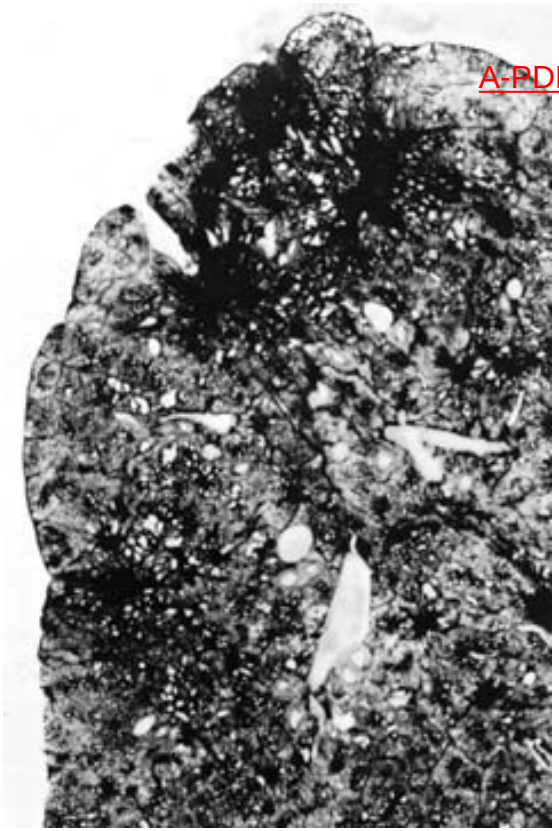

Figure 15-19 Advanced silicosis seen on transection of lung. Scarring has contracted the upper lobe into a small dark mass (*arrow*). Note the dense pleural thickening. *(Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, MA.)*

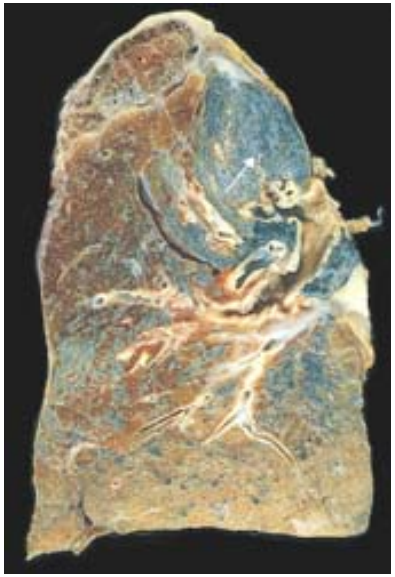

Figure 15-20 Several coalescent collagenous silicotic nodules. *(Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, MA.)*

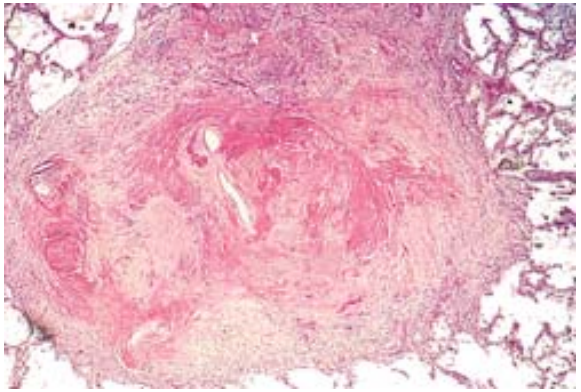

Figure 15-21 High-power detail of an asbestos body, revealing the typical beading and knobbed ends (*arrow*).

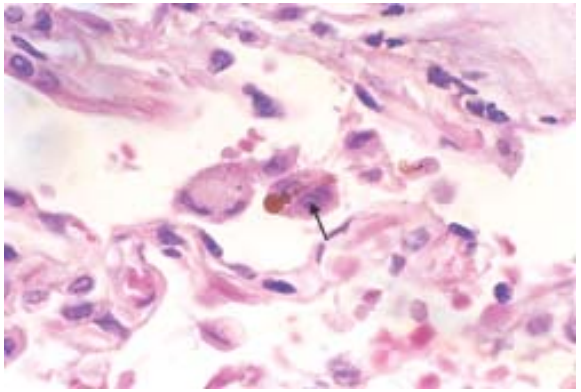

Figure 15-22 Asbestos exposure evidenced by severe, discrete, characteristic fibrocalcific plaques on the pleural surface of the diaphragm. *(Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, MA.)*

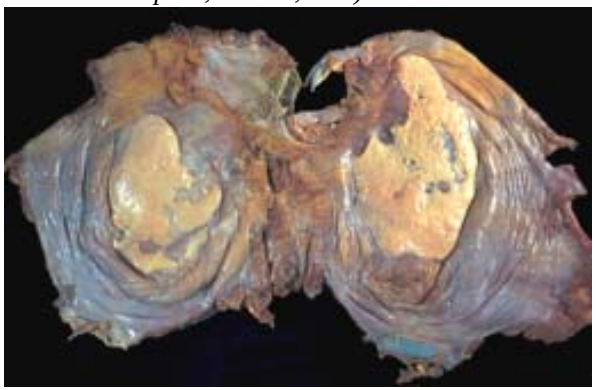

TABLE 15-7 -- Examples of Drug-Induced Pulmonary Disease

Drug	Pulmonary Disease

Cytotoxic drugs	
••Bleomycin	Pneumonitis and fibrosis
••Methotrexate	Hypersensitivity pneumonitis
Amiodarone	Pneumonitis and fibrosis
Nitrofurantoin	Hypersensitivity pneumonitis
Aspirin	Bronchospasm
β-Antagonists	Bronchospasm

changes are those of diffuse alveolar damage, including severe atypia of hyperplastic type II cells and fibroblasts. Epithelial cell atypia and foam cells within vessel walls are also characteristic of radiation damage.

GRANULOMATOUS DISEASES

Sarcoidosis

Sarcoidosis is a systemic disease of unknown cause characterized by noncaseating granulomas in many tissues and organs. Sarcoidosis presents many clinical patterns, but bilateral hilar lymphadenopathy or lung involvement is visible on chest radiographs in 90% of cases. Eye and skin lesions are next in frequency. Since other diseases, including mycobacterial or fungal infections and berylliosis, can also produce noncaseating (*hard*) granulomas, the histologic diagnosis of sarcoidosis is made by exclusion.

The prevalence of sarcoidosis is higher in women than in men but varies widely in different countries and populations. In the United States, the rates are highest in the Southeast; they are 10 times higher in American blacks than in whites. By contrast, among Chinese and Southeast Asians, the disease is rare.

Etiology and Pathogenesis.

Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents.[71] The role of each of these three contributory factors is summarized below.

Immunologic Factors.

There are several *immunologic abnormalities* in the local milieu of sarcoid granulomas that suggest the development of a cell-mediated response to an unidentified antigen. The process is driven by CD4+ helper T cells. These abnormalities include:[72]

- Intra-alveolar and interstitial accumulation of CD4+ T cells, resulting in CD4:CD8 T-cell ratios ranging from 5:1 to 15:1. There is oligoclonal expansion of T-cell subsets as determined by analysis of T-cell receptor rearrangement, suggesting an antigen-driven proliferation.
- Increased levels of T cell-derived T_H 1 cytokines such as IL-2 and interferon-γ (IFN-γ), resulting in T-cell expansion and macrophage activation, respectively.
- Increased levels of several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein 1α [MIP-1α]) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas. TNF in particular is released at high levels by activated alveolar macrophages, and the TNF level in the bronchoalveolar fluid is a marker of disease activity.

Additionally, there are *systemic immunologic abnormalities* in patients with sarcoidosis:

- Anergy to common skin test antigens such as *Candida* or purified protein derivative (PPD)
- Polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation

Genetic Factors.

Evidence of genetic influences can be seen:

- Familial and racial clustering of cases
- Association with certain HLA genotypes (e.g., class I HLA-A1 and HLA-B8)

Environmental Factors.

These are possibly the most tenuous of all the associations in the pathogenesis of sarcoidosis. Several putative microbes have been proposed as the inciting agent for sarcoidosis (e.g., mycobacteria, *Propionibacterium acnes*, and *Rickettsia* species).[73] To date, *there is no unequivocal evidence to suggest that sarcoidosis is caused by an infectious agent*.

Morphology.

Histologically, all involved tissues show the classic **noncaseating granulomas** (Fig. 15-23), each composed of an aggregate of tightly clustered epithelioid cells, often with Langhans or foreign body type giant cells. Central necrosis is unusual. With chronicity, the granulomas may become enclosed within fibrous rims or may eventually be replaced by hyaline fibrous scars. Two other microscopic features are often present in the granulomas: (1) laminated concretions composed of calcium and proteins known as Schaumann bodies and (2) stellate inclusions known as asteroid bodies enclosed within giant cells found in approximately 60% of the granulomas. Although characteristic, these microscopic features are not pathognomonic of sarcoidosis because asteroid and Schaumann bodies may be encountered in other granulomatous diseases (e.g., tuberculosis). Pathologic involvement of virtually every organ in the body has been cited at one time or another.

The **lungs** are common sites of involvement. [74] Macroscopically, there is usually no demonstrable alteration, although at times, the coalescence of granulomas may produce small nodules that are palpable or visible as 1- to 2-cm, noncaseating, noncavitated consolidations. Histologically, the lesions are distributed primarily along the lymphatics, around bronchi and blood vessels, although alveolar lesions are also seen. The relative frequency of granulomas in the bronchial submucosa accounts for the high diagnostic yield of bronchoscopic biopsies. A CD4/CD8 ratio >2.5 and the CD3/CD4 ratio <0.31 in bronchoalveolar lavage lymphocytes is commonly seen in sarcodosis.[75] There appears to be a strong tendency for

Figure 15-23 Characteristic sarcoid noncaseating granulomas in lung with many giant cells. *(Courtesy of Dr. Ramon Blanco, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

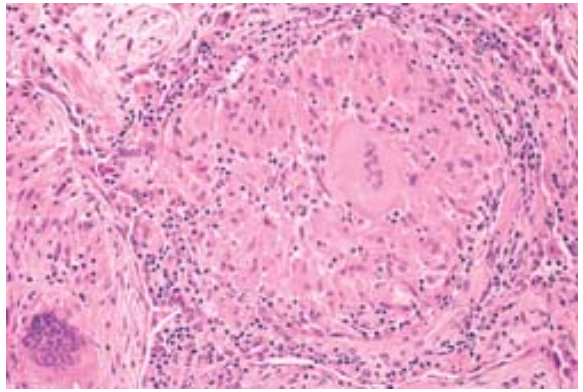

Figure 15-24 Hypersensitivity pneumonitis, histologic appearance. Loosely formed interstitial granulomas and chronic inflammation are characteristic.

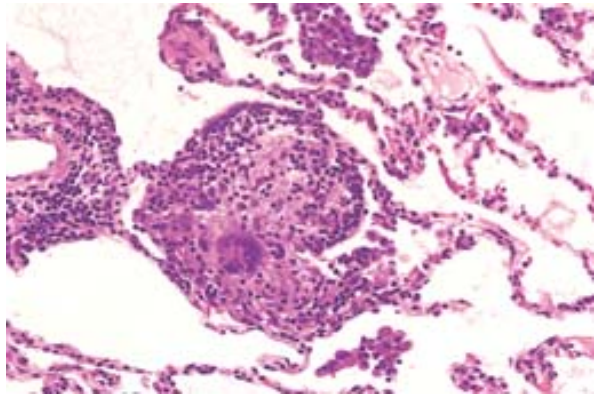

Figure 15-25 Desquamative interstitial pneumonia: medium-power detail of lung to demonstrate the accumulation of large numbers of mononuclear cells within the alveolar spaces with only mild fibrous thickening of the alveolar walls.

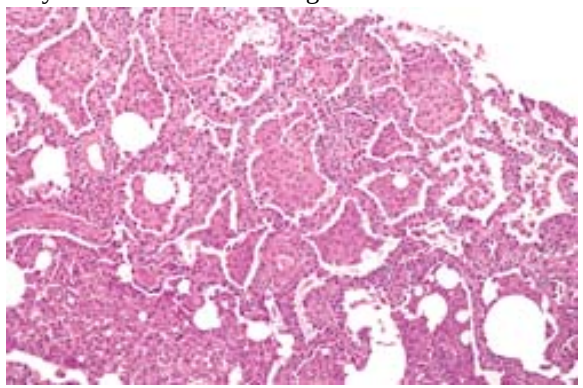

Figure 15-26 Pulmonary alveolar proteinosis, histologic appearance. The alveoli are filled with a dense, amorphous, protein-lipid granular precipitate, while the alveolar walls are normal.

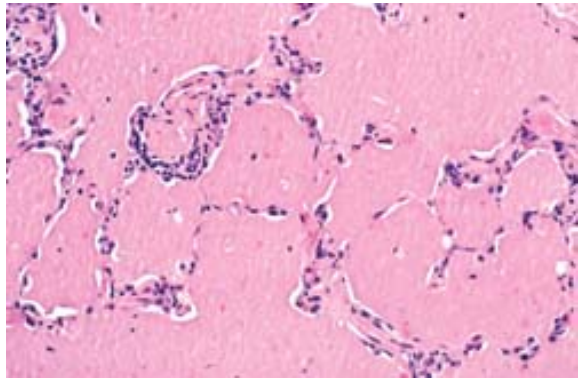

Figure 15-27 Large saddle embolus from the femoral vein lying astride the main left and right pulmonary arteries. *(From the teaching collection of the Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

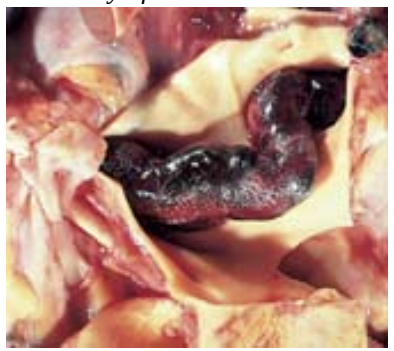

Figure 15-28 Recent, small, roughly wedge-shaped hemorrhagic pulmonary infarct.

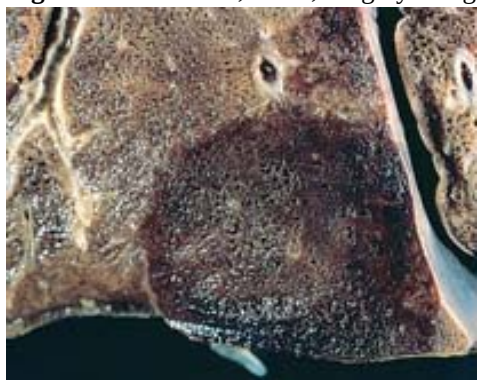

Figure 15-29 Pathogenesis of primary pulmonary hypertension.

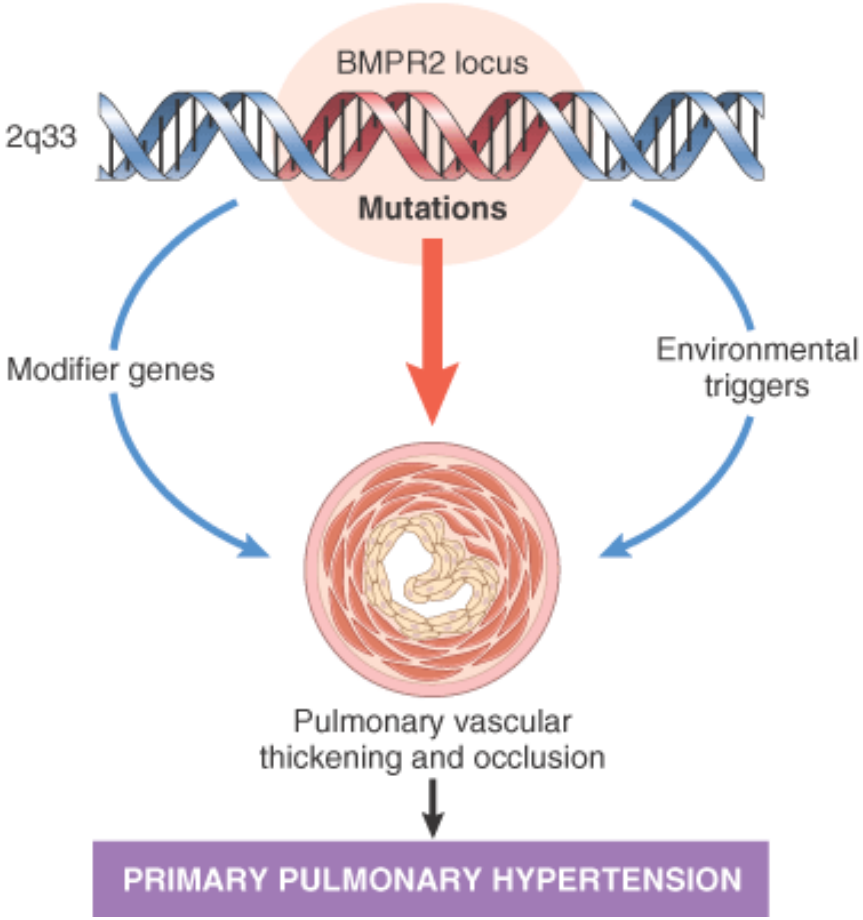

Figure 15-30 Vascular changes in pulmonary hypertension. *A*, Gross photograph of atheroma formation, a finding usually limited to large vessels. *B*, Marked medial hypertrophy. *C*, Plexogenic lesion characteristic of advanced pulmonary hypertension seen in small arteries.

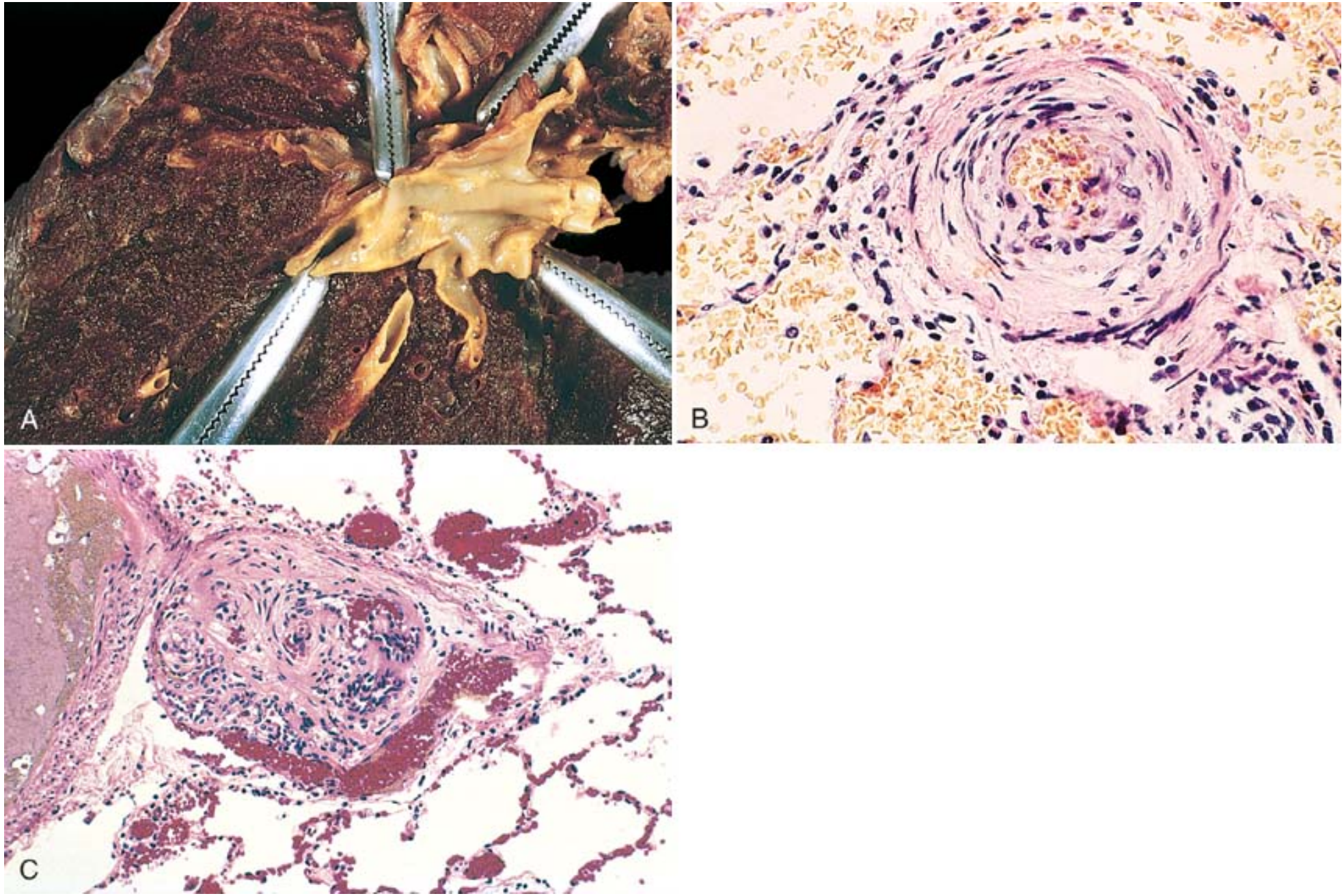

Figure 15-31 Acute intra-alveolar hemorrhage and hemosiderin-laden macrophages, reflecting previous hemorrhage, are common features of the diffuse pulmonary hemorrhage syndromes (Prussian blue stain for iron).

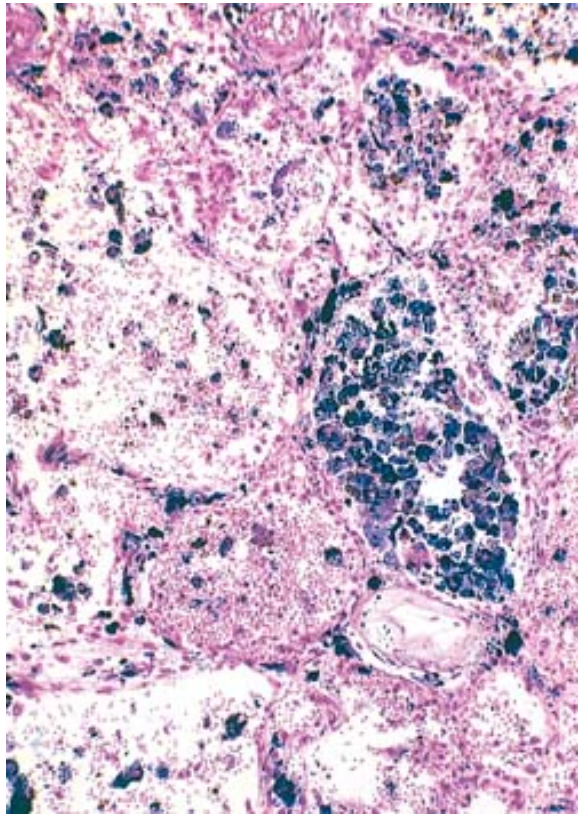

TABLE 15-8 -- The Pneumonia Syndromes

Community-Acquired Acute Pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Legionella pneumophila
Enterobacteriaceae (*Klebsiella pneumoniae*) and *Pseudomonas* spp.
Community-Acquired Atypical Pneumonia
Mycoplasma pneumoniae
Chlamydia spp. (*C. pneumoniae, C. psittaci, C. trachomatis*)
Coxiella burnetti (Q fever)
Viruses: respiratory syncytial virus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits); SARS * virus

Nosocomial Pneumonia
Gram-negative rods belonging to Enterobacteriaceae (*Klebsiella* spp., *Serratia marcescens*, *Escherichia coli*) and *Pseudomonas* spp.
Staphylococcus aureus (usually penicillin-resistant)
Aspiration Pneumonia
Anaerobic oral flora (*Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus*), admixed with aerobic bacteria *(Streptococcus pneumoniae, Staphylococcus aureus, Haemophilas influenzae*, and *Pseudomonas aeruginosa)*
Chronic Pneumonia
Nocardia
Actinomyces
Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis*
Necrotizing Pneumonia and Lung Abscess
Anaerobic bacteria (extremely common), with or without mixed aerobic infection
Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)
Pneumonia in the Immunocompromised Host
Cytomegalovirus
Pneumocystis carinii
Mycobacterium avium-intracellulare
Invasive aspergillosis
Invasive candidiasis
"Usual" bacterial, viral, and fungal organisms (listed above)

*SARS, Severe acute respiratory syndrome

COMMUNITY-ACQUIRED ACUTE PNEUMONIAS

Community-acquired pneumonias may be bacterial or viral. Here we discuss acute pneumonias caused by bacteria, viral pneumonias are considered later in the section on atypical pneumonias. Often, the bacterial infection follows an upper respiratory tract viral infection. Bacterial invasion of the lung parenchyma causes the alveoli to be filled with an inflammatory exudate, thus causing consolidation ("solidification") of the pulmonary tissue. Many variables, such as the specific etiologic agent, the host reaction, and the extent of involvement, determine the precise form of pneumonia. Predisposing conditions include extremes of age, chronic diseases (congestive heart failure, COPD, and diabetes), congenital or acquired immune deficiencies, and decreased or absent splenic function (sickle cell disease or post splenectomy, which puts the patient at risk for infection with encapsulated bacteria such as

pneumococcus). First we describe pneumonias caused by various organisms and then the morphologic and clinical features common to most pneumonias.

Streptococcus Pneumoniae

Streptococcus pneumoniae, or *pneumococcus*, is the most common cause of community-acquired acute pneumonia. Examination of Gram-stained sputum is an important step in the diagnosis of acute pneumonia. The presence of numerous neutrophils containing the typical Gram-positive, lancet-shaped diplococci supports the diagnosis of pneumococcal pneumonia, but it must be remembered that *S. pneumoniae* is a part of the endogenous flora in 20% of adults, and therefore false-positive results may be obtained. Isolation of pneumococci from blood cultures is more specific but less sensitive (in the early phase of illness, only 20% to 30% of patients have positive blood cultures). Pneumococcal pneumonias respond readily to penicillin treatment, but there are increasing numbers of penicillin-resistant strains of pneumococci, so whenever possible, antibiotic sensitivity should be determined. Pneumococcal vaccines containing capsular polysaccharides from the common serotypes are available for use in patients at high risk.

Haemophilus Influenzae

Haemophilus influenzae is a pleomorphic, Gram-negative organism that is a major cause of life-threatening acute lower respiratory tract infections and meningitis in young children. In adults it is a very common cause of community-acquired acute pneumonia.[98] This bacterium is a ubiquitous colonizer of the pharynx, where it exists in two forms: encapsulated (5%) and unencapsulated (95%). Typically, the encapsulated form dominates the unencapsulated forms by secreting an antibiotic called haemocin that kills the unencapsulated *H. influenzae*.[99] Although there are six serotypes of the encapsulated form (types a to f), type b, which has a polyribosephosphate capsule, used to be the most frequent cause of severe invasive disease. With routine use of *H. influenzae* conjugate vaccines, the incidence of disease caused by the b serotype has declined significantly. By contrast, infections with nonencapsulated forms are increasing. Also called nontypable forms, they spread along the surface of the upper respiratory tract and produce otitis media (infection of the middle ear), sinusitis, and bronchopneumonia.

Pili on the surface of *H. influenzae* mediate adherence of the organisms to the respiratory epithelium.[100] In addition, *H. influenzae* secretes a factor that disorganizes ciliary beating and a protease that degrades IgA, the major class of antibody secreted into the airways. Survival of *H. influenzae* in the bloodstream correlates with the presence of the capsule, which, like that of pneumococcus, prevents opsonization by complement and phagocytosis by host cells. Antibodies against the capsule protect the host from *H. influenzae* infection, hence the capsular polysaccharide b is incorporated in the vaccine for children against *H. influenzae*.

H. influenzae pneumonia, which may follow a viral respiratory infection, is a pediatric emergency and has a high mortality rate. Descending laryngotracheobronchitis results in airway obstruction as the smaller bronchi are plugged by dense, fibrin-rich exudate of polymorphonuclear cells, similar to that seen in pneumococcal pneumonias. Pulmonary consolidation is usually lobular and patchy but may be confluent and involve the entire lung lobe. Before a vaccine became widely available, *H. influenzae* was a common cause of suppurative meningitis in children up to 5 years of age. *H. influenzae* also causes an acute, purulent conjunctivitis (pinkeye) in children and, in predisposed older patients, may cause septicemia, endocarditis, pyelonephritis, cholecystitis, and suppurative arthritis. *H. influenzae* is the most common bacterial cause of acute exacerbation of COPD.

Moraxella Catarrhalis

Moraxella catarrhalis is being increasingly recognized as a cause of bacterial pneumonia, especially in the elderly. It is the second most common bacterial cause of acute exacerbation of COPD. Along with *S. pneumoniae* and *H. influenzae, M. catarrhalis* constitutes one of the three most common causes of otitis media in children.

Staphylococcus Aureus

Staphylcocus aureus is an important cause of secondary bacterial pneumonia in children and healthy adults following viral respiratory illnesses (e.g., measles in children and influenza in both children and adults). Staphylococcal pneumonia is associated with a high incidence of complications, such as lung abscess and empyema. *Intravenous drug abusers* are at high risk of developing staphylococcal pneumonia in association with endocarditis. It is also an important cause of nosocomial pneumonia, as will be discussed later.

Klebsiella Pneumoniae

Klebsiella pneumoniae is the most frequent cause of Gram-negative bacterial pneumonia. It commonly afflicts debilitated and malnourished people, particularly *chronic alcoholics*. Thick and gelatinous sputum is characteristic because the organism produces an abundant viscid capsular polysaccharide, which the patient may have difficulty coughing up.

Pseudomonas Aeruginosa

Although *Pseudomonas aeruginosa* most commonly causes nosocomial infections, it is mentioned here because of its

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occurrence in cystic fibrosis patients. It is common in patients who are neutropenic and it has a propensity to invade blood vessels with consequent extrapulmonary spread. *Pseudomonas* septicemia is a very fulminant disease.

Legionella Pneumophila

Legionella pneumophila is the agent of Legionnaires disease, an eponym for the epidemic and sporadic forms of pneumonia caused by this organism. Pontiac fever is a related self-limited upper respiratory tract infection caused by *L. pneumophila*, without pneumonic symptoms. This organism flourishes in artificial aquatic environments, such as water-cooling towers and within the tubing system of domestic (potable) water supplies. The mode of transmission is thought to be either inhalation of aerosolized organisms or aspiration of contaminated drinking water. *Legionella* pneumonia is common in individuals with some predisposing condition such as cardiac, renal, immunologic, or hematologic disease. *Organ transplant recipients are particularly susceptible.* It can be quite severe, frequently requiring hospitalization, and immunosuppressed patients may have fatality rates of up to 50%. Rapid diagnosis is facilitated by demonstration of *Legionella* antigens in the urine or by a positive fluorescent antibody test on sputum samples; culture remains the gold standard of diagnosis.

Morphology.

Bacterial pneumonia has two gross patterns of anatomic distribution: lobular bronchopneumonia and lobar pneumonia (Fig. 15-32). Patchy consolidation of the lung is the dominant characteristic of **bronchopneumonia** (Fig. 15-33). **Lobar pneumonia** is an acute bacterial infection resulting in fibrinosuppurative consolidation of a large portion of a lobe or of an entire lobe (Fig. 15-34). These anatomic but still classic categorizations are often difficult to apply in the individual case because patterns overlap. The patchy involvement may become confluent, producing virtually total lobar consolidation; in contrast, effective antibiotic therapy for any form of pneumonia may limit involvement to a subtotal consolidation. Moreover, the same organisms may produce bronchopneumonia

Figure 15-32 Comparison of bronchopneumonia and lobar pneumonia.

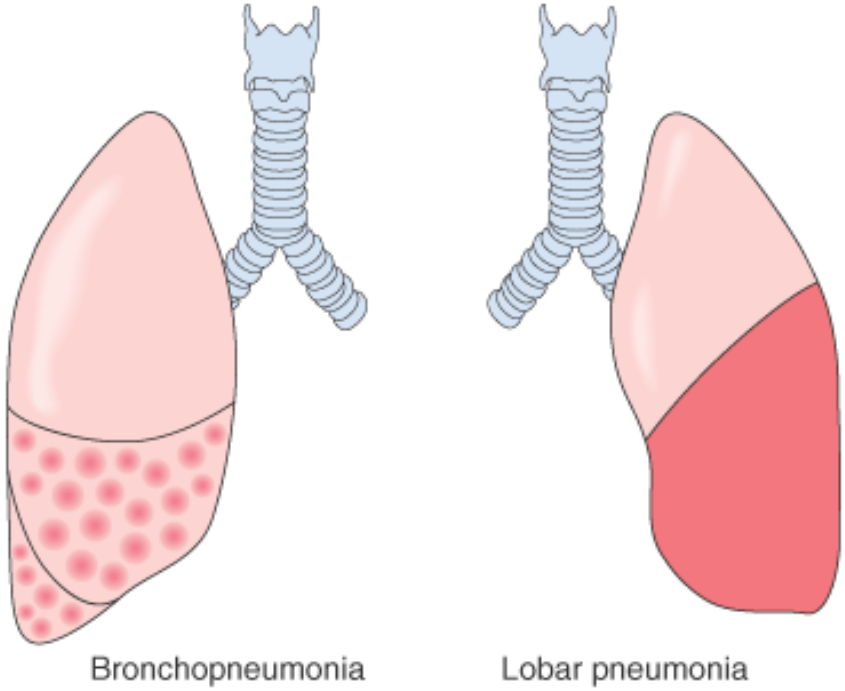

Figure 15-33 Bronchopneumonia. Gross section of lung showing patches of consolidation (*arrows*).

Figure 15-34 Lobar pneumonia—gray hepatization, gross photograph. The lower lobe is uniformly consolidated.

Figure 15-35 *A,* Acute pneumonia. The congested septal capillaries and extensive neutrophil exudation into alveoli corresponds to early red hepatization. Fibrin nets have not yet formed. *B,* Early organization of intra-alveolar exudate, seen in areas to be streaming through the pores of Kohn (*arrow*). *C,* Advanced organizing pneumonia (corresponding to gray hepatization), featuring transformation of exudates to fibromyxoid masses richly infiltrated by macrophages and fibroblasts.

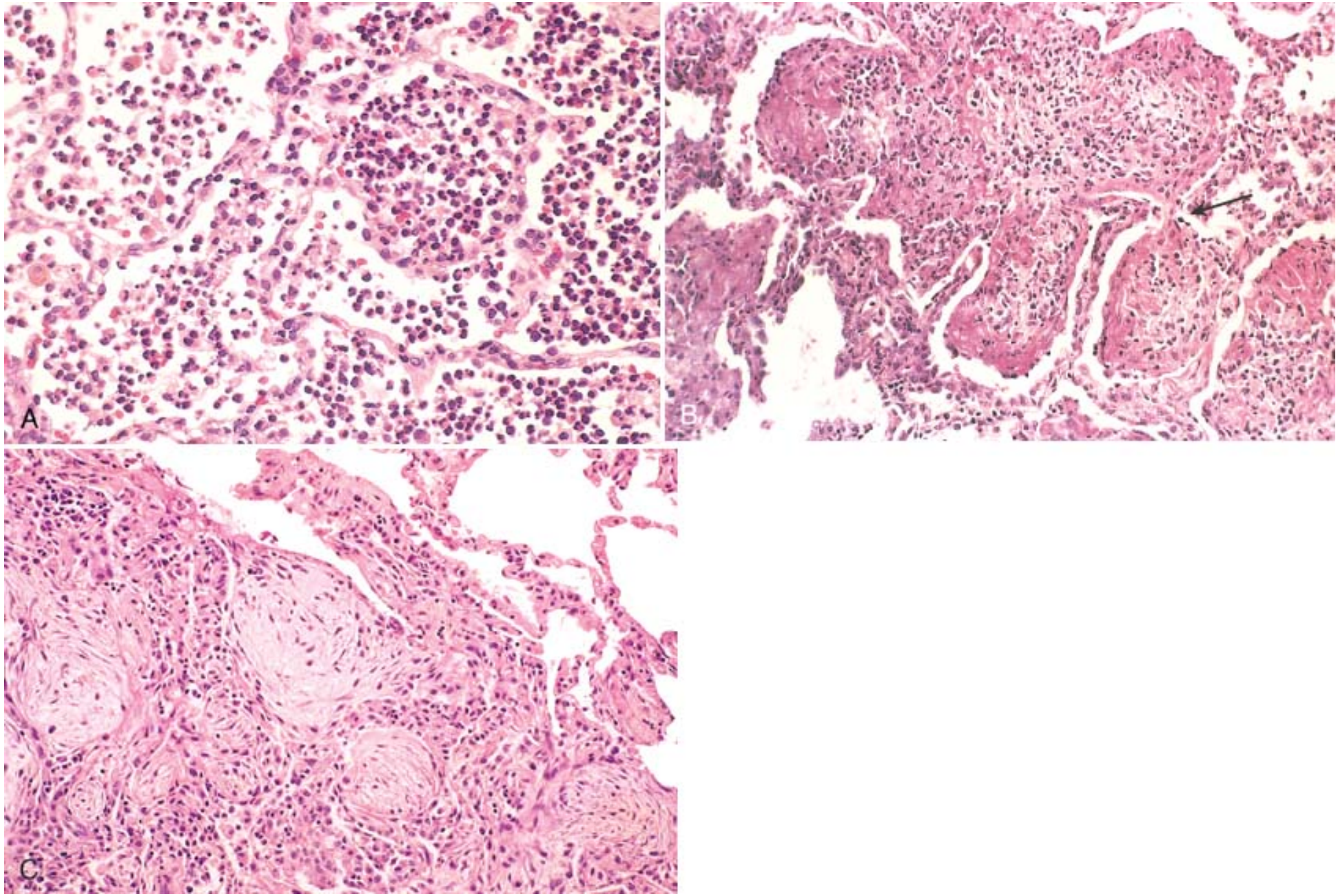

Figure 15-36 Pyemic lung abscess in the center of section with complete destruction of underlying parenchyma within the focus of involvement.

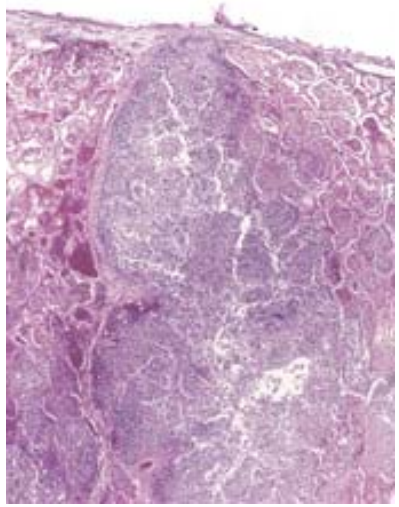

Figure 15-37 Laminated *Histoplasma* granuloma of the lung.

Figure 15-38 *Histoplasma capsulatum* yeast forms fill phagocytes in a lymph node of a patient with disseminated histoplasmosis.

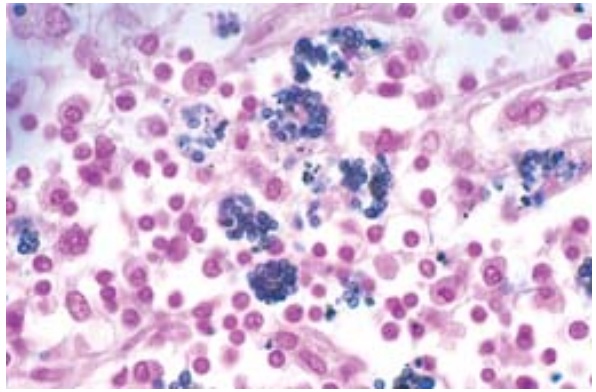

Figure 15-39 Blastomycosis. *A*, Rounded budding yeasts, larger than neutrophils, are present. Note the characteristic thick wall and nuclei (not seen in other fungi). *B*, Silver stain.

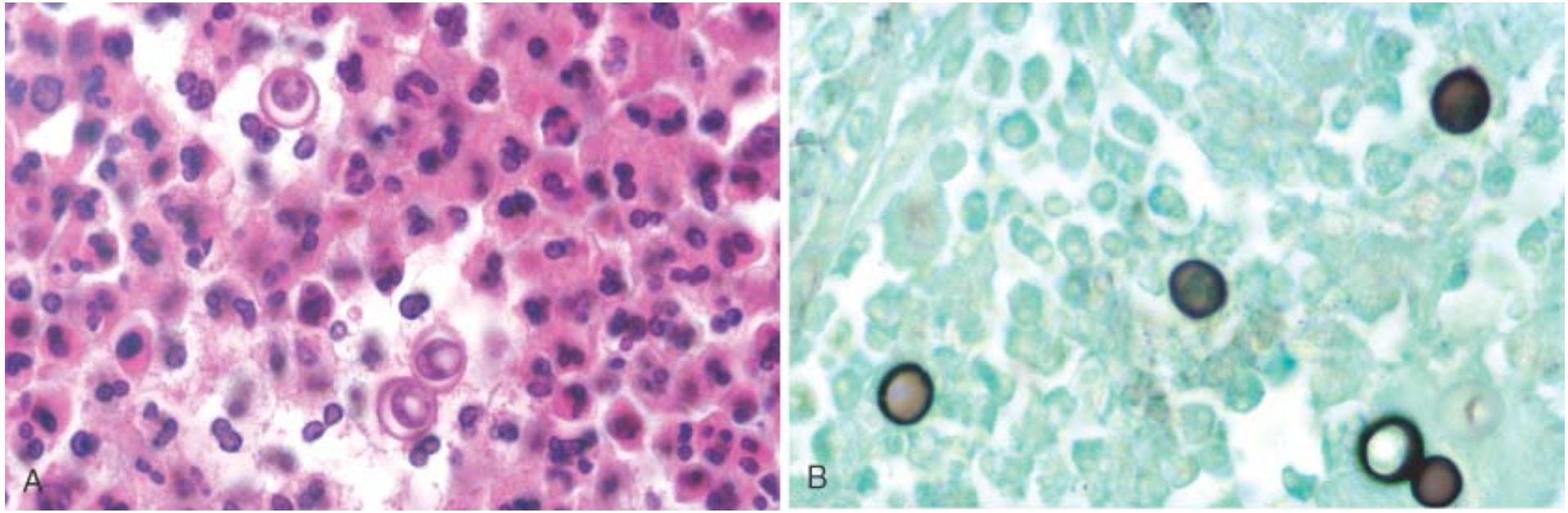

Figure 15-40 Coccidioidomycosis with intact spherules within multinucleated giant cells.

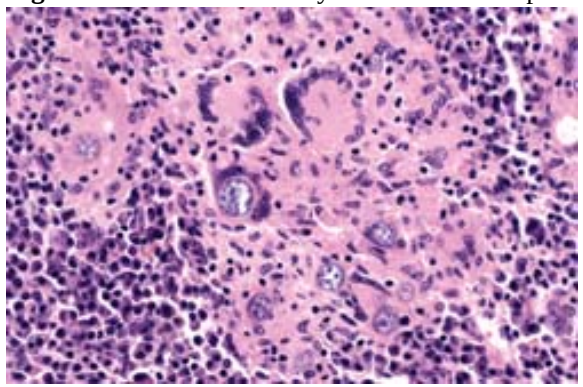

TABLE 15-9 -- Causes of Pulmonary Infiltrates in Immunocompromised Hosts

Diffuse Infiltrate	**Focal Infiltrate**
Common	***Common***
Cytomegalovirus	Gram-negative rods
Pneumocystis carinii	*Staphylococcus aureus*
Drug reaction	*Aspergillus*
	Candida
	Malignancy
Uncommon	***Uncommon***
Bacteria	*Cryptococcus*
Aspergillus	*Mucor*
Cryptococcus	*Pneumocystis carinii*
Malignancy	*Legionella pneumophila*

plethora of entities involved makes diagnosis and treatment a distinct challenge. Some of the individual microbial agents afflicting HIV-infected patients have already been discussed; this section will focus only on the general principles of HIV-associated pulmonary disease.

- Despite the emphasis on "opportunistic" infections, it must be remembered that bacterial lower respiratory tract infection caused by the "usual" pathogens is one of the most serious pulmonary disorders in HIV infection. The implicated organisms include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and Gram-negative rods. Bacterial pneumonias in HIV-infected patients are more common, more severe, and more often associated with bacteremia than in those without HIV infection.
- Not all pulmonary infiltrates in HIV-infected individuals are infectious in etiology. A host of noninfectious diseases, including Kaposi sarcoma (Chapter 6 and Chapter 11), pulmonary non-Hodgkin lymphoma (Chapter 14), and primary lung cancer, occur with increased frequency and need to be excluded.
- *The CD4+ T cell count can define the risk of infection with specific organisms.* As a rule of thumb, bacterial and tubercular infections are more likely at higher CD4+ counts (>200 cells/mm^3). Pneumocystis pneumonia usually strikes at CD4+ counts below 200 cells/mm^3 , while cytomegalovirus and *Mycobacterium avium* complex infections are uncommon until the very late stages of immunosuppression (CD4+ counts <50 cells/mm^3).

Finally, it is useful to remember that pulmonary disease in HIV-infected patients may result from more than one cause, and even common pathogens may present with atypical manifestations. Therefore, the diagnostic workup of these patients may be more extensive (and expensive) than would be mandated in an immunocompetent individual.

Lung Transplantation

Indications for transplantation may include almost all nonneoplastic terminal lung diseases, provided that the patient does not have any other serious disease, which would preclude lifelong immunosuppressive therapy. The most common indications are end-stage emphysema, idiopathic pulmonary fibrosis, cystic fibrosis, and primary pulmonary hypertension. While bilateral lung and heart-lung transplants are possible, in many cases a single lung transplant is performed, offering sufficient improvement in pulmonary function for each of two recipients from a single (and all too scarce) donor. When bilateral chronic infection is present (e.g., cystic fibrosis, bronchiectasis), both lungs of the recipient must be replaced to remove the reservoir of infection.

Morphology.

With improving surgical and organ preservation techniques, postoperative complications (e.g., anastomotic dehiscence, vascular thrombosis, primary graft dysfunction) are happily becoming rare. The transplanted lung is subject to two major complications: infection and rejection.

Pulmonary infections in lung transplant patients are essentially those of any immunocompromised host, discussed earlier. They include bacterial and viral (especially cytomegalovirus) pneumonias, *Pneumocystis carinii* pneumonia (PCP), and fungal infections. In the early posttransplant period (the first few weeks), bacterial infections are most common. With Gancyclovir prophylaxis and matching of donor-recipient CMV status, CMV pneumonia occurs less frequently and is less severe, although some resistant strains are emerging. Most cases occur in the third to twelfth month after transplant. PCP is rare, since almost all patients receive adequate prophylaxis (usually Bactrim™). Fungal infections are mostly due to *Candida* and *Aspergillus* species, and they involve the bronchial anastamotic site and/or the lung.

Acute rejection of the lung occurs to some degree in all patients despite routine immunosuppression postoperatively. It often occurs during the early weeks to months after surgery but may occur years later whenever immunosuppression is decreased. Patients present with fever, dyspnea, cough, and radiologic infiltrates. Since these are similar to the picture of infections, diagnosis often relies on transbronchial biopsy. The morphologic features of acute rejection are primarily those of inflammatory infiltrates (lymphocytes, plasma cells, and few neutrophils and eosinophils), either around small vessels, in the submucosa of airways, or both.[112]

Chronic rejection is a significant problem in at least half of all lung transplant patients by 3 to 5 years. It is manifested by cough, dyspnea, and an irreversible decrease in lung function tests. The major morphologic correlate of chronic rejection is **bronchiolitis obliterans,** the partial or complete occlusion of small airways by fibrosis, with or without active inflammation (Fig. 15-41). Bronchiolitis obliterans is patchy and therefore difficult to diagnose via transbronchial biopsy. Bronchiectasis may develop in long-standing cases.

The acute cellular airway rejection (the presumed forerunner of later, fibrous obliteration of these airways) is generally

Figure 15-41 Chronic rejection of lung allograft, with total occlusion of bronchiole (bronchiolitis obliterans). Adjacent pulmonary artery branch is normal. *(Courtesy of Dr. Thomas Krausz, Department of Pathology, The University of Chicago, Pritzker School of Medicine, Chicago, IL.)*

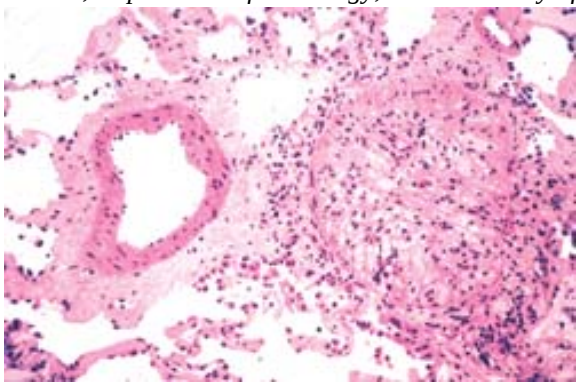

TABLE 15-10 -- Histologic Classification of Malignant Epithelial Lung Tumors

Squamous cell carcinoma
Small cell carcinoma
••Combined small cell carcinoma
Adenocarcinoma
••Acinar; papillary, bronchioloalveolar, solid, mixed subtypes
Large cell carcinoma
••Large cell neuroendocrine carcinoma
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Carcinoid tumor
••Typical, atypical
Carcinomas of salivary gland type
Unclassified carcinoma

interesting postulate is that changes in cigarette type (filter tips, lower tar and nicotine) have caused smokers to inhale more deeply and thereby expose more peripheral airways and cells (with a predilection to adenocarcinoma) to carcinogens.[124] There may be mixtures of histologic patterns, even in the same cancer. Thus, combined types of squamous cell carcinoma and adenocarcinoma or of small cell and squamous cell carcinoma occur in about 10% of patients. For common clinical use, however, the various histologic types of lung cancer can be clustered into two groups on the basis of likelihood of metastases and response to available therapies: *small cell carcinomas* (most often metastatic, high initial response to chemotherapy) versus *non-small cell carcinomas* (less often metastatic, less responsive). The strongest relationship to smoking is with squamous cell and small cell carcinoma.

Morphology.

Lung carcinomas arise most often in and about the hilus of the lung. About three fourths of the lesions take their origin from first-order, second-order, and third-order bronchi. A small number of primary carcinomas of the lung arise in the periphery of the lung substance from the alveolar septal cells or terminal bronchioles. These are predominantly adenocarcinomas, including those of the bronchioloalveolar type, to be discussed separately.

Squamous cell carcinoma of the lung begins as an area of in situ cytologic dysplasia that, over an unknown interval of time, yields a small area of thickening or piling up of bronchial mucosa. With progression, this small focus, usually less than 1 cm^2 in area, assumes the appearance of an irregular, warty excrescence that elevates or erodes the lining epithelium. The tumor may then follow a variety of paths. It may continue to fungate into the bronchial lumen to produce an intraluminal mass. It can also rapidly penetrate the wall of the bronchus to infiltrate along the peribronchial tissue (Fig. 15-42) into the adjacent region of the carina or mediastinum. In other instances, the tumor grows along a broad front to produce a cauliflower-like intraparenchymal mass

Figure 15-42 Lung carcinoma. The gray-white tumor tissue is seen infiltrating the lung substance. Histologically, this large tumor mass was identified as a squamous cell carcinoma.

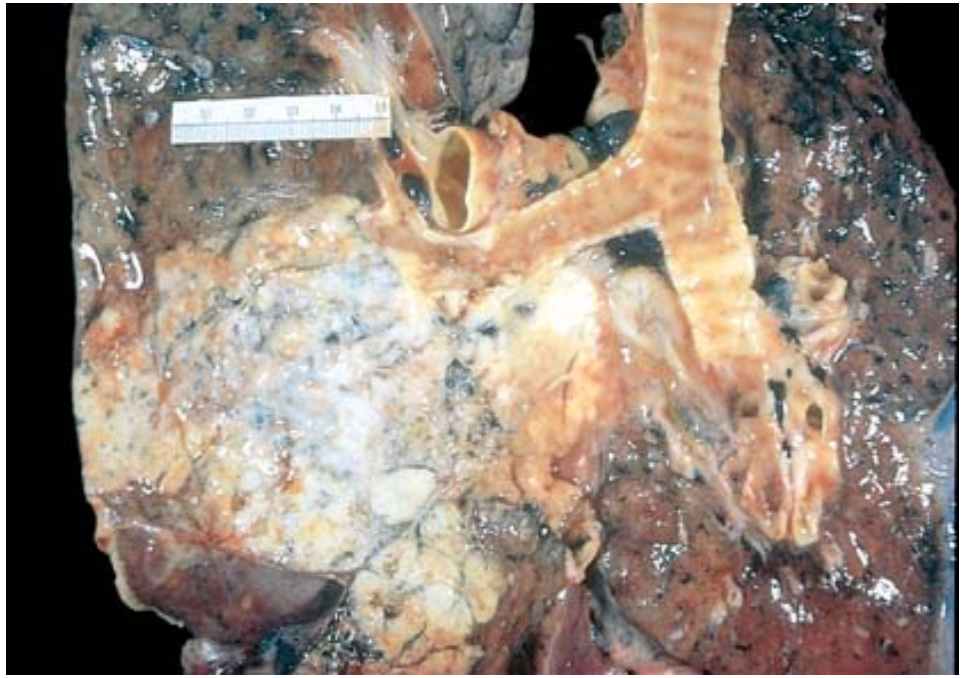

Figure 15-43 Cytologic diagnosis of lung cancer is often possible. *A*, A sputum specimen shows an orange-staining, keratinized squamous carcinoma cell with a prominent hyperchromatic nucleus (*arrow*). *B*, A fine-needle aspirate of an enlarged lymph node shows clusters of tumor cells from a small cell carcinoma, with molding and nuclear atypia characteristic of this tumor (see also Fig. 15-44*C*); note the size of the tumor cells compared with normal polymorphonuclear leukocytes in the left lower corner.

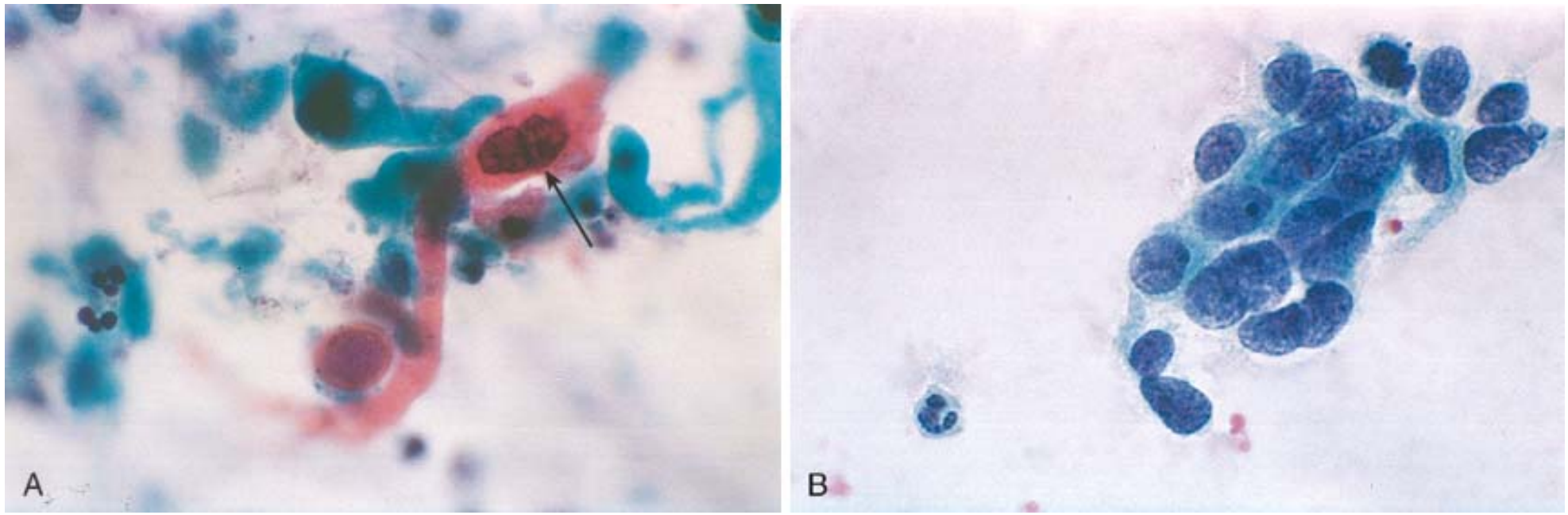

Figure 15-44 Histologic appearance of lung carcinoma. *A*, Well-differentiated squamous cell carcinoma showing keratinization. *B*, Gland-forming adenocarcinoma. *C*, Small cell

carcinoma with islands of small deeply basophilic cells and areas of necrosis. *D,* Large cell carcinoma, featuring pleomorphic, anaplastic tumor cells and absence of squamous or glandular differentiation.

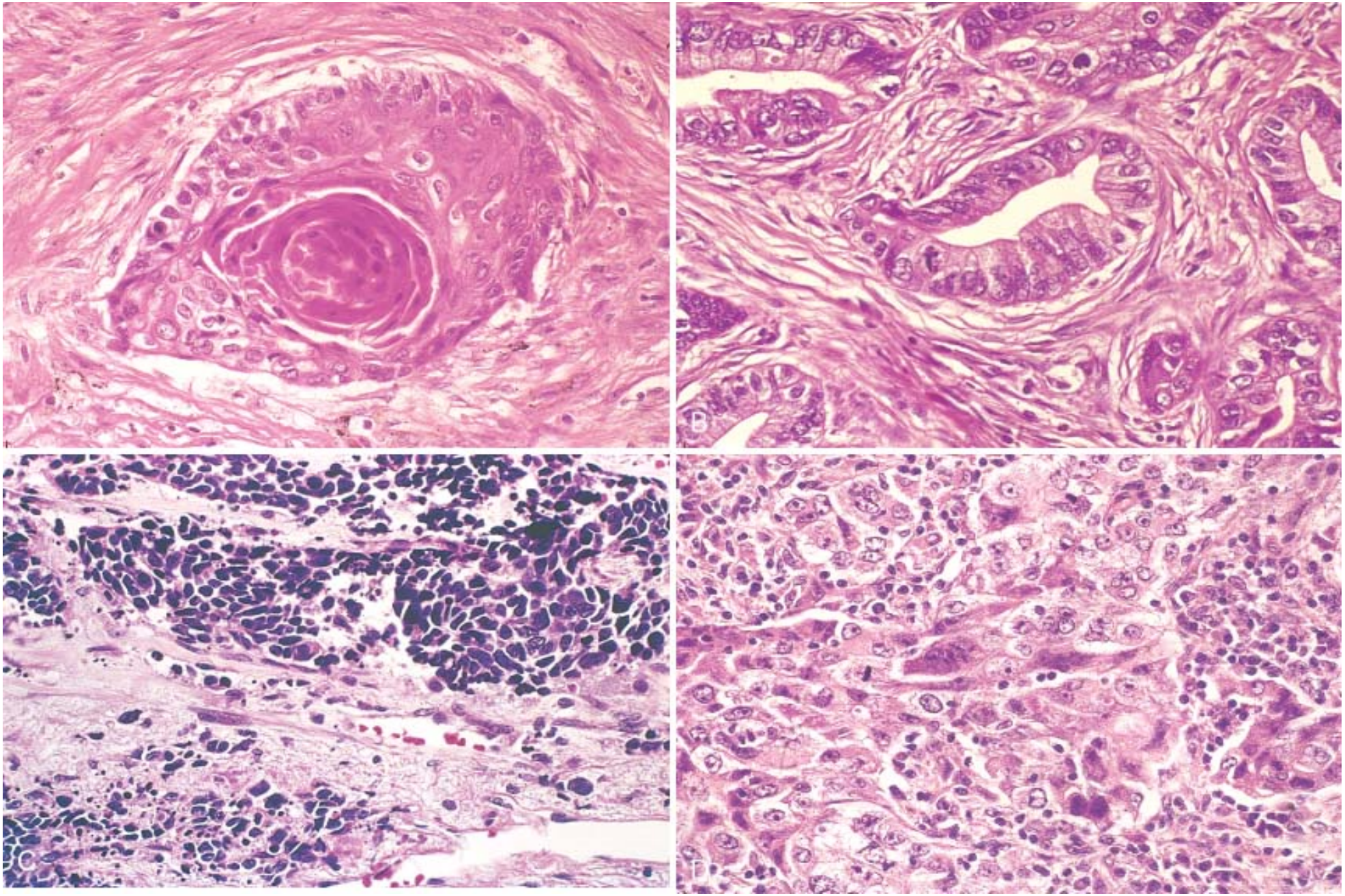

Figure 15-45 Bronchioloalveolar carcinoma with characteristic growth along pre-existing alveolar septa, without invasion. *(Courtesy of Dr. Jerome B. Taxy, Department of Pathology, The University of Chicago, Pritzker School of Medicine, Chicago, IL.)*

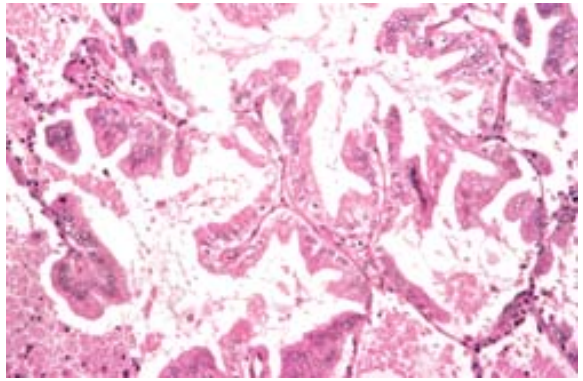

TABLE 15-11 -- New International Staging System for Lung Cancer

T1	Tumor <3 cm without pleural or main stem bronchus involvement
T2	Tumor >3 cm or involvement of main stem bronchus 2 cm from carina, visceral pleural involvement, or lobar atelectasis
T3	Tumor with involvement of chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, pericardium, main stem bronchus 2 cm from carina, or entire lung atelectasis
T4	Tumor with invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina or with a malignant pleural effusion
N0	No demonstrable metastasis to regional lymph nodes
N1	Ipsilateral hilar or peribronchial nodal involvement
N2	Metastasis to ipsilateral mediastinal or subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal or hilar lymph nodes, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
M0	No (known) distant metastasis
M1	Distant metastasis present

	Stage Grouping		
Stage Ia	T1	N0	M0
Stage Ib	T2	N0	M0
Stage IIa	T1	N1	M0
Stage IIb	T2	N1	M0
	T3	N0	M0
Stage IIIa	T1–3	N2	M0
	T3	N1	M0
Stage IIIb	Any T	N3	M0
	T3	N2	M0

	T4	Any N	M0
Stage IV	Any T	Any N	M1
Adapted from Mountain C: Revisions in the International System for Staging Lung Cancer. Chest 111:1710, 1997.			

TABLE 15-12 -- Local Effects of Lung Tumor Spread

Clinical Feature	**Pathologic Basis**
Pneumonia, abscess, lobar collapse	Tumor obstruction of airway
Lipid pneumonia	Tumor obstruction; accumulation of cellular lipid in foamy macrophages
Pleural effusion	Tumor spread into pleura
Hoarseness	Recurrent laryngeal nerve invasion
Dysphagia	Esophageal invasion
Diaphragm paralysis	Phrenic nerve invasion
Rib destruction	Chest wall invasion
SVC syndrome	SVC compression by tumor
Horner syndrome	Sympathetic ganglia invasion
Pericarditis, tamponade	Pericardial involvement
SVC, superior vena cava.	

the overall 5-year survival rate is on the order of 15%. In many large clinics, not more than 20% to 30% of lung cancer patients have lesions sufficiently localized to permit even an attempt at resection. In general, the adenocarcinoma and squamous cell patterns tend to remain localized longer and have a slightly better prognosis than do the undifferentiated cancers, which usually are advanced lesions by the time they are discovered. The survival rate is 48% for cases detected when the disease is still localized. Only 15% of lung cancers are diagnosed at this early stage. Surgical resection for *small cell carcinoma* is so ineffective that the diagnosis essentially precludes surgery. Untreated, the survival time for patients with small cell cancer is 6 to 17 weeks. This cancer is particularly sensitive to radiation and chemotherapy, and potential cure rates of 15% to 25% for limited disease have been reported in some centers. Most patients have distant metastases on diagnosis. Thus, even with treatment, the mean survival after diagnosis is about 1 year.

Despite this discouraging outlook, some patients have been cured by lobectomy or pneumonectomy, emphasizing the continued need for early diagnosis and adequate prompt therapy.

Paraneoplastic Syndromes.

Lung carcinoma can be associated with a number of paraneoplastic syndromes[127] (Chapter 7), some of which may antedate the development of a gross pulmonary lesion. The hormones or hormone-like factors elaborated include

- *Antidiuretic hormone* (ADH), inducing hyponatremia owing to inappropriate ADH secretion
- *Adrenocorticotropic hormone* (ACTH), producing Cushing syndrome
- *Parathormone, parathyroid hormone-related peptide, prostaglandin E, and some cytokines*, all implicated in the hypercalcemia often seen with lung cancer
- *Calcitonin*, causing hypocalcemia

- *Gonadotropins*, causing gynecomastia
- *Serotonin and bradykinin*, associated with the carcinoid syndrome

The incidence of clinically significant syndromes related to these factors ranges from 1% to 10% of all lung cancer

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patients, although a much higher proportion of patients show elevated serum levels of these (and other) peptide hormones. Any one of the histologic types of tumors may occasionally produce any one of the hormones, but tumors that produce ACTH and ADH are predominantly small cell carcinomas, whereas those that produce hypercalcemia are mostly squamous cell tumors. The carcinoid syndrome is more common with the carcinoid tumor, described later, and is only rarely associated with small cell carcinoma. However, small cell carcinoma occurs much more commonly; therefore, one is much more likely to encounter carcinoid syndrome in these patients.

Other systemic manifestations of lung carcinoma include the *Lambert-Eaton myasthenic syndrome* (Chapter 27), in which muscle weakness is caused by auto-antibodies (possibly elicited by tumor ionic channels) directed to the neuronal calcium channel;[127] *peripheral neuropathy*, usually purely sensory; dermatologic abnormalities, including *acanthosis nigricans* (Chapter 25); hematologic abnormalities, such as *leukemoid reactions*; and finally, a peculiar abnormality of connective tissue called *hypertrophic pulmonary osteoarthropathy*, associated with clubbing of the fingers.

Apical lung cancers in the superior pulmonary sulcus tend to invade the neural structures around the trachea, including the cervical sympathetic plexus, and produce a group of clinical findings that includes severe pain in the distribution of the ulnar nerve and *Horner syndrome* (enophthalmos, ptosis, miosis, and anhidrosis) on the same side as the lesion. Such tumors are also referred to as *Pancoast tumors*.

NEUROENDOCRINE PROLIFERATIONS AND TUMORS

Neuroendocrine lesions share morphologic and biochemical features with cells of the *dispersed neuroendocrine cell system* (Chapter 24).[128] The normal lung contains neuroendocrine cells within the epithelium as single cells or as clusters, the neuroepithelial bodies. While virtually all pulmonary neuroendocrine cell hyperplasias are secondary to airway fibrosis and/or inflammation, a rare disorder called diffuse idiopathic pulmonary neuroendocrine cell hyperplasia appears to be a precursor to the development of multiple tumorlets and typical or atypical carcinoids.

Figure 15-46 *A*, Bronchial carcinoid growing as a spherical, pale mass (*arrow*) protruding into the lumen of the bronchus. *B*, Histologic appearance of bronchial carcinoid, demonstrating small, rounded, uniform cells.

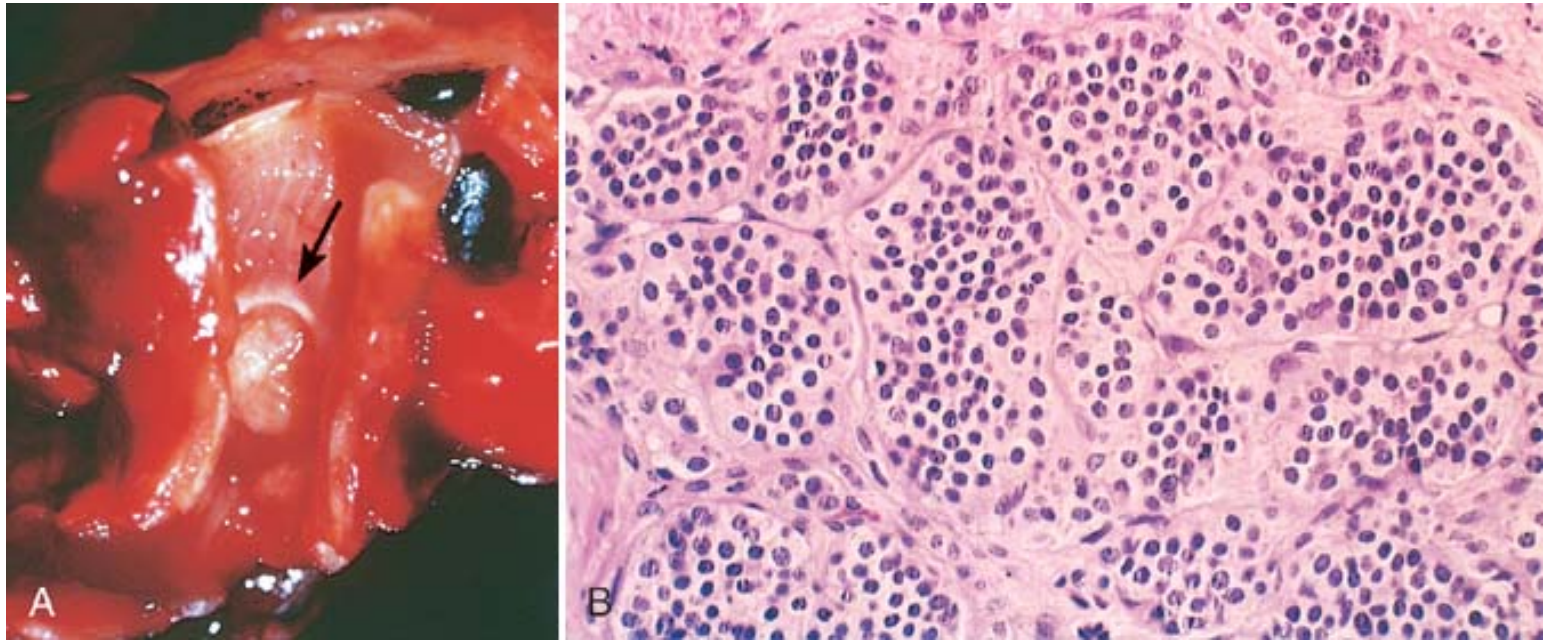


TABLE 15-13 -- Mediastinal Tumors and Other Masses

Superior Mediastinum
Lymphoma
Thymoma
Thyroid lesions
Metastatic carcinoma
Parathyroid tumors
Anterior Mediastinum
Thymoma
Teratoma
Lymphoma
Thyroid lesions
Parathyroid tumors
Posterior Mediastinum
Neurogenic tumors (schwannoma, neurofibroma)
Lymphoma

Gastroenteric hernia
Middle Mediastinum
Bronchogenic cyst
Pericardial cyst
Lymphoma

occurs most often with esophageal carcinomas and mediastinal lymphomas.

Morphology.

The pattern of metastatic growth within the lungs is quite variable. In the usual case, multiple discrete nodules (cannonball lesions) are scattered throughout all lobes (Fig. 15-47). These discrete lesions tend to occur in the periphery of the lung rather than in the central locations of the primary lung carcinoma. Other patterns include solitary nodule, endobronchial, pleural, pneumonic consolidation, and mixtures of the above. Foci of lepidic growth similar to bronchioloalveolar carcinoma are seen occasionally with metastatic carcinomas and may be associated with any of the patterns listed above.

Metastatic growth may be confined to peribronchiolar and perivascular tissue spaces, presumably when the tumor has extended to the lung through the lymphatics. In these cases, the lung septa and connective tissue are diffusely infiltrated with the gray-white tumor. The subpleural lymphatics may be outlined by the contained tumor, producing a gross appearance referred to as lymphangitis carcinomatosa. Least commonly, the metastatic tumor is not apparent on gross examination and becomes evident only on histologic section as a diffuse intralymphatic dissemination dispersed throughout the peribronchial and perivascular channels. In certain instances, microscopic tumor emboli fill the small pulmonary vessels and may result in life-threatening pulmonary hypertension or hemorrhage and hemoptysis.

Pleura

Pathologic involvement of the pleura is, with rare exceptions, a secondary complication of some underlying disease. Secondary infections and pleural adhesions are particularly common findings at autopsy. Occasionally, the secondary pleural disease assumes a dominant role in the clinical problem, as occurs in bacterial pneumonia with the development of empyema. Important primary disorders include (1) primary intrapleural bacterial infections that imply seeding of this space as an isolated focus in the course of a transient bacteremia and (2) a primary neoplasm of the pleura: mesothelioma (discussed later).

PLEURAL EFFUSION

Pleural effusion is a common manifestation of both primary and secondary pleural diseases. Normally, no more

TABLE 15-14 -- Pleural Space Fluid Accumulations

Condition	Type of Fluid	Common Associations
Inflammatory		

Serofibrinous pleuritis	Serofibrinous exudate	Inflammation in adjacent lung
		Collagen vascular disease
Suppurative pleuritis (empyema)	Pus	Suppurative infection in adjacent lung
Hemorrhagic pleuritis	Bloody exudate	Tumor
Noninflammatory		
Hydrothorax	Transudate	Congestive heart failure
Hemothorax	Blood	Ruptured aortic aneurysm, trauma
Chylothorax	Chyle (lymph)	Tumor obstruction of normal lymphatics

Figure 15-47 Numerous metastases from a renal cell carcinoma. *(Courtesy of Dr. Michelle Mantel, Brigham and Women's Hospital, Boston, MA.)*

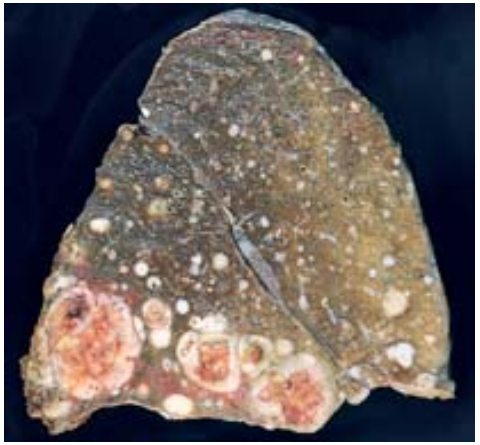


Figure 15-48 Malignant mesothelioma. Note the thick, firm, white pleural tumor tissue that ensheathes this bisected lung.

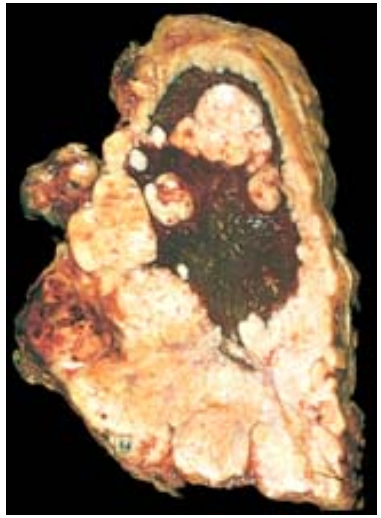


Figure 15-49 *A,* Malignant mesothelioma, epithelial type. *B,* Malignant mesothelioma, mixed type, stained for calretinin (immunoper-oxidase method). The epithelial component is strongly positive (*dark brown*), while the sarcomatoid component is less so. *(Courtesy of Dr. Thomas Krausz, Department of Pathology, The University of Chicago, Pritzker School of Medicine, Chicago, IL.)*

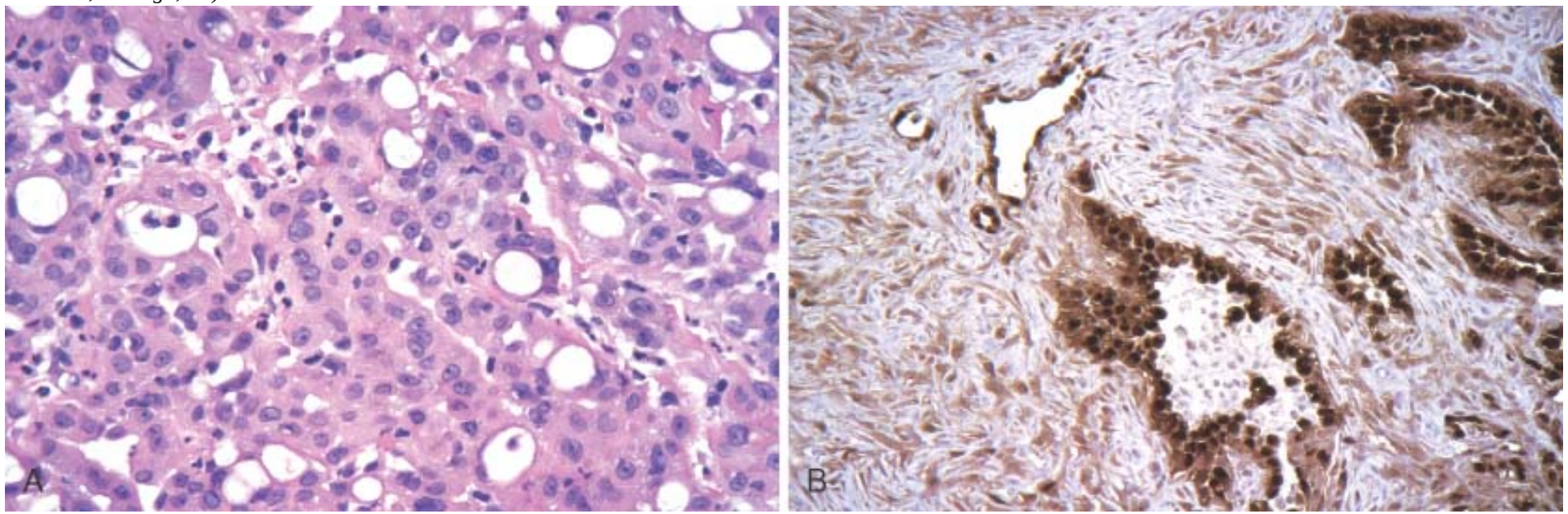
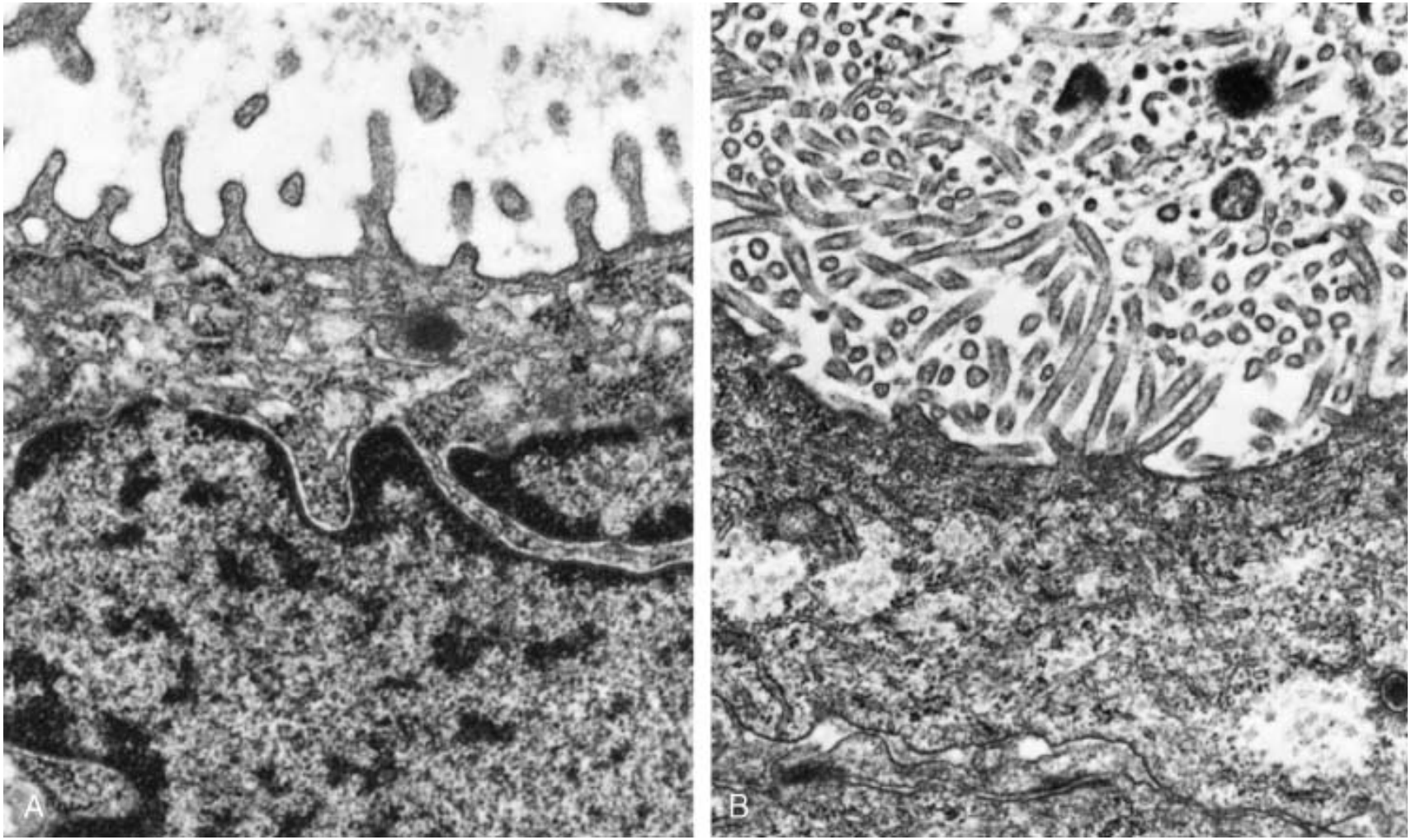


Figure 15-50 Ultrastructural features of pulmonary adenocarcinoma (*A*), characterized by short, plump microvilli, contrasted with those of mesothelioma (*B*), in which microvilli are numerous, long, and slender. *(Courtesy of Dr. Noel Weidner, University of California, San Francisco, School of Medicine, San Francisco, CA.)*



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Chapter 16 - Head and Neck

Mark W. Lingen DDS, PhD
Vinay Kumar MD

Diseases of the head and neck range from the common cold to uncommon neoplasms of the nose. Those selected for discussion are assigned, sometimes arbitrarily, to one of the following anatomic sites: (1) oral cavity; (2) upper airways, including the nose, pharynx, larynx, and nasal sinuses; (3) ears; (4) neck; and (5) salivary glands.

Oral Cavity

The oral cavity is a fearsome orifice guarded by ranks of upper and lower "horns" (lamentably, quite subject to erosion), demanding constant gratification, and teeming with microorganisms, some of which are potentially harmful. Among the many disorders that affect its various parts, only the more important or frequent conditions involving the teeth and supporting structures, oral mucous membranes, lips, and tongue are considered.

Teeth and Supporting Structures

Teeth contribute to a number of important functions, including mastication and proper speech. It is useful to briefly review normal dental anatomy before we delve into the common pathologic conditions affecting teeth. As is well known, teeth are firmly implanted in the jaw and are surrounded by the gingival mucosa (Fig. 16-1). The anatomic crown of the tooth projects into the mouth and is covered by

Figure 16-1 Schematic representation of the normal dental anatomy and surrounding supporting tissues.

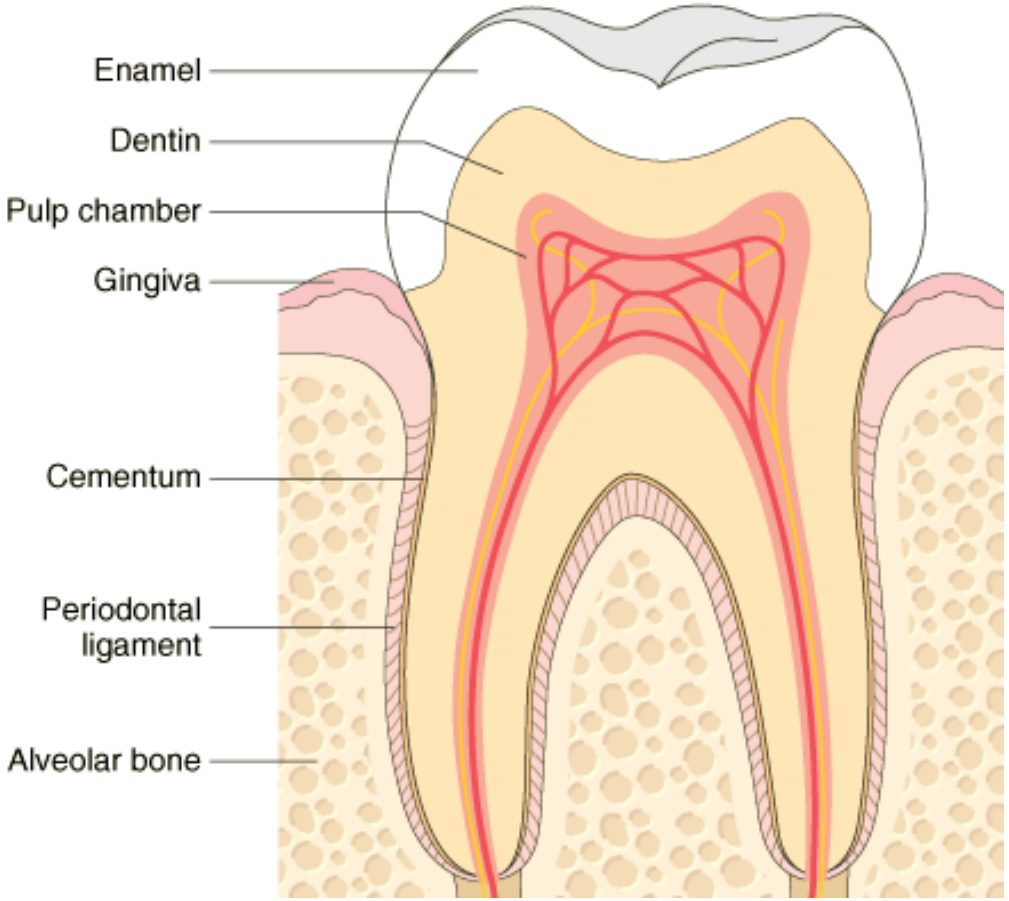

Figure 16-2 Fibroma. Smooth, pink, exophytic nodule on the buccal mucosa.

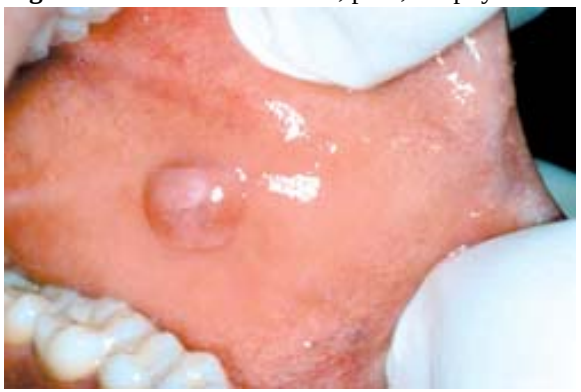

Figure 16-3 Pyogenic granuloma. Erythematous, hemorrhagic, and exophytic mass arising from the gingival mucosa.

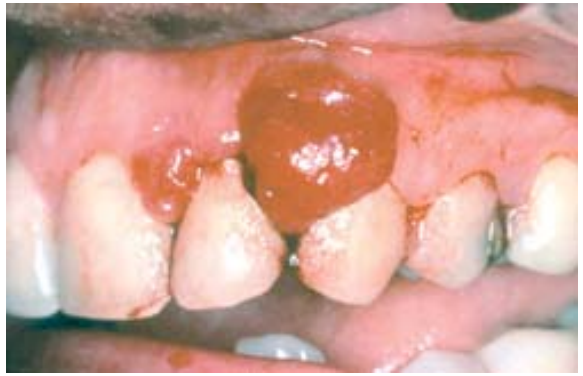

Figure 16-4 Aphthous ulcer. Single ulceration with an erythematous halo surrounding a yellowish fibrinopurulent membrane.

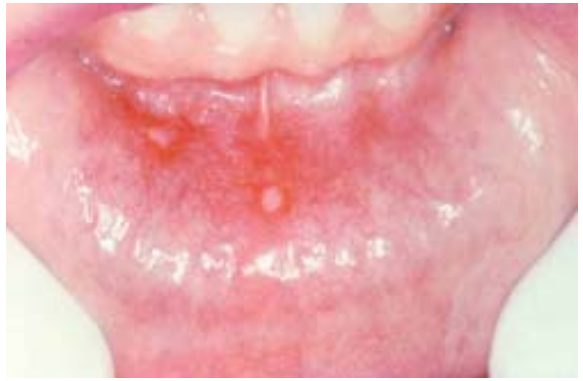

TABLE 16-1 -- Oral Manifestations of Some Systemic Diseases

Infectious Diseases	
Scarlet fever	Fiery red tongue with prominent papillae (raspberry tongue); white coated tongue through which hyperemic papillae project (strawberry tongue)
Measles	A spotty enanthema in the oral cavity often precedes the rash; ulcerations on the buccal mucosa about Stensen duct produce Koplik spots
Infectious mononucleosis	An acute pharyngitis and tonsillitis that may cause coating with a gray-white exudative membrane; enlargement of lymph nodes in the neck
Diphtheria	A characteristic dirty white, fibrinosuppurative, tough, inflammatory membrane over the tonsils and retropharynx
Human immunodeficiency virus infection; AIDS	Predisposition to opportunistic oral infections, particularly with herpesvirus, *Candida*, and other fungi; sometimes oral lesions of Kaposi sarcoma and hairy leukoplakia (described in text)
Dermatologic Conditions *	
Lichen planus	Reticulate, lacelike, white keratotic lesions that rarely become bullous and ulcerated; seen in more than 50% of patients with cutaneous lichen planus; rarely, is the sole manifestation
Pemphigus	Usually vulgaris; vesicles and bullae prone to rupture, leaving hyperemic erosions covered with exudate
Bullous pemphigoid	Oral lesions resemble macroscopically those of pemphigus but can be differentiated histologically

Erythema multiforme	A maculopapular, vesiculobullous eruption that sometimes follows an infection elsewhere, ingestion of drugs, development of cancer, or a collagen vascular disease; when it involves the lips and oral mucosa, it is referred to as *Stevens-Johnson syndrome*
Hematologic Disorders	
Pancytopenia (agranulocytosis, aplastic anemia)	Severe oral infections in the form of gingivitis, pharyngitis, tonsillitis; may extend to cellulitis of the neck *(Ludwig angina)*
Leukemia	With depletion of functioning neutrophils, oral lesions may appear like those in pancytopenia
Monocytic leukemia	Leukemic infiltration and enlargement of the gingivae, often with accompanying periodontitis
Miscellaneous	
Melanotic pigmentation	May appear in Addison disease, hemochromatosis, fibrous dysplasia of bone (Albright syndrome), and Peutz-Jegher syndrome (gastrointestinal polyposis)
Phenytoin (Dilantin) ingestion	Striking fibrous enlargement of the gingivae
Pregnancy	A friable, red, pyogenic granuloma protruding from the gingiva ("pregnancy tumor")
Rendu-Osler-Weber syndrome	Autosomal dominant disorder with multiple aneurysmal telangiectasias from birth beneath the skin or mucosal surfaces of the oral cavity, lips, gastrointestinal tract, respiratory tract, and urinary tract as well as in internal viscera

*See Chapter 25 for details

most cells and is now accepted as the cause of the condition.[7] Sometimes there is superimposed candidal infection on the surface of the lesions, adding to the "hairiness." When the hairy leukoplakia is a harbinger of HIV infection, manifestations of AIDS generally appear within 2 or 3 years.

Tumors and Precancerous Lesions

A number of epithelial and soft tissue neoplasms can arise in the oral cavity. Many of these tumors (e.g., papillomas, hemangiomas, lymphomas) also occur elsewhere in the body and are described adequately in other chapters. Therefore, this discussion will consider only oral squamous cell carcinoma and its associated precancerous lesions.

LEUKOPLAKIA AND ERYTHROPLAKIA

As is discussed in more detail below, oral cancers are common worldwide, with a fairly high mortality. Screening and early detection in populations at risk have been proposed to decrease both the morbidity and mortality associated with oral cancer.[8] [9] However, the visual detection of definitive premalignant oral lesions is problematic. This is in stark contrast to skin lesions, where visual screening for melanomas of the skin has been shown to have sensitivity and specificity rates of 93% and 98%. [10] [11] One explanation for this discrepancy is that the early lesions frequently do not demonstrate any of the clinical characteristics observed in advanced oral cancer: ulceration, induration, pain, or associated cervical lymphadenopathy.[12] In addition, the clinical presentation of potentially premalignant lesions in the oral cavity is highly heterogeneous. We begin our discussion with two premalignant lesions—leukoplakia and erythroplakia.

The term *leukoplakia* is defined by the World Health Organization as "a white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease." Simply put, if a white lesion in the oral cavity can be given a specific diagnosis it is not a leukoplakia. This clinical term is reserved for lesions that are present in the oral cavity for no apparent reason. As such, white patches caused by entities such as lichen planus and candidiasis are not leukoplakias. Approximately 3% of the world's population have

leukoplakic lesions, and somewhere between 5% and 25% of these lesions are premalignant.[13] *Thus, until it is proved otherwise via histologic evaluation, all leukoplakias must be considered precancerous.*

Related to leukoplakia, but much less common and much more ominous, is *erythroplakia*. It represents a red, velvety, possibly eroded area within the oral cavity that usually remains level with or may be slightly depressed in relation to the surrounding mucosa (Fig. 16-5). The epithelium in such

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Figure 16-5 Erythroplakia. *A,* Lesion of the maxillary gingiva. *B,* Red lesion of the mandibular alveolar ridge. Biopsy of both lesions revealed carcinoma in situ.

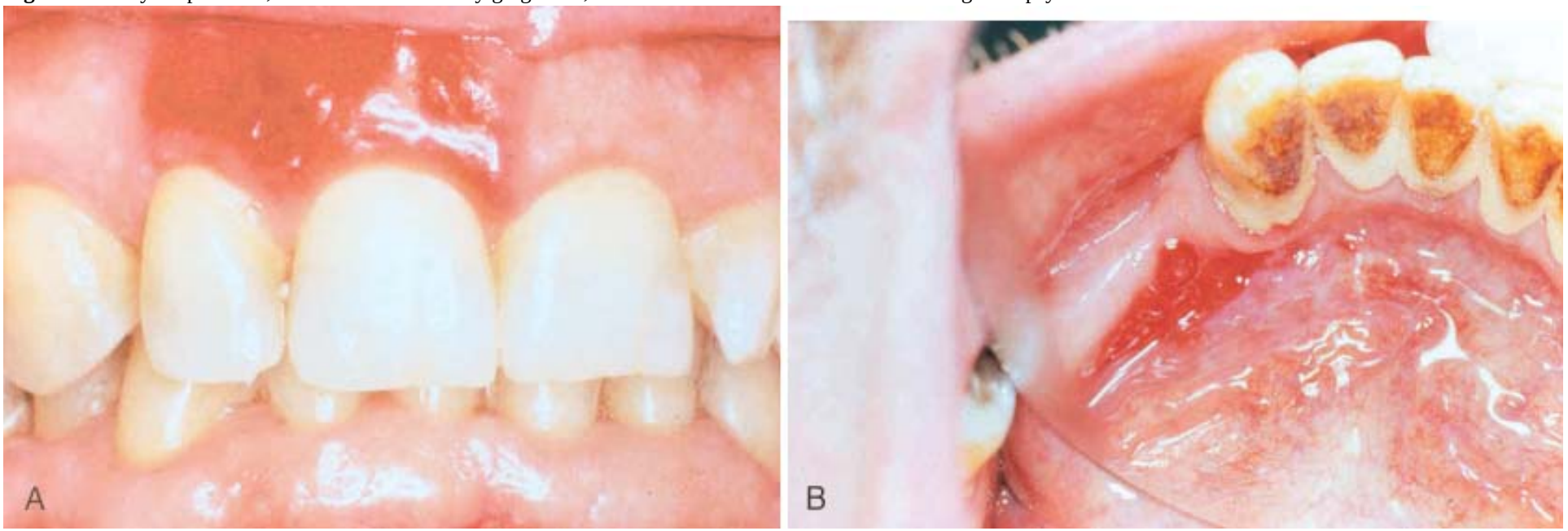


Figure 16-6 Leukoplakia. Clinical appearance of leukoplakias is highly variable and can range from *A,* smooth and thin with well-demarcated borders. *B,* diffuse and thick. *C,* irregular with a granular surface. *D,* diffuse and corrugated. *(Courtesy of Drs. Neville, Damm, Allen, Bouquot [eds], Oral & Maxillofacial Pathology, Philadelphia, WB Saunders, 2002.)*

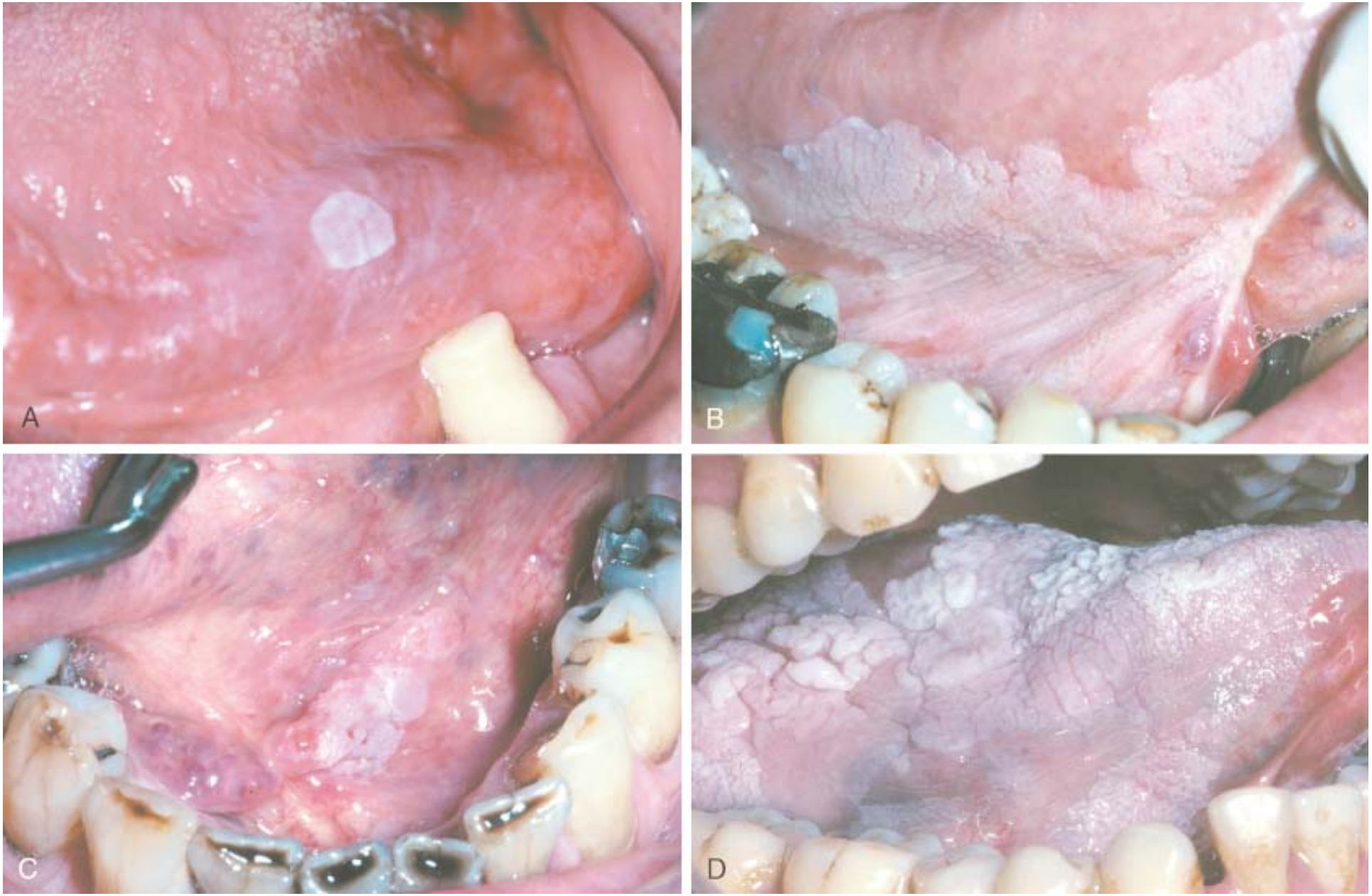


Figure 16-7 Clinical, histologic, and molecular progression of oral cancer. *A,* The typical clinical progression of oral cancer. *B,* The histologic progression of squamous epithelium from normal, to hyperkeratosis, to mild/moderate dysplasia, to severe dysplasia, to cancer. *C,* The sites of the most common genetic alterations identified as important for cancer development. *(Clinical photographs courtesy of Sol Silverman, M.D., from the text Silverman S: Oral Cancer. Hamilton, Ontario, BD Dekker, 2003.)*

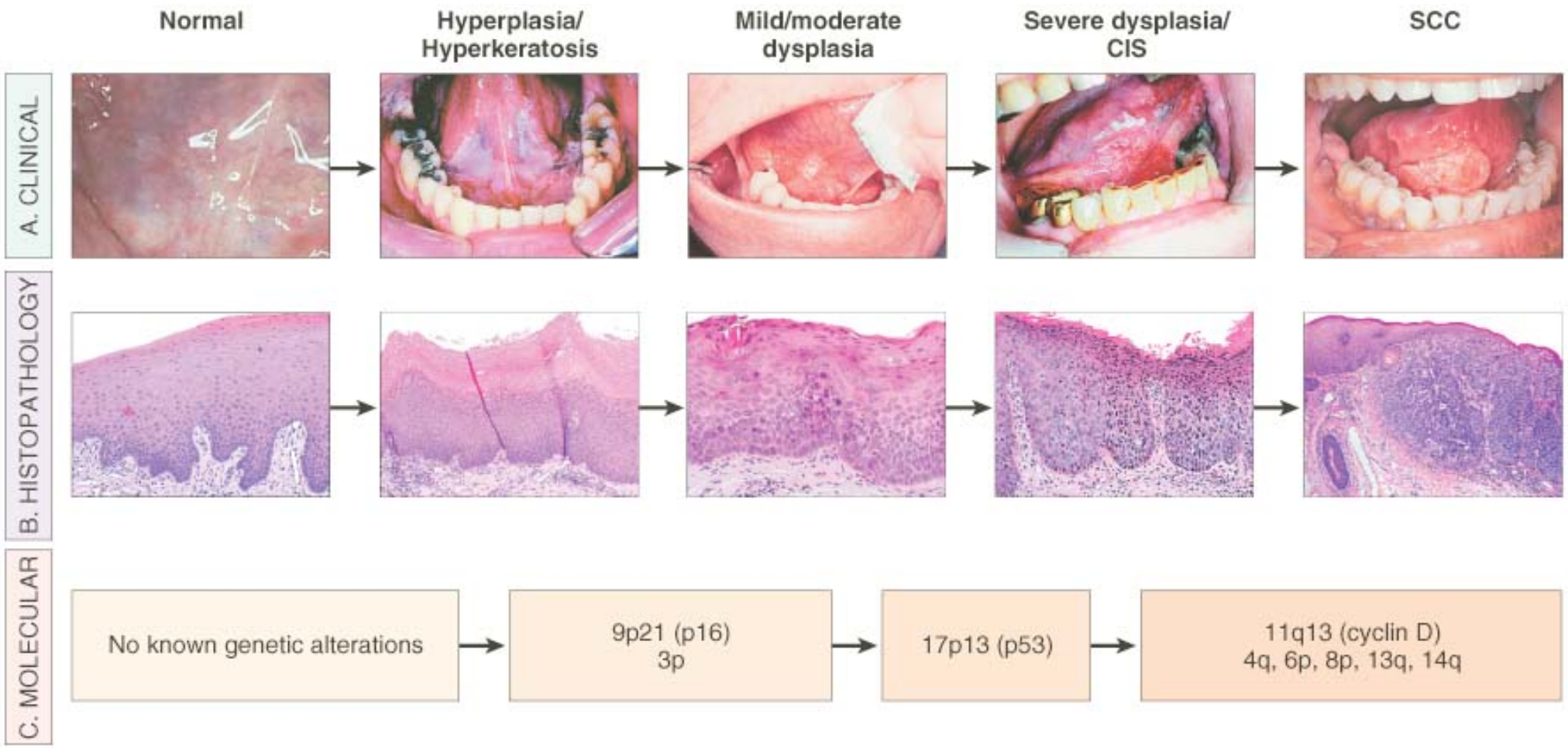


Figure 16-8 Schematic representation of the sites of origin of squamous cell carcinoma of the oral cavity, in numerical order of frequency.

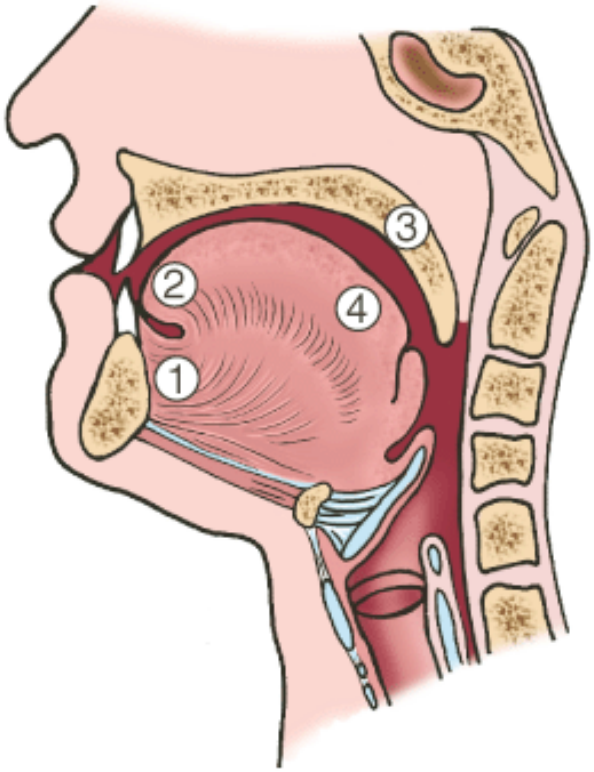


TABLE 16-2 -- Histologic Classification of Odontogenic Cysts

1. Inflammatory
•••a. Periapical cyst
•••b. Residual cyst
•••c. Paradental cyst
2. Developmental
•••a. Dentigerous cyst
•••b. Odontogenic keratocyst
•••c. Gingival cyst of newborn
•••d. Gingival cyst of adult
•••e. Eruption cyst
•••f. Lateral periodontal cyst
•••g. Glandular odontogenic cyst

•••h. Calcifying epithelial odontogenic cyst (Gorlin cyst)

which may be caused by advanced carious lesions or by trauma to the tooth in question. The inflammatory process may result in necrosis of the pulpal tissue, which can traverse the length of the root and exit the apex of the tooth into the surrounding alveolar bone giving rise to a periapical abscess. Over time, like any chronic inflammatory process, a lesion with granulation tissue (with or without an epithelial lining) may develop. While the term *granuloma* is not the most appropriate terminology (as the lesion does not show true granulomatous inflammation), old terminology, like bad habits, is difficult to shed. Periapical inflammatory lesions persist as a result of the continued presence of bacteria or other offensive agents in the area. Successful treatment therefore necessitates the complete removal of offending material and appropriate restoration of the tooth or extraction.

Odontogenic tumors are a complex group of lesions with diverse histology and clinical behavior.[33] Some are true neoplasms (both benign and malignant), while others are more likely hamartomas. Odontogenic tumors are derived from odontogenic epithelium, ectomesenchyme, or both (Table 16-3). The two most common and clinically significant tumors are:

- *Ameloblastoma,* which arises from odontogenic epithelium and shows *no* ectomesenchymal differentiation. It is commonly cystic, slow growing, and locally invasive but has a benign course in most cases.
- *Odontoma,* the most common type of odontogenic tumor, arises from epithelium but shows extensive depositions of enamel and dentin. Odontomas are probably hamartomas rather than true neoplasms and are cured by local excision.

TABLE 16-3 -- Histologic Classification of Odontogenic Tumors

1. Tumors of Odontogenic Epithelium
•••Benign
•••••a. Ameloblastoma
•••••b. Calcifying epithelial odontogenic tumor (Pindborg tumor)
•••••c. Squamous odontogenic tumor
•••Malignant
•••••a. Ameloblastic carcinoma
•••••b. Malignant ameloblastoma
•••••c. Clear cell odontogenic carcinoma
2. Tumors of Odontogenic Ectomesenchyme
•••a. Odontogenic fibroma
•••b. Odontogenic myxoma
•••c. Cementoblastoma
3. Tumors of Odontogenic Epithelium and Ectomesenchyme
•••Benign
•••••a. Ameloblastic fibroma
•••••b. Ameloblastic fibro-odontoma

•••••c. Ameloblastic fibrosarcoma
•••••d. Adenomatoid odontogenic tumor
•••••e. Odontoameloblastoma
•••••f. Complex odontoma
•••••g. Compound odontoma
•••Malignant
•••••a. Ameloblastic fibrosarcoma

Upper Airways

The term *upper airways* is used here to include the nose, pharynx, and larynx and their related parts. Disorders of these structures are among the most common afflictions of humans, but fortunately the overwhelming majority are more nuisances than threats.

Nose

Inflammatory diseases, mostly in the form of the common cold, as everyone knows, are the most common disorders of the nose and accessory air sinuses. Most of these inflammatory conditions are viral in origin, but they are often complicated by superimposed bacterial infections having considerably greater significance. Much less common are a few destructive inflammatory nasal diseases and tumors primary in the nasal cavity or paranasal sinuses.

INFLAMMATIONS

Infectious Rhinitis.

Infectious rhinitis, the more elegant way of saying "common cold," is in most instances caused by one or more viruses. Major offenders are adenoviruses, echoviruses, and rhinoviruses. They evoke a profuse catarrhal discharge that is familiar to all and the bane of the kindergarten teacher. During the initial acute stages, the nasal mucosa is thickened, edematous, and red; the nasal cavities are narrowed; and the turbinates are enlarged. These changes may extend, producing a concomitant pharyngotonsillitis. Secondary bacterial infection enhances the inflammatory reaction and produces an essentially mucopurulent or sometimes frankly suppurative exudate. But as everyone knows, these infections soon clear up—as the saying goes, in a week if treated but after 7 days if ignored.

Figure 16-9 *A*, Nasal polyps. Low-power magnification showing edematous masses lined by epithelium. *B*, High-power view showing edema and eosinophil-rich inflammatory infiltrate.

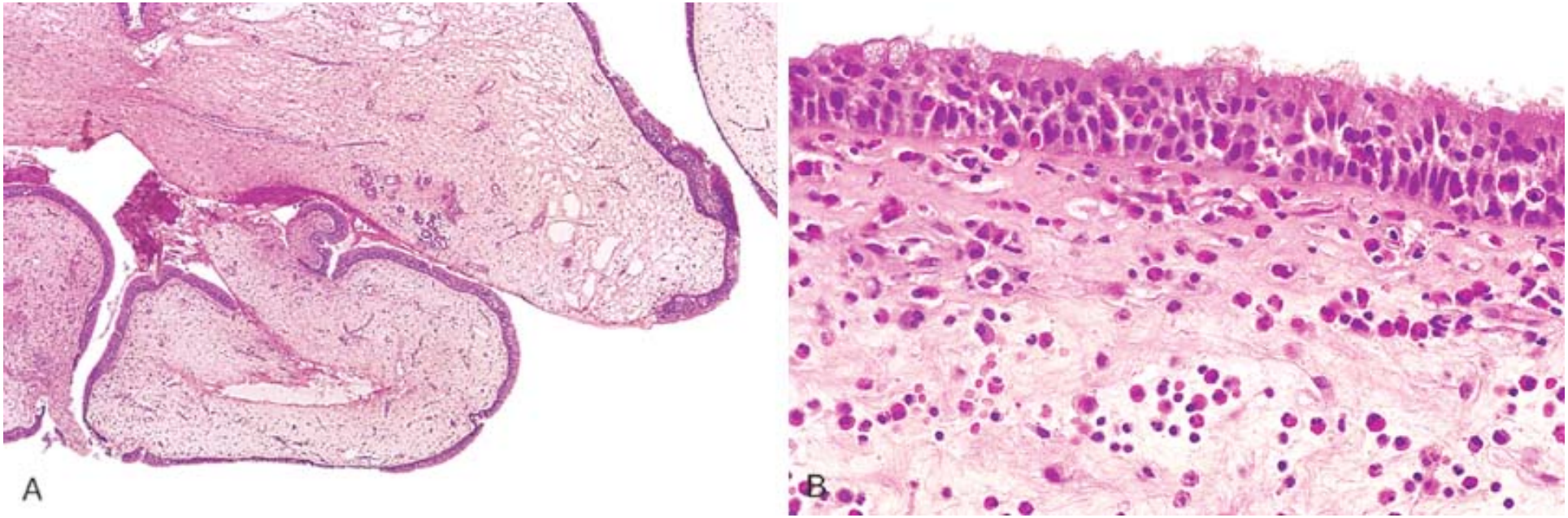


Figure 16-10 Inverted papilloma. The masses of squamous epithelium are growing inward; hence, the term inverted. *(Courtesy of Dr. James Gulizia, Brigham and Women's Hospital, Boston, MA.)*

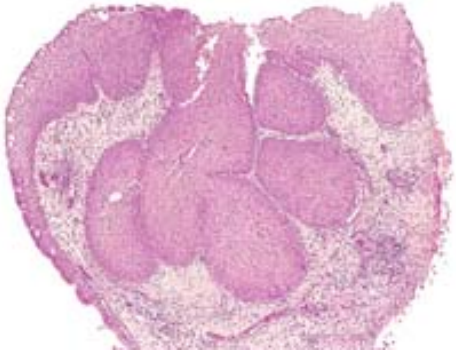


Figure 16-11 Nasopharyngeal carcinoma, lymphoepithelioma type. The syncytium-like nests of epithelium are surrounded by lymphocytes. *(Courtesy of Dr. James Gulizia, Brigham and Women's Hospital, Boston, MA.)*

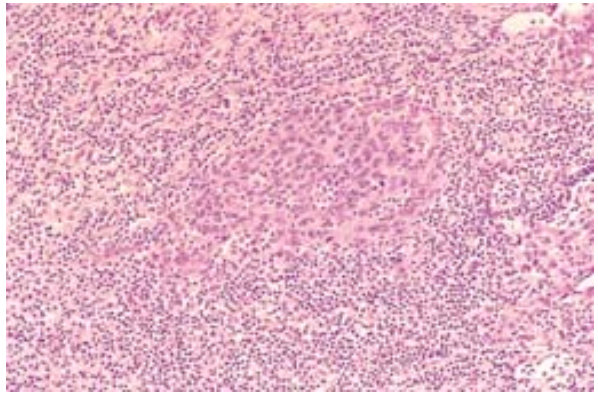
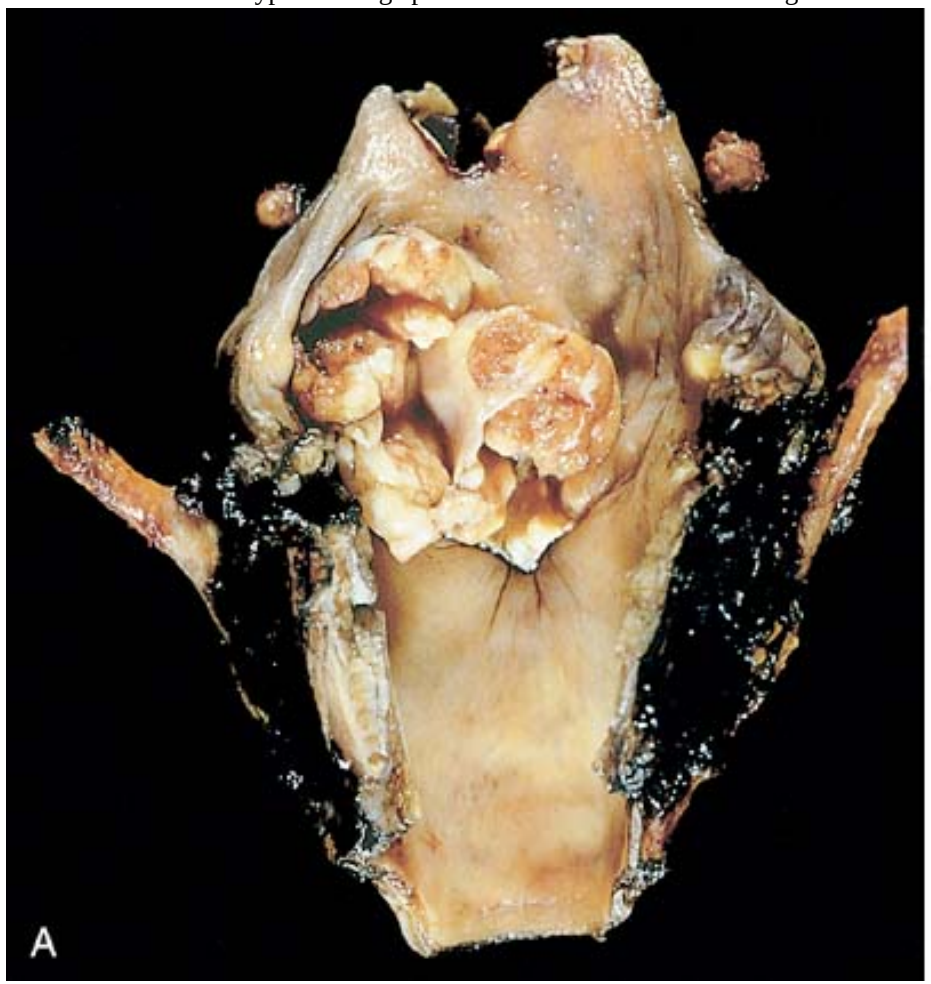


Figure 16-12 *A,* Laryngeal carcinoma. Note the large, ulcerated, fungating lesion involving the vocal cord and piriform sinus. *B,* Histologic appearance of laryngeal squamous cell carcinoma. Note the atypical lining epithelium and invasive keratinizing cancer cells in the submucosa.



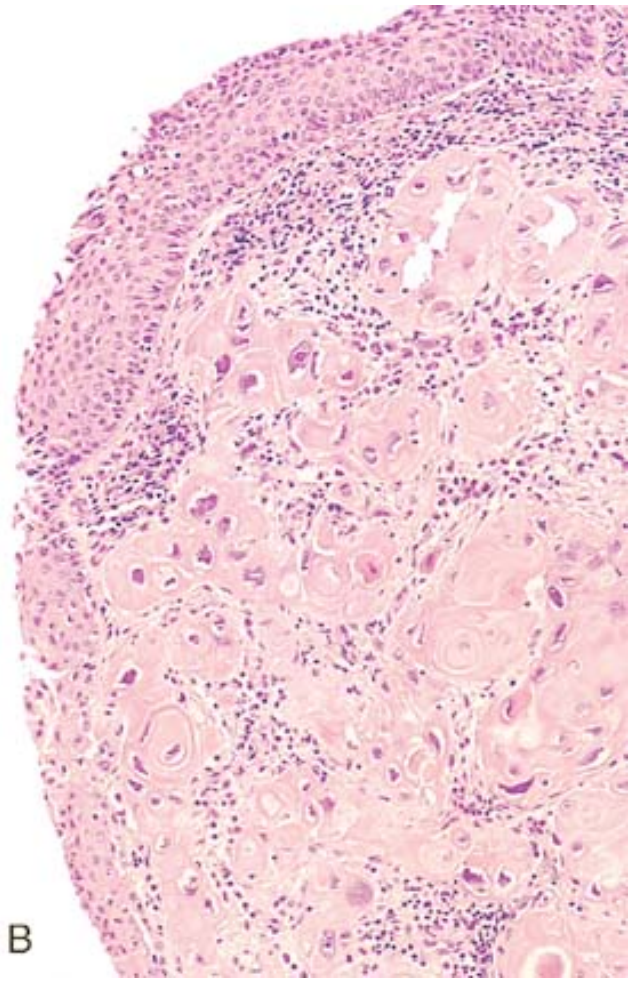


Figure 16-13 Diagrammatic comparison of a benign papilloma and an exophytic carcinoma of the larynx to highlight their quite different appearances.

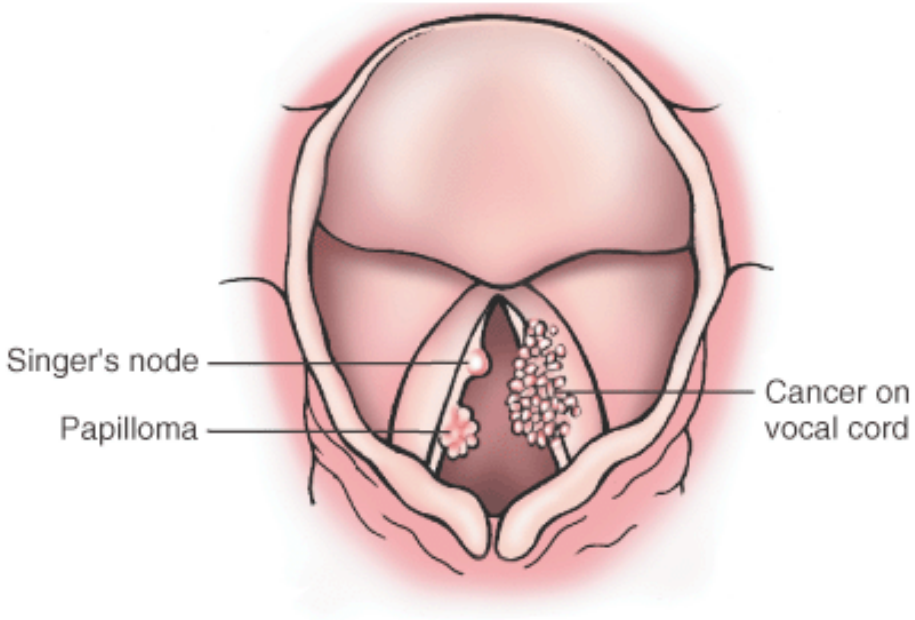


Figure 16-14 Carotid body tumor. *A,* Low-power view showing tumor clusters separated by septa (zellballen). *B,* High-power view of large, eosinophilic, slightly vacuolated tumor cells with elongated sustentacular cells in the septa.

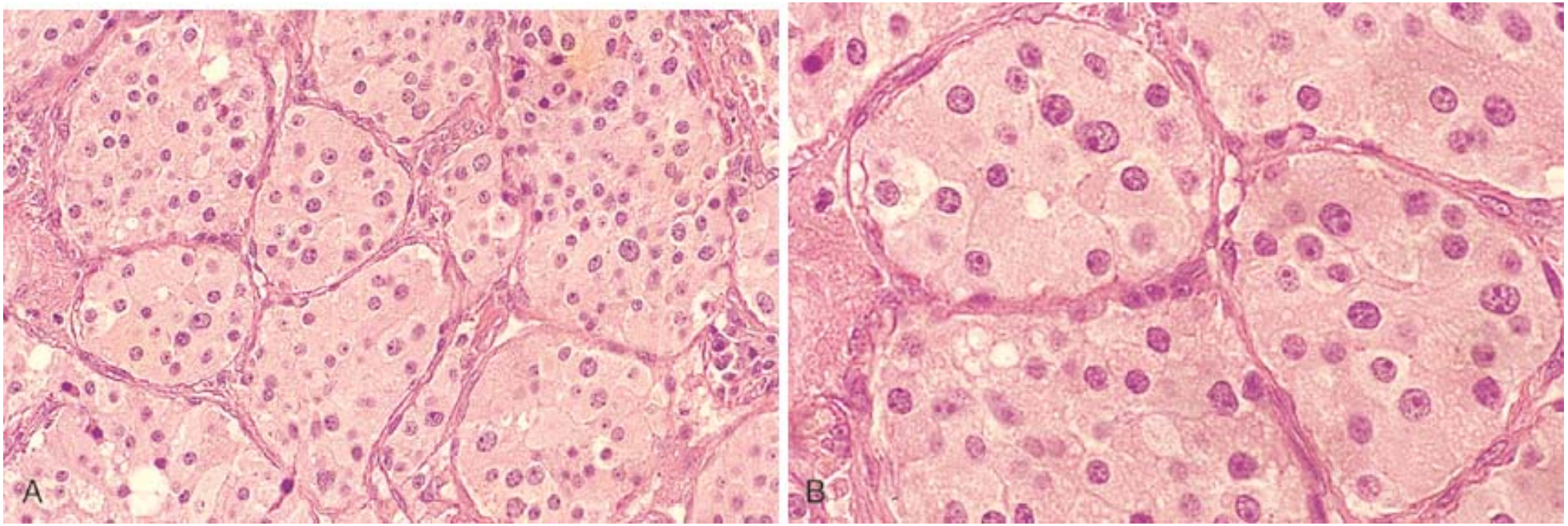
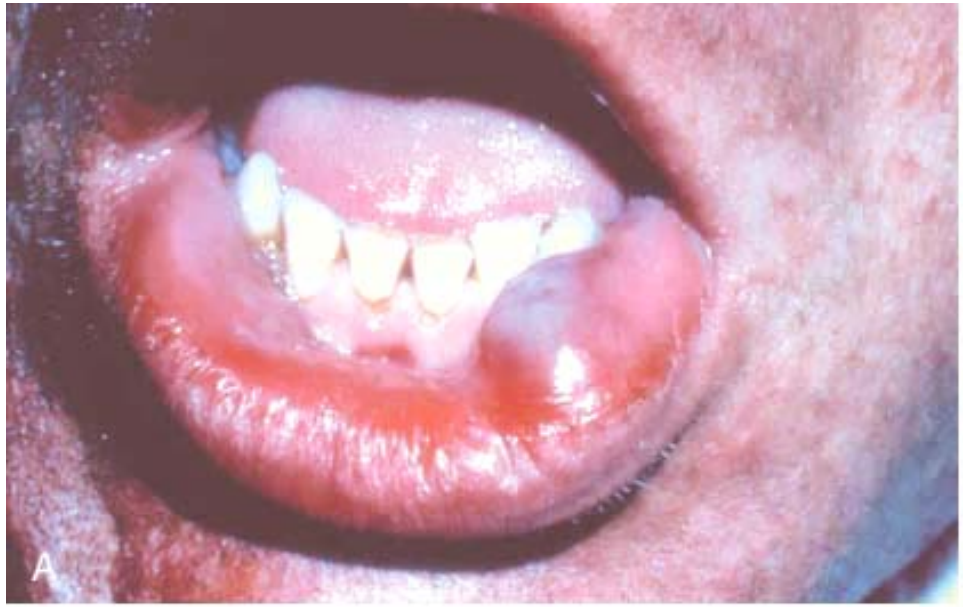


Figure 16-15 Mucocele. *A,* Fluctuant fluid-filled lesion on the lower lip subsequent to trauma. *B,* Cystlike cavity filled with mucinous material and lined by organizing granulation tissue.



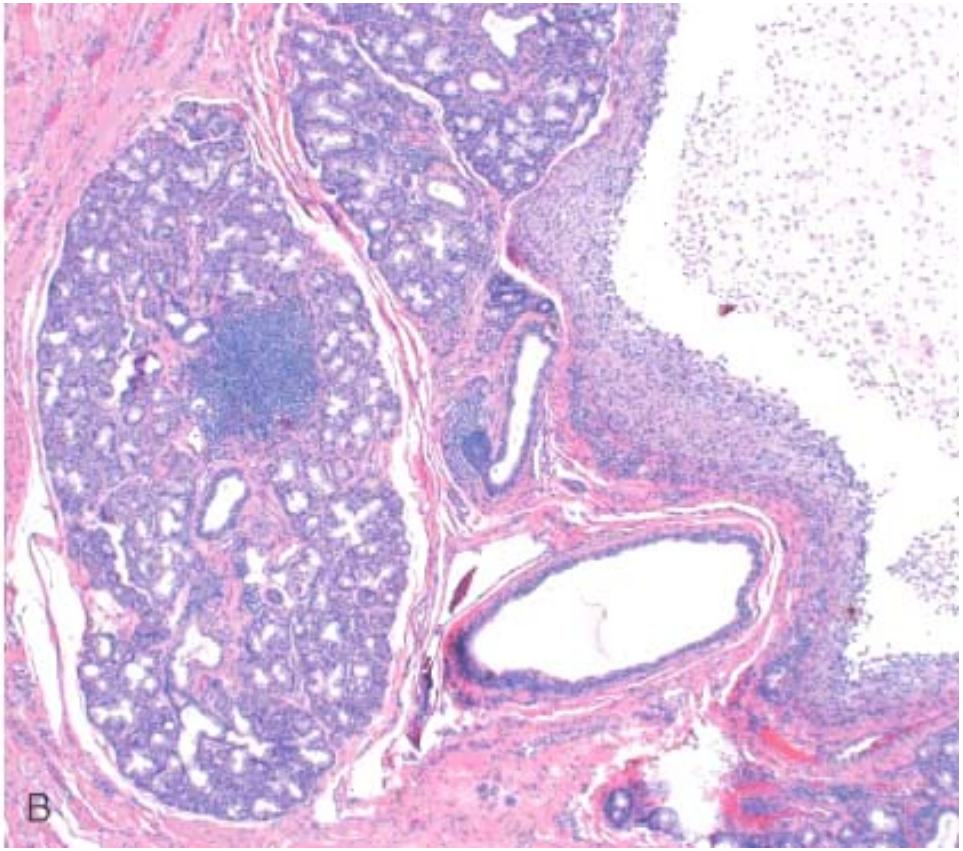


TABLE 16-4 -- Histologic Classification and Approximate Incidence of Benign and Malignant Tumors of the Salivary Glands

Benign	**Malignant**
Pleomorphic adenoma (50%) (mixed tumor)	Mucoepidermoid carcinoma (15%)
Warthin tumor (5%–10%)	Adenocarcinoma (NOS) (10%)
Oncocytoma (1%)	Acinic cell carcinoma (5%)
Other adenomas (5%–10%)	Adenoid cystic carcinoma (5%)
••Basal cell adenoma	Malignant mixed tumor (3%–5%)
••Canalicular adenoma	Squamous cell carcinoma (1%)
Ductal papillomas	Other carcinomas (2%)
NOS, not otherwise specified. *Data from Ellis GL, Auclair PL: Tumors of the Salivary Glands. Atlas of Tumor Pathology, Third Series. Washington, DC, Armed Forces Institute of Pathology, 1996.*	

ear. In general, when they are first diagnosed, both benign and malignant lesions range from 4 to 6 cm in diameter and are mobile on palpation except in the case of neglected malignant tumors. Although benign tumors are known to have been present usually for many months to several years before coming to clinical attention, cancers seem to demand attention more

promptly, probably because of their more rapid growth. Ultimately, however, there are no reliable criteria to differentiate, on clinical grounds, the benign from the malignant lesions, and morphologic evaluation is necessary.

PLEOMORPHIC ADENOMA

Because of their remarkable histologic diversity, these neoplasms have also been called *mixed tumors*. They represent about 60% of tumors in the parotid, are less common in the submandibular glands, and are relatively rare in the minor salivary glands. They are benign tumors that are derived from a mixture of ductal (epithelial) and myoepithelial cells, and therefore they show both epithelial and mesenchymal differentiation. They also reveal epithelial elements dispersed throughout a matrix along with varying degrees of myxoid, hyaline, chondroid (cartilaginous), and even osseous tissue. In some tumors, the epithelial elements predominate; in others, they are present only in widely dispersed foci.

Little is known about the origins of these neoplasms except that radiation exposure increases the risk. Equally uncertain is the histogenesis of the various components. A currently popular view is that all neoplastic elements, including those that appear mesenchymal, are of either myoepithelial or ductal reserve cell origin (hence the designation *pleomorphic adenoma*).

Morphology.

Most pleomorphic adenomas present as rounded, well-demarcated masses rarely exceeding 6 cm in greatest dimension (Fig. 16-16). Although they are encapsulated, in some locations (particularly the palate) the capsule is not fully developed, and expansile growth produces tonguelike protrusions

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Figure 16-16 Pleomorphic adenoma. *A,* Slowly enlarging neoplasm in the parotid gland of many years duration. *B,* The bisected, sharply circumscribed, yellow-white tumor can be seen surrounded by normal salivary gland tissue.

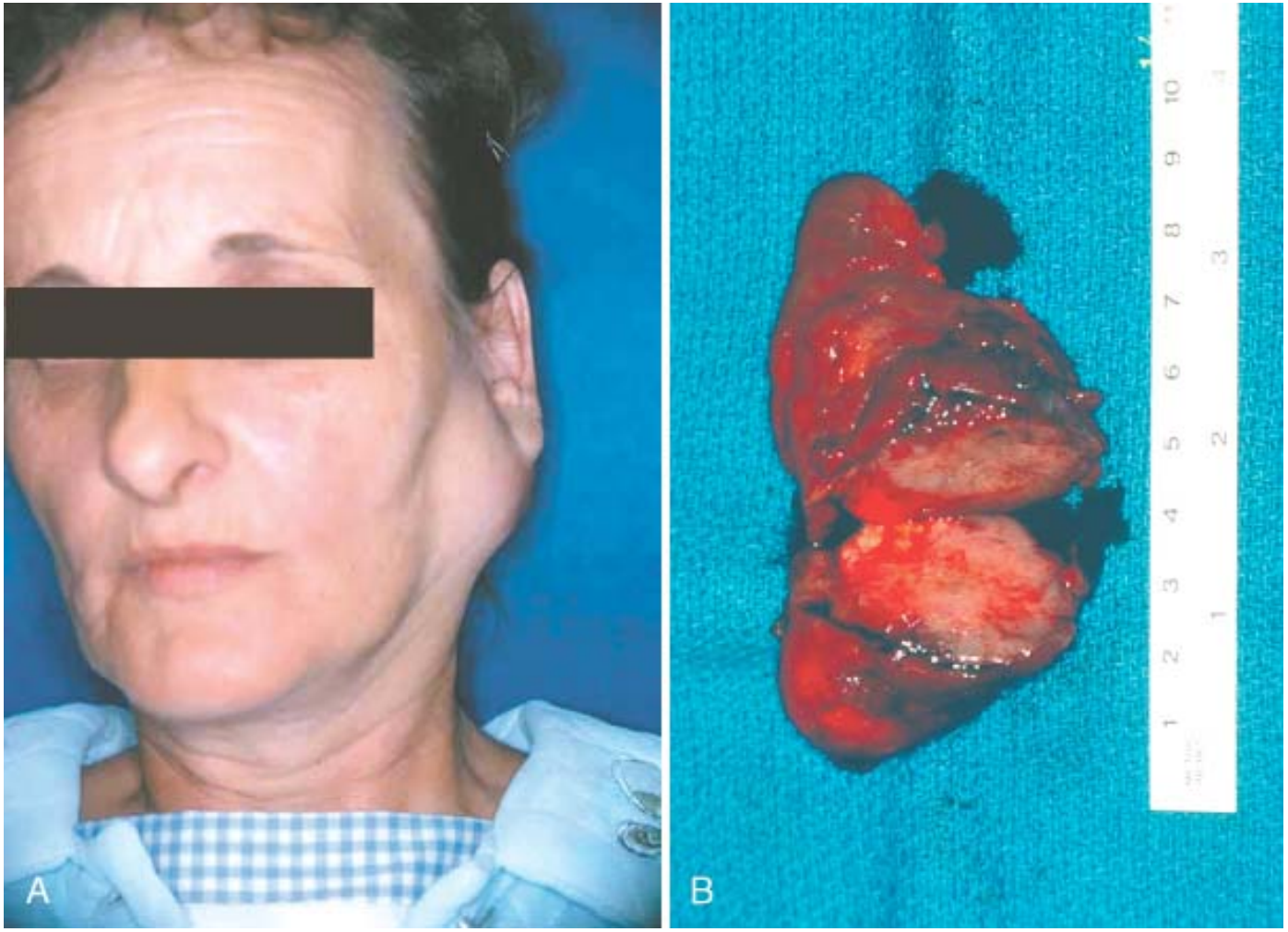


Figure 16-17 Pleomorphic adenoma. *A*, Low-power view showing a well-demarcated tumor with adjacent normal salivary gland parenchyma. *B*, High-power view showing epithelial cells as well as myoepithelial cells found within a chondroid matrix material.

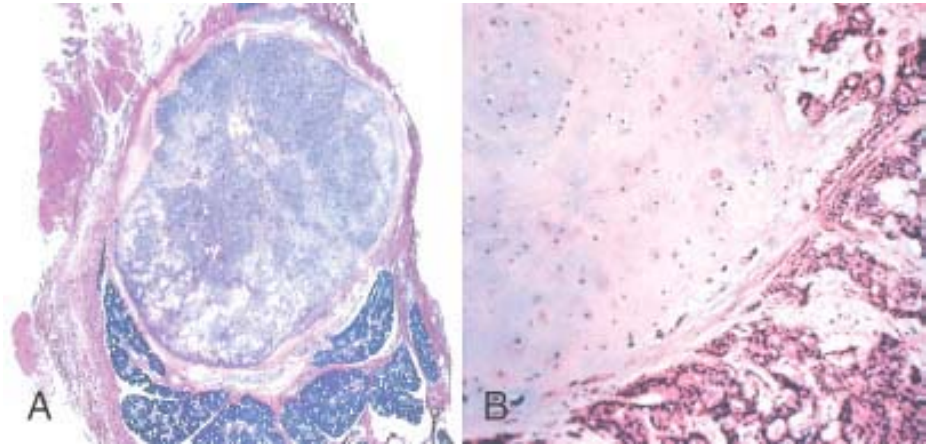


Figure 16-18 Warthin tumor. *A,* Low-power view showing epithelial and lymphoid elements. Note the follicular germinal center beneath the epithelium. *B,* Cystic spaces separate lobules of neoplastic epithelium consisting of a double layer of eosinophilic epithelial cells based on a reactive lymphoid stroma.

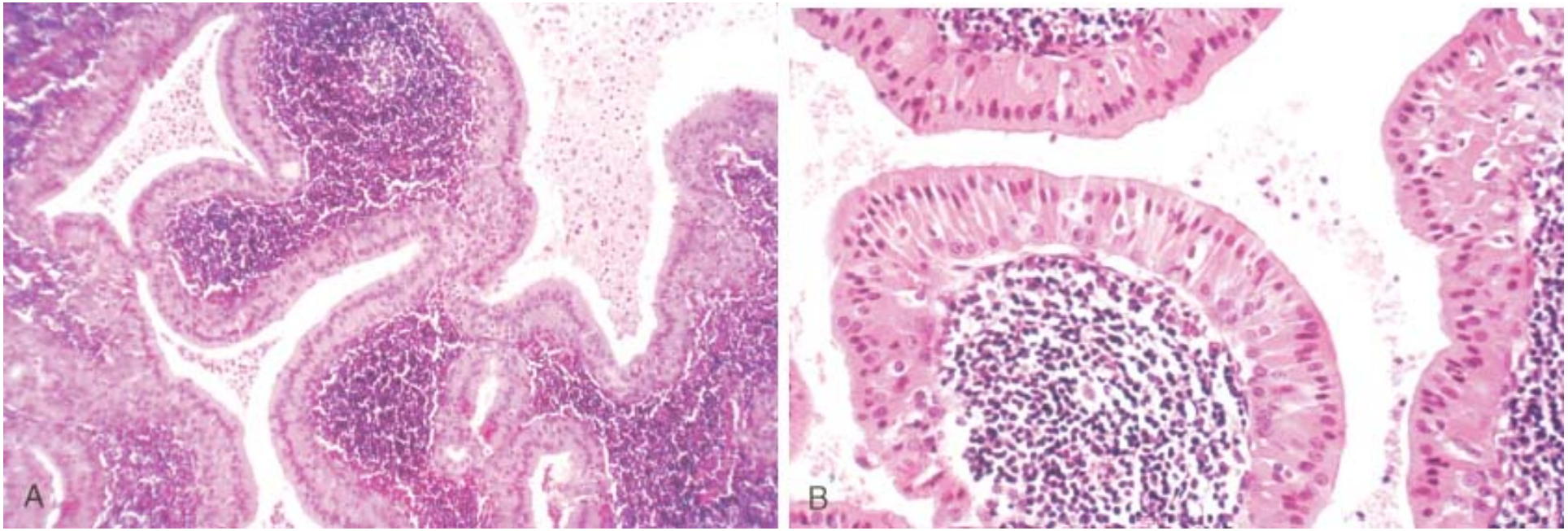


Figure 16-19 *A,* Mucoepidermoid carcinoma showing islands having squamous cells as well as clear cells containing mucin. *B,* Mucicarmine stains the mucin reddish-pink. *(Courtesy of Dr. James Gulizia, Brigham and Women's Hospital, Boston.)*

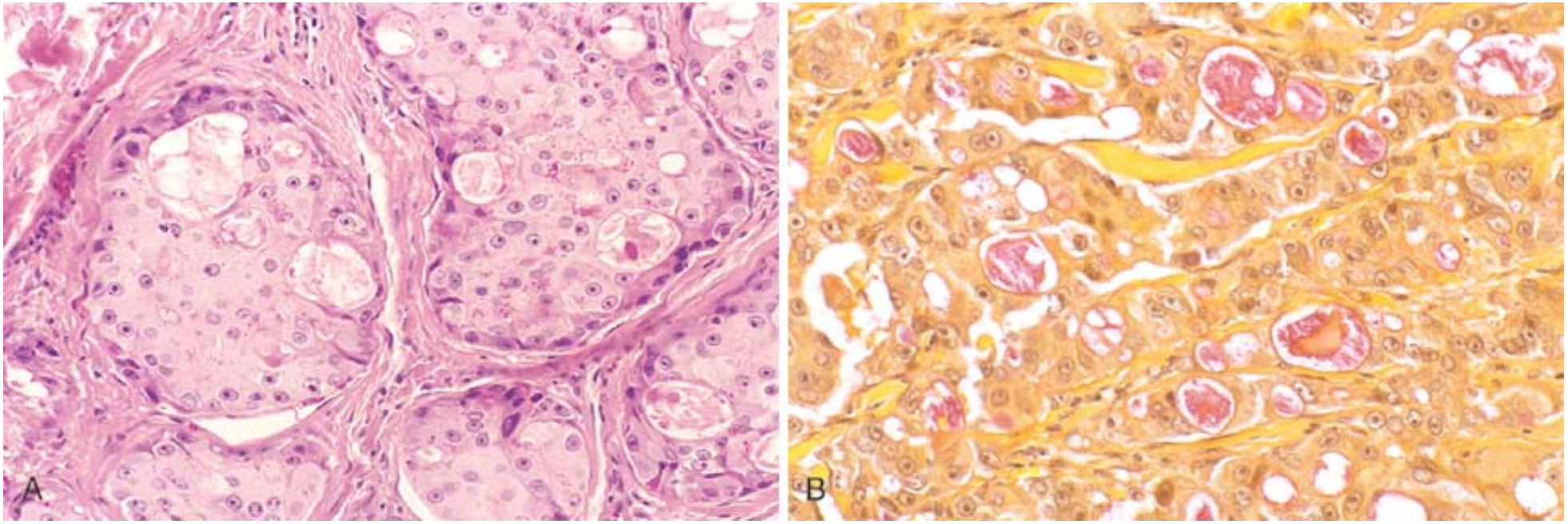
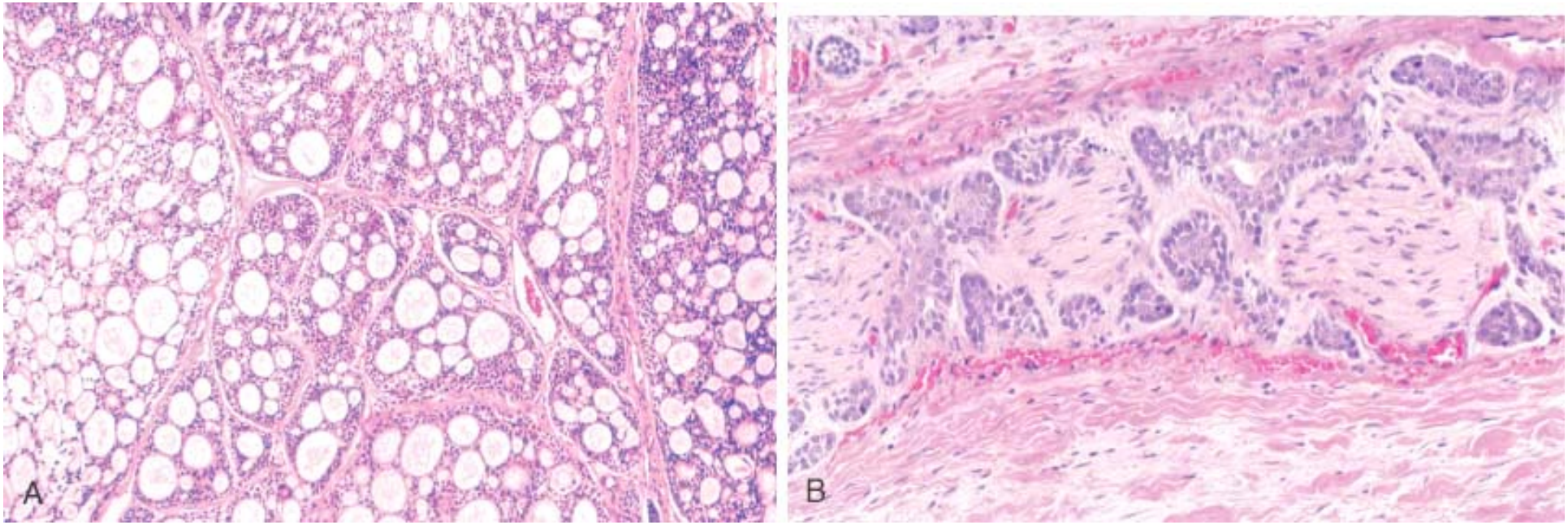


Figure 16-20 Adenoid cystic carcinoma in a salivary gland. *A*, Low-power view. The tumor cells have created a cribriform pattern enclosing secretions. *B*, Perineural invasion by tumor cells.



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Chapter 17 - The Gastrointestinal Tract

Chen Liu MD, PhD
James M. Crawford MD, PhD

Esophagus

Normal

The esophagus develops from the cranial portion of the foregut and is recognizable by the third week of gestation. The normal esophagus is a hollow, highly distensible muscular tube that extends from the epiglottis in the pharynx, at about the level of the C6 vertebra, to the gastroesophageal junction at the level of the T11 or T12 vertebra. Measuring between 10 and 11 cm in the newborn, it grows to a length of about 25 cm in the adult. For the endoscopist, the esophagus is recorded as the anatomic distance between 15 and 40 cm from the incisor teeth, with the gastroesophageal junction located at the 40-cm point. Several points of luminal narrowing can be identified along its course—proximally at the cricoid cartilage, midway in its course alongside the aortic arch and at the anterior crossing of the left main bronchus and left atrium, and distally where it pierces the diaphragm. Although the pressure in the esophageal lumen is negative compared with the atmosphere, manometric recordings of intraluminal pressures have identified two higher-pressure areas that remain relatively contracted in the resting phase. A 3-cm segment in the proximal esophagus at the level of the cricopharyngeus muscle is referred to as the upper esophageal sphincter (UES). The 2- to 4-cm segment just proximal to the

anatomic gastroesophageal junction, at the level of the diaphragm, is referred to as the lower esophageal sphincter (LES). Both "sphincters" are physiologic, in that there are no anatomic landmarks that delineate these higher-pressure regions from the intervening esophageal musculature.

The wall of the esophagus consists of a mucosa, submucosa, muscularis propria, and adventitia, reflecting the general structural organization of the gastrointestinal tract.[1] The

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mucosa has a smooth, glistening, and pink-tan surface. It has three components: a nonkeratinizing stratified squamous epithelial layer, lamina propria, and muscularis mucosa. The epithelial layer has mature squamous cells overlying basal cells. The basal cells, constituting 10% to 15 % of the mucosal thickness, are reserve cells with great proliferative potential. A small number of specialized cell types, such as melanocytes, endocrine cells, dendritic cells, and lymphocytes, are present in the deeper portion of the epithelial layer. The lamina propria is the nonepithelial portion of the mucosa, above the muscularis mucosae. It consists of areolar connective tissue and contains vascular structures and scattered leukocytes. Finger-like extensions of the lamina propria, called *papillae*, extend into the epithelial layer. The muscularis mucosae is a delicate layer of longitudinally oriented smooth-muscle bundles.

The *submucosa* consists of loose connective tissue containing blood vessels, a rich network of lymphatics, a sprinkling of leukocytes with occasional lymphoid follicles, nerve fibers (including the ganglia of the Meissner plexus), and submucosal glands. Submucosal glands connected to the lumen by squamous epithelium-lined ducts are scattered along the entire esophagus but are more concentrated in the upper and lower portions. Their mucin-containing fluid secretions help lubricate the esophagus.

As is true throughout the alimentary tract, the *muscularis propria* consists of an inner circular and an outer longitudinal coat of smooth muscle with an intervening, well-developed myenteric plexus (Auerbach plexus). The muscularis propria of the proximal 6 to 8 cm of the esophagus also contains striated muscle fibers from the cricopharyngeus muscle. Besides creating a unique histologic interplay of smooth muscle and skeletal muscle fibers, this feature explains why skeletal muscle disorders can cause upper esophageal dysfunction.

In sharp contrast to the rest of the gastrointestinal tract, the esophagus is mostly devoid of a serosal coat. Only small segments of the intra-abdominal esophagus are covered by serosa; the thoracic esophagus is surrounded by fascia that condenses around the esophagus to form a sheathlike structure. In the upper mediastinum, the esophagus is supported by this fascial tissue, which forms a similar sheath around adjacent structures, the great vessels and the tracheobronchial tree. This intimate anatomic proximity to important thoracic viscera is of significance in permitting the ready and widespread dissemination of infections and tumors of the esophagus into the posterior mediastinum. The rich network of mucosal and submucosal lymphatics that runs longitudinally along the esophagus further facilitates spread.

The main functions of the esophagus are to conduct food and fluids from the pharynx to the stomach, to prevent passive diffusion of substances from the food into the blood, and to prevent reflux of gastric contents into the esophagus. These functions require motor activity coordinated with swallowing, namely a wave of peristaltic contraction, relaxation of the LES in anticipation of the peristaltic wave, and closure of the LES after the swallowing reflex. The mechanisms governing this motor function are complex, involving both extrinsic and intrinsic innervation, humoral regulation, and properties of the muscle wall itself.

The control of the lower esophageal sphincter (LES) is critical to esophageal function.[2] Maintenance of sphincter tone is necessary to prevent reflux of gastric contents, which are under positive pressure relative to the esophagus. During deglutition, both active inhibition of the muscularis propria muscle fibers by inhibitory nonadrenergic/noncholinergic neurons and cessation of tonic excitation by cholinergic neurons enable the LES to relax. Many chemical agents (e.g., gastrin, acetylcholine, serotonin, prostaglandin $F_{2\alpha}$, motilin, substance P, histamine, and pancreatic polypeptide) increase LES tone, while some agents (nitric oxide, vasoactive intestinal peptide) decrease the tone. However, their precise roles in normal esophageal function remain unclear.

Pathology

Lesions of the esophagus run the gamut from highly lethal cancers to the merely annoying "heartburn" that has affected many a partaker of a large, spicy meal. Esophageal varices, the result of cirrhosis and portal hypertension, are of major importance, since their rupture is frequently followed by massive hematemesis (vomiting of blood) and even death by exsanguination. Esophagitis and hiatal hernias are far more frequent and rarely threaten life. Distressing to the physician is that all disorders of the esophagus tend to produce similar symptoms, namely heartburn, dysphagia, pain, and/or hematemesis.

Heartburn (retrosternal burning pain) usually reflects regurgitation of gastric contents into the lower esophagus. *Dysphagia* (difficulty in swallowing) is encountered both with deranged esophageal motor function and with diseases that narrow or obstruct the lumen. *Pain* and *hematemesis* are sometimes evoked by esophageal disease, particularly by those lesions associated with inflammation or ulceration of the esophageal mucosa. The clinical diagnosis of esophageal disorders often requires specialized procedures such as esophagoscopy, radiographic barium studies, and manometry.

Congenital Anomalies

Ectopic tissue rests are not uncommon in the esophagus. The most common is ectopic gastric mucosa in the upper third of the esophagus ("inlet patch"), occurring in up to 2% of individuals. Sebaceous glands or ectopic pancreatic tissue are much less frequent. The acid secretions of the ectopic gastric mucosa or pancreatic enzymatic secretions can produce localized inflammation and discomfort.

Embryologic formation of the foregut can also give rise to *congenital cysts*. These are usually duplication cysts, containing double smooth muscle layers and derived from the lower esophagus in 60% of cases. Rarely, bronchial or parenchymal pulmonary tissue may arise from the upper gut and is denoted *bronchogenic cyst* or *pulmonary sequestration*, respectively. These lesions usually present as masses. Lastly, impaired formation of the diaphragm may permit herniation of abdominal viscera into the thorax. When severe, this lesion is incompatible with life, since the lungs are severely hypoplastic at the time of birth. This condition is to be distinguished from hiatal hernias, to be discussed presently.

ATRESIA AND FISTULAS

Although developmental defects in the esophagus are uncommon, they must be corrected early because they are incompatible with life. Because they cause immediate regurgitation when feeding is attempted, they are usually discovered soon after birth. *Absence* (agenesis) of the esophagus is extremely rare; much more common are *atresia* and *fistula formation* (Fig. 17-1). In atresia, a segment of the esophagus is represented by only a thin, noncanalized cord, with a proximal blind pouch connected to the pharynx and a lower pouch leading to the stomach. Atresia is most commonly located at or near the tracheal bifurcation. It rarely occurs alone, but is usually associated with a fistula connecting the lower or upper pouch with a bronchus or the trachea. Associated anomalies include congenital heart disease, neurologic disease, genitourinary disease, and other gastrointestinal malformations. Atresia sometimes is associated with the presence of a single umbilical artery.[3] Aspiration and paroxysmal suffocation from food are obvious hazards; pneumonia and severe fluid and electrolyte imbalances may also occur.

WEBS, RINGS, AND STENOSIS

Esophageal mucosal webs are uncommon ledgelike protrusions of the mucosa into the esophageal lumen. These are semicircumferential, eccentric, and most common in the upper esophagus. Well-developed webs rarely protrude more than 5 mm into the lumen, with a thickness of 2 to 4 mm. The webs consist of squamous mucosa and a vascularized submucosal core. Webs can be congenital in origin, or they may arise in association with long-standing reflux esophagitis, chronic graft-versus-host disease (GVHD), or blistering skin diseases. When an upper esophageal web is accompanied by an iron-deficiency anemia, glossitis, and cheilosis, the condition is referred to as the Paterson-Brown-Kelly or Plummer-Vinson syndrome, with an attendant risk for postcricoid esophageal carcinoma.

Esophageal rings are concentric plates of tissue protruding into the lumen of the distal esophagus. One occurring above the squamocolumnar junction of the esophagus and stomach is

referred to as an *A ring*. One located at the squamocolumnar

Figure 17-1 Esophageal atresia and tracheoesophageal fistula. *A*, Blind upper and lower esophageal segments. *B*, Fistula between blind upper segment and trachea. *C*, Blind upper segment, fistula between blind lower segment and trachea. *D*, Blind upper segment only. E, Fistula between patent esophagus and trachea. Type C is the most common variety. *(Adapted from Morson BC, and Dawson IMP, eds., Gastrointestinal Pathology. Oxford, Blackwell Scientific Publications, 1972, p. 8.)*

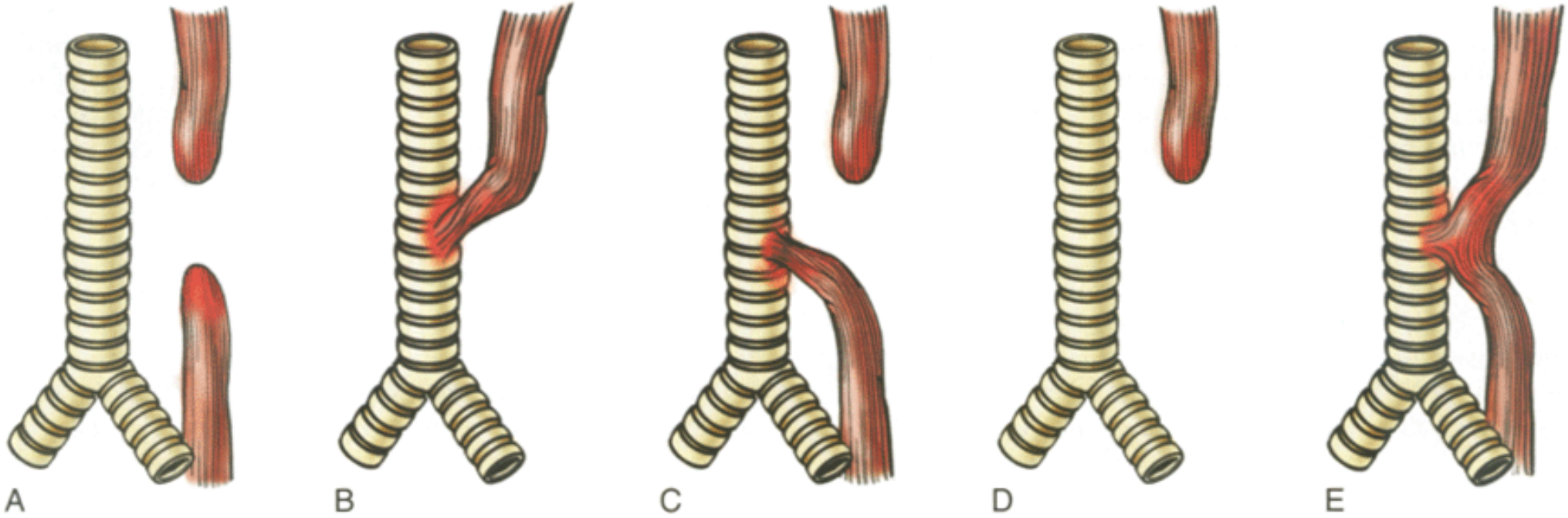


Figure 17-2 Major conditions associated with esophageal motor dysfunction.

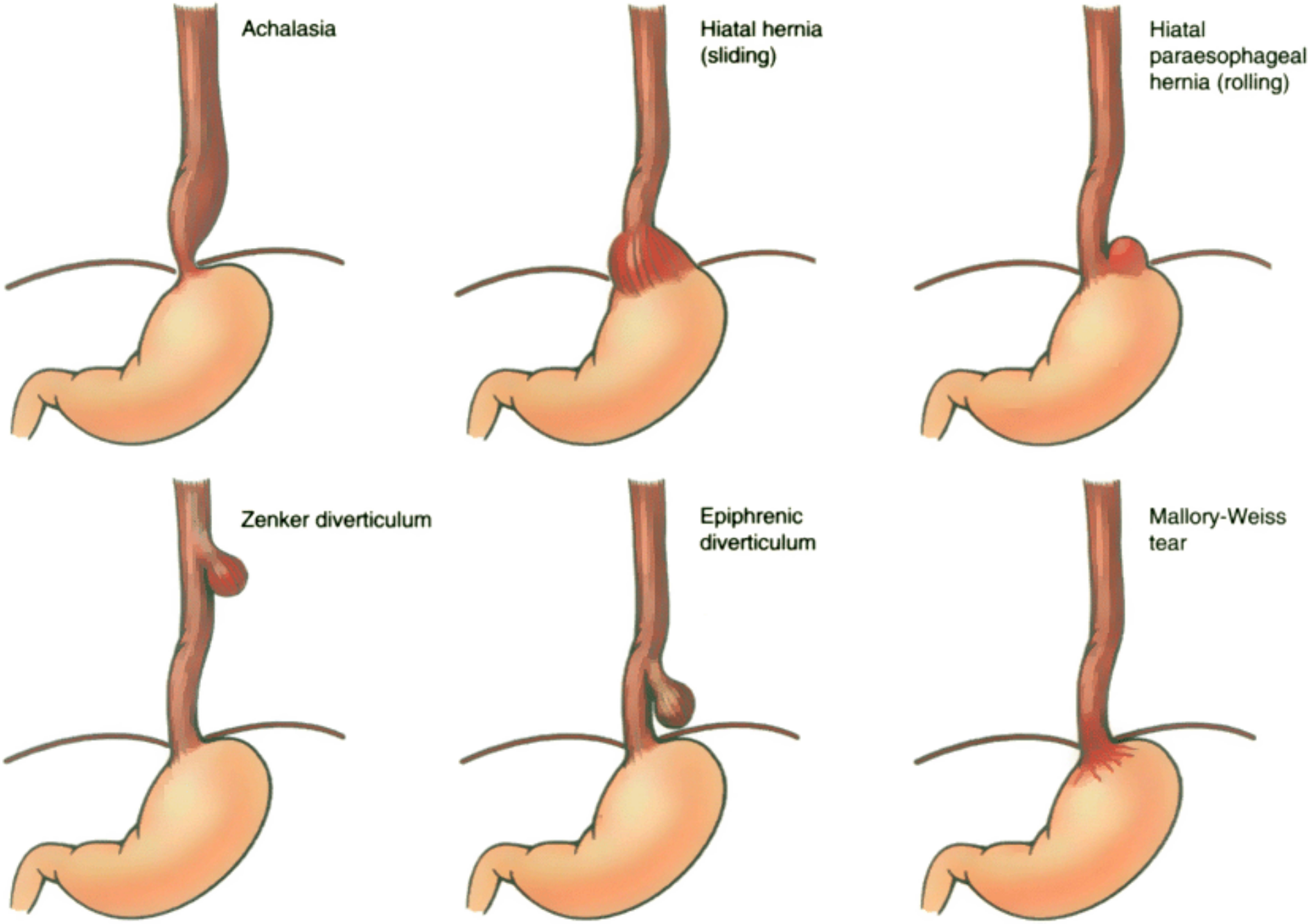


Figure 17-3 Esophageal laceration (Mallory-Weiss tears). Gross view demonstrating longitudinal lacerations extending from esophageal mucosa into stomach mucosa *(arrow)*. *(Courtesy of Dr. Richard Harruff, King County Medical Examiner's Office, Seattle, WA.)*

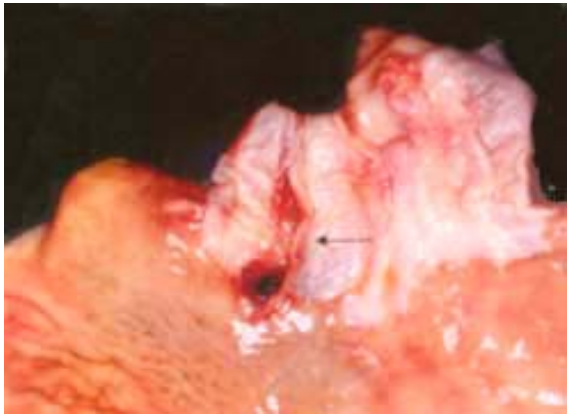


Figure 17-4 Esophageal varices. *A*, A view of the everted esophagus and gastroesophageal junction, showing dilated submucosal veins (varices). The blue-colored varices have collapsed in this postmortem specimen. *B*, Low-power cross-section of a dilated submucosal varix that has ruptured through the mucosa. A small amount of thrombus is present within the point of rupture. *C*, Hepatic venogram after injection of dye into portal veins (PV) to show a large tortuous gastroesophageal varix *(arrow)* extending superiorly from the patent main portal vein. *(C, courtesy of Dr. Emily Sedgwick, Brigham and Women's Hospital, Boston, MA.)*

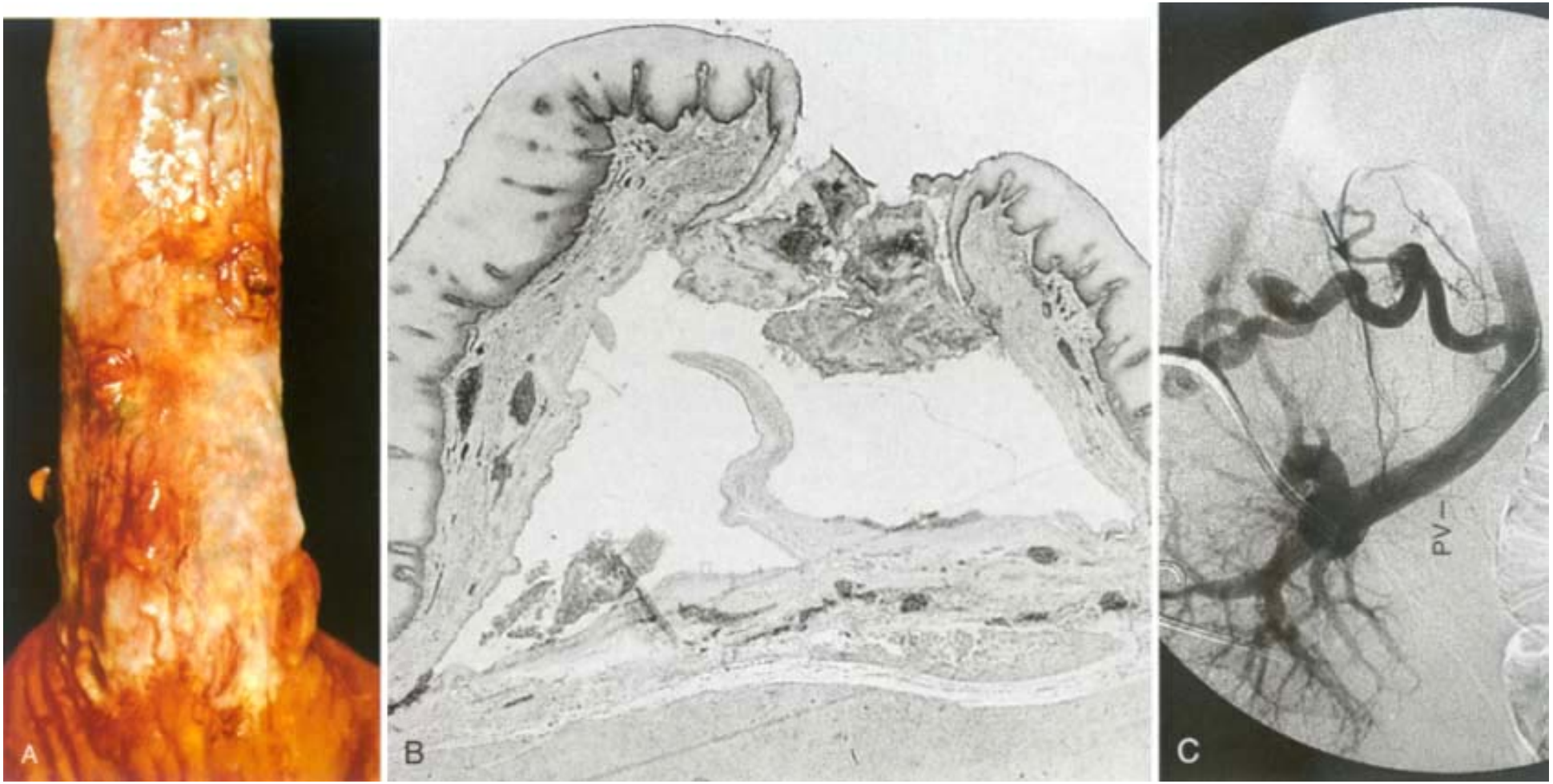


Figure 17-5 Reflux esophagitis. Low-power view of the superficial portion of the mucosa. Numerous eosinophils within the squamous epithelium, elongation of the lamina propria papillae, and basal zone hyperplasia are present.

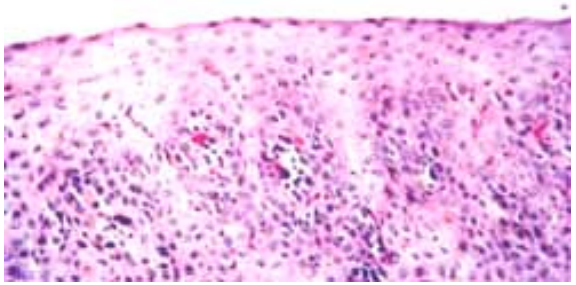


Figure 17-6 Barrett esophagus. *A, B,* Gross view of distal esophagus *(top)* and proximal stomach *(bottom),* showing *A,* the normal gastroesophageal junction *(arrow)* and *B,* the granular zone of Barrett esophagus *(arrow). C,* Endoscopic view of Barrett esophagus showing red velvety gastrointestinal mucosa extending from the gastroesophageal orifice. Note the paler squamous esophageal mucosa.

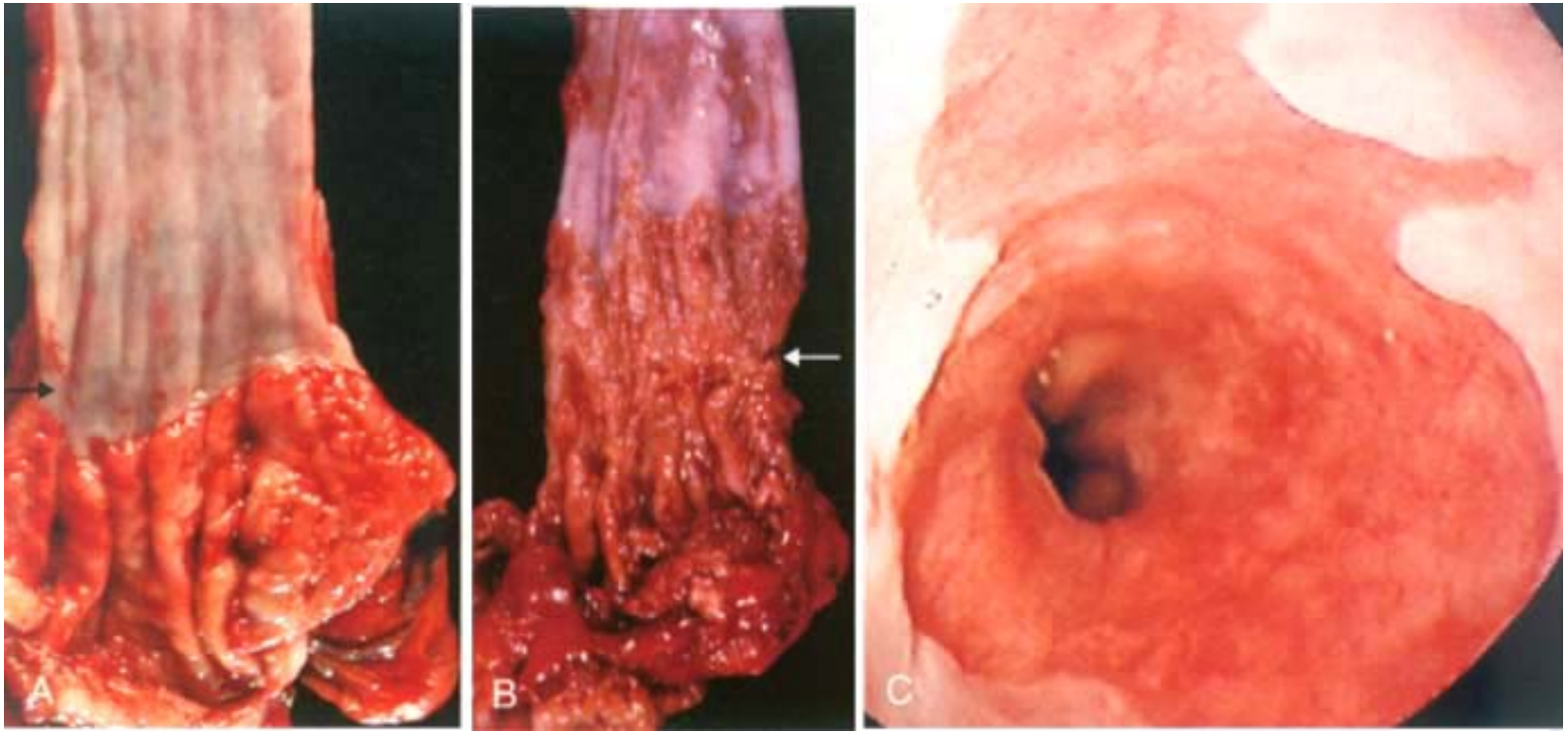


Figure 17-7 Barrett esophagus. Microscopic view showing squamous mucosa and intestinal-type columnar epithelial cells (goblet cells) in a glandular mucosa.

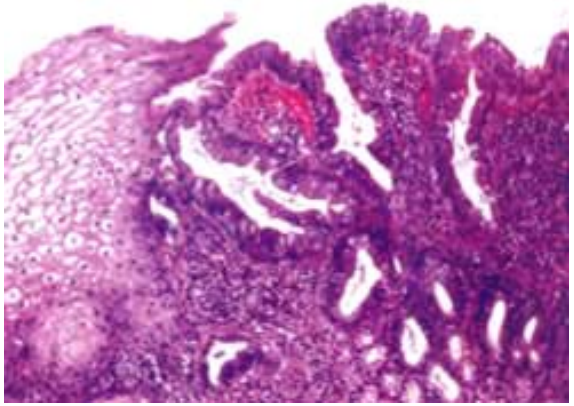


TABLE 17-1 -- Factors Associated with the Development of Squamous Cell Carcinoma of the Esophagus

Dietary
Deficiency of vitamins (A, C, riboflavin, thiamine, pyridoxine)
Deficiency of trace elements (zinc, molybdenum)
Fungal contamination of foodstuffs

High content of nitrites/nitrosamines
Betel chewing
Lifestyle
Burning-hot beverages or food
Alcohol consumption
Tobacco use
Urban environment
Esophageal Disorders
Long-standing esophagitis
Achalasia
Plummer-Vinson syndrome
Genetic Predisposition
Long-standing celiac disease
Ectodermal dysplasia
Epidermolysis bullosa
Racial disposition

States are attributable to alcohol and tobacco usage. Some alcoholic drinks contain significant amounts of such carcinogens as polycyclic hydrocarbons, fuel oils, and nitrosamines, along with other mutagenic compounds. Nutritional deficiencies associated with alcoholism may contribute to the process of carcinogenesis.

Alcohol and tobacco cannot be invoked as risk factors in many high-incidence regions of the world. The presence of carcinogens, such as fungus-contaminated and nitrosamine-containing foodstuffs in China, may play a significant role in the extraordinary high incidence of carcinoma in this region. Dietary deficiencies in vitamins and essential metals have been documented in China and South Africa. Human papillomavirus DNA is found frequently in esophageal squamous cell carcinomas from high-incidence regions, but is infrequent in cancer-bearing patients in North America. [13]

Based on the above considerations, dietary and environmental factors have been proposed to increase risk, with nutritional deficiencies acting as promoters or potentiators of the tumorigenic effects of environmental carcinogens. For example, methylating nitroso compounds in the diet and in tobacco smoke may be the reason for the broad spectrum of *p53* point mutations present in over half of esophageal cancers. Other genetic alterations, such as mutations in *p16INK4*, and amplification of *CYCLIN D1*, C-*MYC*, and epithelial growth factor receptor *(EGFR)*, are prevalent in these cancers as well. This is in keeping with the concept that stepwise acquisition and accumulation of genetic alterations ultimately give rise to cancer. [14] Notably rare in esophageal squamous cell carcinomas are K-*RAS* and adenomatous polyposis coli *(APC)* mutations.

Finally, the chronic esophagitis so commonly observed in persons living in areas of high incidence may itself be the result of sustained exposure to the carcinogens listed earlier. This chronic esophagitis results in an increased epithelial cell turnover, which, over a length of time in a continuously carcinogenic environment, progresses to dysplasia and eventually to carcinoma. The rate of progression along the chronic esophagitis-dysplasia-cancer sequence may well be modified or modulated by genetic or racial factors.

Morphology.

Like squamous cell carcinomas arising in other locations, those of the esophagus begin as apparent in situ lesions **(intraepithelial neoplasm or carcinoma in situ)**. When they become overt, about 20% of these tumors are located in the upper third, 50% in the middle third, and 30% in the lower third of the esophagus. Early lesions appear as small, gray-white, plaque-like thickenings or elevations of the mucosa. In months to years, these lesions become tumorous masses and may eventually encircle the lumen. Three morphologic patterns are described: (1) protruded (60%), a polypoid exophytic lesion that protrudes into the lumen; (2) flat (15%), a diffuse, infiltrative form that tends to spread within the wall of the esophagus, causing thickening, rigidity, and narrowing of the lumen; and (3) excavated (ulcerated, 25%; Fig. 17-8), a necrotic cancerous ulceration that excavates deeply into surrounding structures and may erode into the respiratory tree (with resultant fistula and pneumonia) or aorta (with catastrophic exsanguination) or may permeate the mediastinum and pericardium. The fortunate patient is found at the stage of superficial esophageal carcinoma, in which the malignant lesion is confined to the epithelial layer (in situ) or is superficially invading the lamina propria or submucosa (Fig. 17-9).

Most squamous cell carcinomas are moderately to well differentiated. Several histologic variants may be seen, such as verrucous squamous cell carcinoma, spindle cell carcinoma, and basaloid squamous cell carcinoma. Irrespective of their degree of differentiation, most symptomatic tumors are quite large by the time they are diagnosed and have already invaded the wall or beyond. The rich lymphatic network in the submucosa

Figure 17-8 Large ulcerated squamous cell carcinoma of the esophagus.

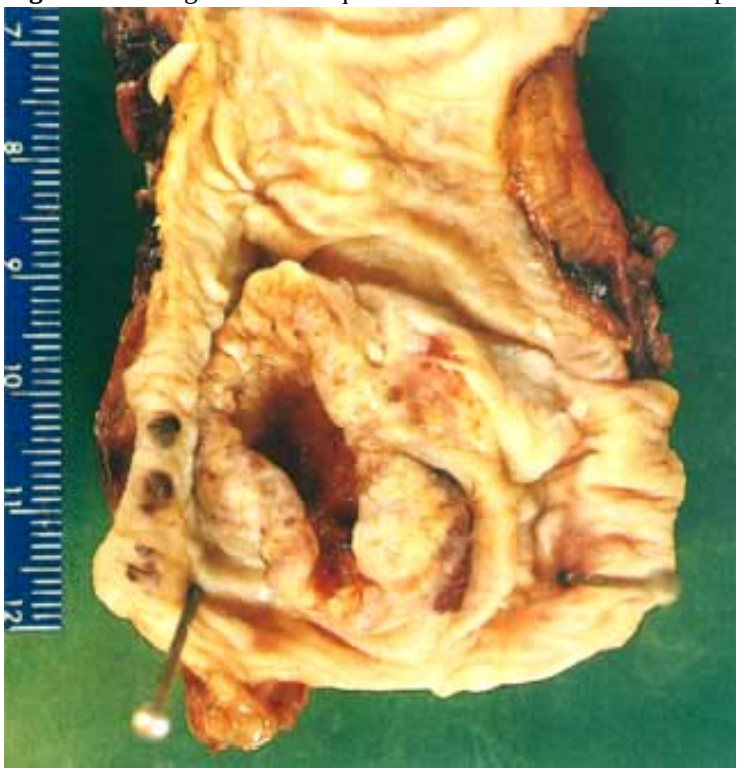


Figure 17-9 Squamous cell carcinoma of the esophagus: low-power microscopic view showing invasion into the submucosa.

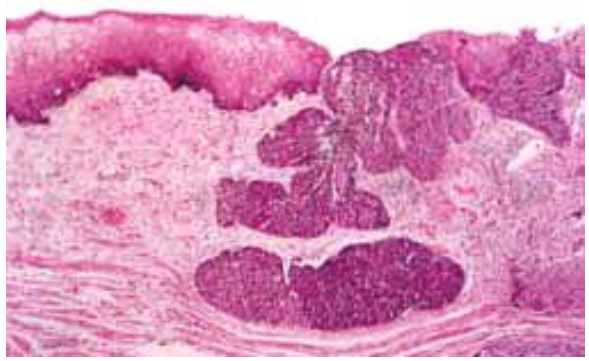


Figure 17-10 Transition from Barrett esophagus to adenocarcinoma.

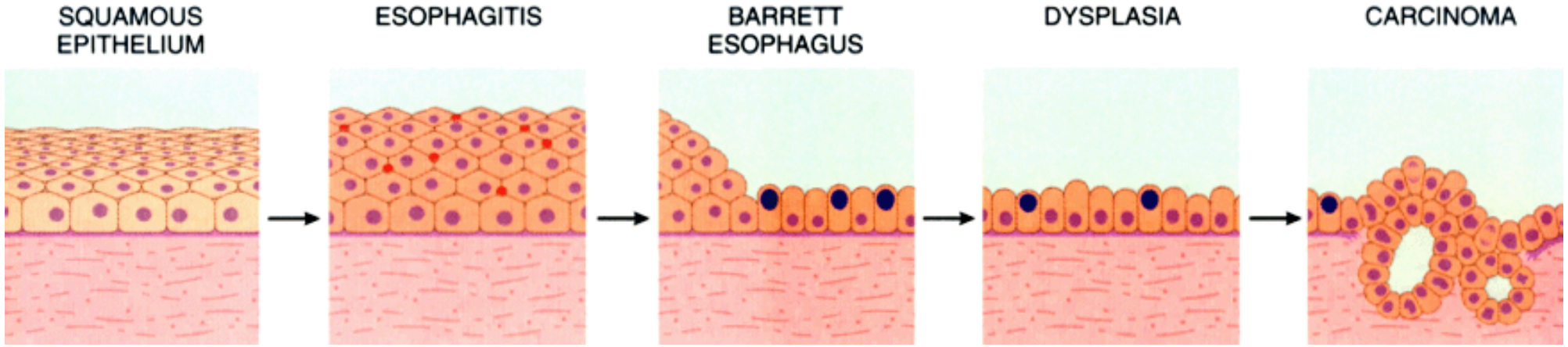
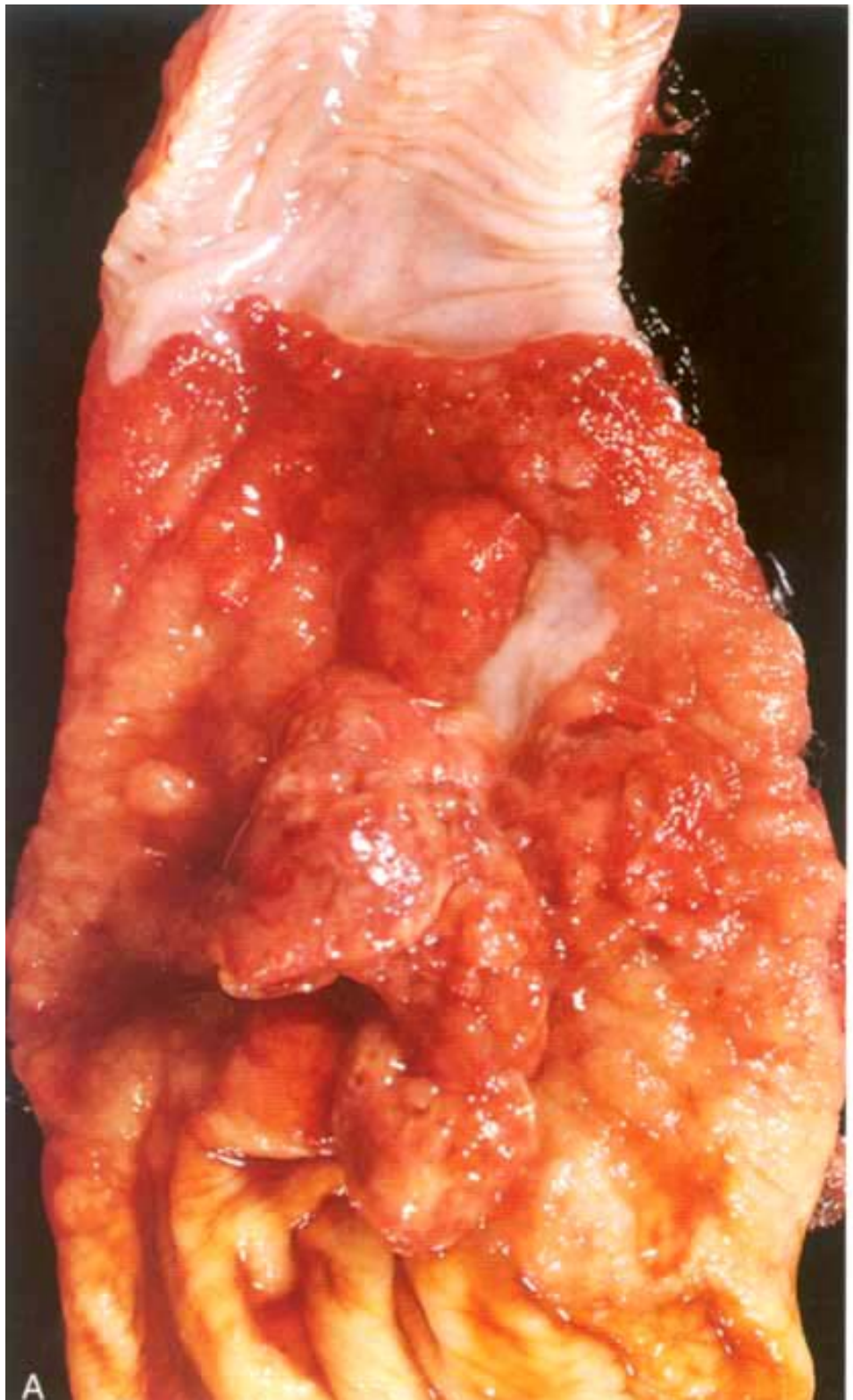
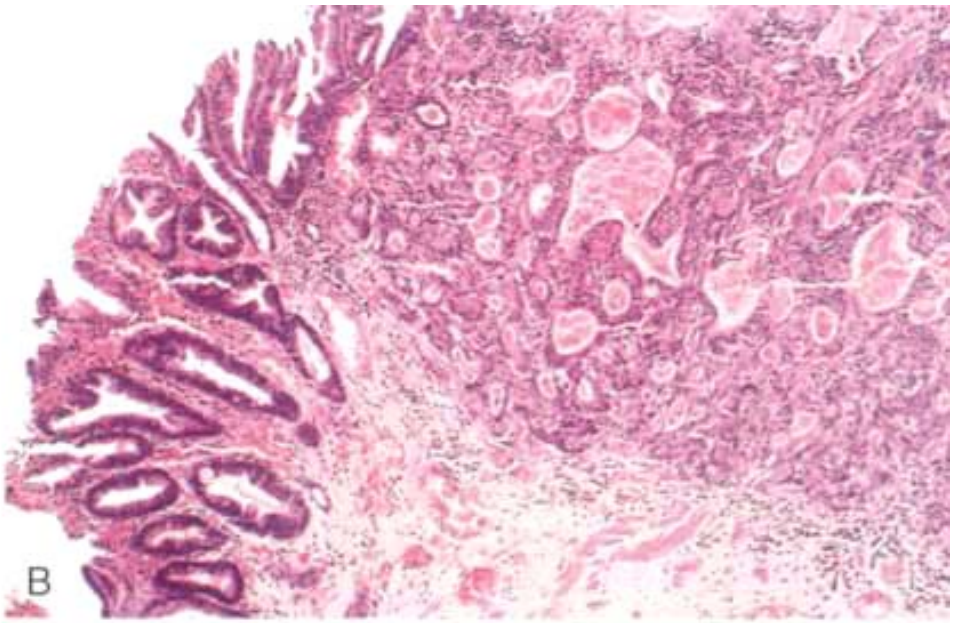


Figure 17-11 Adenocarcinoma of the esophagus. *A*, Gross view of an ulcerated, exophytic mass at the gastroesophageal junction, arising from the granular mucosa of Barrett esophagus. The gray-white esophageal mucosa is on the top, and the folds of gastric mucosa are below. *(A, courtesy of Dr. James Gulizia, Brigham and Women's Hospital, Boston, MA.) B,* Microscopic view of malignant intestinal-type glands in adenocarcinoma arising from Barrett esophagus.

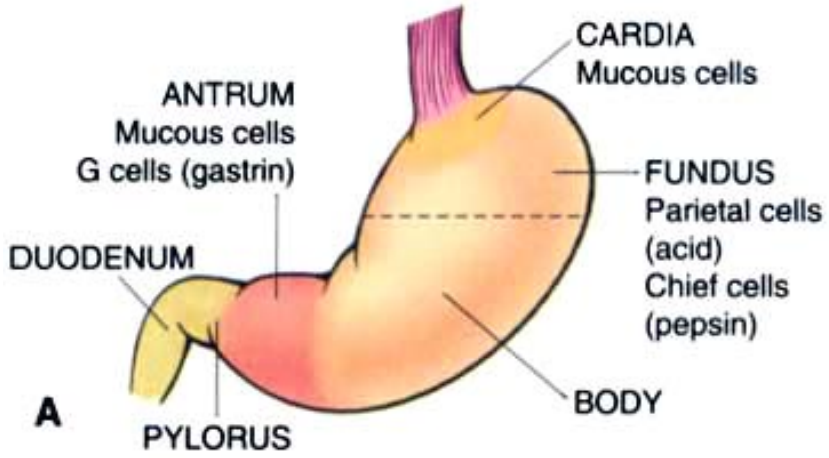


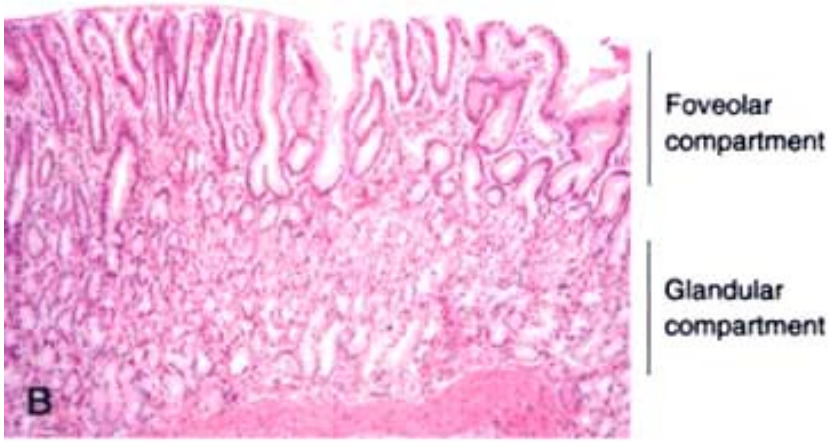
A



B

Figure 17-12 Anatomy and histology of the stomach. *A*, Gross anatomy. *B*, Microscopic view of antral mucosa. *C*, Microscopic view of fundic mucosa.





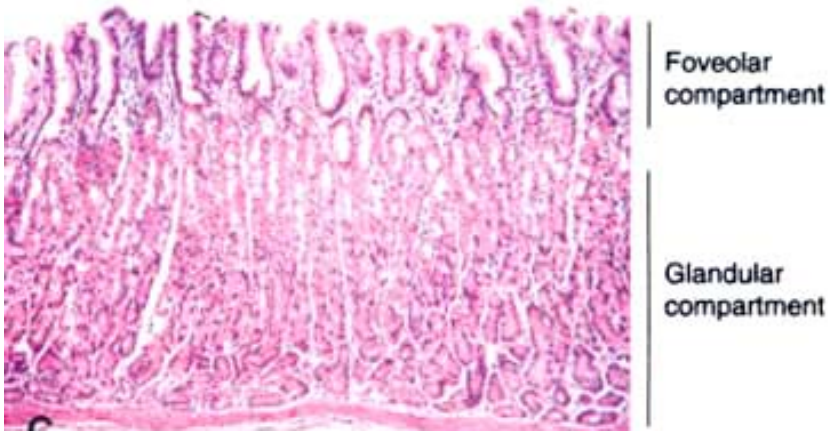
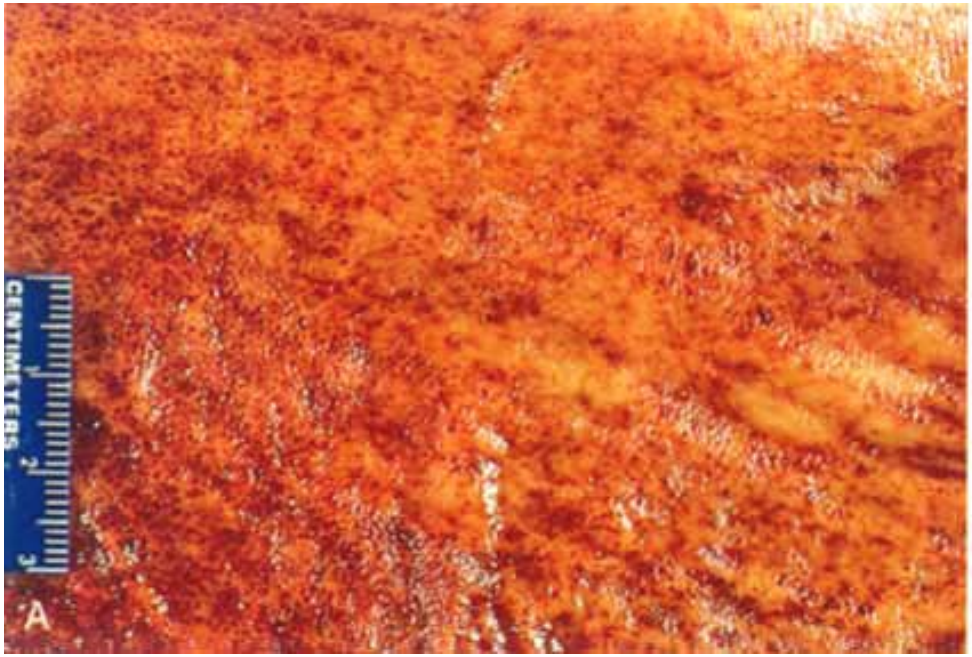


Figure 17-13 Acute gastritis. *A,* Gross view showing punctate erosions in an otherwise unremarkable mucosa; adherent blood is dark due to exposure to gastric acid. *B,* Low-power microscopic view of focal mucosal disruption with hemorrhage; the adjacent mucosa is normal.



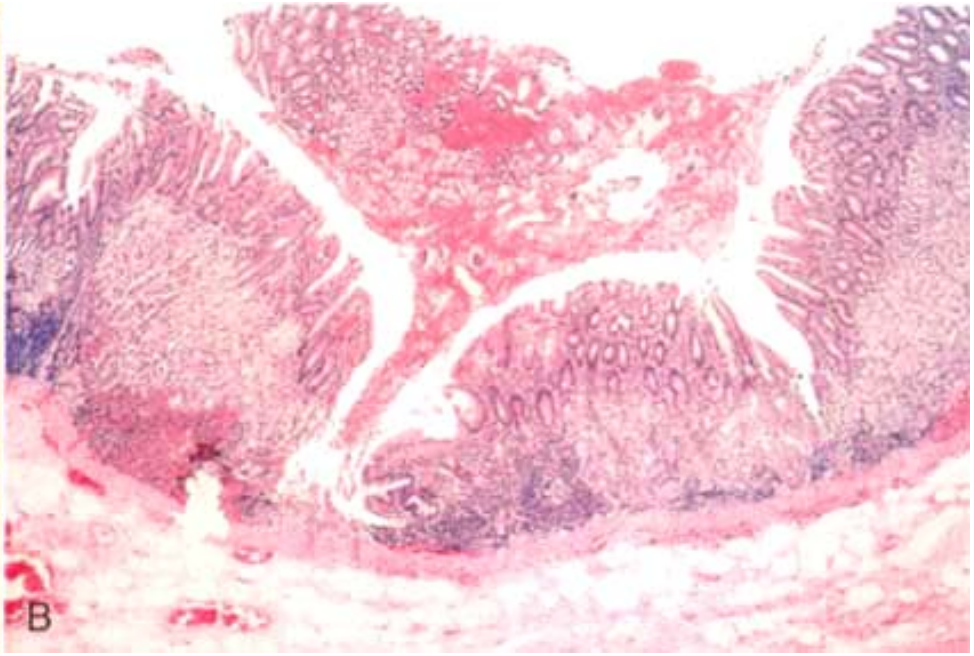


TABLE 17-2 -- Diseases Associated with *Helicobacter pylori* Infection

Disease	Association
Chronic gastritis	Strong causal association
Peptic ulcer disease	Strong causal association
Gastric carcinoma	Strong causal association
Gastric MALT lymphoma *	Definitive etiologic role

* MALT, mucosa-associated lymphoid tissue

areas where infection is endemic, the organism seems to be acquired in childhood and persists for decades. The mode of transmission of *H. pylori* has not been well defined, although oral-oral transmission, fecal-oral transmission, and environmental spread are among the possible routes. *Most infected persons also have the associated gastritis but are asymptomatic.* Nevertheless, infected persons are at increased risk for the development of peptic ulcer disease and possibly gastric cancer.

H. pylori is a nonsporing, curvilinear gram-negative rod measuring approximately 3.5 × 0.5 µm. *H. pylori* is part of a genus of bacteria that have adapted to the ecologic niche provided by gastric mucus, which is lethal to most bacteria. The specialized traits that allow it to flourish include:

- Motility (via flagella), allowing it to swim through viscous mucus
- Elaboration of a *urease*, which produces ammonia and carbon dioxide from endogenous urea, thereby buffering gastric acid in the immediate vicinity of the organism
- Expression of *bacterial adhesins*, such as BabA, which binds to the fucosylated Lewis B blood-group antigens, enhances binding to blood group O antigen bearing cells.[23]
- Expression of bacterial toxins, such as cytotoxin association gene A *(CagA)* and vacuolating cytotoxin gene A *(VacA)*.[24] These are discussed later under "Peptic Ulcer."

The *H. pylori* genome is 1.65 million base pairs and encodes approximately 1500 proteins. Extensive molecular studies suggest that the bacteria cause gastritis by stimulating production of pro-inflammatory cytokines and by directly injuring epithelial cells (discussed later).

After initial exposure to *H. pylori*, gastritis occurs in two patterns: a predominantly antral-type gastritis with high acid production and elevated risk for duodenal ulcer, and a pangastritis that is followed by multifocal atrophy (multifocal atrophic gastritis) with lower gastric acid secretion and higher risk for adenocarcinoma. The underlying mechanisms contributing to this difference are not completely clear, but host-microorganism interplay appears to be critical. IL-1β is a potent pro-inflammatory cytokine and a powerful gastric acid inhibitor. Patients who have higher IL-1β production in response to *H. pylori* infection tend to develop pangastritis, while patients who have lower IL-1β production exhibit antral-type gastritis. [25]

A number of diagnostic tests have been developed for the detection of *H. pylori*. Noninvasive tests include a serologic test for antibodies, fecal bacterial detection, and a urea breath test. The breath test is based on the generation of ammonia by bacterial urease. Invasive tests are based on the identification of *H. pylori* in gastric biopsy tissue. Detection methods in gastric tissue include visualization of the bacteria in histologic sections, bacterial culture, a rapid urease test, and bacterial DNA detection by the polymerase chain reaction.

Patients with chronic gastritis and *H. pylori* usually improve when treated with antibiotics. Relapses are associated with reappearance of the organism. The current treatment regimens include antibiotics and hydrogen pump inhibitors.[22] Prophylactic and therapeutic vaccine development is still in the early research stage, but it holds the promise to eradicate or at least greatly reduce the worldwide prevalence of *H. pylori* infection.

In addition to *H. pylori*, humans can also be infected by *Helicobacter heilmannii*, a spiral bacterium found in dogs, cats, and nonhuman primates.[26] This bacterium causes a relatively mild gastritis.

Autoimmune Gastritis.

This form of gastritis accounts for less than 10% of cases of chronic gastritis. It results from the presence of autoantibodies to components of gastric gland parietal cells, including antibodies against the acidproducing enzyme H^+ ,K^+ -ATPase,[27] gastrin receptor, and intrinsic factor. Gland destruction and mucosal atrophy lead to loss of acid production. In the most severe cases, production of intrinsic factor is lost, leading to pernicious anemia. This uncommon form of gastritis is seen in association with other autoimmune disorders such as Hashimoto thyroiditis, Addison disease, and type 1 diabetes. Patients with autoimmune gastritis have a significant risk for developing gastric carcinoma and endocrine tumors (carcinoid tumor).

Morphology.

Chronic gastritis may affect different regions of the stomach and exhibit varying degrees of mucosal damage.[19] Autoimmune gastritis is characterized by diffuse mucosal damage of the body-fundic mucosa, with less intense to absent antral damage, probably due to the autoantibodies against parietal cells. Gastritis in the setting of environmental etiologies (including infection by *H. pylori*) tends to affect antral mucosa or both antral and body-fundic mucosa (pangastritis). The mucosa is usually reddened and has a coarser texture than normal. The inflammatory infiltrate may create a mucosa with thickened rugal folds, mimicking early infiltrative lesions. Alternatively, with long-standing atrophic disease, the mucosa may become thinned and flattened. Irrespective of cause or location, the histologic changes are similar. An inflammatory infiltrate of lymphocytes and plasma cells is present within the lamina propria (Fig. 17-14). **"Active" inflammation is signified by the presence of neutrophils within the glandular and surface epithelial layer.** Active inflammation may be prominent or absent. Lymphoid aggregates, some with germinal centers, are frequently observed within the mucosa. Several additional histologic features are characteristic:

• ***Regenerative Change.*** A proliferative response to the epithelial injury is a constant feature of chronic gastritis. In the neck region of the gastric glands mitotic figures are increased. Epithelial cells of the

surface mucosa, and to a lesser extent the glands, exhibit enlarged, hyperchromatic nuclei and a higher nuclear-cytoplasmic ratio. Mucus vacuoles are diminished or absent in the superficial cells. When regenerative changes are severe, particularly with ongoing active inflammation, distinguishing regenerative change from dysplasia may be difficult.

• ***Metaplasia.*** The antral, body, and fundic mucosa may become partially replaced by metaplastic columnar absorptive cells and goblet cells of intestinal morphology **(intestinal metaplasia),** both along the surface epithelium and in rudimentary glands. Occasionally, villus-like projections may appear. Although small intestinal features predominate, in some instances, features of colonic epithelium may be present.

• ***Atrophy.*** Atrophic change is evident by marked loss in glandular structures. **Atrophy is quite frequently associated with autoimmune gastritis and pangastritis caused by *H. pylori***. Parietal cells, in particular, may be conspicuously absent in the autoimmune form. Persisting glands frequently undergo cystic dilatation. A particular feature of atrophic gastritis of autoimmune origin or chronic gastritis treated by inhibitors of acid secretion is hyperplasia of gastrin-producing G-cells in the antral mucosa. This is attributed to the hypochlorhydria or achlorhydria arising from severe parietal cell loss. The G-cell hyperplasia is responsible for the increased gastrinemia, which stimulates hyperplasia of enterochromaffin-like cells in the gastric body. As will be discussed later, the ECL cell hyperplasia is the frequent background for gastric carcinoid tumor formation.

• ***Dysplasia.*** With long-standing chronic gastritis, the epithelium develops cytologic alterations, including variation in size, shape, and orientation of epithelial cells, and nuclear enlargement and atypia. Intestinal metaplasia may precede the development of dysplasia. Dysplastic alterations may become so severe as to constitute in situ carcinoma. The development of dysplasia is thought to be a precursor lesion of gastric cancer in atrophic forms of gastritis, particularly in association with pernicious anemia (autoimmune gastritis) and *H. pylori*- associated chronic gastritis.

Figure 17-14 Chronic gastritis, showing partial replacement of the gastric mucosal epithelium by intestinal metaplasia (upper left) and inflammation of the lamina propria (right) containing lymphocytes and plasma cells.

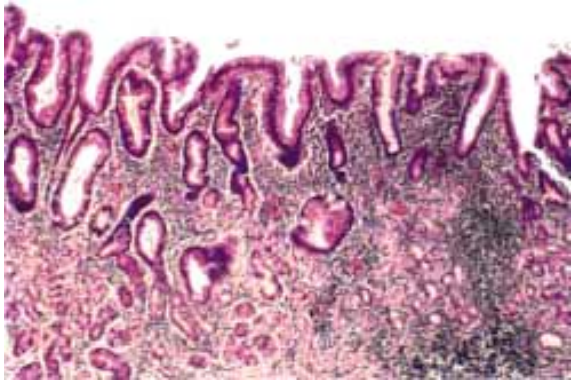


Figure 17-15 *Helicobacter pylori.* A Steiner silver stain demonstrates the numerous darkly stained *Helicobacter* organisms along the luminal surface of the gastric epithelial cells. Note that there is no tissue invasion by bacteria.

Figure 17-16 Reactive gastropathy. Gastric mucosa, showing hyperplasia of foveolar surface epithelial cells, glandular regenerative changes, and smooth muscle fibers extending into lamina propria.

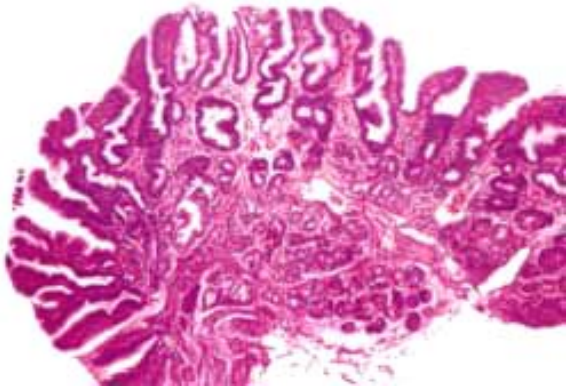


Figure 17-17 Diagram of causes of, and defense mechanisms against, peptic ulceration. Diagram of the base of a nonperforated peptic ulcer, demonstrating the layers of necrosis (N), inflammation (I), granulation tissue (G), and scar (S), moving from the luminal surface at the top to the muscle wall at the bottom.

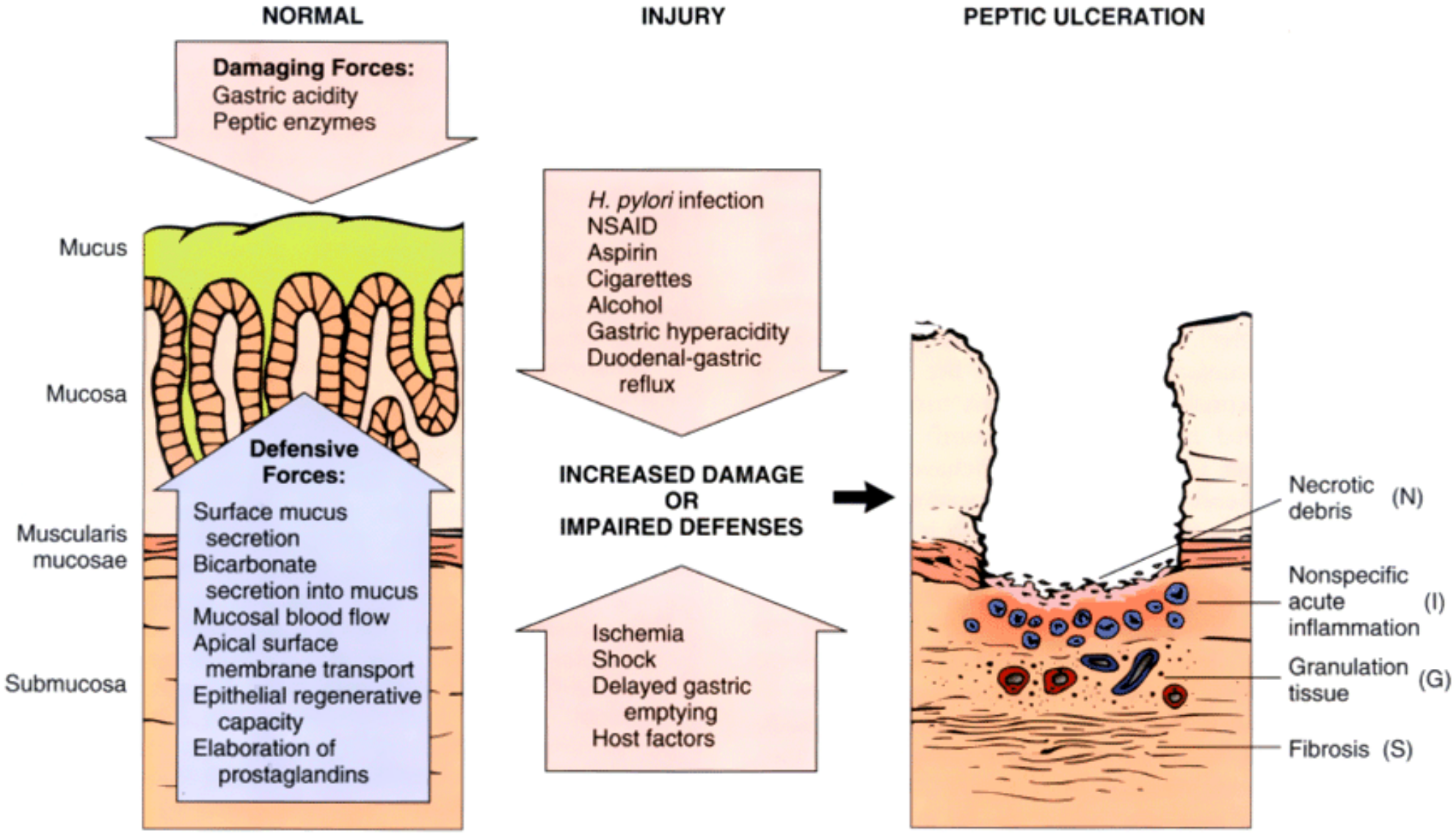


Figure 17-18 Peptic ulcer of the duodenum. Note that the ulcer is small (2 cm) with a sharply punched-out appearance. Unlike cancerous ulcers, the margins are not elevated. The ulcer base is clean. *(Courtesy of Robin Foss, University of Florida, Gainesville, FL.)*

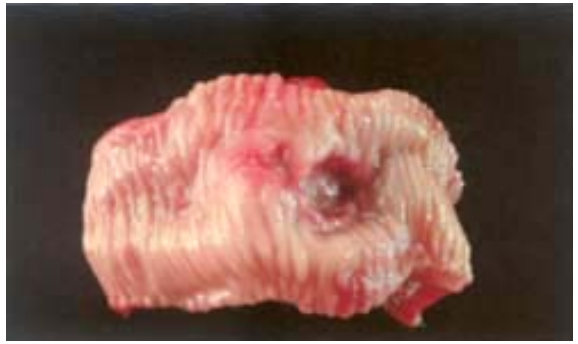


TABLE 17-3 -- Complications of Peptic Ulcer Disease

Bleeding
• Occurs in 15% to 20% of patients
• Most frequent complication
• May be life-threatening
• Accounts for 25% of ulcer deaths
• May be the first indication of an ulcer
Perforation
• Occurs in about 5% of patients
• Accounts for two thirds of ulcer deaths
• Rarely, is the first indication of an ulcer
Obstruction from edema or scarring
• Occurs in about 2% of patients
• Most often due to pyloric channel ulcers
• May also occur with duodenal ulcers
• Causes incapacitating, crampy abdominal pain
• Rarely, may lead to total obstruction with intractable vomiting

tumors are designated *Cushing ulcers* and carry a high incidence of perforation.

The genesis of the acute mucosal defects in these varied clinical settings is poorly understood. No doubt, many factors are shared with acute gastritis, such as impaired oxygenation.

NSAID-induced ulcers are related to decreased prostaglandin production from the inhibition of cyclooxygenase. In the case of lesions associated with intracranial injury, the proposed mechanism involves the direct stimulation of vagal nuclei by increased intracranial pressure, leading to hypersecretion of gastric acid, which is common in these patients. Systemic acidosis, a frequent finding in these clinical settings, may contribute to mucosal injury by lowering the intracellular pH of mucosal cells. These cells are also hypoxic as a consequence of stress-induced splanchnic vasoconstriction.

Morphology.

Acute stress ulcers are usually less than 1 cm in diameter and are circular and small. The ulcer base is frequently stained a dark brown by the acid digestion of extruded blood (Fig. 17-19). Unlike chronic peptic ulcers, acute stress ulcers are found anywhere in the stomach, the gastric rugal pattern is essentially normal and the margins and base of the ulcers are not indurated. While they may occur singly, more often there are multiple stress ulcers throughout the stomach and duodenum. Microscopically, acute stress ulcers are abrupt lesions, with essentially unremarkable adjacent mucosa. Depending on the duration of the ulceration, there may be a suffusion of blood into the mucosa and submucosa and some inflammatory reaction. Conspicuously absent are scarring and thickening of blood vessels, as seen in chronic peptic ulcers. Healing with complete reepithelialization occurs after the causative factors are removed. The time required for complete healing varies from days to several weeks.

Clinical Features.

Most critically ill patients admitted to hospital intensive care units develop histologic evidence of gastric mucosal damage. Bleeding from superficial gastric erosions or ulcers sufficient to require transfusion develops in 1% to 4% of these patients. Although prophylactic H_2 -receptor antagonists and proton pump inhibitors may blunt the impact of stress ulceration, *the single most important determinant of*

Figure 17-19 Multiple stress ulcers of the stomach, highlighted by dark digested blood on their surfaces.

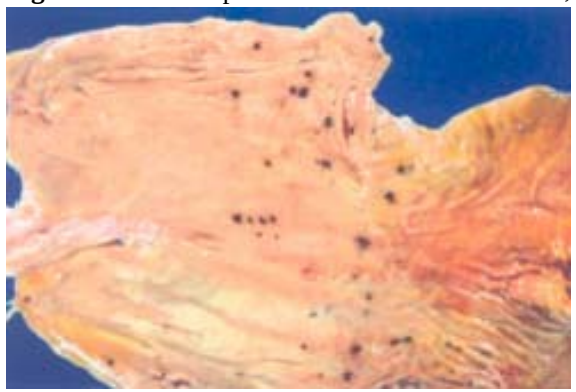


Figure 17-20 Trichobezoar, showing agglomeration of hair, food, and mucus that occurred within the gastric lumen.

Figure 17-21 Hypertrophic gastropathy, showing markedly thickened gastric folds.

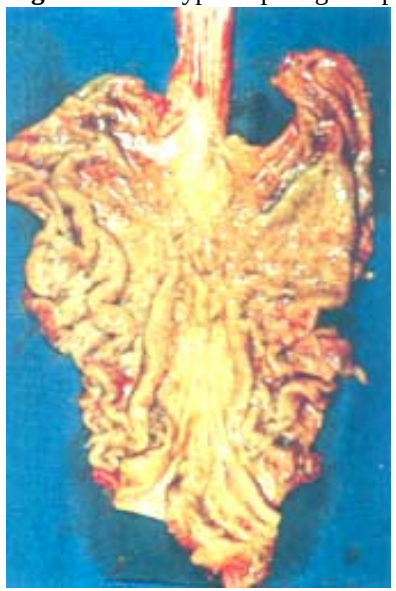


Figure 17-22 Gastric hyperplastic polyp. Low-power microscopic view of the polyp showing hyperplastic foveolar epithelium and inflammation.

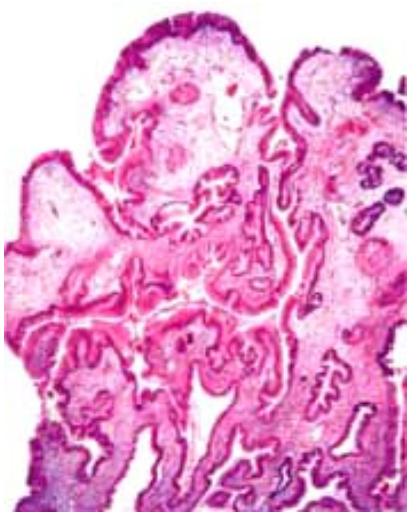


Figure 17-23 Gastric adenoma. Gross photograph showing a large polyp in the stomach.

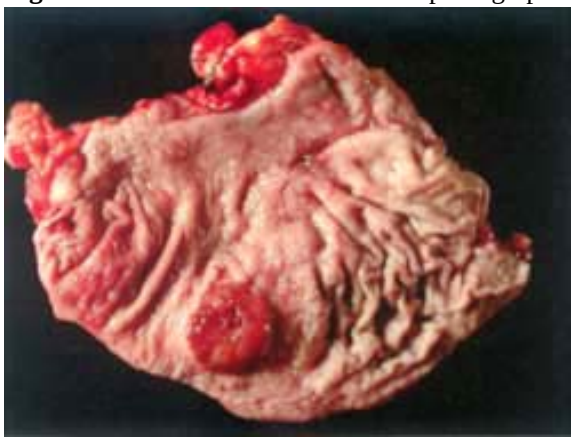


Figure 17-24 Inflammatory fibroid polyp; microscopic photograph showing submucosal growth of inflamed vascularized fibromuscular tissue with prominent eosinophilic infiltrate.

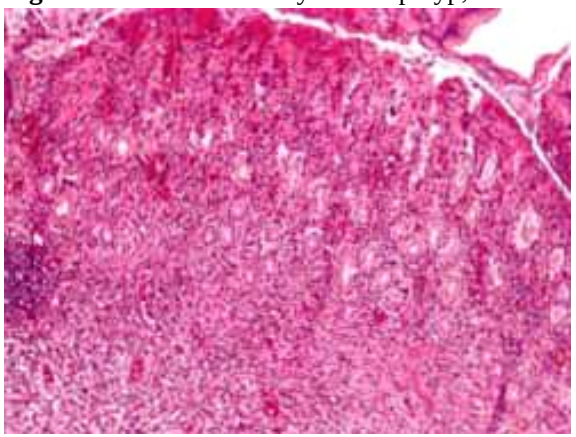


TABLE 17-4 -- WHO Histologic Classification of Gastric Tumors

Epithelial Tumors
Intraepithelial neoplasia: adenoma
Adenocarcinoma*
••• Papillary adenocarcinoma
••• Tubular adenocarcinoma
••• Mucinous adenocarcinoma
••• Signet-ring cell carcinoma
••• Undifferentiated carcinoma
••• Adenosquamous carcinoma
Small-cell carcinoma
Carcinoid tumor
Nonepithelial Tumors
Leiomyoma
Schwannoma
Granular cell tumor
Leiomyosarcoma
Gastrointestinal stromal tumor (GIST) (gradation from benign to malignant)
Kaposi sarcoma
Others
Malignant Lymphoma

* The Laurén classification subdivides adenocarcinomas into intestinal and diffuse types.

pathway by which intestinal-type gastric cancers develop. Adenomas containing mucosal dysplasia can also become malignant.

Environment.

Environmental influences may be critical in gastric carcinogenesis. [35] When families migrate from high-risk to low-risk areas (or the reverse), successive generations acquire the level of risk that prevails in the new locales. The *diet*

TABLE 17-5 -- Factors Associated with Increased Incidence of Gastric Carcinoma

Environmental Factors
Infection by *H. pylori*
• Present in most cases of intestinal-type carcinoma
Diet
• Nitrites derived from nitrates (water, preserved food)
• Smoked and salted foods, pickled vegetables, chili peppers
• Lack of fresh fruit and vegetables
Low socioeconomic status
Cigarette smoking
Host Factors
Chronic gastritis
• Hypochlorhydria: favors colonization with *H. pylori*
• Intestinal metaplasia is a precursor lesion
Partial gastrectomy
• Favors reflux of bilious, alkaline intestinal fluid
Gastric adenomas
• 40% harbor cancer at time of diagnosis
• 30% have adjacent cancer at time of diagnosis
Barrett esophagus
• Increased risk of gastroesophageal junction tumors
Genetic Factors
Slightly increased risk with blood group A
Family history of gastric cancer
Hereditary nonpolyposis colon cancer syndrome
Familial gastric carcinoma syndrome (E-cadherin mutation)

is suspected to be a primary factor, and adherence to certain culinary practices is associated with a high risk of gastric carcinoma. Lack of refrigeration; consumption of preserved, smoked,

cured, and salted foods; water contamination with nitrates; and lack of fresh fruit and vegetables are common themes in high-risk areas. The consumption of dietary carcinogens, such as N-nitroso compounds and benzopyrene, appears to be particularly important. Conversely, intake of green, leafy vegetables and citrus fruits, which contain antioxidants such as ascorbate (vitamin C), alpha-tocopherol (vitamin E), and beta-carotene, is negatively correlated with gastric cancer. A specific protective role for any one of these nutrients cannot be assumed, however, since intake of fresh food may simply displace consumption of preserved foods.

So far there is no conclusive evidence linking alcohol intake and cigarette smoking to the development of gastric cancer. Despite initial concern, *to date there appears to be no increased risk of stomach cancer from the use of antacid drug therapies*.

Host.

Autoimmune gastritis, like *H. pylori* infection, increases the risk of gastric cancer, presumably due to chronic inflammation and intestinal metaplasia. It has been noted that blood group A patients have higher risk but it is not yet clear whether this is related to the binding of *H. pylori* to Lewis B antigen, or to other mechanisms.

Within the United States, blacks, Native Americans, and Hawaiians have a higher risk of developing gastric cancer. But since only about 8% to 10% of patients with gastric cancer have a family history of this disease, genetic factors are unlikely to be a major influence. Environmental factors mentioned above, are likely to play a major role in the higher incidence of gastric cancer among these various groups. Genetic traits play a critical role in some familial cases of gastric cancer, including gastric carcinoma occurring in the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Recently, E-cadherin gene *(CDH1)* germ-line mutations have also been identified as the underlying genetic basis for another familial gastric cancer syndrome that is characterized by early occurrence of diffuse type adenocarcinoma.[36] These patients are also at risk for developing lobular breast cancer.[37]

Other Risk Factors.

Peptic ulcer disease per se does not impart increased risk for development of gastric cancer. However,

Figure 17-25 Diagram of growth patterns and spread of gastric carcinoma. In early gastric carcinoma (*A*), the tumor is confined to the mucosa and submucosa and may exhibit an exophytic, flat or depressed, or excavated conformation. Advanced gastric carcinoma (*B*) extends into the muscularis propria and beyond. Linitis plastica is an extreme form of flat or depressed advanced gastric carcinoma.

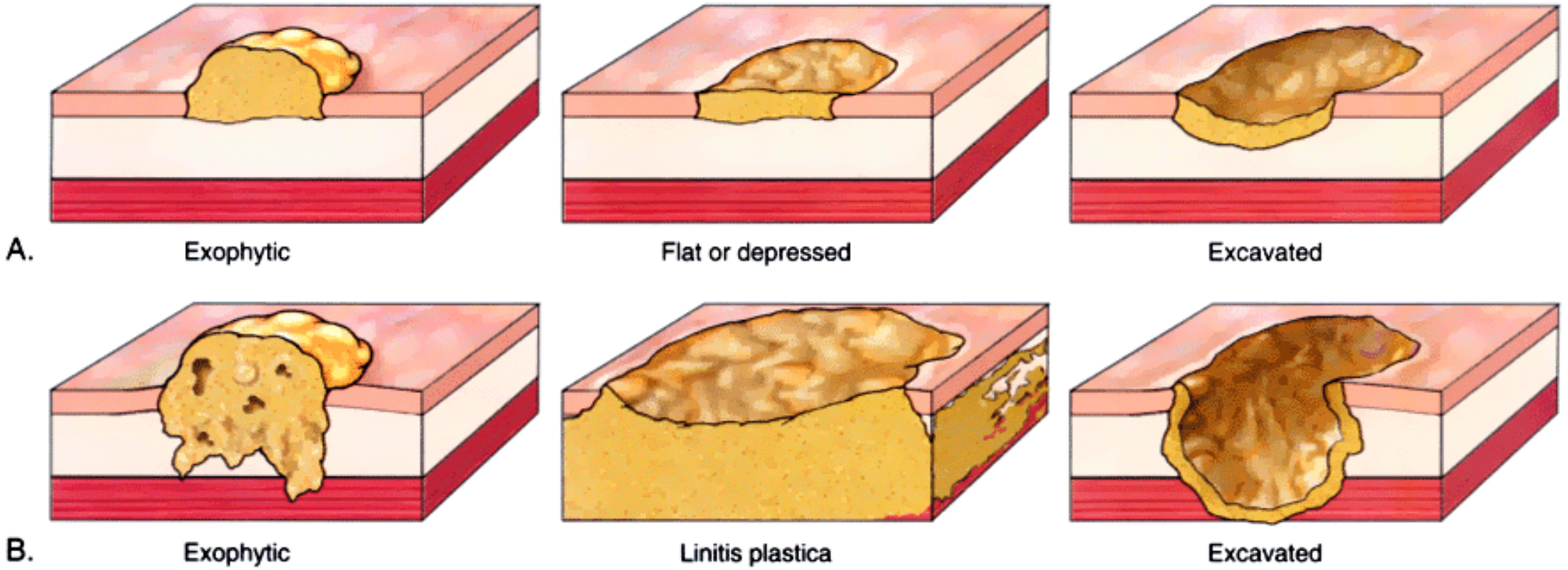


Figure 17-26 Gastric carcinoma. Gross photograph showing an ill-defined, excavated central ulcer surrounded by irregular, heaped-up borders.

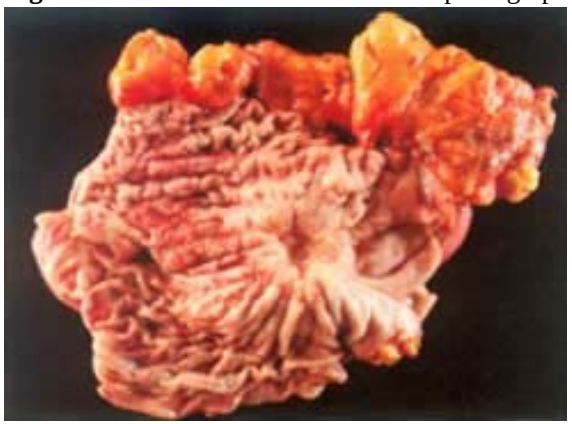


Figure 17-27 Gastric carcinoma. *A*, Intestinal type demonstrating gland formation by malignant cells, which are invading the muscular wall of the stomach. *B*, Diffuse type demonstrating signet-ring carcinoma cells.

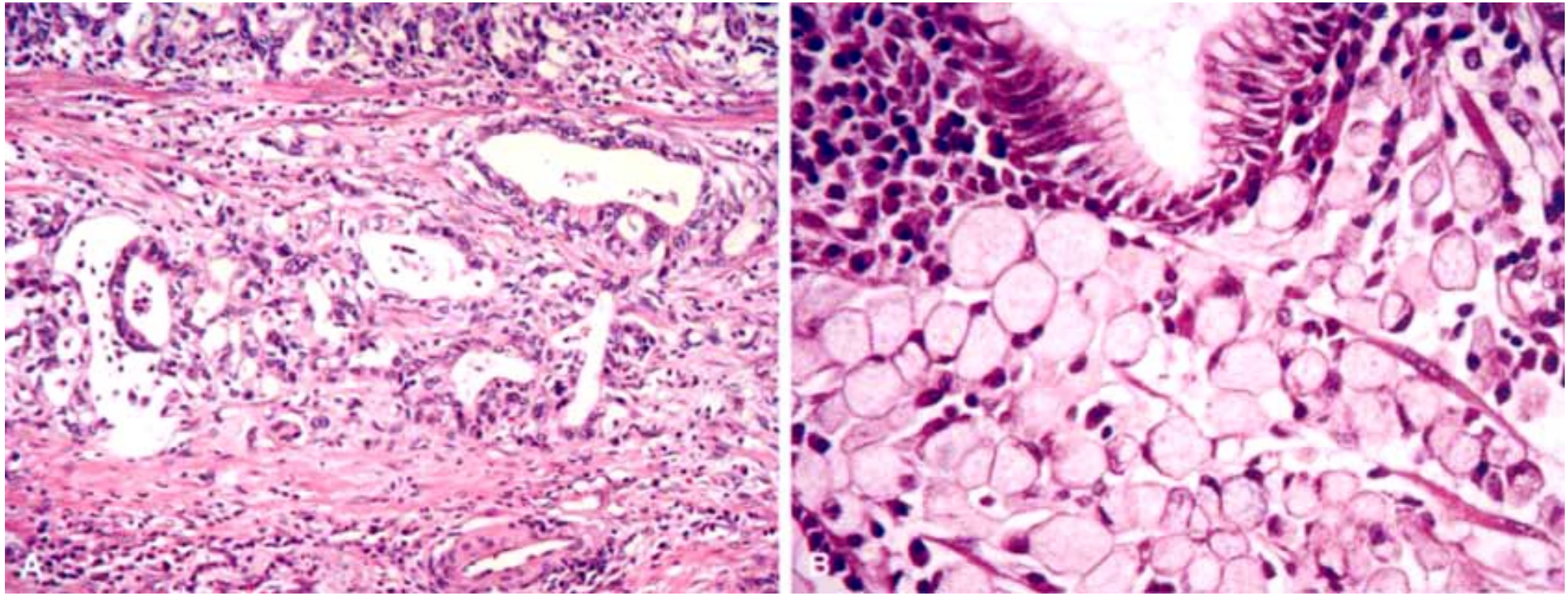


Figure 17-28 Gastric MALT lymphoma. Note the lymphoepithelial lesions *(arrows)*. *(Courtesy of Dr. Melissa Li, University of Florida, Gainesville, FL.)*

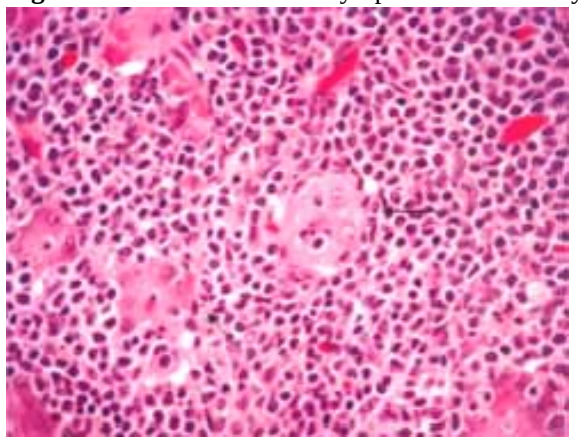


Figure 17-29 Gastrointestinal stromal tumor. *A,* Gross photograph of the tumor arising from the muscularis propria of the gastric wall. *B,* Microscopic view of the tumor showing spindle cell feature. *C,* Immunohistochemical stain showing the tumor cell c-*KIT* positivity.

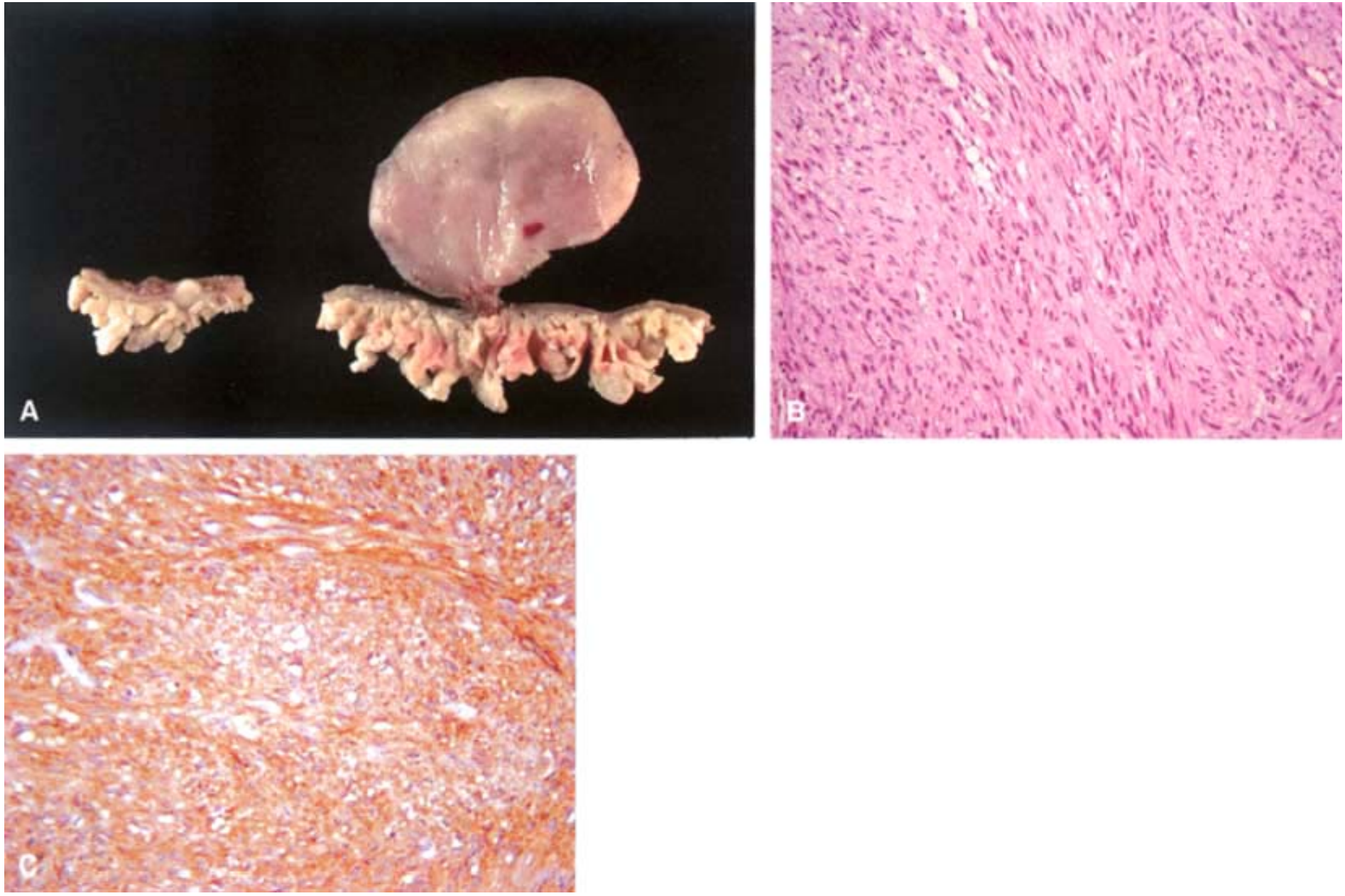


Figure 17-30 *A,* Normal small-bowel histology, showing mucosal villi and crypts, lined by columnar cells. *B,* Normal colon histology, showing flat mucosal surface and abundant vertically oriented crypts.

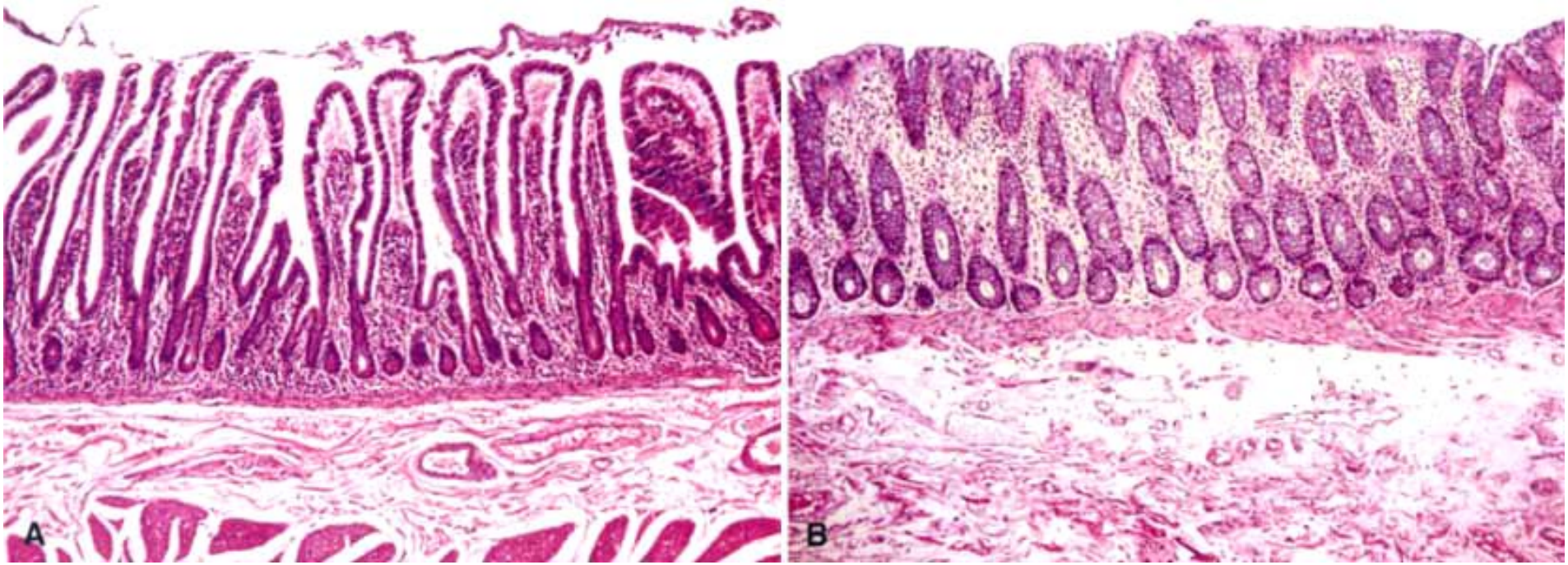


Figure 17-31 Meckel diverticulum. The blind pouch is located on the antimesenteric side of the small bowel.

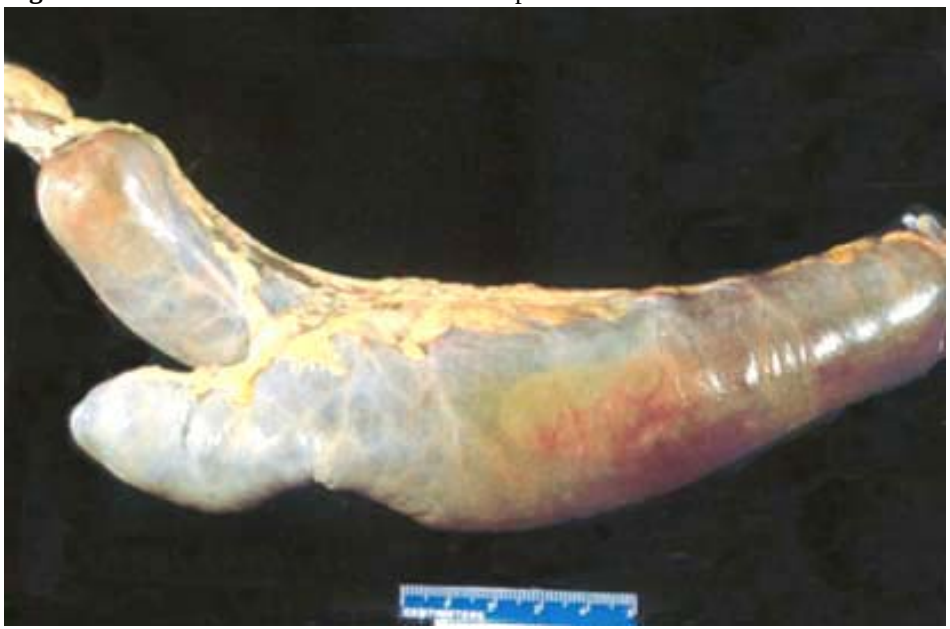


TABLE 17-6 -- Major Causes of Diarrheal Illnesses

Secretory Diarrhea

Infectious: viral damage to mucosal epithelium
• Rotavirus
• Caliciviruses
• Enteric adenoviruses
• Astroviruses
Infectious: enterotoxin mediated
• *Vibrio cholerae*
• *Escherichia coli*
• *Bacillus cereus*
• *Clostridium perfringens*
Neoplastic
• Tumor elaboration of peptides, serotonin, prostaglandins
• Villous adenoma in distal colon (nonhormone mediated)
Excess laxative use
Osmotic Diarrhea
Disaccharidase (lactase) deficiencies
Lactulose therapy (for hepatic encephalopathy, constipation)
Prescribed gut lavage for diagnostic procedures
Antacids ($MgSO_4$ and other magnesium salts)
Primary bile acid malabsorption
Exudative Diseases
Infectious: bacterial damage to mucosal epithelium
• *Shigella*
• *Salmonella*
• *Campylobacter*
• *Entamoeba histolytica*
Idiopathic inflammatory bowel disease
Typhlitis (neutropenic colitis in the immunosuppressed)
Malabsorption

Defective intraluminal digestion
Primary mucosal cell abnormalities
Reduced small intestinal surface area
Lymphatic obstruction
Infectious: impaired mucosal cell absorption
• *Giardia lamblia* infection
Deranged Motility
Decreased intestinal transit time
• Surgical reduction of gut length
• Neural dysfunction, including irritable bowel syndrome
• Hyperthyroidism
• Diabetic neuropathy
• Carcinoid syndrome
Decreased motility (increased intestinal transit time)
• Small intestinal diverticula
• Surgical creation of a "blind" intestinal loop
• Bacterial overgrowth in the small intestine

- *Secretory diarrhea:* Net intestinal fluid secretion leads to the output of more than 500 mL of fluid stool per day, which is isotonic with plasma and persists during fasting.
- *Osmotic diarrhea:* Excessive osmotic forces exerted by luminal solutes lead to output of more than 500 mL of stool per day, which abates upon fasting. Stool exhibits an osmotic gap (stool osmolality exceeds plasma electrolyte concentration by ≥50 mOsm).
- *Exudative diseases:* Mucosal destruction leads to output of purulent, bloody stools that persist on fasting; stools are frequent but may be small or large volume.
- *Deranged motility:* Improper gut neuromuscular function may produce highly variable patterns of increased stool volume; other forms of diarrhea must be excluded.
- *Malabsorption:* Improper absorption of gut nutrients produces voluminous, bulky stools with increased osmolarity combined with excess stool fat (steatorrhea). The diarrhea usually abates on fasting.

INFECTIOUS ENTEROCOLITIS

Intestinal diseases of microbial origin are marked principally by diarrhea and sometimes ulcerative and inflammatory changes in the small and/or large intestine. *Infectious enterocolitis is a global problem of staggering proportions, causing more than 12,000 deaths per day among children in developing countries, and constituting one half of all deaths before age 5 worldwide.* [49] *Although far less prevalent in industrialized nations, these infections still have attack rates of one to two illnesses per person per year, second only to the common cold in frequency.* This results in an estimated 99 million acute cases of either vomiting or diarrhea per year in the United States, equivalent to 40% of the population. The infections are mainly associated with contaminated food and water.

Acute, self-limited infectious diarrhea, which is a major cause of morbidity among children, is most frequently caused by enteric viruses. In infants, infectious diarrhea may cause severe

dehydration and metabolic acidosis, which may result in hospitalization in developed countries and death in developing countries. Bacterial infections, such as enterotoxigenic *Escherichia coli*, are also common offenders. However, *many pathogens can cause diarrhea*; the major offenders vary with the age, nutrition, immune status of the host, environment (living conditions, public health measures), and special predispositions, such as hospitalization, wartime dislocation, or foreign travel. In 40% to 50% of cases, the specific agent cannot be isolated.

Viral Gastroenteritis

Symptomatic human infection is caused by several distinct groups of viruses (Table 17-7). *Rotavirus* accounts for an estimated 140 million cases and 1 million deaths worldwide per year. The target population is children age 6 to 24 months, but young infants and debilitated adults are susceptible to symptomatic infection. This virus accounts for 25% to 65% of severe diarrhea in infants and young children.[50] Rotavirus is an encapsulated virus with a segmented double-stranded RNA genome. *Rotavirus selectively infects and destroys mature enterocytes in the small intestine, without infecting crypt cells.* The surface epithelium of the villus is repopulated by immature secretory cells. With the loss of absorptive function and excess of secretory cells, there is net secretion of water and electrolytes, compounded by an osmotic diarrhea from incompletely absorbed nutrients. The minimal infective inoculum is approximately 10 viral particles, whereas an individual with rotavirus gastroenteritis typically sheds up to 10^{12} particles/mL stool. Thus, outbreaks among pediatric populations in hospitals and day-care centers are very common. The clinical syndrome has an incubation period of approximately 2 days, which is followed by vomiting and watery diarrhea for several days. Viral infection can induce protective immunity, but the protection for reinfection is often short-lived. Antirotavirus

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TABLE 17-7 -- Common Gastrointestinal Viruses

Virus	Genome	Size (nm)	% of U.S. Childhood Viral Enterocolitis	Host Age	Mode of Transmission	Prodrome/Duration of Illness
Rotavirus (Group A)	dsRNA	70	60	6–24 months	Person-to-person, food, water	2 days/3–5 days
Caliciviruses	ssRNA	35–40	20	Child or adult	Person-to-person, water, cold foods, raw shellfish	1–3 days/4 days
••Norwalk-like viruses						
••Sapporo-like viruses						
Enteric adenoviruses	dsDNA	80	8	Child <2 years	Person-to-person	3–10 days/7+ days
Astroviruses	ssRNA	28	4	Child	Person-to-person, water, raw shellfish	24–36 hours/1–4 days

Data from Goodgame RW: Viral causes of diarrhea. Gastroenterol Clin North Am 30:779,2001.

ds, double-stranded; ss, single stranded.

antibodies are present in mother's milk, so rotavirus infection is most frequent at the time of weaning.

Among the numerous types of *adenovirus*, the subtypes (enteric serotypes) Ad40, Ad41, and Ad31 appear to be responsible for enteric infections and are a common cause of diarrhea among infants. They can be distinguished from adenoviruses that cause respiratory disease by their failure to grow easily in culture. Adenoviruses cause a moderate gastroenteritis with diarrhea and vomiting, lasting for a week to 10 days after an incubation period of approximately 1 week. In the small intestine, adenoviral infection causes atrophy of the villi and

compensatory hyperplasia of the crypts similar to rotavirus, resulting in malabsorption and fluid loss. The virus can also cause colitis. Immunohistochemical stain of nuclear inclusions facilitates the diagnosis.

Caliciviruses include two major groups: the classic Caliciviruses (Sapporo-like viruses) and the Norwalk-like viruses (small round structured viruses). Sapporo-like viral infection is rare, while *Norwalk virus*, the prototype of Norwalk-like viruses, is responsible for the majority of cases of nonbacterial food-borne epidemic gastroenteritis in all age groups. Norwalk-like viruses are small icosahedral viruses containing a single-stranded RNA genome. They cause epidemic gastroenteritis with diarrhea, nausea, and vomiting among children. Outbreaks occur following exposure of multiple individuals to a common source. The clinical syndrome has an incubation period of 1 to 2 days, which is followed by 12 to 60 hours of nausea, vomiting, watery diarrhea, and abdominal pain.

Astrovirus is named after its starlike appearance. It primarily affects children, (it accounts for 4% of acute gastroenteritis in young children), and has a worldwide distribution. Those infected develop anorexia, headache, and fever. Other viruses such as enterotrophic coronaviruses and toroviruses are occasionally implicated in human diarrheal disease.

Despite the high incidence of viral gastroenteritis, insights into disease pathogenesis have been slow in coming.

Morphology.

Although the enteric viruses are genetically and morphologically different from each other, the lesions they cause in the intestinal tract are similar. The small intestinal mucosa usually exhibits modestly shortened villi and infiltration of the lamina propria by lymphocytes. Vacuolization and loss of the microvillus brush border in surface epithelial cells may be evident, and the crypts become hypertrophied. Viral particles may be visualized by electron microscopy within surface epithelial cells. In infants, rotavirus can produce a flat mucosa resembling celiac sprue (discussed later).

Bacterial Enterocolitis

Diarrheal illness may be caused by numerous bacteria (Table 17-8). There are several pathogenic mechanisms for bacterial enterocolitis (also termed *food poisoning*):

- *Ingestion of preformed toxin*, present in contaminated food. Major offenders are *Staphylococcus aureus*, *Vibrio*, and *Clostridium perfringens*. Symptoms develop within a matter of hours; explosive diarrhea and acute abdominal distress herald an illness that passes within a day or so. Ingested systemic neurotoxins, as from *Clostridium botulinum*, may produce rapid, and fatal, respiratory failure.
- *Infection by toxigenic organisms*, which proliferate within the gut lumen and elaborate an enterotoxin. An incubation period of several hours to days is followed by *diarrhea and dehydration* if the primary pathogenic mechanism is a secretory enterotoxin, or *dysentery* if the primary mechanism is a cytotoxin. *Traveler's diarrhea* (Montezuma's revenge, turista) usually occurs following ingestion of fecally contaminated food or water; it begins abruptly and subsides within 2 to 3 days. It affects 20% to 50% of the 35 million people who travel worldwide from industrialized countries to developing countries each year.
- *Infection by enteroinvasive organisms*, which proliferate, invade, and destroy mucosal epithelial cells, also leading to dysentery. As with ingestion of toxigenic organisms, the incubation period is several hours to days.

The main properties of bacteria that contribute to the pathogenesis of enterocolitis are: *(1) the ability to adhere to the mucosal epithelial cells and replicate, (2) the ability to elaborate enterotoxins, and (3) the capacity to invade.*

Bacterial Adhesion and Replication.

In order to produce disease, ingested organisms must adhere to the mucosa; otherwise they will be swept away by the fluid stream. Adherence of enterotoxigenic organisms such as *E. coli* and *Vibrio cholerae* is mediated by plasmid-encoded adhesins. These proteins are expressed on the surface of the organism, sometimes in the form of fimbriae or *pili*, which are rigid or wiry surface

TABLE 17-8 -- Major Causes of Bacterial Enterocolitis

Organism	Pathogenic Mechanism	Source	Clinical Features
Escherichia coli			Traveler's diarrhea, including:
• ETEC	Cholera-like toxin, no invasion	Food, water	Watery diarrhea
• EHEC	Shiga-like toxin, no invasion	Undercooked beef products	Hemorrhagic colitis, hemolytic-uremic syndrome
• EPEC	Attachment, enterocyte effacement, no invasion	Weaning foods, water	Watery diarrhea, infants and toddlers
• EIEC	Invasion, local spread	Cheese, water, person-to-person	Fever, pain, diarrhea, dysentery
Salmonella	Invasion, translocation, lymphoid inflammation, dissemination	Milk, beef, eggs, poultry	Fever, pain, diarrhea or dysentery, bacteremia, extraintestinal infection, common source outbreaks
Shigella	Invasion, local spread	Person-to-person, low-inoculum	Fever, pain, diarrhea, dysentery, epidemic spread
Campylobacter	Toxins, invasion	Milk, poultry, animal contact	Fever, pain, diarrhea, dysentery, food sources, animal reservoirs
Yersinia enterocolitica	Invasion, translocation, lymphoid inflammation, dissemination	Milk, pork	Fever, pain, diarrhea, mesenteric adenitis, extraintestinal infection, food sources
Vibrio cholerae, other *Vibrios*	Enterotoxin, no invasion	Water, shellfish, person-to-person spread	Watery diarrhea, cholera, pandemic spread
Clostridium difficile	Cytotoxin, local invasion	Nosocomial environmental spread	Fever, pain, bloody diarrhea, following antibiotic use, nosocomial acquisition
Clostridium perfringens	Enterotoxin, no invasion	Meat, poultry, fish	Watery diarrhea, food sources, "pigbel"
Mycobacterium tuberculosis	Invasion, mural inflammatory foci with necrosis and scarring	Contaminated milk, swallowing of coughed-up organisms	Chronic abdominal pain; complications of malabsorption, stricture, perforation, fistulae, hemorrhage

ETEC, enterotoxigenic *E. coli*; EHEC, enterohemorrhagic *E. coli*; EPEC, enteropathogenic *E. coli*; EIEC, enteroinvasive *E. coli*.

projections. Adherence of enteropathogenic and enterohemorrhagic organisms, including *E. coli* and *Shigella,* is also dependent on plasmid-encoded proteins, but the nature of these proteins is not known. Adherence causes effacement of the apical enterocyte membrane, with destruction of the microvillus brush border and changes in the underlying cell cytoplasm.[35] The factors regulating bacterial replication are not well understood, particularly since pathogenic organisms must compete with the normal bacterial flora to achieve a critical population density.

Bacterial Enterotoxins.

Bacterial enterotoxins are polypeptides that cause diarrhea. Some *enterotoxins* cause intestinal secretion of fluid and electrolytes without causing tissue damage; this is accomplished by binding of the toxin to the epithelial cell membrane, entry of a portion of the toxin into the cell, and massive activation of electrolyte secretion accompanied by water. *Cholera toxin, elaborated by Vibrio cholerae, is the prototype secretagogue toxin.* The toxin causes increased levels of intracellular calcium, resulting in dysfunction of the fluid and electrolyte transport, as discussed below under Cholera. *Strains of E. coli (enterotoxigenic E. coli) that produce heat-labile (LT) and heat-stable (ST) secretagogue toxins are the major cause of traveler's diarrhea.* The LT toxin is similar to cholera toxin, and the ST toxin induces cyclic guanosine monophosphate, resulting in increased fluid excretion. Leukocytes are absent from the stool of patients with traveler's diarrhea. A second group of enterotoxins are *cytotoxins*, exemplified by Shiga toxin produced by *Shigella dysenteriae* and Shiga-like toxins produced by enterohemorrhagic *E. coli* (e.g., *E. coli O157:H7*). These toxins cause direct tissue damage through epithelial cell necrosis. *Staphylococcal enterotoxins*, which are major causes of food poisoning, represent yet another group of enterotoxins; are proteins that bind to the antigen receptors of large numbers of T cells and activate the lymphocytes to secrete cytokines. The cytokines stimulate intestinal motility and fluid secretion.

Bacterial Invasion.

Both enteroinvasive *E. coli* and *Shigella* possess a large virulence plasmid that confers the capacity for epithelial cell invasion, apparently by microbe-stimulated endocytosis. This is followed by intracellular proliferation, cell lysis, and cell-to-cell spread. *Salmonella* quickly pass through intestinal epithelial cells via transcytosis with minimal epithelial damage; entry into the lamina propria leads to a 5% to 10% incidence of bacteremia, which can sometimes cause typhoid fever, meningitis, endocarditis, and osteomyelitis (commonly in the setting of sickle cell disease). *Yersinia enterocolitica* penetrates the ileal mucosa and multiplies within Peyer patches and regional lymph nodes. Bacteremia is rare and usually occurs in the setting of iron-overload disease, since iron is a growth factor for *Yersinia*.

Bacterial cytotoxins and invasion give rise to bacillary dysentery, which generates its own unique misery for its victims: abdominal cramping and tenesmus with loose stools containing blood, pus, and mucus. Bacillary dysentery, which results in as many as 500,000 deaths among children in developing countries each year, is caused by *Shigella dysenteriae, Shigella flexneri, Shigella boydii,* and *Shigella sonnei* as well as certain O type enterotoxic *E. coli*. (Amebic dysentery is caused by the protozoan parasite *Entamoeba histolytica,* discussed later in this chapter).

Shigella Bacillary Dysentery

Shigella species are gram-negative facultative anaerobes that infect only humans. *S. flexneri* is the major cause of endemic bacillary dysentery in locations of poor hygiene, including large regions of the developing world and institutions in the

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developed world. Epidemic shigellosis can occur when individuals consume uncooked foods at picnics or other events.

Pathogenesis.

Transmission is fecal-oral and is remarkable for the small number of organisms that may cause disease (10 ingested organisms cause illness in 10% of volunteers, and 500 organisms cause disease in 50% of volunteers). *Shigella* bacteria invade the intestinal mucosal cells but do not usually go beyond the lamina propria. Dysentery is caused when the bacteria escape the epithelial cell phagolysosome, multiply within the cytoplasm, and destroy host cells. Shiga toxin causes hemorrhagic colitis and hemolytic-uremic syndrome by damaging endothelial cells in the microvasculature of the colon and the glomeruli, respectively (Chapter 20). In addition, chronic arthritis secondary to *S. flexneri* infection, called *Reiter syndrome,* may be caused by a bacterial antigen; the occurrence of this syndrome is strongly linked to HLA-B27 genotype, but the immunologic basis of this reaction is not understood. [51]

Salmonellosis and Typhoid Fever

Salmonellae are flagellated, gram-negative bacteria that cause a self-limited food-borne and water-borne gastroenteritis (*S. enteritidis, S. typhimurium,* and others) or a life-threatening systemic illness, typhoid fever, marked by fever and systemic symptoms *(S. typhi)*. In the United States, *Salmonella* species cause approximately 500,000 reported cases of food poisoning, and many cases go unreported. Because *Salmonella* species other than *S. typhi* infect most commercially raised chickens and many cows, the major sources of *Salmonella* in the United States are feces-contaminated beef and chicken that are insufficiently washed and cooked. Stringent hygiene in the production plants and the home kitchen helps minimize risk of contamination. In contrast, humans are the only host of *S. typhi*, which is shed in the feces, urine, vomitus, and oral secretions by acutely ill persons and in the feces by chronic carriers without overt disease. Therefore, typhoid fever from *S. typhi* is a disease largely of developing countries, where sanitary conditions are insufficient to stop its spread. Typhoid fever is a protracted disease that is associated with bacteremia, fever, and chills during the first week; widespread mononuclear phagocyte involvement with rash, abdominal pain, and prostration in the second week; and ulceration of Peyer patches with intestinal bleeding and shock during the third week.

Pathogenesis.

Salmonella invades intestinal epithelial cells as well as tissue macrophages. Invasion of intestinal epithelial cells is controlled by invasion genes that are induced by the low oxygen tension found in the gut. These genes encode proteins involved in adhesion and in recruitment of host cytoskeletal proteins that internalize the bacterium. Similarly, intramacrophage growth is important in pathogenicity, and this seems to be mediated by bacterial genes that are induced by the acid pH within the macrophage phagolysosome. The enteric nervous system also is a critical regulator of fluid secretion in the normal gut. Neural reflex pathways increase epithelial fluid secretion in response to enteric pathogens such as *Salmonella* and *Clostridium difficile*. [52]

Campylobacter Enterocolitis

This comma-shaped, flagellated, gram-negative organism was once classified with the vibrios. When special culture conditions permitted its isolation in the 1970s, it became apparent that *Campylobacter* was an important cause of enterocolitis and septicemia in humans. In the United States, *Campylobacter jejuni* is responsible for twice the enteric disease of *Salmonella* and four times that of *Shigella*. Most infections with *Campylobacter* are sporadic and are associated with ingestion of improperly cooked chicken, which may be contaminated with *Campylobacter* and/or *Salmonella*. Sporadic infections may also be associated with contact with infected dogs. Outbreaks of *Campylobacter* are usually associated with unpasteurized milk or contaminated water.

Pathogenesis.

Invasiveness is strain dependent. Flagella of *Campylobacter,* which give the organism its comma shape and motility, are necessary for the bacterium to penetrate mucus covering epithelial surfaces. Three clinical outcomes of *Campylobacter* infection are possible: (1) diarrhea, which is independent of bacterial invasion; (2) dysentery with blood and mucus in the stool; and (3) enteric fever when bacteria proliferate within the lamina propria and mesenteric lymph nodes. Postinfectious complications of *Campylobacter* infections include reactive arthritis in HLA-B27 carriers (as with *Shigella* infection) and Guillain-Barré syndrome, a demyelinating disease of peripheral nerves due to autoantibodies against gangliosides G_{M1} and GQ1b, described in Chapter 27 . Recently, *C. jejuni* was found to be associated with the development of immunoproliferative small intestinal disease (discussed later).

Cholera

Vibrio cholerae are comma-shaped, gram-negative bacteria that have been the cause of seven great long-lasting epidemics (pandemics) of diarrheal disease. Many of these pandemics began in the Ganges Valley of India and Bangladesh, which is never free from cholera, and then moved east. Although there are 140 serotypes of *V. cholerae,* until recently only the 01 serotype was associated with severe diarrhea. Beginning in 1992, a new *V. cholerae* serotype (0139, also known as Bengal) has been associated with severe, watery diarrhea.[53]

Pathogenesis.

The vibrios never invade the epithelium but instead remain within the lumen and secrete an enterotoxin, which is encoded by a virulence phage. Flagellar proteins involved in motility and attachment are necessary for efficient bacterial colonization, as has been described for *Campylobacter*. (This is in contrast to *Shigella* species and certain *E. coli* strains, which are

nonmotile and yet invasive.) The *Vibrio* hemagglutinin, which is a metalloprotease, is important for detachment of *Vibrio* from epithelial cells.

The secretory diarrhea characteristic of the disease is caused by release of *cholera toxin* (Fig. 17-32). Cholera toxin is composed of five binding peptides B and a catalytic peptide A. The B peptides, serving as a "landing pad," bind to carbohydrates on G_{M1} ganglioside on the surface of epithelial cells of the small intestine, enabling calveolar-mediated endosomal entry of toxin subunit A into the cell. Reverse transport of the subunit A from the endosome into the cell cytoplasm is followed by cleavage of the disulfide bond linking the two fragments of peptide A (A1 and A2). Catalytic peptide A1 is generated, leading to the following sequence:

- A1 interacts with 20-kD cytosolic proteins called ADP-ribosylation factors (ARF).
- The ARF-A1 complex catalyzes ADP-ribosylation of a 49-kD G-protein (called $G_{s\alpha}$).[54]
- Binding of NAD and GTP generates an activated $G_{s\alpha}$, which in turn binds to and stimulates adenylate cyclase. ADP-ribosylated $G_{s\alpha}$ is permanently in an active GTP-bound

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state, resulting in persistent activation of adenylate cyclase.

- The activated adenylate cyclase generates high levels of intracellular cAMP from ATP.
- Cyclic AMP stimulates secretion of chloride and bicarbonate, with associated sodium and water secretion. Chloride and sodium resorption are also inhibited.

Figure 17-32 Mechanisms of cholera toxin action.

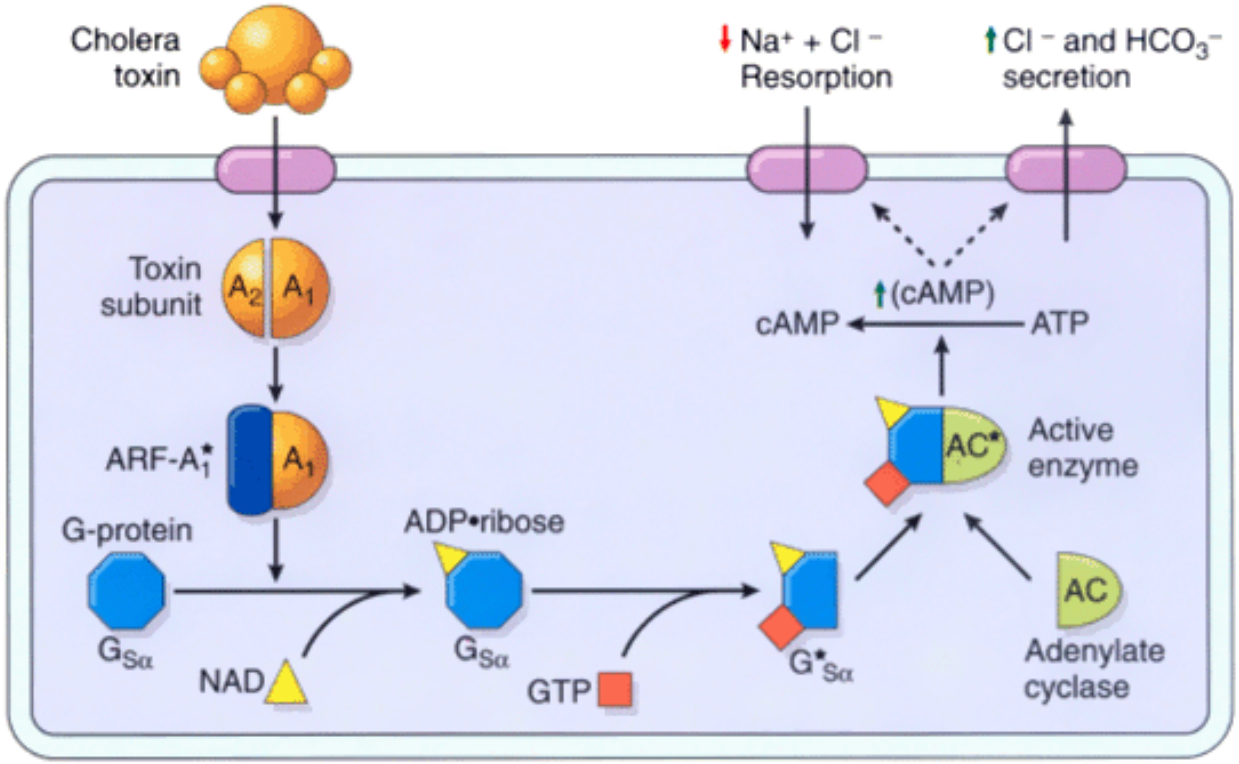


Figure 17-33 Shigella enterocolitis. Segment of colon showing pale, granular, inflamed mucosa with patches of coagulated exudate.

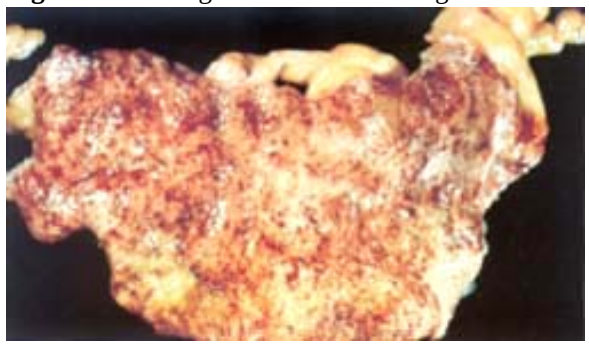


Figure 17-34 Pseudomembranous colitis from *C. difficile* infection. *A,* Gross photograph showing plaques of yellow fibrin and inflammatory debris adherent to a reddened colonic mucosa. *B,* Low-power micrograph showing superficial erosion of the mucosa and an adherent pseudomembrane of fibrin, mucus, and inflammatory debris.

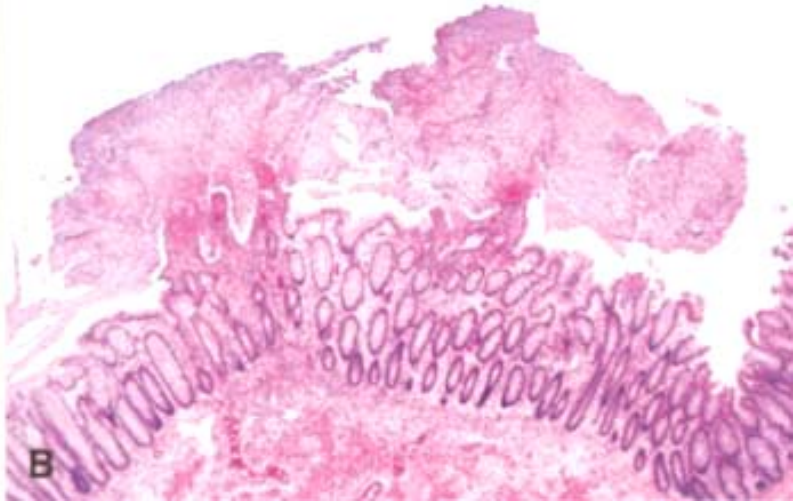


Figure 17-35 *Entamoeba histolytica* in colon. High-power view of the organisms. Note some of the organisms ingesting red blood cells.

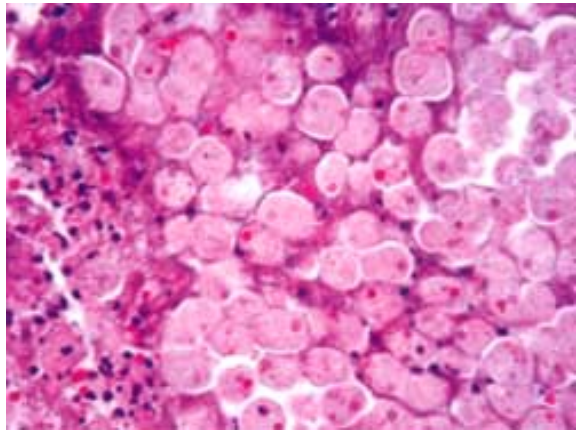


Figure 17-36 *Giardia lamblia.* Trophozoite *(arrow)* of the organism immediately adjacent to the duodenal surface epithelium.

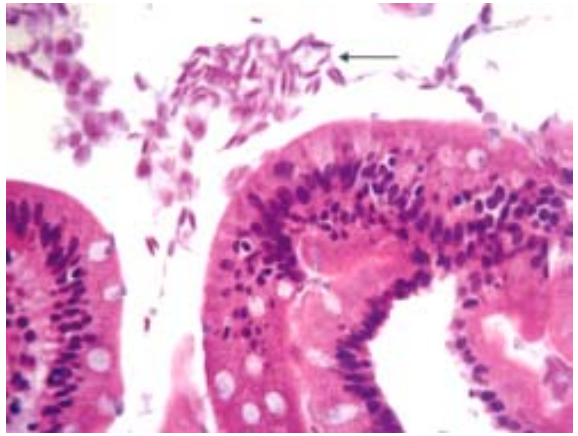


Figure 17-37 Graft-versus-host disease of the colon. Note the apoptotic cell in the crypt *(arrow)*.

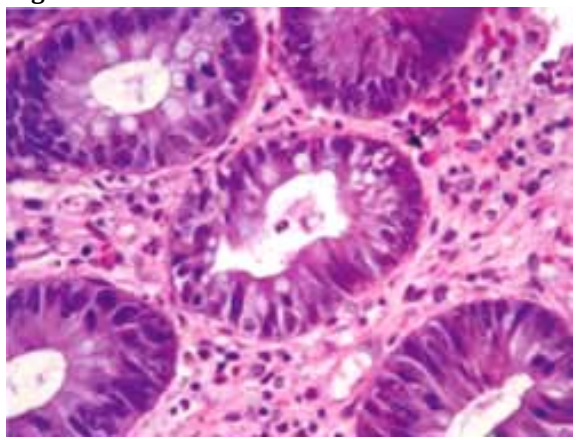


TABLE 17-9 -- Major Malabsorption Syndromes

Defective Intraluminal Digestion
Digestion of fats and proteins
• Pancreatic insufficiency, owing to pancreatitis or cystic fibrosis
• Zollinger-Ellison syndrome, with inactivation of pancreatic enzymes by excess gastric acid secretion
Solubilization of fat, owing to defective bile secretion
• Ileal dysfunction or resection, with decreased bile salt uptake
• Cessation of bile flow from obstruction, hepatic dysfunction
Nutrient preabsorption or modification by bacterial overgrowth
Primary Mucosal Cell Abnormalities
Defective terminal digestion
• Disaccharidase deficiency (lactose intolerance)
• Bacterial overgrowth, with brush border damage
Defective epithelial transport
• Abetalipoproteinemia
• Primary bile acid malabsorption owing to mutations in the ileal bile acid transporter
Reduced Small Intestinal Surface Area
Gluten-sensitive enteropathy (celiac disease)
Crohn disease
Lymphatic Obstruction
Lymphoma
Tuberculosis and tuberculous lymphadenitis
Infection
Acute infectious enteritis
Parasitic infestation
Tropical sprue
Whipple disease (*Tropheryma whippelii*)
Iatrogenic
Subtotal or total gastrectomy
Short-gut syndrome, following extensive surgical resection
Distal ileal resection or bypass

• *Alimentary tract:* diarrhea, both from nutrient malabsorption and excessive intestinal secretions, flatus, abdominal pain, weight loss, and mucositis resulting from vitamin deficiencies
• *Hematopoietic system:* anemia from iron, pyridoxine, folate, and/or vitamin B_{12} deficiency and bleeding from vitamin K deficiency
• *Musculoskeletal system:* osteopenia and tetany from calcium, magnesium, and vitamin D deficiency
• *Endocrine system:* amenorrhea, impotence, and infertility from generalized malnutrition; hyperparathyroidism from protracted calcium and vitamin D deficiency
• *Epidermis:* purpura and petechiae from vitamin K deficiency, edema from protein deficiency, dermatitis and hyperkeratosis from deficiencies of vitamin A, zinc, essential fatty acids and niacin
• *Nervous system:* peripheral neuropathy from vitamin A and B_{12} deficiencies.

The passage of abnormally bulky, frothy, greasy, yellow, or gray stools *(steatorrhea)* is a prominent feature of malabsorption, accompanied by weight loss, anorexia, abdominal distention, borborygmi, and muscle wasting. *The malabsorptive disorders most commonly encountered in the United States are celiac disease, pancreatic insufficiency, and Crohn disease.*

Pancreatic insufficiency, primarily from chronic pancreatitis or cystic fibrosis, is a major cause of *defective intraluminal digestion*. Typical features of defective intraluminal digestion are an osmotic diarrhea from undigested nutrients and steatorrhea. Excessive growth of normal bacteria within the proximal small intestine (*bacterial overgrowth,* discussed earlier) also impairs intraluminal digestion and can damage mucosal epithelial cells, causing impaired terminal digestion and epithelial absorption.

CELIAC DISEASE

Celiac disease (also referred to as celiac sprue, gluten-sensitive enteropathy) is a chronic disease, in which there is a characteristic mucosal lesion of the small intestine and impaired nutrient absorption, which improves on withdrawal of wheat gliadins and related grain proteins from the diet. [63] Celiac disease occurs largely in Caucasians and is rare or nonexistent among native Africans, Japanese, and Chinese. Its prevalence in the United States is somewhat difficult to define; in Europe the prevalence is in the range of 1:100 to 1:200.[64] The disease was first described more than a century ago, but its connection to gluten was not known until the 1940s, changing its clinical management.

Pathogenesis.

The fundamental disorder in celiac disease is a sensitivity to gluten, which is the alcohol-soluble, water-insoluble protein component (gliadin) of wheat and closely related grains (oat, barley, and rye). The hallmark of this disease is a T-cell mediated chronic inflammatory reaction with an autoimmune component, which most likely develops as a consequence of a loss of tolerance to gluten. Interplay between genetic predisposing factors, the host immune response, and environmental factors is central to disease pathogenesis. The small intestinal mucosa, when exposed to gluten, accumulates intraepithelial CD8+ T cells and large numbers of lamina propria CD4+ T cells, which are sensitized to gliadin. The recognized epitopes are confined to residues 57–75 of gliadin. [65]

It has been long known that family history is important in celiac disease. Almost all individuals with celiac disease share the major histocompatibility complex class II HLA-DQ2 or

Figure 17-38 Celiac disease (gluten-sensitive enteropathy). *A,* A peroral jejunal biopsy specimen of diseased mucosa shows diffuse severe atrophy and blunting of villi, with a chronic inflammatory infiltrate of the lamina propria. *B,* A normal mucosal biopsy.

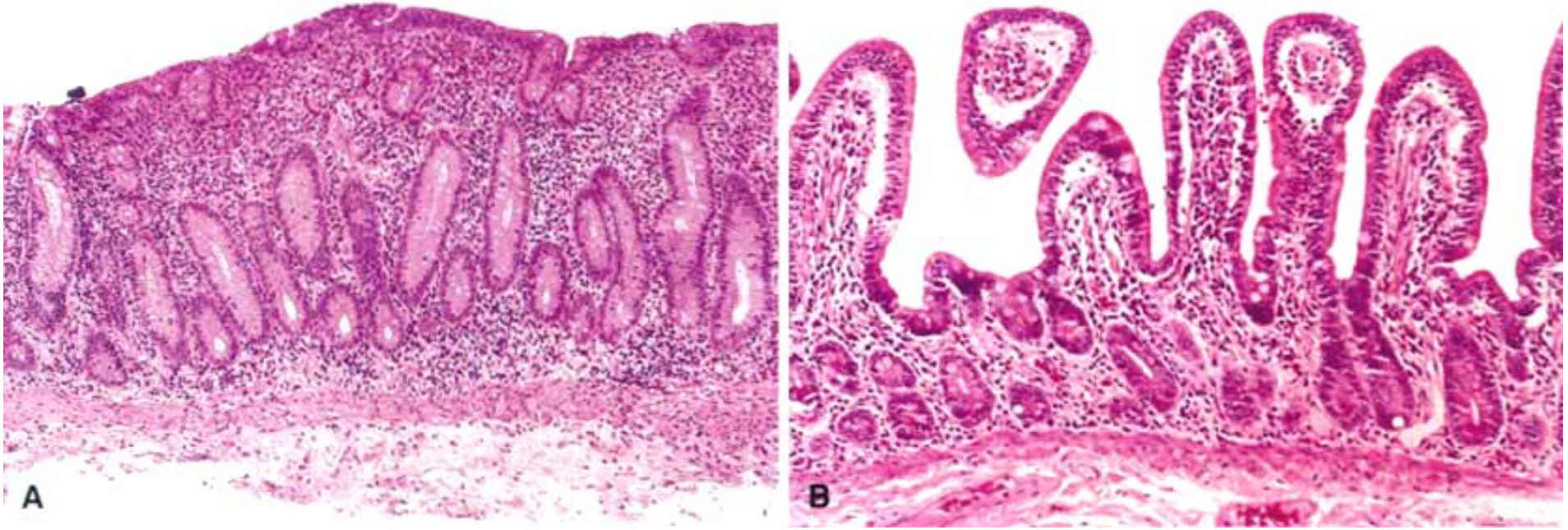
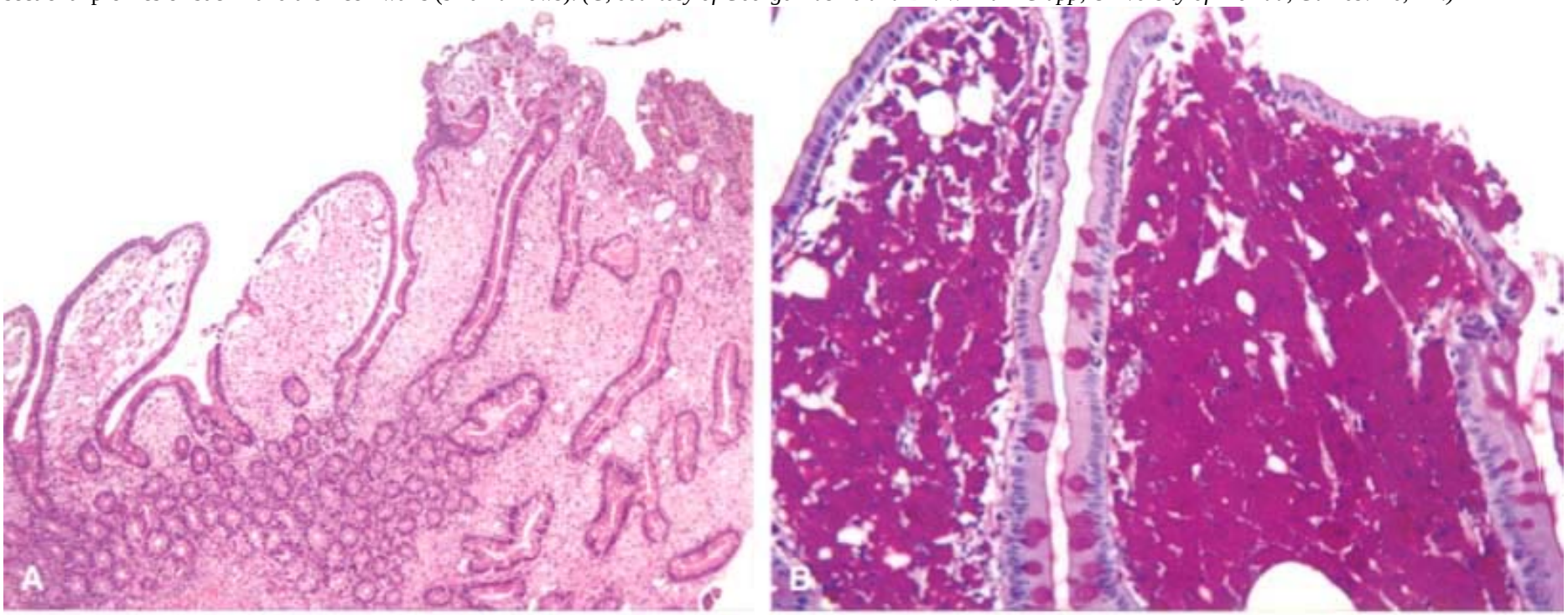


Figure 17-39 Whipple disease. *A,* Note foamy macrophages in the lamina propria. *B,* PAS stain showing the positive granules in the foamy macrophages. *C,* Electron micrograph of a lamina propria macrophage showing many bacilli within the cell (*arrow*) and in the extracellular space (*arrowhead*). *Inset,* Higher magnification of macrophage cytoplasm showing cross-sectional profiles of bacilli and their cell walls (small *arrows*). *(C, courtesy of George Kasnic and Dr. William Clapp, University of Florida, Gainesville, FL.)*



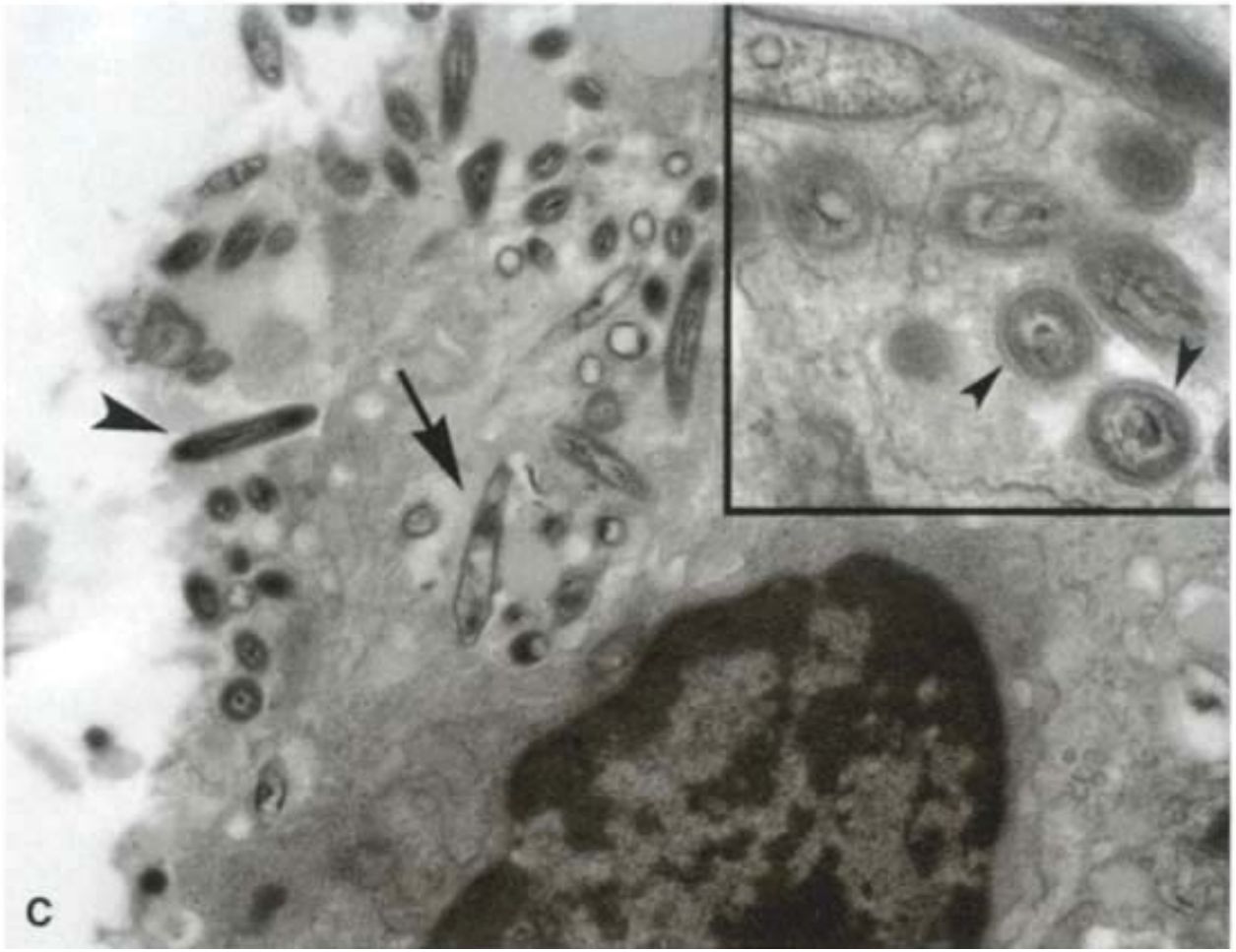


Figure 17-40 Crohn disease of ileum, showing narrowing of the lumen, bowel wall thickening, serosal extension of mesenteric fat ("creeping fat"), and linear ulceration of the mucosal surface *(arrowheads)*.

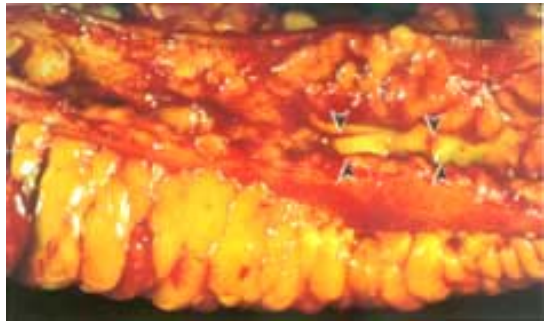


Figure 17-41 Crohn disease of the colon; a deep fissure extending into the muscle wall, a second, shallow ulcer (on the upper right), and relative preservation of the intervening mucosa. Abundant lymphocyte aggregates are present, evident as dense blue patches of cells at the interface between mucosa and submucosa.

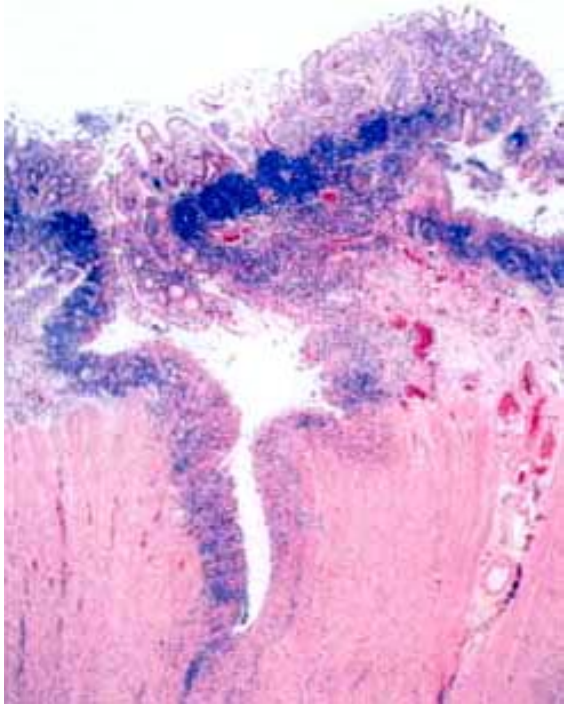


Figure 17-42 Crohn disease of the colon. A noncaseating granuloma is present in the lamina propria of an uninvolved region of colonic mucosa (*arrow*).

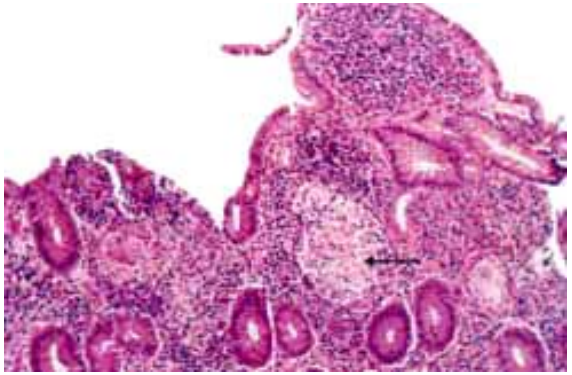


Figure 17-43 Comparison of the distribution patterns of Crohn disease and ulcerative colitis, as well as the different conformations of the ulcers and wall thickenings.