcer complications occur within the first few months of NSAID therapy. There appears to be a degree of adaptation that occurs with continued use of the drug, which protects the mucosa from injury. It remains unclear whether a synergism exists between NSAIDs and *Helicobacter pylori* infection in the formation of ulcers. It is clear, however, that

treatment of *Helicobacter* infection alone is not sufficient to protect the patient from NSAID-related ulcers.

Maneuvers to reduce the gastroduodenal toxicity of NSAIDs include the use of acetaminophen or other analgesics for pain control in place of NSAIDs, the use of the lowest possible dose of NSAID, and the addition of a drug to inhibit gastric acid secretion. High-dose H_2-antagonists have been demonstrated to reduce the incidence of gastric and duodenal ulcers.[155] Proton-pump inhibitors have been shown to be superior to standard doses of H_2-antagonists.[62] Another treatment option to prevent ulcer disease is the use of an oral prostaglandin, such as misoprostil. This agent has been effective in reducing NSAID-related ulcer disease; however, its use is limited because it is expensive, and it is poorly tolerated causing diarrhea in many patients, which leads to its discontinuation. Omeprazole has been shown to be more effective than misoprostil in preventing NSAID ulcer with little risk of toxicity or side effects. Other approaches that may be available in the future include the formulation of NSAIDs that are directed specifically at inhibition of the COX 2 enzyme. This formulation would reduce inflammation and pain without diminishing COX 1 function, thus maintaining mucosal prostaglandin synthesis. Another approach is to combine nitric oxide with the NSAID. Nitric oxide may prevent the formation of ulcers by decreasing mucosal inflammation and increasing mucosal blood flow.[164]

In addition to the more common adverse effect of ulceration of the stomach and duodenum, NSAIDs have been reported to cause ulceration and stricture in the small intestine[4] and in the colon.[69] Rarely the small intestine ulceration presents as a perforation.

NSAIDs also may cause hepatotoxicity.[16] Many drugs in this category are associated with trivial and inconsequential elevations in levels of the liver enzymes; it is rare to develop clinical liver disease. Sulindac is associated with the greatest risk of liver toxicity. This toxicity usually occurs within the first 2 months of therapy and is a hypersensitivity reaction associated with fever, rash, and eosinophilia. Other symptoms include nausea, vomiting, pruritus, and jaundice, and liver biochemistries reveal a cholestatic pattern with elevation of the alkaline phosphatase. Aspirin is also associated with liver disease, especially when used in the treatment of juvenile RA and SLE. Aspirin is also associated with the development of Reye's syndrome causing hepatic inflammation and neurologic disease, which may include seizures and coma. This syndrome is most commonly seen when aspirin is used in patients with viral illness such as varicella.

Corticosteroids

There has been a long-standing controversy about whether the use of corticosteroids is associated with the development of ulcers of the stomach and duodenum. The evidence to support this relationship is weak. There have been anecdotal reports of an increased risk of compli-

cations of ulcers, such as perforation, in those using corticosteroids.[13] Data to support an increased risk for the development of ulcers with steroid use are difficult to assess, however, because many reports are complicated by the additional risk for developing ulcer disease contributed by the underlying illness for which the patients were receiving steroid therapy. In addition, other medications with which these patients were also being treated may contribute to the ulcer risk. It is known that NSAIDs increase the risk of ulcer and additionally increase the risk of complications of ulcers, such as perforation and bleeding. Anticoagulants also increase the risk of gastrointestinal bleeding. Patients who receive these medications in addition to steroids therefore are more likely to be hospitalized for these complications and thereby skew the interpretation of the data regarding the risk of ulcer that can be attributed to corticosteroids. This can be seen in a review of Medicaid patients hospitalized in Michigan for upper gastrointestinal bleeding. A small minority of the group had received prior treatment with steroids; however, the relative risk of bleeding was increased eightfold in those patients receiving steroids and anticoagulants.[24] A second retrospective study also suggested that there is an increased risk of upper gastrointestinal bleeding with concomitant use of corticosteroids and NSAIDs.[24] There was a fourfold increased risk of bleeding in patients using both medications compared with those patients using only steroids. Thus, the true risk of developing an ulcer secondary to corticosteroid therapy is not known but is probably insignificant or, at most, a small relative risk. These studies have shown an increased risk of complications with the concomitant use of steroids and either NSAIDs or anticoagulants.

An adverse side effect that has been well documented is the association of corticosteroids with an increased risk of various gastrointestinal infections. This risk is secondary to the effect of steroids to depress the cellular immune system. There is an expected increase in viral and fungal infections. Patients treated with steroids have an increased risk of oropharyngeal and esophageal candidiasis. There is also an increased risk of esophagitis secondary to herpes simplex and cytomegalovirus infections. Rare reports of hepatitis from these infections have also been attributed to corticosteroid immunosuppression. For similar reasons, tuberculosis and *Strongyloides* infections can also flare during steroid therapy. Patients may present with tuberculous peritonitis or gastrointestinal involvement, such as ileocolitis, and those who had dormant *Strongyloides* infestation may develop a flare with systemic disease. Diagnosis of the latter disease may require duodenal aspirate because stool examination may fail to reveal the parasite.

Also of importance, patients with chronic hepatitis B infection may have a flare of hepatitis, and cases of life-threatening fulminant hepatitis have been reported after the withdrawal of steroid therapy. Hepatitis B virus does not lead to hepatic necrosis directly, but the inflammation and necrosis associated with the infection are secondary to the host immune response to the infection. Therefore it is postulated that hepatitis B viral replication is increased during immunosuppression, and more

hepatocytes become infected with the virus. When steroid therapy is withdrawn and there is a return of the body's immune response, this leads to enhanced necrosis of the infected hepatocytes and a flare of the clinical disease.

Other uncommon gastrointestinal complications are associated with corticosteroid therapy. Pancreatitis rarely occurs. One case report documents the association with temporal relapses after rechallenge with the drug.[94] Fatty infiltration of the liver also may develop, but this is rarely clinically significant. Of more importance, although more difficult to establish from clinical studies, is the impression from clinical experience and anecdotal reports that steroids mask the signs and symptoms of gastrointestinal diseases.[40] Cases of peritonitis secondary to perforation of ulcers and cases related to colonic diverticulitis have had a delay in diagnosis because of diminished pain and masking of the typical physical signs of guarding and tenderness usually associated with this complication. Diagnosis has sometimes relied on the finding of free air in the peritoneum on x-ray. There is also the theoretic concern that decreased inflammatory response and decreased wound healing secondary to corticosteroids could predispose to widespread peritonitis instead of a localized and walled-off perforation as is usually seen with diverticulitis. Another potential complication related to the catabolic state caused by corticosteroids could be an increased risk of dehiscence of surgical wounds and anastomoses, including dehiscence and peritonitis after percutaneous gastrostomy feeding tube placement.

Methotrexate

Methotrexate is used in the treatment of malignancy as well as in the treatment of some benign inflammatory diseases, such as psoriasis and RA. It interferes with DNA synthesis by inhibiting the activity of dihydrofolate reductase, and the risk for adverse side effects is increased in the presence of folate deficiency and in circumstances when the drug's renal excretion is decreased, such as with renal insufficiency or in the presence of drugs that can decrease its renal excretion, such as NSAIDs. Low dosages used for inflammatory diseases can cause liver toxicity. Doses for cancer therapy may be greater than 1000 mg, whereas doses for inflammatory disease are usually not more than 25 mg/week. There is a spectrum of histologic change that can be noted in the liver, including fatty infiltration, portal tract inflammation, and Ito cell enlargement.[16, 156] Fibrosis may initially develop in the space of Disse and can lead to portal fibrosis and cirrhosis. Abnormalities of liver biochemistries include elevations of alkaline phosphatase and the aminotransferases; however, there is a poor correlation between the severity of laboratory abnormalities and the histologic changes in the liver. Risk factors that increase the likelihood of developing methotrexate-related hepatic fibrosis include excessive alcohol consumption, obesity, and diabetes mellitus.[39] The risk of fibrosis appears to increase with increased total dose and duration of methotrexate therapy.[156]

Several protocols have been established to monitor for hepatotoxicity. Criteria have been established for liver biopsy before initiating therapy if the liver enzymes are elevated or if there is a history of diabetes, alcoholism, prior liver disease, or positive viral serology for hepatitis B or C.[39, 85] Patients meeting any of these criteria would also undergo biopsy after receiving every 1000 mg of treatment. Patients without these criteria would undergo biopsy if liver enzymes became abnormal for 3 months during therapy or after every 1500 mg of cumulative dose. The American College of Rheumatology recommendation differs in that there is no pretreatment biopsy for diabetics, and surveillance biopsies are done only if liver enzymes are abnormal five of nine times within 1 year. Liver biopsy is also done after every 1000 to 1500 mg of cumulative dose. One study found that following the recommendations of the American College of Rheumatology greatly reduced the number of liver biopsies performed and avoided the two complications of biopsies that occurred using the Psoriatic Task Force protocol. This protocol missed one of five patients who had been found to have fibrosis or cirrhosis using the more intensive protocol.[39] It is not known what is the natural history of methotrexate hepatic fibrosis and whether fibrosis in the space of Disse or in the portal tracts inevitably leads to cirrhosis. With the limited knowledge now available, it is appropriate to perform liver biopsy on a regular protocol and discontinue methotrexate if early signs of fibrosis are found.

Azathioprine is metabolized to 6-mercaptopurine and acts as a prodrug enhancing its clinical efficacy. Minor gastrointestinal side effects may occur within the first few months of therapy and include nausea and vomiting. A more serious reaction is the apparent hypersensitivity reaction that in addition has symptoms of diarrhea, fever, and rash. This typically occurs within weeks of initiating therapy and would necessitate discontinuation of the drug. Also occurring within weeks of beginning therapy is the uncommon complication of pancreatitis, which presents in the usual fashion with upper abdominal pain and nausea and vomiting. This is a hypersensitivity reaction and would be a contraindication to reinstitution of the drug.

Liver disease rarely is associated with these medications and may be related to damage of the endothelium of the sinusoids and venules. This damage can lead to sinusoidal dilation and centrilobular congestion and necrosis. Peliosis hepatis and veno-occlusive disease may also occur. The latter disease may present with right upper abdominal pain secondary to a congested liver and be accompanied by ascites. Fibrosis of the hepatic veins and nodular regenerative hyperplasia may complicate drug therapy and lead to portal hypertension.

Cyclophosphamide

Cyclophosphamide commonly causes nausea and vomiting; however, more serious gastrointestinal adverse effects are rare. This drug is

well known to cause hemorrhagic cystitis probably related to the urinary excretion of irritant metabolites. There have been rare anecdotal case reports describing the development of hemorrhagic colitis, but this is so uncommon that it raises the possibility that there is no causal relationship with the medication.

Penicillamine

Penicillamine is commonly associated with gastrointestinal side effects. Perhaps one third of patients develop nausea, vomiting, abdominal discomfort, and diarrhea. It also may cause a loss of taste sensation.

Gold Salts

Treatment with gold is often associated with diarrhea, and rare case reports of enterocolitis have been reported.

Sulfasalazine

Sulfasalazine is derived from the binding of a salicylate with a sulfa compound, and the common gastrointestinal side effects are related to the sulfa moiety and include nausea, vomiting, and abdominal discomfort. There may also be a change in taste. A more serious, albeit uncommon, side effect is the development of pancreatitis. As with other sulfonamides, there is also a rare risk of the development of hepatitis, which occurs early after beginning drug therapy.

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