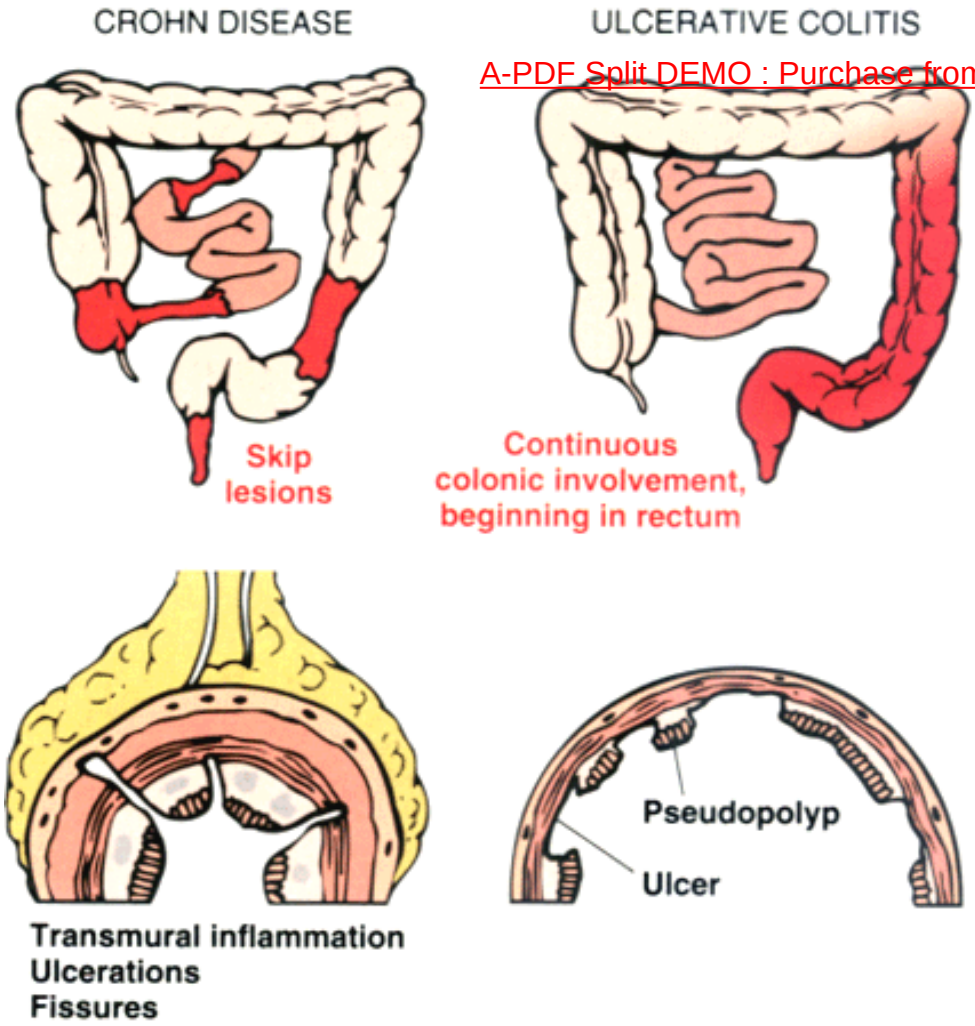

Figure 17-44 Ulcerative colitis. Ulcerated hemorrhagic surface with knobby pseudopolyps. *(Courtesy of Dr. Kim Bechard, Brigham and Women's Hospital, Boston, MA.)*

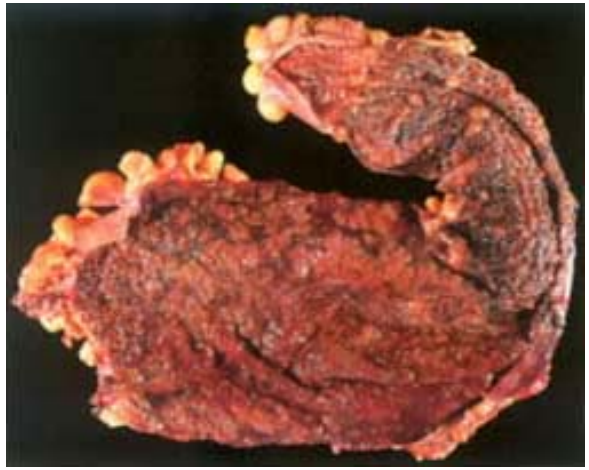

Figure 17-45 Ulcerative colitis. Low-power micrograph showing marked chronic inflammation of the mucosa with atrophy of colonic glands, moderate submucosal fibrosis, and a normal muscle wall.

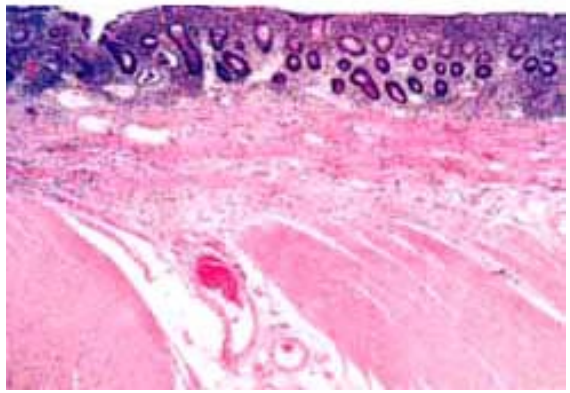

Figure 17-46 Toxic megacolon. Complete cessation of colon neuromuscular activity has led to massive dilatation of the colon and black-green discoloration signifying gangrene and impending rupture.

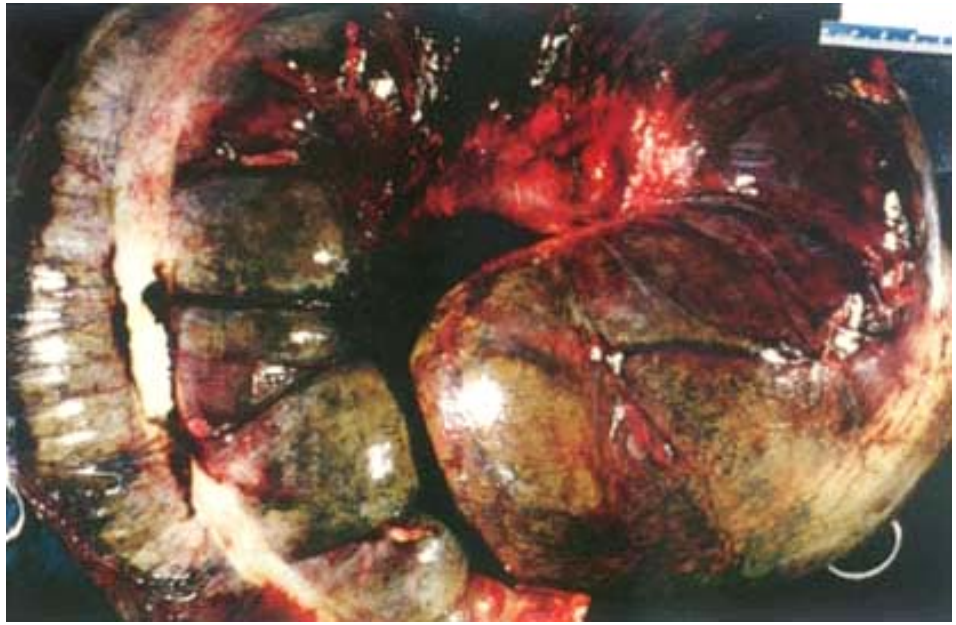

Figure 17-47 Ulcerative colitis. Microscopic view of the mucosa, showing diffuse active inflammation with crypt abscess and glandular architectural distortion.

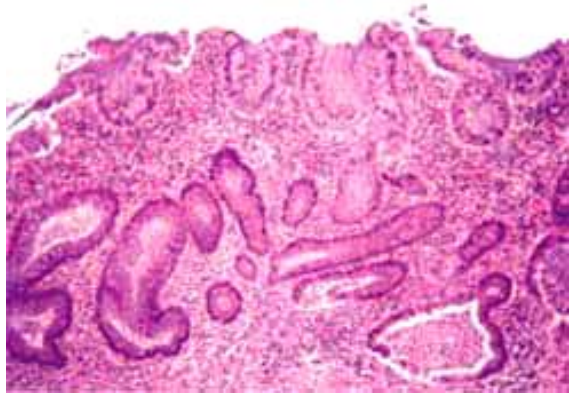

TABLE 17-10 -- Distinctive Features of Crohn Disease and Ulcerative Colitis *

Feature	Crohn Disease - SI	Crohn Disease - C	Ulcerative Colitis
Macroscopic			
Bowel region	Ileum ± colon	Colon ± ileum	Colon only
Distribution	Skip lesions	Skip lesions	Diffuse
Stricture	Early	Variable	Late/rare
Wall appearance	Thickened	Thin	Thin

Dilation	No	Yes	Yes
Microscopic			
Inflammation	Transmural	Transmural	Limited in mucosa
Pseudopolyps	No to slight	Marked	Marked
Ulcers	Deep, linear	Deep, linear	Superficial
Lymphoid reaction	Marked	Marked	Mild
Fibrosis	Marked	Moderate	Mild
Serositis	Marked	Variable	Mild to none
Granulomas	Yes (50%)	Yes (50%)	No
Fistulae/sinuses	Yes	Yes	No
Clinical			
Fat/vitamin malabsorption	Yes	Yes, if ileum	No
Malignant potential	Yes	Yes	Yes
Response to surgery	Poor	Fair	Good

*SI, Crohn disease of the small intestine; C, Crohn disease of the colon. Features are often not all present in a single case.

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the disease runs a fulminant course; unless medically or surgically controlled, this toxic form of the disease can lead to death soon after onset.

The most feared long-term complication of UC is cancer. There is a tendency for dysplasia to arise in multiple sites, and the underlying inflammatory disease may mask the symptoms and signs of carcinoma. UC is characterized by DNA damage with microsatellite instability in mucosal cells. More recently, genomic instability was detected in non-dysplastic areas of patients with UC, suggesting that these patients have DNA repair deficiency and genomic instability throughout the intestinal tract.[77] *The associated carcinomas are often infiltrative without obvious exophytic masses, further underscoring the importance of early diagnosis.* Historically, the risk of cancer is highest in patients with pancolitis of 10 or more years' duration, in whom it is 20- to 30-fold higher than in a control population.[78] However, recent screening programs of patients with UC now indicate that the rate of progression to dysplasia and carcinoma is in fact quite low, provided that initial examinations were negative for dysplasia. Since great cost is involved in mass screening, the debate over the cost-effectiveness of repeated colonoscopies in patients with long-term inactive disease continues; the modest improvement in patient outcome may be related to better patient care, rather than identification of dysplasia per se.

The features of CD and UC are compared in Table 17-10 .

Vascular Disorders

ISCHEMIC BOWEL DISEASE

Ischemic lesions may be restricted to the small or large intestine, or may affect both, depending on the particular vessel(s) affected. Acute occlusion of one of the three major supply trunks

of the intestines—celiac, superior mesenteric, and inferior mesenteric arteries—may lead to infarction of several meters of intestine. However, insidious loss of one

Figure 17-48 Acute ischemic bowel disease. Schematic of the three levels of severity, diagrammed for the small intestine.

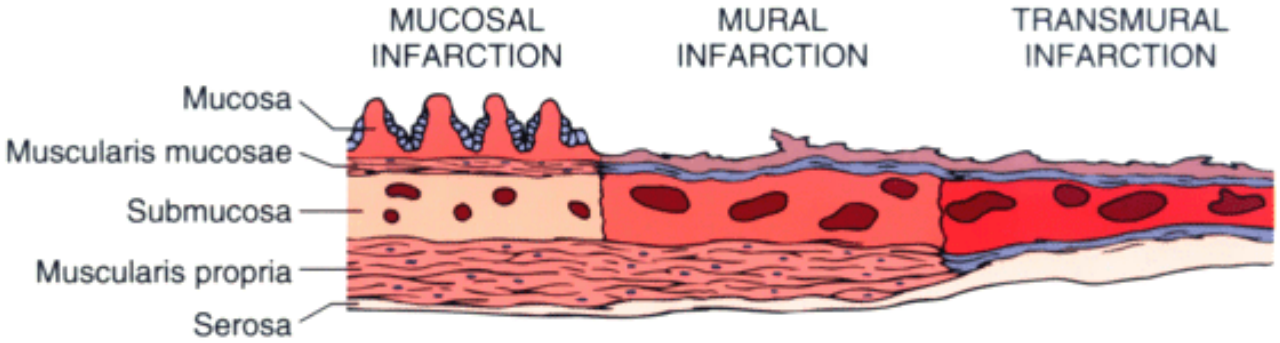


Figure 17-49 Infarcted small bowel, secondary to acute thrombotic occlusion of the superior mesenteric artery.

Figure 17-50 Mucosal infarction of the small bowel. The mucosa is hemorrhagic, and there is no epithelial layer. The remaining layers of the bowel are intact.

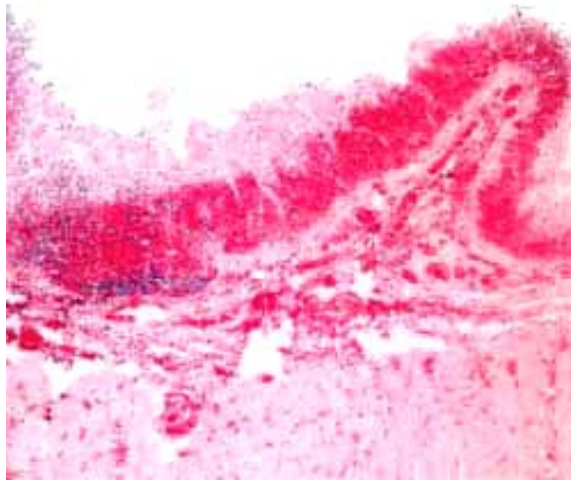


Figure 17-51 Chronic ischemia of the colon, resulting in chronic mucosal damage and a stricture.

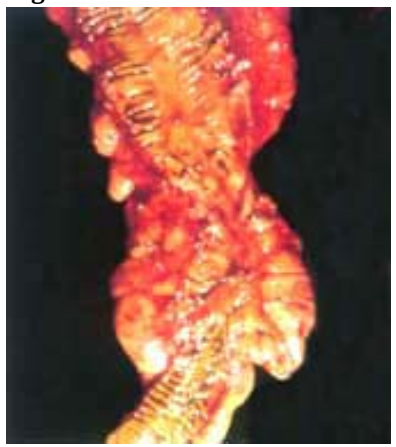
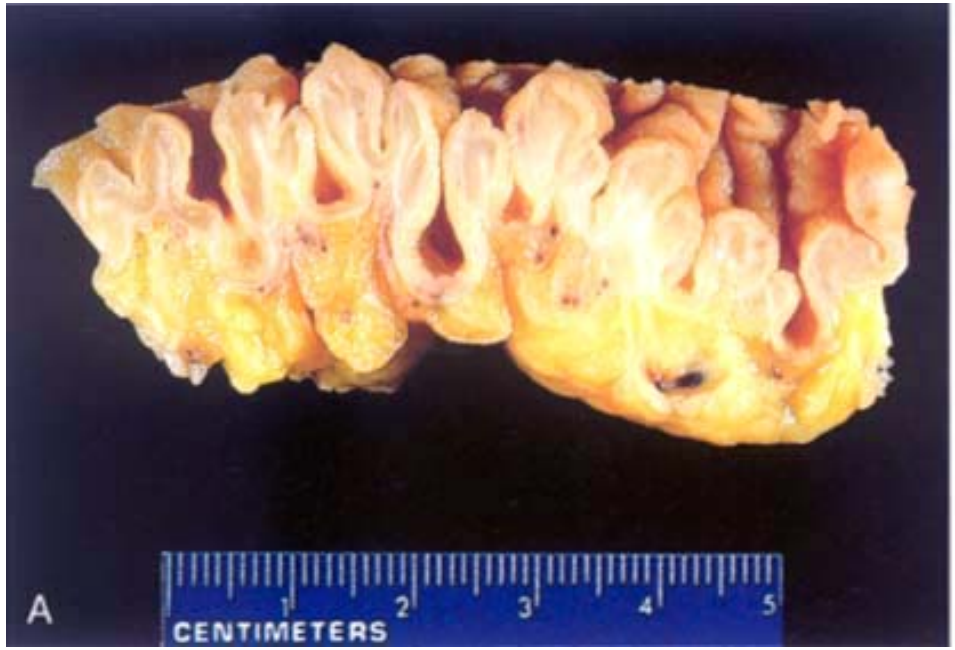


Figure 17-52 Diverticulosis. *A,* Section through the sigmoid colon, showing multiple sac-like diverticula protruding through the muscle wall into the mesentery. The muscularis propria in between the diverticular protrusions is markedly thickened. *B,* Low-power photomicrograph of diverticulum of the colon, showing protrusion of mucosa and submucosa through the muscle wall. A dilated blood vessel at the base of the diverticulum was a source of bleeding; some blood clot is present within the diverticular lumen.



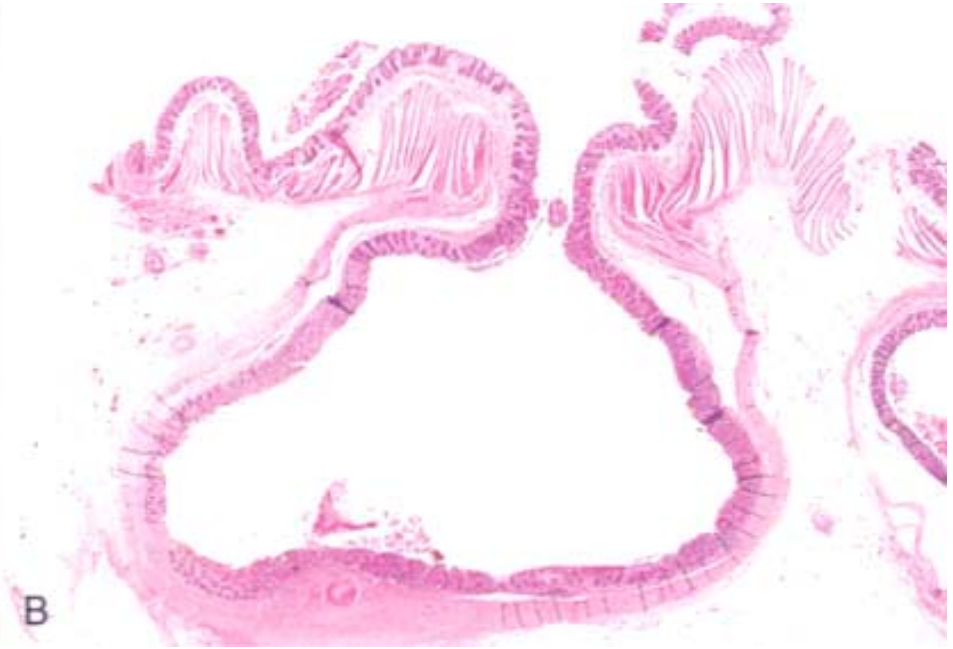


TABLE 17-11 -- Major Causes of Intestinal Obstruction

Mechanical Obstruction
Adhesions
Hernias, internal or external
Volvulus
Intussusception
Tumors
Inflammatory strictures
Obstructive gallstones, fecaliths, foreign bodies
Congenital strictures; atresias
Congenital bands
Meconium in mucoviscoidosis
Imperforate anus
Pseudo-obstruction
Paralytic ileus (e.g., postoperative)
Vascular—bowel infarction

Myopathies and neuropathies (e.g., Hirschsprung)

Figure 17-53 Schematic depicting the four major causes of intestinal obstruction: (1) Herniation of a segment in the umbilical or inguinal regions; (2) adhesion between loops of intestine; (3) intussusception; (4) volvulus formation.

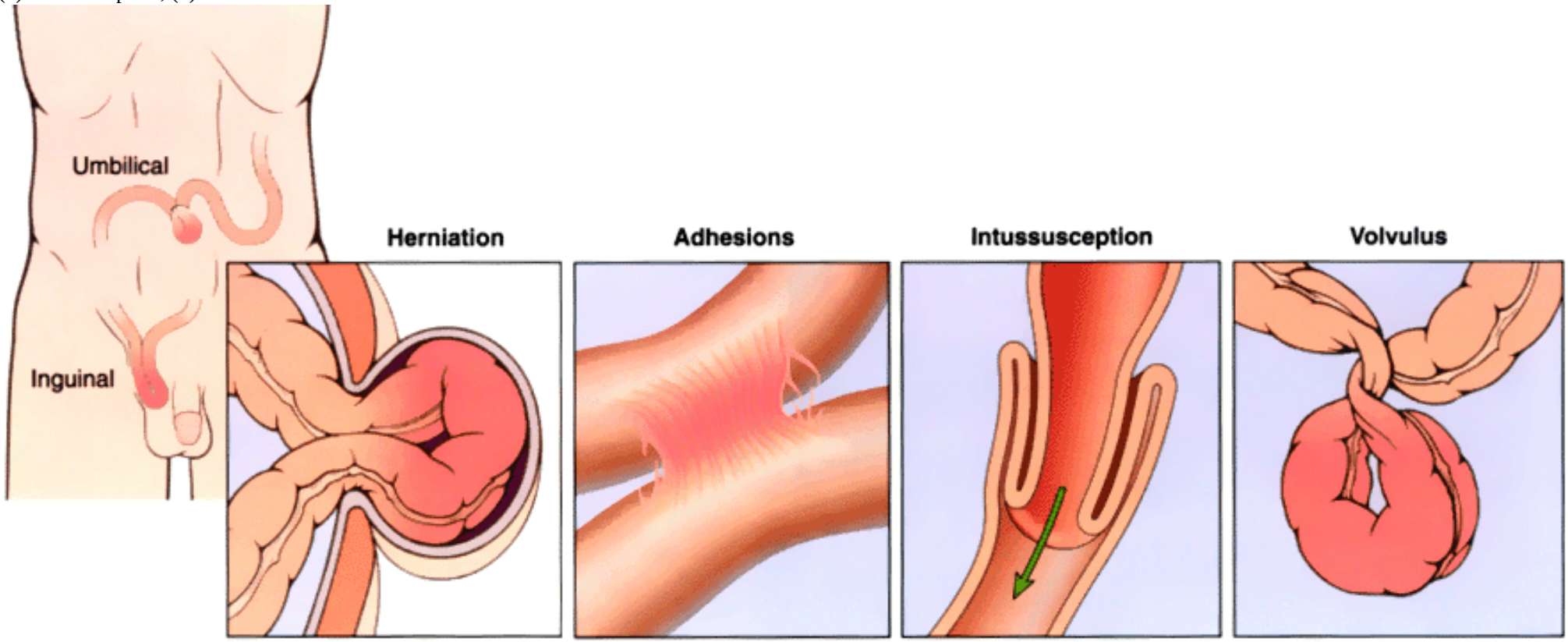


TABLE 17-12 -- Tumors of the Small Intestine and Colon

Non-neoplastic (Benign) Polyps
Hyperplastic polyps
Hamartomatous polyps
• Juvenile polyps
• Peutz-Jeghers polyps

Inflammatory polyps
Lymphoid polyps
Neoplastic Epithelial Lesions
Benign
• Adenoma *
Malignant
• Adenocarcinoma *
• Carcinoid tumor
• Anal zone carcinoma
Mesenchymal Lesions
Gastrointestinal stromal tumor (GIST) (gradation from benign to malignant)
Other benign lesions
• Lipoma
• Neuroma
• Angioma
Kaposi sarcoma
Lymphoma

* Benign and malignant counterparts of the most common neoplasms in the intestines; virtually all lesions are in the colon.

angiomas, and rare hamartomatous mucosal lesions comprise the remainder. One of the enigmas of medicine is the rarity of malignant tumors of the small intestine—annual U.S. death rate is under 1000, representing only about 1% of gastrointestinal malignancies. Small intestinal adenocarcinomas and carcinoids have roughly equal incidence, followed in order by lymphomas and sarcomas. As the latter three exhibit a broader distribution than the small intestine, they are discussed later.

Adenomas

Adenomas account for approximately 25% of benign small intestinal tumors, with benign mesenchymal tumors (especially leiomyomas), lipomas, and neuromatous lesions following in frequency. *Most adenomas occur in the region of the ampulla of Vater.* The usual presentation is that of a 30- to 60-year-old patient with occult blood loss, rarely with obstruction or intussusception; some are discovered incidentally during radiographic investigation. Patients with familial polyposis coli (discussed later) are particularly prone to developing periampullary adenomas. Macroscopically, the ampulla of Vater is enlarged and exhibits a velvety surface (Fig. 17-54). Microscopically, these adenomas resemble their counterparts in the colon (discussed later). Frequently, there is extension of adenomatous tissue into the ampullary orifice, rendering surgical excision difficult, short of a pancreatoduodenectomy to remove the entire ampullary region. Like its counterpart in the colon, the small intestinal adenoma is a premalignant lesion. The adenoma-carcinoma sequence has been demonstrated in small intestinal tumors.

Figure 17-54 Adenoma of the ampulla of Vater, showing exophytic tumor at the ampullary orifice.

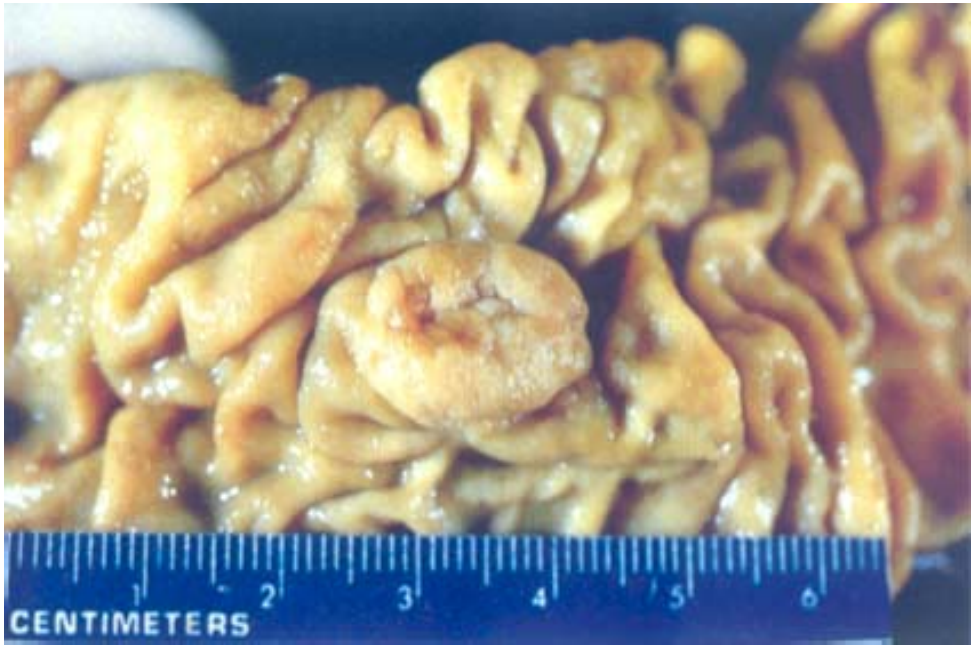


Figure 17-55 Diagrammatic representation of two forms of sessile polyp (hyperplastic polyp and adenoma) and of two types of adenoma (pedunculated and sessile). There is only a loose association between the tubular architecture for pedunculated adenomas and the villous architecture for sessile adenomas.

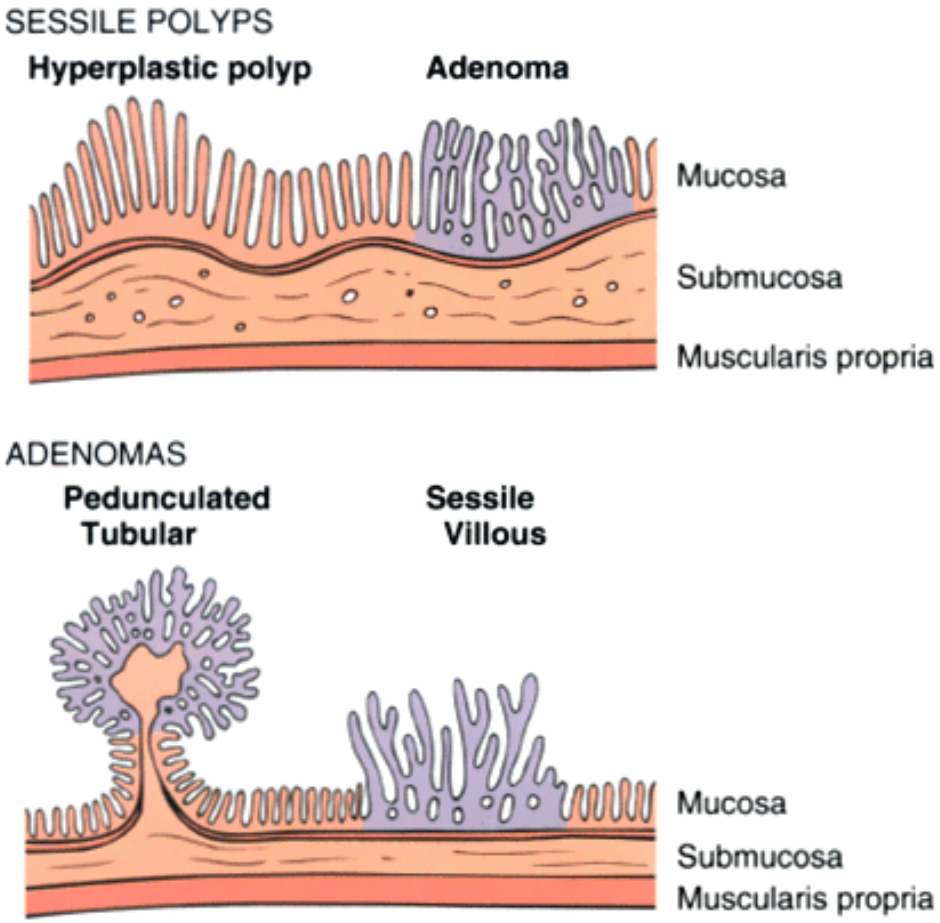


TABLE 17-13 -- Hereditary Syndromes Involving the Gastrointestinal Tract

Syndromes	Altered Gene	Pathology in GI Tract
Familial adenomatous polyposis (FAP)	*APC*	Multiple adenomatous polyps
• Classic FAP		
• Attenuated FAP		
• Gardner syndrome		
• Turcot syndrome		
Peutz-Jeghers syndrome	*STK11*	Hamartomatous polyps
Juvenile polyposis syndrome	*SMAD4*	Juvenile polyps
	BMPRIA	
Hereditary nonpolyposis colorectal carcinoma	Defects in mismatch DNA repair genes	Colon cancer

Tuberous sclerosis	*TSC1*	Inflammatory polyps
	TSC2	
Cowden disease	*PTEN*	Hamartomatous polyps

Non-Neoplastic Polyps

The overwhelming majority of intestinal polyps occur on a sporadic basis, particularly in the colon, and increase in frequency with age. Non-neoplastic polyps include the hyperplastic polyp, the hamartomatous polyp, the inflammatory polyp, and the lymphoid polyp. Hyperplastic polyps represent about 90% of all epithelial polyps in the large intestine. They may arise at any age but usually are discovered incidentally in the sixth and seventh decades. They are found in more than half of all persons age 60 and older. It is believed that the hyperplastic polyp results from decreased epithelial cell turnover and accumulation of mature cells on the surface. Harmatomatous polyps are malformations of the glands and the stroma. They can occur sporadically or occur in the setting of genetic syndromes (Table 17-13). Inflammatory polyps, also known as *pseudopolyps*, represent islands of inflamed regenerating mucosa surrounded by ulceration. These are seen primarily in patients with severe, active IBD. Lymphoid polyps are an essentially normal variant of the mucosal bumps containing intramucosal lymphoid tissue.

Morphology.

Hyperplastic Polyps.

These are small (usually <5 mm in diameter) epithelial polyps that appear as nipple-like, hemispheric, smooth, moist protrusions of the mucosa, usually positioned on the tops of mucosal folds. They may occur singly but more often are multiple, and over half are found in the rectosigmoid colon. Histologically, they are composed of well-formed glands and crypts lined by non-neoplastic epithelial cells, most of which show differentiation into mature goblet or absorptive cells. The delayed shedding of surface epithelial cells leads to infoldings of the crowded epithelial cells and fission of the crypts, creating a serrated epithelial profile and an irregular crypt architecture (Fig. 17-56*A*). Although large hyperplastic polyps may rarely coexist with foci of adenomatous change, **the usual small, hyperplastic polyp is considered to have virtually no malignant potential**. However, the hyperplastic polyps occurring in the setting of the rare hyperplastic polyposis syndrome can harbor epithelial cell dysplasia (adenoma), and hence are considered at risk for carcinoma. The

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underlying genetic basis for this syndrome is not known.

Hamartomatous Polyps.

Juvenile polyps represent focal hamartomatous malformations of the mucosal epithelium and lamina propria. For the most part they are sporadic lesions, with the vast majority occurring in children younger than age 5. Isolated hamartomatous polyps may be identified in the colon of adults; these incidental lesions are referred to as **retention polyps**. In both age groups, nearly 80% of the polyps occur in the rectum, but they may be scattered throughout the colon. Juvenile polyps tend to be large (1 to 3 cm in diameter), rounded, smooth or slightly lobulated lesions with stalks up to 2 cm in length; retention polyps tend to be smaller (<1 cm diameter). Histologically, lamina propria comprises the bulk of the polyp, enclosing abundant cystically dilated glands. Inflammation is common, and the surface may be congested or ulcerated. In general they occur singly and being hamartomatous lesions have no malignant potential. However, the rare autosomal dominant **juvenile polyposis syndrome,** in which there are multiple (50 to 100) juvenile polyps in the gastrointestinal tract, does carry a risk of adenomas and hence adenocarcinoma. Mutations in the *SMAD4/DPC4* gene (which encodes a TGF-β signaling intermediate) account for some cases of juvenile polyposis syndrome.[79]

Peutz-Jeghers polyps are hamartomatous polyps that involve the mucosal epithelium, lamina propria, and muscularis mucosa. These hamartomatous lesions may also occur singly or

multiply in the **Peutz-Jeghers syndrome**. This rare autosomal dominant syndrome is characterized by multiple hamartomatous polyps scattered throughout the entire gastrointestinal tract and melanotic mucosal and cutaneous pigmentation around the lips, oral mucosa, face, genitalia, and palmar surfaces of the hands. Patients with this syndrome are at risk for intussusception, which is a common cause of mortality. Peutz-Jeghers polyps tend to be large and pedunculated with a firm lobulated contour. Histologically, an arborizing network of connective tissue and well-developed smooth muscle extends into the polyp and surrounds normal abundant

Figure 17-56 Non-neoplastic colonic polyps. *A,* Hyperplastic polyp; high-power view showing the serrated profile of the epithelial layer. *B,* Peutz-Jeghers polyp; low-power view showing the splaying of smooth muscle into the superficial portion of the pedunculated polyp.

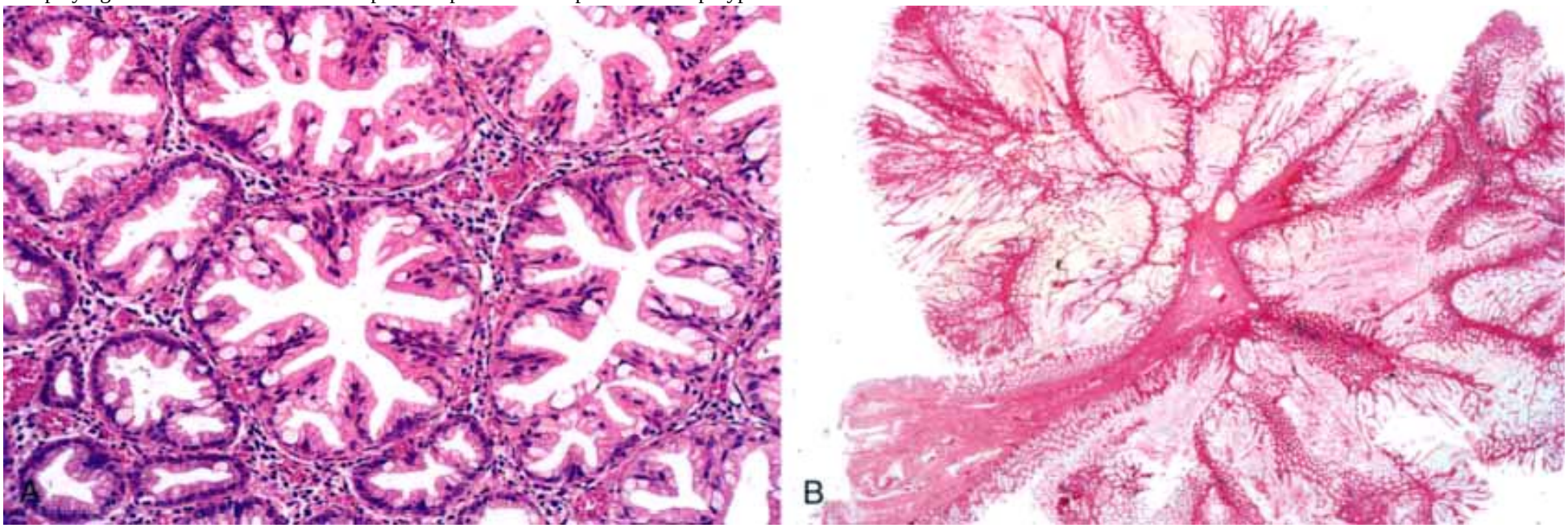


Figure 17-57 *A,* Pedunculated adenoma showing a fibrovascular stalk lined by normal colonic mucosa and a head that contains abundant dysplastic epithelial glands, hence the blue color with the H & E stain. *B,* A small focus of adenomatous epithelium in an otherwise normal (mucin-secreting, clear) colonic mucosa, showing how the dysplastic columnar epithelium (deeply stained) can populate a colonic crypt and create a tubular architecture.

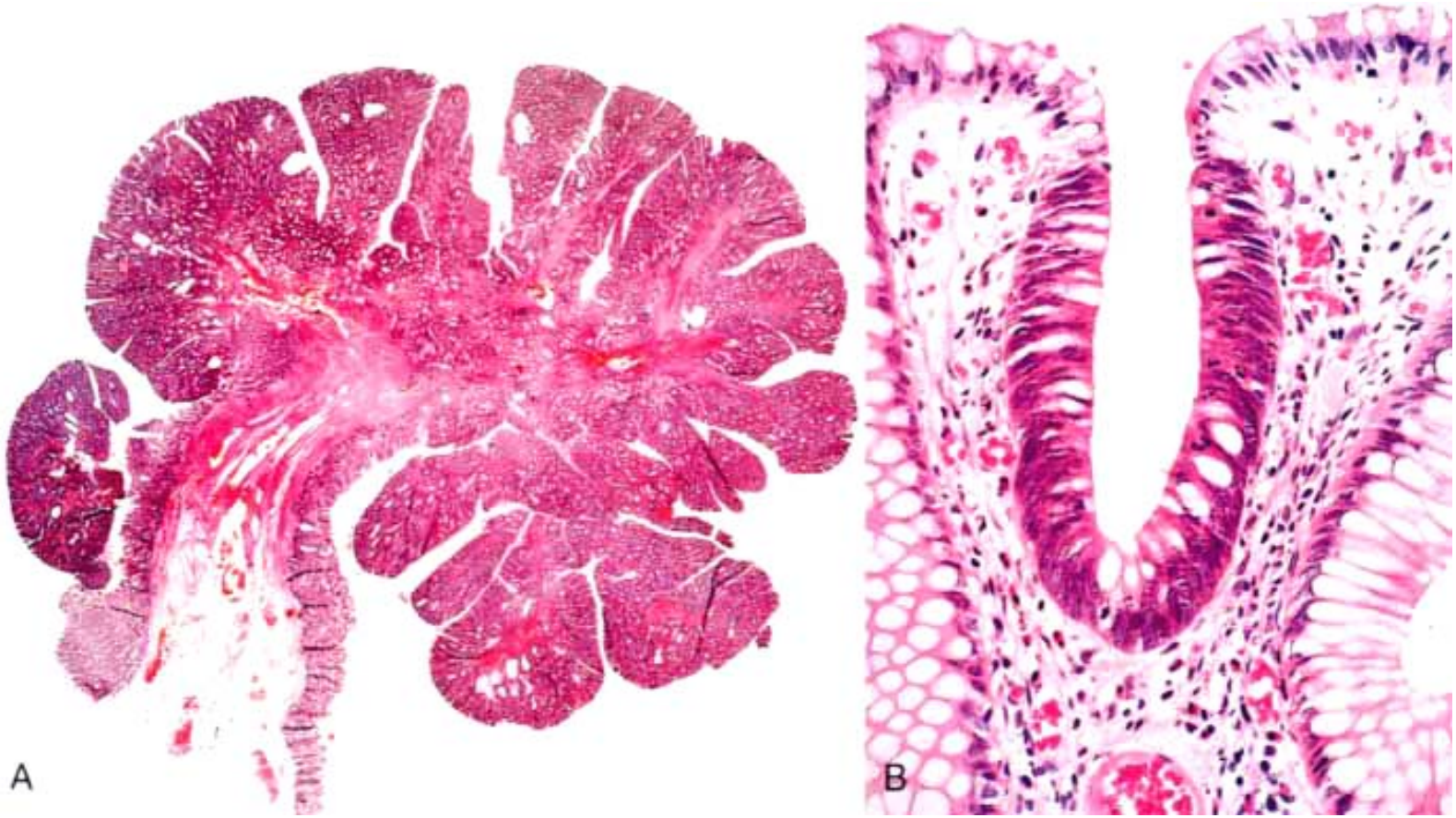


Figure 17-58 *A,* Sessile adenoma with villous architecture. Each frond is lined by dysplastic epithelium. *B,* Portion of a villous frond with dysplastic columnar epithelium on the left and normal colonic columnar epithelium on the right.

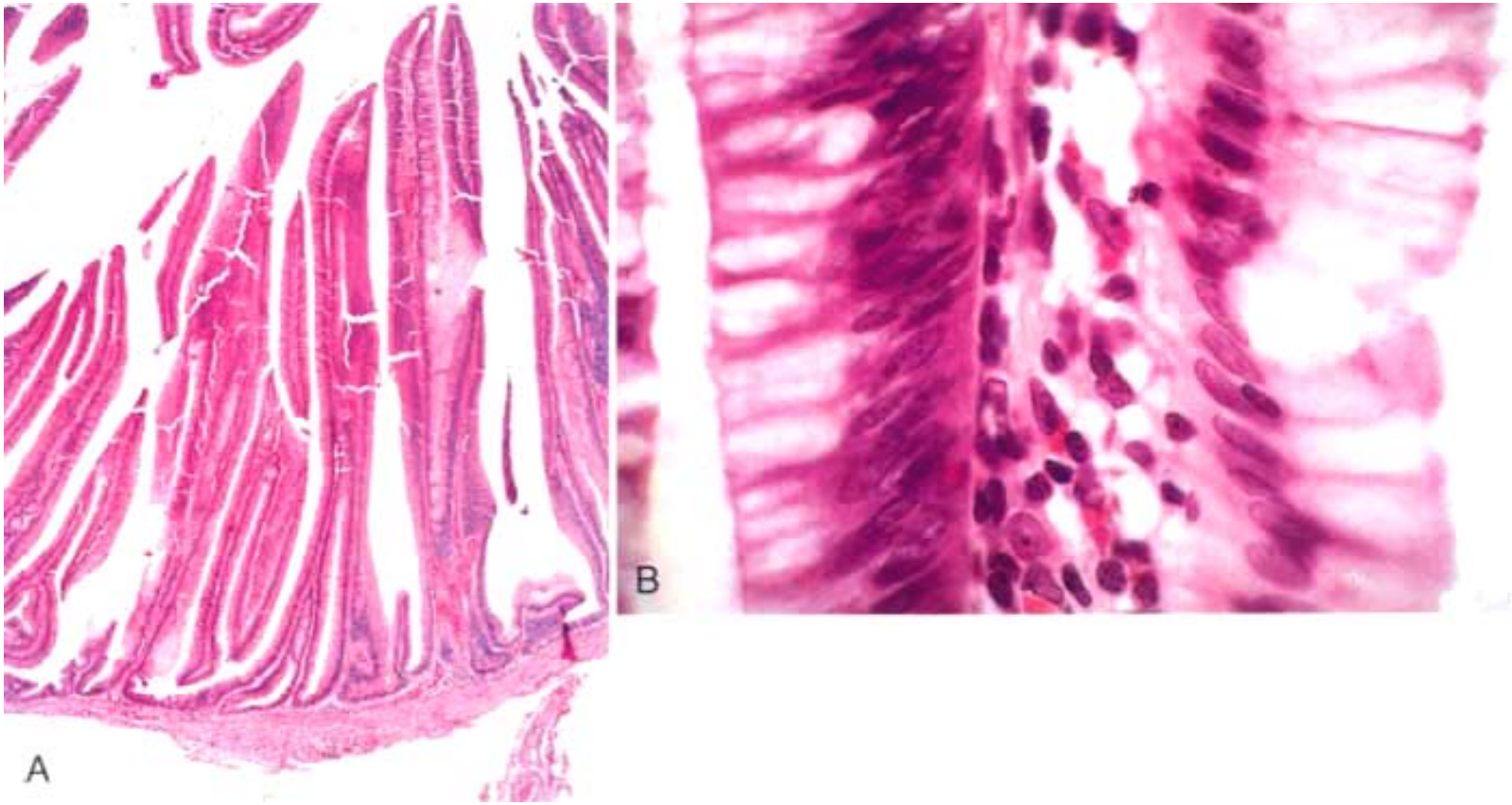


Figure 17-59 Familial adenomatous polyposis in an 18-year-old woman. The mucosal surface is carpeted by innumerable polypoid adenomas.

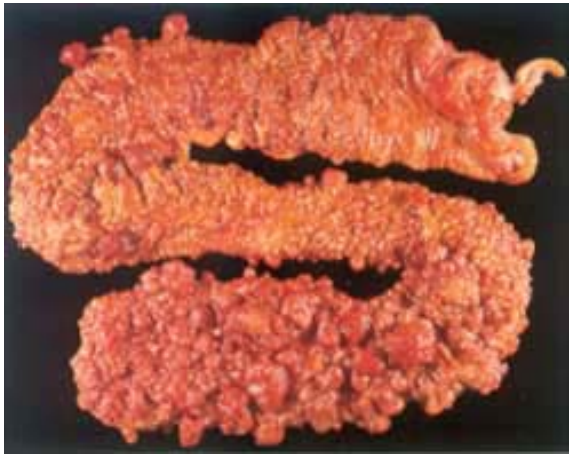


Figure 17-60 Schematic of the morphologic and molecular changes in the adenoma-carcinoma sequence. It is postulated that loss of one normal copy of the tumor suppressor gatekeeper gene *APC* occurs early. Indeed, individuals may be born with one mutant allele of APC, rendering them extremely likely to develop colon cancer. This is the "first hit," according to Knudson's hypothesis. The loss of the normal copy of the *APC* gene follows ("second hit"). Mutations of the oncogene *K-RAS* seem to occur next. Additional mutations or losses of

heterozygosity inactivate the tumor suppressor gene *p53* (on chromosome 17p) and *SMAD*2 and *SMAD*4 on chromosome 18q, leading finally to the emergence of carcinoma, in which additional mutations occur. It is important to note that while there seems to be a temporal sequence of changes, as shown, the accumulation of mutations, rather than their occurrence in a specific order, is more important.

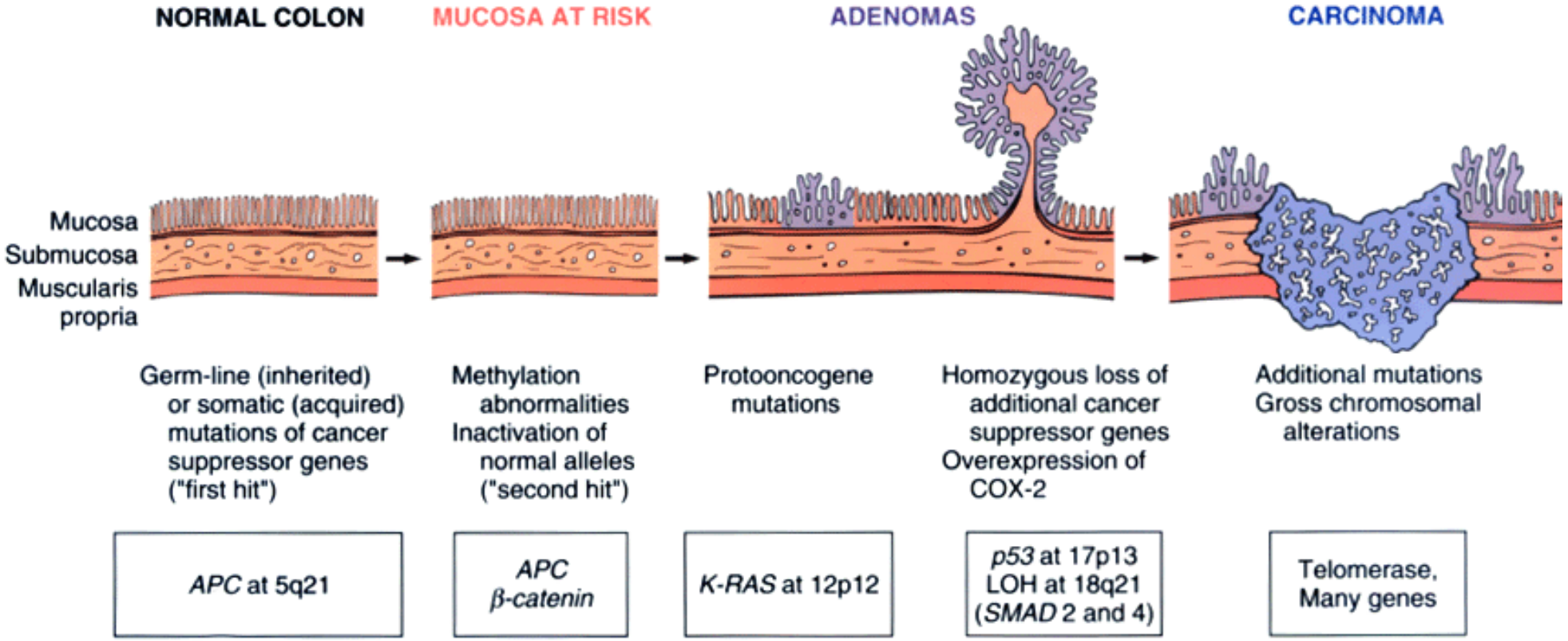


Figure 17-61 Carcinoma of the cecum. The fungating carcinoma projects into the lumen but has not caused obstruction.

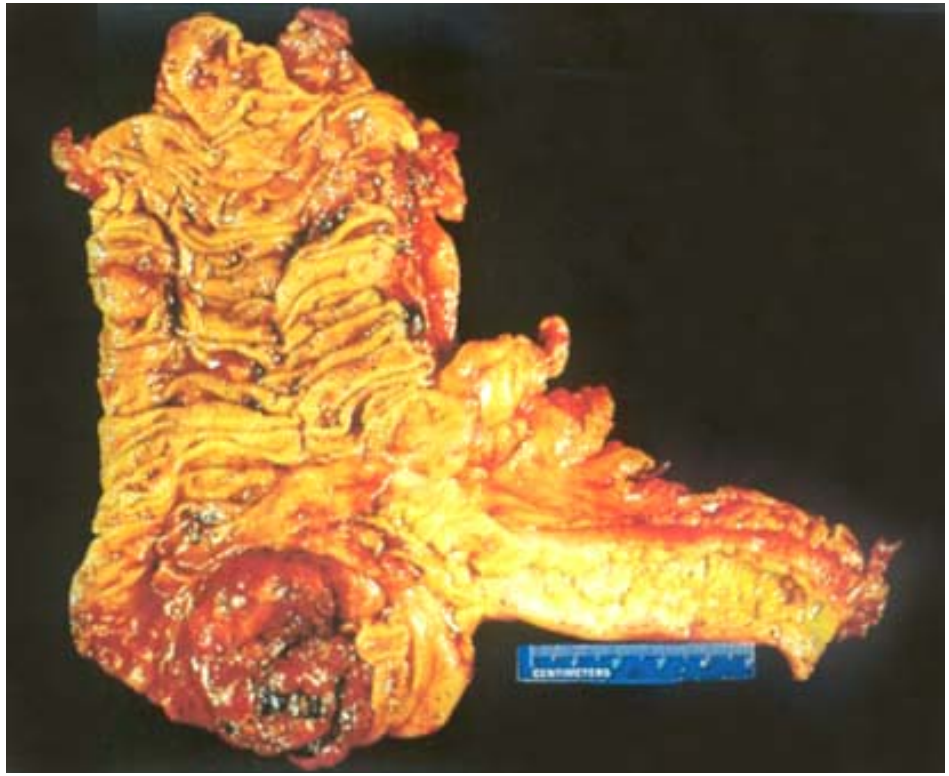


Figure 17-62 Carcinoma of the descending colon. This circumferential tumor has heaped-up edges and an ulcerated central portion. The arrows identify separate mucosal polyps.

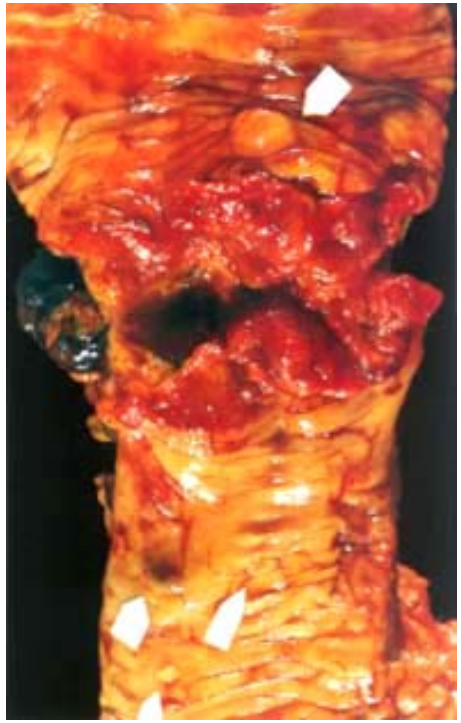


Figure 17-63 Invasive adenocarcinoma of colon, showing malignant glands infiltrating the muscle wall.

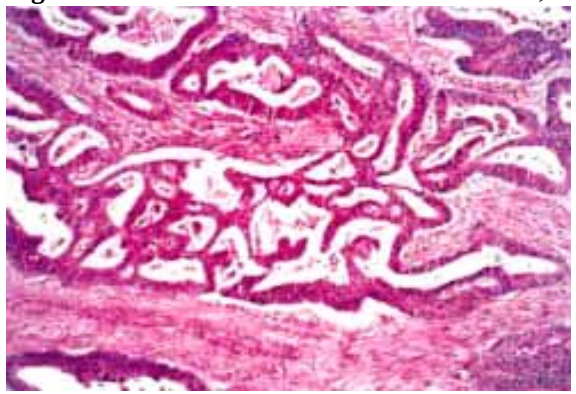


TABLE 17-14 -- TNM Classification of Carcinoma of the Colon and Rectum

Tumor Stage	Histologic Features of the Neoplasm
Tis	Carcinoma in situ (high-grade dysplasia) or intramucosal carcinoma (lamina propria invasion)
T1	Tumor invades submucosa
T2	Extending into the muscularis propria but not penetrating through it
T3	Penetrating through the muscularis propria into subserosa

T4	Tumor directly invades other organs or structures
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 lymph nodes
N2	Metastasis in 4 or more lymph nodes
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Figure 17-64 Pathologic staging of colorectal cancer. Staging is based on the depth of tumor invasion.

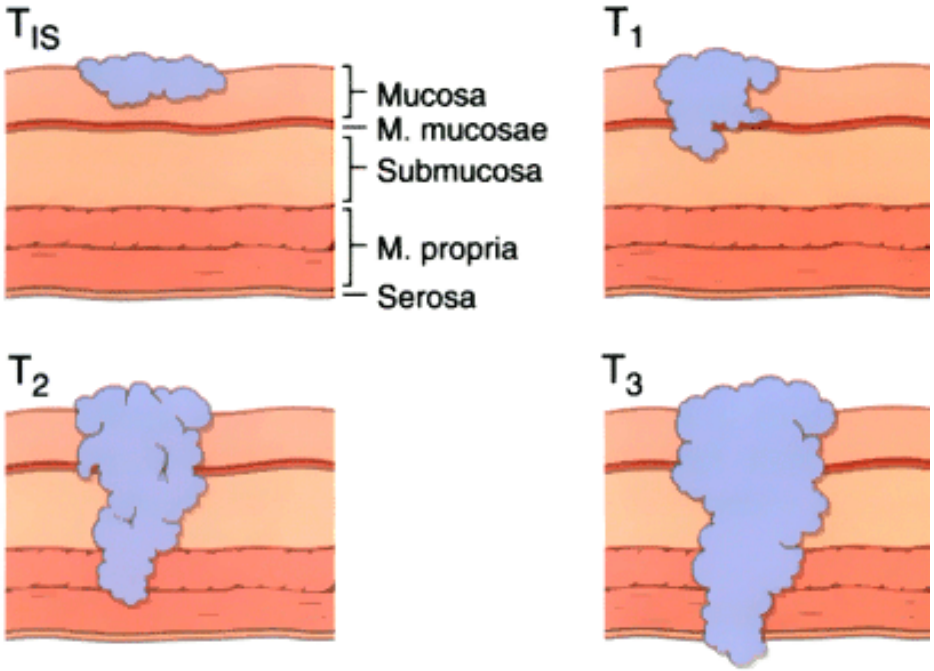
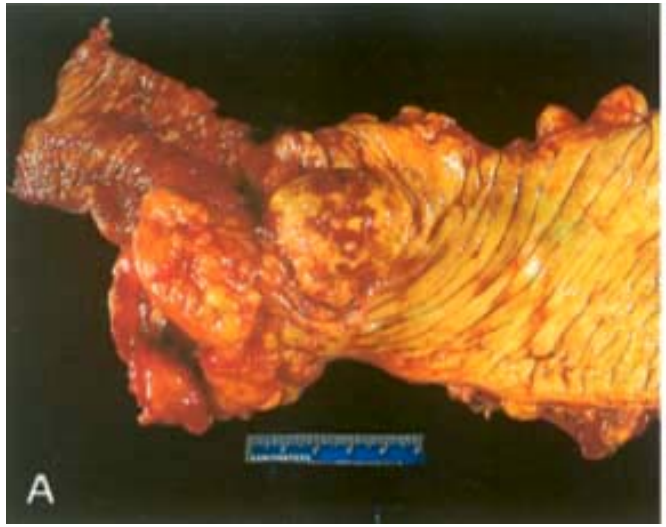
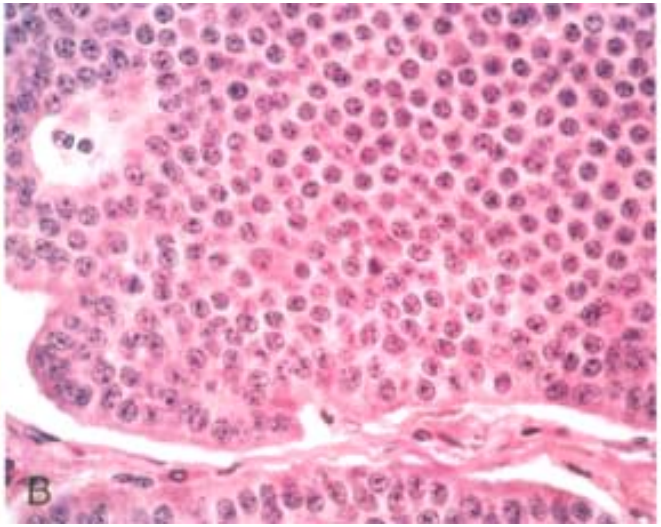


Figure 17-65 Carcinoid tumor. *A,* Multiple protruding tumors are present at the ileocecal junction. *B,* The tumor cells exhibit a monotonous morphology, with a delicate intervening fibrovascular stroma. *C,* Electron micrograph showing dense core bodies in the cytoplasm.





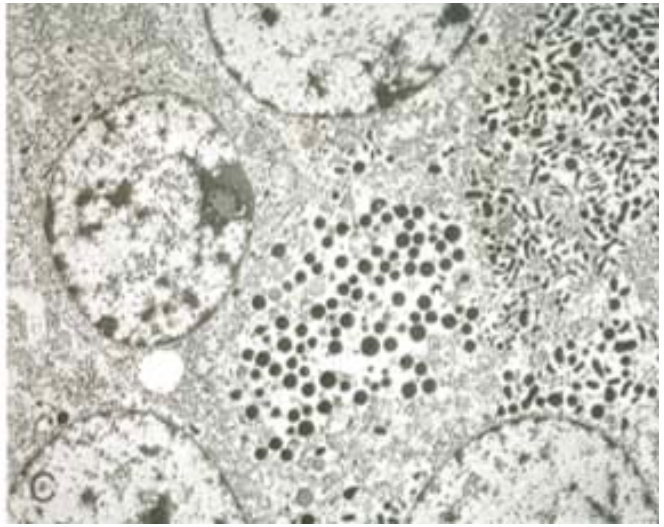


TABLE 17-15 -- Clinical Features of the Carcinoid Syndrome

• Vasomotor distubances
••Cutaneous flushes and apparent cyanosis (most patients)
• Intestinal hypermotility
••Diarrhea, Cramps, nausea, vomiting (most patients)
• Asthmatic bronchoconstrictive attacks
••Couth, wheezing, dyspnea (about one third of patients)
• Hepatomegaly
••Nodular liver owing to hepatic metastases (some patients)
• Systemic fibrosis (some patients)
••Cardiac involvement
••••Pulmonic and tricuspid valve thickening and stenosis
••••Endocardial fibrosis, principally in the right ventricle
••••(Bronchial carcinoids affect the left side)
••Retroperitoneal and pelvic fibrosis
••Collagenous pleural and intimal aortic plaques

metastases are usually not required for the production of a carcinoid syndrome by extraintestinal carcinoids (such as those arising in the lungs or ovaries), because active substances produced by the tumors are directly released into the systemic circulation. Other secretory products of carcinoids such as histamine, bradykinin, kallikrein, and prostaglandins may also contribute to the manifestations of the carcinoid syndrome.

The overall five-year survival rate for carcinoids (excluding appendiceal) is approximately 90%. Even with small-bowel tumors with hepatic metastases, it is better than 50%. However, widespread disease will usually cause death.

GASTROINTESTINAL LYMPHOMA

Any segment of the gastrointestinal tract may be secondarily involved by systemic dissemination of non-Hodgkin lymphomas. However, up to 40% of lymphomas arise in sites other than lymph nodes, and the gut is the most common location. Conversely, about 1% to 4% of all gastrointestinal malignancies are lymphomas. *By definition, primary gastrointestinal lymphomas exhibit no evidence of liver, spleen, mediastinal lymph node, or bone marrow involvement at the time of diagnosis*—regional lymph node involvement may be present. *Primary gastrointestinal lymphomas usually arise as sporadic neoplasms but also occur more frequently in certain patient populations: (1) Chronic gastritis caused by H. pylori, (2) chronic spruelike syndromes, (3) natives of the Mediterranean region, (4) congenital immunodeficiency states, (5) infection with human immunodeficiency virus, and (6) following organ transplantation with immunosuppression.*

Intestinal tract lymphomas can be classified into B-cell and T-cell lymphomas. The B-cell lymphoma can be subdivided into MALT lymphoma, immunoproliferative small-intestinal disease (IPSID), and Burkitt lymphoma.

1. *MALT lymphoma is a sporadic lymphoma, which* arises from the B cells of MALT (mucosa-associated lymphoid tissue, described under gastric lymphoma). *This type of lymphoma is the most common form in the Western hemisphere.* The biologic features of these lymphomas are different from node-based lymphomas in that (1) many behave as focal tumors in their early stages and are amenable to surgical resection; (2) relapse may occur exclusively in the gastrointestinal tract; (3) genotypic changes are different than those observed in nodal lymphomas: the t(11;18) translocation is relatively common in MALT lymphoma; and (4) the cells are usually CD5- and CD10-negative. This type of gastrointestinal lymphoma usually affects adults, has no gender predilection, and may arise anywhere in the gut: stomach (55% to 60% of cases); small intestine (25% to 30%), proximal colon (10% to 15%), and distal colon (up to 10%). The appendix and esophagus are only rarely involved.
   The pathogenesis of these lymphomas is under intense scrutiny. The concept has been advanced that lymphomas of MALT origin arise in the setting of mucosal lymphoid activation and that these lymphomas are the malignant counterparts of hypermutated, postgerminal-center memory B cells. As discussed earlier, *Helicobacter*-associated chronic gastritis, in particular, has been proposed as a driving force for the development of gastric MALT lymphoma, the result of antigen-driven somatic mutation of

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   gastric lymphoid tissue. However, the etiologic factors for intestinal lymphoma are still unknown, although history of IBD appears to increase the risk.
2. *IPSID is also referred to as Mediterranean lymphoma.* It is an unusual intestinal B-cell lymphoma arising in patients with Mediterranean ancestry, having a background of chronic diffuse mucosal plasmacytosis. The plasma cells synthesize an abnormal Igα heavy chain, in which the variable portion has been deleted. A high proportion of patients have malabsorption and weight loss preceding the development of the lymphoma. The diagnosis is made most commonly in children and young adults, and both sexes appear to be affected equally. The exact etiology of this type of lymphoma is not known, although infection appears to play a role.[95]
3. *The intestinal T-cell lymphoma* is usually associated with a long-standing malabsorption syndrome (such as celiac disease) that may not constitute a true gluten-sensitive enteropathy. This lymphoma occurs in relatively young individuals (age 30 to 40), often following a 10- to 20-year history of symptomatic malabsorption. Alternatively, a diffuse enteropathy with malabsorption may accompany the development of a lymphoma. Intestinal T-cell lymphoma arises most often in the proximal small bowel, and its overall prognosis is poor (reported 11% five-year survival rate).

Morphology.

Gastrointestinal lymphomas can assume a variety of gross appearances. Since all the gut lymphoid tissue is mucosal and submucosal, early lesions appear as plaque-like expansions of the mucosa and submucosa. Diffusely infiltrating lesions may produce full-thickness mural thickening, with effacement of the overlying mucosal folds and focal ulceration. Others may be polypoid, protruding into the lumen, or form large, fungating, ulcerated masses. Tumor infiltration into the muscularis propria splays the muscle fibers, gradually destroying them. Because of this feature, advanced lesions frequently cause motility problems with secondary obstruction. Large tumors sometimes perforate because of lack of stromal support; reduction in tumor

bulk during chemotherapy also may lead to perforation.

In the earliest histologic lesions, atypical lymphoid cells may be seen infiltrating the mucosa, with effacement and loss of glands and massive expansion of lymphoid tissue. Extreme numbers of atypical lymphoid cells may populate the superficial or glandular epithelium (lymphoepithelial lesion). With established lymphomas, the mucosa, submucosa, and even muscle wall are replaced by a monotonous infiltrate of malignant cells, consisting of a mixture of small lymphocytes and immunoblasts in varying proportions. Lymphoid follicles are occasionally formed. Most gut lymphomas are of B-cell type (over 95%) and are evenly split between low- and high-grade tumors. The small fraction of T-cell lymphomas occurring in the intestine are commonly high-grade lesions.

Clinical Features.

With the exception of T-cell lymphomas, primary gastrointestinal lymphomas generally have a better prognosis than do those arising in other sites. Ten-year survival for patients with localized mucosal or submucosal disease approaches 85%. Early discovery is key to survival; thus, gastric lymphomas generally have a better outcome than those of the small or large bowel. In general, the depth of local invasion, size of the tumor, the histologic grade of the tumor, and extension into adjacent viscera are important determinants of prognosis.

MESENCHYMAL TUMORS

Mesenchymal tumors may occur anywhere in the alimentary tract. The nomenclature for these tumors is largely based on the tumor cell phenotypes. Lipomas show a propensity for the submucosa of the small and large intestines, and lipomatous hypertrophy may occur in the ileocecal valve. A variety of spindle-cell lesions may arise in the muscle wall of any gut segment. The great majority of these tumors are of smooth muscle origin, and hence can be termed *leiomyomas* and *leiomyosarcomas*. Gastrointestinal stromal tumors (GISTs), are now considered to be a distinctive tumor type, characterized by c-KIT immunoreactivity, as discussed earlier (see "Gastric Tumors"). The small intestine is the second most common location for this tumor, (the stomach being the most common). Both benign and malignant versions of GIST may occur at any age and in either sex. Vascular tumors such as *Kaposi sarcomas* are considered elsewhere (see Chapter 11).

Morphology.

Lipomas are usually well-demarcated, firm nodules (almost always less than 4 cm in diameter) arising within the submucosa or muscularis propria. The overlying mucosa is stretched and attenuated. Rarely, they grow to larger size and produce hemispheric elevation of the mucosa with ulceration over the dome of the tumor. Malignant stromal tumors (primarily leiomyosarcoma) tend to produce large, bulky, intramural masses that eventually fungate and ulcerate into the lumen or project subserosally into the abdominal space. Histologically, lipomas, leiomyomas, and leiomyosarcomas resemble their counterparts encountered elsewhere (Chapter 26). In the case of the stromal tumors (e.g., leiomyomas and leiomyosarcomas), large size and a high mitotic rate are correlated with an aggressive course.

Clinical Features.

Most mesenchymal tumors are asymptomatic. In the stomach, larger lesions (benign or malignant) may produce symptoms resembling those of peptic ulcer, particularly bleeding that is sometimes massive. Intestinal lesions may present with bleeding, and for the small intestine, rare obstruction or intussusception. Benign lesions are easily resectable. Surgical removal is usually possible for the malignant lesions as well, since they tend to grow as cohesive masses. Five-year survival rate for leiomyosarcoma, for example, is 50% to 60%. Metastases, however, are present in about one third of cases.

TUMORS OF THE ANAL CANAL

The anal canal is the terminal portion of the large intestine. It is divided into three zones: the upper (covered with rectal mucosa), the middle (partially covered with a transitional mucosa), and the lower (covered by stratified squamous mucosa). The tumors located in this anatomic location are designated as carcinoma of the anal canal. Patterns of differentiation

include a basaloid pattern, squamous cell carcinoma, and adenocarcinoma.

Anal canal carcinoma with basaloid differentiation is a tumor populated by immature proliferative cells derived from the basal layer of a stratified squamous epithelium. These tumors may occur sporadically and be uniform in their histologic features. Alternatively, basaloid differentiation may be a component of a tumor that exhibits more genuine squamous cell differentiation and/or the mucin vacuole-containing features of adenocarcinoma. All such tumors remain classified as anal canal carcinoma.

Pure squamous cell carcinomas of the anal canal are closely associated with chronic HPV infection.[96] Some rare cases are also related to immunosuppression, as encountered in renal transplantation and in AIDS patients. As with the genital tract, chronic HPV infection of the anal canal often causes precursor lesions such as condyloma acuminatum, squamous epithelium dysplasia, and carcinoma in situ.

Pure adenocarcinoma of the anal canal is often the extension of rectal adenocarcinoma. Rarely, other tumors may arise from the anal canal, notably *Paget disease,* small-cell carcinoma, and melanoma.

Appendix

Normal

The appendix is an underdeveloped residuum of the otherwise voluminous cecum. The adult appendix averages 6 to 7 cm in length, is partially anchored by a mesenteric extension from the adjacent ileum, and has no known function. The appendix has the same four layers as the remainder of the gut and possesses a colonic-type mucosa. A distinguishing feature of this organ is the extremely rich lymphoid tissue of the mucosa and submucosa, which in young individuals forms an entire layer of germinal follicles and lymphoid pulp. This lymphoid tissue undergoes progressive atrophy during life to the point of complete disappearance in advanced age. In the elderly the appendix, particularly the distal portion, sometimes undergoes fibrous obliteration.

Pathology

Diseases of the appendix loom large in surgical practice; appendicitis is the most common acute abdominal condition the surgeon is called on to treat. Appendicitis is one of the best-known medical entities and yet may be one of the most difficult diagnostic problems to confront the emergency physician. A differential diagnosis must include virtually every acute process that can occur within the abdominal cavity, as well as some emergent conditions affecting organs of the thorax.

Acute Appendicitis

Inflammation in the right lower quadrant was considered a nonsurgical disease of the cecum (typhlitis or perityphlitis) until Fitz recognized acute appendicitis as a distinct entity in 1886. Appendiceal inflammation is associated with obstruction in 50% to 80% of cases, usually in the form of a fecalith and, less commonly, a gallstone, tumor, or ball of worms *(oxyuriasis vermicularis).* Continued secretion of mucinous fluid in the obstructed viscus presumably leads to a progressive increase in intraluminal pressure sufficient to cause eventual collapse of the draining veins. Ischemic injury then favors bacterial proliferation with additional inflammatory edema and exudation, further embarrassing the blood supply. Nevertheless, a significant minority of inflamed appendices have no demonstrable luminal obstruction, and the pathogenesis of the inflammation remains unknown.

Morphology.

At the earliest stages, only a scant neutrophilic exudate may be found throughout the mucosa, submucosa, and muscularis propria. Subserosal vessels are congested, and often there is a modest perivascular neutrophilic infiltrate. The inflammatory reaction transforms the normal glistening serosa into a dull, granular, red membrane; this transformation signifies **early acute appendicitis** for the operating surgeon. At a later stage, a prominent neutrophilic exudate generates a fibrinopurulent reaction over the serosa (Fig. 17-66). As the inflammatory process worsens, there is abscess formation within the wall, along with ulcerations and foci of suppurative necrosis in the mucosa. This state constitutes **acute suppurative appendicitis**. Further appendiceal compromise leads to large areas of hemorrhagic green ulceration of the mucosa and green-black gangrenous necrosis through the wall, extending to the serosa, creating **acute gangrenous appendicitis,** which is quickly followed by rupture and suppurative peritonitis.

The histologic criterion for the diagnosis of acute appendicitis is neutrophilic infiltration of the muscularis propria. Usually, neutrophils and ulcerations are also present within the mucosa. Since drainage of an exudate into the appendix from alimentary tract infection may also induce a mucosal neutrophilic infiltrate, evidence of muscular wall inflammation is requisite for the diagnosis.

Figure 17-66 Acute appendicitis. The inflamed appendix shown below is red, swollen, and covered with a fibrinous exudate. For comparison, a normal appendix is shown above.

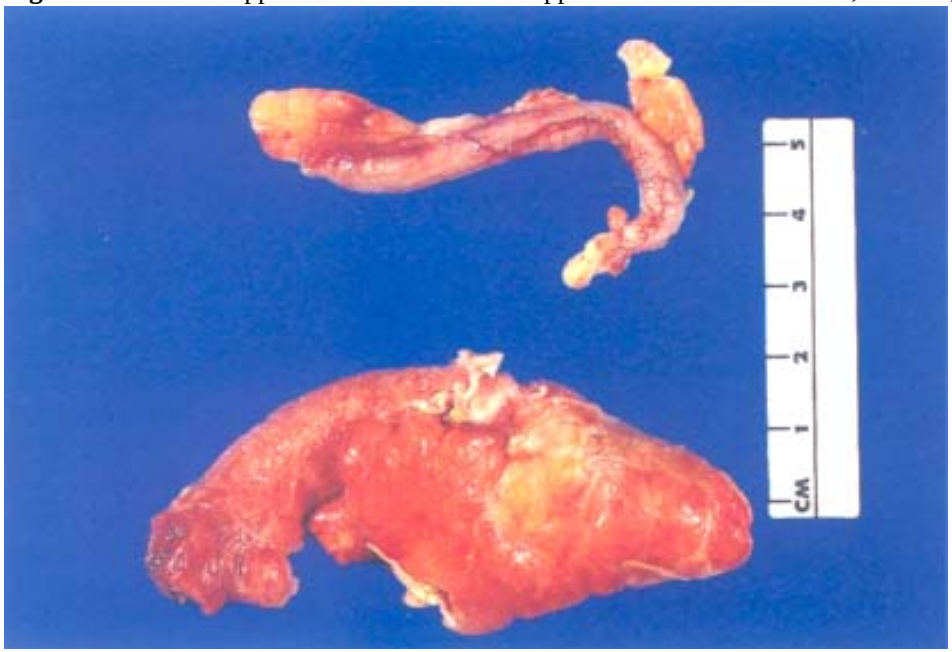
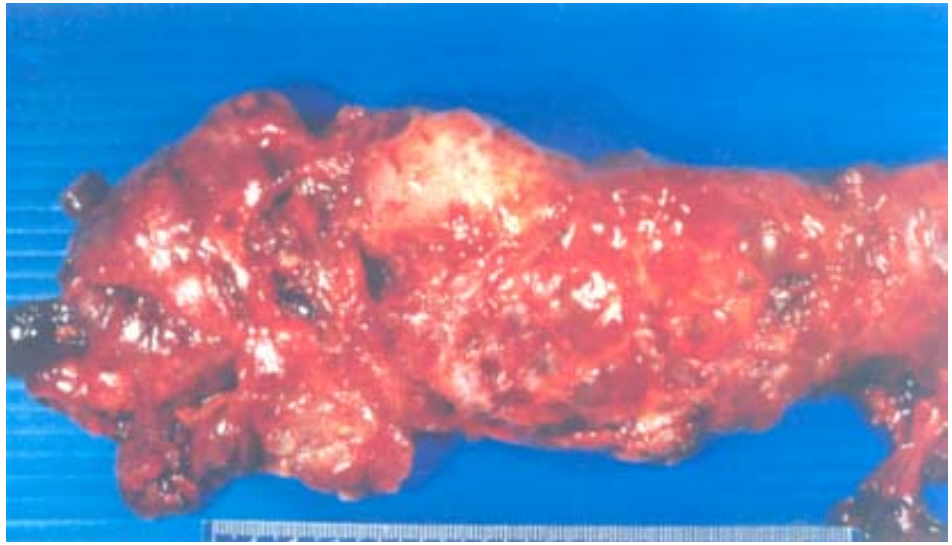


Figure 17-67 Mucinous cystadenocarcinoma of the appendix, with spread into the immediate periappendiceal tissues.



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Chapter 18 - Liver and Biliary Tract

James M. Crawford MD, PhD

The Liver

Normal

The liver and biliary tree and the gallbladder occupy the right upper quadrant of the abdomen. The liver resides between the digestive tract and the rest of the body and functions as a way station between the splanchnic and systemic circulation. As the headwater of the biliary tree, the liver sits astride the enterohepatic circulation. The liver has the critical job of maintaining the body's metabolic homeostasis. This includes the processing of dietary amino acids, carbohydrates, lipids, and vitamins; removal of microbes and toxins in splanchnic blood en route to the systemic circulation; synthesis of many plasma proteins; and detoxification and excretion into bile of endogenous waste products and pollutant xenobiotics. Hepatic disorders, therefore, have far-reaching consequences.

The mature liver lies in the right hypochondrium under the rib cage and extends from the right fifth intercostal space at the midclavicular line to just below the costal margin. It projects slightly below the costal margin at the right intercostal line and under the xyphoid process in the midline. The conventional division of the liver into the right, left, caudate, and quadrate lobes is a topographic classification that does not correspond to the functional lobes or segments of the liver. The physiologic or functional right and left lobes are defined by the distribution of the right and left portal vein systems. The watershed between these two vascular beds corresponds to a plane that passes superiorly through the left side of the sulcus of the inferior vena cava to the middle of the gallbladder fossa inferiorly. The quadrate lobe and the greater part of the caudate lobe on the posterior aspect of the liver belong functionally to the left hemiliver. Of greater significance to the surgeon is the functional organization of the liver into eight segments, numbered I to VIII, the caudate lobe being segment I and the remainder, II to VIII, moving roughly from left to right across the liver. Each segment has its own independent vascular and biliary pedicle and venous drainage. *This anatomic arrangement facilitates limited segmental resections of the liver* as is sometimes performed for partial hepatectomy.

The normal adult liver weighs 1400 to 1600 gm, representing 2.5% of body weight. Incoming blood—approximately 25% of total cardiac output—arrives via the portal vein (60% to 70% of hepatic blood flow) and the hepatic artery (30% to 40%) through the hilum, the "gateway" of the liver (*porta hepatis*). The major bile ducts exit in this same region. The initial right and left branches of the portal vein, hepatic artery, and bile duct lie just outside the liver. The remaining branches travel in parallel within the liver in *portal tracts*, ramifying variably through 17 to 20 orders of branches. The vast expanse of hepatic parenchyma is serviced via approximately 450,000 terminal branches of the portal tract system. Portal vein blood enters the parenchyma via penetrating *septal venules*; hepatic arteriolar twigs supply the parenchyma, the major bile ducts, the vasa vasorum of the major portal veins and hepatic veins, and the hepatic capsule. Blood from all sources is collected into ramifications of the hepatic vein, which exits by the "back door" of the liver into the closely apposed inferior vena cava.

Microarchitecture.

Classically, the liver has been divided into 1- to 2-mm diameter hexagonal *lobules* oriented around the terminal tributaries of the hepatic vein (*terminal hepatic veins*), with portal tracts at the periphery of the lobule. Accordingly, the hepatocytes in the vicinity of the terminal hepatic vein are called "centrilobular" (or centrolobular); those near the portal tract are "periportal." However, since hepatocytes near the terminal hepatic veins are most remote from the blood supply, it has been argued that they are at the distal apices of roughly triangular *acini*, with the bases formed by penetrating septal venules from the portal vein extending out from the portal tracts (Fig. 18-1). [1] In the "acinus," the parenchyma is divided into three zones, zone 1 being closest to the vascular supply, zone 3 abutting the terminal hepatic venule, and zone 2 being intermediate. This zonation is of considerable metabolic consequence, since a lobular gradient of activity exists for many hepatic enzymes.[2] Moreover, many forms of hepatic injury exhibit a zonal distribution. While acinar architecture is of greater physiologic significance, the anatomic terminology of the liver remains anchored in the older lobular terminology.

The hepatic parenchyma is organized into cribiform, anastomosing sheets or "plates" of hepatocytes, seen in microscopic sections as cords of cells (Fig. 18-2). Hepatocytes immediately abutting the portal tract are referred to as the *limiting plate*, forming a discontinuous rim around the mesenchyme of the portal tract. There is a radial orientation of the hepatocyte cords around the terminal hepatic vein. Hepatocytes exhibit minimal variation in overall size, but nuclei may vary in size, number, and ploidy, particularly with advancing age. Uninucleate,

diploid cells tend to be the rule, but with increasing age, a significant fraction are binucleate, and the karyotype may range up to octaploidy.

Between the cords of hepatocytes are vascular sinusoids. Blood traverses the sinusoids and exits into the terminal hepatic vein through innumerable orifices in the vein wall. Hepatocytes are thus bathed on two sides by well-mixed portal venous and hepatic arterial blood, placing hepatocytes among the most richly perfused cells in the body. The sinusoids are lined by fenestrated and discontinuous endothelial cells, which demarcate an extrasinusoidal *space of Disse*, into which protrude abundant microvilli of hepatocytes. Scattered *Kupffer cells* of the mononuclear phagocyte system are attached to the luminal face of endothelial cells, and scattered fat-containing *perisinusoidal stellate cells* are found in the space of Disse. These stellate cells play a role in the storage and metabolism of vitamin A and are transformed into collagen-producing myofibroblasts when there is inflammation of the liver.

Between abutting hepatocytes are *bile canaliculi*, which are channels 1 to 2 μm in diameter, formed by grooves in the

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Figure 18-1 Microscopic anatomy of the liver. The portal tract carries branches of the portal vein, hepatic artery, and bile duct system. The portal vein gives rise to branching septal veins, which penetrate the hepatocellular parenchyma at regular intervals. Blood from the septal veins enters directly into the parenchymal sinusoids between hepatocytes. The hepatic artery gives off capillaries that supply the bile duct system; these capillaries usually dump into the portal vein but may deposit blood directly into sinusoids. Arterioles also occasionally convey blood directly to the sinusoids. The bile duct system gives off bile ductules, which traverse the mesenchyme of the portal tract to penetrate the parenchyma; at that point, they become hemicircular, abutting hepatocytes (not shown) to form the canals of Hering. Bile traveling through the bile canalicular system between hepatocytes enters into the biliary tree through these canals of Hering. Blood from the portal vein and hepatic artery travels through the sinusoids of the parenchyma toward the terminal hepatic vein, leaving the liver by this route. On the basis of blood flow, three zones can be defined, zone 1 being the closest to the blood supply and zone 3 being the farthest. Pathologists refer to the regions of the parenchyma as "periportal, midzonal, and centrilobular," the last term owing to the historical concept that the terminal hepatic vein was at the center of a "lobule."

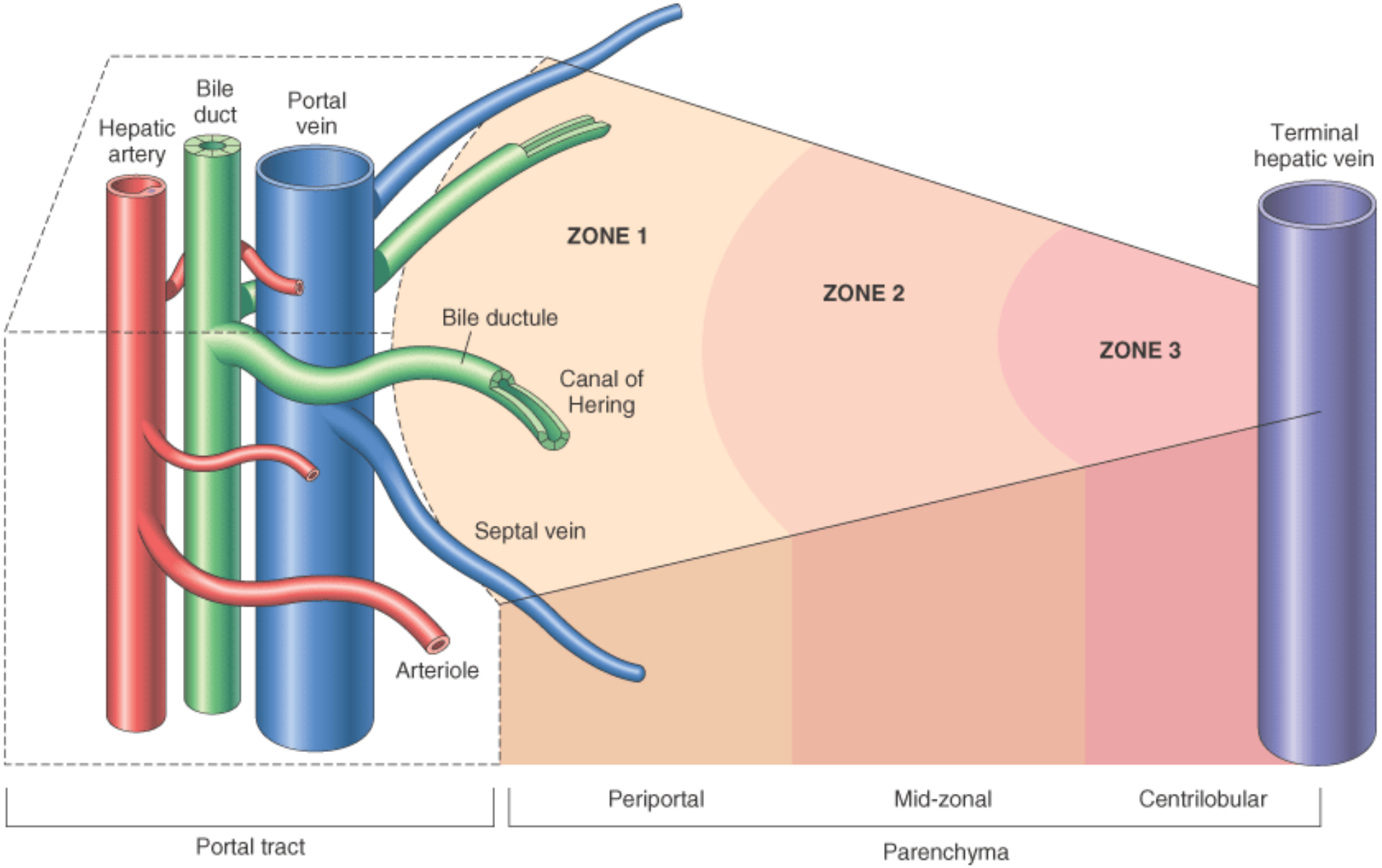
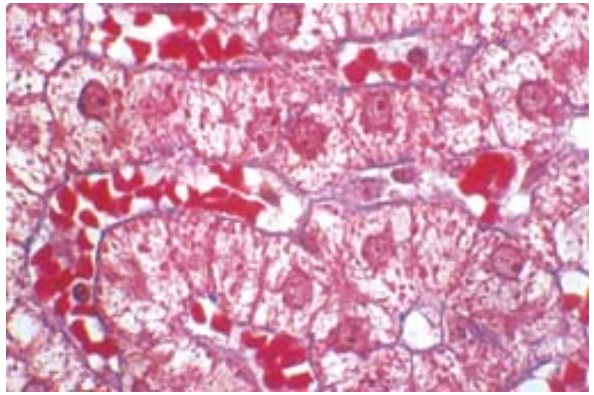


Figure 18-2 Photomicrograph of liver (trichrome stain). Note the blood-filled sinusoids and cords of hepatocytes; the delicate network of reticulin fibers in the subendothelial space of Disse stains light blue.



Necrosis frequently exhibits a zonal distribution. The most obvious is necrosis of hepatocytes immediately around the terminal hepatic vein (so-called **centrilobular necrosis,** using the historical terminology), an injury that is characteristic of ischemic injury and a number of drug and toxic reactions. Pure **midzonal** and **periportal necrosis** are rare; the latter may be seen in eclampsia. With most other causes of hepatic injury, a variable mixture of hepatocellular death through the parenchyma is encountered. The hepatocyte necrosis may be limited to scattered cells within hepatic lobules (**focal** or **spotty necrosis**) or to the interface between the periportal parenchyma and inflamed portal tracts (**interface hepatitis**). With more severe inflammatory injury, necrosis of contiguous hepatocytes may span adjacent lobules in a portal-to-portal, portal-to-central, or central-to-central fashion (**bridging necrosis**). Necrosis of entire lobules (**submassive necrosis**) or of most of the liver (**massive necrosis**) is usually accompanied by hepatic failure. With disseminated candidal or bacterial infection, macroscopic **abscesses** may occur.

• **Inflammation.** Injury to the liver associated with an influx of acute or chronic inflammatory cells is termed **hepatitis**. Direct toxic or ischemic hepatocyte necrosis incites an inflammatory reaction. With toxic damage, inflammation may also precede the onset of inflammation. Destruction of antigen-expressing liver cells by cytotoxic lymphocytes is a common mechanism of liver damage, especially during viral infection. In viral hepatitis, quiescent lymphocytes may collect in the portal tracts as a reflection of mild smoldering inflammation, spill over into the periportal parenchyma as activated lymphocytes (**interface hepatitis**) causing a moderately active hepatitis, or suffuse the entire parenchyma in severe hepatitis. Once killed, apoptotic hepatocytes do not incite an inflammatory reaction per se. However, scavenger macrophages (Kupffer cells and circulating monocytes recruited to the liver) engulf the apoptotic cell fragments within a few hours, generating clumps of inflammatory cells. Hence, identification of apoptotic hepatocytes is a sign of very recent hepatocyte destruction. Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction.

• **Regeneration.** Hepatocytes have long life spans, and they proliferate in response to tissue resection or cell death (see Chapter 3). Regeneration occurs in all but the most fulminant hepatic diseases. Hepatocellular proliferation is marked by mitoses, thickening of the hepatocyte cords, and some disorganization of the parenchymal structure. The canal of Hering-bile ductule unit constitutes a reserve compartment for restitution of severe parenchymal injury; when it is activated, innumerable serpentine profiles resembling bile ductules appear —so-called **ductular reaction**. This compartment also proliferates during large bile duct obstruction. When hepatocellular necrosis occurs and

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leaves the connective tissue framework intact, almost perfect restitution of liver structure can occur, even when the necrosis is submassive or massive.

• **Fibrosis.** Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver. Unlike other responses, which are reversible, **fibrosis points toward generally irreversible hepatic damage**. However, there is now considerable debate about the irreversibility of liver fibrosis and even cirrhosis (see below). Deposition of collagen has lasting consequences on patterns of hepatic blood flow and perfusion of hepatocytes. In the initial stages, fibrosis may develop around portal tracts or the terminal hepatic vein or may be deposited directly within the space of Disse. **With continuing fibrosis, the liver is subdivided into nodules of proliferating hepatocytes surrounded by scar tissue, termed "cirrhosis."** This end-stage form of liver disease is discussed later in this section.

The ebb and flow of hepatic injury may be imperceptible to the patient and detectable only by abnormal laboratory tests (Table 18-1). Alternatively, hepatic function may be so impaired as to be life threatening. The major clinical consequences of liver disease are listed in Table 18-2 and are discussed next.

HEPATIC FAILURE

The most severe clinical consequence of liver disease is *hepatic failure*. This may be the result of sudden and massive hepatic destruction, with about 2500 new cases per year in the United States. More often, it is the end point of progressive damage to the liver as part of chronic liver disease, either by insidious destruction of hepatocytes or by repetitive discrete

TABLE 18-1 -- Laboratory Evaluation of Liver Disease

Test Category	**Serum Measurement**
Hepatocyte integrity	Cytosolic hepatocellular enzymes
	••*Serum aspartate aminotransferase* (AST) *
	••*Serum alanine aminotransferase* (ALT) *
	••Serum lactate dehydrogenase (LDH) *
Biliary excretory function	Substances normally secreted in bile
	••*Serum bilirubin*
	••••*Total:* unconjugated plus conjugated *
	••••*Direct:* conjugated only *
	••••Delta: covalently linked to albumin *
	••Urine bilirubin *
	••Serum bile acids *
	Plasma membrane enzymes (from damage to bile canaliculus)
	••*Serum alkaline phosphatase* *
	••Serum γ-glutamyl transpeptidase *
	••Serum 5'-nucleotidase *
Hepatocyte function	Proteins secreted into the blood
	••*Serum albumin* †
	••*Prothrombin time* * (factors V, VII, X, prothrombin, fibrinogen)
	Hepatocyte metabolism
	••Serum ammonia *
	••Aminopyrine breath test (hepatic demethylation) †

	••Galactose elimination (intravenous injection) †
The most common tests are in italics.	

*An elevation implicates liver disease.
†A decrease implicates liver disease.

TABLE 18-2 -- Clinical Consequences of Liver Disease

Characteristic signs	Hepatic dysfunction:
	••Jaundice and cholestasis
	••Hypoalbuminemia
	••Hyperammonemia
	••Hypoglycemia
	••Fetor hepaticus
	••Palmar erythema
	••Spider angiomas
	••Hypogonadism
	••Gynecomastia
	••Weight loss
	••Muscle wasting
	Portal hypertension from cirrhosis:
	••Ascites
	••Splenomegaly
	••Hemorrhoids
	••Caput medusae—abdominal skin
Life-threatening complications	Hepatic failure
	••Multiple organ failure
	••Coagulopathy
	••Hepatic encephalopathy
	••Hepatorenal syndrome

	Portal hypertension from cirrhosis
	••Esophageal varices, risk of rupture
	Malignancy with chronic disease
	••Hepatocellular carcinoma

waves of parenchymal damage. Whatever the sequence, 80% to 90% of hepatic functional capacity must be eroded before hepatic failure ensues. In many cases, the balance is tipped toward decompensation by intercurrent diseases that place demands on the liver. These include gastrointestinal bleeding, systemic infection, electrolyte disturbances, and severe stress such as major surgery or heart failure. In most cases of severe hepatic dysfunction, liver transplantation is the only hope for survival. Overall, mortality from hepatic failure without liver transplantation is 70% to 95%.

The morphologic alterations that cause liver failure fall into three categories:

- *Massive hepatic necrosis.* This is most often drug- or toxin-induced, as from acetaminophen (38% of massive hepatic necrosis cases in the United States), halothane, antituberculosis drugs (rifampin, isoniazid), antidepressant monoamine oxidase inhibitors, industrial chemicals such as carbon tetrachloride, and mushroom poisoning (*Amanita phalloides*), collectively accounting for an additional 14% of cases. The mechanism may be direct toxic damage to hepatocytes (e.g., acetaminophen, carbon tetrachloride, mushroom toxins) but more often is a variable combination of toxicity and inflammation with immune-mediated hepatocyte destruction. Hepatitis A infection accounts for 4% of cases, hepatitis B infection accounts for 8%, and other causes (including unknown) account for 37%. Hepatitis C infection does not cause massive hepatic necrosis.
- *Chronic liver disease.* This is the most common route to hepatic failure and is the endpoint of relentless chronic hepatitis ending in cirrhosis. The many causes of cirrhosis will be discussed shortly.
- *Hepatic dysfunction without overt necrosis.* Hepatocytes may be viable but unable to perform normal metabolic function, as with Reye syndrome, tetracycline toxicity, and acute fatty liver of pregnancy.

Clinical Features.

Regardless of cause, the clinical signs of hepatic failure are much the same. *Jaundice* is an almost invariable finding. *Hypoalbuminemia*, which predisposes to peripheral edema, and *hyperammonemia*, which may play a role in cerebral dysfunction, are extremely worrisome developments. *Fetor hepaticus* is a characteristic body odor that is variously described as "musty" or "sweet and sour" and occurs occasionally. It is related to the formation of mercaptans by the action of gastrointestinal bacteria on the sulfur-containing amino acid methionine and shunting of splanchnic blood from the portal into the systemic circulation (portosystemic shunting). Impaired estrogen metabolism and consequent hyperestrogenemia are the putative causes of *palmar erythema* (a reflection of local vasodilatation) and *spider angiomas* of the skin. Each angioma is a central, pulsating, dilated arteriole from which small vessels radiate. In the male, hyperestrogenemia also leads to *hypogonadism* and *gynecomastia*.

Hepatic failure is life-threatening because *with severely impaired liver function, patients are highly susceptible to failure of multiple organ systems*. Thus, respiratory failure with pneumonia and sepsis combine with renal failure to claim the lives of many patients with hepatic failure. A *coagulopathy* develops, attributable to impaired hepatic synthesis of blood clotting factors II, VII, IX, and X. The resultant bleeding tendency can lead to massive gastrointestinal bleeding as well as petechial bleeding elsewhere. Intestinal absorption of blood places a metabolic load on the liver, which worsens the extent of hepatic failure. The outlook of full-blown hepatic failure is grave: A rapid downhill course is usual, death occurring within weeks to a few months in about 80% of cases. A fortunate few can endure an acute episode until hepatocellular regeneration restores adequate hepatic function. Alternatively, liver transplantation might save the patient.

Two particular complications merit separate consideration, as they herald the most grave stages of hepatic failure.

Hepatic encephalopathy is manifested by a spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to marked confusion and stupor to deep coma and death. These changes may progress over hours or days in fulminant hepatic failure or more insidiously in a patient with marginal hepatic function from chronic liver disease. Associated fluctuating neurologic signs include rigidity, hyperreflexia, and particularly *asterixis*: nonrhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists. *Hepatic encephalopathy is regarded as a disorder of neurotransmission in the central nervous system and neuromuscular system*[5] and appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema. *In the great majority of instances, there are only minor morphologic changes in the brain, such as edema and an astrocytic reaction,* and the encephalopathy is reversible if the underlying hepatic condition can be corrected.

Hepatorenal syndrome refers to the appearance of renal failure in patients with severe chronic liver disease, in whom there are no intrinsic morphologic or functional causes for the renal failure. Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities.[6] Several factors are involved in its development, including a decreased renal perfusion pressure due to systemic vasodilation, activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arteriolae, and increased synthesis of renal vasoactive mediators, which further decrease glomerular filtration. Onset of this syndrome is typically heralded by a drop in urine output, associated with rising blood urea nitrogen and creatinine. *The ability to concentrate urine is retained, producing a hyperosmolar urine devoid of proteins and abnormal sediment, and surprisingly low in sodium* (unlike renal tubular necrosis). Rapid development of renal failure is usually associated with a precipitating stress factor such as infection, gastrointestinal hemorrhage, or a major surgical procedure. Insidious development of renal failure is the result of progressive destabilization of circulatory physiology, frequently in the setting of severe refractory ascites. The prognosis is poor, with a median survival of only 2 weeks in the rapid-onset form and 6 months with the insidious-onset form.

CIRRHOSIS

Cirrhosis is among the top 10 causes of death in the Western world. The chief worldwide contributors are alcohol abuse and viral hepatitis. Other causes include biliary disease, and iron overload. An example of the progression to cirrhosis is given under the subsequent discussion on alcohol. Cirrhosis as the end-stage of chronic liver disease is defined by three characteristics:

- Bridging *fibrous septae* in the form of delicate bands or broad scars linking portal tracts with one another and portal tracts with terminal hepatic veins
- *Parenchymal nodules* containing proliferating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) to large (several centimeters, macronodules)
- *Disruption of the architecture of the entire liver*

Several features of cirrhosis should be underscored:

- *The parenchymal injury and consequent fibrosis are diffuse,* extending throughout the liver. Focal injury with scarring does not constitute cirrhosis, nor does diffuse nodular transformation without fibrosis.
- *Nodularity is part of the diagnosis* and reflects the balance between regenerative activity and constrictive scarring. It should be noted that rapid development of fibrosis, as in alcoholic hepatitis, may leave little time for the development of spherical nodules.
- *Vascular architecture is reorganized* by the parenchymal damage and scarring, with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow channels. As a result, portal vein and arterial blood partially bypasses the functional hepatocyte mass through these abnormal channels.
- *Fibrosis is the key feature of progressive damage to the liver.* With cessation of the causal injury, slow regression of fibrosis may occur. Once cirrhosis has developed, reversal is thought to be rare. However, the liver contains abundant metalloproteinases and collagenases that are capable of degrading extracellular matrix. Collagen degradation is a slow process, since collagen I sustains extensive crosslinking after its deposition and hence becomes more resistant to collagenases over time. Nevertheless, there are a sufficient number of clinical reports of patients whose full-blown cirrhosis has subsided to a form of incomplete septation of the liver or apparent absence of fibrosis, to raise

hopes that even patients with cirrhosis may improve without resorting to liver transplantation.

The only satisfactory classification of cirrhosis is based on the presumed underlying etiology. The descriptive terms "micronodular" and "macronodular" should not be used as primary classifications. Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with time, counterbalanced by the constraints imposed by fibrous scarring.

The etiology of cirrhosis varies both geographically and socially. The following is the approximate frequency of etiologic categories in the Western world, most of which are discussed in detail later:

Alcoholic liver disease	60% to 70%
Viral hepatitis	10%
Biliary diseases	5% to 10%
Primary hemochromatosis	5%
Wilson disease	Rare
α_1 -Antitrypsin deficiency	Rare
Cryptogenic cirrhosis	10% to 15%

Infrequent types of cirrhosis also include the cirrhosis developing in infants and children with galactosemia and tyrosinosis (Chapter 10), and drug-induced cirrhosis, as with α-methyldopa. Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis," discussed later). After all the categories of cirrhosis of known causation have been excluded, a substantial number of cases remain. Referred to as *cryptogenic cirrhosis*, the magnitude of this "wastebasket" category speaks eloquently to the difficulties in discerning the many origins of cirrhosis. A growing concern is that many of these cases are due to undiagnosed *nonalcoholic fatty liver disease*, to be discussed. *Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.*

Pathogenesis.

The central pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver.[7] In the normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins, with occasional bundles in the space of Disse. The collagen (reticulin) coursing alongside hepatocytes is composed of delicate strands of type IV collagen in the space of Disse. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. New vascular channels in the septae connect the vascular structures in the portal region (hepatic arteries and portal veins) and terminal hepatic veins, shunting blood around the parenchyma. Continued deposition of collagen in the space of Disse within preserved parenchyma is accompanied by the loss of fenestrations in the sinusoidal endothelial cells. In the process, the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma. In particular, hepatocellular secretion of proteins (e.g., albumin, clotting factors, lipoproteins) is greatly impaired.

The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells, which lie in the space of Disse. Although normally functioning as vitamin A fat-storing cells, during the development of cirrhosis they become activated, a process that includes (1) robust mitotic activity in areas developing new parenchymal fibrosis, (2) a shift from the resting-state lipocyte phenotype to a transitional myofibroblast phenotype, and (3) increased capacity for synthesis and secretion of extracellular matrix. It is predominantly the cytokines secreted by activated Kupffer cells and other inflammatory cells that stimulate perisinusoidal stellate cells to divide and to produce large amounts of extracellular matrix. Moreover, the greatest activation of stellate cells is in areas of severe hepatocellular necrosis and inflammation. As depicted in Figure 18-3 , the stimuli for stellate cell activation may come from several sources:

- Chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin-1 (IL-1).
- Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells), including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and lipid peroxidation products.
- Disruption of the extracellular matrix, as stellate cells are extraordinarily responsive to the status of their substrate.
- Direct stimulation of stellate cells by toxins.

Acquisition of myofibers by perisinusoidal stellate cells also increases vascular resistance within the liver parenchyma, since tonic contraction of these "myofibroblasts" constricts the sinusoidal vascular channels.

Throughout the process of liver damage and fibrosis, remaining hepatocytes are stimulated to regenerate and proliferate as spherical nodules within the confines of the fibrous septae. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely compromised, as is the ability of hepatocytes to secrete substances into plasma. Disruption of the interface between the parenchyma and portal tracts obliterates biliary channels as well. Thus, *the cirrhotic patient may develop jaundice and even hepatic failure, despite having a liver of normal mass.*

Clinical Features.

All forms of cirrhosis may be clinically silent. When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation. Incipient or overt hepatic failure may develop, usually precipitated by a superimposed metabolic load on the liver, as from systemic infection or a gastrointestinal hemorrhage. Imbalances of pulmonary blood flow, which are poorly understood, may lead to severely impaired oxygenation (*hepatopulmonary syndrome*), further stressing the patient. *The ultimate mechanism of most cirrhotic deaths is (1) progressive liver failure (discussed earlier), (2) a complication related to portal hypertension, or (3) the development of hepatocellular carcinoma.*

PORTAL HYPERTENSION

Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into *prehepatic, intrahepatic, and posthepatic causes*. The major *prehepatic conditions* are obstructive thrombosis and narrowing of the portal vein before it ramifies within the liver. Massive splenomegaly may also shunt excessive blood into the splenic vein. The major *posthepatic causes* are severe right-sided heart failure, constrictive pericarditis, and hepatic vein outflow obstruction. *The dominant intrahepatic cause is cirrhosis, accounting for most cases of portal hypertension.* Far less frequent are schistosomiasis, massive fatty change, diffuse fibrosing granulomatous disease such as sarcoidosis and miliary

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Figure 18-3 Schematic of stellate cell activation and liver fibrosis in comparison to the normal liver. Kupffer cell activation leads to secretion of multiple cytokines; cytokines also may be released by endothelial cells, hepatocytes, and inflammatory cells entering the liver (not shown). These cytokines "activate" stellate cells, whereby they loose their lipid droplets (which are present in the quiescent state) and acquire a myofibroblastic state. Stellate cell proliferation is stimulated in particular by platelet-derived growth factor (PDGF); tumor necrosis factor (TNF) is a potent stimulant of the change to a myofibroblastic phenotype. Contraction of the activated stellate cells is stimulated by endothelin-1 (ET-1). Deposition of extracellular matrix (fibrogenesis) is stimulated especially by transforming growth factor β (TGF-β). Chemotaxis of activated stellate cells to areas of injury, such as where hepatocytes have undergone apoptosis, is promoted by PDGF and monocyte chemotactic protein-1 (MCP-1). Kupffer cells also are a major source of TNF released into the system circulation. *(Schematic based on concepts presented in Friedman SL: Molecular regulation of hepatic fibrosis: an integrated cellular response to tissue injury. J Biol Chem 275:2247–2250, 2000; and Crawford JM: Cellular and molecular biology of the liver. Curr Op Gastroenterol 13:175–185, 1997.)*

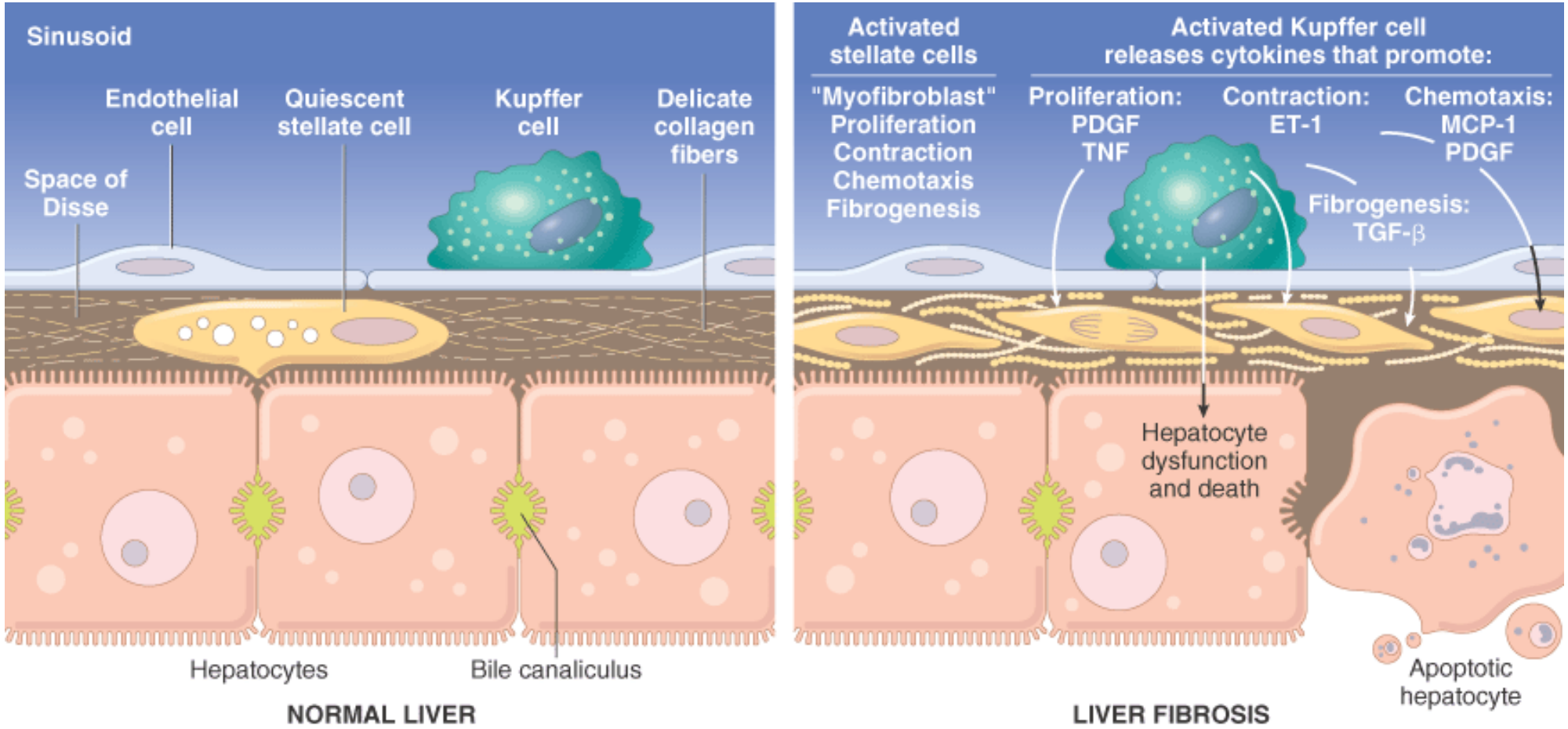


Figure 18-4 The major clinical consequences of portal hypertension in the setting of cirrhosis, shown for the male. In women, oligomenorrhea, amenorrhea, and sterility are frequent, owing to hypogonadism.

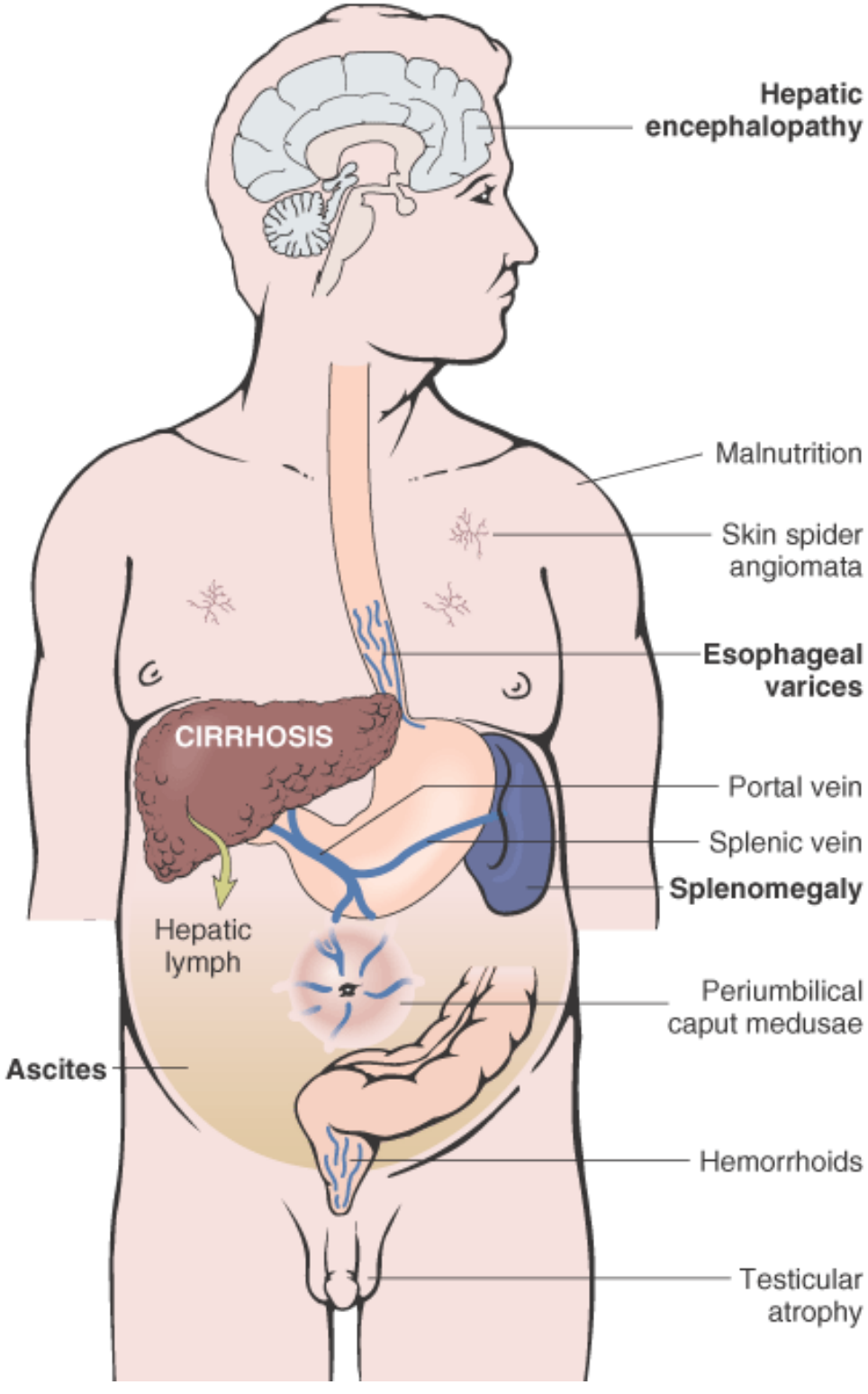
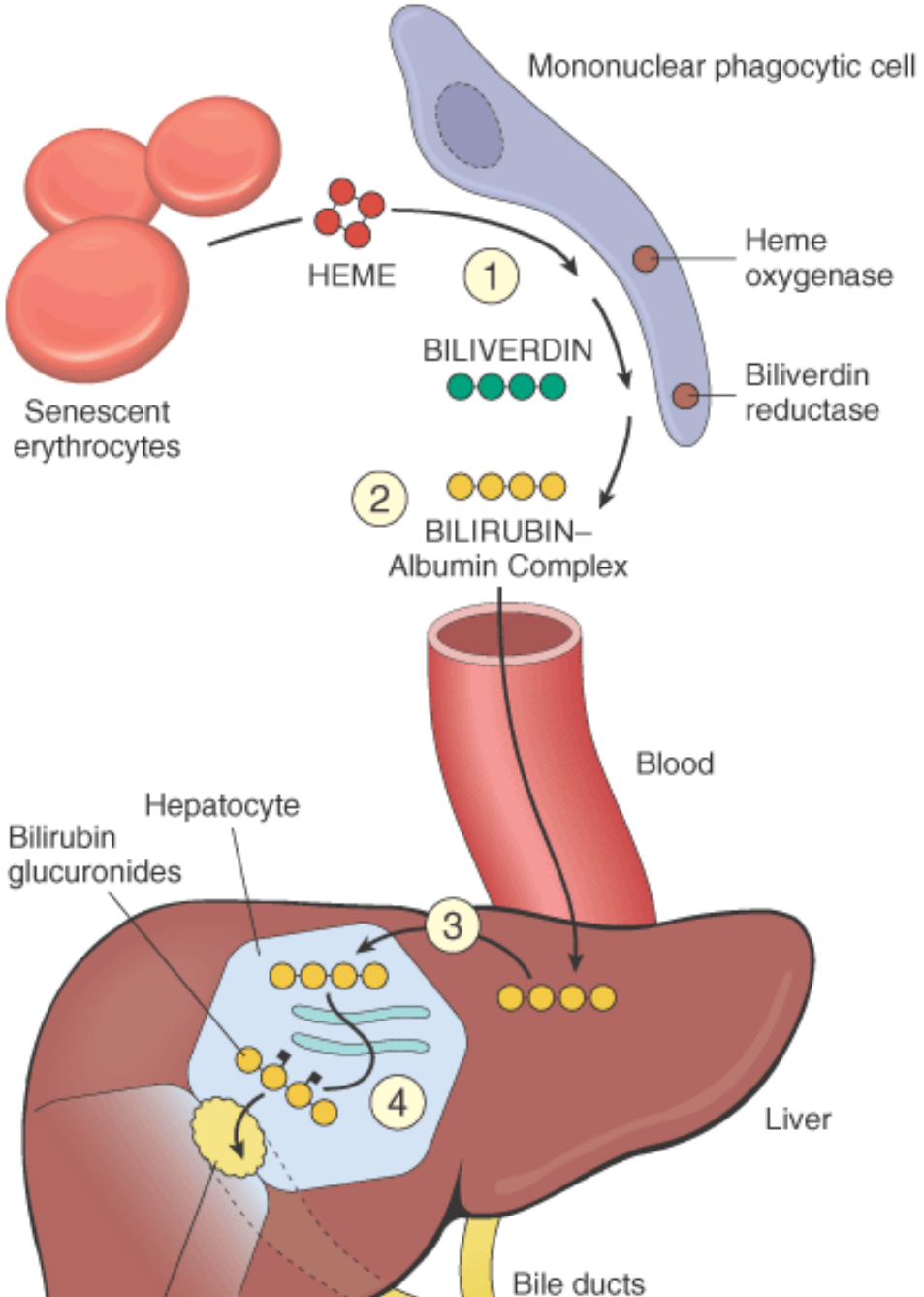

Hepatic encephalopathy
Malnutrition
Skin spider angiomata
Esophageal varices
CIRRHOSIS
Portal vein
Splenic vein
Splenomegaly
Hepatic lymph
Periumbilical caput medusae
Ascites
Hemorrhoids
Testicular atrophy

Figure 18-5 Bilirubin metabolism and elimination. 1, Normal bilirubin production from heme (0.2 to 0.3 gm/day) is derived primarily from the breakdown of senescent circulating erythrocytes, with a minor contribution from degradation of tissue heme-containing proteins. 2, Extrahepatic bilirubin is bound to serum albumin and delivered to the liver. 3, Hepatocellular uptake and (4) glucuronidation in the endoplasmic reticulum generate bilirubin monoglucuronides and diglucuronides, which are water soluble and readily excreted into bile. 5, Gut bacteria deconjugate the bilirubin and degrade it to colorless urobilinogens. The urobilinogens and the residue of intact pigments are excreted in the feces, with some reabsorption and excretion into urine.



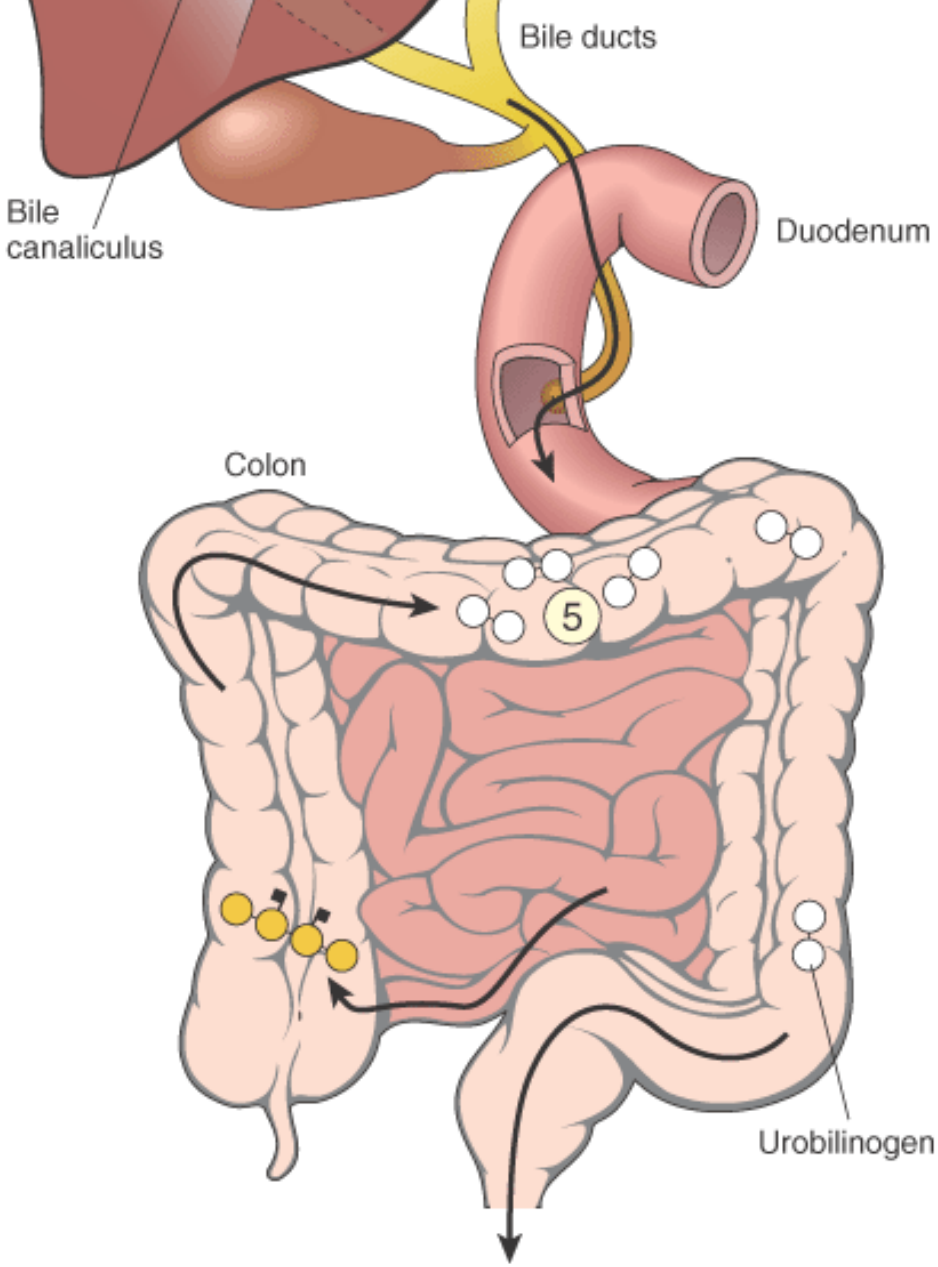


TABLE 18-3 -- Causes of Jaundice

Predominantly Unconjugated Hyperbilirubinemia
Excess production of bilirubin
••Hemolytic anemias

••Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas)
••Ineffective erythropoiesis syndromes (e.g., pernicious anemia, thalassemia)
Reduced hepatic uptake
••Drug interference with membrane carrier systems
••Some cases of Gilbert syndrome
Impaired bilirubin conjugation
••Physiologic jaundice of the newborn (decreased UGT1A1 activity, decreased excretion)
••Breast milk jaundice (β-glucuronidases in milk)
••Genetic deficiency of UGT1A1 activity (Crigler-Najjar syndrome types I and II)
••Gilbert syndrome (mixed etiologies)
••Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
Predominantly Conjugated Hyperbilirubinemia
Deficiency of canalicular membrane transporters (Dubin-Johnson syndrome, Rotor syndrome)
Impaired bile flow
UGT, uridine diphosphate-glucuronyltransferase.

Neonatal Jaundice.

Because the hepatic machinery for conjugating and excreting bilirubin does not fully mature until about 2 weeks of age, almost every newborn develops transient and mild unconjugated hyperbilirubinemia, termed neonatal jaundice or *physiologic jaundice of the newborn*. Breast-fed infants tend to exhibit jaundice with greater frequency, possibly the result of β-glucuronidases present in maternal milk. These enzymes deconjugate bilirubin glucuronides in the gut, increasing intestinal reabsorption of unconjugated bilirubin. Sustained jaundice in the newborn is indicative of a disease condition, discussed later under *neonatal hepatitis*.

Hereditary Hyperbilirubinemias.

In rare instances, there may be a genetic lack of UGT1A1 (Table 18-4). In *Crigler-Najjar syndrome type I*, the enzyme is completely absent. Multiple genetic defects in the locus coding for UGT1A1 may give rise to this disorder.[10] The liver is incapable of synthesizing a functional enzyme, and the colorless bile contains only trace amounts of unconjugated bilirubin. The liver is morphologically normal by light and electron microscopy. However, serum unconjugated bilirubin reaches very high levels, producing severe jaundice and icterus. Without liver transplantation, this condition is invariably fatal, causing death within 18 months of birth secondary to kernicterus.

Crigler-Najjar syndrome type II is a less severe, nonfatal disorder in which UGT1A1 enzyme activity is greatly reduced, and the enzyme is capable of forming only monoglucuronidated bilirubin. Unlike Crigler-Najjar syndrome type I, the only major consequence is extraordinarily yellow skin from moderate to high levels of circulating unconjugated bilirubin; phenobarbital treatment can improve bilirubin glucuronidation by inducing hypertrophy of the hepatocellular endoplasmic reticulum. Mutations either reduce the affinity of UGT1A1 toward bilirubin or reduce enzyme activity.[11] Almost

TABLE 18-4 -- Hereditary Hyperbilirubinemias

Disorder	Inheritance	Defects in Bilirubin Metabolism	Liver Pathology	Clinical Course
Unconjugated Hyperbilirubinemia				
Crigler-Najjar syndrome type I	Autosomal recessive	Absent UGT1A1 activity	Normal	Fatal in neonatal period
Crigler-Najjar syndrome type II	Autosomal dominant with variable penetrance	Decreased UGT1A1 activity	Normal	Generally mild, occasional kernicterus
Gilbert syndrome	Autosomal dominant?	Decreased UGT1A1 activity	Normal	Innocuous
Conjugated Hyperbilirubinemia				
Dubin-Johnson syndrome	Autosomal recessive	Impaired biliary excretion of bilirubin glucuronides due to mutation in canalicular multidrug resistance protein 2 (MRP2)	Pigmented cytoplasmic globules; ?epinephrine metabolites	Innocuous
Rotor syndrome	Autosomal recessive	Decreased hepatic uptake and storage?	Normal	Innocuous
		Decreased biliary excretion?		

UGT, uridine diphosphate-glucuronyltransferase.

all patients develop normally, but there is a risk for some neurologic damage from kernicterus.

Gilbert syndrome is a relatively common, benign, somewhat heterogeneous inherited condition presenting with mild, fluctuating hyperbilirubinemia. The primary cause is reduction in hepatic bilirubin glucuronidating activity to about 30% of normal levels. In most patients, two extra bases (TA) are found in the TATAA element of the 5' promoter region (creating an A $(TA)_7$ TAA element rather than the normal A$(TA)_6$ TAA, resulting in reduced expression of UGT1A1. Alternatively, patients may be heterozygous for missense mutations in the *UGT1A1* gene. Affecting some 6% of the population, the mild hyperbilirubinemia may go undiscovered for years and is not associated with functional derangements. When detected in adolescence or adult life, it is typically in association with stress, such as an intercurrent illness, strenuous exercise, or fasting. Gilbert syndrome has no clinical consequence except for the anxiety that a jaundiced sufferer might justifiably experience with this otherwise innocuous condition.

Dubin-Johnson syndrome results from a hereditary defect in hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. The defect is due to absence of the canalicular protein, the *multidrug resistance protein 2* (MRP2; located on chromosome 10q24), that is responsible for transport of bilirubin glucuronides and related organic anions into bile.[12] The liver is darkly pigmented owing to coarse pigmented granules within the cytoplasm of hepatocytes (Fig. 18-6). Electron microscopy reveals that the pigment is located in lysosomes, and it appears to be composed of polymers of epinephrine metabolites, not bilirubin pigment. The liver is otherwise normal. Apart from chronic or recurrent jaundice of fluctuating intensity, most patients are asymptomatic and have a normal life expectancy.

Rotor syndrome is a rare form of asymptomatic conjugated hyperbilirubinemia with multiple defects in hepatocellular uptake and excretion of bilirubin pigments. The liver is not pigmented. As with Dubin-Johnson syndrome, patients with Rotor syndrome exhibit jaundice but otherwise live normal lives.

Cholestasis

Cholestatic conditions, which result from hepatocellular dysfunction or intrahepatic or extrahepatic biliary obstruction, also may present with jaundice. Alternatively, *pruritus* is a presenting symptom, related to the elevation in plasma bile acids and their deposition in peripheral tissues, particularly skin. *Skin xanthomas* (focal accumulations of cholesterol) sometimes appear, the result of hyperlipidemia and impaired excretion of cholesterol. *A characteristic laboratory finding is elevated serum alkaline phosphatase*, an enzyme present in bile duct epithelium and in the canalicular membrane of hepatocytes that is released into the circulation because of the detergent action of retained bile salts on hepatocyte membranes. An isozyme derived from posttranscriptional changes is normally present in many other tissues such as bone, so the increased levels must be verified as being hepatic in origin. Another canalicular ectoenzyme, *γ-glutamyl transpeptidase*, is also released into the circulation. The elevated levels of these

Figure 18-6 Dubin-Johnson syndrome, showing abundant pigment inclusions in otherwise normal hepatocytes (H&E).

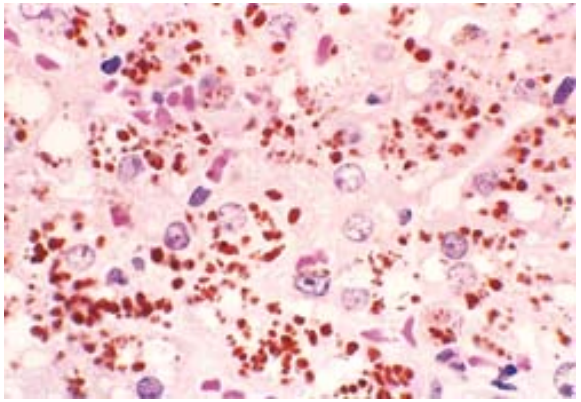
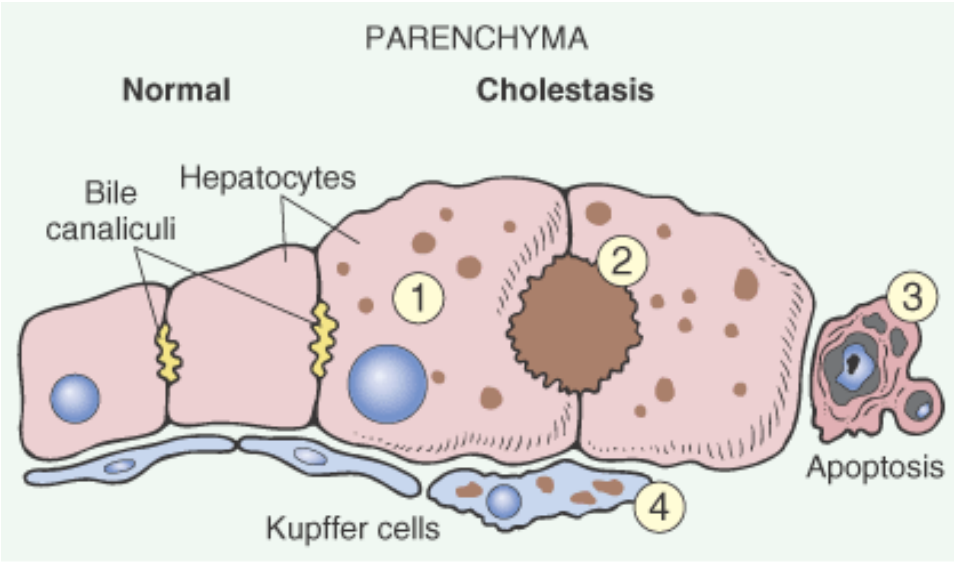


Figure 18-7 Illustration of the morphologic features of cholestasis (*right*) and comparison with normal liver (*left*). In the parenchyma (*upper panel*), cholestatic hepatocytes (1) are enlarged with dilated canalicular spaces (2). Apoptotic cells (3) may be seen, and Kupffer cells (4) frequently contain regurgitated bile pigments. In the portal tracts of obstructed liver (*lower panel*), there is also bile ductular proliferation (5), edema, bile pigment retention (6), and eventually neutrophilic inflammation (not shown). Surrounding hepatocytes (7) are swollen and undergoing degeneration.



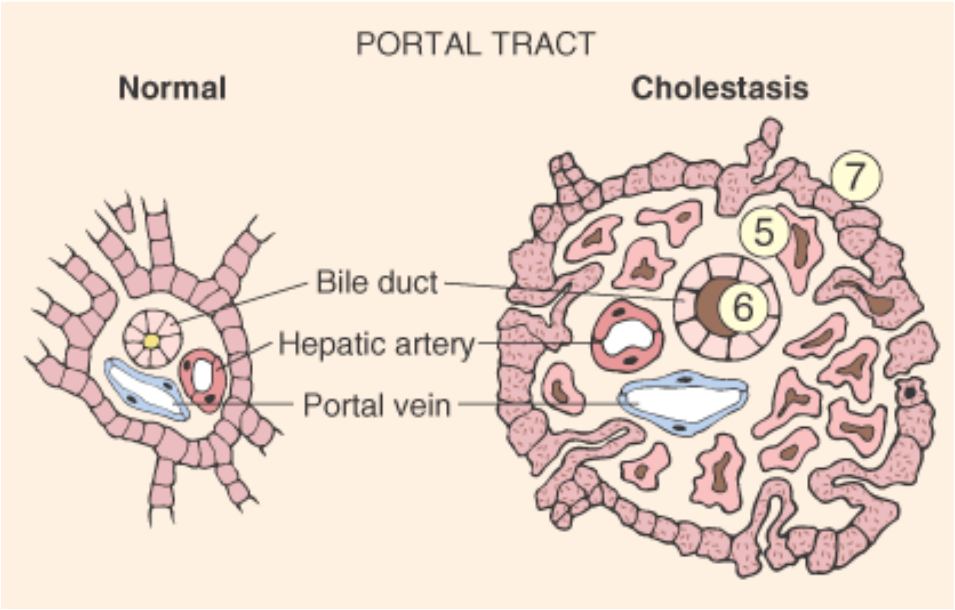


TABLE 18-5 -- Inherited Cholestatic Conditions

Common Names	Gene	Chromosome	Ligands	Location	Diseases
ABC1	ABCAI	9q22-q31	Lipids?	Many tissues	Tangier disease type 1
			Cholesterol?		
MDR3	ABCB4	7q21	Phosphatidylcholine	Hepatocyte apical (canalicular) membrane	PFIC-3

BSEP	ABCB11	2q24	Bile Salts	Hepatocyte apical (canalicular) membrane	PFIC-2
MRP2 (cMOAT)	ABCC2	10q24	Anionic conjugates with glutathione, sulfate, and glucuronate	Liver, intestine, kidney apical membranes	Dubin-Johnson Syndrome
CFTR	ABCC7	7q31-2	Organic anions? GSH?	Lung, intestine (crypt), cholangiocytes: apical membranes	Cystic Fibrosis
IBST	SLC10A2	13q33	Bile Salts	Cholangiocytes, intestine: apical membranes	PBAM
FIC1	ATP8B1	18q21-22	Aminophospholipid?	Cholangiocytes, hepatoctyes: apical membranes	PFIC-1, BRIC, Byler disease, Byler syndrome
ATP7B	ATP7B	13q14.3	Copper	Hepatocyte endoplasmic reticulum	Wilson disease

ABC, of the ABC transporter family; ATP, adenosine triphospatase; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane regulator; cMOAT, canalicular multiple organic anion transporter; PFIC, progressive familial intrahepatic cholestasis; IBST, intestinal bile salt transporter; MRP, multidrug resistant protein; PBAM, primary bile acid malabsorption; PFIC, progressive familial intrahepatic cholestasis.

(PFIC-3), due to mutations in the *ABCB4* gene on chromosome 7q21. The encoded protein, MDR3, is a canalicular transport protein that is responsible for flipping phosphatidylcholine from the internal to the external hemileaflet of the canalicular membrane. In patients with this disorder, the absence of secreted phosphatidylcholine in bile leaves the apical surfaces of the biliary tree epithelia subject to the full detergent action of secreted bile salts, with resultant toxic destruction of these epithelia and release of GGT into the circulation.

Children with severe cholestasis but with absence of elevated serum GGT and absence of pruritus may also have inherited defects in bile acid synthesis. The most common condition is a deficiency of *3β-hydroxysteroid dehydrogenase*, an enzyme located early in the pathway for bile acid synthesis from cholesterol.

Infectious Disorders

Inflammatory disorders of the liver dominate the clinical practice of hepatology. This is due in part to the fact that virtually any insult to the liver can kill hepatocytes and recruit inflammatory cells, but also because inflammatory diseases are frequently long-term chronic conditions that must be managed medically. Among inflammatory disorders, infection is by far the most frequent. The liver is almost inevitably involved in blood-borne infections, whether systemic or arising within the abdomen. The foremost hepatic infections are viral in origin. Other infections in which the hepatic lesion is prominent include miliary tuberculosis, malaria, staphylococcal bacteremia, the salmonelloses, candida, and amebiasis.

VIRAL HEPATITIS

Unless otherwise specified, the term "viral hepatitis" is reserved for infection of the liver caused by a group of viruses having a particular affinity for the liver (Table 18-6). [14] [15] Systemic viral infections that can involve the liver include (1) infectious mononucleosis (Epstein-Barr virus), which may cause a mild hepatitis during the acute phase; (2) cytomegalovirus, particularly in the newborn or immunosuppressed patient; and (3) yellow fever, which has been a major and serious cause of hepatitis in tropical countries. Infrequently, in children and immunosuppressed patients, the liver is affected in the course of rubella, adenovirus, herpesvirus, or enterovirus infections. Hepatotropic viruses cause overlapping patterns of disease. Each hepatotropic virus and the disease conditions it causes will be introduced before a general discussion of hepatitis.

Hepatitis A Virus

Hepatitis A virus (HAV), the scourge of military campaigns since antiquity, is a benign, self-limited disease with an incubation period of 2 to 6 weeks.[16] *HAV does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis, so the fatality rate associated with HAV is about 0.1%.* The outcome of HAV infection may be more severe if it is superimposed on chronic hepatitis due to Hepatitis B virus (HBV), Hepatitis C virus (HCV), or alcohol. HAV occurs throughout the world and is endemic in countries with substandard

hygiene and sanitation, so populations there may have detectable anti-HAV by the age of 10 years. Clinical disease tends to be mild or asymptomatic and rare after childhood. In developed countries, the prevalence of seropositivity increases gradually with age, reaching 50% by age 50 years in the United States. In this population, acute HAV tends to be a sporadic febrile illness. Overall, HAV accounts for about 25% of clinically evident acute hepatitis worldwide and an estimated 270,000 new cases per year in the United States.[4]

HAV is a small, nonenveloped, single-stranded RNA picornavirus that occupies its own genus, *Hepatovirus*. Ultrastructurally, HAV is an icosahedral capsid 27 nm in diameter. HAV

TABLE 18-6 -- The Hepatitis Viruses

	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus	Hepatitis D Virus	Hepatitis E Virus	Hepatitis G Virus *
Agent	Icosahedral capsid, ssRNA	Enveloped dsDNA	Enveloped ssRNA	Enveloped ssRNA	Unenveloped ssRNA	ssRNA virus
Transmission	Fecal-oral	Parenteral; close contact	Parenteral; close contact	Parenteral; close contact	Waterborne	Parenteral
Incubation period	2–6 wk	4–26 wk	2–26 wk	4–7 wk	2–8 wk	Unknown
Carrier state	None	0.1–1.0% of blood donors in U.S. and Western world	0.2–1.0% of blood donors in U.S. and Western world	1–10% in drug addicts and hemophiliacs	Unknown	1–2% of blood donors in U.S.
Chronic hepatitis	None	5–10% of acute infections	>50%	<50% coinfection, 80% upon superinfection	None	None
Hepatocellular carcinoma	No	Yes	Yes	No increase above HBV	Unknown, but unlikely	None

*At present, hepatitis G virus is not considered pathogenic.

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is spread by ingestion of contaminated water and foods and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice. Thus, close personal contact with an infected individual or fecal-oral contamination during this period accounts for most cases and explains the outbreaks in institutional settings such as schools and nurseries and the waterborne epidemics in places where people live in overcrowded, unsanitary conditions. HAV is not shed in any significant quantities in saliva, urine, or semen. In developed countries, sporadic infections may be contracted by the consumption of raw or steamed shellfish (oysters, mussels, clams), which concentrate the virus from seawater contaminated with human sewage. Infected workers in the food industry may also be the source of outbreaks. Outbreaks of the disease in September and November, 2003, in the United States involved more than 600 infected persons and caused at least three deaths. Consumption of raw green onions contaminated with HAV was the most likely cause of these outbreaks. *Because HAV viremia is transient, blood-borne transmission of HAV occurs only rarely; therefore, donated blood is not specifically screened for this virus.*

Serologic Diagnosis.

Specific antibody against HAV of the immunoglobulin (Ig) M type appears in blood at the onset of symptoms, constituting a reliable marker of acute infection (Fig. 18-8). Fecal shedding of the virus ends as the IgM titer rises. The IgM response usually begins to decline in a few months and is followed by the appearance of IgG anti-HAV. The latter persists for years,

perhaps for life, providing protective immunity against reinfection by all strains of HAV. Hence, the HAV vaccine is effective.

Hepatitis B Virus

Hepatitis B virus (HBV) can produce (1) acute hepatitis with resolution, (2) chronic hepatitis, which may evolve to cirrhosis, (3) fulminant hepatitis with massive liver necrosis, and (4) the backdrop for hepatitis D virus infection. Patients with chronic hepatitis represent carriers of actively replicating virus and hence are a source of infection to other individuals.[17] HBV also plays an important role in the development of hepatocellular carcinoma. The approximate frequencies of clinical outcomes of HBV infection are depicted in Figure 18-9 .

Liver disease due to HBV is an enormous problem globally, with an estimated worldwide carrier rate of 350 million. It is estimated that HBV has infected over 2 billion of the individuals alive today at some point in their lives. Seventy-five percent of all chronic carriers live in Asia and the Western Pacific rim. The global prevalence of chronic hepatitis B infection varies widely, from high (>8%) in Africa, Asia, and the Western Pacific to intermediate (2% to 7%) in Southern and Eastern Europe to low (<2%) in Western Europe, North America, and Australia. In the United States alone, there are

Figure 18-8 Sequence of serologic markers in acute hepatitis A viral hepatitis.

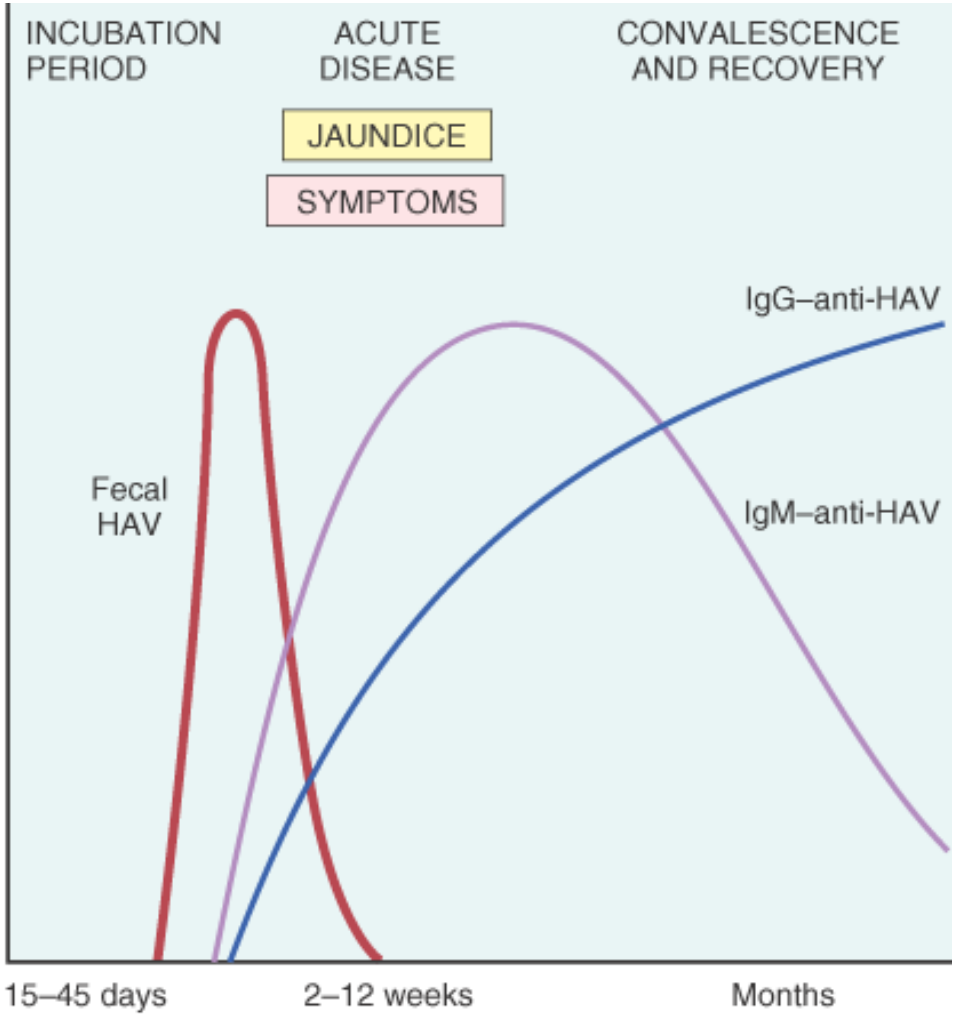

Figure 18-9 Schematic of the potential outcomes of hepatitis B infection in adults, with their approximate frequencies in the United States.

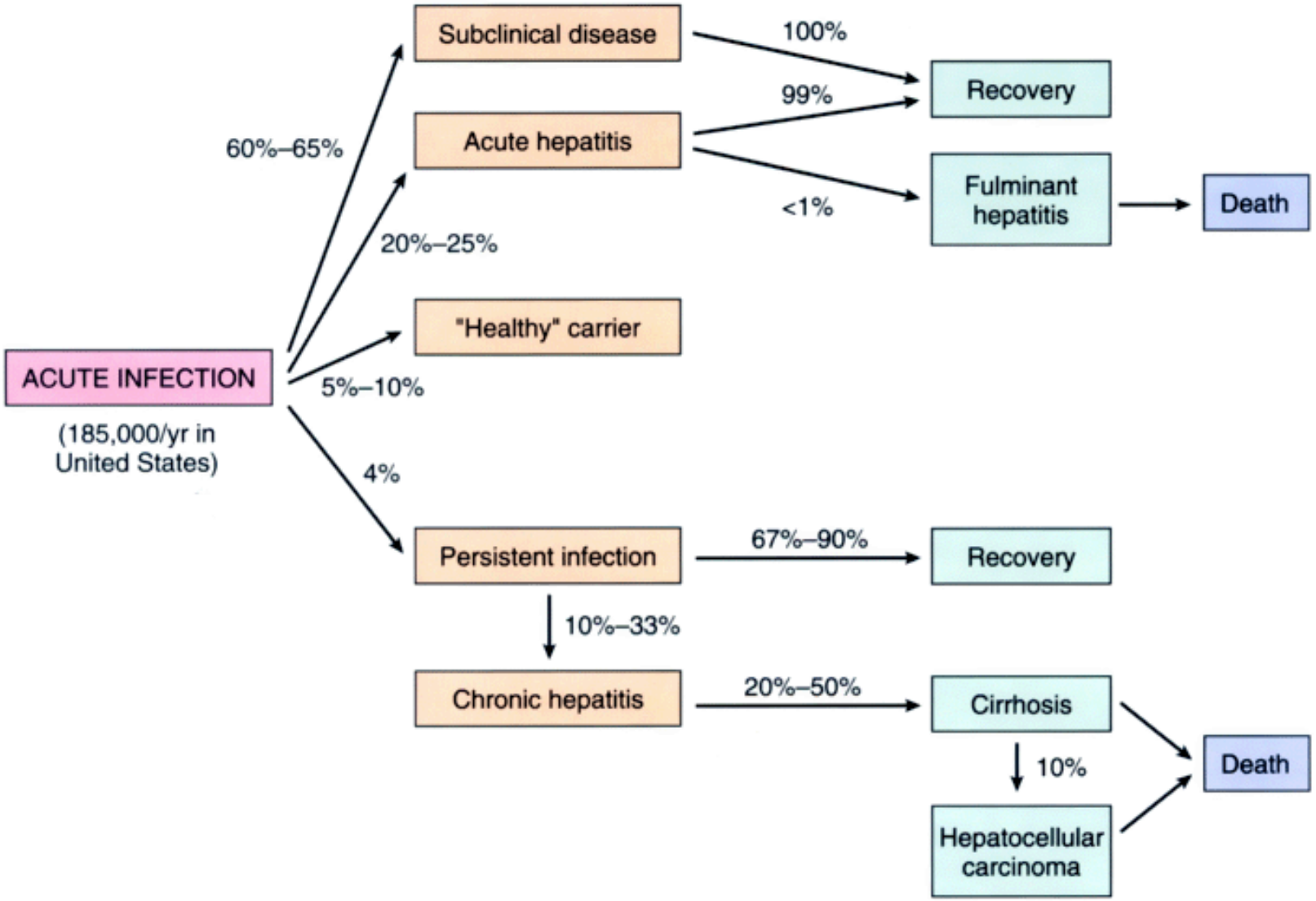

Figure 18-10 Diagrammatic representation of genomic structure and transcribed components of the hepatitis B virion. The innermost circles represent the DNA (+) strand and the DNA (-) strand of the virion. The thick bars labeled "P," "X," "pre-C," "C," "pre-S1," "pre-S2," and "S" denote the peptides derived from the virion. The outermost lines denote the mRNA transcripts of the virion. *(After Kidd-Ljunggren K, Myakawa Y, Kidd AH: J Gen Virol 83:1267–1280, 2002.)*

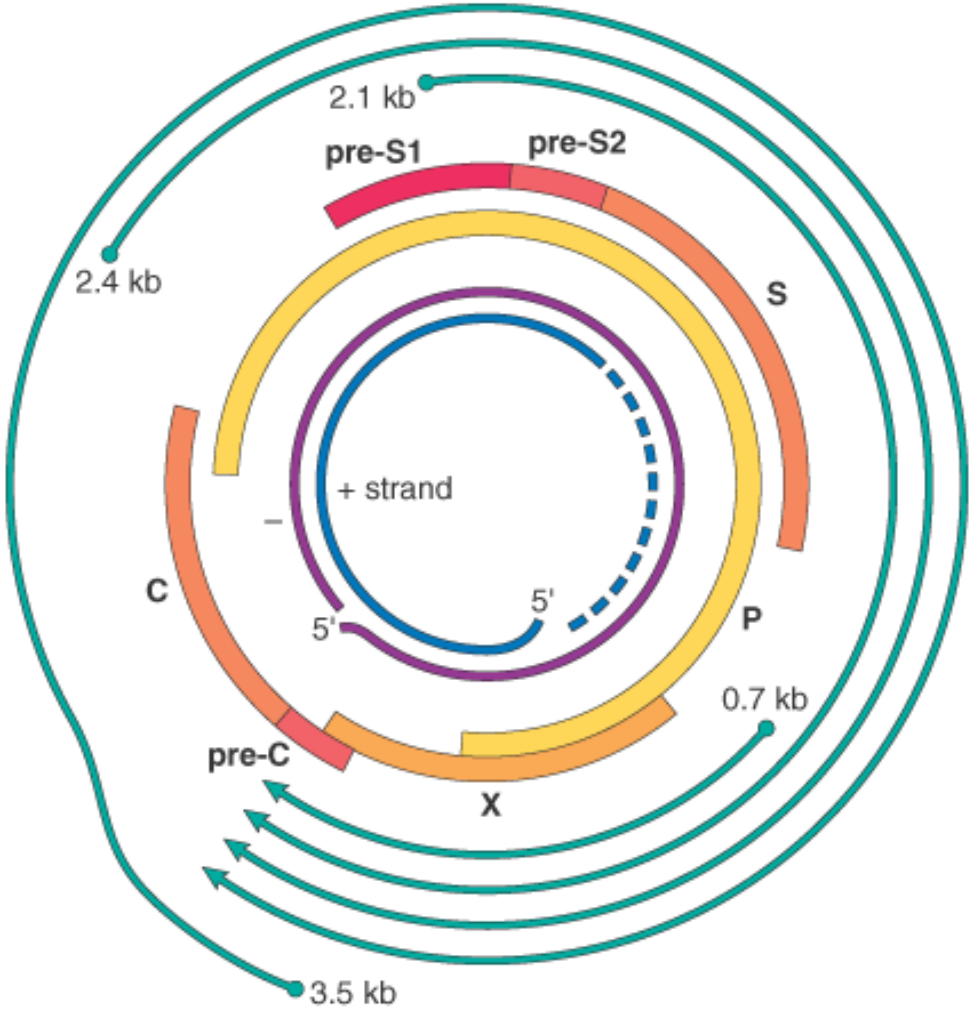

Figure 18-11 Sequence of serologic markers for hepatitis B viral hepatitis demonstrating *(A)* acute infection with resolution and *(B)* progression to chronic infection.

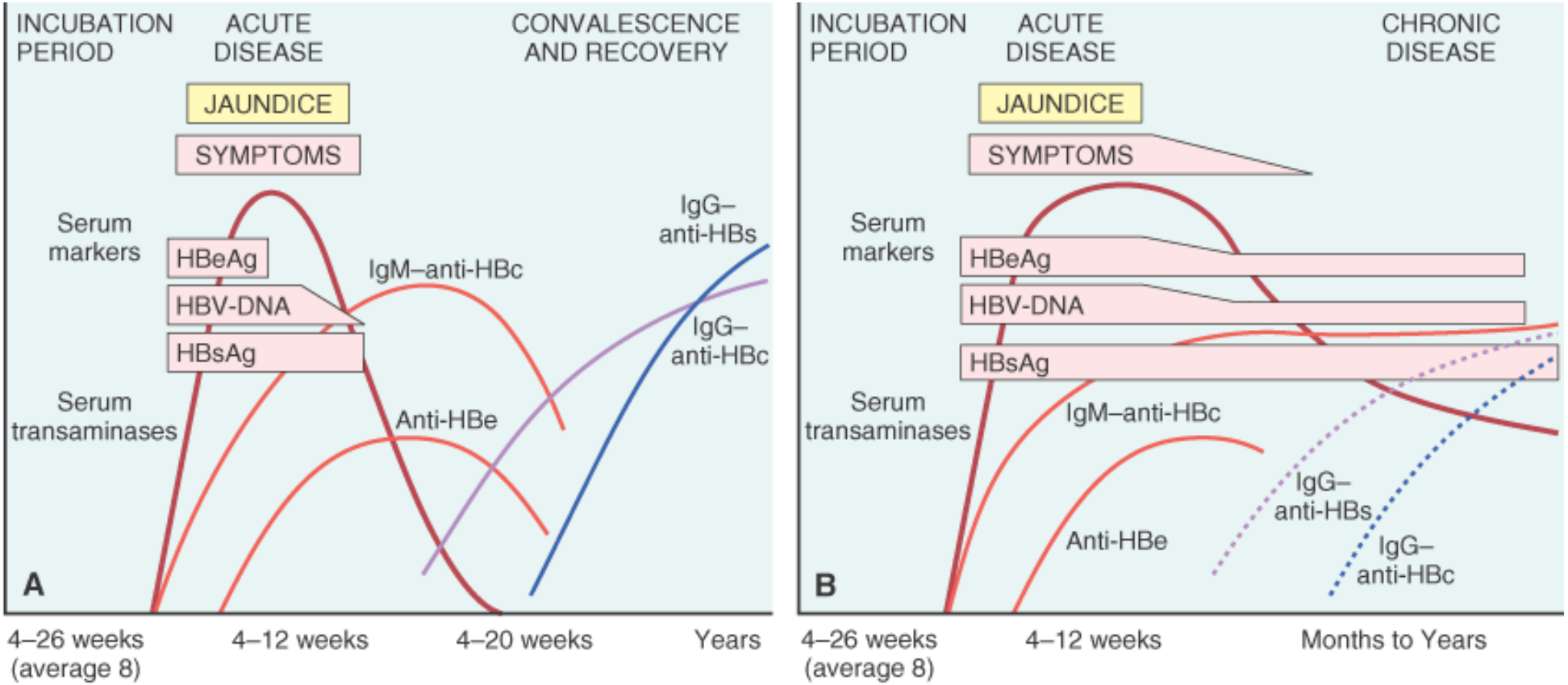

Figure 18-12 Schematic of the potential outcomes of hepatitis C infection in adults, with their approximate frequencies in the United States.

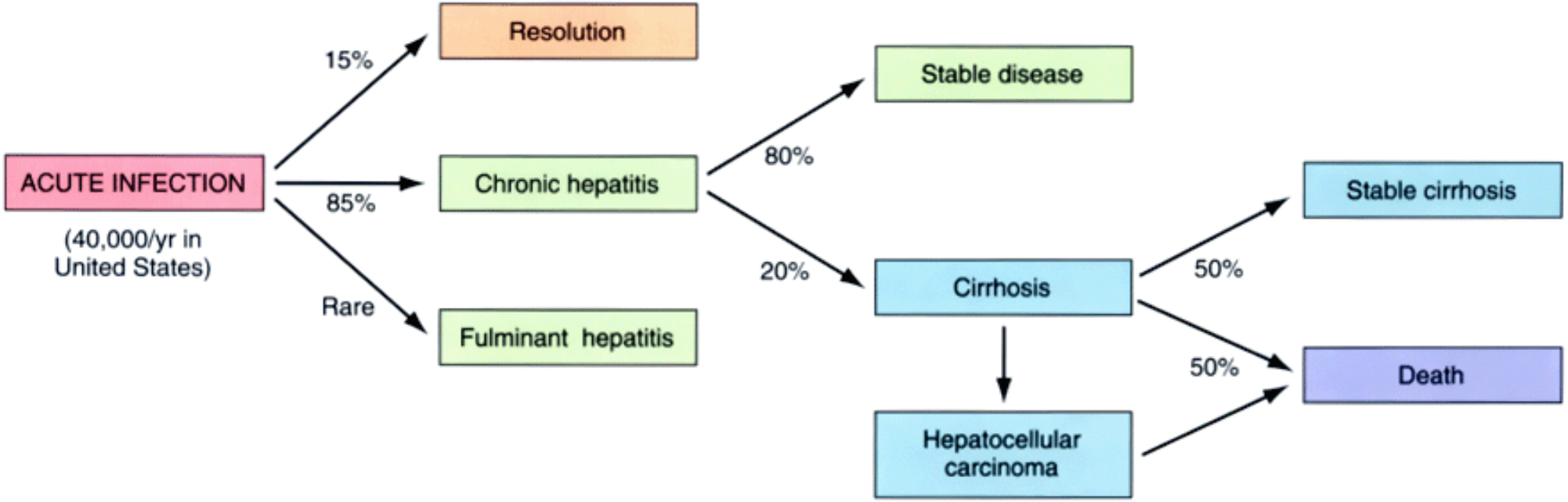

Figure 18-13 Diagrammatic representation of the genomic structure and transcribed components of the hepatitis C virion. The hepatitis C virion is transcribed in one single transcript, as depicted in the top line; 340 nucleotides at the 5' end and 128 nucleotides at the 3' end are not translated into protein. The protein products cleaved from the single translated peptide are shown in the bottom bar.

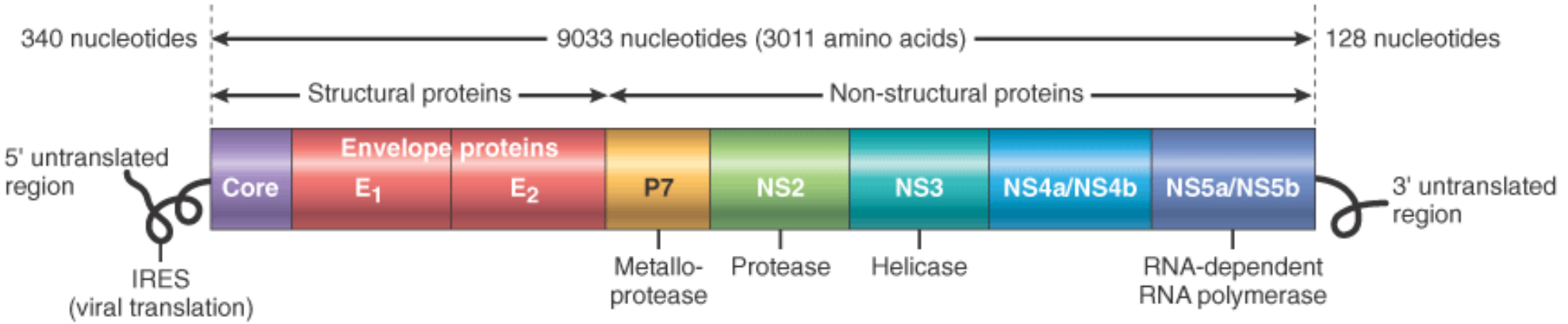

Figure 18-14 Sequence of serologic markers for hepatitis C viral hepatitis demonstrating (*A*) acute infection with resolution and (*B*) progression to chronic relapsing infection.

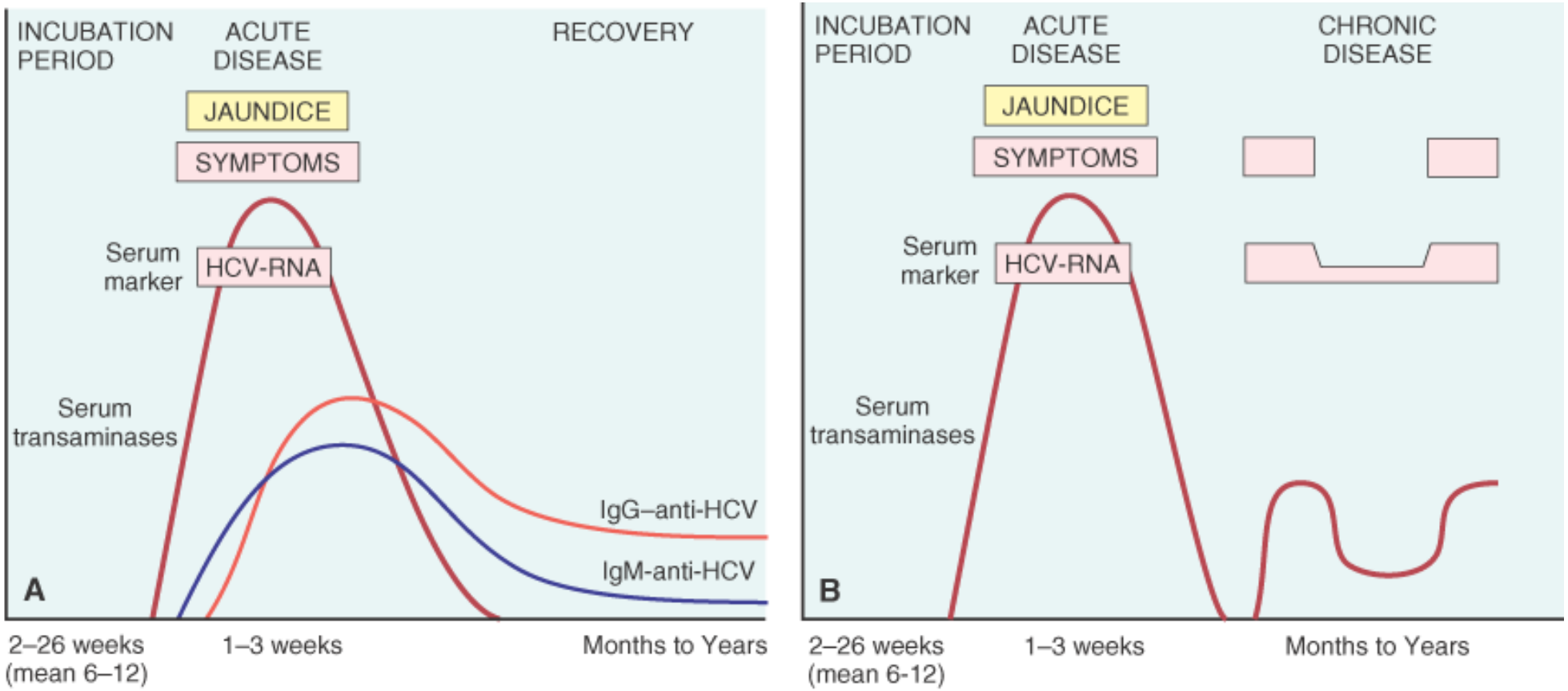

Figure 18-15 Differing clinical consequences of two patterns of combined hepatitis D virus and hepatitis B virus infection.

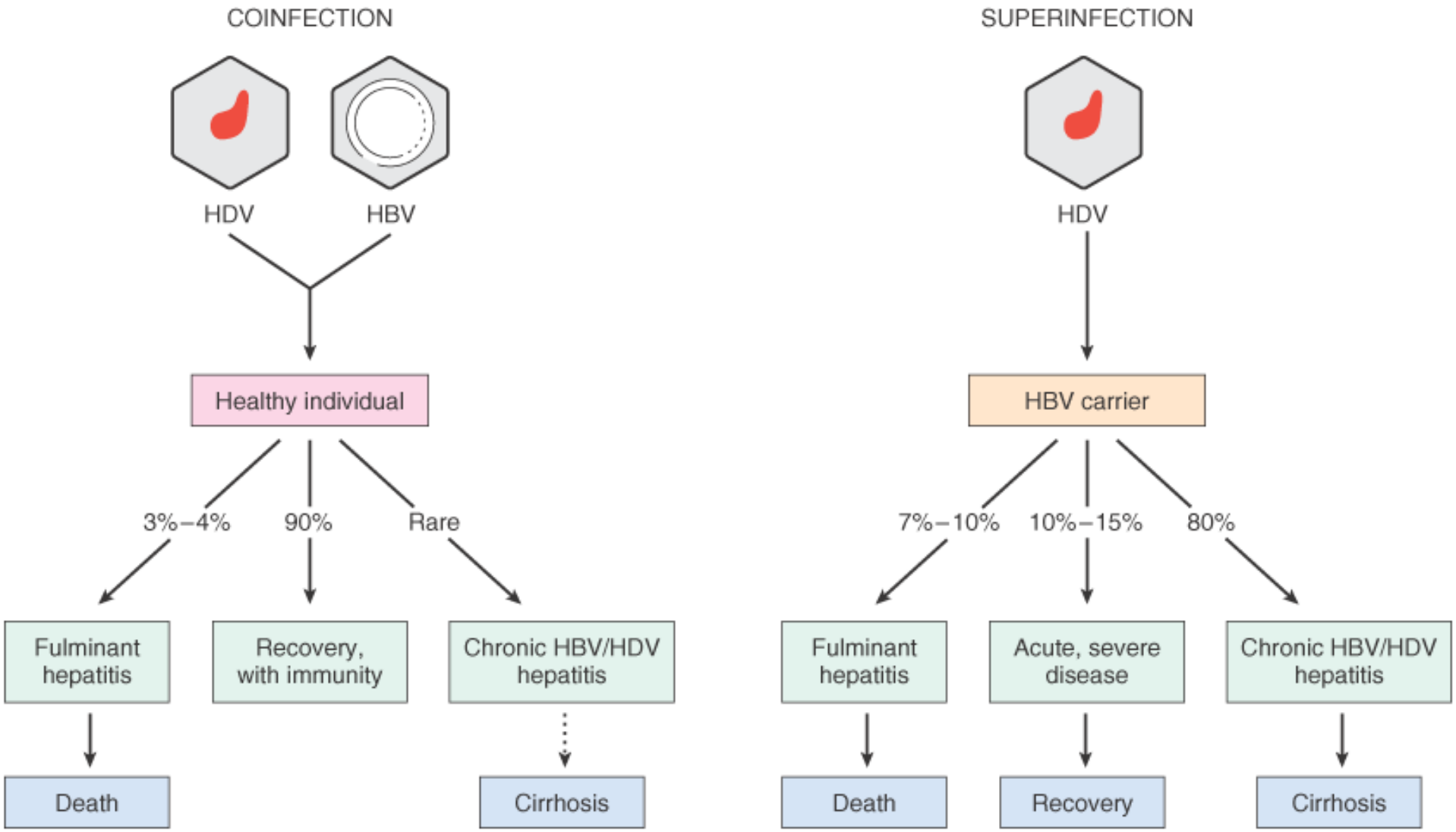

Figure 18-16 Sequence of serologic markers for hepatitis D viral hepatitis depicting (*A*) coinfection with hepatitis B virus (HBV) and (*B*) superinfection of an HBV carrier.

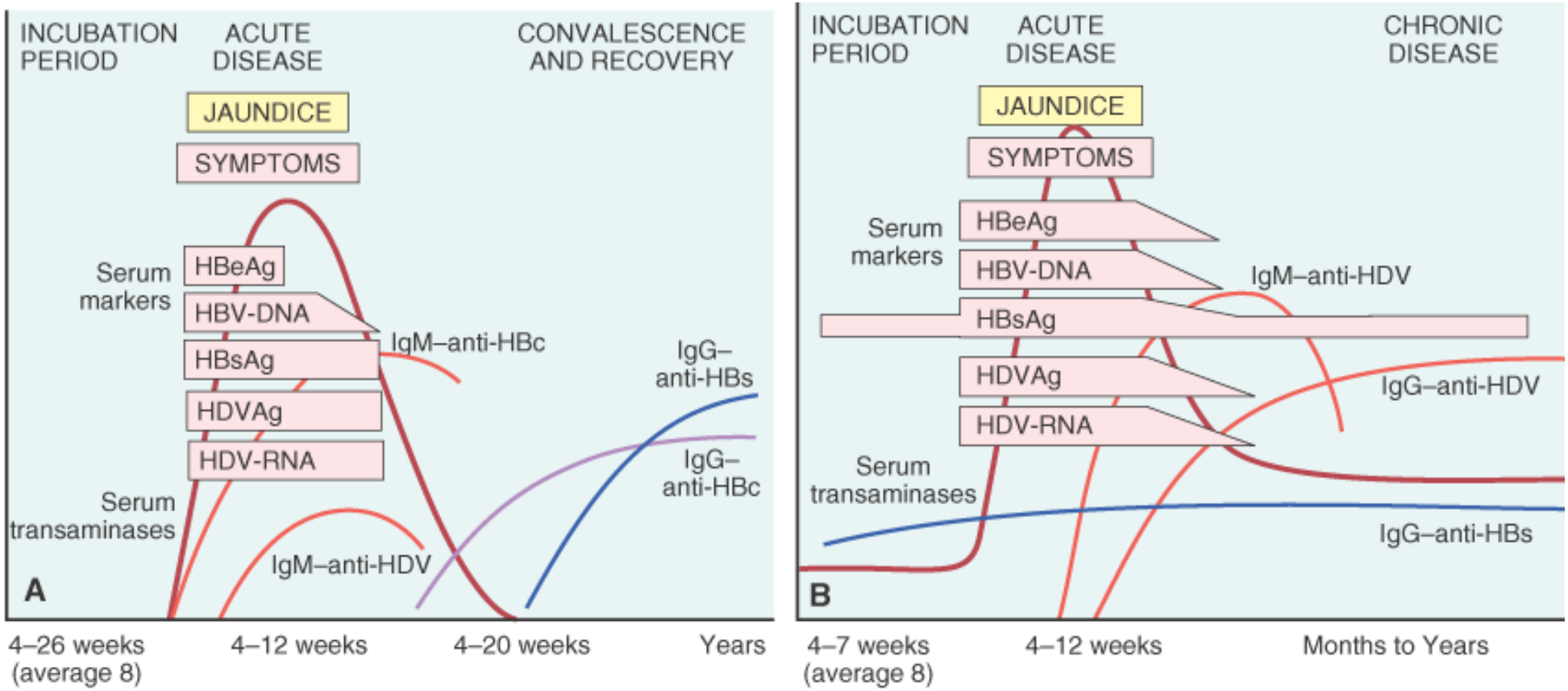

TABLE 18-7 -- Key Morphologic Features of Viral Hepatitis

Acute Hepatitis
Enlarged, reddened liver; greenish if cholestatic
Parenchymal changes:
••Hepatocyte injury: swelling (ballooning degeneration)
••••Cholestasis: canalicular bile plugs
••••HCV: mild focal fatty change of hepatocytes
••Hepatocyte necrosis: isolated cells or clusters
••••Cytolysis (rupture) or apoptosis (shrinkage)
••••If severe: bridging necrosis (portal-portal, central-central, portal-central)
••••Lobular disarray: loss of normal architecture
••Regenerative changes: hepatocyte proliferation

••Sinusoidal cell reactive changes:
••••Accumulation of phagocytosed cellular debris in Kupffer cells
••••Influx of mononuclear cells into sinusoids
••Portal tracts:
••••Inflammation: predominantly mononuclear
••••Inflammatory spillover into adjacent parenchyma, with hepatocyte necrosis
Chronic Hepatitis
Changes shared with acute hepatitis:
••Hepatocyte injury, necrosis, and regeneration
••Sinusoidal cell reactive changes
Portal tracts:
••Inflammation:
••••Confined to portal tracts, *or*
••••Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), *or*
••••Bridging inflammation and necrosis
••Fibrosis:
••••Portal deposition, *or*
••••Portal and periportal deposition, *or*
••••Formation of bridging fibrous septa
HBV: "ground-glass" hepatocytes, "sanded" nuclei
HCV: bile duct epithelial cell proliferation, lymphoid aggregate formation
Cirrhosis: The end-stage outcome

The canalicular bile plugs result from cessation of the contractile activity of the hepatocyte pericanalicular actin microfilament web. Two patterns of hepatocyte cell death are seen. In the first, rupture of cell membranes leads to cytolysis and focal loss of hepatocytes. The sinusoidal collagen reticulin framework collapses where the cells have disappeared, and scavenger **macrophage aggregates** mark sites of hepatocyte loss. The second pattern of cell death, **apoptosis**, is more conspicuous. It is caused by anti-viral cytotoxic T cells. Apoptotic hepatocytes shrink, become intensely eosinophilic, and have fragmented nuclei; effector T cells may still be present in the immediate vicinity. Apoptotic cells also are phagocytosed within hours by macrophages and hence might be difficult to find despite a brisk rate of hepatocyte injury. In severe cases of acute hepatitis (not depicted in Fig. 18-17*A*), confluent necrosis of hepatocytes may lead to **bridging necrosis** connecting portal-to-portal, central-to-central, or portal-to-central regions of adjacent lobules. Hepatocyte swelling and regeneration compress sinusoids, and the more or less radial array of the parenchyma is lost.

Inflammation is a characteristic and usually prominent feature of acute hepatitis. **Kupffer cells undergo hypertrophy and hyperplasia** and are often laden with lipofuscin pigment due to phagocytosis of hepatocellular debris. **The portal tracts are usually infiltrated with a mixture of inflammatory cells.** The inflammatory infiltrate may spill over into the adjacent parenchyma to cause necrosis of periportal hepatocytes; this **"interface hepatitis"** can occur in both acute and chronic hepatitis. Finally, bile duct epithelia may become reactive and even

proliferate to form poorly defined ductular structures (ductular reaction), particularly in cases of HCV hepatitis.

Chronic Hepatitis.

The histologic features of chronic hepatitis (Fig. 18-17*B* and Fig. 18-20) range from exceedingly mild to severe. In the mildest forms, significant inflammation is limited to portal tracts and consists of lymphocytes, macrophages, occasional plasma cells, and rare neutrophils or eosinophils. Liver architecture is usually well preserved, but smoldering hepatocyte necrosis throughout the lobule may occur in all forms of chronic hepatitis. Even in mild chronic hepatitis due to HCV infection, common findings are **lymphoid aggregates** and **bile duct damage** in the portal tracts and focally mild to moderate macrovesicular **steatosis**. In all forms of chronic hepatitis, continued **interface hepatitis** and **bridging necrosis** are harbingers of progressive liver damage. **The hallmark of irreversible liver damage is the deposition of fibrous tissue.** At first, only portal tracts exhibit increased fibrosis, but with time, **periportal** septal **fibrosis** occurs, followed by linking of fibrous septa between lobules (**bridging fibrosis**).

Continued loss of hepatocytes and fibrosis results in cirrhosis, with fibrous septae and hepatocyte regenerative nodules. This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad scars (Fig. 18-21). Historically, this pattern of cirrhosis has been termed **postnecrotic cirrhosis**, but it should be noted that the term "postnecrotic cirrhosis" has been applied to all forms of cirrhosis in which the liver shows large, irregular-sized nodules with broad scars, regardless of etiology. Autoimmune hepatitis, hepatotoxins (carbon tetrachloride, mushroom poisoning), pharmaceutical drugs (acetaminophen, α-methyldopa), and even alcohol (discussed later) may give rise to a cirrhotic liver with irregular-sized large nodules. In some cases that come to autopsy, the inciting cause of the so-called postnecrotic cirrhosis cannot be determined at all ("cryptogenic cirrhosis"). In essence, the morphology of the end-stage cirrhotic liver is neither helpful in determining the basis of the liver injury, nor can it be easily related to any specific set of clinical circumstances.

The clinical course of viral hepatitis is unpredictable. Patients may experience spontaneous remission or may have indolent disease without progression for many years. Conversely, some patients have rapidly progressive disease and develop cirrhosis within a few years. The major causes of death are cirrhosis, with liver failure and hepatic encephalopathy or massive hematemesis from esophageal varices, and hepatocellular carcinoma in those with long-standing HBV (particularly neonatal) or HCV infection.

Fulminant Hepatitis

When hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks, it is

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Figure 18-17 Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Bridging necrosis (and fibrosis) is shown only for chronic hepatitis; bridging necrosis may also occur in acute hepatitis (not shown).

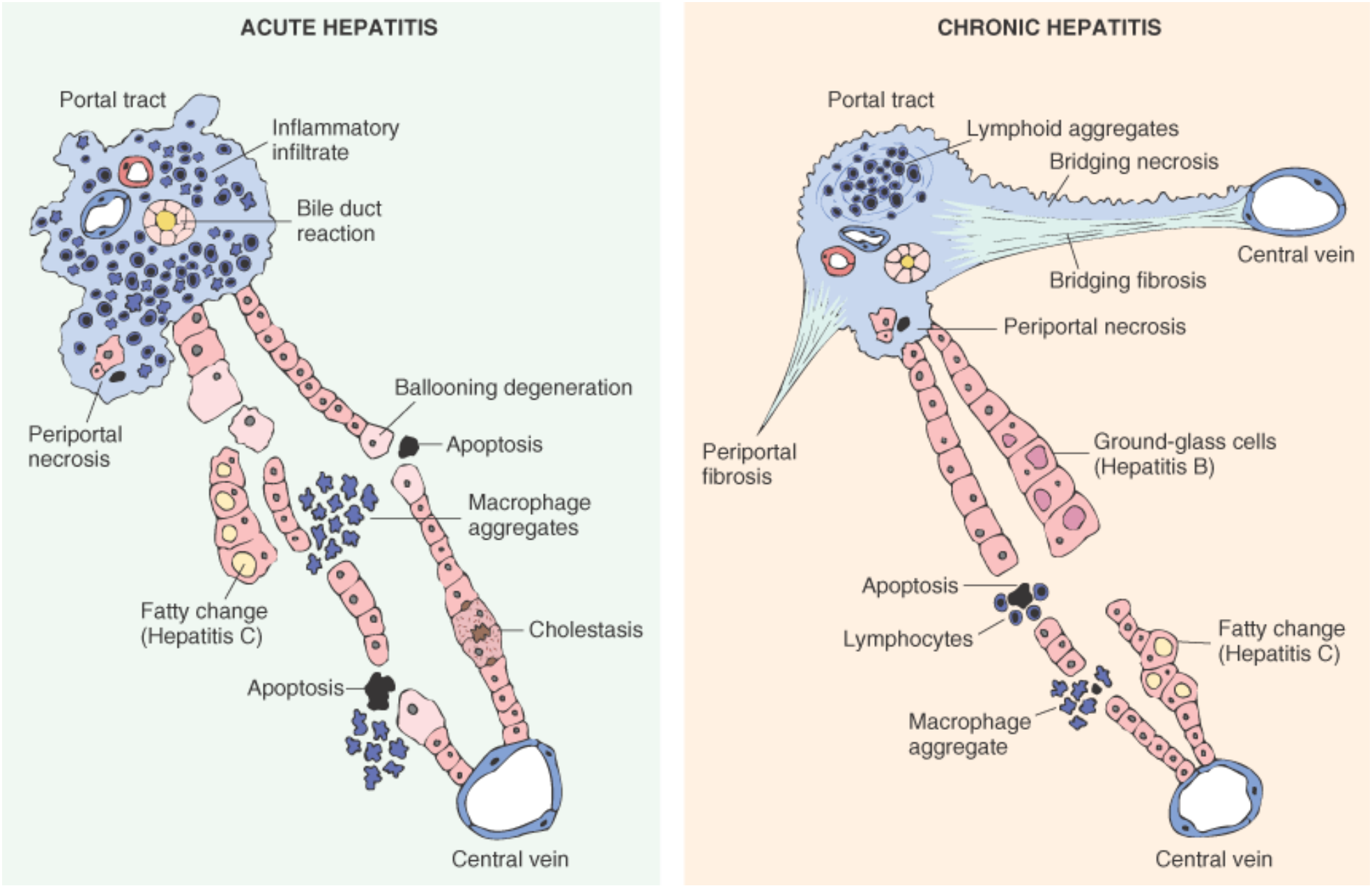


Figure 18-18 Hepatitis B viral infection. *A,* Liver parenchyma showing hepatocytes with diffuse granular cytoplasm, so-called ground glass hepatocytes. (H&E) *B,* Immunoperoxidase stain for HBsAg from the same case, showing cytoplasmic inclusions of viral particles.

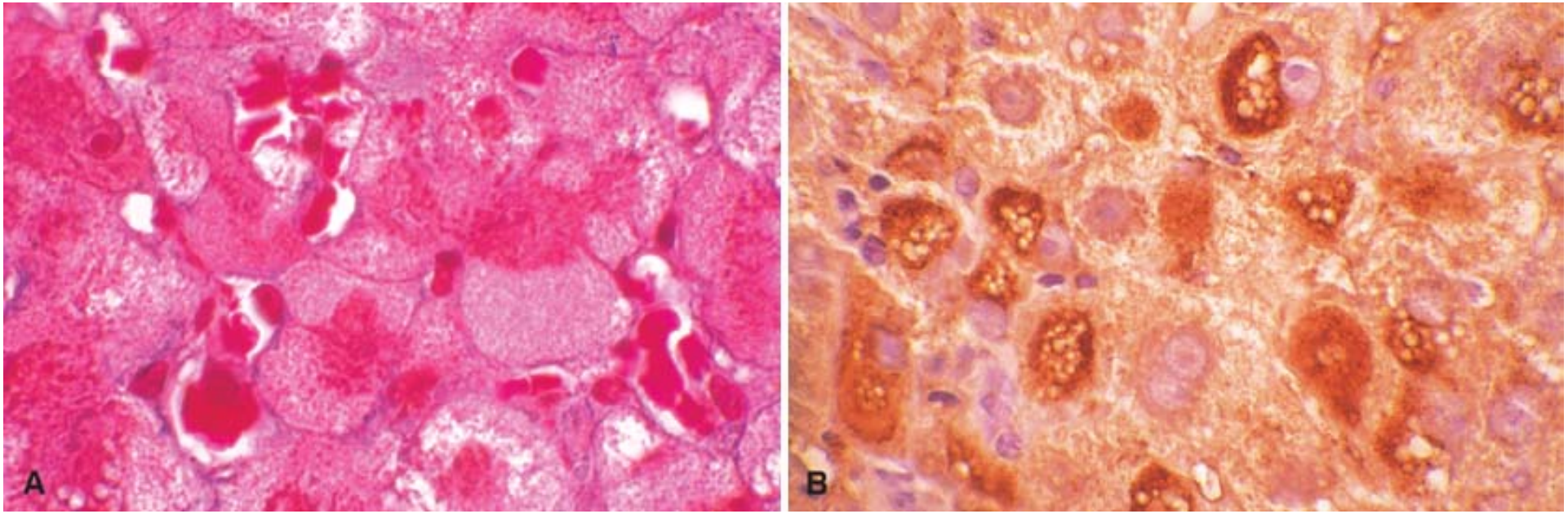


Figure 18-19 Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in the sinusoids, and hepatocellular apoptosis (*arrow*).

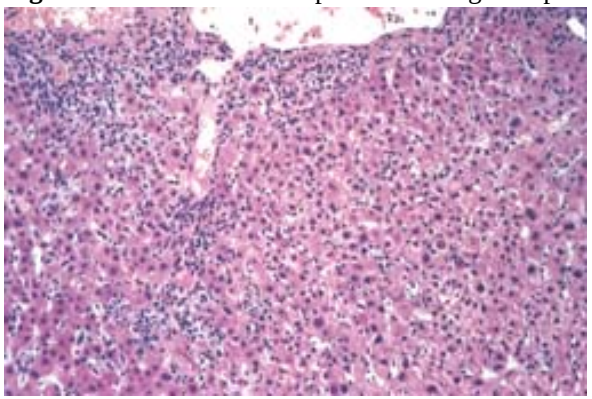


Figure 18-20 Chronic viral hepatitis due to hepatitis C virus, showing portal tract expansion with inflammatory cells and fibrous tissue and interface hepatitis with spillover of inflammation into the adjacent parenchyma. A lymphoid aggregate is present.

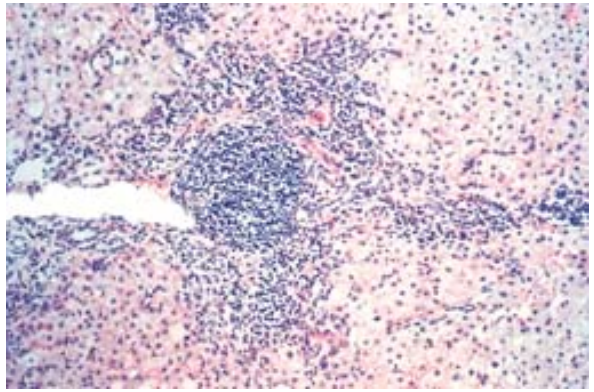


Figure 18-21 Cirrhosis resulting from chronic viral hepatitis. Note the broad scar and coarse nodular surface.

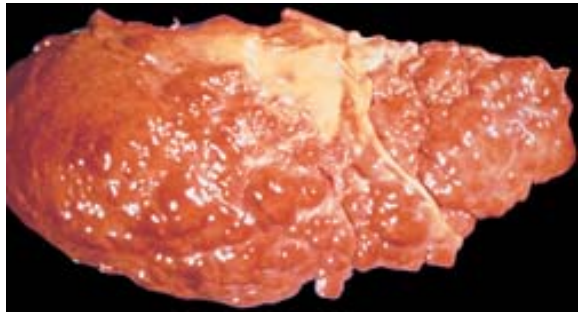
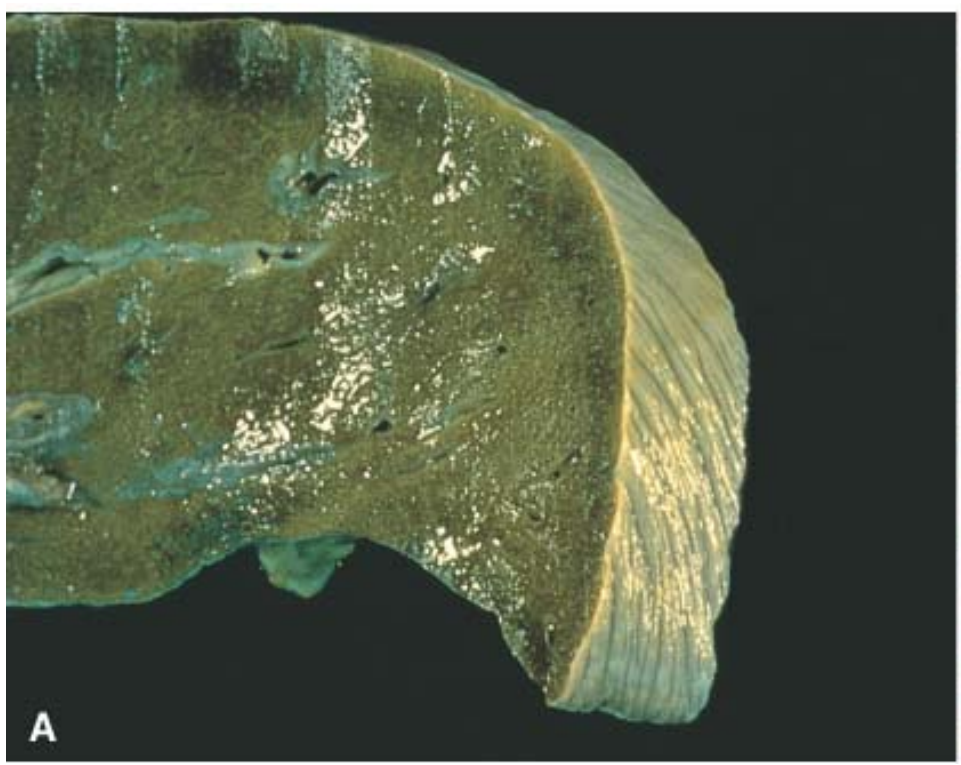


Figure 18-22 Massive necrosis. *A*, Cut section of liver. The liver is small (700 gm), bile-stained, and soft. The capsule is wrinkled. *B*, Microscopic section. Portal tracts and terminal hepatic veins are closer together than normal, owing to necrosis and collapse of the intervening parenchyma. The rudimentary ductal structures are the result of early ductular regeneration. An infiltrate of mononuclear inflammatory cells is present.



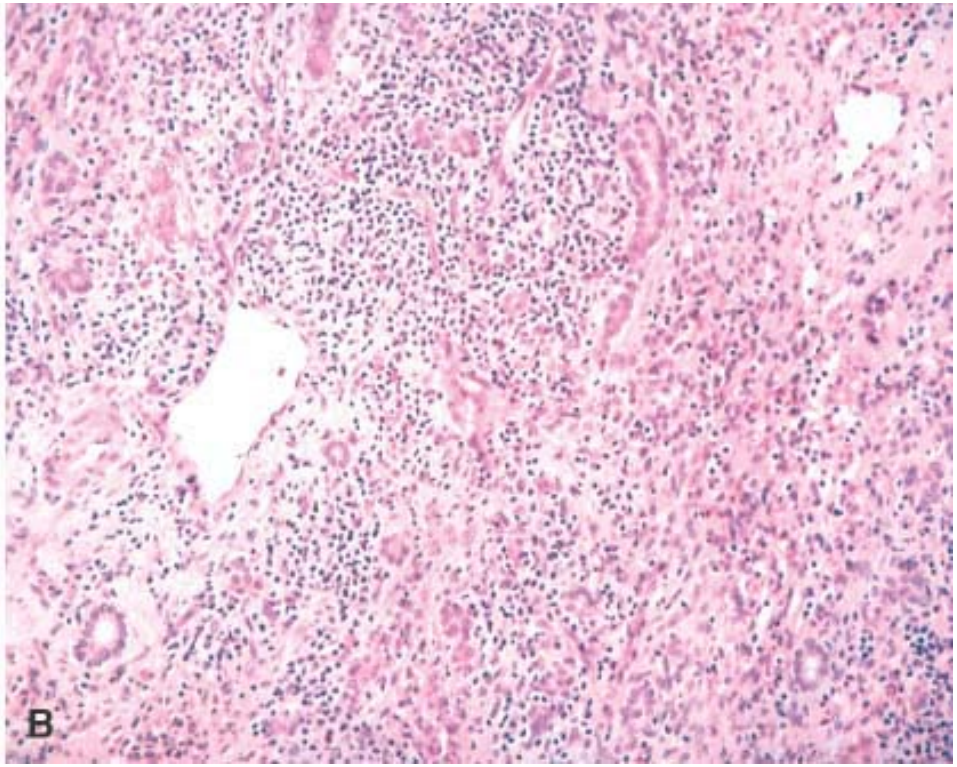


TABLE 18-8 -- Drug- and Toxin-Induced Hepatic Injury

Hepatocellular Damage	Examples
Microvesicular fatty change	• Tetracycline, salicylates, yellow phosphorus, ethanol
Macrovesicular fatty change	• Ethanol, methotrexate, amiodarone
Centrilobular necrosis	• Bromobenzene, CCl_4 , acetaminophen, halothane, rifampin
Diffuse or massive necrosis	• Halothane, isoniazid, acetaminophen, methyldopa, trinitrotoluene, *Amanita phalloides* (mushroom) toxin
Hepatitis, acute and chronic	• Methyldopa, isoniazid, nitrofurantoin, phenytoin, oxyphenisatin
Fibrosis-cirrhosis	• Ethanol, methotrexate, amiodarone, most drugs that cause chronic hepatitis
Granuloma formation	• Sulfonamides, methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol
Cholestasis (with or without hepatocellular injury)	• Chlorpromazine, anabolic steroids, erythromycin estolate, oral contraceptives, organic arsenicals

Among the agents listed in Table 18-8 , hepatic injury is considered predictable from overdoses of acetaminophen (also called phenacetin or paracetamol) and exposure to *Amanita phalloides* toxin, carbon tetrachloride, and, to a certain extent, alcohol. However, individual genetic differences in the hepatic metabolism of xenobiotics through activating and detoxification pathways play a major role in individual susceptibility to "predictable" hepatotoxins. Many other xenobiotics, such as sulfonamides, α-methyldopa, and allopurinol, cause idiosyncratic reactions. *Reye syndrome*, a potentially fatal syndrome of mitochondrial dysfunction in liver, brain, and elsewhere, occurs predominantly in children who are given acetylsalicylic acid (aspirin) for the relief of virus-induced fever. This disease, which features extensive accumulation of fat droplets within hepatocytes (microvesicular steatosis), is

exceedingly rare. A causal relationship with use of salicylates was never established, but a national campaign in the 1970s and 1980s warning against the use of aspirin in children with febrile illness might have served to break the Reye syndrome epidemic.

Drug-induced liver disease is usually followed by recovery upon removal of the drug. *Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of liver disease.*

Figure 18-23 Alcoholic liver disease. The interrelationships among hepatic steatosis, hepatitis, and cirrhosis are shown, along with a depiction of key morphologic features at the morphologic level.

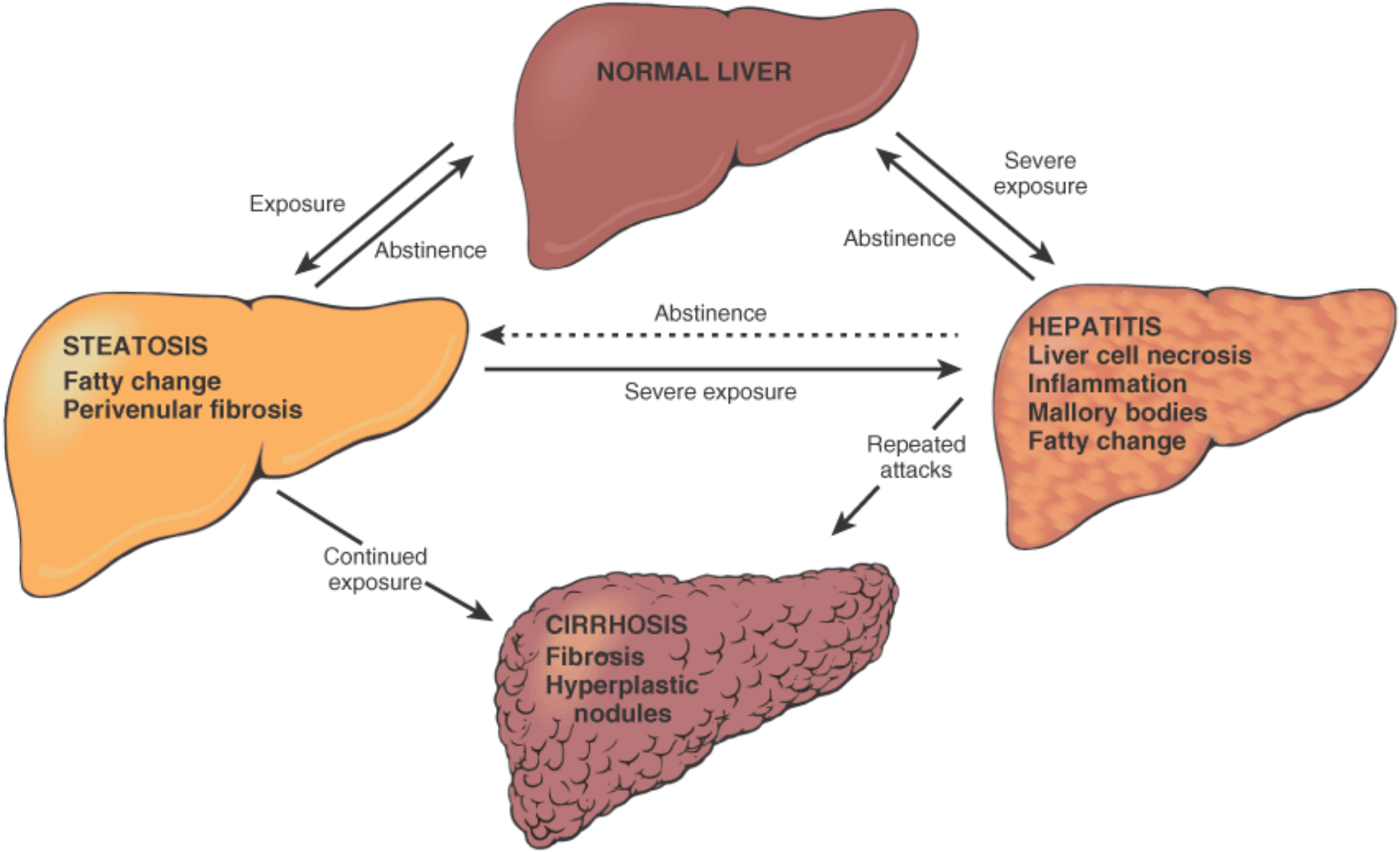


Figure 18-24 Alcoholic liver disease: macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles. Some early fibrosis (stained blue) is present (Masson trichrome).

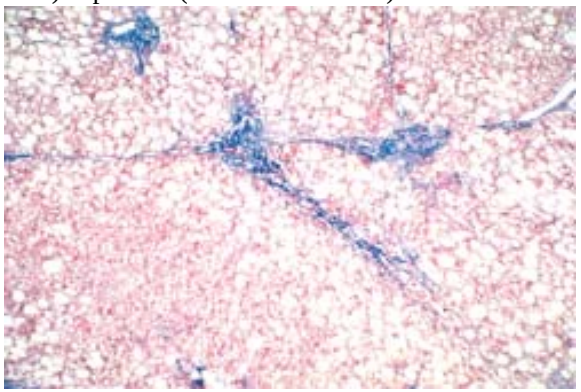


Figure 18-25 Alcoholic hepatitis. *A*, The cluster of inflammatory cells marks the site of a necrotic hepatocyte. A Mallory body is present in a second hepatocyte (*arrow*). *B*, Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue (H&E).

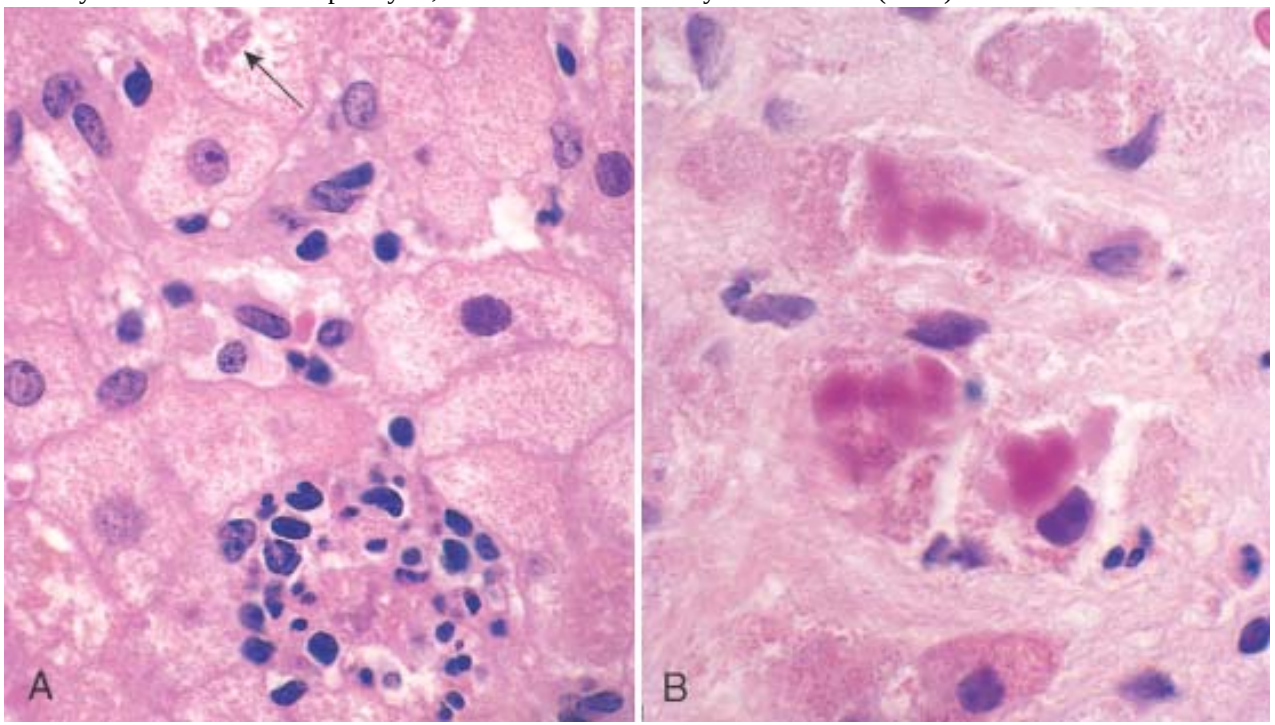
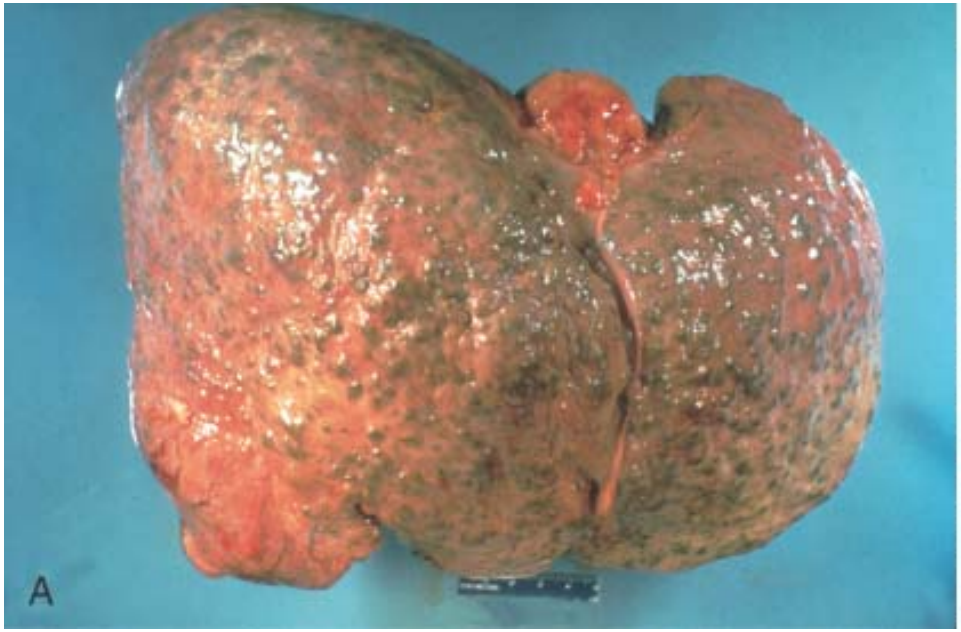


Figure 18-26 Alcoholic cirrhosis. *A*, The characteristic diffuse nodularity of the surface reflects the interplay between nodular regeneration and scarring. The greenish tint of some nodules is due to bile stasis. A hepatocellular carcinoma is present as a budding mass at the lower edge of the right lobe (lower left of figure). *B*, The microscopic view shows nodules of varying sizes entrapped in blue-staining fibrous tissue. The liver capsule is at the top (Masson trichrome).



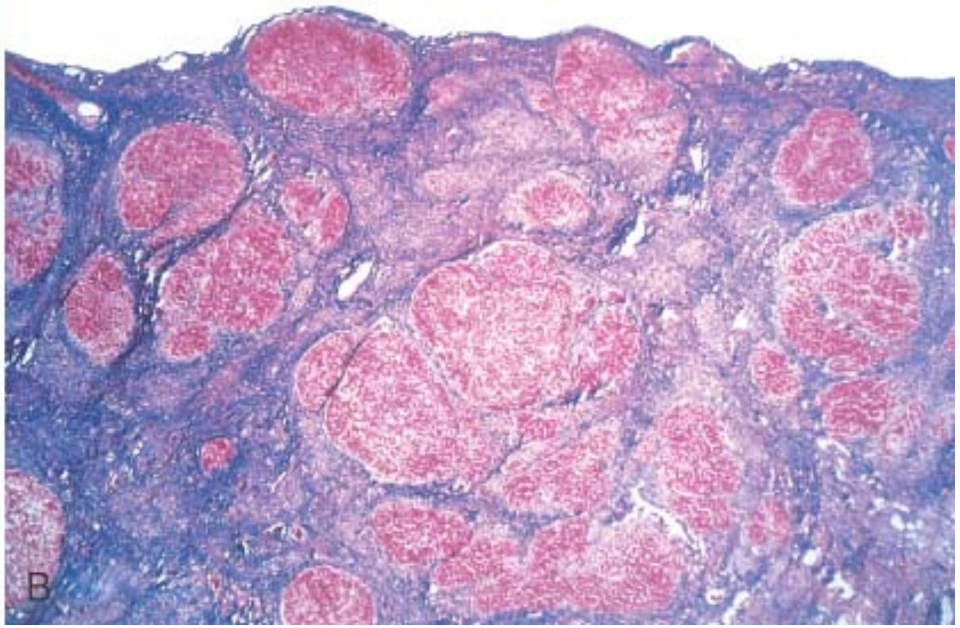


TABLE 18-9 -- Classification of Iron Overload

I. Hereditary Hemochromatosis
II. Secondary Hemochromatosis
••••A. Parenteral iron overload
•••••••Transfusions
••••••••••Long-term hemodialysis
••••••••••Aplastic anemia
••••••••••Sickle cell disease
••••••••••Myelodysplastic syndromes
••••••••••Leukemias
•••••••Iron-dextran injections
••••B. Ineffective erythropoiesis with increased erythroid activity
•••••••β-Thalassemia
•••••••Sideroblastic anemia
•••••••Pyruvate kinase deficiency
••••C. Increased oral intake of iron
•••••••African iron overload (Bantu siderosis)

••••D. Congenital atransferrinemia
••••E. Chronic liver disease
•••••••Chronic alcoholic liver disease
•••••••Porphyria cutanea tarda

In white populations of northern European extraction, the frequency of the C282Y mutation is estimated at 6.4% to 9.5%.[4] The frequency of homozygosity is 0.45% (1 of every 220 persons), and that for heterozygosity is 11% (1 of every 9 persons), making hereditary hemochromatosis one of the most common genetic disorders in humans. However, the penetrance of this disorder is only about 20% in patients with the homozygous C282Y mutation, so the genetic condition does not lead to disease in all individuals.

Pathogenesis.

It may be recalled that the total body content of iron is tightly regulated, as the limited daily losses of iron are matched by gastrointestinal absorption. *In hereditary hemochromatosis, regulation of intestinal absorption of dietary iron is lost, leading to net iron accumulation of 0.5 to 1.0 gm/year.* The disease manifests itself typically after 20 gm of storage iron have accumulated.

The critical site for HFE expression appears to be the basolateral surface of the small intestinal crypt epithelial cell, where it is prominently expressed. According to the current hypothesis (Fig. 18-27),[32] [33] HFE complexes with the transferrin receptor, TfR, enabling the binding of plasma transferrin and its bound iron. The TfR-Tf-iron complex is endocytosed into the crypt enterocyte; acidification of the endosome releases iron into the regulatory iron pool of the crypt cell. This is a sensing mechanism for the systemic iron balance, as increased levels of circulating iron bound to transferrin will lead to an increased iron regulatory pool in enterocytes. This pool "sets" the level of expression of apical iron uptake systems. *Crypt cells with mutant HFE lack the facilitating effect on TfR-dependent iron uptake, thus decreasing the regulatory iron pool in the crypt cell.* As small intestinal crypt cells are the progenitors of villus absorptive cells, these cells are preprogrammed to absorb dietary iron regardless of the systemic iron overload.

Excessive iron appears to be directly toxic to host tissues, by the following mechanisms: (1) lipid peroxidation via iron-catalyzed free radical reactions, (2) stimulation of collagen formation, and (3) interactions of reactive oxygen species and of iron itself with DNA, leading to lethal injury or predisposition to hepatocellular carcinoma. Whatever the actions of iron, they are reversible in cells that are not fatally injured, and removal of excess iron during therapy promotes recovery of tissue function.

The most common causes of secondary hemochromatosis are the hemolytic anemias associated with ineffective erythropoiesis, discussed in Chapter 13 . In these disorders, the excess iron may result not only from transfusions, but also from increased absorption. Transfusions alone, as in aplastic

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Figure 18-27 Schematic diagram of HFE function in the intestine. The *crypt epithelial cell* expresses HFE on its basolateral surface; complexing of HFE with β_2 -microglobulin is required for its expression on the cell surface. HFE-β_2 -microglobulin complexes with the transferrin receptor (TfR) to bind circulating transferring (Tf). Endocytosis ensues; on acidification of the recycling endosome, transferrin-bound iron (Fe(II)) is released and enters into the cytoplasm. High levels of cytoplasmic iron downregulate levels of the iron-regulatory proteins (IRP), a family of proteins with potent effects on nuclear transcription. With low levels of cytoplasmic iron, the IRP content of the cell remains high. IRPs upregulate nuclear transcription of the genes for several proteins required for intestinal absorption of dietary iron: Dcytb (duodenal cytochrome B), DMT1 (divalent metal transporter 1), ferritin (a cytoplasmic iron-binding protein), and FP1 (ferroportin 1). *A mutation in HFE prevents "sensing" of circulating iron levels by the crypt epithelial cell, leading to unregulated expression of these four proteins.* The

crypt epithelial cell is the precursor cell of the *mature absorptive enterocyte* on the tip of the villus, through migration up the villus axis. On the apical membrane of the absorptive enterocyte, Dcytb reduces dietary ferric iron (Fe(III)) to ferrous iron (Fe(II)). Fe(II) is then taken up by DMT1 into the enterocyte. Iron can be bound to ferritin (and hence sloughed back into the gut lumen) or transported across the basolateral plasma membrane by FP1 for binding to transferrin and entry into the systemic circulation. *In the patient with mutant HFE, the inability to downregulate expression of these four proteins leads to lifelong excessive absorption of dietary iron.*

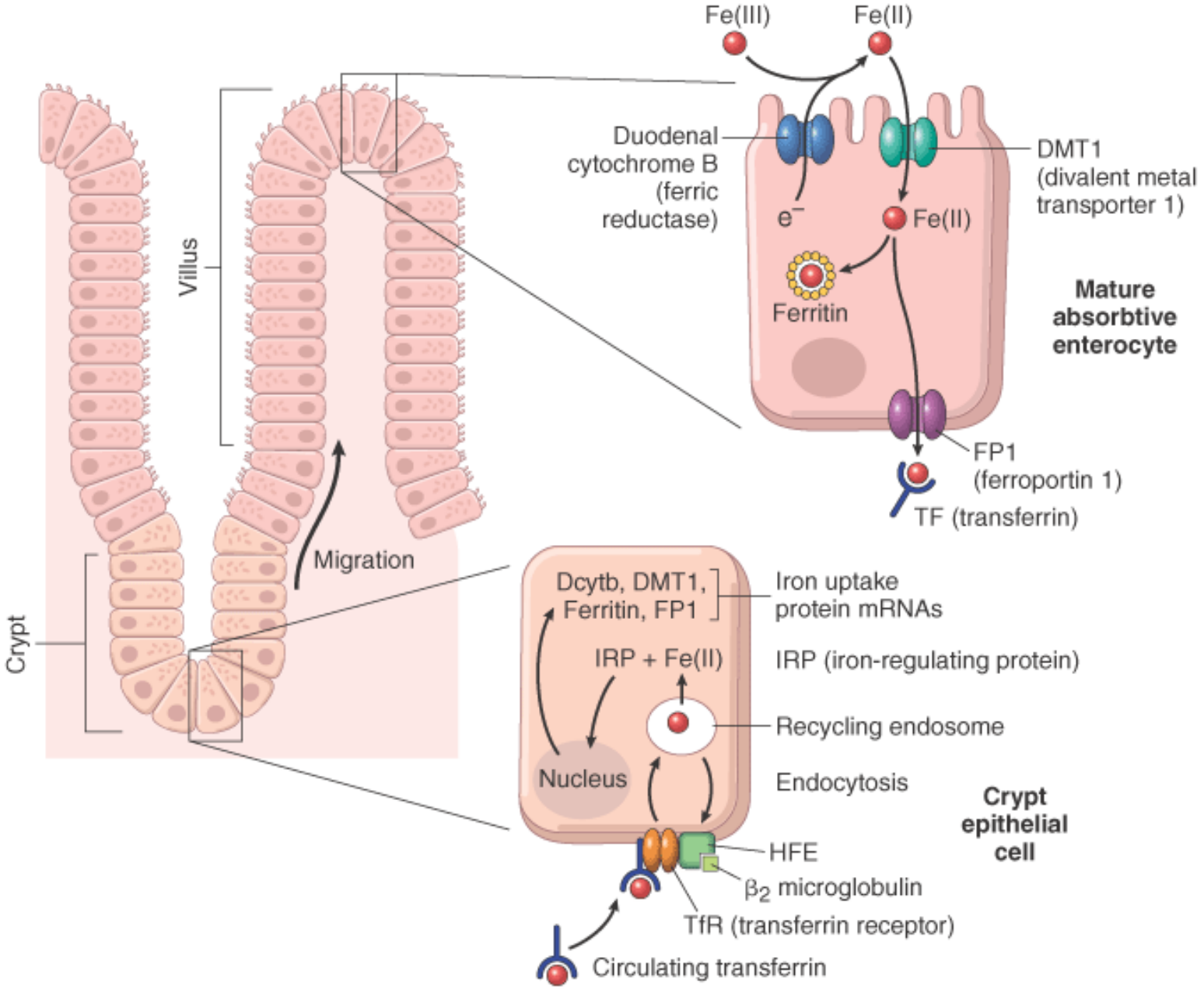

Figure 18-28 Hereditary hemochromatosis. Hepatocellular iron deposition is blue in this Prussian blue-stained section of an early stage of the disease, in which parenchymal architecture is normal.

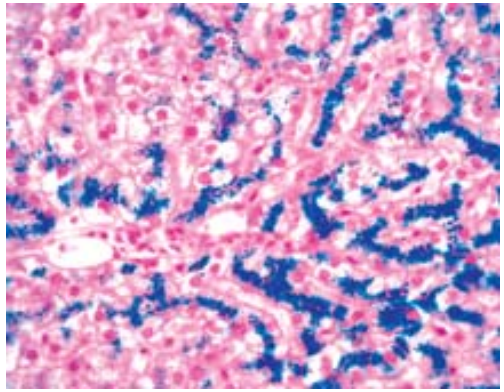

Figure 18-29 α_1 -Antitrypsin deficiency. Periodic acid-Schiff stain of the liver, highlighting the characteristic red cytoplasmic granules. *(Courtesy of Dr. I. Wanless, Toronto General Hospital, Toronto, Ontario, Canada.)*

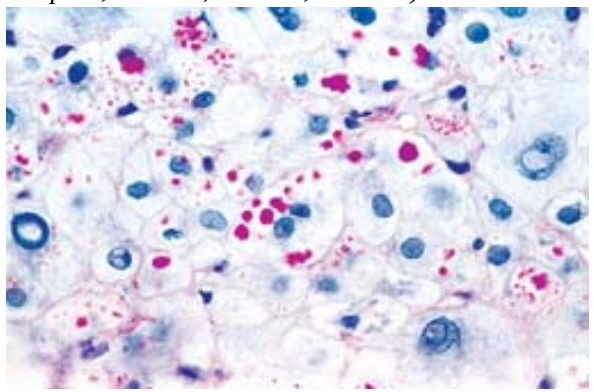

TABLE 18-10 -- Major Causes of Neonatal Cholestasis

Bile duct obstruction
••Extrahepatic biliary atresia
Neonatal infection
••Cytomegalovirus
••Bacterial sepsis
••Urinary tract infection
••Syphilis
Toxic
••Drugs
••Parenteral nutrition

Metabolic disease
••Tyrosinemia
••Niemann-Pick disease
••Galactosemia
••Defective bile acid synthetic pathways
••α_1 -Antitrypsin deficiency
••Cystic fibrosis
Miscellaneous
••Shock/hypoperfusion
••Indian childhood cirrhosis
••Alagille syndrome (paucity of bile ducts)
Idiopathic neonatal hepatitis

NEONATAL CHOLESTASIS

Prolonged conjugated hyperbilirubinemia in the neonate, termed *neonatal cholestasis*, affects approximately 1 in 2500 live births. The major conditions causing it are (1) cholangiopathies, primarily *biliary atresia* (discussed later) and (2) a variety of disorders causing conjugated hyperbilirubinemia in the neonate, collectively referred to as *neonatal hepatitis*. *Neonatal cholestasis and hepatitis are not specific entities, nor are the disorders necessarily inflammatory.* Instead, the finding of "neonatal cholestasis" should evoke a diligent search for recognizable toxic, metabolic, and infectious liver diseases, the more common of which are listed in Table 18-10 .[38] Once identifiable causes have been excluded, one is left with the syndrome of "idiopathic" neonatal hepatitis, which shows considerable clinical overlap with biliary atresia.

Affected infants have jaundice, dark urine, light or acholic stools, and hepatomegaly. Variable degrees of hepatic synthetic dysfunction may be identified, such as hypoprothrombinemia. Thus, liver biopsy is critical in distinguishing neonatal hepatitis from an identifiable cholangiopathy.

Morphology.

The morphologic features of neonatal hepatitis are:

- Lobular disarray with focal liver cell necrosis
- Panlobular giant cell transformation of hepatocytes and formation of hepatocyte "rosettes": radially arrayed hepatocytes
- Prominent hepatocellular and canalicular cholestasis
- Mild mononuclear infiltration of the portal areas
- Reactive changes in the Kupffer cells
- Extramedullary hematopoiesis

This predominantly parenchymal pattern of injury may blend imperceptibly into a ductal pattern of injury, with bile ductular proliferation and fibrosis of

portal tracts. Clear distinction from an obstructive cholangiopathy may therefore be impossible. Specific features that point toward a particular etiology include the inclusions of cytomegalovirus, or fatty change with cirrhosis in galactosemia and tyrosinemia. Electron microscopy may be helpful, for example, by showing phospholipid whorls in Neimann-Pick disease.

Despite the long list of disorders associated with neonatal cholestasis, most are quite rare. "Idiopathic" neonatal hepatitis represents up to 50% of cases, biliary atresia represents another 20%, and α_1 -antitrypsin deficiency represents 15%. Differentiation of biliary atresia from nonobstructive neonatal cholestasis assumes great importance, since definitive treatment of biliary atresia requires surgical intervention, whereas surgery may adversely affect the clinical course of a child with other disorders. Fortunately, discrimination can be made with clinical data, without or with liver biopsy, in about 90% of cases.

Intrahepatic Biliary Tract Disease

In this section, we discuss three disorders of intrahepatic bile ducts: secondary biliary cirrhosis, primary biliary cirrhosis, and primary sclerosing cholangitis, (summarized in Table 18-11). Secondary biliary cirrhosis is a condition resulting most often from uncorrected obstruction of the extrahepatic biliary tree. Primary biliary cirrhosis is a destructive disorder of the intrahepatic biliary tree. Primary sclerosing cholangitis involves both the extrahepatic and intrahepatic biliary tree. It should also be noted (although not discussed here) that intrahepatic bile ducts are frequently damaged as part of more general liver disease, as in drug toxicity, viral hepatitis, and transplantation—both orthotopic liver transplantation and graft-versus-host disease after bone marrow transplantation.

TABLE 18-11 -- Distinguishing Features of the Major Intrahepatic Bile Duct Disorders

	Secondary Biliary Cirrhosis	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head	Possibly autoimmune	Unknown, possibly autoimmune; 50–70% associated with inflammatory bowel disease
Sex predilection	None	Female to male: 6:1	Female to male: 1:2
Symptoms and signs	Pruritus, jaundice, malaise dark urine, light stools, hepatosplenomegaly	Same as secondary biliary cirrhosis; insidious onset	Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol	Same as secondary biliary cirrhosis, plus elevated serum IgM autoantibodies (especially M2 form of antimitochondrial antibody-AMA)	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts	Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

SECONDARY BILIARY CIRRHOSIS

Prolonged obstruction of the extrahepatic biliary tree results in profound alteration of the liver itself. The most common cause of obstruction in adults is extrahepatic cholelithiasis

(gallstones, described later), followed by malignancies of the biliary tree or head of the pancreas and strictures resulting from previous surgical procedures. Obstructive conditions in children include biliary atresia, cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree, see later), and syndromes in which there are insufficient intrahepatic bile ducts (paucity of bile duct syndromes).[39] The initial morphologic features of *cholestasis* were described earlier and are entirely reversible with correction of the obstruction. However, secondary inflammation resulting from biliary obstruction initiates periportal fibrosis, which eventually leads to hepatic scarring and nodule formation, generating secondary biliary cirrhosis. Subtotal obstruction may promote secondary bacterial infection of the biliary tree (*ascending cholangitis*), which aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common culprits.

Morphology.

The end-stage obstructed liver exhibits extraordinary yellow-green pigmentation and is accompanied by marked icteric discoloration of body tissues and fluids. On cut surface, the liver is hard, with a finely granular appearance (Fig. 18-30). The histology is characterized by coarse fibrous septae that subdivide the liver in a jigsaw-like pattern. Embedded in the septa are distended small and large bile ducts, which frequently contain inspissated pigmented material. There is extensive proliferation of smaller bile ductules and edema, particularly at the interface between septa (formerly portal tracts) and the parenchyma. Cholestatic features in the parenchyma may be severe, with extensive feathery degeneration and formation of bile lakes. However, once regenerative nodules have formed, bile stasis

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Figure 18-30 Biliary cirrhosis. Sagittal section through the liver demonstrates the fine nodularity and bile staining of end-stage biliary cirrhosis.

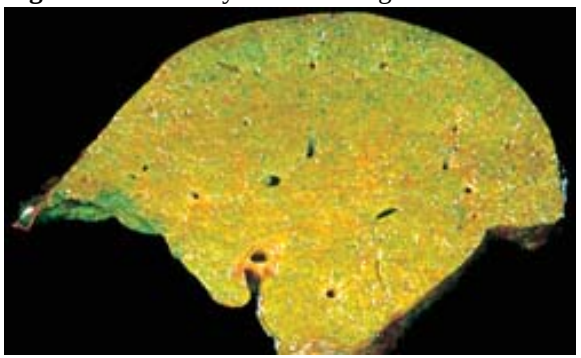


Figure 18-31 Primary biliary cirrhosis. A portal tract is markedly expanded by an infiltrate of lymphocytes and plasma cells. The granulomatous reaction to a bile duct undergoing destruction (florid duct lesion) is highlighted by the arrowheads.

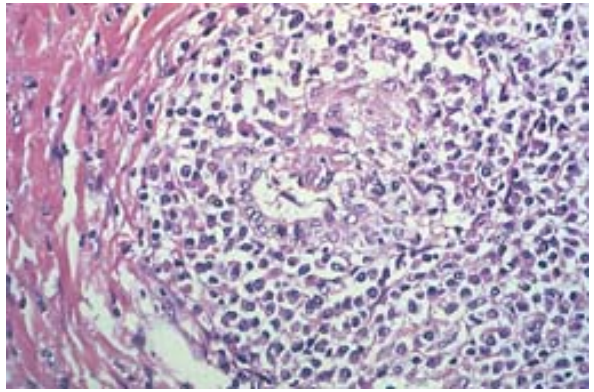


Figure 18-32 Primary sclerosing cholangitis. A bile duct under-going degeneration is entrapped in a dense, "onion-skin" concentric scar.

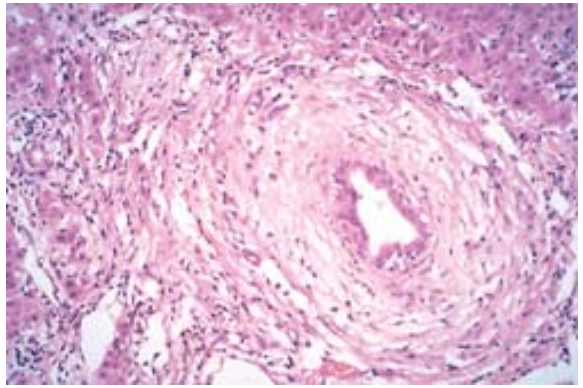
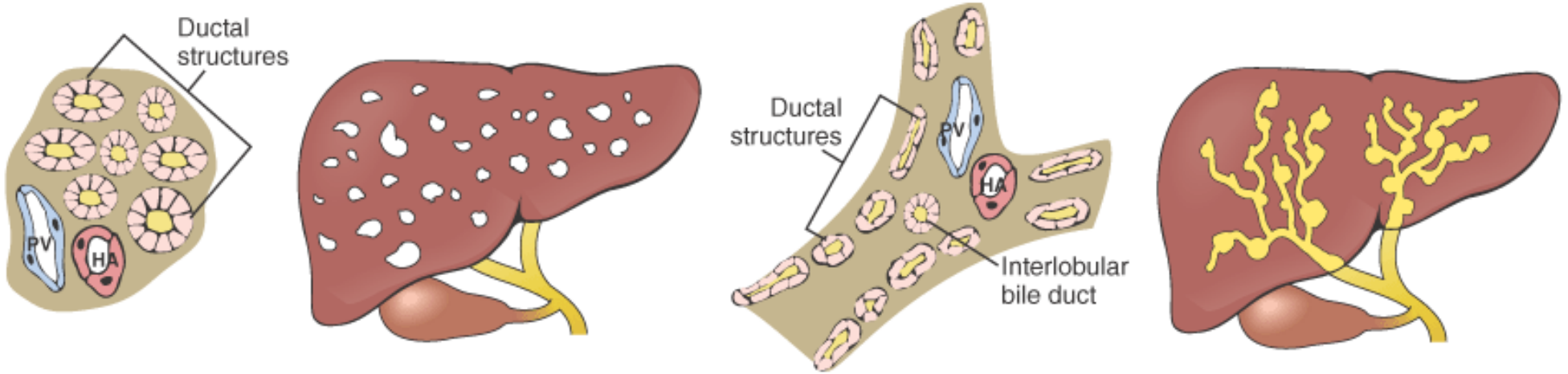


Figure 18-33 Bile duct anomalies. The morphologic features of the four major groups are diagrammed, along with apparent patterns of inheritance and associations with polycystic kidney disease. PV, portal vein. HA, hepatic artery.



	von Meyenburg Complex	Polycystic Liver Disease	Congenital Hepatic Fibrosis	Caroli Disease
INHERITANCE:	Sporadic	Autosomal Dominant	Autosomal Recessive	Autosomal Recessive
ASSOCIATION WITH POLYCYSTIC KIDNEY DISEASE (PKD)				
Autosomal dominant PKD:	+	+ + +	+	+
Autosomal recessive PKD:	-	-	+ + +	+

Figure 18-34 Hepatic circulatory disorders. The forms and clinical manifestations of impaired blood flow are contrasted.

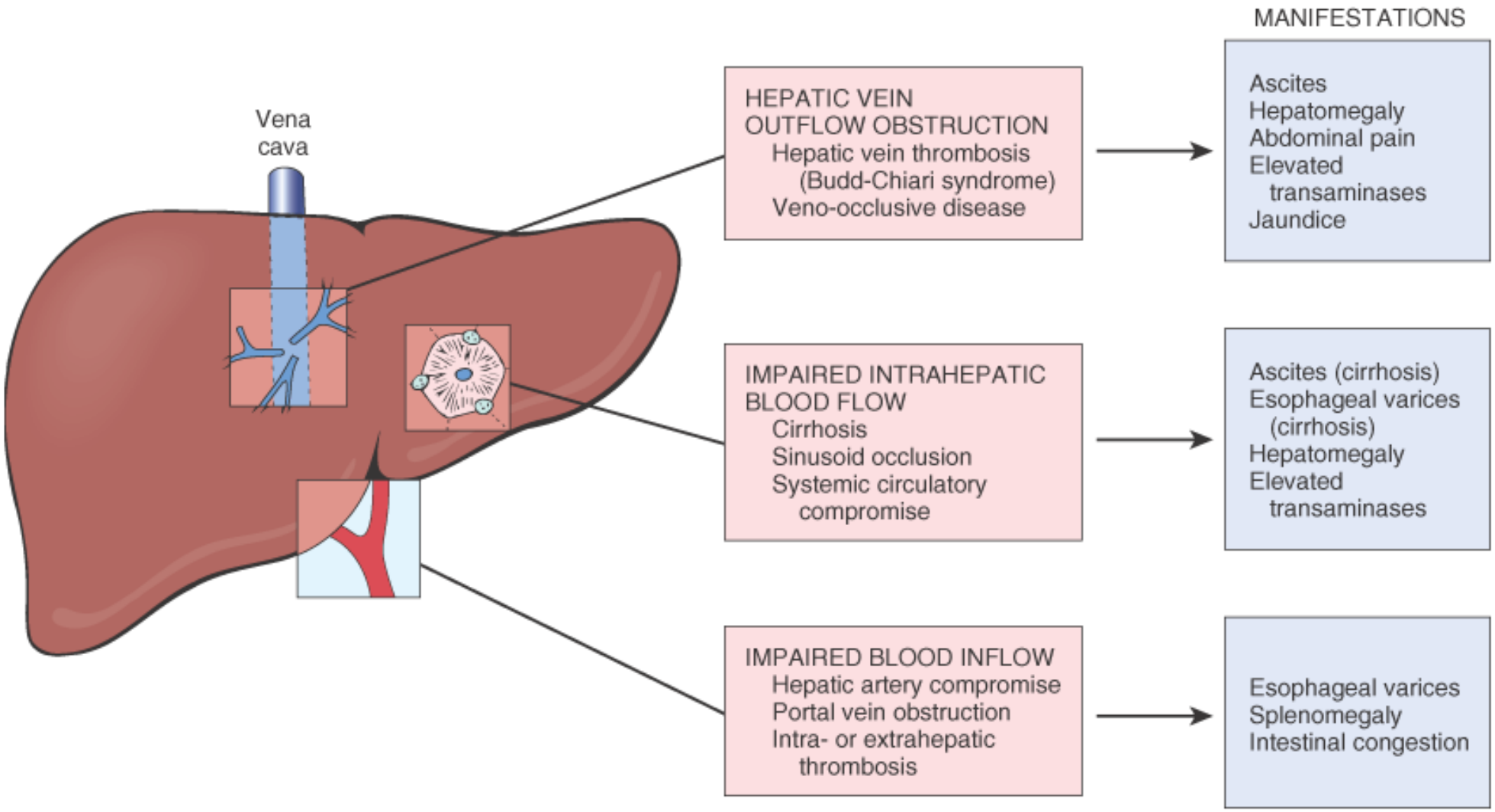


Figure 18-35 Liver infarct. A thrombus is lodged in a peripheral branch of the hepatic artery and compresses the adjacent portal vein; the distal hepatic tissue is pale, with a hemorrhagic margin.

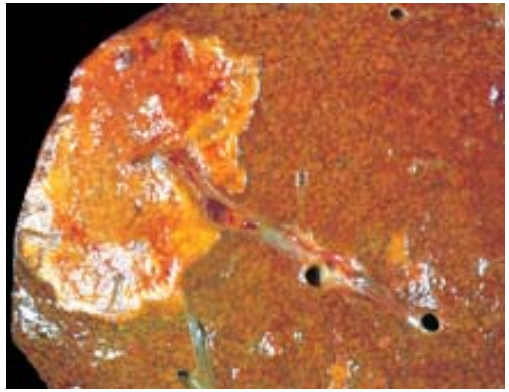


Figure 18-36 Centrolobular hemorrhagic necrosis. The cut liver section, in which major blood vessels are visible, is notable for a variegated, mottled, red appearance (nutmeg liver).

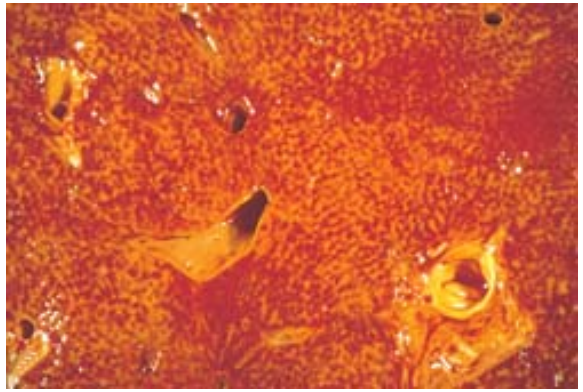


Figure 18-37 Budd-Chiari syndrome. Thrombosis of the major hepatic veins has caused extreme blood retention in the liver.

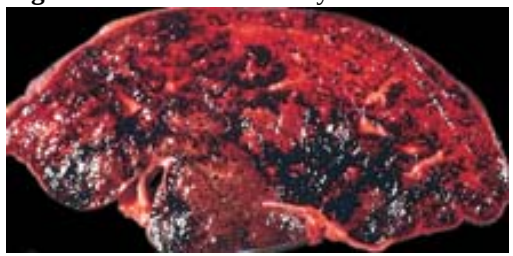


Figure 18-38 Veno-occlusive disease. A reticulin stain reveals the parenchyma framework of the lobule and the marked deposition of collagen within the lumen of the central vein.

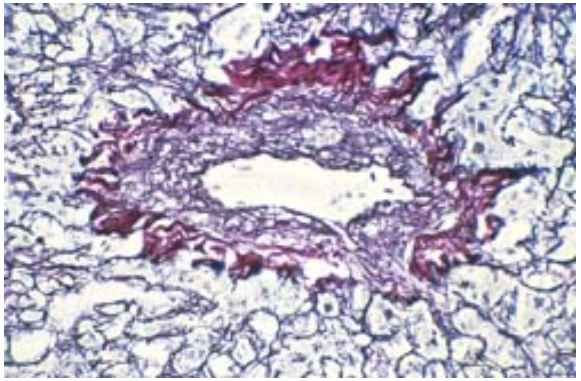


Figure 18-39 Eclampsia. Subcapsular hematoma dissecting under Glisson's capsule in a fatal case of eclampsia. *(Courtesy of Dr. Brian Blackbourne, Office of the Medical Examiner, San Diego, CA.)*

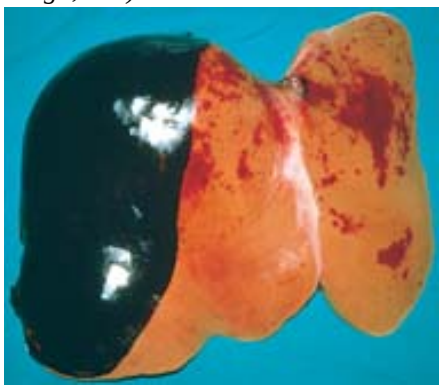


Figure 18-40 Focal nodular hyperplasia. *A,* Resected specimen showing lobulated contours and a central stellate scar. *B,* Low-power photomicrograph showing a broad fibrous scar with hepatic arterial and bile duct elements and chronic inflammation, present within hepatic parenchyma that lacks the normal sinusoidal plate architecture (H&E).

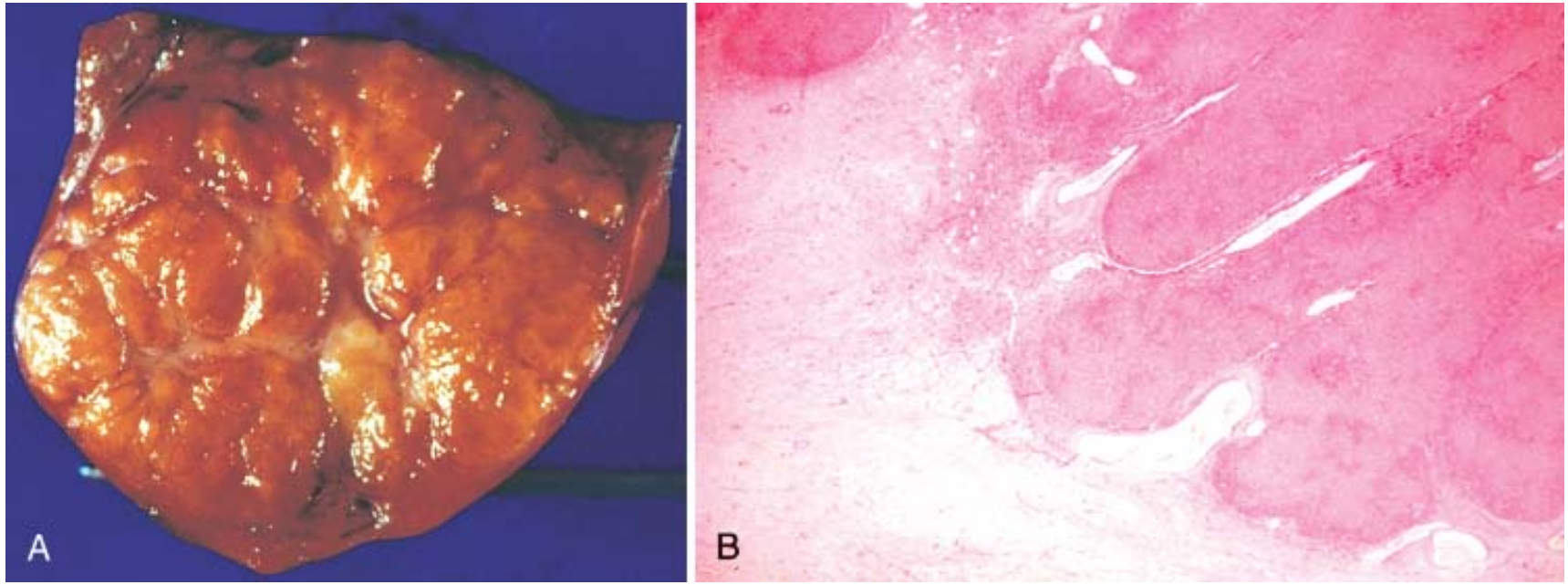


Figure 18-41 Nodular regenerative hyperplasia. Autopsied liver showing diffuse nodular transformation.

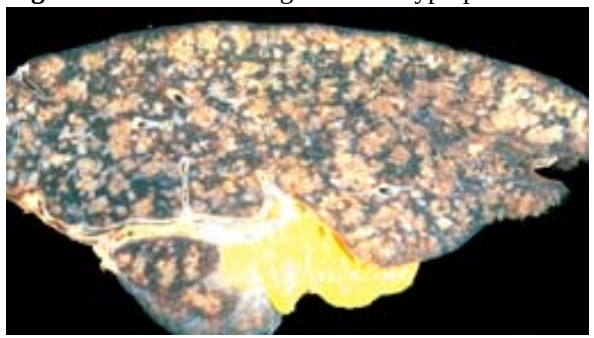


Figure 18-42 Liver cell adenoma. *A*, Resected specimen presenting as a pendulous mass arising from the liver. *B*, Microscopic view showing cords of hepatocytes, with an arterial vascular supply (*arrows*) and no portal tracts.

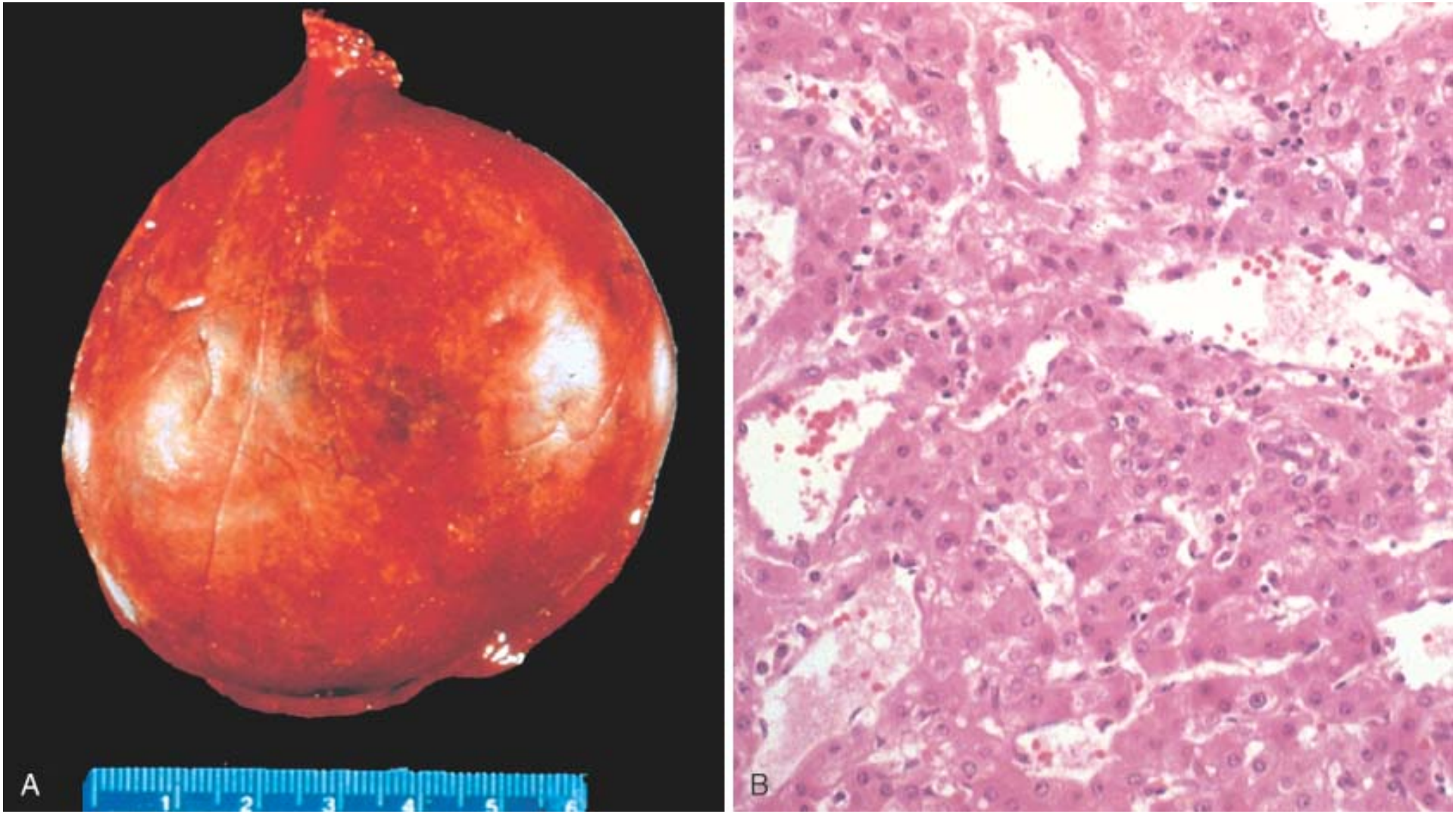


Figure 18-43 Hepatocellular carcinoma. *A,* Autopsied liver showing a unifocal, massive neoplasm replacing most of the right hepatic lobe in a noncirrhotic liver; a satellite tumor nodule is directly adjacent. *B,* In this microscopic view of a well-differentiated lesion, tumor cells are arranged in nests, sometimes with a central lumen, one of which contains bile (*arrow*). Other tumor cells contain intracellular bile pigment.

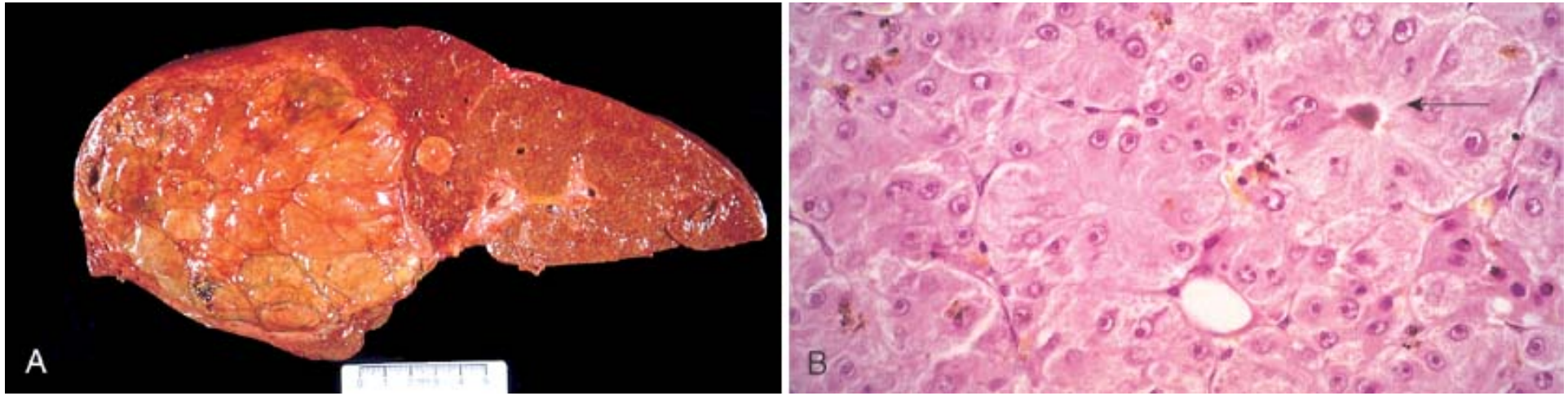


Figure 18-44 Fibrolamellar carcinoma. *A*, Resected specimen showing a demarcated nodule in an otherwise normal liver. *B*, Microscopic view showing nests and cords of malignant-appearing hepatocytes separated by dense bundles of collagen.

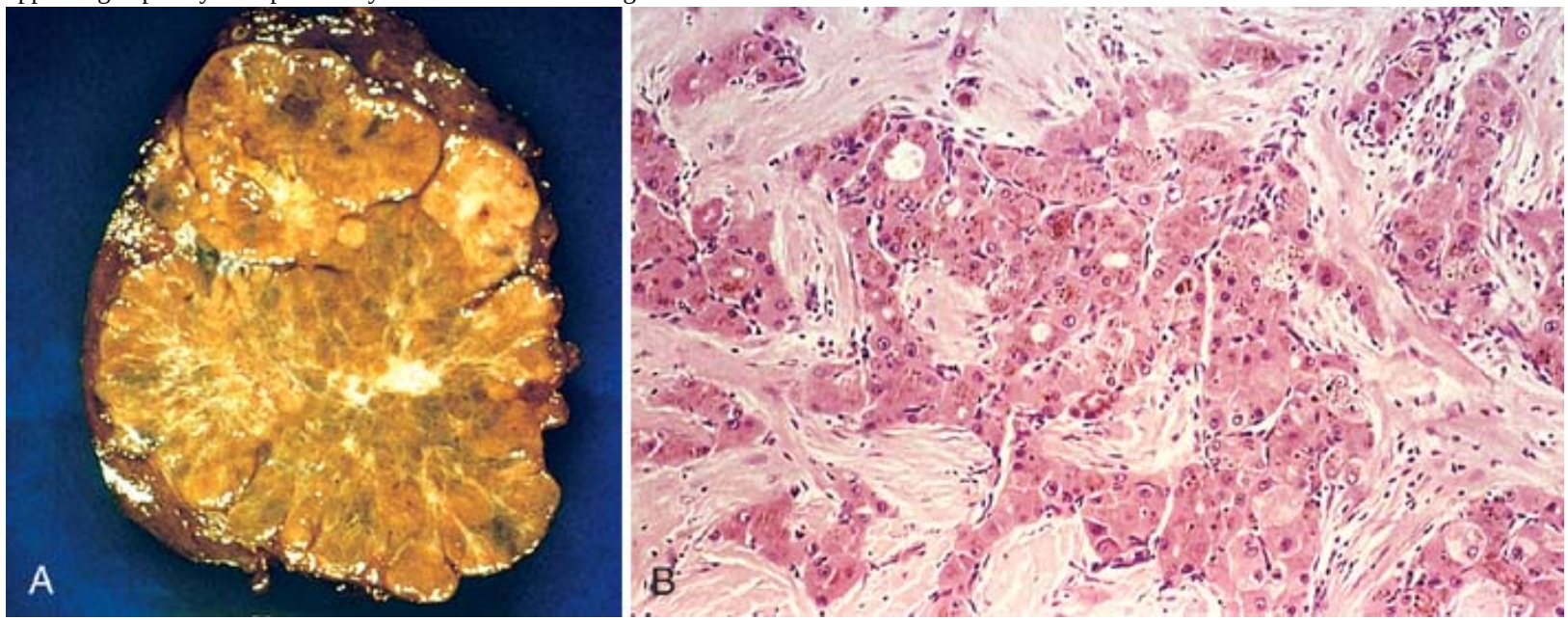


Figure 18-45 Cholangiocarcinoma. *A*, Autopsied liver showing a massive neoplasm in the right hepatic lobe and innumerable metastases permeating the entire liver. *B*, Microscopic view showing tubular glandular structures embedded in a dense sclerotic stroma.

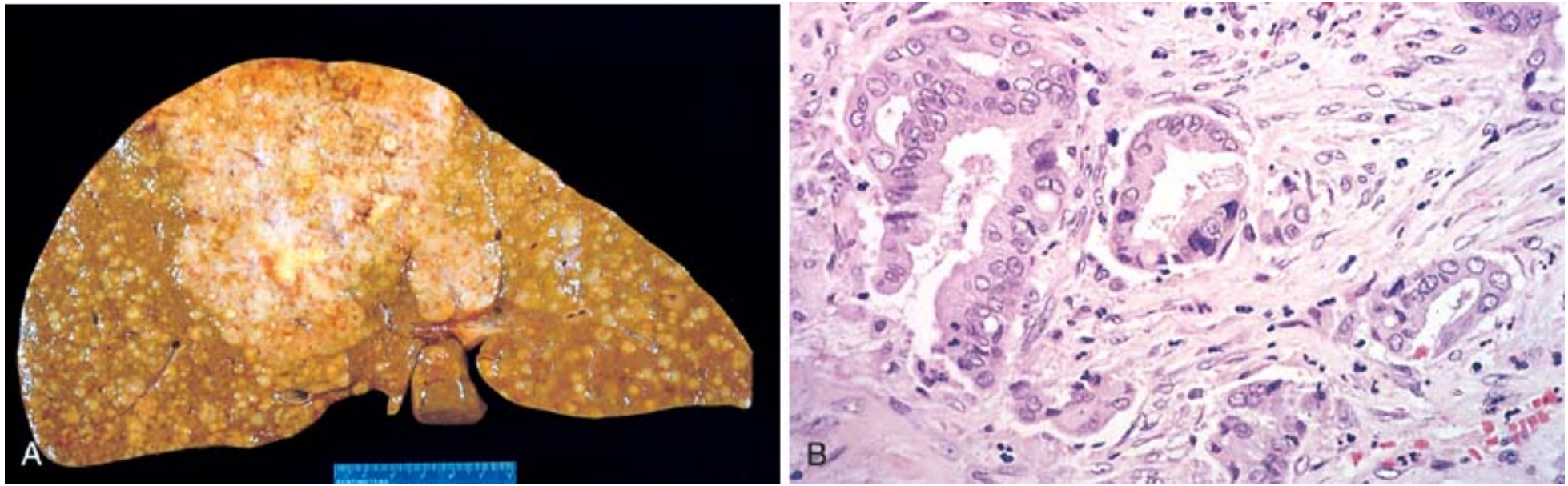


Figure 18-46 Multiple hepatic metastases from a primary colon adenocarcinoma.

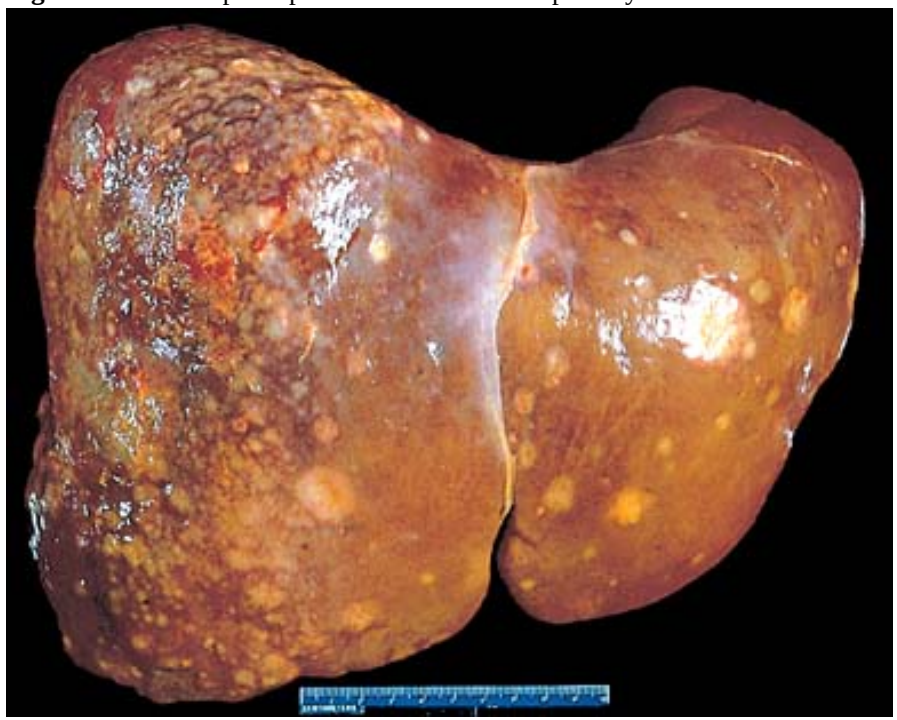


Figure 18-47 Normal gallbladder histology. The undulating mucosal epithelium overlies a delicate lamina and only one smooth muscle layer. This is different from elsewhere in the gut, where two muscle layers exist (muscularis mucosa and muscularis propria).

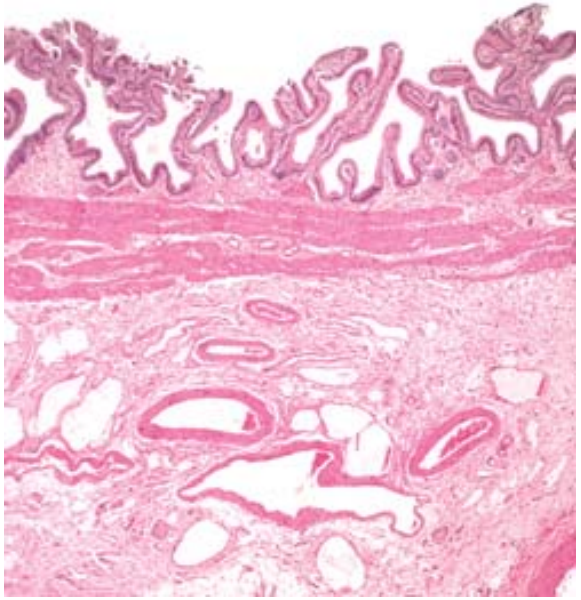


Figure 18-48 Phrygian cap of the gallbladder; the fundus is folded inward.

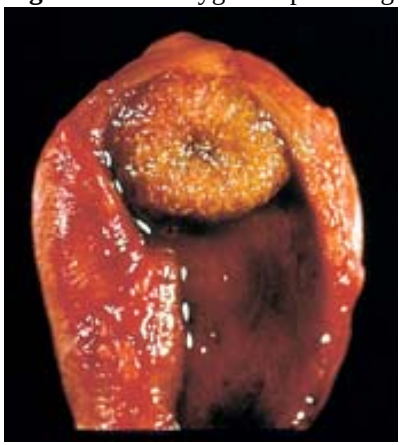


TABLE 18-12 -- Risk Factors for Gallstones

Cholesterol Stones
Demography: Northern Europe, North and South America, Native Americans, Mexican Americans
Advancing age
Female sex hormones
••Female gender
••Oral contraceptives

••Pregnancy
Obesity
Rapid weight reduction
Gallbladder stasis
Inborn disorders of bile acid metabolism
Hyperlipidemia syndromes
Pigment Stones
Demography: Asian more than Western, rural more than urban
Chronic hemolytic syndromes
Biliary infection
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

Hereditary Factors.

In addition to ethnicity, family history alone imparts increased risk, as do a variety of inborn errors of metabolism that (1) lead to impaired bile salt synthesis and secretion or (2) generate increased serum and biliary levels of cholesterol, such as defects in lipoprotein receptors (hyperlipidemia syndromes), which engender marked increases in cholesterol biosynthesis. Animal studies strongly implicate specific genetic susceptibilities, many attributable to aberrant regulation of the transport proteins responsible for the secretion of biliary solutes into bile. [61]

Certain risk factors are well established for the development of pigment stones. Disorders that are associated with elevated levels of unconjugated bilirubin in bile include hemolytic syndromes, severe ileal dysfunction (or bypass), and bacterial contamination of the biliary tree.

Pathogenesis of Cholesterol Stones.

Cholesterol is rendered soluble in bile by aggregation with water-soluble bile salts and water-insoluble lecithins, both of which act as detergents. *When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals. Cholesterol gallstone formation involves four simultaneous defects* (Fig. 18-49):

- Bile must be supersaturated with cholesterol.
- Gallbladder hypomotility promotes nucleation.
- Cholesterol nucleation in bile is accelerated.
- Mucus hypersecretion in the gallbladder traps the crystals, permitting their aggregation into stones.

Supersaturation of bile with cholesterol is the result of hepatocellular hypersecretion of cholesterol. This appears to be a primary defect, mediated by abnormal regulation of hepatic mechanisms for delivering cholesterol to bile.[62] The abundant free cholesterol is toxic to the gallbladder, penetrating the wall and exceeding the ability of the mucosa to detoxify it by esterification. *Gallbladder hypomotility ensues.* Muscular stasis appears to result both from intrinsic neuromuscular dysmotility and from diminished muscular responsiveness to cholecystokinin, the hormone secreted by the gut that promotes gallbladder contraction. The relative composition of trace proteins in bile also may be altered, such that the balance of antinucleating and pronucleating proteins shifts in favor of *accelerated nucleation of cholesterol crystals*. Nucleation is further promoted by the presence of microprecipitates of inorganic or organic calcium salts. As a result of these events, supersaturated bile is sequestered in a hypomotile gallbladder under favorable nucleating conditions. *Hypersecretion of gallbladder*

mucus completes the tetralogy, as the cholesterol crystals are trapped for sustained periods, enabling their growth into macroscopic concretions. Superimposed conditions exacerbate defective gallbladder emptying and the likelihood of forming cholesterol stones: prolonged fasting, pregnancy, rapid weight loss, total parenteral nutrition, and spinal cord injury.

Pathogenesis of Pigment Stones.

Pigment gallstones are complex mixtures of abnormal insoluble calcium salts of unconjugated bilirubin along with inorganic calcium salts.[63] Unconjugated bilirubin is normally a minor component of bile but increases when infection of the biliary tract leads to release of microbial β-glucuronidases, which hydrolyze bilirubin glucuronides. Thus, infection of the biliary tract, as with *Escherichia coli* or *Ascaris lumbricoides* or by the liver fluke *Opisthorchis sinensis*, increases the likelihood of pigment stone

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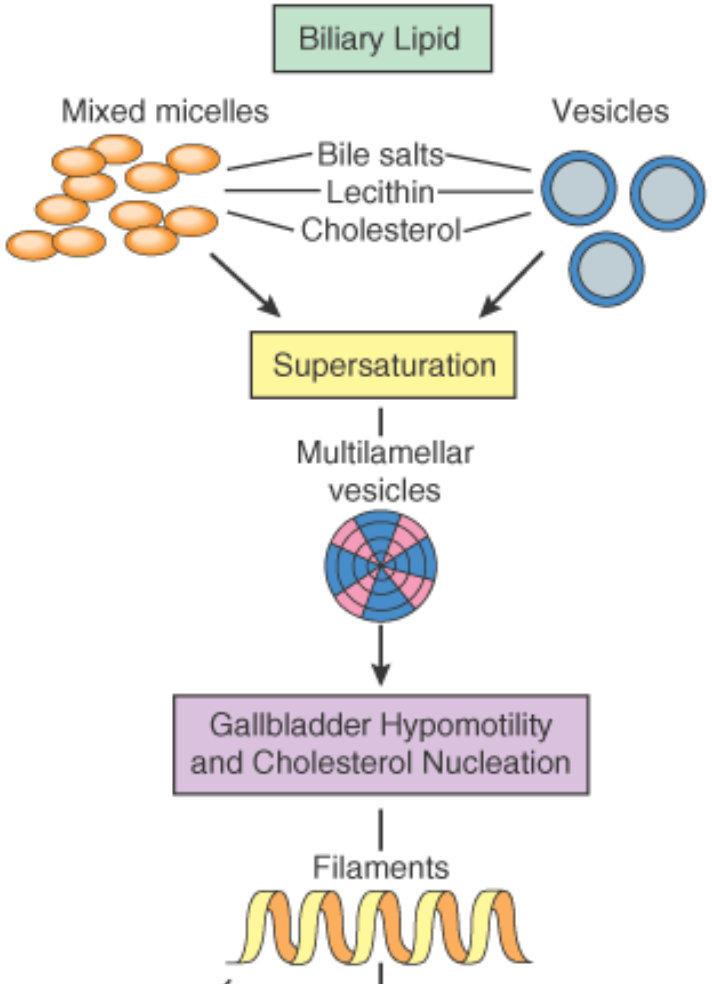
Figure 18-49 Schematic representation of the four contributing factors for cholelithiasis: supersaturation, gallbladder hypomotility, crystal nucleation, and accretion within the gallbladder mucous layer.



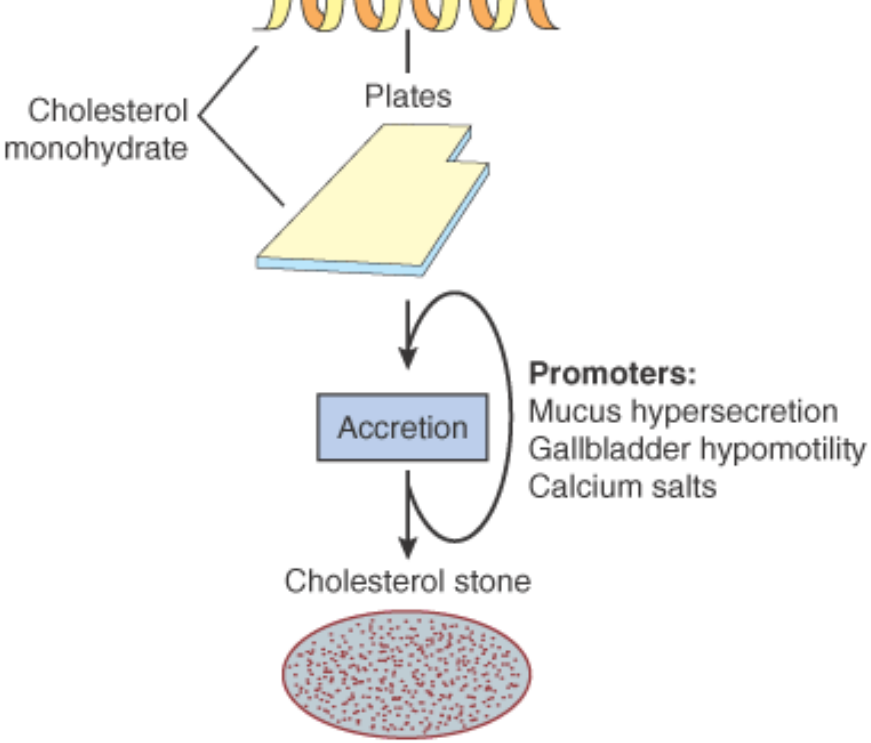


Figure 18-50 Cholesterol gallstones. Mechanical manipulation during laparoscopic cholecystectomy has caused fragmentation of several cholesterol gallstones, revealing interiors that are pigmented because of entrapped bile pigments. The gallbladder mucosa is reddened and irregular as a result of coexistent chronic cholecystitis.

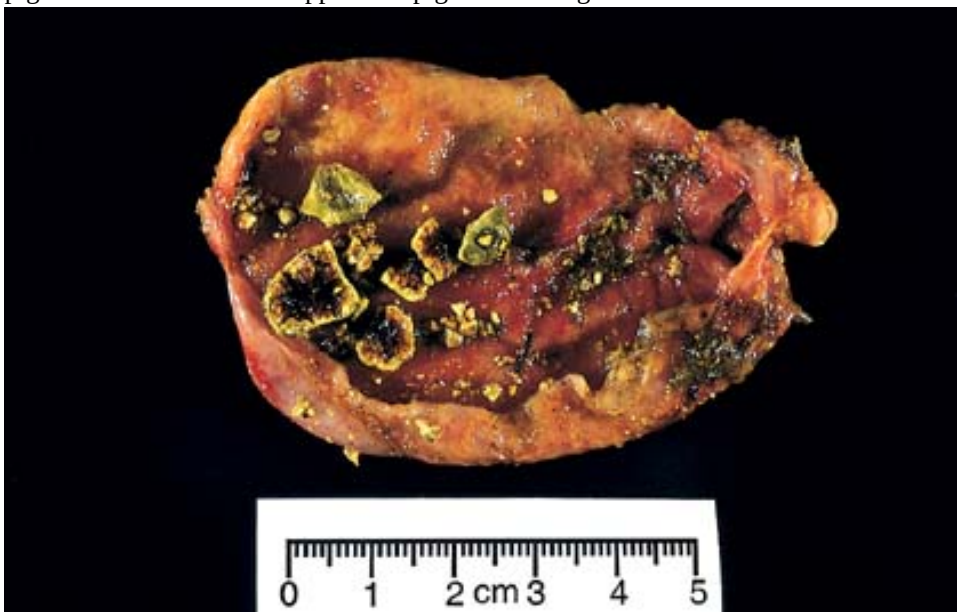


Figure 18-51 Pigment gallstones. Several faceted black gallstones are present in this otherwise unremarkable gallbladder from a patient with a mechanical mitral valve prosthesis, leading

to chronic intravascular hemolysis.

Figure 18-52 Acute calculous cholecystitis; the stone was not photographed.

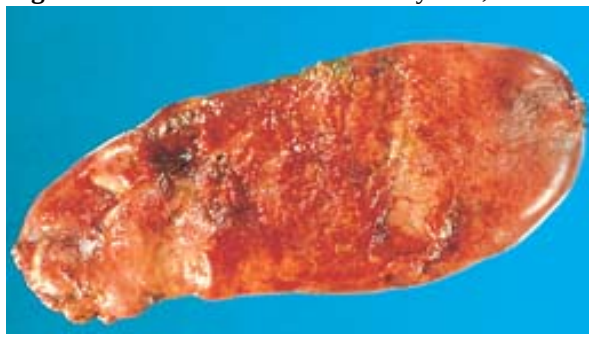


Figure 18-53 Chronic cholecystitis with cholesterol stones. The gallbladder wall is thickened and gray-white, owing to fibrosis and inflammation. The mucosa is effaced. Multiple faceted cholesterol gallstones are present within the lumen. The exterior of the specimen is black as a result of India ink application.

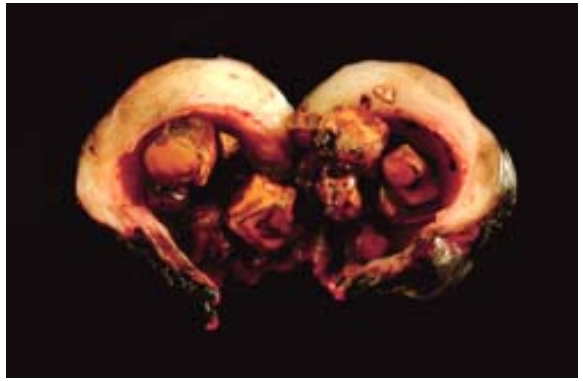


Figure 18-54 Biliary atresia, schematized to show the pattern of biliary tract injury.

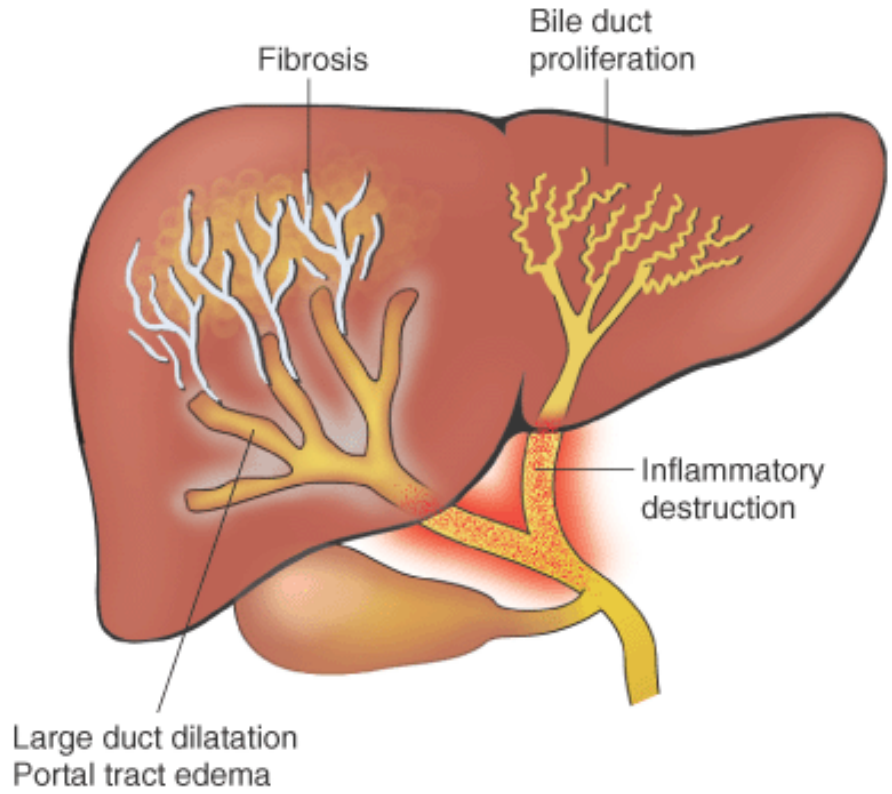
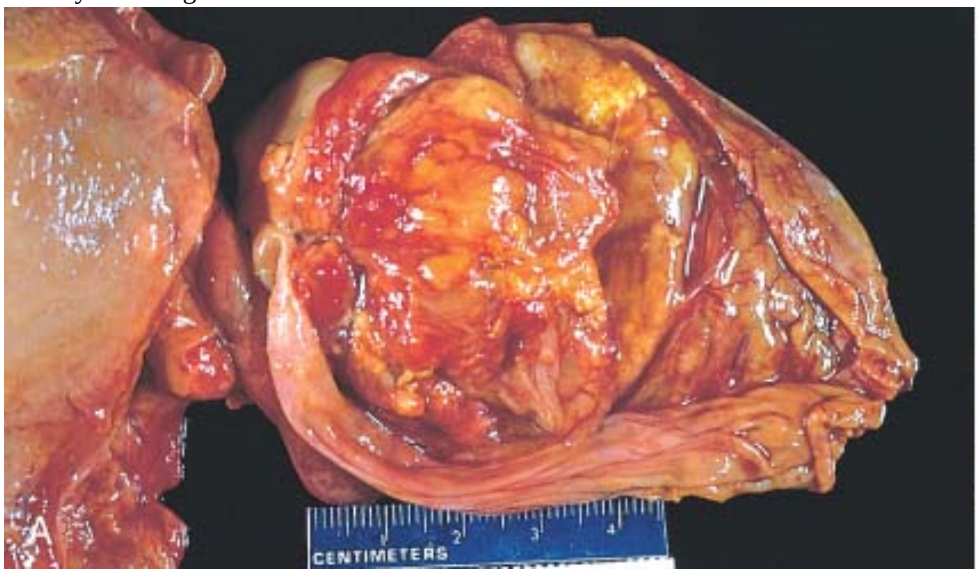
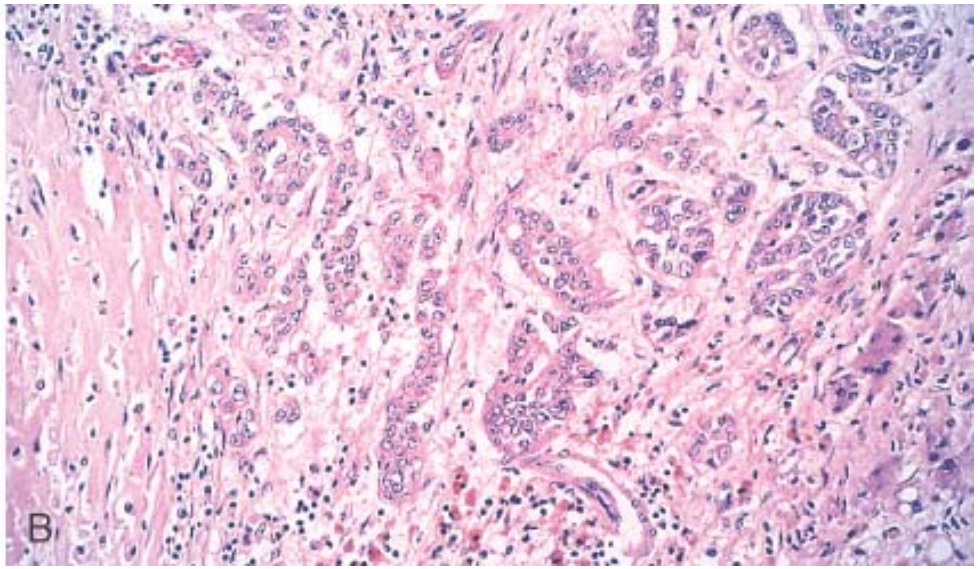


Figure 18-55 Gallbladder adenocarcinoma. *A*, The opened gallbladder contains a large, exophytic tumor that virtually fills the lumen. *B*, Malignant glandular structures are present within a densely fibrotic gallbladder wall.





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Chapter 19 - The Pancreas

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Normal

The pancreas has important endocrine and exocrine functions, and diseases of the pancreas cause significant morbidity and mortality. Despite the physiologic importance of the pancreas, the retroperitoneal location of the gland and the vague signs and symptoms associated with injury to the gland allow many diseases to progress relatively unnoticed for extended periods of time. Diseases of the pancreas thus remain a continuing source of frustration in modern medicine.

The adult pancreas is a transversely oriented retroperitoneal organ extending from the "C" loop of the duodenum to the hilum of the spleen (Fig. 19-1). On average, the pancreas measures 20 cm in length and weighs 90 gm in men and 85 gm in women.[1] Although the pancreas does not have well-defined anatomic subdivisions, the adjacent vasculature can be used to separate the pancreas into three parts: the head, body, and tail.

The pancreatic duct system is highly variable. The main pancreatic duct, also known as the duct of Wirsung, most commonly drains into the duodenum at the papilla of Vater, whereas the accessory pancreatic duct, also known as the duct of Santorini, most often drains into the duodenum through a separate minor papilla approximately 2 cm cephalad (proximal) to the major papilla of Vater (Fig. 19-2*A*). In many adults, the main pancreatic duct merges with the common bile duct proximal to the papilla of Vater, thus creating the ampulla of Vater, a common channel for biliary and pancreatic drainage. Owing to developmental variability, however, this ductal architecture can differ tremendously from patient to patient.

Embryologically, the pancreas arises from the fusion of dorsal and ventral outpouchings of the foregut.[1] During early embryonic development, the dorsal and ventral pancreatic primordia rotate and fuse at approximately the seventh week of gestation to form a single gland.[2] The majority of the gland, including the body, the tail, the superior/anterior aspect of the head, and the accessory duct of Santorini, is derived from the dorsal primordium. Although the ventral primordium gives rise only to the posterior/inferior part of the head of the pancreas, the ventral primordium is important because it drains into the papilla of Vater. Fusion of the dorsal and ventral duct systems allows the majority of the gland to drain through the larger Vaterian papilla.

Although the organ gets its name from the Greek *pankreas*, meaning "all flesh," the pancreas is, in fact, a complex lobulated organ with distinct exocrine and endocrine components. The exocrine portion of the gland, which produces digestive

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Figure 19-1 Anatomic relationships of the pancreas seen in a cross-section of the abdomen at the level of the upper lumbar vertebrae. *(From Go VW, et al (eds): The Pancreas: Biology, Pathobiology, and Disease, 2nd ed. New York, Raven Press, 1993.)*

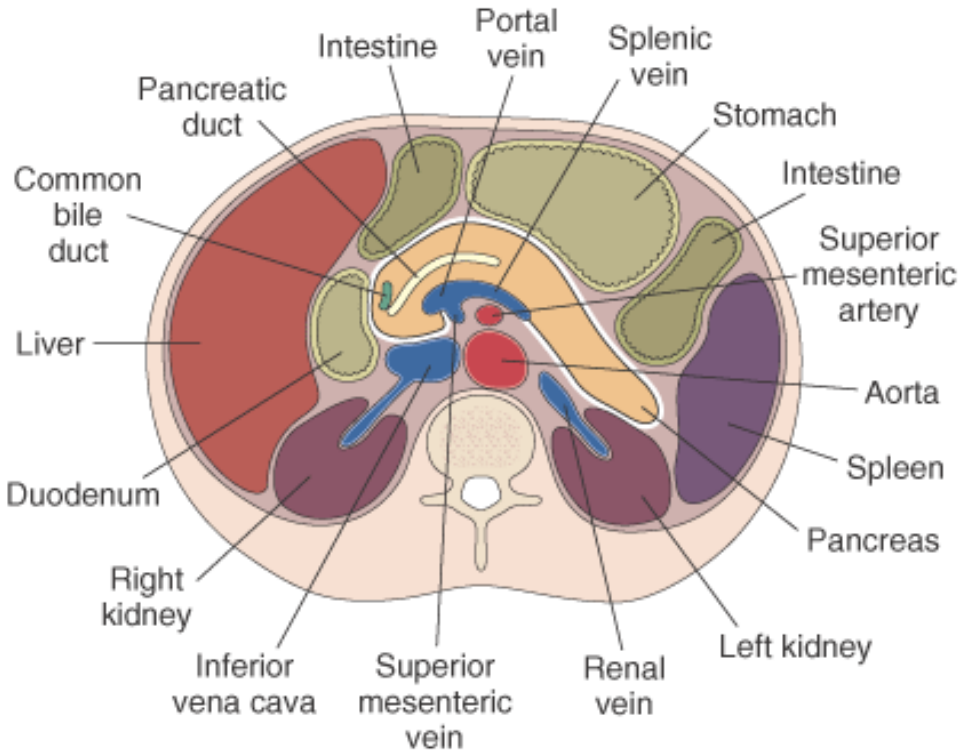

Figure 19-2 Pancreatic ductal anatomy. *A*, The normal ductal anatomy. *B*, The ductal anatomy in pancreatic divisum. *(Adapted from Gregg JA, Monaco AP, McDermott WV: Pancreas divisum: results of surgical intervention. Am J Surg 145:488–492, 1983.)*

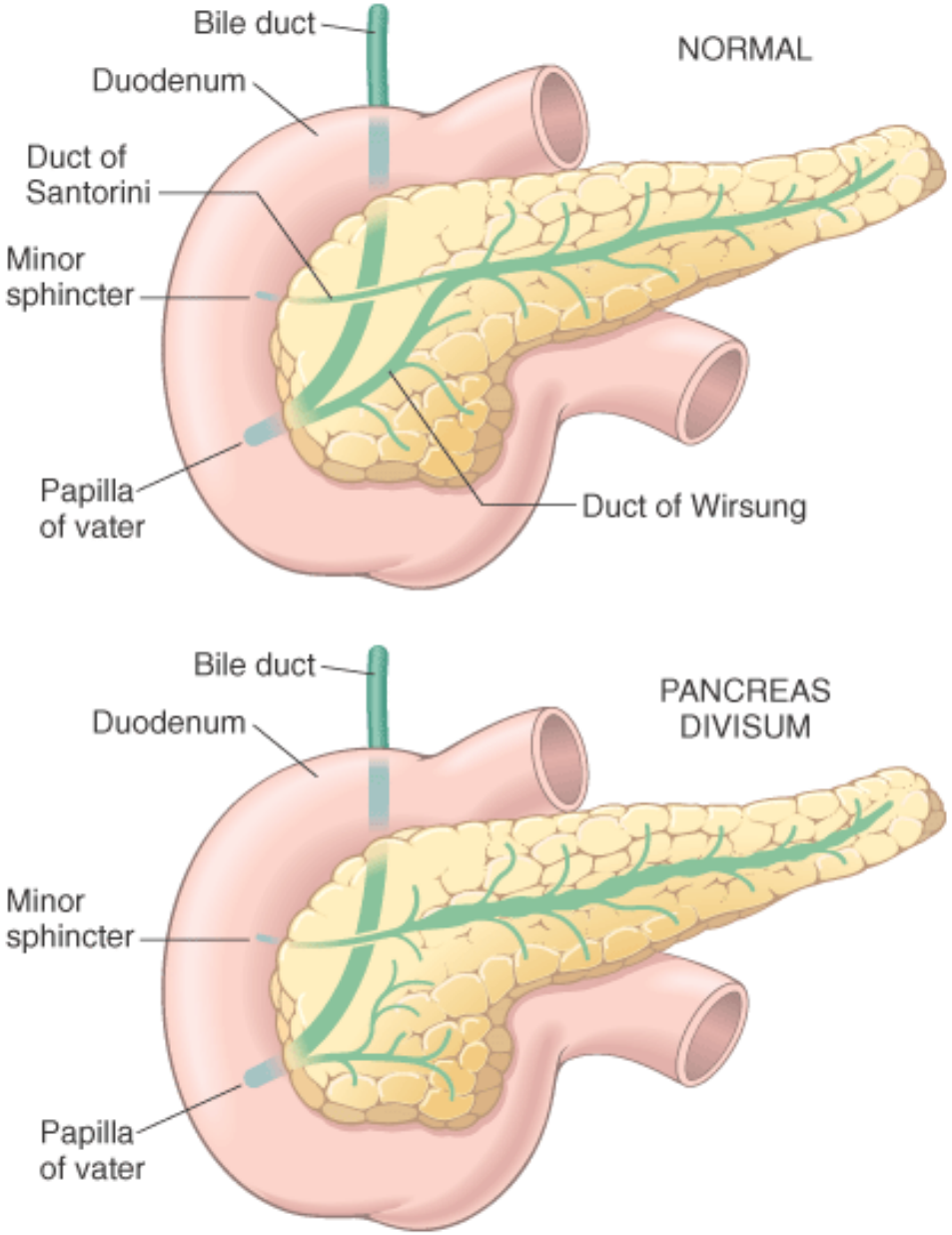

Figure 19-3 Pancreatic acini, showing the radial orientation of the pyramidal exocrine acinar cells. The cytoplasm is devoted to the synthesis and packaging of digestive enzymes for secretion into a central lumen.

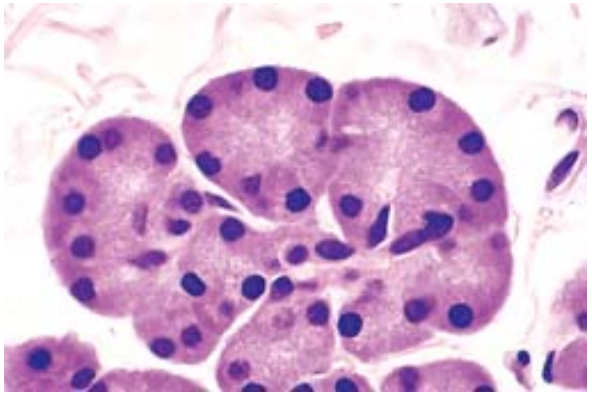

TABLE 19-1 -- Etiologic Factors in Acute Pancreatitis

Metabolic
Alcoholism
Hyperlipoproteinemia
Hypercalcemia
Drugs (e.g., thiazide diuretics)
Genetic
Mechanical
Trauma
Gallstones
Iatrogenic injury
••Perioperative injury
••Endoscopic procedures with dye injection
Vascular
Shock
Atheroembolism
Polyarteritis nodosa
Infectious
Mumps
Coxsackievirus
Mycoplasma pneumoniae

Of note, 10% to 20% of patients with acute pancreatitis have no known associated processes. Although this condition is currently termed *idiopathic*, a growing body of evidence suggests that many, in fact, have a genetic basis. The genetic alterations associated with the development of pancreatitis therefore deserve special note.[22]

Cationic Trypsinogen (PRSS1).

Hereditary pancreatitis is an autosomal-dominant disease with an 80% penetrance characterized by recurrent attacks of severe pancreatitis usually beginning in childhood.[19] This disorder is caused by germ line (inherited) mutations in the *cationic trypsinogen* gene (also known as *PRSS1*).[18] Most are point mutations, with G to A transitions, that result in an arginine (R) to histidine (H) substitution (called R122H).[19] This mutation abrogates a critical failsafe mechanism, by affecting a site on the cationic trypsinogen molecule that is essential for the cleavage (inactivation) of trypsin by trypsin itself.[23] When this site is mutated, trypsinogen and trypsin become resistant to inactivation, and the abnormally active trypsin activates other digestive proenzymes, resulting in the development of pancreatitis.

Serine Protease Inhibitor, Kazal Type 1 (SPINK1).

The *SPINK1* gene codes for a pancreatic secretory trypsin inhibitor that, as the name suggests, inhibits trypsin activity, helping to prevent the autodigestion of the pancreas by activated trypsin.[20] As one might suspect, inherited homozygous inactivating mutations in the *SPINK1* gene can also lead to the development of pancreatitis.

Morphology.

The morphology of acute pancreatitis ranges from trivial inflammation and edema to severe extensive necrosis and hemorrhage. The basic alterations are **(1) microvascular leakage causing edema, (2) necrosis of fat by lipolytic enzymes, (3) an acute inflammatory reaction, (4) proteolytic destruction of pancreatic parenchyma, and (5) destruction of blood vessels with subsequent interstitial hemorrhage.** The extent and predominance of each of these alterations depend on the duration and severity of the process.

In the milder form, acute interstitial pancreatitis, histologic alterations are limited to interstitial edema and focal areas of fat necrosis in the pancreatic substance and peripancreatic fat (Fig. 19-4). Fat necrosis, as we have seen, results from enzymatic destruction of fat cells. The released fatty acids combine with calcium to form insoluble salts that precipitate in situ (Chapter 1).

In the more severe form, **acute necrotizing pancreatitis**, necrosis of pancreatic tissue affects acinar and

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Figure 19-4 Acute pancreatitis. The microscopic field shows a region of fat necrosis on the right and focal pancreatic parenchymal necrosis (*center*).

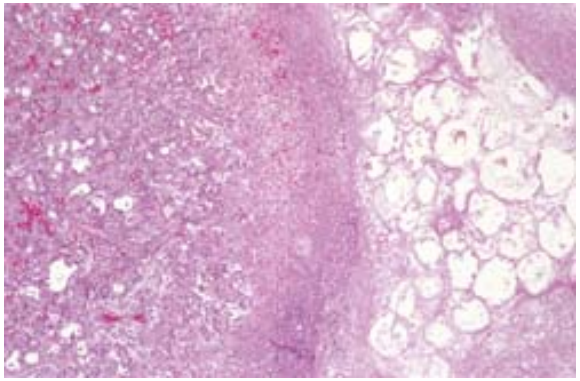

Figure 19-5 Acute pancreatitis. The pancreas has been sectioned across to reveal dark areas of hemorrhage in the head of the pancreas and a focal area of pale fat necrosis in the peripancreatic fat (*upper left*).

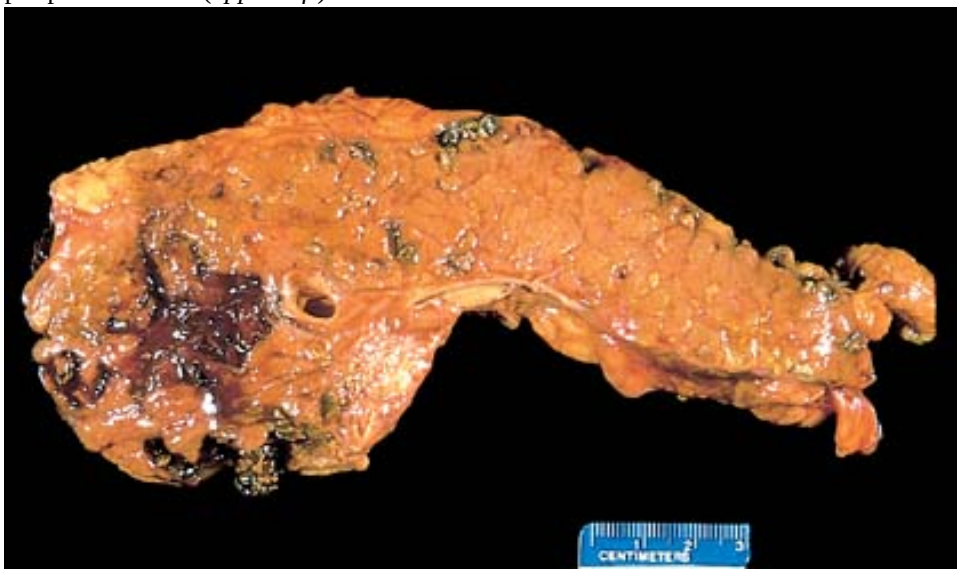

Figure 19-6 Three proposed pathways in the pathogenesis of acute pancreatitis.

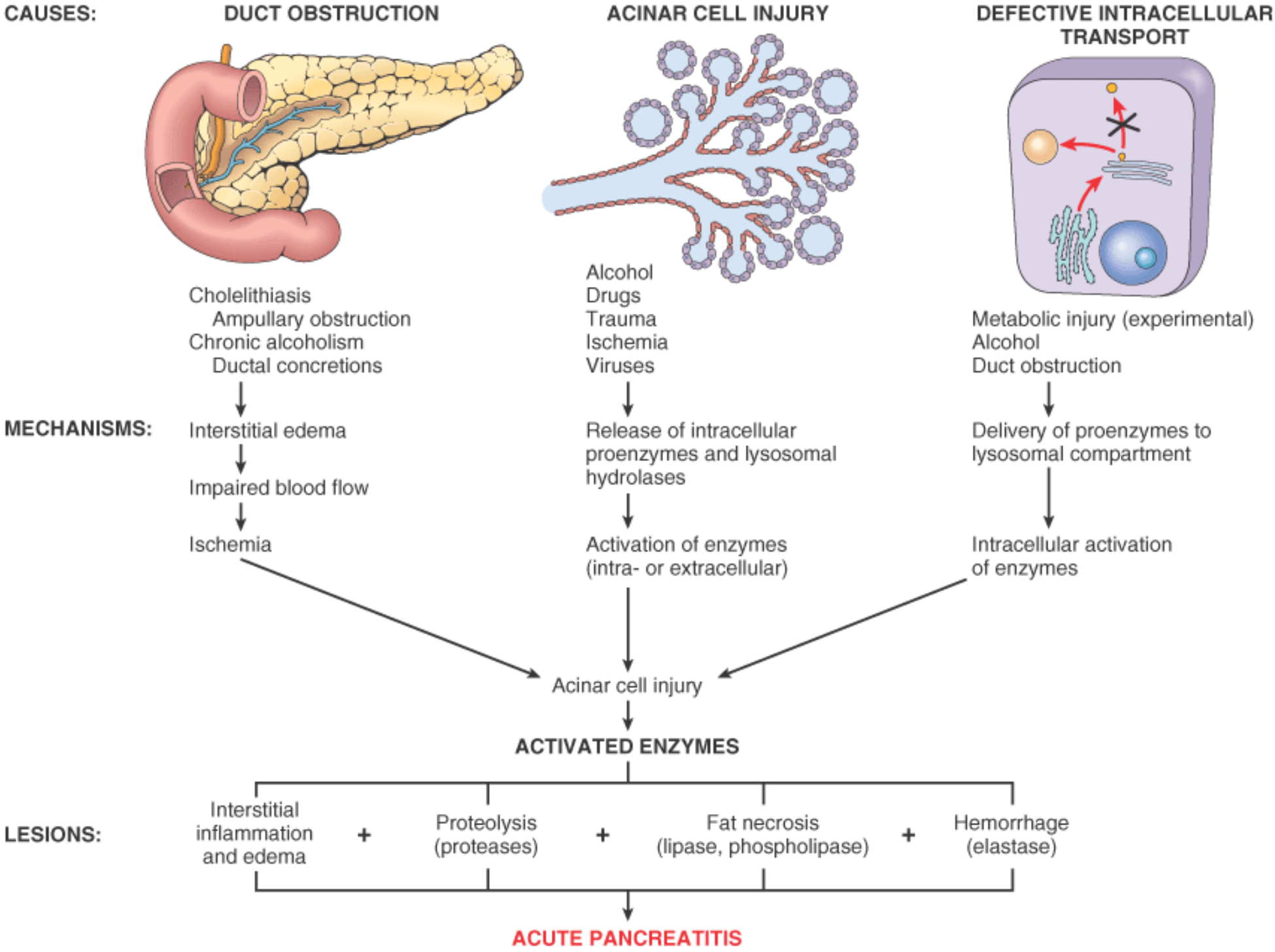

Figure 19-7 Comparison of the sequelae of acute and chronic pancreatitis. (ARDS = acute respiratory distress syndrome)

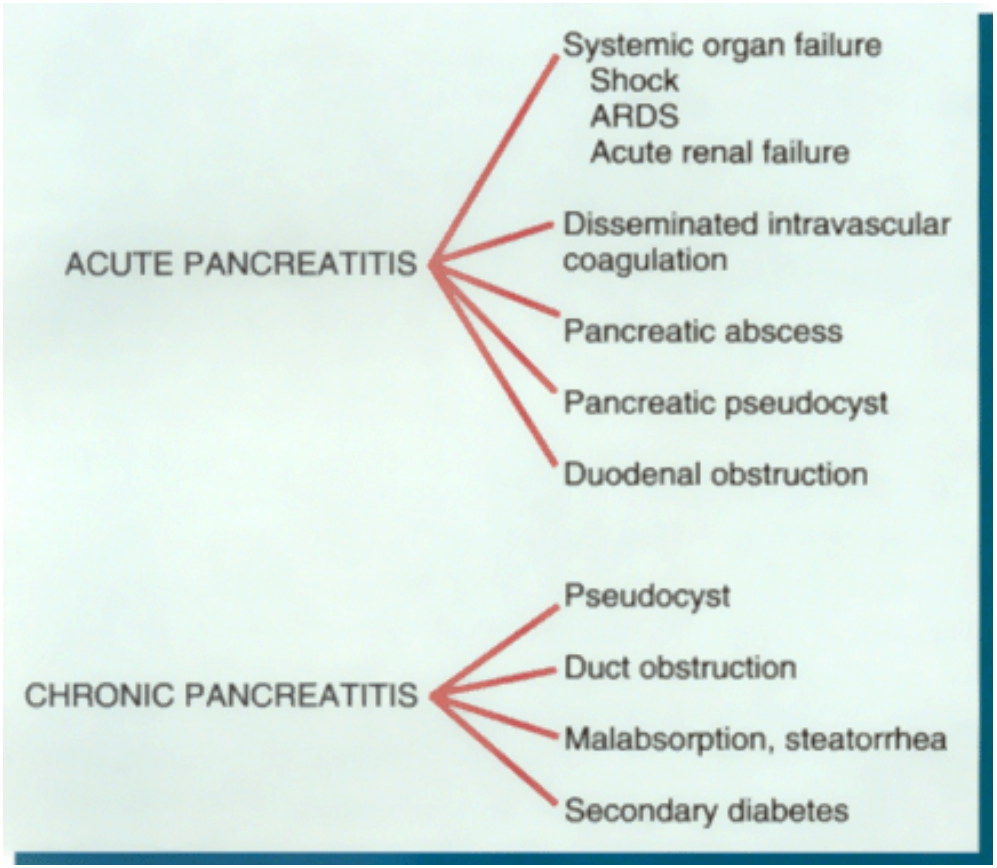

Figure 19-8 Chronic pancreatitis. *A*, Extensive fibrosis and atrophy has left only residual islets (*left*) and ducts (*right*), with a sprinkling of chronic inflammatory cells and acinar tissue. *B*, A higher-power view demonstrating dilated ducts with inspissated eosinophilic ductal concretions in a patient with alcoholic chronic pancreatitis.

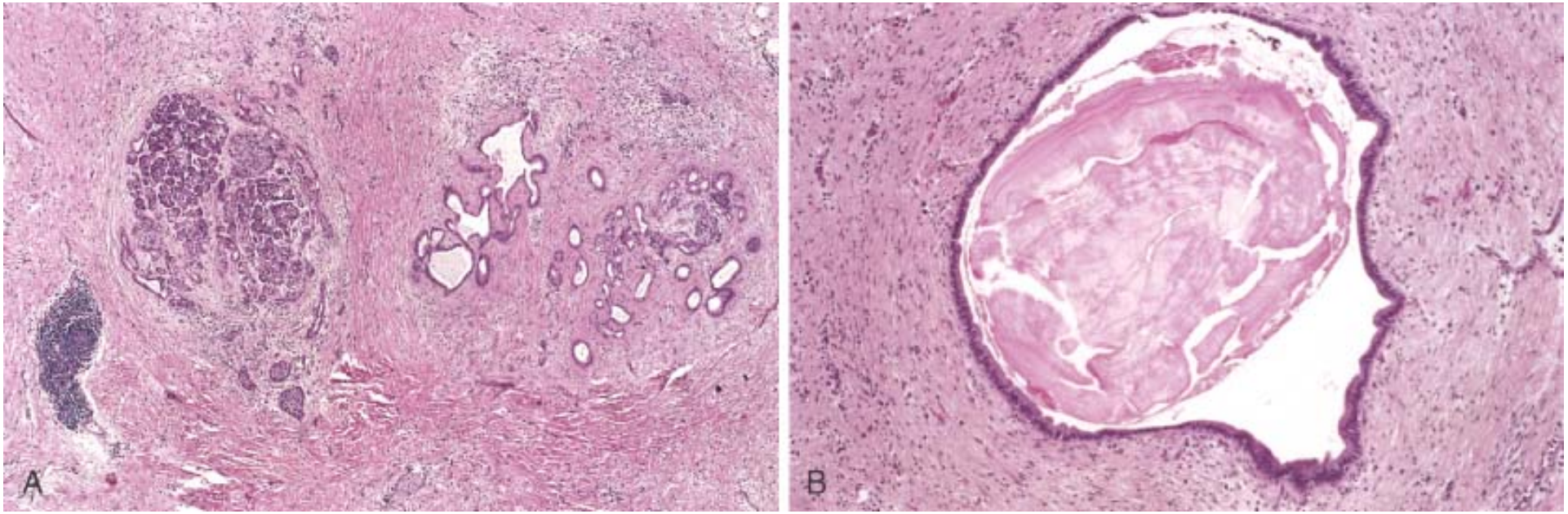

Figure 19-9 Pancreatic pseudocyst. *A,* Cross-section through this previously bisected lesion revealing a poorly defined cyst with a necrotic brown-black wall. *B,* Histologically, the cyst lacks a true epithelial lining and instead is lined by fibrin and granulation tissue.

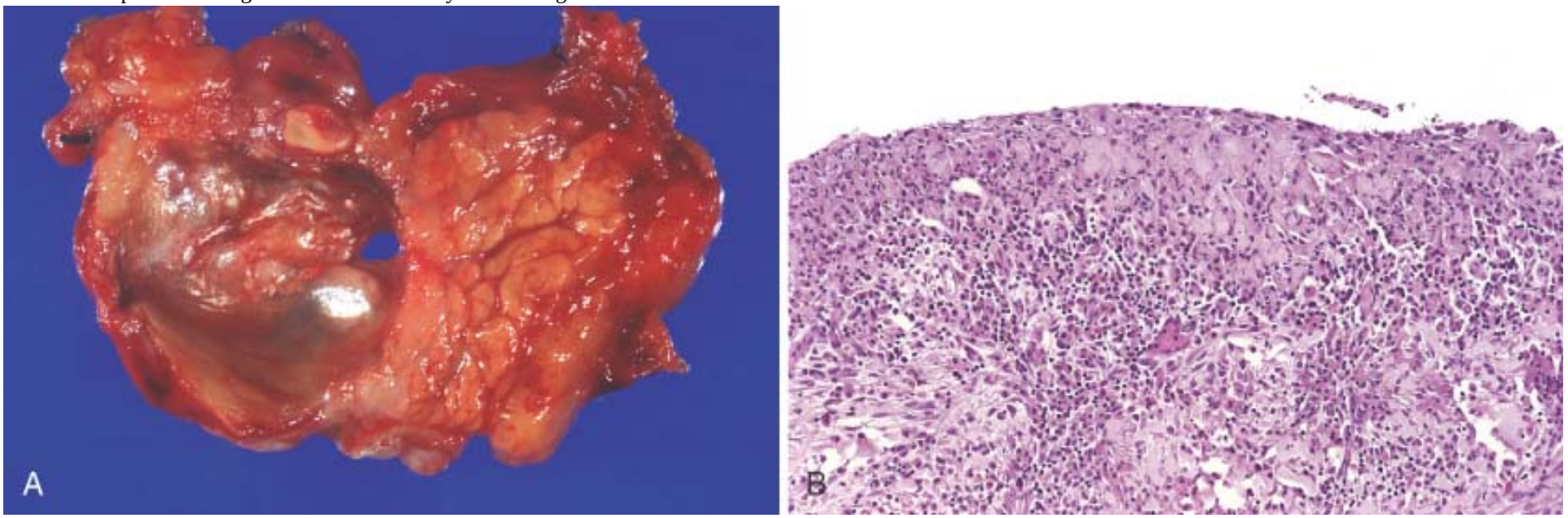

Figure 19-10 Serous cystadenoma. *A,* Cross-section through a serous cystadenoma. Only a thin rim of normal pancreatic parenchyma remains. The cysts are relatively small and contain clear, straw-colored fluid. *B,* The cysts are lined by cuboidal epithelium without atypia.