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CHAPTER 6

The Respiratory System

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General Considerations

The responses of the respiratory tract to injury, and the resulting patterns of disease, are determined largely by the structural and functional complexity of the system. Most of the diseases of the respiratory system are caused by damaging agents arriving by either the airborne (aerogenous) or blood-borne (hematogenous) routes, each with its own special pathogenetic considerations.

There is constant exposure of the respiratory system to potentially harmful agents in the ambient air. The defenses of the respiratory tract against **aerogenous injury** are remarkably effective but are not always successful. Airborne infectious agents commonly cause respiratory diseases, and in some intensive systems of animal management they constitute the most important cause of morbidity and mortality. Each instance represents a breach of pulmonary defenses. An understanding of the pathogenesis of the diseases requires knowledge of the defensive mechanisms and the factors leading to their being overcome. A variety of inhaled noninfectious agents cause disease less frequently, notably organic allergens, caustic gases, fumes and chemicals, and inorganic dusts. The respiratory tract can also serve as a portal of entry of infectious agents that do not primarily affect the respiratory system.

Respiratory defenses serve principally to protect the delicate alveolar parenchyma of the lung from damage. This is accomplished by removing harmful agents as much as possible in the nasal passages and conducting airways. Alveolar mechanisms form a second level of defense. The upper respiratory tract functions to warm and humidify inspired air and to remove larger particles and water-soluble gases by means of the mucous lining. Warming and humidifying principally occurs during passage of air through the nose. It is facilitated by the extensive surface area and the rich, readily engorged vascular plexus in the submucosa, particularly of the turbinates, and nasal septum. Many particles in inspired air are first deposited on the mucous lining of nasal passages and conducting airways and are then cleared by movement of the mucociliary blanket. The larger the particles, the more efficient their removal in the upper airways. Deposition on surfaces is mainly by inertial impaction, gravitational sedimentation, diffusion, or a combination of these. Inertial impaction is chiefly in the nasal passages and pharynx and at points of branching of airways, where the airstream changes its direction and where turbulence occurs. The efficiency of nasopharyngeal trapping depends on the anatomic complexity of the nasal passages, especially with regard to the turbinates, and on the pattern of respiration. The gravitational settlement of particles is directly proportional to their size and density and is favored in the relatively still air of deeper parts of the respiratory system. Diffusion of particles is due to molecular collision and affects only the very smallest of them, that is, particles of less than ~0.3 μm in size. Since displacement velocity by diffusion is low, deposition by this method is effective only in the alveoli, where movement of gases is also by diffusion rather than linear flow.

Deposition of particles greater than ~10 μm aerodynamic diameter is virtually complete above the larynx. With decreasing particle size, an increasing proportion of inhaled particles pass into the deep lung, although many are subsequently exhaled. The critical feature, from the point of view of pulmonary homeostasis, is that droplet nuclei and other irritant or infectious particles around 1–2 μm in diameter mostly deposit at the bronchiolar–alveolar junction. This is because the total cross-sectional area of airspaces increases suddenly, linear velocity of the airstream falls to zero, and there is time for the particles to deposit by gravitational settling. As will be discussed later, this is one of the reasons for the vulnerability of the bronchiolar–alveolar junction to damage by inhaled irritants.

Statements on relationship between particle size and deposition are relative rather than absolute. Sizes quoted for mathematical modeling of particle deposition are in terms of equivalent cross-sectional diameters of unit-density spheres (aerodynamic diameter). The most obvious exception to the generalization that particles greater than 10 μm in diameter do not penetrate beyond the larynx is that fine fibers up to 100 μm or longer, notably of asbestos, do reach alveolar parenchyma. Additionally, there might be opportunity for redistribution of particles deposited in the proximal respiratory tract by reflux of excess secretions or aspiration of fluid.

Once particles are deposited on the mucus of airways, clearance by normally functioning mucociliary transport is highly efficient. Most particles are removed from central airways within a few hours, and even from distal airways within 24 hr. The mucociliary blanket consists of cilia bathed in a watery sol on top of which lies mucus with physical properties of a viscoelastic gel. Whether the mucus usually forms a patchy or continuous surface layer is still debated, but it will probably prove to be continuous in healthy individuals. In any event, the cilia beat mostly in the watery hypophase, except during the active forward stroke when their tips contact the overlying mucus. The net effect of a ciliary frequency of around 1000 beats a minute is to propel the mucus toward the pharynx at a linear velocity of the order of 10 mm/min. The greater density of ciliated cells in proximal airways, the more rapid ciliary beat, and possibly, absorption of a portion of the aqueous periciliary fluid are believed to prevent swamping of these airways, especially the trachea, by fluid collected from the large number of distal airways.

Most of the mucous secretions of the respiratory tract, and the particulate matter they carry, reach the pharynx and are swallowed. The concentration of material into the nasopharynx coincides with well-developed diffuse and focal lymphoid tissue of the tonsillar region and dorsal nasopharynx. This enhances the efficiency of development of immune responses but also makes the region vulnerable to primary infections by organisms such as *Brucella* spp. and *Mycobacterium paratuberculosis*. Swallowing of material originating in the lungs also serves as a mode of spread of diseases such as tuberculosis and as part of the migratory pathway of helminth eggs and larvae.

The specific roles and controlling influences of mucous cells, serous cells, and other secretory cells in surface epithelium and submucosal glands, and the differences among species, are still poorly understood. In addition to the physical aspects of the sol and gel phases of the secretion, however, a variety of other components with defensive capabilities are recognized. The major immunoglobulin is locally synthesized IgA, although IgE, IgG, and other classes are present. Immunoglobulin A is produced by plasma cells resident in the lamina propria of the respiratory mucosa and secreted through epithelial serous cells. A major function of organized lymphoid tissue in the walls of the nasal passages, nasopharynx, and airways is believed to be to populate, through the circulation, the respiratory mucosa with precursors of IgA-secreting plasma cells. This includes bronchus-associated lymphoid tissue. The principal functions of IgA are thought to be viral neutralization, aggregation of macromolecular antigens to impede their mucosal absorption, and inhibition of bacterial colonization. Important nonspecific humoral components of the secretions are interferon, which helps limit viral infection in nonimmune hosts, and lysozyme (muramidase) and lactoferrin, which have selective antibacterial activity. The normal bacterial flora of the nose and nasopharynx are important in that by specific adherence of their specialized surface structures (pili) to receptors on cilia and surfaces of epithelial cells, they prevent adherence and colonization by more pathogenic flora. Most current investigations of bacterial interference are on flora of the alimentary tract and skin of humans. By analogy, however, the phenomenon is undoubtedly important in the upper respiratory tract of animals.

The physical and humoral defenses of the mucociliary blanket, which are constantly in operation, are boosted by cellular and humoral mechanisms recruited from blood at the onset of inflammation, and by sneezing, coughing, and bronchoconstriction provoked by irritation of airway receptors. Normal mucociliary function depends on structurally and functionally intact ciliated epithelium as well as normal viscous properties and quantity of secretions. Interference with any one or more of these predisposes to infection, and is considered under Bronchopneumonia.

Alveolar defense against small-sized particles depends heavily on phagocytosis by alveolar macrophages. Phagocytosis of readily ingested particles, for instance, opsonized bacteria, is largely complete by 4 hr after alveolar deposition. Actual physical removal of particulates from alveoli is inefficient, in contrast to their removal when deposited on the mucociliary blanket. Fifty per cent clearance of particles deposited in alveoli takes from several days to months or longer, depending on their physical nature and irritant capability. Most particles are therefore phagocytosed by macrophages and either inactivated or sequestered. The alveolar macrophages move toward the bronchioles and hence eventually onto the mucociliary blanket. Reasons for their centripetal movement are not known, but the surface-lining liquid in alveoli is also believed to move centripetally, possibly because of its continual secretion and a "milking" action of respiratory movements. Alternative fates of particles in alveoli are clearance in the lining liquid without phagocytosis, or penetration into the pulmonary interstitium. The latter becomes of increasing importance as the particulate load increases. Although not completely proven, it appears that most particles reach the interstitium by endocytosis across the alveolar type I epithelial cells. Once in the interstitial space, particles move with the flow of lymph and are phagocytosed by interstitial macrophages. Particle-laden macrophages associated with lymphatics occur in peribronchiolar and perivascular clusters, and some eventually find their way to the local lymph nodes. Overloading the alveolar macrophage system favors accumulation of particles in the interstitium, as occurs in the pneumoconioses.

Sterility of alveoli is thus maintained largely by the ability of macrophages to kill ingested bacteria and to secrete interferon. These activities are enhanced by immunoglobulin, particularly through the opsonizing effect of IgG, which is the predominant immunoglobulin in the alveolar lining liquid. Alveolar macrophages are also capable of initiating a variety of amplification mechanisms, particularly by their recruitment of neutrophils and sensitized T lymphocytes. The latter in turn can cause macrophage activation. Macrophage factors are also important in the pathogenesis of emphysema and pulmonary fibrosis, as mentioned in the sections on those diseases.

Lysozyme, lactoferrin, and complement are also present in alveolar lining liquid. Humoral components capable of inhibiting inflammatory mediators or destructive enzymes are now recognized to be of great importance. The components of most active study are superoxide dysmutase, which helps protect

against injury by reactive oxygen radicals, and α_1-protease inhibitor, which is important in protection against the development of alveolar emphysema.

Just as factors interfering with mucociliary defense mechanisms of airways predispose to bronchopneumonia, so will factors depressing alveolar defenses, especially the alveolar macrophage (see Bronchopneumonia).

The entire output of the right ventricle flows through the low-pressure pulmonary circulation. The densely anastomosing network of capillaries in alveolar septa provides the equivalent of "sheet" flow when they are all patent. This arrangement both provides for easy trapping of emboli in the pulmonary vascular bed and for minimizing the deleterious effects of blockage. Effects of blockage are minimized further by the dual pulmonary and bronchial arterial blood supplies to the lung. Nevertheless, emboli carry a risk and are associated with a variety of lesions, according to the nature of the emboli. The types of emboli vary greatly. Unusual ones are epidermal fragments and hair inadvertently introduced into the blood at the time of injection, or fragments of nucleus pulposus from intervertebral disks. More commonly they are bacteria, fungi, protozoa, endogenous fat, normal cells (which may be represented by megakaryocytes), or abnormal cells (which are principally neoplastic). They can also be fragments of bland or septic thrombi, helminth parasites for which the respiratory system is a natural or accidental habitat, or even parasitic ova, as required by *Pneumostrongylus tenuis* of deer for the continuation of its life cycle. In general, the benefit of the lung acting as a blood filter is the prevention of emboli reaching the systemic circulation and the protection of organs such as the brain, heart, and kidneys against infarction. The detriments are spread of infection, metastasis of tumors, and pulmonary thromboembolism causing shock. The last named is rare in animals.

The lung is also prone to injury by a variety of blood-borne toxic agents, both exogenous and endogenous, and can be affected by certain metabolic abnormalities. These will be considered further under Interstitial Pneumonia. The reasons for the special vulnerability of the lung are only now emerging. Pulmonary capillary endothelium as a whole forms a highly metabolic organ, particularly with respect to vasoactive substances and the blood-clotting, fibrinolytic, and arachidonic acid cascades. For reasons still unclear, in conditions such as shock and septicemia there is a tendency in pulmonary capillaries for activation of Hageman factor, release of prostaglandins and leukotrienes, and aggregation of platelets and neutrophils. This causes the acute pulmonary injury seen in these conditions.

Patterns of Respiratory Tract Disease

Respiratory diseases can be caused by a large variety of infectious or noninfectious agents. The site of damage in the respiratory tract is determined by the interplay of portal of entry of the agent, the nature and concentration of the agent, and the relative susceptibility of the tissues exposed to the agent. The portal of entry is the major determinant.

Aerogenous insult, as would be expected, usually leads to damage centered on airways. Nasal passages and upper airways are mostly affected by irritants contained in large particles, by highly soluble gases, or by infectious agents whose cell receptors are most numerous or more readily accessible in upper respiratory epithelium. Distal airways are more affected by fine particles, weakly soluble gases, and infectious agents with affinity for bronchiolar or alveolar epithelium. The greater vulnerability of the bronchiolar–alveolar junction to damage is also an extremely important determinant at this level (see Bronchopneumonia).

Hematogenous insult usually affects the lungs and is manifest, depending on the cause, as diffuse, patchy, or discrete focal lesions without orientation on airways. An important exception to the generalization that blood-borne agents affect alveolar septa and pulmonary interstitium more than airways is where a toxin specifically damages bronchiolar epithelium. The best example of this for present purposes is the necrosis of nonciliated bronchiolar epithelial (Clara) cells of the horse caused experimentally by 3-methylindole. Localization of damage to Clara cells in the horse is because that is where cellular binding of 3-methylindole and metabolism to the toxic intermediate by the cytoplasmic microsomal monooxygenase (mixed-function oxidase) system occur in this species.

Other, less common types of injury to the respiratory tract are traumatic, as by penetration of a foreign body, or by extension of lesions along fascial planes and lymphatics from adjacent tissues or cavities.

Differences in patterns of lesions among species of animals are well recognized, but few have been formally studied. An obvious example is the complete lobular septation and absence of collateral ventilation (low interdependence) in the bovine lung, which predisposes it to poor resolution of bronchopneumonia and to the development of acute interstitial emphysema under conditions of excessively labored breathing. Another example is the acute pulmonary congestion and edema almost invariably found in sheep dying as a result of any acute disease process. More precise mechanistic reasons for differences in species response are coming to light as more is learned about the interspecies variations in specific cell types and their metabolic capabilities. One example already alluded to is that the selectivity of damage caused by some pneumotoxins depends on the distribution of enzymes capable of metabolizing them. This is the basis for 3-methylindole's causing mostly nonciliated bronchiolar cell necrosis in the horse, in contrast to extensive pulmonary endothelial and alveolar epithelial damage in the cow.

Nasal Cavity and Sinuses

Congenital Anomalies

Congenital anomalies of the nasal region are rare but occur in all species. They are usually part of more extensive craniofacial defects in which they accompany various combinations of malformations of mouth and eyes. Animals with absent, underdeveloped, or severely distorted nasal regions are usually stillborn or die immediately after birth, often because of an imperforate buccopharyngeal membrane (choanal atresia). The milder

defect of cleft palate is compatible with life, but affected animals generally die because of aspiration pneumonia.

A variety of localized, developmentally related defects, which take time to become apparent, can affect the nasal region, particularly those of tooth germ origin. Maxillary cysts in foals or young adult horses can distort the profile of the maxillary bone sufficiently to cause obstruction of the ipsilateral nasal passage, destruction of the nasal turbinates, and deviation of the nasal septum.

Metabolic Disturbances

Deposits of amyloid sometimes occur in the nasal submucosa of horses. The deposition is not part of a generalized amyloidosis, and the cause is unknown. The nasal vestibule and anterior portions of the septum and turbinates are involved. The amyloid might be in nodules of various sizes or occur as a diffuse deposition. Resulting stenosis can be severe enough to cause clinical signs of nasal obstruction. The nodules or diffuse thickenings have a smooth surface and the usual waxy sheen of amyloid on the cut surface. The amyloid is deposited in the walls of submucosal vessels and the basement membrane of mucosal glands as well as in the connective tissues. There might be mild inflammatory changes in the mucous membrane.

Circulatory Disturbances

The arteries, veins, and capillaries of the nasal mucosa are capable of remarkable adaptive changes in the content of blood. Vascular engorgement occurs by relaxation of the arteries and contraction of the thick tunica media of the veins. This lability of the vessels is responsible for the frequency of hyperemia and edema. Active hyperemia is part of the acute stage of inflammation. Passive congestion is the result of local or general circulatory failure.

Of rather more concern is nasal hemorrhage, which is known as **epistaxis**. The term epistaxis is used in a general sense to refer to hemorrhage from the nose, but this does not necessarily mean that the source of bleeding is within the nasal passages or sinuses. The hemorrhage might be from the nasopharynx or from deep within the respiratory tract. This distinction is particularly important in horses, where in epistaxis associated with heavy exercise the blood originates from the lung. The condition is more appropriately termed exercise-induced pulmonary hemorrhage and will be described under Pulmonary Hemorrhage. Bloodstained foam is frequently present in and issues from the nose of cadavers, especially sheep. This is an indication of terminal pulmonary congestion, edema, and hemorrhage.

Hemorrhage originating within the nasal region is most commonly caused by traumatic, inflammatory, or neoplastic breakdown of vessels. It might also be part of any of the hemorrhagic diatheses (see the Hematopoietic System, Volume 3). In some of the hemorrhagic diatheses, such as those of thrombocytopenic origin, the bleeding might be copious. Hemorrhage in rhinitis is associated with mucosal ulceration, a frequent happening in acute inflammation, and in some specific types of chronic inflammation. In most inflammatory hemorrhages, the extravasation is initially submucosal. Mycotic infections of the guttural pouches can cause epistaxis in horses. Rarely, nasal hemorrhage might be the result of hypertension or vascular aneurysms.

Inflammation of the Nasal Cavity

Rhinitis

The nasopharyngeal mucous membrane has a normal resident microbial flora, established by specific adherence between the bacterial pili and sugar-containing surface binding sites on epithelial cells. An important role of the normal flora is to exclude adherence and subsequent colonization of the mucosa by more pathogenic organisms, particularly Gram-negative ones. Injury to the mucosal surface can lead to pathogenic activity by certain of the normal flora or, more importantly, affect surface binding sites such that adherence and colonization by pathogenic microorganisms can occur. Similar changes can occur because of systemic immunodeficiency states or nonspecific stress situations, such as occur postoperatively. The frequency of fungal and other opportunistic infections following prolonged antibiotic therapy probably has the same basis, that is, removal of the normal "blocking" bacterial flora.

Primary injurious agents are usually viruses. Allergens are probably important in cattle and, to a lesser extent, in dogs and cats. Irritant volatile gases, dust, and excessive dryness of the atmosphere are occasional causes of injury to the nasal epithelium. In summary, rhinitis is usually related to the interaction between viruses, or other devitalizing influences, and bacteria or fungi.

Rhinitis can be differentiated, according to its course, as acute or chronic. It can be differentiated morphologically, according to the nature of the response, into serous, catarrhal, purulent, ulcerative, pseudomembranous, hemorrhagic, or granulomatous inflammation. Most acute cases of rhinitis begin with a serous exudation, which changes in the course of the disease to a catarrhal and then purulent inflammation. Pseudomembranous, ulcerative, or hemorrhagic rhinitis is a sign of very severe damage. Chronic rhinitis is most commonly manifested by proliferative changes, but occasionally it causes atrophy.

During the initial **serous** stages of rhinitis, whether viral, allergic, or nonspecific, the mucosa is swollen and gray to red, depending on the degree of hyperemia. Histologically, the epithelial cells show hydropic degeneration and loss of cilia. There is hyperactivity of the goblet cells and submucosal glands. The secretion is a thin, clear seromucin that contains a few leukocytes and epithelial cells. The underlying lamina propria is edematous and sparsely infiltrated by inflammatory cells. The swelling of the mucous membrane tends to cause mild respiratory discomfort and the familiar sneezing and snuffling.

Within hours or a few days, serous rhinitis is modified partly by changes in glandular secretion and partly by bacterial infection. The hyperemia, edema, and swelling are then aggravated and the discharge becomes catarrhal (mucous) or frankly purulent because of the emigration of large numbers of leukocytes and desquamation of epithelial cells. Erosion and regenerative hyperplasia of the epithelium occur, and in purulent rhinitis extensive ulcerations might be evident.

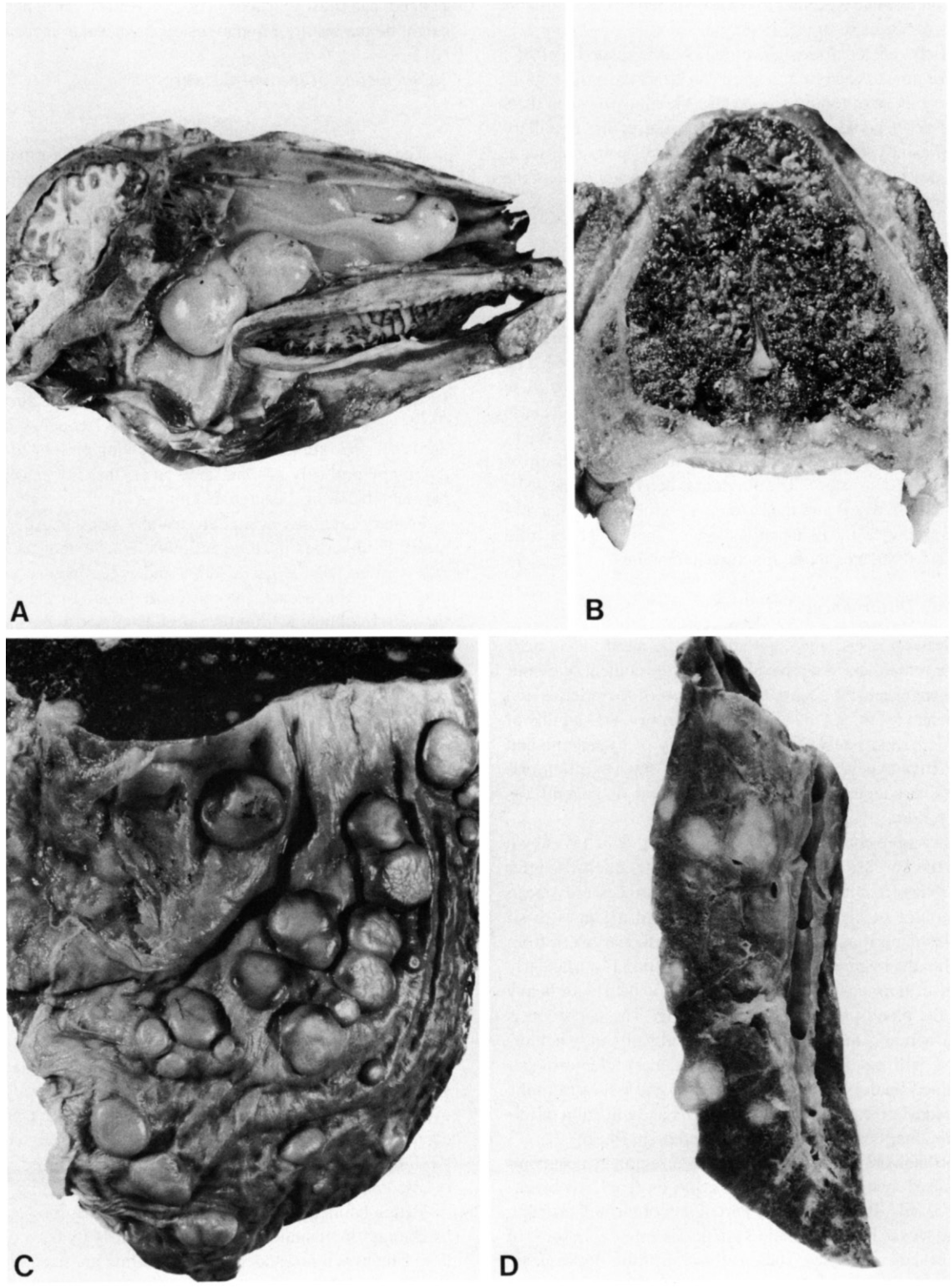

Fig. 6.1. (**A**) Myxomatous polyps in chronic rhinitis. Sheep. (**B**) Chronic diffuse, proliferative rhinitis. Cat. (**C**) Splenic abscessation in melioidosis. Sheep. (**D**) Chronic pulmonary abscessation in melioidosis. Sheep. (**C** and **D** courtesy of W. T. Hall and the Queensland Department of Agriculture.)

In subacute to chronic rhinitis, diffuse or localized polypous thickenings of the mucosa develop (Fig. 6.1A). The polyps are initially sessile but can, when larger, become pedunculated. They consist of a core of edematous stroma resembling myxoma tissue and a covering epithelium that is variously hyperplastic, squamous, or ulcerated. Chronic **catarrhal** or **suppurative rhinitis** causes progressive fibrosis of the lamina propria with atrophy of the glands and atrophy with focal squamous metaplasia of nasal epithelium. The atrophic epithelium is dry and shiny.

Pseudomembranous rhinitis may be fibrinous or fibrinonecrotic (diphtheritic), but it is usually the former, and the membranes can be peeled off without leaving gross underlying defects. The deeper, fibrinonecrotic inflammations are associated with severe bacterial infections and frequently have a dry, yellowish quality that indicates infection with *Fusobacterium necrophorum*. The fibrinonecrotic membrane is firmly adherent to the underlying tissue and when removed leaves a raw, ulcerated surface.

Granulomatous rhinitis is a typical lesion in some specific diseases. The lesions are nodular and polypoid or become large, space-occupying masses. The smaller ones are more firm, the larger ones more friable or gelatinous. The histologic structure is specific for the disease.

Rhinitis occurs commonly as part of a more generalized disease process. Important specific entities in which rhinitis is the sole or a major lesion will be covered subsequently. A chronic nonspecific rhinitis is an important condition in the dog, and to a lesser extent in the cat. There is a chronic unilateral or bilateral mucopurulent discharge, and the inflammatory proliferation leads to diffuse or polypoid thickening of the nasal mucosa and obstruction of nasal passages (Fig. 6.1B). The glandular elements are hyperplastic, the epithelium is variously ulcerated, hyperplastic, and metaplastic (squamous), and the edematous, fibrotic stroma is heavily infiltrated by lymphocytes and plasma cells. There is no sign of foreign bodies, at least in the chronic lesion, and bacterial cultures do not reveal significant organisms. The pathogenesis is unclear, but following initial damage that is no longer detectable there is probably a vicious cycle involving impaired local defenses, further infection and damage by normally nonpathogenic flora, and self-sustaining inflammation by release of mediators from the large numbers of inflammatory cells. Pooling of exudate in obstructed portions of the lumen and compromised venous and lymphatic drainage in the hyperplastic mucosa are also likely to be factors leading to progression of the lesion.

Rhinitis of itself can have unfortunate sequelae. Aspiration of nasal exudate might lead to bronchopneumonia. The potentiality for reflex flow in the valveless veins of the head explains the occurrence of intracranial thrombophlebitis, abscess, or meningitis; these are, however, rare. Sinusitis probably is the sequel most common to rhinitis.

Sinusitis

Inflammation of the paranasal sinuses often goes undetected unless it has caused facial deformity or a fistula in the overlying skin. Sinusitis is very common in sheep as a response to larvae of *Oestrus ovis*. It also follows penetration of infection in dehorning wounds, fractures, and periodontitis. Seromucinous sinusitis of little significance occurs in viral infections of the upper respiratory tract. In acute catarrhal or purulent rhinitis, the mucosal swelling tends to occlude the orifices of the sinuses. The secretions and exudates then accumulate and render chronic purulent sinusitis almost inevitable. The histologic features of sinusitis are the same as those of rhinitis. The accumulation of seromucinous secretion is referred to as mucocele, and the accumulation of purulent exudate is referred to as empyema of the sinus. Purulent inflammations of the sinuses are more significant than rhinitis because of proximity to the brain. They are also less liable to spontaneous drainage and resolution. Therefore, they are more likely to cause epithelial atrophy and metaplasia, and distortion of the bony walls of the sinuses by pressure or osteomyelitis.

Rhinitis in Specific Diseases

In addition to the specific diseases to be discussed below, rhinitis is a prominent feature of a variety of respiratory or more generalized infectious diseases. The nature, cause, and specificity of the various forms of rhinitis differ according to species. Examples are canine distemper, the feline respiratory disease complex, bovine virus diarrhea, rinderpest and malignant catarrhal fever of cattle, bluetongue of sheep, and equine influenza, equine rhinopneumonitis, and equine viral arteritis.

INCLUSION-BODY RHINITIS OF SWINE. Inclusion-body rhinitis is widespread in Europe, but its prevalence in the United States and other major pig-raising areas of the world is unknown. It is caused by a cytomegalovirus that characteristically produces large, basophilic intranuclear inclusions in swollen glandular epithelia of the nasal cavity.

Inclusion-body rhinitis is an acute to subacute disease of suckling piglets about 1–5 weeks of age. The signs are those usual for rhinitis with modest fever. The early discharge is seromucinous, but it might become catarrhal or purulent if the course is prolonged, probably owing to secondary bacterial infection. The morbidity is high, but the mortality in the absence of suppurative complications is low; the complications include sinusitis, otitis media, and pneumonia.

The uncomplicated histologic changes in the mucosa are those of a nonsuppurative rhinitis, with a tendency to squamous metaplasia, and the presence of specific basophilic inclusions in the epithelial cells of the glands and their ducts (Fig. 6.2C). The inclusions are large and readily visible at low magnification. Affected glands occur in irregular clusters, and all their epithelial cells tend to contain inclusions. The inclusion bodies can persist for a month but become less numerous as the course of the disease advances.

As the inclusion develops, the nucleus and cytoplasm of the affected cell expand. The cytoplasm becomes clear and finely granular, and cell borders become indistinct. The inclusion body fills the nucleus, except for small peripheral indentations in which minute neutrophilic or acidophilic bodies may be found. The affected nuclei continue to swell and the nuclear membrane loses its distinctiveness; by this time the inclusion bodies resemble bluish gray smears among degenerating cytoplasm. Sloughing of the epithelium is followed by liquefaction and the accumulation of leukocytic debris. The necrotic glands are obliterated by collapse of the lamina propria and infiltration by

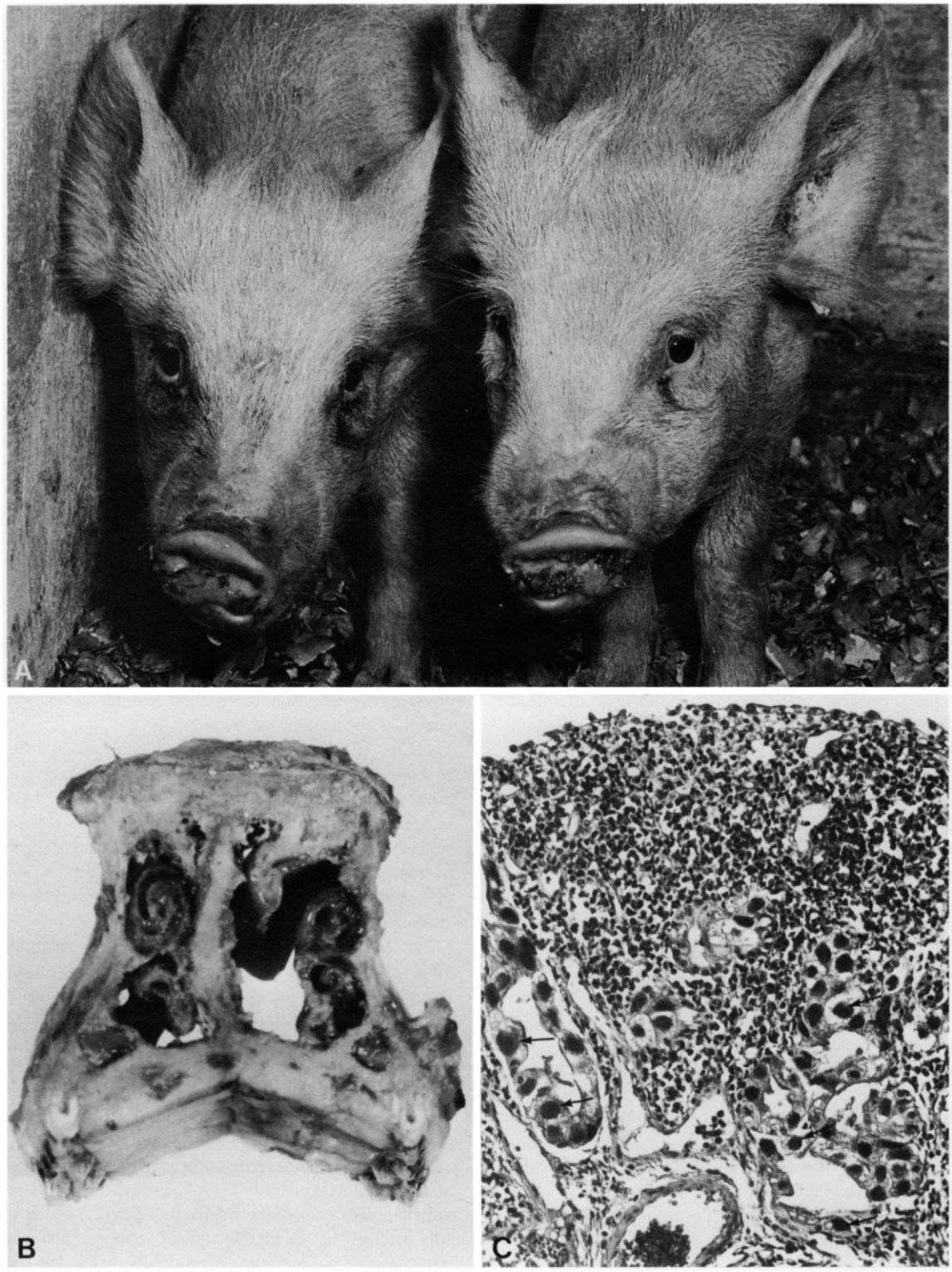

Fig. 6.2. (**A**) Atrophic rhinitis with deviation of snout. (**B**) Asymmetry of turbinates and facial skeleton with deviation of septum in atrophic rhinitis. Pig. (**C**) Large, basophilic intranuclear inclusions (arrows) in inclusion-body rhinitis. Pig.

lymphocytes. There is slight vascular reaction in this disease. The infiltrating cells are predominantly lymphocytes, and although distributed diffusely, they tend to form more dense aggregates in the superficial layers of the lamina propria. Regeneration of glands may take place by downgrowth and differentiation from the superficial epithelium.

Occasionally, in addition to rhinitis, there is severe generalized cytomegalovirus infection, with focal necrotizing lesions associated with intranuclear inclusions in adrenal, liver, kidney, lung, and central nervous system. Although further substantiation is needed, it appears likely that cytomegalovirus infection is one of the factors that may lead to persistent infection with *Bordetella bronchiseptica* or *Pasteurella multocida* and subsequent development of atrophic rhinitis.

ATROPHIC RHINITIS OF SWINE. Atrophic rhinitis of swine is a disease of uncertain cause characterized by atrophy of the nasal turbinates (conchae). Less constant features are irregular atrophy of the nasal bones and plates of paranasal sinuses, and with variation from case to case, there is also irregular hypertrophy of facial bones and remnants of turbinates. On clinical and experimental grounds, the disease is generally regarded as being principally of infectious origin, but the proportional involvement of the various agents that have been incriminated and the role of enhancing factors have to be clarified. A variety of inflammatory stimuli can cause atrophy of turbinates, often of a temporary nature. The morphologic features of atrophic rhinitis are therefore not particularly specific. There is growing evidence that the naturally occurring disease is mainly the result of adherence and persistent colonization of nasal mucosa by virulent strains of *Bordetella bronchiseptica, Pasteurella multocida,* or perhaps more importantly, both organisms. Other bacteria found on the nasal mucosa, such as *Haemophilus parasuis,* probably play a lesser role. Factors known to be capable of enhancing the severity of the clinical disease, for instance, cytomegalovirus infection (inclusion-body rhinitis) or adverse environmental and nutritional circumstances, probably act by facilitating the colonization and persistence of the pathogenic bacteria. Nutritional defects, particularly those involving calcium and phosphorus, can also interfere with metabolism of bone at the time when rapid growth and remodeling of turbinates in young pigs make them most susceptible to the effects of the infectious agents. Nutritional deficiencies alone, however, do not cause atrophic rhinitis. The precise proportional mix of factors resulting in chronic, irreversible atrophy undoubtedly varies according to local geographic influences. The mechanism by which *B. bronchiseptica* or *P. multocida* cause the atrophy of turbinates is uncertain. The basic abnormality, as will be described, appears to be defective osteoblast function, leading to osteoporosis and hypoplasia of the turbinate bone. Studies with *B. bronchiseptica* implicate diffusible toxin, although in one experimental study, bacteria believed to be *B. bronchiseptica* were detected ultrastructurally within the cytoplasm of degenerating osteoblasts and extracellularly in the vicinity of the surface of bone.

Atrophic rhinitis occurs with high incidence in most of the major pig-raising areas of the world. It is an important cause of economic loss because in young pigs it causes decreased rate of growth and reduced efficiency of feed conversion. The endemic disease is insidious in onset and progression, but there can be acute episodes when a herd first becomes affected.

Acute signs are observed in young piglets and consist of rhinitis with sneezing, coughing, and a serous or mucopurulent nasal discharge. Large or small flecks of blood may be expelled by sneezing when damage is severe, and occasionally the hemorrhage is profuse. There is not a constant association between clinical signs of acute rhinitis and atrophic changes. Rhinitis occasionally is found not to have resulted in atrophy, at least of a permanent nature, and in some herds a high incidence of atrophy of the turbinates might be present in slaughtered pigs without there having been at any time clinical signs of rhinitis or facial deformity.

Facial deformity, which is an expression of severe disease in the rapidly growing young pig, is seldom evident before the fifth or sixth week of age. It consists of shortening and distortion of the snout and facial bones (Fig. 6.2A). As a result of the shortening, the overlying skin forms thick transverse folds. Asymmetry of the disease process causes deviation of the snout toward the more severely affected side; when the intranasal lesions are symmetric, the nose may be shortened and turned upward. Characteristically, there is often patchy encrustation of dried tears and dirt just below the medial canthus of the eye; this is usually attributed to lacrimal spillage caused by obstruction of the nasolacrimal duct, but increased lacrimation might also play a role.

The lesions of atrophic rhinitis range from indefinite to severe, and as is often the case, no clear dividing line separates the normal from the diseased. The lesions are most severe anterior to the nasofrontal suture. When mild, they may be detectable only in the ventral scroll of the ventral turbinate, but with increasing severity gross changes become detectable in the entire ventral turbinate, in the dorsal turbinate, and further back in the nasal cavity until even the ethmoids are involved. The nasal mucosa usually has less gross changes. It might be edematous and covered by a thin seromucinous exudate on the anterior portions and thick purulent exudate in posterior recesses and cells of the ethmoid, or it might be pale and dry.

The grossly detectable changes in the conformation of bones are always of the same type, but there are wide variations in the extent of the lesions. In the least affected specimens, the ventral scrolls of the ventral turbinates are reduced in size and are pliable and soft. The width of the ventral meatus is increased. This is often accompanied by slight bulging of the nasal septum toward the less affected side. With progression of the lesions in the turbinates, there is loss of both scrolls of the ventral turbinate and then of the dorsal turbinate (Fig. 6.2B). In extreme cases, nothing remains of the turbinates save for folds of mucosa on the lateral aspect of the empty nasal chamber. The bones surrounding the nasal cavity are frequently thinned. In some animals, especially those whose general health is not significantly affected by the disease and who continue to grow, hypertrophic changes frequently coexist with atrophic changes in the facial bones and rarely with hypertrophic changes in the turbinates. Combined hypertrophic and atrophic changes in the turbinates produce a series of longitudinal folds. Hypertrophy of the facial bones affects chiefly the dorsal part of the nasal bones so that the conformation is broad and flat rather than narrow and convex.

The alveolar processes may also be thickened, although the lateral plates of the maxillae tend to be attenuated.

Microscopically, the turbinate atrophy is associated with loss of cancellous bone in the core of the turbinates. Histologic and ultrastructural observations support the concept that the basic defect is decreased osteoid synthesis by severely damaged, differentiated osteoblasts. The disappearance of turbinates appears to be due more to defective osteogenesis during a period of rapid growth and remodeling of the nasal region than the result of excessive osteoclastic activity.

Histologically, there is hypoplasia of the cancellous bone of the turbinates and reduction or absence of the osteoid layer normally present between osteoblasts and the surface of the bone. The periosteum in some instances has increased cellularity of the proliferative (osteoprogenitor) cell layer, and in other instances is narrowed and composed mainly of fibroblast-like cells. Osteoclasts are not significantly changed in number or structure.

Ultrastructurally, degeneration of osteoblasts is associated with irregular folding of nuclear and plasma membranes, loss of the Golgi apparatus, and dilatation of cisternae of the endoplasmic reticulum. The types of mitochondrial and cytoplasmic changes preceding atrophy and death of the cells are less certain. Osteocytes are similarly but less severely affected. Although pigs with atrophic rhinitis sometimes have more widespread skeletal abnormalities, there is no clear evidence that they have the same cause.

The inflammatory lesions in the nasal mucous membranes are usually nonspecific and vary according to the stage of the disease. In early stages, there is loss of ciliated and goblet cells and proliferation of cuboidal cells to form layers one to several cells deep. Submucosal glands become hyperactive and distended with mucus. Neutrophils infiltrate the superficial and glandular epithelium and occasionally form microabscesses. Subsequently, there is infiltration of the lamina propria by lymphocytes and plasma cells. The only indication of a specific acute infection occurs in piglets from herds where cytomegalovirus infection is prevalent. There is no direct correlation between severity of the acute rhinitis and the later development of permanent atrophy of the turbinates. In established cases of atrophic rhinitis, there is chronic nonspecific mucosal inflammation with variation from epithelial ulceration to squamous metaplasia, and atrophy or cystic dilation of the glands within a fibrotic lamina propria.

STRANGLES IN HORSES. Strangles is an acute contagious disease of horses characterized by inflammation of the upper respiratory tract and abscessation in the regional lymph nodes. It is caused by *Streptococcus equi*. This organism is an obligate parasite on upper respiratory mucous membranes of Equidae. Other hemolytic streptococci of Lancefield's group C are frequent commensals in the upper respiratory tract of horses. The main species are *S. zooepidemicus* and *S. equisimilis*. The former is much more commonly pathogenic and can be isolated from a variety of suppurative processes such as wound infections, sinusitis, and pneumonia secondary to respiratory viral infection. It can cause endometritis and abortion in mares, and umbilical infection, septicemia, and polyarthritis in newborn foals. *Streptococcus zooepidemicus* and, rarely, *S. equisimilis* are causes of respiratory catarrh in horses that might on other than bacteriologic grounds be indistinguishable from strangles. This is especially true for mild cases of the latter in which lymphadenitis is absent or is mild and nonsuppurative.

Streptococcus equi in exudates is very resistant to the external environment and can survive for many months in stables. The initial source of infection, however, is usually a carrier animal or one with active but not necessarily clinically obvious disease. Outbreaks of the disease occur mainly in young animals under crowded conditions. Carrier horses are difficult to detect because shedding of organisms is intermittent and the site of recovery can shift between nasal and pharyngeal regions in a single animal. The distribution of *S. equi* in populations of horses is roughly parallel to the incidence of strangles in such populations.

The incubation period of strangles is 3 or 4 days, although it might be as short as 2 or as long as 15 days; the onset is indicated by fever, slight cough, and nasal discharge. The nasal discharge is bilateral, and in a few days it changes from serous to catarrhal and then purulent. Coincidentally, there is catarrhal conjunctivitis and, in cases that pursue a typical course, inflammatory swelling of the lymph nodes of the head and neck. The submandibular and retropharyngeal nodes are the first and usually the most severely affected. The acute inflammatory swelling is firm, but the nodes begin to fluctuate as liquefaction and suppuration develop. The typical and favorable outcome of the lymphadenitis is for the abscesses to rupture onto the skin 1–3 weeks after onset of infection. Rupture is preceded by depilation and oozing of serum. The discharged pus is copious, creamy, and yellow-white. Abscessation of lymph nodes is not an invariable feature of strangles, but the diagnosis is seldom made in its absence.

The nasal lesions are those of a purulent rhinitis but are otherwise nonspecific. Large amounts of creamy, yellow pus collect in the folds of the turbinates and may produce temporary distortion. The mucosa is edematous, hyperemic, and occasionally ulcerated.

In the typical course of strangles described above, the outcome is favorable. The course, however, may be either milder or more severe and with an unfavorable outcome. In older horses, the course tends to be milder and confined to catarrhal rhinitis and pharyngitis without nodal abscessation, or the nodal abscesses may become sterile and encapsulated. When the course is severe, infection may spread to the paranasal sinuses and by way of the Eustachian tubes to the guttural pouches to cause chronic empyema of these cavities. Extensive cellulitis might develop in the connective tissues of nose, pharynx, or throat. Retropharyngeal abscesses might discharge into the pharynx, allowing pus to be aspirated into the lungs. Metastatic abscesses ("bastard strangles") occasionally form in the liver, kidneys, synovial structures, and brain. The internal organs most frequently affected, however, are the mediastinal and mesenteric lymph nodes. In each of these locations, the abscessations tend to be very large, and although frank rupture is unusual, the suppurative process can permeate to the respective serous membranes and cause a purulent pleuritis or peritonitis. Two other

important sequelae are purpura hemorrhagica and local damage to cranial nerves, resulting in laryngeal paralysis (roaring), facial nerve paralysis, or Horner's syndrome.

Glanders

Glanders is an infectious disease caused by a Gram-negative bacillus, *Pseudomonas mallei*. It is mainly an equine infection, but it does occur occasionally in humans and it can be acquired naturally by carnivorous animals that eat diseased flesh of horses. Goats are susceptible to contact infection, but cattle, sheep, and pigs are not. A variety of other generic names have been used for the organism, most commonly, *Loefflerella, Pfeifferella, Malleomyces,* and *Actinobacillus*. The disease in horses is characterized by nodular lesions in the lungs, and ulcerative and nodular lesions of the skin and respiratory mucosa. "Farcy" is the term often applied to the cutaneous lesions.

Glanders is, historically, a very old disease and flourished especially among cavalry horses. Since the advent of motorized vehicles and accurate serologic diagnostic procedures, it has virtually or completely disappeared from many countries. It still exists, however, in some parts of eastern Europe and Asia.

Pseudomonas mallei is sensitive to the external environment, and infection is acquired directly or indirectly from excretions and discharges of affected animals. In horses, the disease is usually chronic and the organisms confined to the lesions and discharges, especially those of the skin and nasal mucosa. In the acute disease, which occurs in some horses and is the usual form in donkeys, the organism is distributed in most tissues and may be excreted in feces, urine, saliva, and tears. Although the most common form of the disease in horses is respiratory, the route of infection is probably oral because this is the only experimental way to produce the typical chronic respiratory disease; intranasal or intratracheal inoculation reproduces the acute disease. Percutaneous infection can occur, but this is unusual.

In the absence of definitive information it is assumed that the organisms traverse the pharyngeal mucosa, and perhaps the intestinal mucosa, and are conveyed to the lungs, where lesions almost always occur. From there, hematogenous spread is believed to result in the nasal, cutaneous, and nodal lesions. This sequence of events is speculative, however, and not entirely satisfying. The chronic syndrome of glanders is frequently divided into nasal, pulmonary, and cutaneous varieties. The division is convenient for description, but the varieties are not distinct, emphasis may at any time change from one to the other, and the same animal may suffer the three varieties at the same time. Involvement of all three sites is common in acute glanders as it is seen in donkeys and in exacerbations of the chronic disease in horses.

Rhinitis in glanders usually commences as a unilateral nasal catarrh, but the inflammation might be bilateral and also involve the pharynx and larynx. The nasal excretion is copious, purulent, and greenish yellow. It is frequently flecked with blood and fragments of desquamated epithelium. The typical nasal lesions are multiple small nodules lying in the submucosa and surrounded by a narrow hyperemic halo. Each nodule consists of a focus of intense cellular infiltration with an inner core of neutrophils and a periphery of macrophages. The core liquefies, and the overlying mucosa might slough. The nodules might be isolated or semiconfluent, with suppurative cores separated by granulation tissue. A discrete slough of the necrotic tissue over individual nodules can occur, leaving a crateriform ulcer with a sharp margin and smooth base. The ulcers sometimes perforate the septum in severe cases. New generations of nodules develop, ulcerate, and heal irregularly; it is usual to find nodules, ulcers, and white stellate scars mixed together in an affected horse. There is variation from case to case in the number of lesions that can be found. In the milder cases, a few discrete foci are present in the posterior portions of the nasal cavity, and the anterior portions show only hyperemia and catarrh. Lymphadenitis of the submaxillary and retropharyngeal nodes is regularly present. Depending on the age and activity, nodules or scars might be found. When lesions occur on the larynx, they are of the same type as those in the nose. Lesions in the tracheal mucosa are usually ulcerative but are occasionally pyogranulomatous nodules.

Lesions of glanders can be found in lungs in all but a very small percentage of cases. The typical lesion is the nodule, but in some acute cases there may be a more diffuse pneumonia. The nodules have a miliary distribution throughout the lungs, but most of them are detected beneath the pleura. They are basically pyogranulomatous lesions, but the relative proportion of exudative and proliferative components varies. The more exudative foci typically have necrotic centers composed of karyorrhectic neutrophils. In acute stages, they have hemorrhagic and fibrinous exudation. In more mature lesions, liquefied or caseonecrotic centers are surrounded by epithelioid cells, occasional giant cells, and lymphocytes, which blend with an outer layer of granulation tissue (Fig. 6.3C). The core may be gritty because of dystrophic calcification, but the salts are deposited irregularly and incompletely. In old lesions, the capsule is thin and fibrous (Fig. 6.3D). The more proliferative nodules develop a grayish semitranslucent core of granulomatous tissue consisting of epithelioid and giant cells with an admixture of leukocytes in a fibroblastic stroma. The more diffuse lobular pneumonia has the same range of components as the nodules but extends without clear demarcations other than those provided by interlobular septa.

Lesions of glanders in the alimentary tract are rare, although they do occur in experimental infections in which large doses of the organism are given by mouth. Hematogenous metastases are common in the spleen and less common in other viscera or in locomotor organs. Metastatic lesions are similar in structure to the pulmonary nodules.

In equine "farcy," the cutaneous lesions of glanders, the cordlike thickening of the subcutaneous lymphatics has caused them to be referred to as "farcy pipes." Chains of nodules ("buds") that tend to ulcerate are distributed along the corded lymphatics (Fig. 6.3A,B), and the regional nodes are enlarged. The lymphangitis is purulent and remarkable only for the unusual degree of leukocyte necrosis.

Melioidosis

Melioidosis is occasionally known as "pseudoglanders." The causative organism is *Pseudomonas (Malleomyces) pseudomallei,* which is closely related to *P. mallei*. Melioidosis is

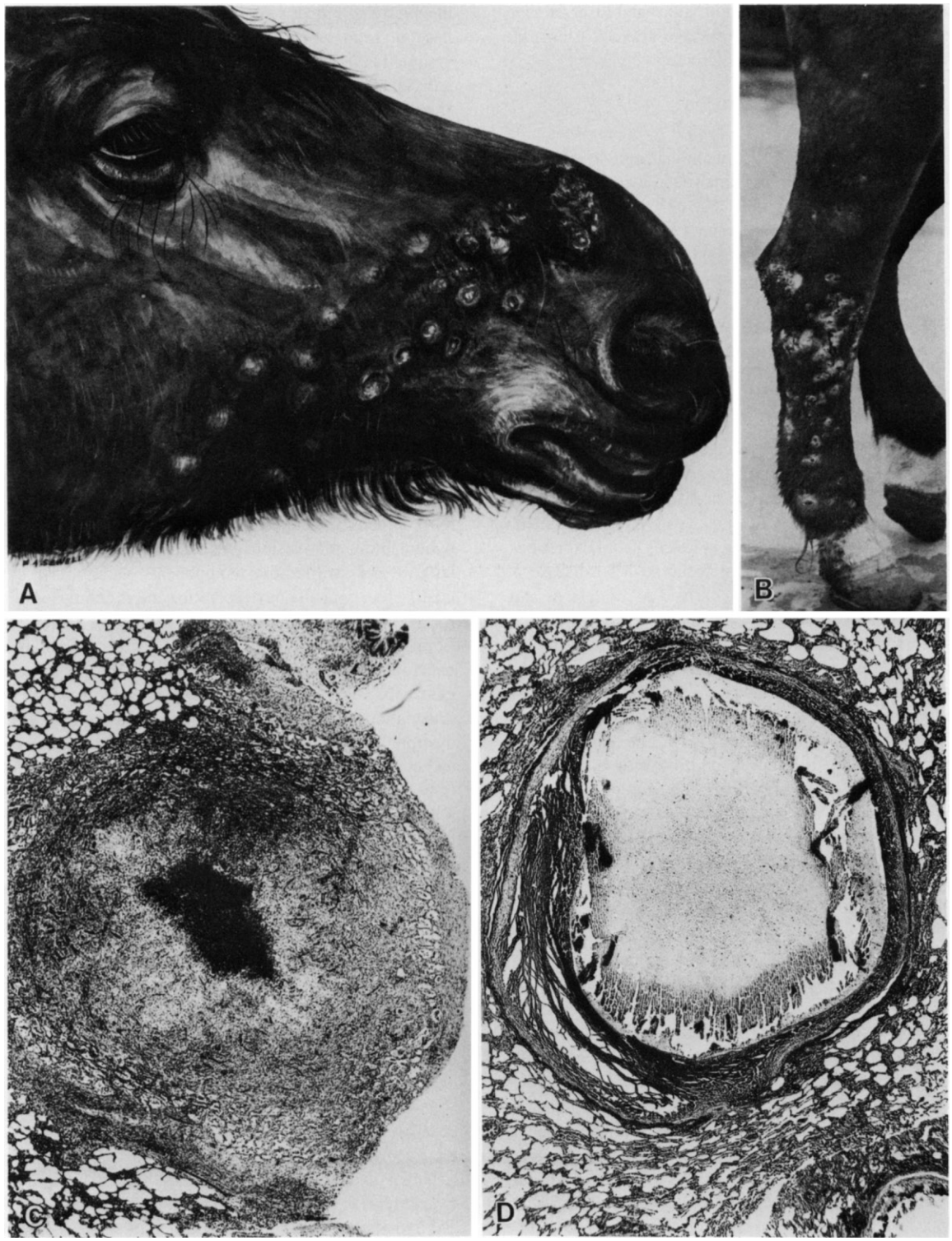

Fig. 6.3. Glanders. Horse. (**A**) Ulcers and farcy buds along facial lymphatics. (**B**) Cutaneous glanders with nonulcerated buds. (**A** and **B** from W. Hunting, *Glanders*, H. and W. Brown and Co., London, 1908.) (**C**) Pyogranulomatous pulmonary nodule with central necrosis. (**D**) Chronic pulmonary nodules with irregular calcification and thin fibrous capsules.

primarily a disease of rodents, but is occasionally a highly fatal disease of humans. All domestic species have been reported as occasionally infected, sometimes in small outbreaks in regions where the infection is endemic. The principal occurrence has been in Southeast Asia, but it is also present in parts of western Europe, the Caribbean, and Australia. Rats have been regarded as the usual source of infection, but since the organism can be found in soil and water of endemic areas, it is probably an accidental pathogen. Infection can occur through cutaneous wounds, and it can be transmitted by insects. Ingestion is probably the most important natural route of infection.

The usual course following clinical infection is pyemia followed by localization of the organism and abscessation in a wide variety of tissues, particularly lymph nodes, spleen, lung, liver, joints, and central nervous system. Depending on the severity of the process, there might be an acute disease associated with fulminating suppuration, or a more indolent one associated with chronic abscessation. Melioidosis in dogs can also cause dermal abscesses and epididymitis. In cattle, acute fatal infection, pneumonia, placentitis, and endometritis are important lesions.

Outbreaks of melioidosis, as well as isolated cases, occur in sheep, goats, and pigs, and the infection can be transmitted to these species more regularly than to other domestic animals. Pneumonia and arthritis are common in the clinical course of the disease, which otherwise is nonspecific. Goats may develop a chronic infection or recover. The lesions are those of a pyemia with multiple abscesses in the lungs, regional lymph nodes, spleen, and less often in other viscera and joints. The splenic abscesses are less than a centimeter in diameter, and they project from the surface of the organ (Fig. 6.1C). Larger purulent cavities, as well as multiple small abscesses, occur in the lungs and are associated with focal adhesive pleuritis (Fig. 6.1D). The abscesses are encapsulated and contain a creamy or caseous, yellow-green pus. In some cases, there is a purulent exudation in the bronchi. Except for the lamination that occurs in old lesions of caseous lymphadenitis caused by *Corynebacterium pseudotuberculosis,* there is nothing in the morphology of the lesions to distinguish the two diseases in sheep and goats. Experimental infections in sheep can produce, in addition to the lesions of the natural disease, microabscesses in the brain and lesions in the nasal mucosa similar to those of glanders.

INFECTIOUS BOVINE RHINOTRACHEITIS. This is an acute contagious disease of cattle caused by bovine herpesvirus-1 characterized by inflammatory lesions in the upper respiratory tract and trachea. The virus also can cause a wide variety of other syndromes, notably conjunctivitis, infectious pustular vulvovaginitis or balanoposthitis, abortion, and meningoencephalitis, enteritis, or more generalized infection in young calves. Although other members of the herpesvirus family collectively share similar tissue tropisms, bovine herpesvirus-1 is unusual in the wide variety of the disease syndromes it can cause. It is not certain to what extent different manifestations of disease are due to differences in strains of the virus or to epidemiologic factors such as density of susceptible populations, route of transmission, and management practices.

On clinical and virologic evidence the disease is widely distributed in the world, and on serologic evidence the infection is more widespread than is any clinical evidence of it. As rhinotracheitis, the disease occurs chiefly where cattle are crowded, and most outbreaks occur among animals kept in feedlots or indoor fattening pens. The disease in dairy cattle is usually milder. The onset in feed lots is usually preceded by introduction of animals from an outside source, and from there on, the pattern is typically that of an epidemic maintained by the continual movement of cattle into and out of the feedlots. The morbidity is high, and many cases are mild and unrecognized. The fatality rate is usually low, but it can be more than 30% in exceptional outbreaks.

The clinical course is characterized by fever, increased respiratory rate, coughing, and serous nasal discharge. Lacrimation sometimes occurs. If the course is prolonged, the nasal discharge becomes mucopurulent and inspiratory dyspnea develops. The lesions in typical and uncomplicated cases are those of seromucinous rhinotracheitis and possibly conjunctivitis. In cases of greater severity, and those with bacterial complications, there is a glairy or mucopurulent exudate with acute diffuse inflammation and focal hemorrhages, erosions, and ulcerations. In the most severe cases, and especially in fatal ones, there are widespread fibrinopurulent or fibrinonecrotic membranes on nasopharyngeal, laryngeal, and tracheal surfaces (Fig. 6.4A). The region of most severe damage varies, but in field outbreaks the necrotizing and diphtheritic inflammation is often most dramatic in the larynx and adjacent pharynx and trachea (Fig. 6.4C). Bacteria contribute to the severity of these lesions, particularly *Pasteurella* spp., *Mycoplasma* spp., and *Fusobacterium necrophorum.*

The histologic changes can be anticipated from the gross appearance of the lesions. In mild cases, there are the expected features of serous to mucopurulent inflammation with minor amounts of epithelial necrosis. In fatal cases, the emphasis is on extensive epithelial necrosis and formation of a surface layer of admixed fibrin and necrotic debris (Fig. 6.4B). There is an intense vascular, neutrophilic, and mononuclear response in the underlying viable tissue. Acidophilic intranuclear viral inclusion bodies, best demonstrated after use of acid fixatives, can sometimes be found in infected cells. Because they usually appear for a transient period around 2 or 3 days after infection, they are mostly seen in experimental situations. They can rarely be detected in autopsy samples from field cases, although they occasionally persist long enough to be found in bronchial or alveolar epithelium. They are of little practical diagnostic value.

Assessment of the role of bovine herpesvirus-1 in causing pneumonia is complicated because in most descriptions of both the experimental and naturally occurring respiratory form of the disease it is impossible to distinguish between the effect of the virus itself, its role in predisposing to severe secondary bacterial pneumonia, or even the confounding effect of preexisting pneumonic lesions, which are common in calves or feedlot animals. Currently, it seems fairly safe to conclude that the lung is not significantly affected in the mild viral disease. At the other end of the disease spectrum, severe viral infection seriously impairs pulmonary defenses and leads to the extensive secondary bacterial pneumonia usually present in fatal cases. *Pasteurella* species are usually involved in such instances. The appearance of lungs is commonly that of severe fibrinous pneumonia with or

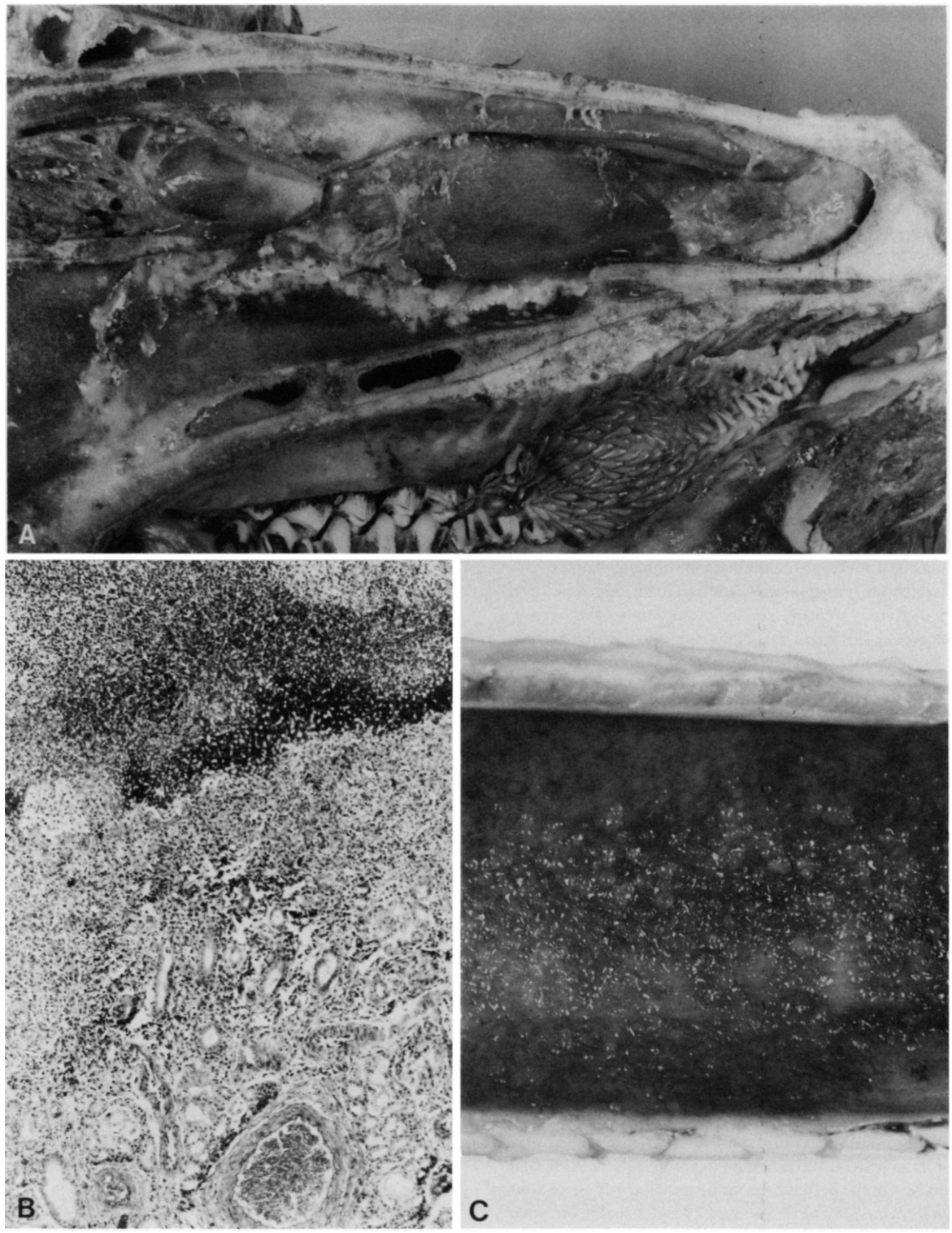

Fig. 6.4. Infectious bovine rhinotracheitis. (**A**) Inflamed mucous membranes of nasal cavity partially covered by fibrinopurulent exudate. (**B**) Acute rhinitis with ulceration and fibrinonecrotic covering. (**C**) Granular surface of ulcerated tracheal mucosa.

without pleuritis, as described under Pasteurellosis. An additional feature is interstitial emphysema, which frequently follows the labored respiration caused by upper and lower airway obstruction. The most severe viral lesion, in which secondary organisms might not play a significant role, is in fulminating infections. In these instances there is a severe necrotizing bronchitis and bronchiolitis, and there is extensive serofibrinous flooding of alveoli.

The pattern of generalized disease in newborn calves is rare but spectacular. Affected calves are young, less than ~1 month of age, and part of a herd in which infectious bovine rhinotracheitis affects all age groups. They are febrile and have serous ocular and nasal discharge, inspiratory difficulty, anorexia, and depression, and sometimes a laryngeal stertor suggesting laryngeal necrobacillosis. There is acute rhinitis and erosive pharyngitis, with intense hyperemia under the eroded areas and yellowish pellicles of epithelium at the margin. The epiglottis might be similarly involved, but the more distal parts of the respiratory tract remain unaffected. The most prominent changes are in the epithelium of the esophagus and forestomachs, which appear as if plastered with clumps of curdled milk. This caseous material is adherent epithelial debris. The necrosis involves the epithelium to its full depth, with intense neutrophil infiltration. Surviving epithelial cells and those at the margins of the lesions contain inclusion bodies in their vesicular nuclei. Additional lesions of systemic viral action include acute lymphadenitis with focal cortical necrosis, especially in nodes draining the upper respiratory tract. Necrotic foci can also be seen in the kidney, spleen, and liver. Miliary white necrotic foci 1–2 mm in diameter are particularly prominent in the liver. They are either uniformly distributed or concentrated in the right lobe.

The pathogenesis of meningoencephalitis, which mostly occurs in calves, is not fully understood. The virus apparently can travel to the brain from the mouth and nasopharynx by way of cranial nerves, and it can persist for long periods in the trigeminal ganglion. On the other hand, calves are also susceptible to viremic infection, so this is a possible alternative route. The lesions are those of a nonsuppurative meningoencephalitis in which granular acidophilic intranuclear inclusions are present in astrocytes and degenerating neurons.

When abortion is caused by the virus, the fetuses are edematous, and advanced autolysis indicates death of the fetus perhaps 2 days before abortion. There are no characteristic gross lesions, but microscopic lesions occur in many parenchymatous organs and lymph nodes as well as in the placenta. These lesions take the form of foci of intense necrosis and leukocytic infiltration. They are most prominent and consistent in the liver and could be confused with listeriosis. Specific inclusion bodies might not be found in autolyzed fetuses. Vaccinal strains of virus, prepared for this purpose in tissue culture, are as effective as field virus in causing abortion, and the natural infections may not be preceded or accompanied by signs of rhinitis or other illness. Thus far, it appears that cows pregnant less than ~5 months are less likely to abort following exposure to bovine herpesvirus-1.

FELINE VIRAL RHINOTRACHEITIS. Feline viral rhinotracheitis is principally an upper respiratory disease caused by feline **herpesvirus-1** and is one of the major components of the feline respiratory disease complex. The other major component is feline calicivirus infection. Feline reovirus and the feline-adapted strain of *Chlamydia psittaci* (feline pneumonitis agent) are minor causes. *Mycoplasma felis* is probably relegated to the role of an opportunist capable of causing mucopurulent conjunctivitis, usually in association with viral or chlamydial infection.

Feline viral rhinotracheitis is characterized by fever, sneezing, salivation, oral respiration, coughing, and serous to mucopurulent nasal and conjunctival discharges. Most cats recover in 7 to 14 days, but mortality can be high in young kittens or debilitated animals, including those whose immune system is depressed by feline leukemia virus infection.

The distribution of gross lesions corresponds to the predilection sites for viral replication, namely, the epithelium of nasal passages, pharynx, soft palate, conjunctivae, tonsils, and to a lesser extent, trachea. The initial serous inflammation becomes mucopurulent or fibrinous within a few days. Lethal cases usually have the more extensive fibrinous rhinotracheitis, possibly with extension to an acute viral or secondary bacterial pneumonia. Tonsils are enlarged and often petechiated. The regional lymph nodes are also usually enlarged, reddened, and edematous. Ulcerations of the tongue are only rarely seen, and then only in severely affected cats. This contrasts with the frequent finding of vesicular to ulcerative lesions on tongue, hard palate, or nostrils of cats with calicivirus infection. The ocular involvement is usually limited to purulent conjunctivitis, but it can progress to an ulcerative keratitis.

Microscopically, the respiratory and conjunctival lesions are associated with intranuclear viral replication causing epithelial cell death and the multifocal necrosis characteristic of active herpesvirus infection. The virus is pathogenic enough in its own right to cause extensive lesions, but mixed secondary bacterial infection by organisms such as *Pasteurella multocida, Bordetella bronchiseptica, Streptococcus* spp., and *Mycoplasma felis* enhance the suppurative response. Most active viral replication and cell necrosis occur from 2 to 7 days after infection, and during this period herpesvirus inclusions are present in the nuclei of affected cells. They are typically large, acidophilic, and surrounded by a clear halo (Cowdry type A). Fixation in acid fixative such as Bouin's solution is best for their demonstration. They might be found in lesions from cats dying of the disease, but they are rarely detected beyond 7 days after infection and cannot be relied upon for diagnosis. Cells bearing inclusion bodies become large and pale, with a perinuclear clear zone, or ballooned and granular, with loss of epithelial organization. The disrupted epithelium is soon eroded or ulcerated, and there is an acute inflammatory reaction with exudation of fibrin and many neutrophils. Focal necrosis accompanied by acute inflammation might be found in tonsils and local lymph nodes. Necrosis and resorption of turbinates have also been described.

Pulmonary involvement is uncommon except in fatal cases. In fulminating cases of viral infection, there is widespread multifocal necrotizing bronchitis, bronchiolitis, and interstitial pneumonia, with extensive serofibrinous flooding of airspaces. In other instances, there is a secondary bacterial bronchopneumonia.

Naturally occurring infection by feline herpesvirus-1 rarely

causes manifestation of the wider tissue tropisms seen with other members of the family, such as bovine herpesvirus, but they occur occasionally. The virus is suspected of being a cause of abortion, but this has been difficult to prove in natural outbreaks. Experimentally, it has been possible to produce abortion and generalized neonatal infection by intravenous or intravaginal inoculation of the virus into pregnant cats. Necrosis accompanied by inclusion bodies has also been found in sites of osteogenesis in a wide variety of bones of kittens after intravenous inoculation. Degeneration of olfactory nerve fibers and focal lymphocytic infiltration of the olfactory bulbs has occurred in experimentally infected, germ-free cats, but the extent of lesions in the brain has not been properly documented.

Feline **calicivirus** infection is the other main component of the feline respiratory disease complex. Although clinical signs overlap with those of feline herpesvirus infection, and occasionally both viruses occur together, the caliciviruses have more affinity for epithelium of the mouth and lung than for that of the upper respiratory tract and conjunctiva. The tendency of virulent strains of calicivirus to affect lungs is discussed under Calicivirus Infections.

The cat-adapted strain of *Chlamydia psittaci* (*C. felis*) is mostly a cause of persistent conjunctivitis more analogous to trachoma in humans. The disease is misleadingly called feline pneumonitis, although there might be a mild or inapparent bronchointerstitial pneumonia.

Allergic Rhinitis

Sporadic instances of what probably is an allergic rhinitis are observed occasionally in dogs and less commonly in cats. The disease, clinically and in response to treatment, resembles hay fever in humans, but the immunologic basis has not been adequately established. Frequently in cattle, and occasionally in sheep, there is a rhinitis that in its clinicopathologic features is consistent with an allergic pathogenesis, but here also rigorous proof is lacking. The disease has been mainly reported from Australia, but it does occur elsewhere. It is more common in Channel Island breeds. It occurs chiefly in the summertime, when the pastures are in bloom, and affects individuals or most of a herd or flock. The nasal mucosa is pale and thick from edema fluid, and mucosal erosions might be visible in the anterior nares. The exudate is at first serous but later becomes mucopurulent or contains floccules of detritus and mucus. Eosinophils are a prominent component of the exudate.

Histologically, the surviving nasal epithelium is hyperplastic or eroded and is infiltrated by eosinophils. The glandular epithelium can be hypertrophied, and mucus is produced in excess; if the orifices of excretory ducts are occluded by the superficial reaction, the mucus accumulates in the ducts and eventually lifts off the debris on the surface. In more severe cases, in which there is extensive superficial diphtheresis, many of the small mucosal vessels show fibrinoid necrosis.

Nasal "granuloma" is considered to be generally a more chronic form of allergic rhinitis. The affected mucosa is mainly in the posterior portion of the nasal vestibule and the anterior region of the nasal septum and ventral meatus. The hyperplastic epithelium is granular or has multiple nodular projections covered by intact epithelium (Fig. 6.5A). Histologically, the nodules typically consist of hyperplastic and metaplastic epithelium covering a superficial edematous lamina propria with a central core of inflammatory granulation tissue (Fig. 6.5B). Nonkeratinizing squamous epithelium usually covers the surface of the nodules, and goblet-cell hyperplasia is more pronounced in the terminal portions of nasal gland ducts, which often form the lateral boundaries of the nodules. Active lesions have prominent eosinophil infiltration of the superficial lamina propria and epithelium. They are associated with increased numbers of submucosal mast cells. Vascular proliferation, fibroplasia, and accumulation of mostly lymphocytes and plasma cells in the cores of nodules are features of chronicity. Correlation of acute inflammatory events with degranulation of mast cells and accumulation of eosinophils is strong evidence that an immediate (type I) hypersensitivity is involved. Further support for this hypothesis has been provided by experimental production of closely similar lesions by repeated intranasal exposure of cattle to powdered ovalbumin. In view of the varied components of chronic lesions, however, it is probable that other classes of hypersensitivity (types III and IV) also play some role. It is believed that the condition is due to hypersensitivity to a variety of plant pollen grains or fungal spores. Because there appears to be a familial predisposition in Jersey cattle, the existence of susceptible "atopic" animals has been proposed. The condition is therefore sometimes referred to as atopic rhinitis.

Less commonly, nasal granulomas in cattle are attributable to fungal infection. They also occur mostly in the anterior portion of the nasal cavity but tend to be larger polypoid masses. They frequently have yellow-green cores associated with massive eosinophil accumulation. Histologically, components of the lesions are similar to those described for the chronic allergic "granulomas," but hyphae and chlamydospores of fungi surrounded by macrophages, giant cells, and eosinophils are present. Various fungi normally saprophytic on plants have been isolated. It is tempting to speculate that the mycotic granulomas represent the small proportion of the more nonspecific allergic granulomas in which the causative allergen is able to vegetate.

Granulomatous Rhinitis

Local damage to nasal mucosa or reduced defenses because of depressed immune response or other systemic influence make the nasal cavity prey to occasional opportunistic fungal or yeast infections. The range of fungi varies with species of animal affected.

Aspergillus fumigatus is the commonest cause in the dog, but it is rare in other species. The usual lesion is a chronic necrotizing to granulomatous lesion causing large amounts of friable exudate that often consists mainly of necrotic fungal hyphae. Viable surface hyphae can sometimes be seen grossly as a blue-green mat. The lesion is slowly aggressive and causes destruction of turbinates and sometimes the nasal septum, but it rarely erodes through the nasal, maxillary, or palatine bones. Similar lesions can be caused by *Penicillium* spp.

Cryptococcus neoformans is the most frequent cause of granulomatous rhinitis in cats and also occurs in horses and dogs (in descending order of frequency). The lesion in cats is more gelatinous than granulomatous, since it consists mainly of massed organisms with their abundant mucopolysaccharide capsular

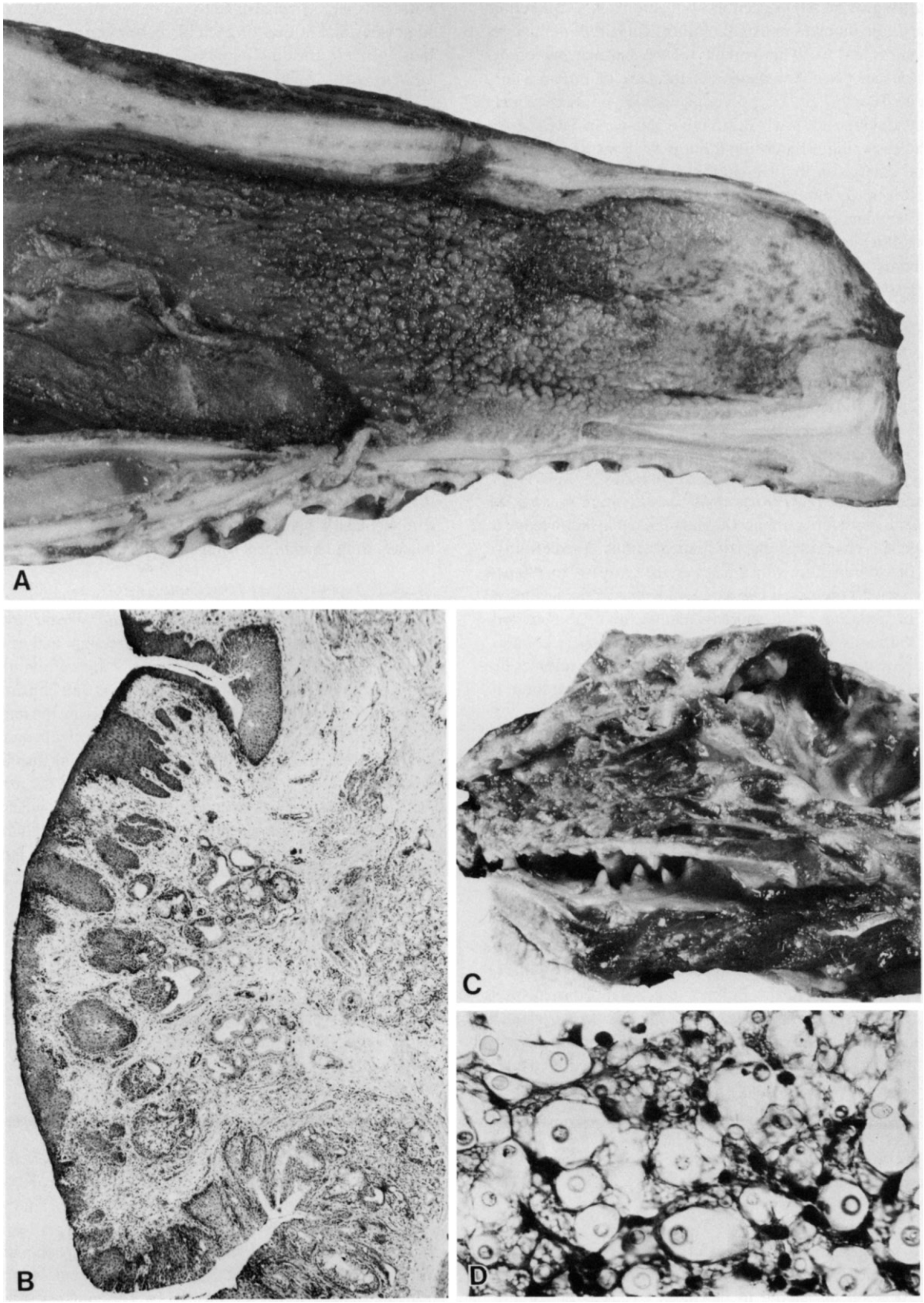

Fig. 6.5. (**A** and **B**) Hyperplastic mucosa of anterior nasal septum in "nasal granuloma." Ox. (**C**) Filling of nasal passages and obliteration of turbinates in nasal cryptococcosis. Cat. (**D**) *Cryptococcus neoformans* surrounded by clear zones of unstained capsular material.

material (Fig. 6.5C,D). Reaction by macrophages, epithelioid cells, and lymphocytes is usually minor. Impaired immune responsiveness and weak antigenicity of the capsular mucopolysaccharide are possible reasons for the lack of inflammatory response. The lesions are polypoid nodules or more widely space-occupying and slowly destructive masses. In cats, there is often facial swelling. Extension through the bony boundaries of the nasal cavity can involve skin and, possibly, oral mucosa. Local extension occurs to eyes or brain, and occasionally there is wider dissemination to local lymph nodes and lung or a variety of visceral organs (see Pulmonary Mycoses).

Actinomycosis and actinobacillosis, the latter in sheep especially, sometimes involve or are limited to the nasal cavities.

Rhinosporidiosis

Rhinosporidiosis in animals is a chronic polypous rhinitis caused by *Rhinosporidium seeberi*. The disease occurs in horses, cattle, and to a lesser extent, dogs, goats, and waterfowl. It also occurs in humans, sometimes in a more generalized form. The disease is endemic in India and Sri Lanka, and it is sporadic in some other tropical and subtropical countries.

Rhinosporidium seeberi has resisted cultivation *in vitro*. Its mode of transmission is unknown, and the sketchy knowledge of its life cycle is based on studies of tissue sections. The definitive stage is the sporangium, which has a diameter of 100 to 300 μm and is visible to the naked eye as a white spot in the lesions or squash preparations. The sporangia have thick, double-contoured, chitinous walls and contain numerous spherical endospores ~2 μm in diameter. The mature sporangium releases the endospores into tissue or into the nasal discharge, and these in turn form new sporangia to complete the cycle.

The source of the organism is unknown; the only recognized association is with proximity to water. Initiation of the disease is thought to be influenced by local trauma to the nasal mucosa; an association has been observed between rhinosporidiosis and the nasal lesions produced by *Schistosoma nasalis*, as well as with punctures of the nasal septum for nose leads in draft oxen.

The lesion is a polyp, usually single and unilateral. The polyps range from sessile to pedunculated and cauliflower-like. They vary in size up to a diameter of 2 to 3 cm. They are soft, pink, and bleed easily because of their insubstantial myxomatous nature. On section, the sporangia may be visible grossly. Histologically, the bulk of the polyp consists of a stroma of fibrous or fibromyxoid tissue covered by usually intact epithelium. The organisms are present in the stromal tissues as spherical bodies of various sizes. There is scant reaction to them except when sporangia rupture. Then there is a granulomatous and occasionally a neutrophilic response.

Parasitic Diseases of the Nasal Cavity and Sinuses

Myiasis

The larvae of a number of flies of the family Oestridae are parasites of nasal cavities of domestic animals. *Cephalopina titillator* deposits its larvae in the nasal passages of camels. Species of the genus *Cephenomyia* are the "head bots" of deer. *Rhinoestrus purpureus*, the Russian gadfly, is parasitic in horses; its larvae can also be found in the conjunctival sac. The life cycles and effects of each of these parasites are similar to those of their most ubiquitous relative, the nasal bot of sheep, *Oestrus ovis*.

The first-stage larvae of *Oestrus ovis* are deposited by the flies on the nares and molt twice as they migrate through the nasal passages. Larvae that find their way through small openings into sinuses or recesses of turbinates are unable to leave after they have grown, so they remain and eventually die there. Development in the nasal passages can take up to 10 months, although larvae deposited early in summer are able to mature in that season. Pupation occurs on the ground.

The larvae attach themselves to the mucous membrane by their mouthparts. They produce mucosal defects at the points of attachment and, since the cuticle is spinous, a more general irritation as they move about. Affected sheep develop a catarrhal rhinitis, with a discharge that may be copious. Irritation of the mucosa of the sinuses, especially the frontal, can cause a gelatinous hypertrophy of the mucous membrane that may almost obliterate the sinus. Apart from persistent annoyance, and the debility that this may cause, there are seldom untoward effects of the parasitism. Sometimes larvae penetrate the cranial cavity, and secondary bacterial infections spread from the olfactory mucosa to the meninges; such complications are rare.

Linguatulosis

The cause of linguatulosis is *Linguatula serrata*, a tongue-shaped, degenerate arthropod 1–2 cm in length and of cosmopolitan distribution. The definitive hosts are carnivorous animals, but in aberrant parasitisms, herbivores and humans might be host to the final stage. Herbivorous animals are the intermediate hosts, and the nymphs can be detected in their mesenteric lymph nodes. Carnivores are infected by eating the infected viscera of herbivores, and the nymphs migrate to the nasal passages and mature. The parasites may be found anywhere in the nasal cavity, and occasionally they find their way into the paranasal sinuses or pass via the Eustachian tube to the inner ear. They lie on the surface of the nasal mucosa and produce, at most, a mild catarrh.

The gravid females discharge a large number of eggs, which are removed by sneezing. The larvae develop in the alimentary tract of the intermediate host and migrate to the mesenteric nodes and other organs, where they encyst and develop into the infective nymphs. The cysts are common in mesenteric nodes of cattle and sheep in some countries. They appear as brownish, fluid-containing foci 2–3 mm in diameter; older lesions may calcify and resemble tubercles.

Miscellaneous Parasitisms

Schistosoma nasalis, which is a cause of granulomatous rhinitis in cattle, goats, and horses in India, is described with other species of the genus under the Cardiovascular System (Volume 3). The only other trematode parasitic in the upper respiratory tract of animals is *Troglotrema acutum*, a European parasite of mink, skunks, and foxes. The first and second intermediate hosts are snails and frogs, respectively. The adult parasites occur in the paranasal sinuses. In foxes, they are attached to the mucous membrane. In mink and skunks, however, they lie in

cysts beneath the mucosa. The cysts, which also contain the eggs, are formed by suppurative granulation tissue. The reaction extends to cause a local rarefying osteomyelitis, which might eventually perforate and release purulent discharge into the cranial cavity, nasal cavity, or to the exterior.

The larvae of the genus *Habronema* may be deposited by flies in the anterior nares to burrow through the skin and produce granulomas similar to those of cutaneous habronemiasis. *Capillaria aerophila,* whose final habitat is the tracheobronchial system of carnivores, is found occasionally in the nasal passages and frontal sinuses. The leeches *Limnatis nilotica* and *L. africana* are taken in while drinking and attach to the mucosa of the pharynx and nasopharynx. They suck large quantities of blood, but the emergency caused by their presence depends on the development of large, edematous swellings in the affected areas, leading to dyspnea and, in severe cases, asphyxiation. The nematode *Syngamus nasicola* is found in the nasal passages of ruminants in tropical countries.

The mite *Pneumonyssoides* (*Pneumonyssus*) *caninum* is occasionally found in the nasal passages and sinuses of dogs. It is usually an incidental finding not associated with clinical signs or the development of lesions, but there are occasional reports of the mites causing mild rhinitis and sinusitis, and one in which they were associated with bronchitis.

Nasal Polyps

Polyps tend to be a sequel to focal chronic inflammation in the nasal mucosa. The ease with which the nasal lamina propria becomes engorged and edematous, plus the tendency of protruberances into the nasal meatus to compromise venous and lymphatic drainage because of constriction in their basal regions, are probable factors in the persistence or progression of inflammatory polyps. They occur occasionally in horses, less commonly in other species. Polyps are soft, pink-gray, irregularly nodular, pedunculated, or sessile masses. They have a chronically inflamed edematous core covered by variously hyperplastic, metaplastic, or ulcerated epithelium. Old polyps can become more fibrous.

Two special types of polyp deserve mention. One is the **hemorrhagic nasal polyp** (progressive hematoma) arising from the ethmoid region of the horse. This is a unilateral hemorrhagic mass, which can extend to the nostril or choanae. It tends to enlarge progressively and might recur after surgical excision. Histologically, it consists mostly of organizing hemorrhages of various ages, with extensive siderosis and calcification of connective tissue fibers. The extent to which capillary angiomatous changes are the forerunner of hemorrhage and hematoma formation is uncertain. The other special form of polyp affecting the region is the **nasopharyngeal polyp** of **cats**, which arises in the middle ear or Eustachian tube.

Neoplastic Diseases of the Nasal Cavity

With the exception of endemic ethmoidal tumors to be described subsequently, primary nasal and paranasal tumors are uncommon. They occur frequently enough, however, to be an important entity in dogs and, to a lesser extent, cats and horses. There is no clear relationship between frequency of nasal tumors in various breeds of dogs and length of their noses. The breeds with significantly increased risk, such as collie and German shepherd, do have long noses, however, and this has led to the mistaken generalization that dolichocephalic breeds as a whole are at greater risk. Origin from the nasal cavity is usual in dogs and cats, but in horses, tumors of the paranasal sinuses arise almost as frequently as those from the nasal cavity. Any of the tissues forming the lining or present in the boundaries of the nasal cavity and sinuses can give rise to either benign or malignant tumors. In general, most are carcinomas (Fig. 6.6A,B,D), followed in decreasing frequency by sarcomas of cartilage (Fig. 6.6C), fibrous tissue, and bone. The precise mix of types varies according to species.

Epithelial tumors of the nasal cavity and sinuses are classified as follows:

Papilloma
Adenoma
Squamous-cell (epidermoid) carcinoma
  Spindle-cell variant
Transitional carcinoma
Adenocarcinoma
Undifferentiated (anaplastic) carcinoma

Squamous-cell carcinomas predominate in the cat and horse. In the cat, a large proportion originates from the nasal vestibule, whereas in the horse, the maxillary sinus is a common site (Fig. 6.6A). It is speculated that the latter might arise from the epithelium of dental alveoli. Transitional carcinomas and adenocarcinomas are the most common in dogs. Transitional carcinomas are so called because they assume the characteristics of transitional epithelium. They typically consist of thick, stratified layers of dysplastic surface epithelial cells with a distinct basement membrane (Fig. 6.6D). Large transitional carcinomas have complex infolding or pleating of the thick epithelial sheets, with the basement membranes usually separated by inconspicuous stroma. Small, acinar-like spaces often appear within the epithelial sheets, frequently by swelling and necrosis of cells, and can cause difficulty in separation between transitional carcinomas and adenocarcinomas. Adenocarcinomas have a more obvious glandular pattern, however, with numerous acini lined by cells usually only one or two layers deep.

The tendency of the stroma of large, more rapidly growing tumors to become edematous can result in difficulty in distinguishing between the more undifferentiated carcinomas and sarcomas. Regardless of histogenic type, malignant nasal tumors tend to be soft, pale and fleshy to friable masses that slowly invade and destroy adjacent structures but rarely metastasize.

Tumors arising from the ethmoturbinate region have been reported to be endemic in a variety of species. They have the most widespread geographic distribution in sheep; cattle are affected less often. Whether endemic tumors occur at present in horses or pigs is uncertain. The tumors in sheep are adenopapillomas or locally invasive adenocarcinomas that arise from olfactory mucosa of the ethmoid region. Ultrastructural evidence indicates their origin from sustentacular cells of olfactory mucosa or the dark cells of Bowman's glands. Epidemiologic evidence does not differentiate between genetic, environmental, or infectious influences in causing the clusters of

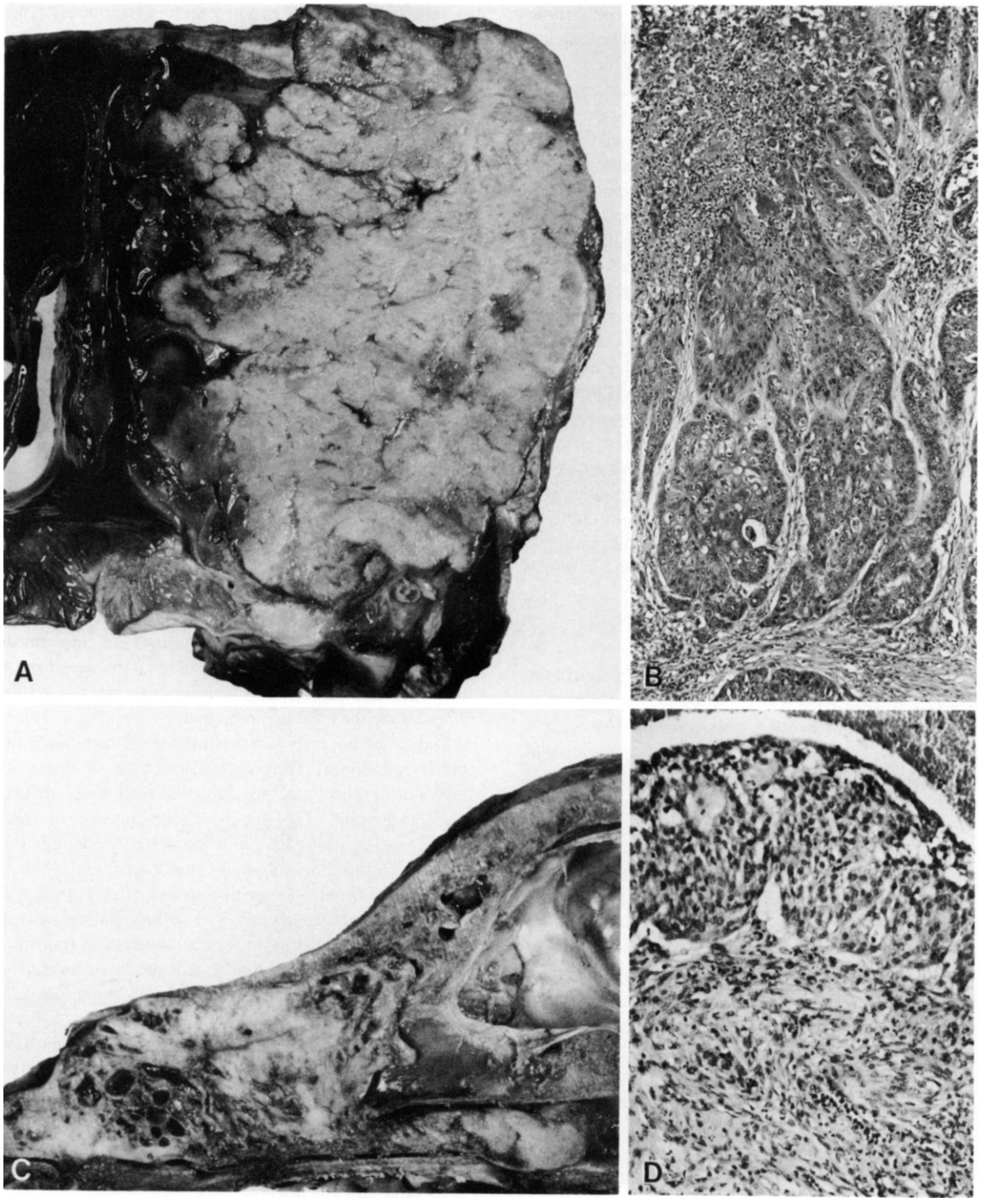

Fig. 6.6. (**A**) Squamous-cell carcinoma of maxillary sinus. Horse. (**B**) Squamous-cell carcinoma of nasal cavity. Dog. (**C**) Chondrosarcoma filling nasal cavity and extending into caudal nares. Dog. (**D**) Transitional carcinoma of nasal cavity with chronic inflammation and fibroplasia of lamina propria. Dog.

affected animals. Transmission experiments have had inconsistent results. The occasional ultrastructural finding of viral particles structurally resembling retroviruses (type C particles) led to the suggestion that a slow virus of the maedi–visna type might be responsible. In view of the fact that *jaagsiekte* (pulmonary adenomatosis) in sheep is now known to be caused by a retrovirus, this too becomes a candidate. Both carcinomatous and sarcomatous ethmoidal tumors have been found in cattle. There is one report of viral particles being detected ultrastructurally, but it has also been suggested that carcinogenic mycotoxins such as aflatoxin might play a causative role.

Pharynx and Guttural Pouches

The pharynx, being common to upper respiratory and alimentary systems, shares the misfortunes of both. Because of the complicated organogenesis of the region, various congenital malformations are occasionally encountered. Most attention is drawn to defects in the dog and horse. In the dog, the excess of soft tissue over skeletal framework that occurs in brachycephalic breeds leads to a variety of conditions of which excessive length of the soft palate, eversion of laryngeal saccules, and laryngeal collapse are most common. In the horse, complications are signaled by exercise intolerance and associated noisy respiration. Subepiglottic cysts believed to arise from thyroglossal duct remnants and entrapment of the epiglottis appear to be most frequent. Entrapment of the epiglottis below the aryepiglottic fold in horses is usually associated with congenital hypoplasia of the epiglottis or acquired shortening or distortion of the structure. A short epiglottis also predisposes to dorsal displacement of the soft palate, and sometimes epiglottal entrapment and dorsal displacement of the palate occur together.

A posterior diverticulum of the pharynx lies immediately dorsal to the esophagus in pigs. In young pigs, awns of barley and similar foreign materials occasionally lodge in the diverticulum and cause inflammation. The local reaction may cause dysphagia and death from starvation. In some cases, the pharyngeal wall is perforated and an ultimately fatal cellulitis spreads down the fascial planes of the neck. Perforation of the posterior–dorsal wall of the pharynx by drenching guns also occurs in sheep and is usually fatal.

Pharyngeal inflammation is a part of inflammatory diseases affecting the upper respiratory system, upper alimentary system, or both. These have been covered elsewhere. An entity deserving of brief mention here is **equine chronic pharyngitis** with **lymphoid hyperplasia**. It is detected mostly by endoscopy in thoroughbred racehorses less than 5 years of age. In its most severe manifestation, there are polypoid projections in the dorsolateral boundaries of the pharynx, with prominent white plaques or nodules representing lymphoid aggregates. The extent of lymphoid hyperplasia found in biopsies sometimes raises the suspicion of neoplastic proliferation, except for the follicular structure and predominance of mature lymphocytes. Although presumed due to persistent lymphoproliferative stimulus by an infective agent or combination of agents, possibly aided by excessive drying or other factors leading to reduced local defenses, nothing definite is known about the cause and pathogenesis. It is the equine analog of adenoids in children.

The guttural pouches of Equidae are ventral diverticula of the Eustachian tubes. They tend to become involved in inflammatory processes in analogous fashion to the paranasal sinuses. Complications differ, however, because severe guttural pouch inflammation can extend to involve nearby cranial nerves (VII, IX, X, XI, XII), vessels, and the cranial sympathetic trunk or even spread to adjacent bones, middle ear, brain, or atlantooccipital joint. Suppurative inflammation leading to empyema occurs mostly after upper respiratory infections, particularly *Streptococcus equi* or other streptococcal infection. Fibrinous or fibrinonecrotic (diphtheritic) inflammation is usually associated with fungal infection, generally *Aspergillus* spp., and hence is commonly referred to as guttural pouch mycosis. The lesion is highly suggestive of, but not pathognomonic for, fungal infection. Because the fibrinonecrotic inflammation extends deeply, and fungi when present can frequently invade vessels and other structures, complications such as rupture of the internal carotid artery with epistaxis, ischemic lesions, or osteitis are much more likely to follow than is the case from guttural pouch empyema. A less common condition is guttural pouch tympany. This is seen mostly in young animals, where the accumulation of air is presumed to be due to valvular action of the nasopharyngeal orifice of the Eustachian tube. Tumors of the guttural pouches are rare but when encountered are most likely to be squamous-cell carcinomas. Pharyngeal tumors are discussed with neoplasia of the mouth (in the Alimentary System, this volume).

Larynx and Trachea

Laryngeal Paralysis

Unilateral or bilateral paralysis of the larynx is the most common cause of abnormal respiratory noise (roaring) in horses. The condition is almost always a left-sided hemiplegia and is due to degeneration of the left recurrent laryngeal nerve. Resulting denervation atrophy affects all intrinsic laryngeal muscles supplied by this nerve, but not all are affected equally. The most obvious atrophy occurs in the cricoarytenoid muscle, which may be reduced to fascial remnants. Atrophy of the other muscles, which is less severe, is indicated by pallor and a reduction in size. The cricothyroid muscle, which is supplied by the cranial laryngeal nerve, is the only intrinsic muscle not affected. The cricoarytenoid muscle is the main abductor of the larynx. As a result of its paresis and atrophy, the left arytenoid cartilage droops into the lumen, thus interfering with airflow, particularly during the inspiration associated with severe exercise.

In cases detected clinically, microscopic examination reveals severe loss of myelinated fibers in middle and distal portions of the left recurrent laryngeal nerve. Less obvious loss occurs in subclinical cases. Ultrastructural features indicate progressive loss of fibers in the left recurrent nerve, accompanied by chronic demyelination, remyelination, and abortive regenerative attempts. Similar but milder changes can be detected electron microscopically in the distal right recurrent nerve. The reasons for the axonal disease are still disputed. The axons in the left recurrent laryngeal nerve are much longer than those in the right recurrent nerve, and this presumably makes them more susceptible to damage. The extent to which damage is caused by trau-

matic interruption of axoplasmic flow, neuritis by extension from guttural pouch disease, vitamin deficiency, or neurotoxins has still to be established. It is unlikely that there is a single cause, as evidenced by the circumstantial implication of delayed neurotoxicity by oral haloxon administration as a cause in Arabian foals. Another organophosphate, trichlorfon, also is linked circumstantially with an incident of left recurrent laryngeal nerve degeneration in horses.

Neurogenic atrophy of laryngeal muscles occurs occasionally in large breeds of dogs. It is usually bilateral and associated with lesions in the recurrent laryngeal nerves or, rarely, occurs as part of generalized degeneration of the nervous system. The condition appears to follow an autosomal dominant hereditary pattern in Bouviers. Laryngeal paralysis occurs rarely in the cat.

Congenital Anomalies

Congenital anomalies of the larynx are rare. Hypoplasia of the epiglottis has been observed in horses and swine. Partial or complete agenesis of the trachea is a rare finding. Tracheal hypoplasia characterized by reduction in the luminal diameter of the entire trachea, sometimes associated with bronchial hypoplasia, occurs in dogs. The higher frequency in English bulldogs indicates the possibility of an inherited basis. Malformations of the cross-sectional shape are important in the dog and to a lesser extent in the horse. The condition in dogs referred to as tracheal collapse occurs principally in miniature breeds. The trachea becomes flattened dorsoventrally. The cartilages form shallow arcs, and the dorsal tracheal membrane is widened and flaccid. The membrane is thin in uncomplicated cases but becomes thickened when there is chronic or periodic acute tracheitis. These are frequent complications of the mechanical obstruction. The nature of the basic defect is still unclear. The major feature appears to be slowly progressive loss of cartilage in tracheal rings, but the extent to which there is a congenital cartilaginous defect or how else the process might be related to miniaturization in the affected breeds is not known.

In horses, lateral compression of the trachea produces the so-called scabbard trachea. In this species also, a scroll-like curling affects the ends of the cartilages.

Acquired malformations of the trachea are caused by external pressure, in most cases from enlarged thyroid or regional lymph nodes, or inflammatory or neoplastic lesions within the wall.

Circulatory Disturbances

Active hyperemia occurs in acute inflammation, which is common. Laryngeal hemorrhages particularly affect the mucous membrane on the dorsal surface of the epiglottis and occur in many septicemic diseases. They are of some diagnostic significance in salmonellosis of swine and hog cholera. The hemorrhagic speckling of the tracheal mucosa in slaughtered cattle is produced by small extravasations in the submucosal lymphoid follicles. In cattle that die with severe dyspnea, and to a lesser extent in sheep, these follicular hemorrhages spread in a linear form. In severe cases the whole mucosa is red-black. The hemorrhages are reflected in the regional lymph nodes, which are also red-black, firm, and enlarged.

Edema of the larynx is usually inflammatory and part of acute respiratory infections, or caused by inhalation of irritant materials or by local trauma or inflammation (Fig. 6.7A). Mild edema of the glottis is occasionally observed in edema disease of swine. Edema occurs in cattle with acute interstitial pneumonia. It is also observed in cattle as part of a rapidly developing edema of the face and throat; this latter syndrome is probably of allergic origin and responds well to antihistamines. If neglected, it leads to asphyxiation. It can also be part of the localized anaphylactic response to insect stings in most species. Edema of the fauces and larynx occurs in equine purpura hemorrhagica and in the same species as a response to the leech *Limnatis nilotica* or lead poisoning.

The amount of edema varies but in any case is most severe in the region of the epiglottis, the aryepiglottic folds, and the ventricles. Severe cases are obvious; mild cases show a soft swelling of the mucosa. The edema fluid is usually bloodstained when associated with acute inflammation, and clear or pale yellow at other times. The fluid might disappear postmortem, but wrinkling of the mucous membrane remains to indicate the prior presence of fluid.

Severe mucosal and submucosal edema of the dorsal region of the distal half of the trachea occasionally causes death by asphyxiation in feedlot cattle. The loud inspiratory noise made by severely affected cows has given rise to the clinical term "honker" syndrome. There is correlation with increased respiratory movements brought about by exercise or hot weather, usually in heavy cattle, but it is not known whether the condition is triggered by trauma, tracheal compression, inhalation of dusts, toxins in feed, or a combination of these.

Laryngitis and Tracheitis

The location of the larynx and trachea is such that frequently they become inflamed as part of inflammatory diseases of either the upper or lower parts of the respiratory tract. Their involvement in major upper respiratory tract diseases has already been covered. Tracheitis frequently accompanies bronchitis and is sometimes a minor component of pneumonias that do not arise by extension from severe upper respiratory disease. Laryngitis can, however, occur without wider involvement of the respiratory tract (Fig. 6.7B). Laryngitis can occur as a part of oral necrobacillosis (calf diphtheria) caused by *Fusobacterium necrophorum* in calves and swine, or it might occur without lesions elsewhere. Ulcers or scarred sites of previous ulceration are found in a small proportion of larynges in slaughtered feedlot cattle. They occur mainly at points of apposition of vocal processes and medial angles of arytenoid cartilages. It is speculated that mucosal damage by the repeated trauma of laryngeal closure is the main predisposing cause of ulceration. It has also been suggested that *Haemophilus somnus* infection may sometimes be a factor. Lesions of acute or chronic diphtheria (*F. necrophorum*) and papillomatosis occur occasionally at the same sites and are believed to develop secondarily to mucosal ulceration.

Small foci of mineralization, often with accompanying granulomatous inflammation, occur in the lamina propria of dorsal trachea and ventral turbinate of adult pigs, particularly males. A causal association with inhalation of dusty, mineral-containing feed has been suggested, but this is unlikely. More widespread

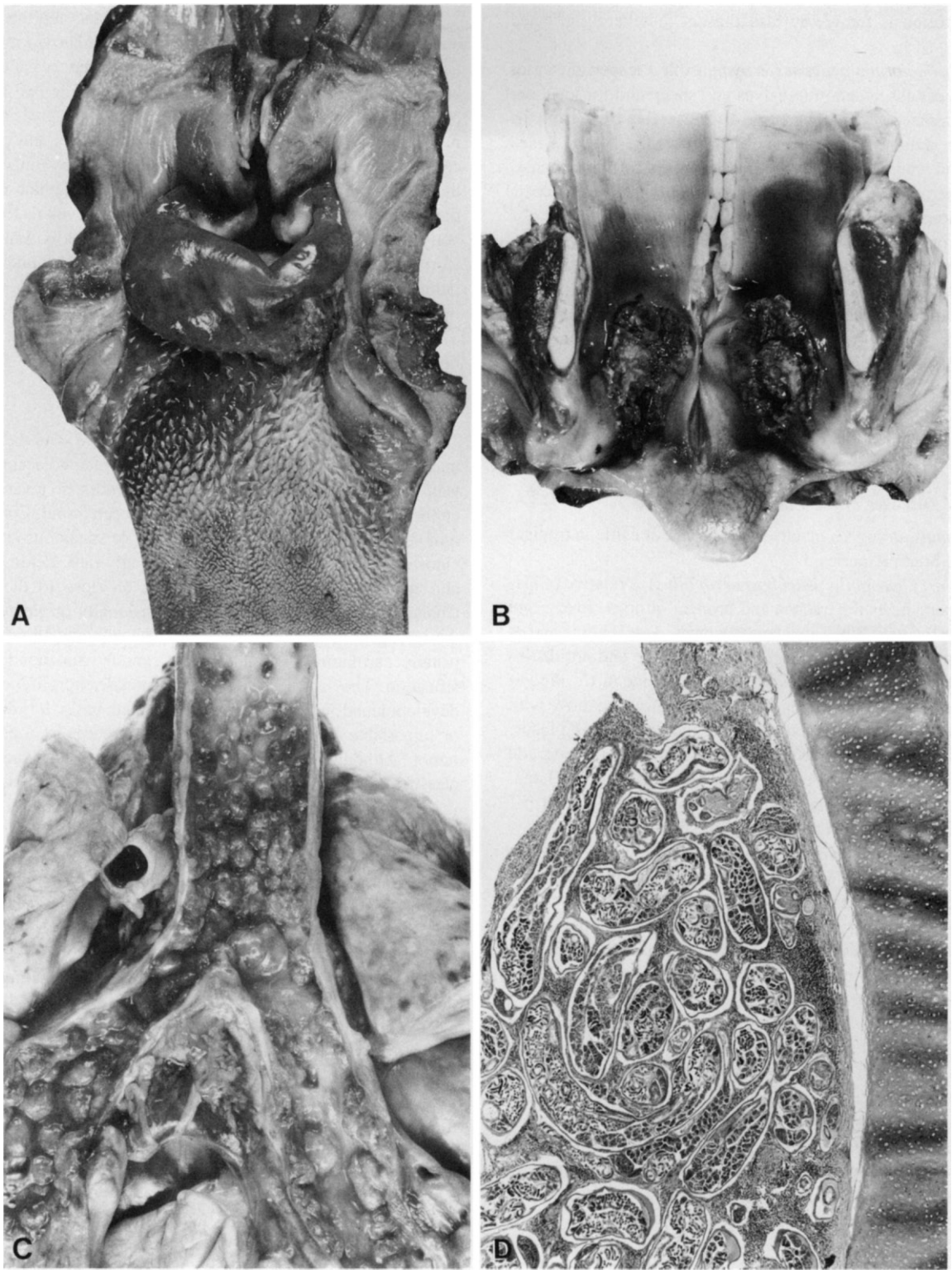

Fig. 6.7. (**A**) Inflammatory edema of epiglottis associated with abscess in base of tongue. Dog. (**B**) Necrotic laryngitis. Calf. (**C**) Parasitic tracheobronchitis. Nodules contain coiled *Filaroides osleri*. Dog. (**D**) Histologic section of nodule in (**C**), showing cross sections of worms and mononuclear-cell reaction.

mineralization is frequently also present in severely affected pigs.

Corynebacterium pyogenes is responsible for sporadic cases of laryngeal abscessation in calves and sheep and for local endemics in sheep grazing on mature dry grass. Recovery from the infection results in scarring and deformity; the latter is most prominent when inflammatory necrosis of the cartilage occurs. A diphtheritic laryngotracheitis caused by untyped streptococci is occasionally observed in litters of piglets.

A chronic and diffuse tracheitis can develop following tracheotomy. The reaction is most severe adjacent to the wound; the mucosa is swollen and, in the late stages, heavily scarred. Foci of chronic polypoid tracheitis are occasionally observed in dogs and cats. The thickening may be sufficient to cause significant stenosis and dyspnea. The cause is unknown, but the various pathogenetic factors involved are probably similar to those responsible for nasal polyps. Squamous metaplasia of tracheal epithelium is a feature of vitamin A deficiency and severe iodide toxicosis.

Parasitic Diseases of the Larynx and Trachea

Syngamus laryngeus occurs in the larynx of cattle in tropical Asia and South America.

Capillaria aerophila (*Eucoleus aerophilus*), a relative of *Trichuris*, parasitizes the trachea and bronchi of dogs, foxes, and occasionally, cats. They are slender worms, 4–6 cm long and of a faint greenish tinge. The eggs are operculate and not distinguishable from those of *T. vulpis* of the intestine or *C. plica* of the urinary bladder. The eggs are laid in the airways, move with mucus to the pharynx, are swallowed, and passed in the feces. The larvae develop to the infective stage within the egg and remain there until the egg is swallowed by a suitable host. Hatching occurs in the intestine. The larvae reach the lungs in ~1 week and are mature in the trachea in ~6 weeks.

The effects of *Capillaria aerophila* depend on the numbers present. Mild infestations are asymptomatic and provoke nothing more than a mild catarrhal inflammation. Heavy infestations cause more severe irritation as well as some obstruction to the lumen of the airways. Chronic coughing and intermittent dyspnea may then be observed, and secondary bacterial bronchopneumonia might occur.

Filaroides (*Oslerus*) *osleri* is an ovoviviparous, filiform worm 0.5–1.5 cm long, parasitizing the dog and related species. The typical lesions are protruding submucosal nodules in the region of the tracheal bifurcation (Fig. 6.7C). The parasite has a wide geographic distribution but is uncommon and seldom seen. Pups are infected by larvae in the saliva or feces of their mother. Larvae migrate from gut to lung through the blood. Efficient transmission depends on pups being licked by the dam and also on the habit of disgorgement of food by the adults to feed the young.

The lesions vary in size from nodules that are barely visible to larger nodules or plaques that project 1.0 cm or more into the lumen of the trachea (Fig. 6.7C). The larger masses are oval, with the long axis parallel to that of the trachea. The parasites do not typically incite acute bronchitis or tracheitis, although they can provoke paroxysmal coughing and dyspnea. The nodules are gray or whitish in color, and the worms are visible through the intact overlying mucosa.

The small nodules contain immature worms, and the larger ones a mass of tightly coiled adults (Fig. 6.7D). The worms lie in tissue spaces between the cartilage rings of the trachea and large bronchi, and in the adventitia and lymphatics. The live worms provoke a minimal reaction consisting of a thin capsule and an infiltration of the lamina propria by lymphocytes and plasma cells. Superficially, the nodules are covered by intact epithelium, except for small pores through which female worms protrude their tails to lay eggs. Dead worms provoke a foreign-body reaction with neutrophils and a few giant cells. Immature worms without significant tissue reaction may be found in the pulmonary lymphatics and occasionally in the alveoli. These immature worms are probably still migrating toward the trachea.

Spirocerca lupi occasionally forms nodules in the trachea or bronchi, examples of aberrant localization.

Neoplastic Diseases of the Larynx and Trachea

Neoplasms of the larynx and trachea are rare, and the information is therefore fragmentary. Any tissue in or adjacent to the wall of these structures can give rise to tumors, so a variety of epithelial and mesenchymal tumors have been found. Epithelial tumors are most likely to be papillomas or squamous-cell carcinomas. Adenocarcinomas are exceedingly rare. Leiomyomas and rhabdomyosarcomas can arise in or close to the wall. Chondromas or osteochondromas occasionally originate from the laryngeal or tracheal cartilages. The osteochondromas are usually cartilaginous nodules with central endochondral ossification. They are derived from perichondrial proliferation of developmental, inflammatory, or neoplastic basis. It is difficult or impossible to decide what the basic process is in any one tumor. Although it has been argued that the lesions should be classified as osteochondral dysplasias, the term osteochondroma is well established and can be understood to embrace the full range of pathogenetic possibilities. Chondrosarcomas and osteosarcomas are also rare findings. Mucosal involvement in lymphosarcoma or malignant mast-cell tumor is an uncommon occurrence in cats and dogs, and possible deformation or invasion by adjacent neoplasms in the thyroid or lymph nodes has already been mentioned.

Oncocytomas have been reported as rare, benign tumors arising as solitary projecting nodules in or close to the lateral ventricle of the canine larynx. They consist of lobular masses of pleomorphic cells with abundant, deeply eosinophilic, granular or foamy cytoplasm. Ultrastructurally, there is an excessive number of mitochondria and intermitochondrial glycogen granules. Oncocytes (oxyphil cells) occur in a variety of endocrine glands and epithelial tissues of humans, where they occasionally give rise to tumors. Evidence indicates that they are atypical neuroendocrine cells, hence oncocytomas are related to carcinoid tumors.

Bronchi

Major bronchi form the conducting zone between the upper and lower respiratory tract and therefore tend to be involved either as an extension of severe upper respiratory tract diseases on the one hand, or as part of pulmonary diseases on the other. Distal orders of bronchi and the bronchioles are mostly involved as part of pulmonary diseases, to be addressed later in this chap-

ter. There are important acquired conditions, however, in which the bronchi are the principal sites of abnormality, and these will be presented here. Congenital malformations are included under Congenital Abnormalities (of the Lungs), and tumors arising in bronchi are considered under Neoplastic Diseases (of the Lungs).

Bronchitis

In postmortem situations, **acute bronchitis** is usually overshadowed by more severe upper respiratory lesions or by pneumonia. The same range of inflammation described for upper airways can be encountered. Catarrhal, mucopurulent, fibrinous, fibrinopurulent, or purulent exudates are most common. Lesions in the inflamed bronchial tree depend to some extent on the causes; for instance, eosinophils are present in immediate hypersensitivity reactions, and inclusion bodies may be found at certain stages of some viral infections, but to a large degree the lesions are not specific and reflect the severity and duration of injury more than its cause.

Catarrhal bronchitis is the simplest form of inflammation. Acute mild irritation of the bronchial mucosa causes discharge of secretion from goblet and serous cells and from such seromucinous glands as are present. Since the types, relative numbers of epithelial secretory cells, and density of the glands differ from species to species, fine details of the response vary accordingly. Hyperemia and edema of the lamina propria accompany the secretory discharge. Ciliated epithelial cells are most sensitive to injury; they lose their cilia, become necrotic, and slough. The usual traffic of leukocytes through the epithelium becomes exaggerated. If the inflammation is transient, the integrity of the epithelium is rapidly restored by proliferation of residual basal and intermediate cells. Peripheral surviving secretory cells can also proliferate to play a part in the regenerative phase if the defect is large.

The course of bronchitis after the initial catarrhal phase depends on the nature of the irritant and the duration of exposure. In common bacterial infections, **purulent bronchitis** occurs, and the exudate in the bronchi becomes characteristically yellowish and viscid. The exuded dead and dying neutrophils collect in the lumen together with mucus and sloughed epithelial cells. **Ulcerative bronchitis**, in which large areas of epithelium are destroyed and the lamina propria directly involved, is usually an extension of prolonged purulent bronchitis. **Fibrinous** or **fibrinonecrotic bronchitis** is characterized by a thick, yellow membrane firmly attached to many points. Reactions of this severity usually also involve the larynx, trachea, and cranioventral portions of the lungs. This form of bronchitis is seldom observed. Primary bacterial infections might sometimes be responsible, but the masses of organisms seen in the membrane are probably mostly superimposed on a primary viral lesion, such as in malignant catarrhal fever or infectious bovine rhinotracheitis. A necrotizing **putrid bronchitis** can occur in bronchiectasis or as a result of aspiration of foreign materials. In such lesions, the microflora is mixed, and the greenish or brown putrid debris is characteristic. Gangrene might supervene.

Inflammation of large bronchi often heals without trace, which indicates that although the surface epithelium of bronchi might be severely damaged, there is seldom significant damage to the deeper structures of the wall. Polyps of granulation tissue are rare. Inflammation of small bronchioles, on the other hand, frequently leads to bronchopneumonia.

Bronchiolitis fibrosa obliterans or organizing bronchiolitis is a nonspecific response to a variety of severe forms of damage to bronchioles and adjacent alveoli. It can follow viral infections such as influenza, inhalation of toxic gases (including 100% oxygen), or damage by lungworms or pneumotoxins such as those associated with acute interstitial pneumonia in cattle. Prerequisites are necrosis of epithelium at the bronchiolar–alveolar junction and the presence of a fibrin-rich exudate that stimulates the infiltration and maturation of fibroblast precursors. The lesion is typically a polypoid projection of fibroblastic tissue partially or completely obliterating the bronchiolar lumen (Fig. 6.15,A,B). Different stages of fibroblastic organization of exudate composed of fibrin and necrotic cell debris can usually be seen in any one lung. In species with well-developed respiratory bronchioles, for instance, the dog, organization of exudate is often seen to be taking place from septa of alveoli situated at intervals along the length of the bronchioles. Organization of exudate into cellular granulation tissue can take place in as few as 7 to 10 days after onset of severe damage, and regeneration of epithelium over its surface can occur in the same time period.

The major causes of bronchitis, as alluded to earlier, are those already mentioned as causes of upper respiratory disease or those to be given later as causes of bronchopneumonia. Although bronchitis most commonly results from an aerogeneous portal of injury, an ascending route of involvement can be of importance. This applies to the verminous pneumonias and to several granulomatous infections. Thus metastatic tubercules frequently erode into the airways to produce tuberculous bronchitis, with subsequent spread as tuberculous bronchopneumonia, and pulmonary abscesses of caseous lymphadenitis might be evacuated into bronchi, resulting in persistent caseous bronchitis.

The consequences of inflammation limited to larger bronchi are much less serious than the consequences of inflammation of small bronchi and especially of bronchioles. The larger bronchi lie in interstitial tissue outside the pulmonary lobules. The epithelium is pseudostratified and well supplied with secretory and ciliated cells. The peribronchial connective tissue is mature and relatively abundant. The lumen is large enough to remain patent even in the presence of copious exudate, and the exudate is so placed as to be expelled by an effective cough reflex. In contrast, the small bronchi and bronchioles lie within the parenchyma. There is a paucity of peribronchial connective tissue. The epithelium is simple, and under normal circumstances the ciliated and mucus-secreting cells dwindle and disappear from the smallest branches. The walls are thin, and the small lumen is easily occluded by exudate that may be too far distal for the cough reflex to be properly effective, especially in lungs with little collateral ventilation. It follows that while inflammation of larger bronchi might not have significant consequences for the lung, inflammation of bronchioles frequently leads to parenchymal damage. Bronchopneumonia, atelectasis, or emphysema are the most important forms of damage.

From the previous discussion, it will be evident that limited bronchitis or tracheobronchitis rarely causes death and is observed mainly as a clinical problem for which detailed pathologic (necropsy) information on the naturally occurring disease is

seldom available. This should change as data obtained from bronchial biopsies accumulate. A good example of this situation is the **infectious tracheobronchitis** causing "**kennel cough**" in dogs. The disease is characterized clinically by a hard, persistent, and usually nonproductive cough that can become paroxysmal. Affected dogs usually recover, although signs can persist for 3 weeks or longer. Available evidence indicates that clinical signs are accompanied either by no significant gross lesions or, with about equal frequency, by catarrhal or mucopurulent tracheobronchitis. There is sometimes extension to a cranioventral bronchopneumonia, and occasionally, serous to mucopurulent rhinitis. Palatine tonsils and tracheobronchial and retropharyngeal lymph nodes are usually enlarged and reddened. Microscopically, various degrees of tracheobronchitis and bronchiolitis are usually present. These range from a focal, superficially necrotizing tracheobronchitis and bronchiolitis to a more severe process characterized by mucopurulent inflammation. There is epithelial degeneration and necrosis, with disorganization of the normal pseudostratified pattern in the necrotizing lesions. The response in the underlying lamina propria is limited. The necrosis is associated mainly with viral infection, particularly canine parainfluenza type 2 virus. Extensive infiltration of neutrophils characteristic of mucopurulent tracheobronchitis is associated with *Bordetella bronchiseptica* infection, and the bacteria can be found by electron microscopy to be attached to cilia by fibrillar material (pili). Bacteria might be in sufficient numbers to be visible by light microscopy after staining for Gram-negative bacteria. The etiology of the disease in dogs is complex, as is that of many respiratory conditions. The most important agent appears to be *B. bronchiseptica,* often acting in concert with canine parainfluenza type 2 virus or canine adenovirus-2. All possible variations of these organisms, singly or mixed, have been recovered at one time or another, however. Mixed infection with canine distemper virus also occurs occasionally. The role of agents such as reovirus, *Mycoplasma, Pasteurella multocida,* and other Gram-negative bacteria is unclear but probably not large.

Acute bronchitis of presumed allergic cause is part of the condition referred to clinically as "asthma" or **allergic bronchitis**. Since cases are frequently episodic or chronic and what little information available on the lesions relates to the longer-standing cases, allergic manifestations are considered in more detail under the next heading.

Chronic Bronchitis

Chronic bronchitis is usually of infectious, parasitic, or presumed allergic cause. The relative importance of these causes varies according to species. Chronic catarrhal or mucopurulent bronchitis is of most importance in dogs, where bronchial irritation and hypersecretion of mucus causes a chronic intractable cough. The condition is seen mostly in small breeds, particularly in obese animals.

At postmortem examination the major finding is excess mucus or mucopus in the tracheobronchial tree. This ranges from pooling of turbid, viscous fluid at the tracheobronchial junction to large amounts of tenacious, white or green to brown exudate in all airways. Sometimes the exudate is profuse enough to cause terminal foamy filling of the airways. The bronchial mucosa is thickened, often hyperemic and edematous. Occasional polypoid projections into the lumen can be seen grossly in advanced cases, as can pale foci representing lymphoid nodules. Microscopically, the mucosal thickening and folding are caused mostly by increase in number and size of the mucosal glands and extensive infiltration of the lamina propria by lymphocytes, plasma cells, and occasional macrophages and neutrophils (Fig. 6.8C). The superficial epithelium has prominent hyperplasia of goblet cells and usually has foci of ulceration or squamous metaplasia. Histochemical techniques reveal a shift in the character of secretions from sulfomucins to more viscous sialomucins. The intraluminal mucus is commonly mixed with abundant neutrophils.

The amount of fibrosis, hyperemia, and edema in the bronchial wall depends on the age and severity of the lesion and whether there has been recent acute exacerbation. The airway involvement usually extends to involve bronchioles, and in ~25% of cases, there is extension to a usually minor degree of bronchopneumonia. Hypertrophy of the smooth muscle in the wall of medium- and small-sized pulmonary arteries accompanies severe chronic bronchitis. The resulting pulmonary hypertension causes the cor pulmonale occasionally detected clinically. Significant lesions of emphysema are not associated with chronic bronchitis in the dog, although there is often exaggeration of the marginal emphysema commonly found along the sharp ventral borders of the lungs in older dogs. A more frequent complication is alveolar atelectasis and bronchiectasis.

The pathogenesis of the disease in dogs is uncertain, as it is in humans. The multiple factors believed to be involved in the development of chronic bronchitis in humans are episodes of viral bronchitis, particularly in childhood, continued damage by cigarette smoking or, to lesser extent, air pollution, and superimposed bacterial infection. In dogs, it is likely that chronic bronchitis occurs mostly in those dogs that fail to recover from a syndrome similar to that described above as infectious tracheobronchitis (kennel cough). Whatever reasons there are for initial failure of the acute episode to resolve, eventually there occurs a vicious cycle of disruption of normal defense mechanisms and persistent interaction of bacteria and leukocytes capable of mediating continued inflammation. The most important infectious agent in dogs is *Bordetella bronchiseptica.*

Chronic suppurative bronchitis is a frequent sequel to bronchopneumonia in cattle and is usually associated with bronchiectasis. The greater frequency with which bronchopneumonia fails to resolve in cattle compared to other species is presumably due, at least in part, to the complete lobular separation in this species. A variety of bacteria can be isolated from the suppurative lesions, of which *Corynebacterium pyogenes* and *Pasteurella* spp. are the most important.

Although circumstantially there is evidence that allergens can be an important cause of bronchitis, rigorous proof is lacking in most instances. The role of allergens in causing the chronic bronchiolitis–emphysema complex in the horse and the airway lesions associated with hypersensitivity pneumonitis are dealt with later. There remains a broad clinical syndrome, mostly in cats and dogs, commonly referred to as **asthma**, **allergic bronchitis**, or **allergic pneumonia**. Diagnosis is usually made on the

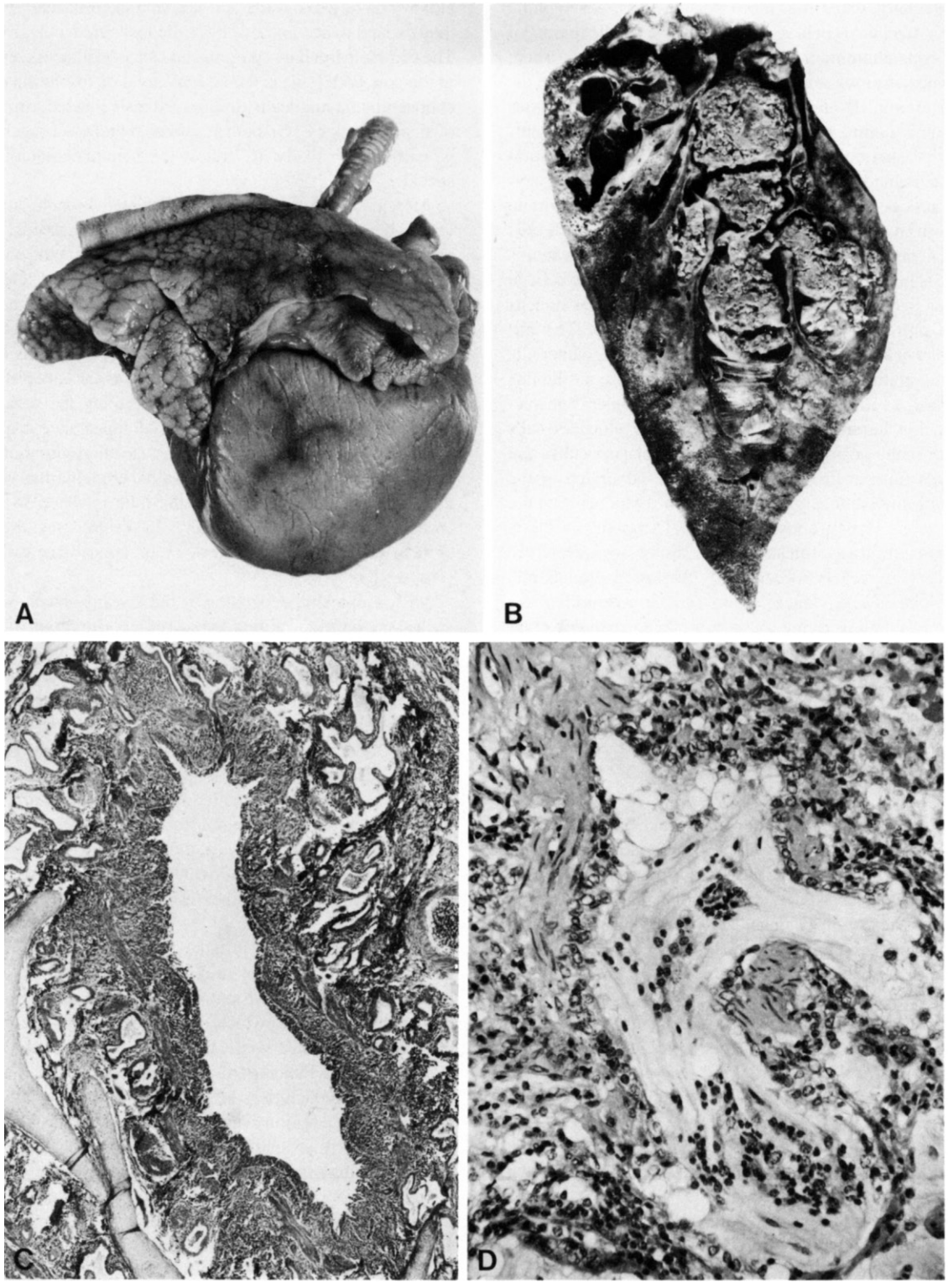

Fig. 6.8. (**A**) Hypoplastic lung. Calf. (**B**) Cylindric bronchiectasis with inspissated exudate filling dilated airways. Dog. (**C**) Chronic bronchitis. Dog. (**D**) Chronic bronchiolitis of presumed allergic origin with smooth muscle hypertrophy, mucus plugging, and eosinophils. Cat.

basis of coughing, wheezing, respiratory distress, eosinophilia in blood or tracheobronchial lavage fluid, and alleviation of signs by sympathomimetic drugs and corticosteroids. There have been no definitive studies of the lesions associated with the clinical syndrome. Bronchial biopsies indicate an edematous and hyperemic lamina propria, with infiltration of eosinophils and fewer plasma cells and lymphocytes. The epithelium is highly susceptible to sloughing, which is exaggerated by sampling and processing artifacts. The lesions found postmortem usually are in an animal that has had repeated episodes or chronic involvement and therefore have features of a chronic bronchitis in which eosinophils are the predominant inflammatory cell. In the cat, for instance, there is narrowing of bronchial lumens because of prominent hyperplasia of mucosal glands. The epithelial goblet cells are also hyperplastic. Numerous eosinophils infiltrate the epithelium and the edematous hyperemic lamina propria. Plasma cells and lymphocytes are usually less conspicuous. Bronchial lumina are filled with mucus and sloughed cells mixed with many eosinophils. Eosinophils, plasma cells, and lymphocytes form an irregular collar in the adventitia of the bronchi, and small numbers of these cells infiltrate between the glandular acini. Hypertrophy of bronchial smooth muscle is common but not always present. Bronchioles are affected in severe cases (Fig. 6.8D). Occasionally the lesion extends into peribronchiolar alveoli. Since lesions seen at postmortem are usually from an animal dying as a result of acute exacerbation, there is also a widespread patchy alveolar and interstitial edema. In other instances, particularly in the dog, the numbers of eosinophils may be low relative to the other inflammatory cells of a chronic bronchitis, making the assumption of an allergic mechanism more tenuous.

Bronchiectasis

Bronchiectasis is dilation of bronchi. Rarely it is a congenital malformation. More commonly it is an acquired lesion secondary to some form of bronchitis. There are two main anatomic varieties of bronchiectasis, saccular and cylindric. **Saccular bronchiectasis** is less common and consists of thin-walled, circumscribed outpouchings of bronchial or bronchiolar walls. It is much more easily detected in lungs fixed by intratracheal infusion of fixative under pressure. This type of bronchiectasis can result from focal necrotizing bronchitis and bronchiolitis and occurs occasionally in sheep and cattle. It can also be found to a mild degree in the small airways of horses with the bronchiolitis–emphysema complex to be described later (Fig. 6.10C).

Cylindric bronchiectasis affects bronchi partially or along their entire lengths (Fig. 6.8B). In cattle it is almost always a sequel to chronic suppurative bronchitis, which is a frequent aftermath of bronchopneumonia. It therefore affects airways in cranioventral portions of the lung where bronchopneumonia occurs. Although the mechanism of bronchiectasis has never been formally investigated, two main requirements appear to be necessary. One is accumulation of exudate in the lumen, and inflammatory weakening of the bronchial wall. The other is extensive atelectasis of alveolar parenchyma supplied by the affected airways. The loss of alveolar volume leads to traction on the walls of the airways, especially during inspiration. Since the airways have weak walls and are ventilated during breathing, they expand to accommodate for the lost parenchymal volume. The complete lobular septation and lack of collateral ventilation in the cow both lessens the effectiveness of resolution of bronchopneumonia and leads to more extensive atelectasis because of airway blockage. On both accounts, therefore, bronchiectasis is particularly likely to follow bronchopneumonia in this species.

Affected lungs have irregularly dilated bronchi in cranioventral regions. They are filled with viscous to caseous, yellow-green pus. The intervening parenchyma is atelectatic and sometimes fibrotic. In the anterior lobes the atelectasis tends to be complete, but in the caudal lobe there is often a mixture of areas of bronchopneumonia, hyperinflated lung and atelectasis. In the bovine lung, in which the demarcation of lobules is distinct, dilation of the central bronchiole and alveolar collapse make a small "hillock" of each lobule, resembling the surface of a pineapple (Fig. 6.9A). The superficial appearance is often obscured by fibrous pleural adhesions, so the induration of the parenchyma and the dilated, thin-walled bronchi filled with exudate are best appreciated when the lobe is sliced so that the bronchi are sectioned transversely. In severe cases, the dilated bronchi give a honeycombed or cystic appearance to the lobe (Fig. 6.9B).

Microscopically, depending on the severity and chronicity of the lesion, there are various degrees of reconstruction of the wall of the bronchus by granulation tissue. The lumen contains mucus, detritus, large collections of inflammatory cells, and frequently some blood. The mucosa might be destroyed by ulceration almost to the muscularis, or it might show a combination of ulcerative, atrophic, metaplastic, and hyperplastic changes. The bronchial walls are densely infiltrated with all types of leukocytes, and the lamina propria takes on the histologic properties of granulation tissue with progressive fibrosis. When the necrotizing process extends more deeply than the mucosa and involves the full width of the wall and some of the adjacent alveolar tissue, the lesion is equivalent to a lung abscess.

Cylindric bronchiectasis in the dog (Fig. 6.8B) arises against the background of severe chronic bronchitis, but in contrast to the cow, it is not as consistent a sequel. A major determinant is probably the extent to which alveolar atelectasis occurs in the dog. Since there is very effective collateral ventilation in dogs, atelectasis is less likely to follow airway obstruction. This could be the reason bronchitis is less prone to cause bronchiectasis in this species. In addition to generalized bronchiectasis associated with severe, diffuse, chronic, mucopurulent bronchitis, the condition sometimes is limited to only one or two lobes, more often the middle lobes. Whether localized or generalized, the greatly dilated bronchi often contain casts of either crumbly or tenacious and rubbery, partially dehydrated exudate.

Chronic mucopurulent bronchitis with bronchiectasis and bronchiolectasis is rare in cats. A case in which there was accompanying miliary broncholithiasis has been recorded. In pigs, sheep, and goats, bronchiectasis is usually associated with severe parasitic bronchitis. Occasionally in all species, localized bronchiectasis follows obstruction by a foreign body, granuloma, or tumor.

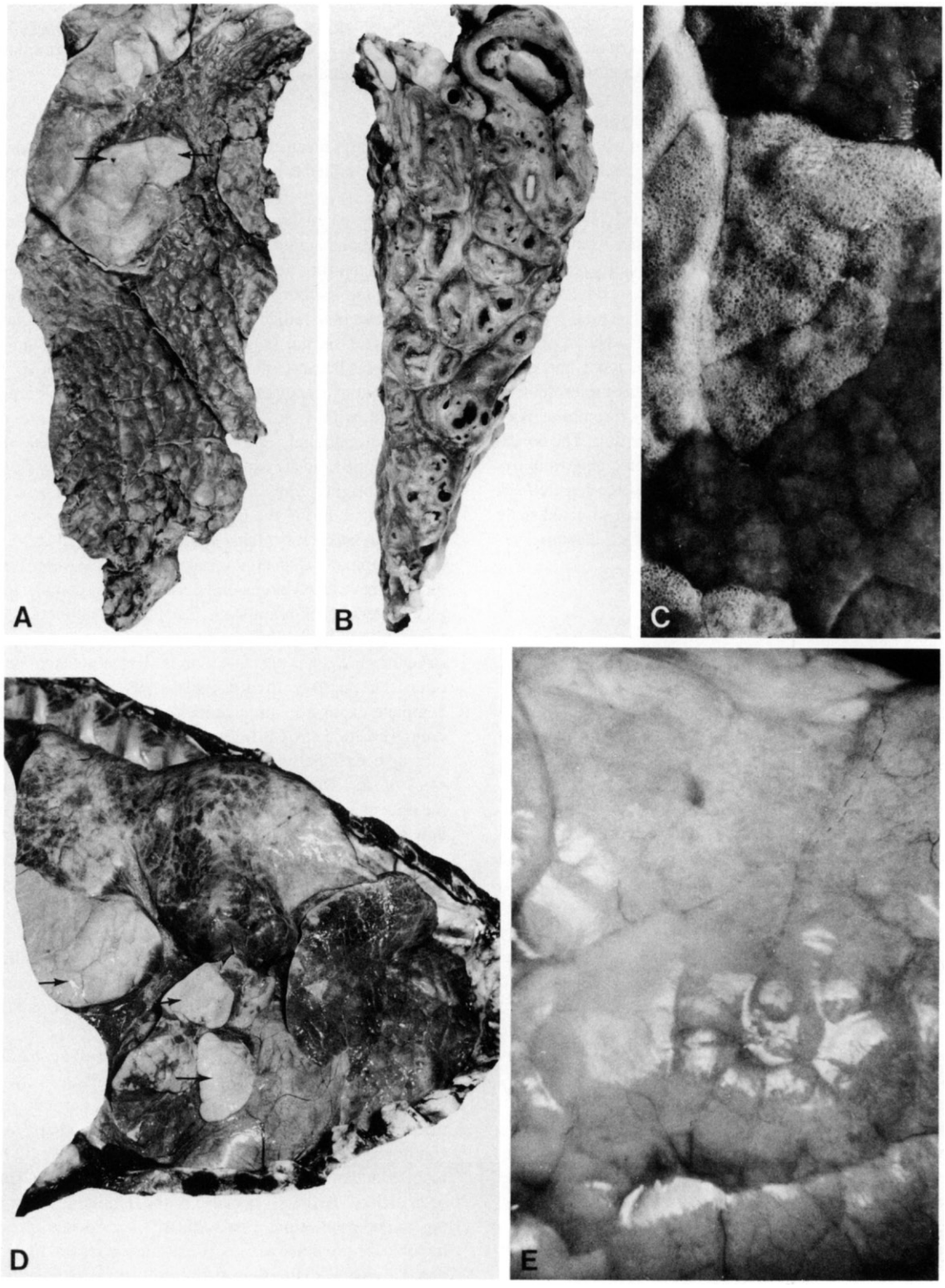

Fig. 6.9. (**A**) Bronchiectasis in cranial lobe. Air trapping in lobules above (arrows). Ox. (**B**) Cut surface of (**A**). (**C**) Hyperinflation (compensatory emphysema) in lobules bordering areas of consolidation. Note the relative smallness of the consolidated lobules and mottling produced by peribronchial infiltrates. Ox. (**D**) Chronic bronchopneumonia. Cranial bronchiectasis, widespread lobular consolidation, interstitial bulla protruding in caudal lobe, and a few pale lobules caused by air trapping (arrows). Calf. (**E**) Pale, puffy emphysematous lung associated with chronic obstructive bronchiolitis. Horse.

The course of bronchiectasis is chronic and unfavorable. Complications, other than bronchopneumonia, include bronchopleural fistula, septic thrombosis and hemorrhage or production of septic emboli with metastatic abscessation, and secondary amyloidosis.

Kartagener's syndrome was the eponym applied to a congenital and often familial disorder in infants in which there was coexisting situs inversus, sinusitis, and bronchiectasis. Investigations have revealed that Kartagener's syndrome is a subset of various abnormalities now referred to collectively as the immotile cilia syndrome or primary ciliary dyskinesia. Abnormalities are referable to improper function of ciliated cells, particularly of respiratory and reproductive organs. The basic defect in each case is now known to be one of several ultrastructural or metabolic abnormalities of cilia throughout the body. The most common defect is absence of one or both of the inner and outer dynein arms attached to the peripheral doublets of microtubules in the cilia. Several isolated cases with features resembling Kartagener's syndrome have been recorded for the dog. The condition has been found in three littermates in which abnormal dynein arms and excessive ciliary rotation were detected. A deliberate father–daughter mating produced an affected male without situs inversus and indicated a possible autosomal recessive pattern of inheritance.

Lungs

Congenital Anomalies

Congenital anomalies are rare. Various forms have been recorded, more for calves than for other species. Major malformations are incompatible with life but are extremely rare. Accessory lungs are the most common finding. These are edematous, lobulated masses and can be found within the abdominal or thoracic cavities or subcutaneously. The main histologic features are dilated bronchiolar structures, hypoplastic bronchi, and various degrees of development of alveolar ducts and alveoli. Bronchial hypoplasia also appears to be the basic defect in what is usually referred to as congenital adenomatoid malformation or adenomatoid hamartoma. This is where one or more lobes of the normal lung are replaced by swollen, spongy or cystic, lobulated tissue. Histologically, as in accessory lungs, there are dilated bronchioles, which sometimes are large enough to be noted grossly as cystic spaces. Bronchi are hypoplastic and lack cartilage and smooth muscle in their walls. Alveolar structures appear more normal.

Pulmonary hypoplasia (Fig. 6.8A) is particularly likely to accompany congenital diaphragmatic hernia. Congenital cysts and congenital bronchiectasis are localized variations on the same theme. Other rare findings are pulmonary agenesis, usually accompanying other major developmental defects, and ectopic lungs. Congenital alveolar dysplasia has been observed in pups. The gross form of the lungs is regular, but they retain a fetal appearance and become poorly aerated and poorly crepitant. The distribution, size, and shape of the alveoli are uneven, they are reduced in number, and there is too much interstitial tissue. Many dilated capillaries are present in the interstitial tissue. The formed alveoli are lined by mature alveolar epithelium. In such cases it is difficult or impossible to determine whether infection of the fetal lung played a pathogenetic role.

Abnormal lobulations and fissures are quite common and are found incidentally at postmortem examination.

Atelectasis

Atelectasis means incomplete expansion of the lung and was originally applied to defective aeration of fetal lung at the time of birth. It is now also applied to collapse of previously air-filled pulmonary parenchyma. Atelectasis is therefore divided into congenital and acquired forms.

In **congenital (neonatal) atelectasis** the lungs range from those of the stillborn animal, which have never been aerated (**fetal atelectasis**), to minor degrees of incomplete expansion. In fetal atelectasis the lungs appear as in the fetus but are dark reddish blue because of dilation of alveolar capillaries. They are of fleshy consistency and do not float. The alveoli are partially distended with fluid, and the epithelial cells are rounded. Sloughed epithelial cells (squames) from the oronasal regions and amniotic fluid are usually present in the alveolar fluid, possibly with bright yellow particles of meconium. These materials are aspirated during the exaggerated respiratory movements of the asphyxiated fetus *in utero*. Patchy congenital atelectasis due to incomplete expansion is usually due to weak respiratory movements caused by general debilitation or damage to respiratory centers in the brain stem. Laryngeal dysfunction, obstruction of airways, and abnormalities of the lung or related thoracic structures are other possible causes. In the neonatal period it is often not possible to distinguish between atelectasis of incomplete expansion and acquired atelectasis of briefly aerated lung. The atelectasis is frequently seen affecting groups of lobules or occasionally more widespread regions during the first week of life. The larger zones are more likely to occur in weak, recumbent animals and mostly affect the lowermost region of the down side (Fig. 6.12A). The atelectic lobules are distinct because they are dark red, depressed below the surface of the surrounding aerated lung, and in contrast to pneumonic lung, have a flabby consistency. The sectioned surface is homogeneous and dark red, and free blood is easily expressed from it. Microscopically, the alveolar walls are in close apposition. Only small amounts of fluid, epithelial debris (including "squames" from the upper oronasal regions or amniotic fluid), and alveolar macrophages are present.

Extensive neonatal atelectasis is a feature of neonatal hyaline membrane disease (neonatal respiratory distress syndrome). This is a common disease in human infants, particularly in premature babies and those born to diabetic mothers. A similar condition in animals is best recognized in foals, but it has been reported in lambs, pigs, puppies, and a calf. Foals and pigs have been called "barkers" because of the doglike sound made during forced expiration. Foals that show evidence of presumed hypoxic brain damage are sometimes referred to as "wanderers." Affected lungs are extensively atelectatic, although the borders of the lobes might be spared. They are heavy, fleshy, and often edematous. Cream-colored or bloodstained foam frequently exudes from cut surfaces and is present in large airways. The lungs sink or almost submerge in fixative. The main microscopic abnormalities are alveolar septal congestion, variably

collapsed or edema-containing alveoli, and presence of acidophilic hyaline membranes lining alveolar ducts and distal portions of bronchioles. Focal hemorrhages and interstitial edema are common.

There is general agreement that lack of normal surface-tension-reducing capacity of the alveolar-lining liquid plays the central pathogenetic role. This in turn is linked to defective production by alveolar type II epithelial cells of the phospholipid surfactant material, which consists mainly of dipalmitoylphosphatidylcholine. There is still debate, however, about the extent to which decreased surfactant activity is due to immaturity of type II cells or to a more specific metabolic derangement of their surfactant synthesis. Fetal hypothyroidism and, possibly, hypoadrenocorticism also play a role in the condition in piglets by being responsible for delayed maturation of type II cells. Other pathogenetic factors are fetal asphyxia, reduction in pulmonary arteriolar blood flow, and inhibition of surfactant by fibrinogen or other serum constituents in edema fluid.

Acquired atelectasis and **alveolar collapse** are used synonymously. Acquired atelectasis is most commonly the **obstructive** type, caused by complete airway obstruction. Whether atelectasis follows obstruction depends on the size of the airway obstructed and the degree of collateral ventilation. Complete blockage of lobar or segmental bronchi is necessary for atelectasis in the dog and cat, where collateral ventilation is extensive. Blockage of small bronchi or even bronchioles can result in atelectasis in bovine lungs, where there is insignificant collateral ventilation. Lungs of sheep are also prone to atelectasis, pigs less so, and the horse is intermediate between ruminants and dogs. Atelectasis is more likely to develop in dependent lung regions, where alveoli are smallest and airways most easily compressed. Atelectatic lung caused by obstruction has the appearance of other forms of atelectasis. It is sunken relative to aerated lung, homogeneously dark red, and flabby. Evidence of bronchial obstruction by exudate, parasites, aspirated foreign material, granulomas, or tumors can often be seen grossly. Resorption of oxygen from nonventilated lung occurs quickly, but nitrogen is resorbed very slowly. Obstruction of airways by aspirated material or foamy exudate shortly before death does not, therefore, produce atelectasis in animals breathing air.

Microscopically, simple atelectasis appears as slightly congested alveolar walls lying in close apposition with slitlike residual lumina having sharp angular ends (Fig. 6.12E). Atelectasis, which is sometimes seen preceding the development of bronchopneumonia or during the final phase of its resolution, is usually associated with small amounts of edema fluid and excess alveolar macrophages in the alveolar lumina. The edema accompanying large zones of atelectasis is due partly to leakage because of hypoxic damage and partly to the hypoxic vasoconstriction of vessels in the affected region. Reduced surfactant activity also plays a role. Microatelectasis of small groups of alveoli is often an artifact of immersion fixation, and the apparent blending of several alveolar septa is easily mistaken for interstitial pneumonia.

Acquired atelectasis of **compression** type is caused by pleural or intrapulmonary space-occupying lesions. Examples are hydrothorax, hemothorax, exudative pleuritis, and mediastinal and pulmonary tumors. In large animals, the atelectasis caused by pleural effusions often occurs below a sharply demarcated fluid line. Abdominal distension, as in severe ascites and ruminal tympany, may cause partial atelectasis, typically in the cranial regions, where ventilatory movements are most easily compromised by intraabdominal pressure.

What might be termed *hypostatic atelectasis* occurs in the lowermost zone of the lung of the down side in recumbent large animals. This is a hazard of prolonged anesthesia or of weakened animals, particularly if there is a condition causing chest pain. The contributing factors are shallow amplitude of respiration (causing impaired ventilation of dependent lung), gradual loss of surfactant activity, and pooling of secretions in the lower airways.

Sharp-bordered, ribbon-shaped or lobular zones of atelectasis are present to some extent in the cranioventral regions of the lungs of slaughtered sheep. Although many of these are associated with blockage of bronchioles and small bronchi with purulent exudate, some have no detectable blockage of airways, and the reason for the atelectasis is not known.

Massive atelectasis is seen mostly as a sequel to pneumothorax. What appears to be total atelectasis is seen in animals, usually dogs and cats, that die during the course of breathing 80–100% oxygen as part of intensive care. Because of the speed with which the oxygen is resorbed into the tissues, the lungs are usually completely degassed by the time they are examined postmortem. They are uniformly shrunken, dark red, and flabby and ooze blood on cut section.

Emphysema of the Lungs

Emphysema in its widest sense refers to tissue puffed up by air or other gas. In the lung there are two major forms. **Alveolar (vesicular) emphysema** is excessive amounts of air within airspaces of the lung. **Interstitial emphysema** is the presence of air within interlobular, subpleural, and other major interstitial zones of the lung. **Emphysema**, unless otherwise qualified, should only be used for alveolar emphysema. The most widely accepted definition of human emphysema is abnormal enlargement of airspaces distal to the terminal bronchioles, with evidence of loss or destruction of their walls. Some broaden the definition to include abnormal enlargement of airspaces, with or without evidence of destruction. The advantages of requiring evidence of destruction of walls of the airspaces is that it enables more precise recognition of an irreversible, functionally significant lesion. Simple enlargement, or hyperinflation, can be a temporary and relatively insignificant lesion. An example of this is the so-called compensatory emphysema, which occurs along the margin of a consolidated lung (Fig. 6.9C). What appear to be emphysematous lesions in lungs removed postmortem are often not significant antemortem changes but mostly result from failure of the lung to deflate normally (Fig. 6.9A,D). This is caused by air trapping, usually by blockage or spasm of airways. Accurate assessment of emphysema therefore can only be obtained in lungs inflated with fixative to a volume approximating the *in vivo* state. In the following discussion, *emphysema* will refer to abnormal enlargement of airspaces distal to terminal bronchioles with evidence of destruction of their walls.

Several morphologic types of emphysema are recognized in human lungs, according to the distribution of the enlarged air-

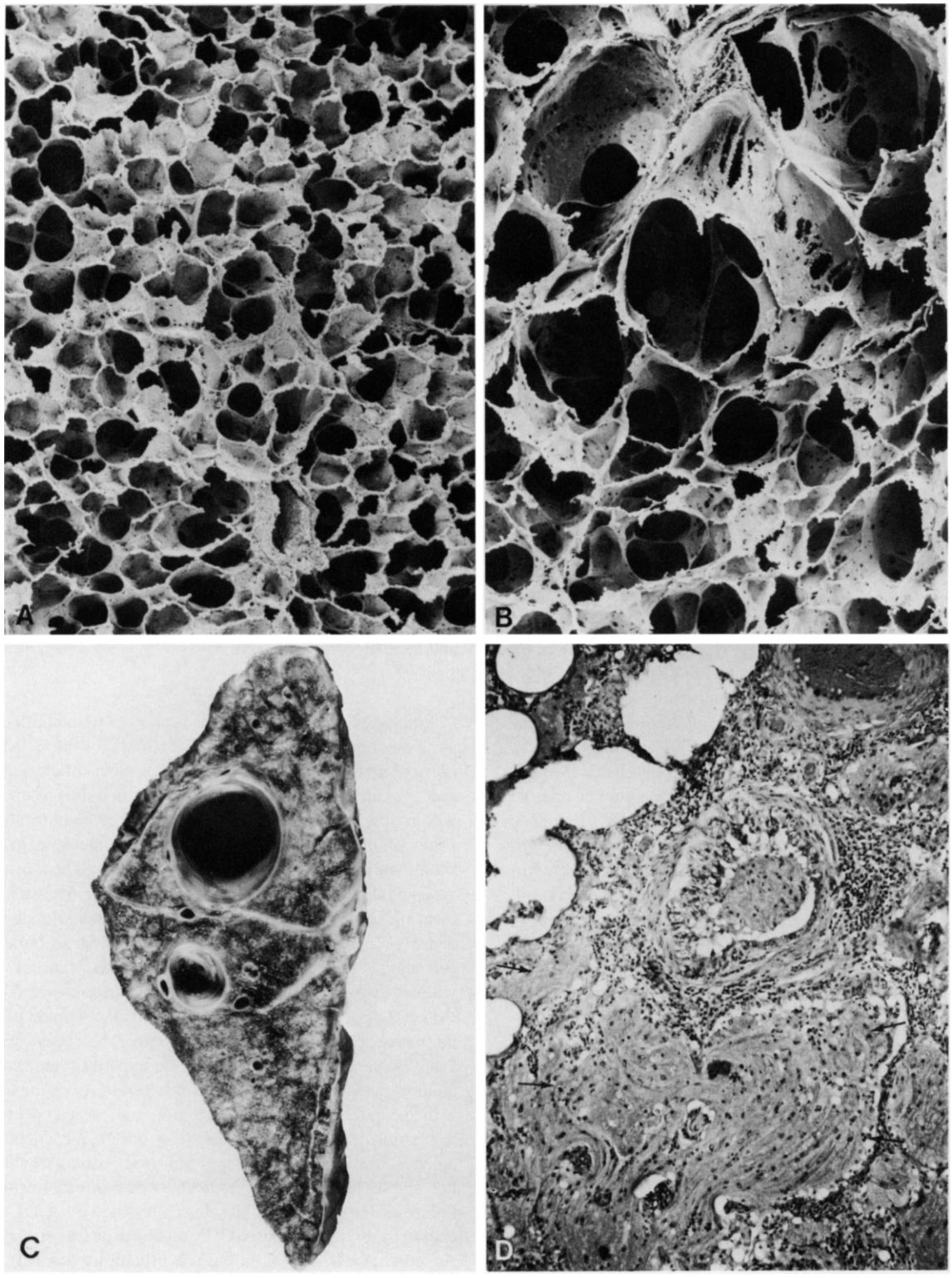

Fig. 6.10. (**A**) Scanning electron micrograph of normal lung. Horse. (**B**) Scanning electron micrograph of emphysematous lung. Same magnification as (**A**). Horse. Note alveolar enlargement and alveolar wall destruction. (**C**) Saccular bronchiectasis in chronic obstructive bronchiolitis. Horse. (**D**) Histologic detail of bronchiolitis in (**C**). Note mucous plugging of bronchiole and mucus reflux into adjacent alveoli (arrows).

spaces. **Centriacinar (centrilobular) emphysema** principally affects respiratory bronchioles and adjacent central portions of the respiratory acini. **Panacinar (panlobular) emphysema** more uniformly involves all portions of acini. An acinus is defined as the terminal unit of lung supplied by a single terminal (nonrespiratory) bronchiole. These two major anatomic types of emphysema in humans also differ with regard to other clinicopathologic features. Less important forms of emphysema are **paraseptal emphysema**, which affects distal alveoli bordering interlobular septa or pleura, and **irregular** or **paracicatricial emphysema**, which results from distortion of airspaces by adjacent contracted scar tissue.

Regardless of distribution, severely emphysematous lung is grossly voluminous, pale, and puffy. When the lesion is diffuse, the lungs fill the thoracic cavity even after the chest has been opened, and they might bear imprints of the ribs. The enlarged airspaces are often visible as small vesicles, and in severe cases coalescence of airspaces can produce large, air-filled bullae one to several centimeters in diameter. Enlargement and coalescence of airspace in inflation-fixed lungs can readily be detected in moderate to severe cases. Scanning electron microscopy, which dramatically reveals the moth-eaten appearance (Fig. 6.10A,B), is best for visualization of early lesions.

With the exception of the chronic bronchiolitis–emphysema complex in the horse, which is to be addressed later, naturally occurring emphysema is rarely of significance in animals. It can be found postmortem in the apices and along the sharp ventral border of the lungs of old animals and is therefore seen mostly in dogs (Fig. 6.11A,B), cats, and horses. Emphysematous bullae also occasionally occur in these regions, and in rare instances rupture to cause fatal pneumothorax. Even where not noted grossly, subpleural airspaces, particularly along cranioventral margins of the lung, are often noted to be larger than more central ones on microscopic examination.

In contrast to animals, emphysema is an extremely important condition in humans, where it frequently coexists with chronic bronchitis and bronchiolitis in causing chronic obstructive pulmonary disease. Most of what is known about the pathogenesis of emphysema is therefore derived from the human condition or, more recently, from experimental animal models. With regard to pathogenetic factors in emphysema, there has been considerable speculation over the years concerning the relative importance of genetic factors, inflammatory alveolar destruction, atrophy of alveolar septa due to ischemic or unknown cause, and mechanical factors leading to widening and rupture of airspaces. Two important findings led to convergence of these ideas. One was the discovery that persons deficient in α_1-antitrypsin (now referred to as α_1-protease inhibitor) have increased incidence and earlier onset of emphysema. The other was that intratracheal injection of papain in hamsters produced an emphysematous lesion. Further developments led to the current basic hypothesis that emphysema is caused by excessive proteolysis in the lung because of protease–antiprotease imbalance. The critical structural component undergoing lysis is elastin, because experimentally the development of emphysema is only correlated well with elastolytic activity and evidence of elastin breakdown. In homozygous α_1-protease-inhibitor deficiency, the emphysema is panacinar in distribution, and the protease–antiprotease imbalance is presumed to be due mainly to the reduction in the antiprotease. In centriacinar emphysema, such as associated with cigarette smoking, there is a slowly smoldering inflammation at the bronchiolar–alveolar junctions, where the emphysema develops. This inflammation is associated with release of elastases by neutrophils and macrophages acting in concert.

Chronic bronchiolitis–emphysema complex in the **horse** has long been associated with the lay terms "heaves" or "broken wind," and more recently with the pathophysiologic term "chronic obstructive pulmonary disease." The term chronic bronchiolitis–emphysema complex is used here because it emphasizes the lesions, which tend to coexist, and the fact that the causes and pathogenesis are both complex and poorly understood. The most consistent finding in horses with clinical signs of chronic obstructive pulmonary disease is a generalized chronic bronchiolitis. Emphysema, as defined by enlargement and destruction of airspaces, is less common (Fig. 6.9E and 6.10B), although in excised lungs the alveoli might appear hyperinflated because of air trapping. Rarely, emphysema is present without significant bronchiolitis. The emphysema is mostly in cranial regions, even when it accompanies a more generalized bronchiolitis.

Constant features of the chronic bronchiolitis are epithelial hyperplasia, goblet-cell metaplasia, and peribronchiolar fibrosis and infiltration by lymphocytes and plasma cells. Lumina of bronchioles are narrowed by accumulation of exudate and the peribronchiolar fibrosis. Mucus is usually a major component of the exudate and sometimes occurs in such large quantities that reflux into adjacent alveolar ducts and alveoli occurs (Fig. 6.10D). The major variable component of the bronchiolitis is the eosinophil. This is sometimes the most obvious feature, both of the intraluminal exudate and within the epithelial and peribronchiolar sites. At other times, relatively few eosinophils are scattered within the mucus and the bronchiolar wall. There often seems to be an inverse relationship between the amount of mucus and the number of eosinophils. There are usually increased numbers of mast cells surrounding the bronchioles. Neutrophils are less common than eosinophils, but sometimes the lesion has the characteristics of a mucopurulent bronchiolitis.

The relative importance of allergy, infection, and toxicity in causing the bronchiolitis is not established; it almost certainly can differ across a series of cases. The frequent presence of eosinophils, circumstantial evidence of clinical exacerbation on exposure to moldy hay, bedding, or stable dust, and limited information from aerosol challenges using suspect fungal antigens all indicate that an allergic response to inhaled allergens is an important mechanism. Infection probably plays some part in a proportion of cases. Experimental evidence that blood-borne toxins, specifically 3-methylindole in the horse, can selectively damage bronchiolar epithelium introduces a further possible set of causes. From the point of view of the characteristic goblet-cell metaplasia and mucus hypersecretion, there is evidence that histamine, prostaglandins, and leukotrienes released during type I allergic responses (anaphylaxis) have a stimulatory effect on mucus secretion. This could explain the association of goblet-

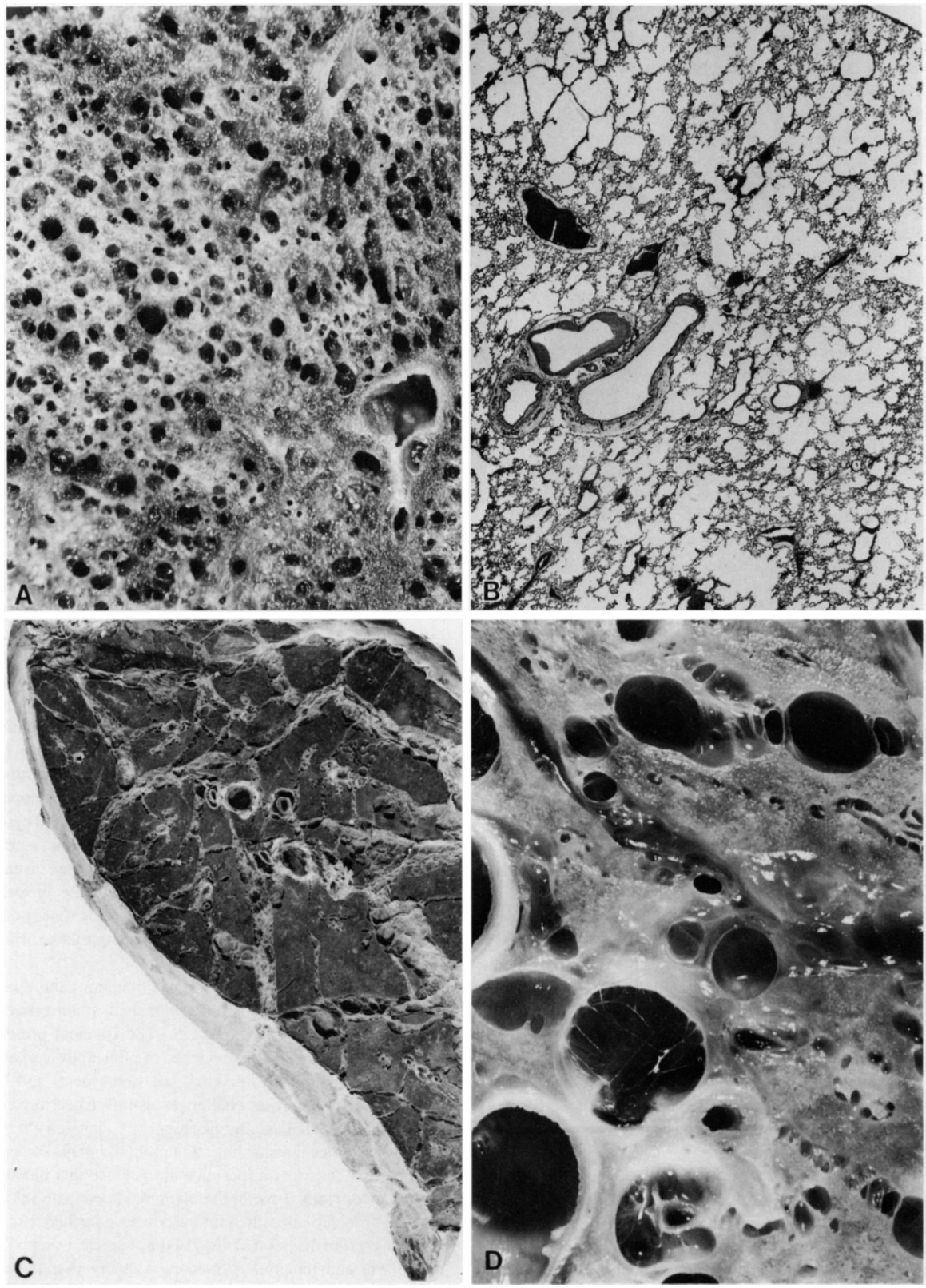

Fig. 6.11. (**A** and **B**) Emphysema. Lung. Dog. (**C** and **D**) Interstitial emphysema secondary to acute interstitial pneumonia. Ox. Note bubbles of air in interstitial tissues and lymphatics of interlobular septa.

cell increases, mucus hypersecretion, eosinophils, and mast cells. As indicated previously, asthma and chronic allergic bronchitis and bronchiolitis are not clearly separable in animals.

Interstitial emphysema is distinguished from alveolar emphysema by the presence of air in the connective tissues and lymphatics of the lung, chiefly the interlobular septa but also beneath the pleura and around vessels and airways (Fig. 6.11C,D). Interstitial emphysema occurs mainly in lungs with well-developed interlobular septa. Lungs of the cow, sheep, and pig have this feature, but only the cow is readily susceptible to the lesion. Any condition causing forced expiratory maneuvers, even agonally, can cause the condition in the cow. It is common in slaughtered cattle. It occurs in most dramatic form as a prominent feature of acute interstitial pneumonia in cattle (acute bovine pulmonary emphysema and edema). A point to be emphasized most strongly is that there is no connection whatsoever between the pathogenesis of alveolar emphysema, as described previously, and interstitial emphysema in the cow. Although there is as yet no proof, it is presumed that air is forced into the complete but delicate interlobular septa because bronchioles are collapsed during forced expiration. For this to occur, there has to be a lack of collateral ventilation and highly uneven deflation among neighboring lobules. In cows surviving sufficient length of time with severe interstitial emphysema, the air can extend along lymphatics to the bronchial and mediastinal lymph nodes, or along fascial planes of the mediastinum to beneath the skin of the back.

Circulatory Disturbances of the Lungs

The lungs are affected by a large variety of circulatory disturbances. They are caused by abnormalities principally involving the pulmonary vessels and heart, or by vascular changes secondary to pulmonary disease. The most important functional consequence is hypoxemia due to mismatching of ventilation and perfusion or shunting of blood through nonventilated regions of lung.

Pulmonary **ischemia** occurs following emphysematous or fibrotic attenuation of alveolar capillaries and can be associated with severe reduction in blood volume. Because of the dual blood supply from pulmonary and bronchial arteries, and the extensive collateral circulation, congestion rather than ischemia is the usual sequel to arterial obstruction. Active **hyperemia** is part of the acute inflammatory response and is a feature of acute pulmonary injury of many types. Pulmonary **congestion** is most commonly caused by left-sided or bilateral cardiac failure. It can also be due to changes in vascular tone causing shifting of blood from the systemic to the pulmonary circulation. Such shifts can be caused by autonomic disturbances, such as those produced by traumatic or other acutely damaging lesions in the hypothalamic region of the brain. The main importance of pulmonary congestion is that it leads to pulmonary edema, as explained below.

Pulmonary Edema

Starling's equation for flow of liquid across a capillary membrane applies in general to pulmonary capillaries; that is, flow is dependent on the permeability characteristics of the vascular wall and the balance of hydrostatic and osmotic pressures between the intravascular and interstitial compartments. The situation is more complicated in the lung, however, because the set of factors involved in the pathogenesis of alveolar edema also includes the permeability of the alveolar epithelium, air pressure and surface tension acting on the alveolar surfaces, and preferential drainage of liquid through the pulmonary interstitium. Uncertainty still exists about the exact magnitude of some of the factors and the routes by which water, solutes, and macromolecular substances cross endothelial and epithelial boundaries.

Despite the low capillary hydrostatic pressure in the pulmonary circulation, there is a slow but steady flow of liquid from the alveolar interstitium into pulmonary lymphatics. Two factors are important in ensuring that alveoli do not become flooded under normal circumstances. One is that alveolar epithelium and its intercellular junctions are much less permeable than endothelial structures and therefore effectively seal off the alveolar lumen. The other is that the interstitial space is at lower pressure than intraalveolar pressure. The interstitial pressure in the loose fascia surrounding vessels and airways where lymphatics are situated becomes increasingly subatmospheric ("negative") toward the pulmonary hilus. The net effect is that liquid is drained from alveolar interstitium to lymphatics and thence to the hilus of the lung. The bronchovascular interstitium and lymphatics therefore constitute a highly compliant sump. Providing the alveolar epithelium remains undamaged, alveolar edema does not occur until the capacity of the sump is overwhelmed. In slowly developing cardiogenic edema, the volume of interstitial liquid can be increased severalfold before alveolar flooding occurs. This explains why the first morphologic evidence of edema due to cardiac insufficiency is excess liquid in interstitium and lymphatics, particularly in the more compliant hilar regions. The increased capillary hydrostatic pressure and higher interstitial pressures caused by gravitational effects in dependent regions of the lungs predispose these sites to edema in large animals.

Physiologic studies indicating different rates of movement of water and molecules of various size ranges and polarity have led to the development of mathematical models postulating the presence of pores of differing size ranges in the air–blood barrier. There is as yet no good correlation between the mathematical pore concept and ultrastructural evidence for sites of the pores. Probably, water and small solutes pass through the endothelium by a transcellular route, and larger solutes by way of intercellular junctions. Macromolecules appear to be largely transported by pinocytotic vesicles. Under some circumstances, water and protein are also actively transported across the alveolar epithelium. It is usually assumed that alveolar edema occurs by passage of edema fluid locally from interstitium to lumen. This is unquestionably the case for edema associated with increased capillary and type I epithelial permeability. It is not necessarily true for edema caused by increased capillary hydrostatic pressure (cardiogenic edema). There is the possibility that in this form of edema, excess fluid accumulates in the perivascular and peribronchiolar interstitium before overflowing into the alveoli through an as yet unidentified pathway close to the bronchiolar–alveolar junction. Although there is experimental evidence supporting this mechanism, its importance in naturally occurring,

clinically significant cardiogenic edema remains to be established.

Pulmonary edema is a frequent complication of many diseases and is therefore one of the most commonly encountered pulmonary abnormalities. Most causes of edema act by increasing capillary hydrostatic pressure or by increasing permeability of the air–blood barrier. Decreased plasma oncotic pressure, such as occurs in hypoalbuminemia, and lymphatic obstruction caused, for instance, by widespread tumor infiltration of lymphatics and pulmonary lymph nodes, are less important.

Edema due to increased capillary hydrostatic pressure is usually the result of increased left atrial pressure in left-sided or bilateral cardiac failure and is commonly referred to as **cardiogenic edema**. The congestion and edema are important parts of the pulmonary complications of congestive heart failure (see the Cardiovascular System, Volume 3). Increased capillary hydrostatic pressure is also the basis for the edema of hypervolemia developing in some cases of excessive fluid transfusion, and the systemic vasoconstriction induced by autonomic discharge following acute brain injury ("**neurogenic**" edema).

Many agents cause pulmonary edema by damaging alveolar type I epithelium and capillary endothelium. The increase in permeability leads to edema of more rapid onset and of higher protein concentration than in cardiogenic forms. Inhaled corrosive gases (including 80–100% oxygen), systemic toxins, anaphylaxis in certain species (e.g., cow and horse), endotoxins, and shocklike states all can cause acute pulmonary edema. As in edema elsewhere, there is no clear dividing line between these "inflammatory" edemas and serous exudates. Many of the toxic or shocklike states causing the edema accompanying acute pulmonary injury may be sufficiently severe to cause acute interstitial pneumonia. They will be considered further under Interstitial Pneumonia. Loss or inhibition of phospholipid-rich surfactant in the alveolar lining layer can enhance edema formation because high surface tension at the air–liquid interface tends to draw fluid into the alveolus. This is probably not of primary importance except in neonatal hyaline membrane disease (respiratory distress syndrome) and perhaps in loss of surfactant activity accompanying prolonged shallow respiration.

Clinically evident pulmonary edema is a sign of serious underlying disturbance. Cardiogenic edema is not fatal if the cardiac insufficiency can be controlled, but pulmonary edema is often the cause of death from sudden cardiac decompensation. Whether other forms of pulmonary edema cause death depends on the severity and speed of onset of the underlying disease process and the edema it produces. Alveolar edema prevents ventilation of flooded alveoli. In the presence of surfactant material, it becomes stable foam by mixing with air in small airways, and the foam further compromises ventilation. Edema fluid can be removed slowly from alveoli if the animal survives, but the details of the mechanisms are not established.

Edematous lungs are wet, heavy, and do not collapse completely when the thorax is opened. Frequently there is excess fluid in the thoracic cavity. Subpleural and interstitial tissues are edematous, and in lungs with well-developed interlobular septa, there is an accentuated pattern because the septa become distended by edema fluid (Fig. 6.12C). Air can be mixed with edema in the bovine lung and distended, tortuous, and beaded lymphatics become visible grossly. Foam is discharged from the nostrils in severe cases, and foam variously mixed with fluid is often present in trachea (Fig. 6.12D) and intrapulmonary airways. Presence of foam indicates edema of at least moderate severity and the presence of alveolar surfactant not inhibited by fibrinogen or other high molecular weight constituents of serum. Fluid oozes from cut surfaces of edematous lungs.

The color of edema fluid and foam depends on the amount of hemorrhage. If absent, the interstitial edema is clear, colorless, to slightly yellow, and the foam is white. Various amounts of hemorrhage cause corresponding degrees of bloodstaining of fluid and foam. The pulmonary parenchyma varies from dark pink to reddish black, according to the amount of congestion or hyperemia. When severe, the distinction between acute pulmonary edema and peracute pneumonia is not possible grossly and can be blurred even on microscopic examination.

Histologically, edema fluid is acidophilic, homogeneous or faintly granular material filling alveoli, except for occasional discrete holes that represent trapped air bubbles. The same material is usually present in interstitial tissue and lymphatics around vessels and airways, and in interlobular septa and subpleural zones in those species where these are well developed. The amount of protein present in cardiogenic edema is small enough, particularly in dogs and cats, that it does not stain well after the leaching that occurs in formalin fixative. It can therefore easily be overlooked. Noting the presence of foam or fluid at gross examination, and distension of interstitial tissue and lymphatics microscopically, then takes on added importance. Coagulant fixatives containing mercury are best for demonstration of protein in edema fluid. Edema due to permeability defects stains more acidophilic than cardiogenic edema, even after formalin fixation, and frequently contains strands or clumps of fibrin. The postmortem seepage of fluid into the alveoli of animals killed by barbiturate euthanasia solutions can easily be mistaken for edema. This artifact usually prevents detection of any antemortem edema unless the latter is revealed by dilatation of interstitial lymphatics.

When the lungs are congested, the capillaries are distended and intraalveolar hemorrhages are common. Alveolar macrophages containing erythrocytes or hemosiderin are present and increase in number with duration of the congestion. These cells are known as "heart failure" cells (Fig. 6.12B). They are not usually a prominent feature of congestive heart failure in animals, however. This is at least partly because of the shorter time animals with severe failure are kept alive compared to humans. A more usual feature accompanying the pulmonary hypertension of chronic cardiogenic edema, as in the dog and cat, is hypertrophy of the muscular walls of small pulmonary vessels and thickening of pulmonary capillary walls by fibrous tissue (Fig. 6.12B). Occasionally in terminal cardiac failure in the dog and cat, there is accumulation of leukocytes in pulmonary capillaries, severe damage to endothelium and alveolar type I epithelium, and filling of alveoli with fibrin-rich fluid. The cause is not established, but the morphologic evidence indicates acute pulmonary injury of shocklike antecedents, described under Interstitial Pneumonia.

Pulmonary Hemorrhage

Hemorrhages occur frequently in the lung and beneath the pleura in the hemorrhagic diatheses, septicemias, and severe

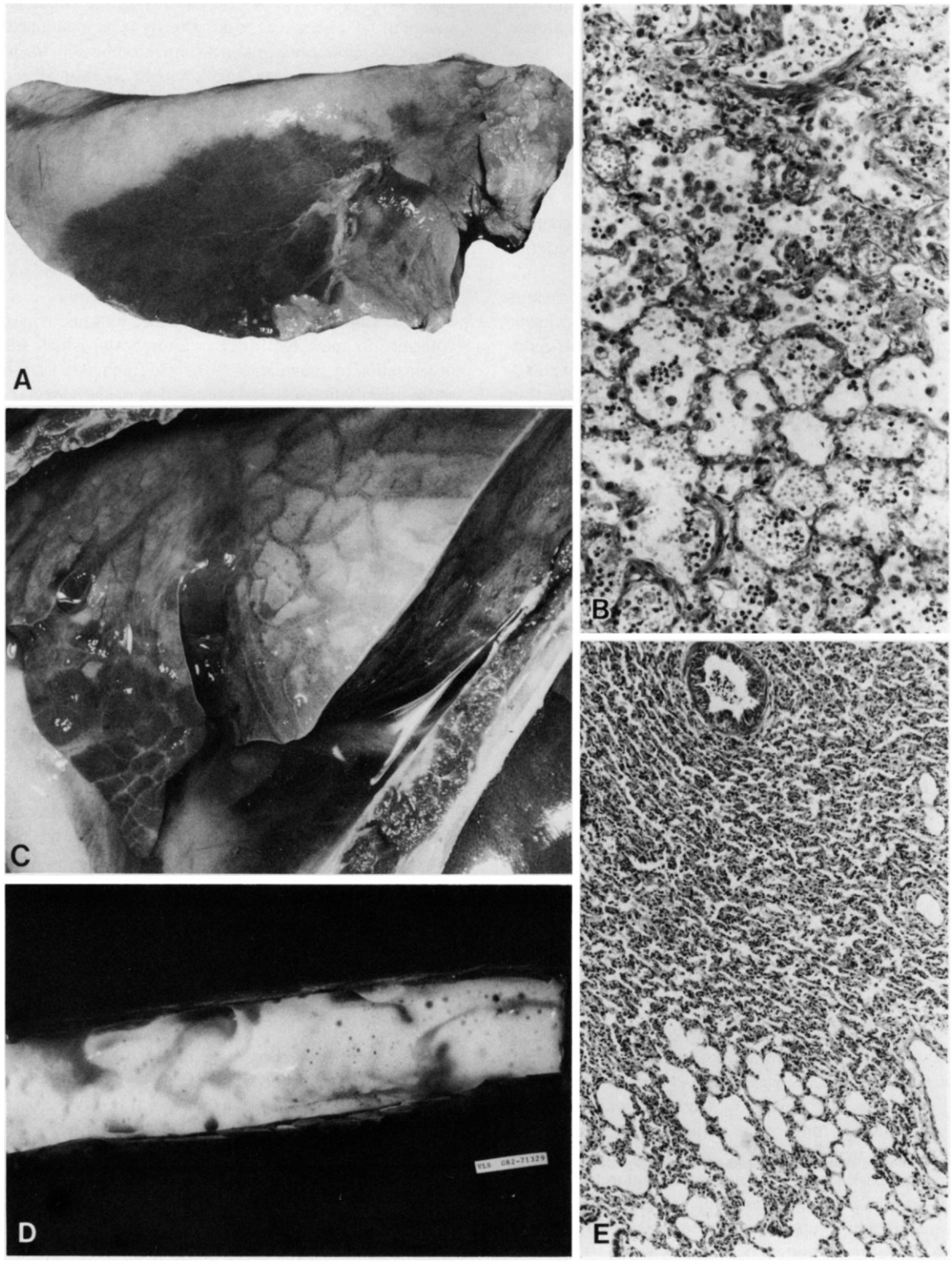

Fig. 6.12. (**A**) Atelectasis of lateral aspect of right caudal lobe. Lamb. (**B**) Chronic pulmonary congestion due to heart failure. Dog. (**C**) Pulmonary edema and hydrothorax. Ox. Interstitial accumulation of fluid accentuates the lobular pattern. (**D**) Tracheal foam due to severe terminal pulmonary edema. Horse. (**E**) Atelectasis. Lamb.

congestion. They can also be caused by infarction, ruptured aneurysms, and trauma. Hemorrhages vary from petechiation to massive filling of large regions by blood. Aspiration of blood is frequent at slaughter. It has a characteristic pattern of multiple, small, bright red foci with feathery or indistinct borders. Massive hemorrhage sufficient to cause hemoptysis or epistaxis is occasionally observed in cattle. It is caused by erosion of a large vessel and rupture into a bronchus. It can be a complication of a bronchogenic abscess but is more often the sequel to septic thromboembolism and arteritis, usually caused by embolism from a septic thrombus in a large hepatic vein or the posterior vena cava.

Exercise-induced pulmonary hemorrahge is the term currently used for hemorrhage occurring in horses during racing or training. It used to be referred to as epistaxis, but with endoscopic examination it has been shown that close to 50% of horses examined soon after racing have detectable hemorrhage, but only 1% or fewer have blood at the nostrils. The frequency of the exercise-induced hemorrhage increases with age and severity of exertion. The exact locations and cause, or more likely, contributory causes, of the hemorrhage are not known. The main debate is whether pulmonary hypertension and mechanical stressing of normal pulmonary tissue during severe exertion is sufficient to cause hemorrhage, or whether preexisting pulmonary lesions are necessary. Since few, if any, lungs of horses are structurally perfect, this is a difficult matter to address. The argument that hypertension alone is unlikely to be the cause because there is no accompanying edema is, however, a forceful one. It appears likely that localized, partial obstruction of small airways or pulmonary scars will be found to play an important part. This is in accord with the hypothesis that distending pressures applied to poorly ventilated regions of lung during inflation of adjacent normal parenchyma are sufficient either to tear lung tissue or produce capillary transmural pressures high enough to cause rupture of the capillary walls. The critical feature is that the transmural pressure of the capillary is the difference between the blood pressure in the capillary and the intraalveolar pressure. Since the intraalveolar pressure becomes reduced well below atmospheric pressure in regions of limited mobility during inspiration, the capillary transmural pressure could become large enough to cause rupture.

Embolism, Thrombosis, and Infarction

The lungs are strategically situated to catch emboli carried in venous blood. In accordance with the general pathology of **embolism**, the outcome will depend on the nature of the embolic material and on the features of the pulmonary circulation. Because the lung is supplied by both pulmonary and bronchial arteries and has extensive collateral channels, infarction usually does not follow embolism and thrombosis unless the pulmonary circulation is already compromised. It is possible, for instance, to find a major pulmonary artery occluded by large, pale, friable thromboembolic material without gross abnormality of the pulmonary parenchyma. Bacterial emboli are associated with fulminating septicemias and cause acute pulmonary edema or interstitial pneumonia. Septic emboli arising from infected thrombi cause thromboembolism, arteritis, usually multiple abscessation, and possibly more extensive chronic suppurative pneumonia. The tendency for aneurysms to occur and be a source of fatal hemorrhage has already been mentioned. In the cow, septic emboli arise mainly from thrombosis of the posterior vena cava due to local spread of a hepatic abscess. They can also originate in uterine and pelvic veins. They arise mainly from mesenteric veins in horses; they can originate from vegetative endocarditis in any species.

Tumor emboli vary in number from a few widely separated foci to extensive showering of capillaries and larger vessels with neoplastic cells. The latter is more common with highly invasive anaplastic carcinomas, such as sometimes occur with mammary carcinomas in bitches. An unusual form of embolism occurs where carcinoma cells lodge and proliferate within vessels, producing multiple discrete foci surrounded by smooth muscle and collagen. In some foci there is thrombosis, which stimulates organization by granulation tissue and frequently leads to death of the neoplastic cells and obliteration of the vascular lumen. Malignant cells usually proliferate more in perivascular lymphatics than in the vessels themselves.

Fat embolism is only occasionally important in animals. The fat can originate from bone marrow at sites of fracture and from severe hepatic lipidosis. The emboli lodge in alveolar capillaries and produce sausage-shaped distensions that are empty in routine paraffin sections. Megakaryocytes are frequently found in pulmonary capillaries, particularly in dogs. A small number of megakaryocytes derived from bone marrow are present in circulating blood and lodge in the lungs, where they continue to produce platelets. This is a normal occurrence, but might be accentuated when there is compensatory extramedullary hematopoiesis.

Pulmonary thrombosis can be triggered, as elsewhere, when there is hypercoagulability, stasis of blood, or vascular endothelial damage. Embolism and endarteritis as causes have been mentioned already. There is an association between pulmonary thrombosis and renal amyloidosis in dogs. The endarteritis caused by *Dirofilaria immitis* or *Angiostrongylus vasorum* is also a cause of thrombosis in dogs; less commonly thrombosis is secondary to ulceration of intimal atherosclerotic plaques. Disseminated intravascular coagulation in septicemic, toxic, and advanced neoplastic states is also an important cause of pulmonary thrombosis (see the Cardiovascular System, Volume 3). Pulmonary thrombosis of unexplained cause is found occasionally in any species.

Pulmonary infarction is an unlikely event unless the pulmonary circulation is already compromised. Thrombosis of large vessels is more likely to lead to congestion, edema, and atelectasis of the affected regions. Most infarctions occur in lungs that have generalized passive congestion. Thrombi occurring in conditions associated with general circulatory collapse, such as disseminated intravascular coagulation, are therefore particularly likely to cause infarction.

All recent infarcts are hemorrhagic. They occur most frequently in the caudal lobes. They usually extend to the pleura and are particularly prone to affect the sharp costophrenic borders of the lung. At the costophrenic margin they are wedge-shaped, with the broad base toward the hilus of the lung. When they involve only one pleural surface they are cone-shaped, with the base at the pleura. The shape is difficult to appreciate when

they are small because their margins blend laterally with adjacent congested parenchyma. Infarcted areas bulge on the pleural aspect and are red-blue to black. They are firm, and the overlying pleura becomes roughened, opaque, and covered by blood-stained exudate if the infarct is more than a few hours old. When the infarct is large, the occluded vessel can usually be detected at or near its apex. Histologically, an early infarct has extensive hemorrhage against a background of necrotic parenchyma. If the animal survives, there is lysis of red cells, and a border of neutrophils and macrophages appears within 1 or 2 days. Organization by peripheral encroachment of granulation tissue occurs subsequently and eventually results in scar formation. The sequelae to septic infarction consist of the more severe changes described previously for septic thromboembolism.

Pulmonary Hypertension

Pulmonary hypertension can be initiated by high-pressure flow of blood from the right heart, such as occurs in congenital ventricular septal defect, or by increased resistance in the pulmonary vascular system. The increased resistance to flow may be the result of left-sided heart failure, luminal narrowing of vessels by arteriosclerotic changes, or hypoxic vasoconstriction, as seen in high-altitude disease of cattle (see the Cardiovascular System, Volume 3). Regardless of initial cause, there occurs a vicious cycle of hypertension, causing arteriosclerosis, which in turn leads to more hypertension.

Any subacute or chronic lesion causing narrowing or obliteration of pulmonary vessels can cause pulmonary hypertension. Thromboembolic situations mentioned previously may therefore produce hypertension and "cor pulmonale." Widespread fibrosis in chronic interstitial pneumonias can also cause pulmonary hypertension by occluding small vessels. Chronic bronchitis and bronchiolitis stimulate muscular hypertrophy in the walls of small arteries, and this too can result in cor pulmonale. The effects of hypertension alone are mainly in the small muscular arteries, where there is proliferation of myointimal and medial smooth muscle cells, and in arterioles, which develop prominent muscle coats by proliferation of pericytes. Severe hypertension causes endothelial degeneration and intimal and adventitial fibroplasia. Eventually, leakage of plasma protein into the degenerating muscular and collagenous components of the wall can produce fibrinoid necrosis.

Inflammation of the Lungs

Pneumonia is the usual term for inflammation of the lungs involving alveolar parenchyma. There has been a tendency to use the term **pneumonia** for the more acute and exudative inflammations and **pneumonitis** for the more chronic, proliferative lesions. Since proliferative components are mostly within or become incorporated into the interstitium of the lung, pneumonitis and chronic interstitial pneumonia are largely synonymous terms. Separate and sometimes conflicting use of pneumonia and pneumonitis has more potential for confusion than clarification, however, so the term pneumonia will be in general use for pulmonary inflammation throughout this chapter. Salient morphologic and pathogenetic features of the various types of pneumonia are conveyed by additional descriptive terms.

Alveolar Response to Injury

Alveoli are completely lined by a mosaic of two types of epithelial cells. The **type I cell (membranous pneumonocyte)** has a flattened nucleus and thin cytoplasmic extensions covering large areas of alveolar wall. Its thin cytoplasmic layer provides a minimal barrier for diffusion of oxygen, but the presence of few organelles and high surface-to-volume ratio makes the cell's plasma membrane, and hence the cell itself, extremely vulnerable to injury. The **type II cell (granular** or **secretory pneumonocyte)**, in contrast, is more numerous than the type I cell, but because of its compactness it covers far less of the alveolar wall. It has a cuboidal shape, surface microvilli, a rich complement of organelles, and the specific osmiophilic lamellar inclusions that are the sites of surfactant storage prior to its release into the alveoli. In addition to its secretory activity, the type II cell's other main function is that of epithelial renewal and repair, as described below. A third cell type, the brush cell, has been found rarely in the alveoli of various species of animals. Its function is unknown.

The type I epithelial cell, having little reparative capacity and no regenerative capability, is highly susceptible to acute injury. The opposite is true for the type II cell. The usual pattern of alveolar response is for necrosis and sloughing of type I cells, accompanied by the acute exudative phase of inflammation. Providing the severity of the process is not sufficient to cause necrosis of type II cells and other components of the alveolar septa, the type II cells begin to proliferate within 24 hr and eventually completely line the previously denuded alveolar wall. Histologically, small clusters of alveolar cells can be detected 2 or 3 days after loss of type I cells, and by 6 days there can be complete lining of alveoli by cuboidal type II cells. This is the appearance commonly referred to as epithelialization. During the active proliferation of type II cells, it is common to see small syncytial clusters and individual atypical cells with increased nuclear and cytoplasmic volumes, abnormal shape, and increased basophilia. Atypical cells are particularly likely to be seen in canine lungs. This active proliferation is sometimes erroneously interpreted as a neoplastic process. The complete lining of alveoli by type II cells, which is a common response to injury, has also misleadingly been referred to as "adenomatosis." Proliferation of type II cells marks the shift from the exudative to the proliferative stage of pneumonia and is usually accompanied by an alveolar exudate increasingly composed of macrophages and other mononuclear cells. Resolution of the epithelial lesion, once inflammation has subsided and provided there has not been scarring of the alveolar wall, is accomplished by transformation of type II cells into type I epithelium. An important aspect of the proliferative response of type II cells is their increased susceptibility to the toxic effects of 60 to 100% oxygen during this phase.

The character of alveolar exudate depends on its cause. In general, it changes with time from serous fluid (inflammatory edema) containing various quantities of fibrin, through a neutrophil phase that predominates in most bacterial infections, to an accumulation mostly consisting of alveolar macrophages.

Both the dominant features and the rate of change vary according to cause of the inflammation. The quantity of fibrin in alveolar exudate is an index of the amount of damage to the alveolar–capillary membrane because it reveals leakage of its precursor fibrinogen. Fibrin forms, together with other serum constituents and cell debris, the hyaline membranes found in conditions involving severe damage to the alveolar wall. The amount of fibrin is an important determinant of fibrosis. When alveolar epithelium is denuded, fibrinous membranes or plugs are infiltrated by fibroblast precursors from the alveolar wall, and collagen-containing fibrous tissue can be detected as early as 7 days after initial fibrinous exudation. There is usually an associated defect in fibrinolytic systems in such instances. The prominence of fibrin in acute alveolar injury in cattle is related to the high fibrinogen content of bovine blood, a low level of plasminogen (precursor of plasmin, a major fibrinolytic enzyme), and a high concentration of a plasmin inhibitor in pulmonary tissue.

Alveolar macrophages are derived mainly from the interstitial compartment in normal lungs, but in inflammatory conditions they come mostly from blood monocytes. Local proliferation can also play a role as evidenced by the occasional finding of mitotic figures in macrophages within alveolar lumina. Once inflammation supervenes, they take their place in an intricate interplay of amplifying and inhibitory processes. Among the more important are chemotactic attraction and stimulation of neutrophils and lymphocytes, increased phagocytic and bactericidal activity in the activated state, release of lysosomal hydrolases, and enhancement of fibrinolysis by activation of plasminogen. They are also involved in pulmonary fibrosis by the secretion, under certain conditions, of fibroblast-stimulating factors. Acute damage to alveolar septa is also accompanied by the usual vascular components of acute inflammation, with accumulation of inflammatory fluid and leukocytes in the interstitium as well as in the alveoli. The inflammatory fluid in the interstitium, as in edema, is mostly accommodated in the compliant fascia and lymphatics surrounding airways and vessels, and in interlobular septa and subpleural tissue. It is most pronounced in those species having more complete interlobular septa, particularly ruminants and pigs. Cellular accumulation in alveolar walls can become pronounced in acute processes involving cell-mediated immune mechanisms, such as influenza virus infection, but they are more often associated with chronic conditions.

Chronic inflammation of the alveolar septa is the major feature of chronic interstitial pneumonias and will be discussed more fully under Interstitial Pneumonia. Chronic bronchopneumonia, on the other hand, is much more likely to lead to destruction of alveolar walls and abscessation because of persistent suppuration caused by pyogenic bacteria. An aspect of the response of alveolar type II cells to **chronic injury** deserving of mention is their potential for undergoing metaplasia to squamous, ciliated or fetal-type, glycogen-containing cells. One of the most important general features to emerge concerning the response of pulmonary epithelial cells to both acute and chronic injury is the extent to which transdifferentiation (metaplasia of one cell type to another) can occur in airways and alveoli. Persistent irritation or disruption of the normal epithelial interaction with basement membrane and alveolar stroma, as in scarring, leads to persistence of atypical alveolar type II cells and the possibility that they might occasionally give rise to bronchioloalveolar tumors. This seems to be the case with "scar cancers" of humans and some bronchioloalveolar tumors of dogs and rodents.

Anatomic Patterns of Pneumonia

The pulmonary inflammatory response varies according to the nature of the causative agents, their distribution (particularly the route by which they reach the lung), and their persistence. Pneumonia can be classified on a temporal basis as acute, subacute, or chronic, on an etiologic basis by major categories of causative agent, or according to morphologic features. Morphologically, there are two approaches. One approach is to classify according to the type of inflammation. Here there are two main subcategories: **exudative** pneumonias, in which the emphasis is on filling of alveoli by exudate with predominant **catarrhal, fibrinous, suppurative, hemorrhagic**, or **necrotizing** characteristics; and **proliferative** pneumonias, in which the emphasis is on proliferation of alveolar type II cells, fibroblasts, macrophages, and possibly additional elements. The second, and more useful, morphologic approach is to classify pneumonias according to initial site of involvement and the pattern of spread of the lesion. On this basis, most pneumonias fall into three main categories: **bronchopneumonia, lobar pneumonia**, and **interstitial pneumonia**. The importance of this form of classification lies in its providing the most important clues regarding pathogenesis and possible cause of pneumonia.

There is often a good link between the various classifications. For example, acute pneumonias are commonly of infectious cause, exudative in nature, and of bronchopneumonic pattern. Chronic pneumonias are of highly varied cause, proliferative in nature, and often of interstitial pattern. Other correlations, and exceptions to these generalizations, will become evident.

Bronchopneumonia

The hallmark of bronchopneumonia is the originating of inflammation in the bronchiolar–alveolar junction, as the name implies. This is correlated with an aerogenous portal of entry of the causative agents, involvement usually of cranioventral regions of the lungs, and a patchy or variegated gross appearance. The irregular lobular involvement is reflected in the older term **lobular pneumonia**.

The defenses of the healthy lung are remarkably effective. Whether or not inflammation results from the constant bombardment of the lung by inhaled irritants depends on the balance between the intensity of the insult and the effectiveness of local defense mechanisms at each structural level of airways and parenchyma. The bronchiolar–alveolar junctions are the loci of greatest vulnerability to damage by many types of inhaled particles and vapors, including droplet nuclei carrying infectious agents. There are three main reasons for the vulnerability of these regions. First, they are the major site of deposition of small particles (0.5–3.0 μm in diameter) capable of reaching deep lung. Second, the epithelium of bronchioles is probably susceptible to damage because it is not protected by the mucous blanket of larger airways nor an effective alveolar macrophage system. Third, the cellular (mostly macrophage) and noncellular mate-

rial cleared from large volumes of alveolar parenchyma has to pass through the narrow lumen of its parent bronchiole, an easily plugged "funnel" or "bottleneck," especially where lack of collateral ventilation hampers expulsion of material.

Epidemiologic and experimental evidence indicates that the important infectious bronchopneumonias of animals usually develop only when the balance is tipped in favor of disease by an increase in number of pathogenic microorganisms reaching vulnerable bronchiolar–alveolar regions of the lung or when pulmonary defenses are impaired. In most situations, both of these circumstances are present. Increased exposure to pathogenic microorganisms is particularly likely to occur in crowding of animals collected from a variety of sources. This is often associated with lack of specific immunity to the organisms involved. Lack of nonspecific defense mechanisms occurs in congenital or acquired immunodeficiency states or is caused by a variety of factors impairing one or both of the mucociliary blanket and alveolar macrophage defensive systems. Dehydration, extreme chilling, viral infection, inhalation of toxic gases and particles, certain anesthetics, and ciliary abnormalities inhibit mucociliary clearance and can predispose to bacterial colonization. Functions of alveolar macrophages are impaired by severe chilling, starvation, viral infection, toxic gases, metabolic disorders such as uremia and acidosis, and immunosuppressants such as corticosteroids. Chronic diseases of heart or lungs also reduce pulmonary defensive capability.

Various combinations of the factors just mentioned exist in circumstances recognized as predisposing to a high risk of bronchopneumonia. The same holds true for the more aggressive lobar pneumonias. Most outbreaks are in young, intensively managed animals, especially soon after stresses associated with shipping. Mixing of animals with different microbial floras and levels of acquired immunity is often involved as well. Sporadic cases of bronchopneumonia in individual animals are likely to be associated with interactive predisposing causes such as debility, immunodeficiency, preexisting cardiopulmonary disease, and prolonged anesthesia or recumbency of illness. Aspiration of foreign material can cause bronchopneumonia but because of its severity more commonly has the distribution of a lobar pneumonia.

The characteristic cranioventral distribution of infectious bronchopneumonias in animals indicates that in these regions the balance between insult and defense is most precarious. This is supported by the fact that pneumonia caused by inhalation of acutely irritant particles or gases does not have a cranioventral distribution. All the reasons for the cranioventral involvement have not been determined. It is reasonable to hypothesize that there is increased deposition of infectious particles in these regions, that defenses are more easily compromised, or both. There is slightly increased deposition of particles in cranial regions. This is believed to be due to the shorter and more abruptly branching airways. Gravitational influences impeding clearance of cranioventral regions, and possibly leading to pooling or reflux of secretions, are probably more important contributory factors. The smaller size of ventral airspaces and their greater vulnerability to collapse or blockage may also be a factor.

Bacteria are the main causes of clinically significant bronchopneumonia, most commonly after pulmonary defenses have been lowered by viral infection, severe stress, or other predisposing factors. Many species of bacteria are involved, the particular set of agents varying with species and sometimes geographic location. In sheep and cattle, *Pasteurella* spp. and *Corynebacterium pyogenes* are common. In swine, *P. multocida, Haemophilus* spp., *C. pyogenes, Bordetella bronchiseptica,* and *Salmonella choleraesuis* are often involved. In horses, the chief offenders are *Streptococcus* spp. and *C. equi.* In dogs, *B. bronchiseptica, Klebsiella* spp., *Streptococcus* spp., *Staphylococcus* spp., and *Escherichia coli* are important. In cats, in which the disease is less common, *P. multocida* and a variety of other Gram-negative organisms are found. Bacteria generally tend to cause a suppurative pneumonia. Exceptions, such as the fulminating fibrinonecrotic pneumonias that can be caused by *Pasteurella* and *Haemophilus,* will be addressed later in the chapter. The involvement of viruses, mycoplasmas, and chlamydiae will also be considered further under specific pneumonias, as will their roles in causing the enzootic pneumonias of cattle, sheep, and swine.

The typical gross appearance of bronchopneumonia is of irregular consolidation in cranioventral regions. The cranial and middle lobes are most often affected in those species having well-defined lobation. Consolidated lung varies from dark red, through gray-pink, to more gray, depending on the age and nature of the process. Palpable firmness (consolidation) of the tissue is the single most important gross criterion of pneumonia. The extent to which there is a lobular or sublobular mosaic of consolidated, atelectatic, congested, and more normal lung tissue depends partly on the severity and rate of spread of the pneumonia and partly on the degree of septation. It is most common in relatively slow-spreading bronchopneumonias of ruminants and swine, which have well-developed septation. (Fig. 6.13C). The more uniform and rapidly spreading the pneumonia, the more homogeneous and extensive the consolidation. Even where complete lobes become involved, however, the bronchopneumonic pattern can often be detected on careful gross examination by the presence of multiple, small, evenly spaced, gray-white, bulging foci separated by narrow, deep red zones. The bulging pale foci denote areas of exudation centered on bronchioles, and the deeper red zones represent more congested, edematous, and atelectatic alveolar parenchyma in peripheral acinar regions. This gross pattern is more usual in bronchopneumonia of dogs and cats, which have rudimentary interlobular septa, and in the "enzootic" bronchopneumonias of ruminants and swine (Fig. 6.36A). The pleura overlying mild to moderately inflamed pulmonary parenchyma usually has its normal smooth, glistening sheen. Where the inflammatory process is severe, however, it extends to produce reddening, roughening, and superficial accumulation of yellow-gray fibrinous or fibrinopurulent exudate, indicating pleuritis (Fig. 6.28A). The cut surface of affected lung reflects the variability of involvement seen on the pleural surface. In catarrhal or suppurative bronchopneumonias, the section of consolidated lobules is moist; mucopurulent or purulent material can be expressed from small airways and can be seen in fluid or foamy state in the large airways. Frank abscesses can be present in severe suppurative inflammation (Fig. 6.14C). The cut surface of fibrinous inflammation, in contrast, has a dull, dryish appearance (Fig. 6.16B).

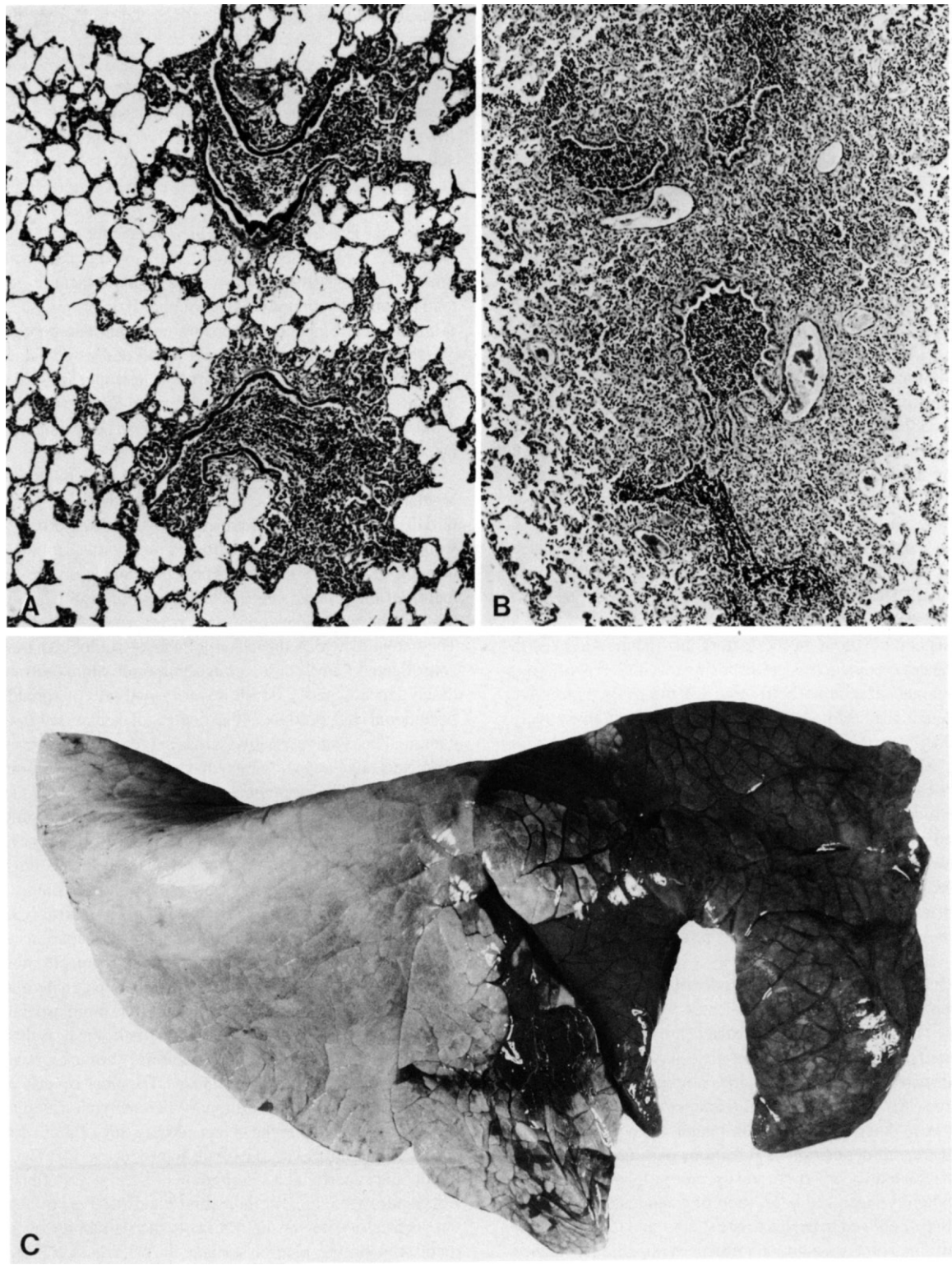

Fig. 6.13. Bronchopneumonia. (**A**) Initial lesion of bronchopneumonia at bronchioloalveolar junction. Dog. (**B**) Later stage of bronchopneumonia. Dog. (**C**) Acute bronchopneumonia. Calf. Lobulation is emphasized in dark areas of consolidation by interlobular edema. Note focal pattern within affected lobules.

Histologically, the nidus of inflammation in bronchopneumonia is in the bronchiolar–alveolar junctions (Fig. 6.13A,B). In early bronchopneumonia, bronchioles and immediately adjacent alveoli are filled with neutrophils, and sometimes an admixture of various amounts of cell debris, mucus, fibrin, and macrophages. The bronchiolar epithelium varies from necrotic to hyperplastic, depending on the nature and pathogenicity of causative agents, and there is a mild acute inflammation in the peribronchiolar connective tissue. Bronchi often show similar but usually less severe changes. Necrotizing (Fig. 6.14A) or proliferative lesions indicating the possibility of prior viral infection may be present (see specific viral infections), but pathognomonic inclusion bodies can be found only occasionally in clinical material. Adenovirus inclusion bodies are the exception, and these inclusion bodies can be found readily in infection caused by this virus. Care must be taken not to interpret the apparently thickened epithelium of collapsed airways as evidence of epithelial hyperplasia. Alveoli peripheral to the severely inflamed bronchiolar regions are partially atelectatic and contain various amounts of edema or serofibrinous exudate, erythrocytes, macrophages, and a sprinkling of leukocytes. Vessels in the early acute stage are engorged and are responsible for the predominant red color of the lung noted macroscopically. Edematous or serofibrinous fluid can be found in interstitial sites but is not an important feature of this early mild to moderate form of catarrhal bronchopneumonia.

The spread of infection after its initial foothold in the bronchiolar–alveolar regions is mostly by airways, both proximally through bronchioles and bronchi and distally through alveolar ducts and alveoli within a respiratory acinus (Fig. 6.14B). The rate and extent of spread depends mainly on the balance between virulence of the causative agent and host defense. Rapid bacterial proliferation leads to severe suppurative pneumonias if pyogens (e.g., streptococci) are involved, and fibrinous through hemorrhagic and necrotizing pneumonias if highly toxigenic bacteria such as *Pasteurella haemolytica* and *Haemophilus pleuropneumoniae* are the cause. In the latter instances, the pneumonia is likely to take on the lobar characteristics; spread of infection through edematous interlobular septa can become important in these cases.

The time sequence of inflammatory events obviously varies with the severity and speed of onset, which in turn depend on the balance between the virulence of the agent and host defense. The red stage of consolidation is present for only 2 or 3 days in a typical bacterial pneumonia. The increasing amount of leukocytic or fibrinous exudation reduces capillary volume and results in an gray appearance within 5 to 7 days. Proliferation of alveolar type II cells can also occur during this period unless there is severe purulent or fibrinonecrotic inflammation. Variations on this theme will be dealt with under the headings of the special types of pneumonia or under those on the specific etiologic agents.

Just as the rate at which bronchopneumonia reaches maturity and the type of inflammation attained vary greatly, so the rate and degree of resolution vary. A catarrhal or mild purulent bronchopneumonia can begin to resolve within 7 to 10 days and the lung return to normal within 3 to 4 weeks. Once the agent has been overcome by the cellular and humoral defenses, macrophages become the predominant cell. They phagocytose debris and aid in lysis of fibrin. The macrophages and extracellular debris are mostly cleared through the airways with the aid of coughing and collateral ventilation (if present). Treatment facilitates this process. This milder inflammation is not associated with significant damage to alveolar basement membranes or capillaries, and resolution can occur without recognizable trace. In these cases, there is a stage as the inflammation begins to wane when the alveoli are lined by alveolar type II cells. Transformation to type I cells occurs as the inflammatory exudate is cleared. A transitory stage of partial atelectasis is usually present between clearance of exudate and regeneration of the pulmonary parenchyma. If there is a residual bronchiolitis or bronchitis, however, and especially if the lack of collateral ventilation impedes expulsion of exudate from small airways, the atelectasis, bronchiolitis, and bronchitis persist. This probably explains why resolution of bronchopneumonia is frequently incomplete in ruminants and swine, and why cattle in particular are prone to develop chronic suppurative bronchiectasis and bronchopneumonia.

Severe bronchopneumonia causes death mostly by a combination of hypoxemia and toxemia. Complete resolution can occur but requires integrity of alveolar basement membranes, readily cleared exudate, and rapid killing of the infectious agent. Necrosis of alveolar septa, intractable exudate, or persistence of the agent therefore preclude complete resolution, even if the animal survives. Often all three conditions occur together. The resulting complications range from healing with scarring, through atelectasis, chronic bronchopneumonia, and bronchiectasis, to abscessation or necrosis with sequestration.

Atelectasis is both a prelude and a sequel to bronchopneumonia. As a complication of bronchopneumonia it follows resolution of parenchymal inflammation with persistence of obstructive bronchiolitis and bronchitis. Obstructive bronchiolitis can occur in three ways. In the simplest form there is a chronic bronchiolitis, with persistent plugging of the lumen by exudate. The second form occurs when there is necrosis of bronchiolar epithelium, presence of fibrin-rich exudate, and development of plugs or polypoid projections of granulation tissue (Fig. 6.15A). These can cause complete obliteration of the bronchiole if epithelial necrosis is total. An alternative finding is that reepithelialization of incompletely obliterating granulation tissue can occur to produce multiple, small, rudimentary lumina analagous to a recanalized thrombus (Fig. 6.15B). These bronchiolar lesions are referred to as bronchiolitis fibrosa obliterans. The third form of bronchiolar obstruction is by compression or constriction of peribronchiolar origin. This can be caused by constricting fibrous tissue, in which case it denotes a preceding severe acute inflammation and usually occurs with obliterative bronchiolitis, or by lymphoid proliferations, such as occur in *Mycoplasma* pneumonias.

Bronchopneumonia may become chronic. This is seen most commonly in cattle and, to a lesser extent, sheep and swine. It is reasonable to associate the tendency for poor resolution of bronchopneumonia with complete lobular septation and lack of collateral ventilation. The extent to which this is true is not known. The pathogenicity of the bacteria involved also undoubtedly plays some part. The lesions of chronic bronchopneumonia are

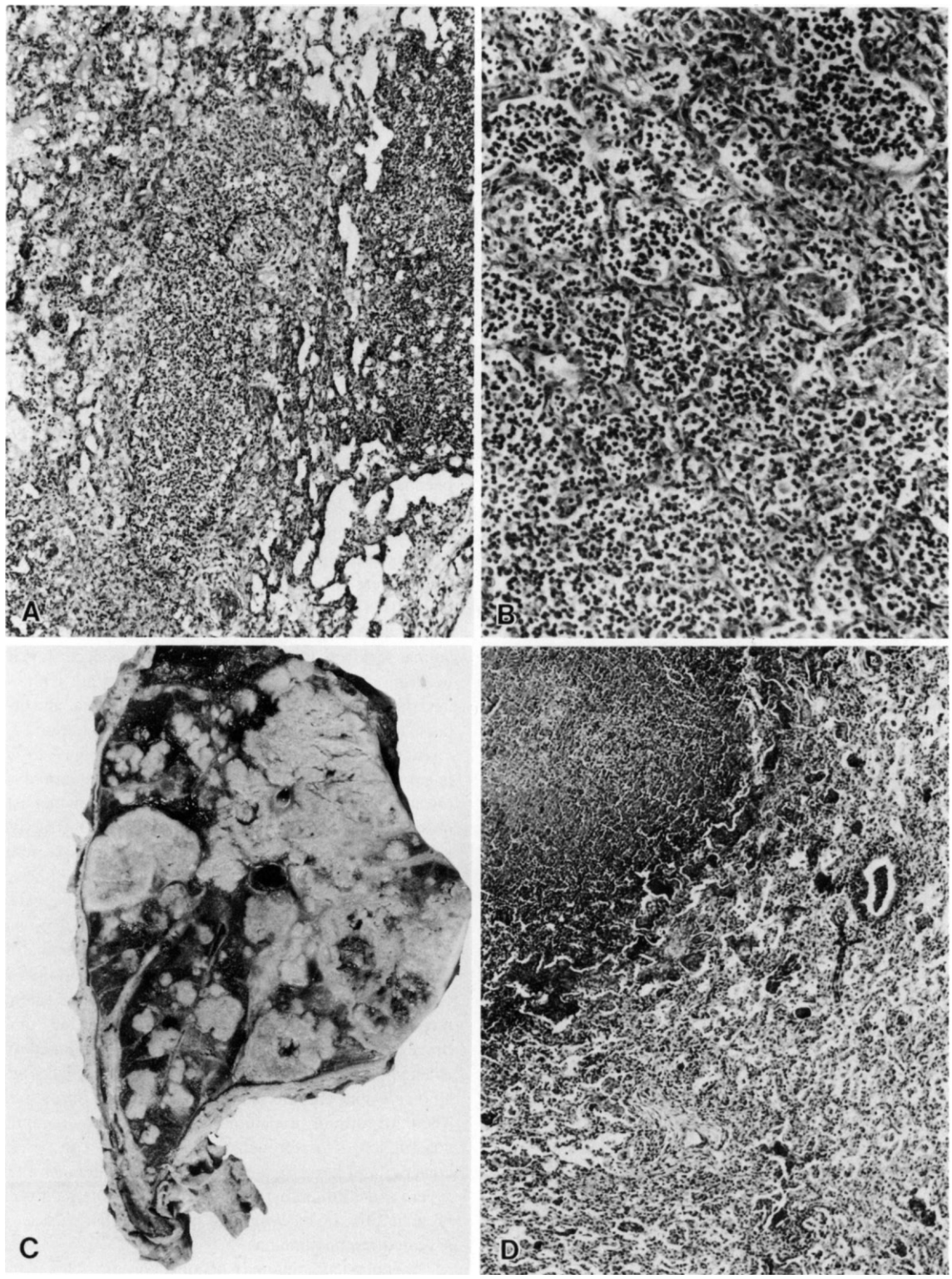

Fig. 6.14. (**A**) Acute bronchopneumonia based on necrotizing bronchiolitis caused by adenovirus. Foal. (**B**) Subacute suppurative bronchopneumonia. Pig. (**C**) Suppurative bronchopneumonia with abscessation and fibrinous pleuritis caused by streptococci. Horse. (**D**) Periphery of abscess in (**C**).

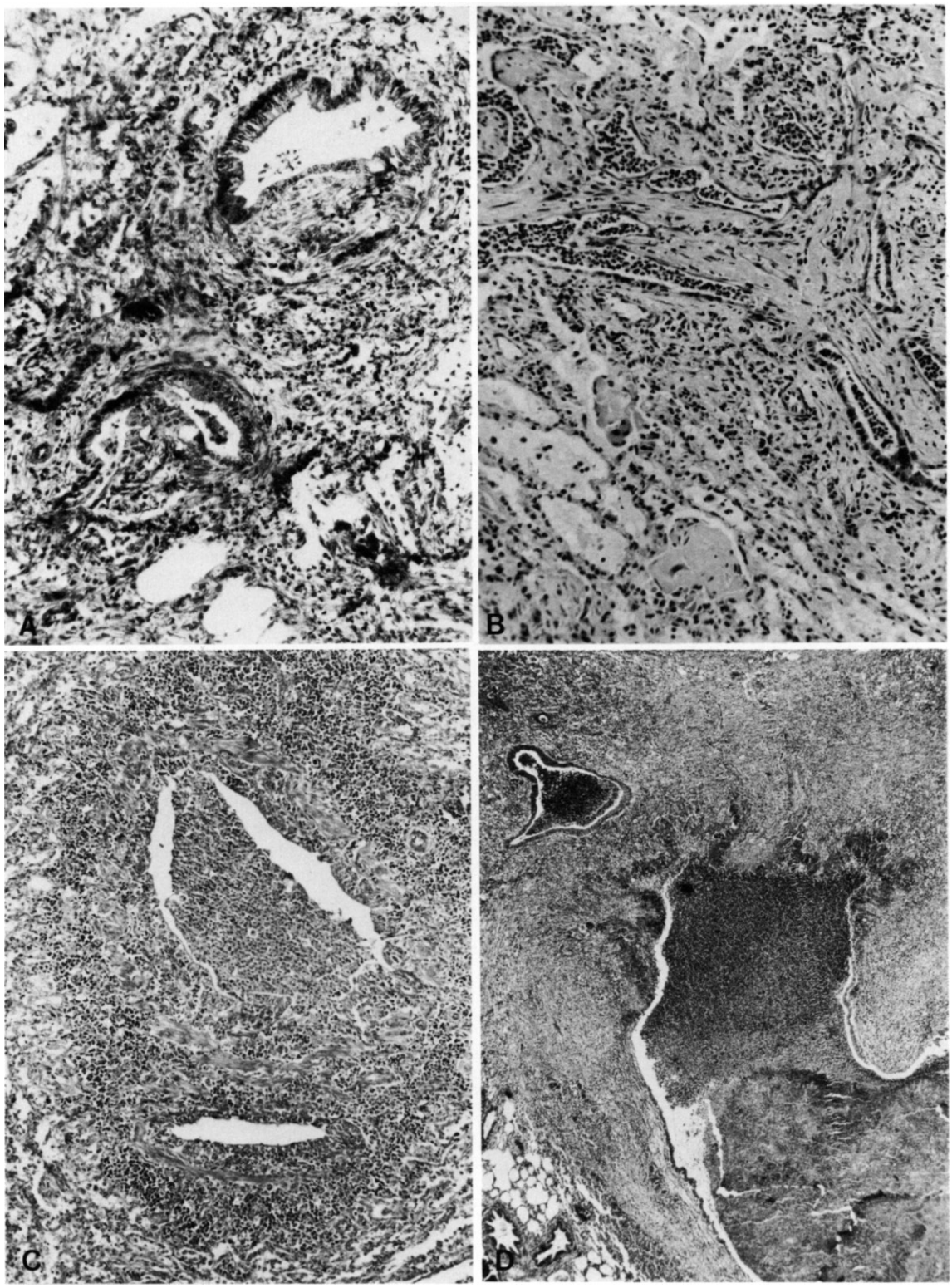

Fig. 6.15. (**A** and **B**) Patterns of obliterative bronchiolitis (bronchiolitis fibrosa obliterans). Calf. (**C** and **D**) Development of bronchogenic abscess in chronic suppurative bronchopneumonia. Sheep.

those of chronic suppuration with fibrosis. The suppurative lesions in ruminants and swine tend to involve mostly the airways (Fig. 6.15C,D), and in cattle especially, there is bronchiectasis and abscessation (see Bronchiectasis). Alveolar parenchyma is mainly atelectatic and fibrotic. Severe acute exudative pneumonias cause prominent widening of interlobular, subpleural, and peribronchial zones by accumulation of serofibrinous or fibrinopurulent exudate in the loose fascia and lymphatics. This becomes organized and visible as broad seams of moist fibrous tissue. It is mostly seen as an aftermath of lobar pneumonias in ruminants and swine and will be mentioned again under Lobar Pneumonia. It also affects the subpleural region and irregular interlobular septa of the horse as a sequel to severe exudative pneumonia. Organization of fibrin-containing pleural exudate often produces pleural adhesions.

Severe suppuration and abscessation of pulmonary parenchyma can be caused by pyogenic organisms. Suppuration is common in dogs when the pneumonia is caused by *Bordetella bronchiseptica*. The exudate has a grayish yellow, slimy quality. Bronchopneumonia in the horse commonly causes abscessation because the organisms are usually pyogenic streptococci (Fig. 6.14C,D). The suppuration usually begins deep in the consolidated areas. The alveolar tissues undergo necrosis in volumes large enough to be visible as many gray nodules, around each of which is a narrow hyperemic zone. These nodules coalesce, and most of the lobe might be converted into a fragile mass of dull gray detritus. Some of this can liquefy and be discharged into a bronchus so that a cavity remains. With *C. pyogenes*, typical abscesses occur in sheep, cattle, and swine. The abscesses might develop first in the alveolar tissue, or they might be associated with chronic suppurative bronchitis, bronchiolitis, and bronchiectasis. The abscesses can be numerous and very large. The reaction usually extends to the pleura to produce dense, adhesive pleuritis, or abscesses may fistulate to produce pleural empyema. Metastatic abscessation can occur in other organs. Erosion of a blood vessel might lead to severe fatal pulmonary hemorrhage. A variety of other bacteria can occasionally cause abscesses, the set of possible agents varying according to species of animal affected.

Lobar Pneumonia

Lobar pneumonia, as the term implies, is one in which entire pulmonary lobes, or major portions of lobes, are diffusely and uniformly consolidated. Pathogenetically, lobar pneumonias are rapidly confluent, fulminating bronchopneumonias in which gross evidence of bronchiolar orientation and spread is not evident. Since lobar pneumonias have this close relationship to bronchopneumonias, it is not surprising that separation between the two is difficult, often arbitrary, and prone to cause confusion. This is further complicated by the fact that even though large areas of uniform consolidation might be seen on gross examination, microscopic evidence often reveals orientation of the inflammation about bronchioles, and hence basically a bronchopneumonic pathogenesis. The term *lobar* is entrenched, however, and is useful to indicate a fulminating or highly aggressive bronchopneumonia. To use this term with as little confusion as possible, it is best applied as a gross designation of extensive pneumonic consolidation in which the parenchymal involvement appears uniform (Fig. 6.16A). Exceptions to the uniform appearance are the necrotic foci that can develop, as in pneumonic pasteurellosis of cattle or contagious bovine pleuropneumonia (Fig. 6.16B,C), and the exudative distension of interlobular septa in ruminants and swine.

Since lobar pneumonia can be regarded as a fulminating bronchopneumonia, it follows that similar pathogenetic factors are involved. Lobar pneumonia is the result of overwhelming spread of the inflammatory process and is usually caused by the action of a virulent organism in an animal with severely impaired pulmonary defense. The prototype in animals is lobar pneumonia caused by *Pasteurella haemolytica* in cattle that have recently been stressed by transportation and that frequently have a predisposing respiratory viral infection. A strong correlation exists between a fulminating pulmonary inflammation and production of a profuse fibrinous exudate, as exemplified by the condition in cattle. Therefore, a tendency has arisen to use the terms lobar and fibrinous interchangeably. This is unwarranted, however, because although there is considerable overlap, not all lobar pneumonias are fibrinous and vice versa. Other than overwhelming *Pasteurella* infection, *Haemophilus* species sometimes cause lobar pneumonia in ruminants and swine. *Mycoplasma mycoides* is an etiologic agent in cattle and goats. Lobar pneumonia can occasionally be caused by *P. multocida* in cats. In horses, massive proliferation of streptococci or, occasionally, *Corynebacterium equi* can be responsible. Another cause in all species is the aspiration of foreign fluids or gastric contents.

Infectious lobar pneumonias diffusely affect large portions of cranioventral lung (Fig. 6.16A). Those caused by aspiration affect portions of lung lowermost at the time of aspiration, and therefore in a recumbent animal might involve the lateral zones of the caudal lobe of one side or the dorsal zones of both sides. As would be expected from their peracute or acute nature, lobar pneumonias are hemorrhagic, fibrinous, fibrinopurulent or necrotizing, and sometimes gangrenous (usually caused by aspiration). The gross appearance therefore varies with age of the lesion from reddish black through deep red, to reddish brown or gray. In all but the peracute hemorrhagic cases, there is usually roughening of the overlying pleura and a coating of fibrin. Two additional features are often seen in ruminants, swine, and to a lesser extent, horses. One is the prominent distension of interlobular septa by serofibrinous exudate, and the other is the development of irregular, discrete zones of necrosis with swollen pale borders (Fig. 6.16B). The cut surface in early cases exudes bloody fluid and, later, in the fibrinous lobar pneumonias, becomes grayish brown, finely granular, dry, and friable. Necrotic areas might become crumbly and cavitated.

The intial stage of red consolidation (hepatization) is characterized by hyperemia of alveolar capillaries and flooding of alveoli with serofibrinous exudate admixed with various amounts of hemorrhage, small numbers of alveolar macrophages, and neutrophils (Fig. 6.17A). The amount of fibrin precipitated in alveoli as dense, pink, fibrillar or more homogeneous clumps rapidly increases. It is accompanied by neutrophils, which predominate in some regions. The capillaries are compressed by

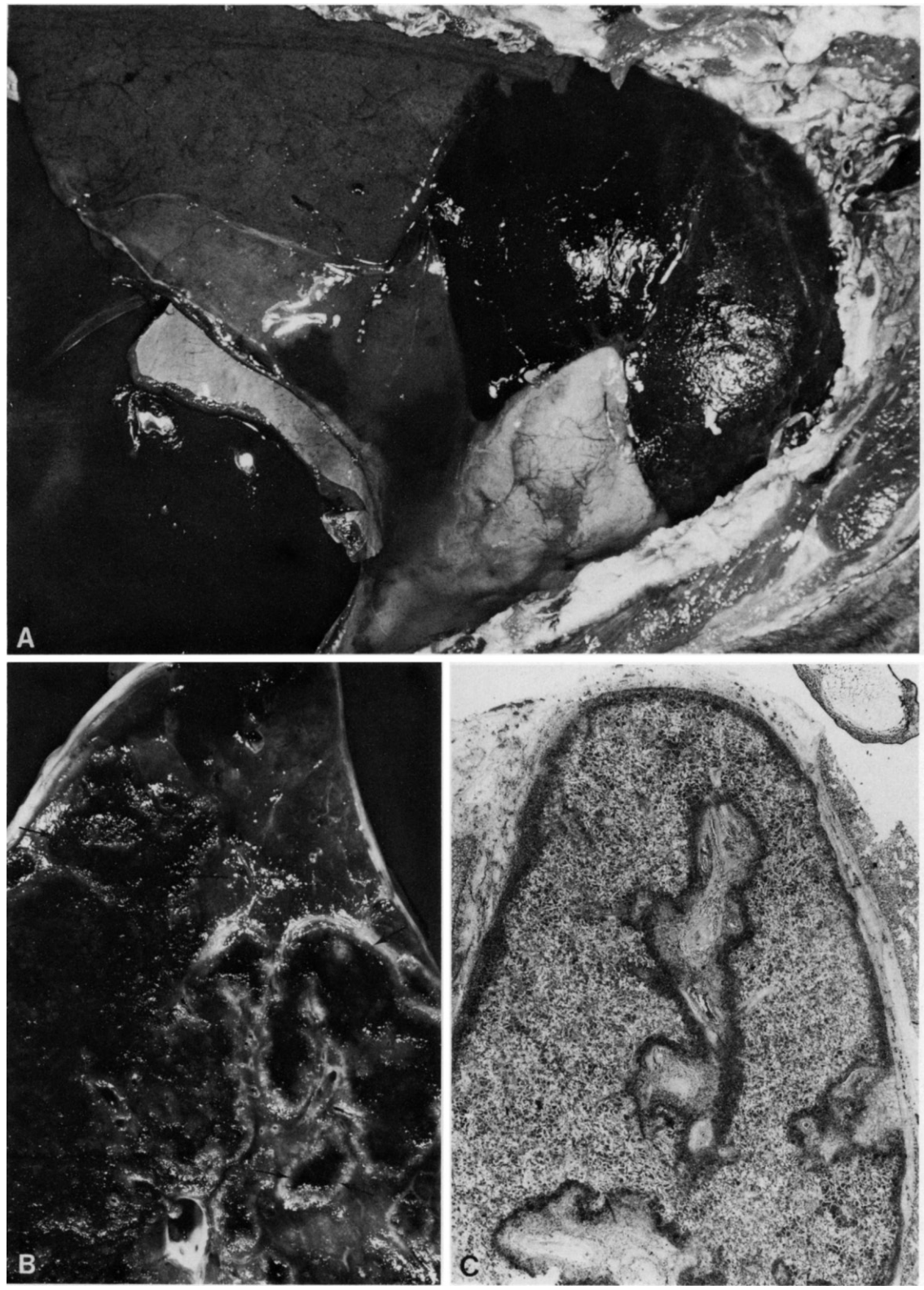

Fig. 6.16. (**A**) Acute, fibrinous, lobar pneumonia and serofibrinous pleuritis of pneumonic pasteurellosis. Lamb. (**B**) Areas of necrosis (arrows) in lobar pneumonia. Cow. (**C**) Necrotic lobule in contagious bovine pleuropneumonia. Connective tissues of septa and surrounding bronchioles and blood vessels are viable and separated from necrotic parenchyma by zones of leukocytes.

pressure of exudate, and many become occluded by thrombi. This is the stage of red-brown or gray consolidation, depending on the degree of ischemia and extent of hemorrhage and lysis of extravasated red cells. During this time, the interlobular septa (when present) and perivascular, peribronchial, and subpleural sheaths become widely distended by serofibrinous or fibrinous exudate within the loose connective tissue, and especially in the lymphatics. The latter often become greatly distended by fibrin thrombi (Fig. 6.17B). Small airways in affected regions are filled either with a purulent exudate or more fibrinous exudate similar to that filling alveoli. Arteries and especially veins passing through severely inflamed regions can develop vasculitis by local extension across their walls, and occasionally thrombi are formed. There is a tendency for leukocytic aggregates in alveoli to become condensed or spindle-shaped (oat-shaped) under the influence of toxins from Gram-negative bacteria such as *Pasteurella* (Fig. 6.17C) and to the development of necrotic foci (Fig. 6.17D). A feature common to most lobar pneumonias is massive proliferation of bacteria, which can be readily detected even in sections stained by hematoxylin and eosin. They are especially prominent within developing necrotic foci and tend to be concentrated close to the leukocytic boundary zones.

This description of lobar pneumonia has drawn heavily on the fibrinous lobar pneumonias, best exemplified by pneumonic pasteurellosis in cattle. However, the features of predominantly fibrinous pneumonia in a series of affected cattle often present a mix of lobar and bronchopneumonic patterns. This should be expected as the difference between lobar and bronchopneumonia is mostly a matter of degree.

The **complications** of lobar pneumonia are obviously more frequent and serious than those of the less severe bronchopneumonias. Death is frequent, usually with accompanying pleuritis, and sometimes with pericarditis. If the animal survives, resolution without some degree of scarring is well nigh impossible. Extensive organization by granulation tissue leading to fleshy fibrous tissue (carnification) is likely, as is chronic abscessation. Peritonitis may arise by hematogenous spread of the infection or direct extension from the pleura through the diaphragmatic lymphatics. Additional complications include toxemic degeneration of parenchymatous organs, endocarditis, fibrinous polyarthritis, meningitis, and hemolytic icterus. A late complication might be empyema of the pleural cavity, following rupture of an abscess peripherally. Erosion and rupture of an abscess into a bronchus can cause a rapid onset of purulent bronchopneumonia, or hemorrhage if an artery is affected.

Interstitial Pneumonia

Diffuse or patchy damage to alveolar septa is the essential feature of interstitial pneumonia. It can be caused by many forms of pulmonary injury. The lack of a completely satisfactory morphologic designation embracing the variants of interstitial pulmonary disease has led to a confusing array of terms. Two terms are most commonly used: **interstitial pneumonia** and **diffuse fibrosing alveolitis**. The former is preferred because it more appropriately covers the necessarily broad range of morphologic, etiologic, and pathogenetic aspects. Other relevant terms, with emphasis on more chronic diseases, are chronic diffuse infiltrative lung disease and diffuse interstitial pulmonary fibrosis.

Interstitial pneumonias have been thought of as chronic inflammatory conditions in which there is predominantly a proliferative response involving alveolar walls and supporting stroma. However, increasing attention has been drawn to a variety of circumstances in which there is acute diffuse damage of alveolar walls. This causes an early intraalveolar exudative phase, which can be quickly followed by proliferative and fibrotic responses. The acute pulmonary injury can be caused by, or associated with, a wide variety of conditions, such as severe viral pneumonia, chemical lung injury, acute pancreatitis, shock, and septicemia. Often there is superimposed toxicity caused by the high concentrations of oxygen used therapeutically. In human medicine, a variety of terms were used that referred to the various circumstances under which acute damage occurred, for instance, "shock lung," "respirator lung," and "traumatic wet lung." Clinically, however, the common feature is acute respiratory distress, and so the collective term "adult respiratory distress syndrome" has come into increasing usage. The syndrome was originally called acute respiratory distress syndrome in adults, to distinguish it from neonatal respiratory distress syndrome in human infants. For veterinary medicine, it is more apt to refer to acute respiratory distress syndrome because there is no established need to distinguish between the adult form and the less often encountered neonatal form. The clinician evaluating a patient with acute respiratory distress and the pathologist interpreting an acute interstitial pneumonia (alveolitis) are both dealing with acute pulmonary injury and therefore need to consider the same set of differential diagnoses.

Most of the literature on interstitial pneumonia and related entities refers to human diseases or experimental animal models of human diseases. There has been preoccupation in veterinary medicine with the common and economically important infectious lobar and bronchopneumonias. Interstitial pneumonias do comprise a significant proportion of veterinary diseases, however, particularly those of infectious, toxic, or allergic cause.

Pathogenetically, interstitial pneumonia results from diffuse or patchy damage to alveolar septa. The absence of obvious orientation of the lesions around small airways differentiates interstitial pneumonia from bronchopneumonia. Grossly, the lesions are distributed widely throughout the lungs, often with greater involvement of dorsocaudal regions (Figs. 6.18A,C and 6.20A,B). This pattern is in sharp contrast to the cranioventral distribution of affected regions in the common infectious lobar and bronchopneumonias.

The alveolar septal damage is caused by a blood-borne insult in most instances. This accounts for the widespread or random distribution of lesions within affected acini, as opposed to the centriacinar localization of damage caused by most inhaled irritants. There are two notable exceptions to this generalization. One is that certain blood-borne chemicals exert their toxic effect only after they are metabolized to reactive intermediates by microsomal enzyme systems, particularly monooxygenases (mixed-function oxidases). Depending on the chemical and the species of animal affected, damage can be limited to nonciliated

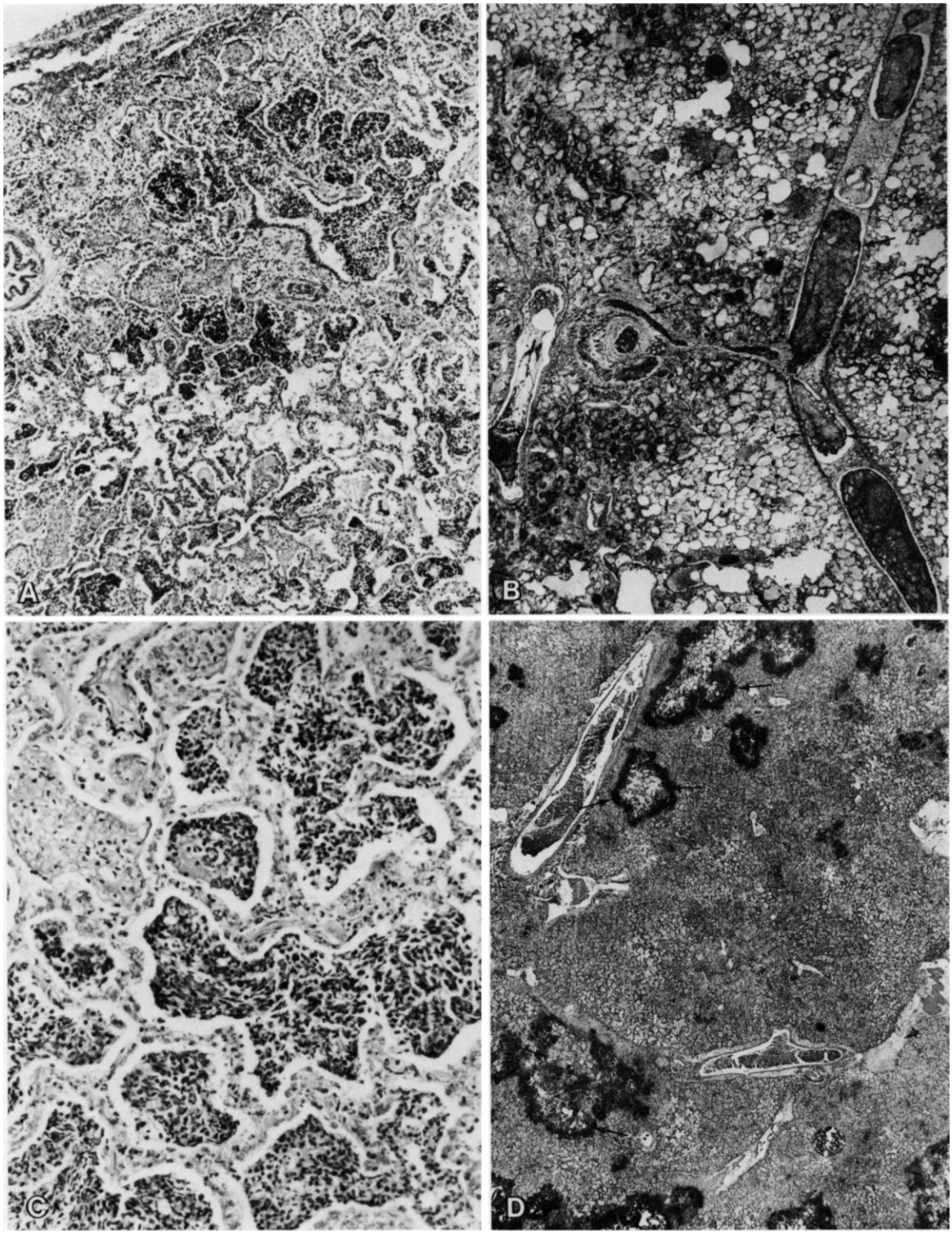

Fig. 6.17. (**A**) Acute lobar pneumonia with bronchiolar orientation. Ox. Alveoli filled with fibrin and leukocytes. (**B**) Acute fibrinous lobar pneumonia. Ox. Fibrin clots in septal and perivascular lymphatics (arrows). (**C**) Streaming, oat-shaped leukocytes. Pneumonic pasteurellosis. Ox. (**D**) Necrotic foci (arrows) in acute fibrinous pneumonia of pasteurellosis. Pig. Necrotic tissue surrounded by dark-staining zones of leukocytes.

bronchiolar epithelial (Clara) cells, sparing the pulmonary alveolar parenchyma, even though the parent chemical is in the blood. The effect of 3-methylindole in the horse is the best known example in domestic animals. The second exception to the generalization is that inhalation of irritants that become widely distributed in the lung causes sufficiently diffuse damage to present as interstitial pneumonia. Severe, acute diffuse damage is associated with inhalation of high concentrations of toxic gases or fumes because there is not an appreciable concentration gradient of the toxic substance between small airways and distal portions of the pulmonary acini. Inhalation of 100% oxygen is the best example. The pneumoconioses, on the other hand, are chronic progressive lesions caused by inhalation of inorganic dusts. Here, although there might initially be a greater tendency for the granulomatous or fibrotic foci to be located close to terminal airways, this often becomes obscured by the time the lesions progress to the point of causing clinical pulmonary dysfunction. There is no precise information explaining why interstitial pneumonias, whether of hematogenous or aerogenous origin, tend to be more severe in dorsocaudal regions of the lung.

Histologically, the interstitial pneumonias as defined here can range from acute to chronic. Although the term implies that the inflammatory response takes place predominantly within the alveolar walls and the interstitial tissues of the lung, interstitial pneumonias of acute onset have an initial phase in which the most obvious feature is exudate into alveolar lumina. The interstitial components soon come to predominate, however, if the animal survives. The apparent paradox that some interstitial pneumonias can have an acute exudative phase is the principal reason for the alternative term "diffuse alveolitis." It was also the reason for the initial designation of acute interstitial pneumonia in cattle as "atypical" interstitial pneumonia.

As in other organs, the morphologic responses following damage by a large variety of agents have many features in common. The lesions therefore frequently lack etiologic specificity. Acute injury, whether of toxic, metabolic, or infectious origin, causes damage principally to alveolar–capillary endothelial cells and type I epithelial cells. Whether the endothelium or epithelium is damaged first depends on the nature, portal of entry, intensity of the insult, and to some extent, the species affected. Usually, however, the alveolar type I cells eventually suffer most damage because of their poor reparative capacity and inability to regenerate. During this acute phase, the most dramatic features of the lesion are flooding of alveoli with serofibrinous exudate, and congestion and edema of alveolar walls. Fibrin, other serum proteins, and cell debris frequently condense to form hyaline membranes lining airspaces, or aggregates plugging their lumina (Fig. 6.18B). There is usually some admixture of leukocytes and erythrocytes in the alveolar exudate, and an initial accumulation of mixed leukocytes within the alveolar interstitium that tends to become mostly mononuclear cells if the inflammation persists. Replacement of necrotic type I epithelium takes place on intact basement membranes by proliferation of type II epithelium, as described under Alveolar Response to Injury. The resulting lining of alveoli by cuboidal cells (epithelialization) is a common feature of subacute to chronic interstitial pneumonias (Figs. 6.18D and 6.19A–C). Once the inflammation has subsided, and if there is not severe scarring of the alveolar wall, complete resolution can be effected by differentiation of type II cells into type I epithelium.

Proliferation of alveolar type II cells marks the shift from the exudative to the proliferative stage of interstitial pneumonia. Onset of fibrosis is a critical feature of the proliferative phase because it is irreversible, at least in its mature form. Fibroblast proliferation can occur as early as 72 hr after severe alveolar damage. It is most evident when alveoli are filled with fibrinous exudate. Immature or "pro-" fibroblasts can appear within alveoli in the lungs by 3 days after severe fibrinous exudation, such as caused by paraquat toxicity. Mature fibroblasts can be seen by 4 days, and collagen fibers can be detected histologically by 5 to 7 days. Interstitial fibrosis also occurs in such instances, though not to such a dramatic degree. It occurs more rapidly when there is considerable interstitial edema or serofibrinous exudation. Both intra- and interalveolar (interstitial) fibrosis, therefore, are sequelae to severe exudative lesions and can be a striking feature by 14 days after onset. If the animal survives and residual scarring is present, it is no longer possible to determine the relative contributions of intra- and interalveolar fibrosis (Fig. 6.19C). Chronic, smoldering lesions in which there are prominent interstitial cellular accumulations, mostly of mononuclear cells, cause fibrosis within the alveolar walls.

The rate of fibrosis is therefore heavily dependent on the intensity of inflammation. Studies on mechanisms underlying fibrosis focus on two major areas. One is the biochemistry of collagen; the other the nature of factors influencing collagen synthesis and degradation. A relative increase of type I collagen (dense fibers of high tensile strength) over type III (reticulin-type fibers) occurs wherever active fibroplasia can be recognized histologically or where there is extensive scarring. There might be an early, transient increase in type III collagen in conditions where the rate of accumulation of fibrous tissue is slow.

Factors influencing the balance of synthesis and degradation of collagen are extremely complex. Potentially any of the cellular and biochemical alterations in an inflammatory site might have an influence, and presumably most of them do. Biochemical mediators, disruptions between cells and their normal extracellular matrices, and cell-to-cell interactions are presumed to be involved.

If the animal survives, most acute interstitial pneumonias of animals resolve with various amounts of residual scarring (Fig. 6.19C). Chronic, progressive inflammation is not ofen encountered in animals. The chronic inflammation, where a specific cause can be identified, is usually associated with persistence of, or repeated exposure to, the causative agent (e.g., dusts, drugs, or infectious agents). Often, immunologic processes are known or suspected to be at least partly involved in the pathogenetic mechanisms. In those instances where a specific cause cannot be identified, immunologic mechanisms are also often incriminated.

The central features of chronic interstitial pneumonia are intraalveolar accumulation of various mononuclear cells (mostly macrophages), proliferation and persistence of alveolar type II cells, and interstitial thickening by accumulations of lymphoid cells and fibrous tissue. Granulomatous interstitial pneumonia is

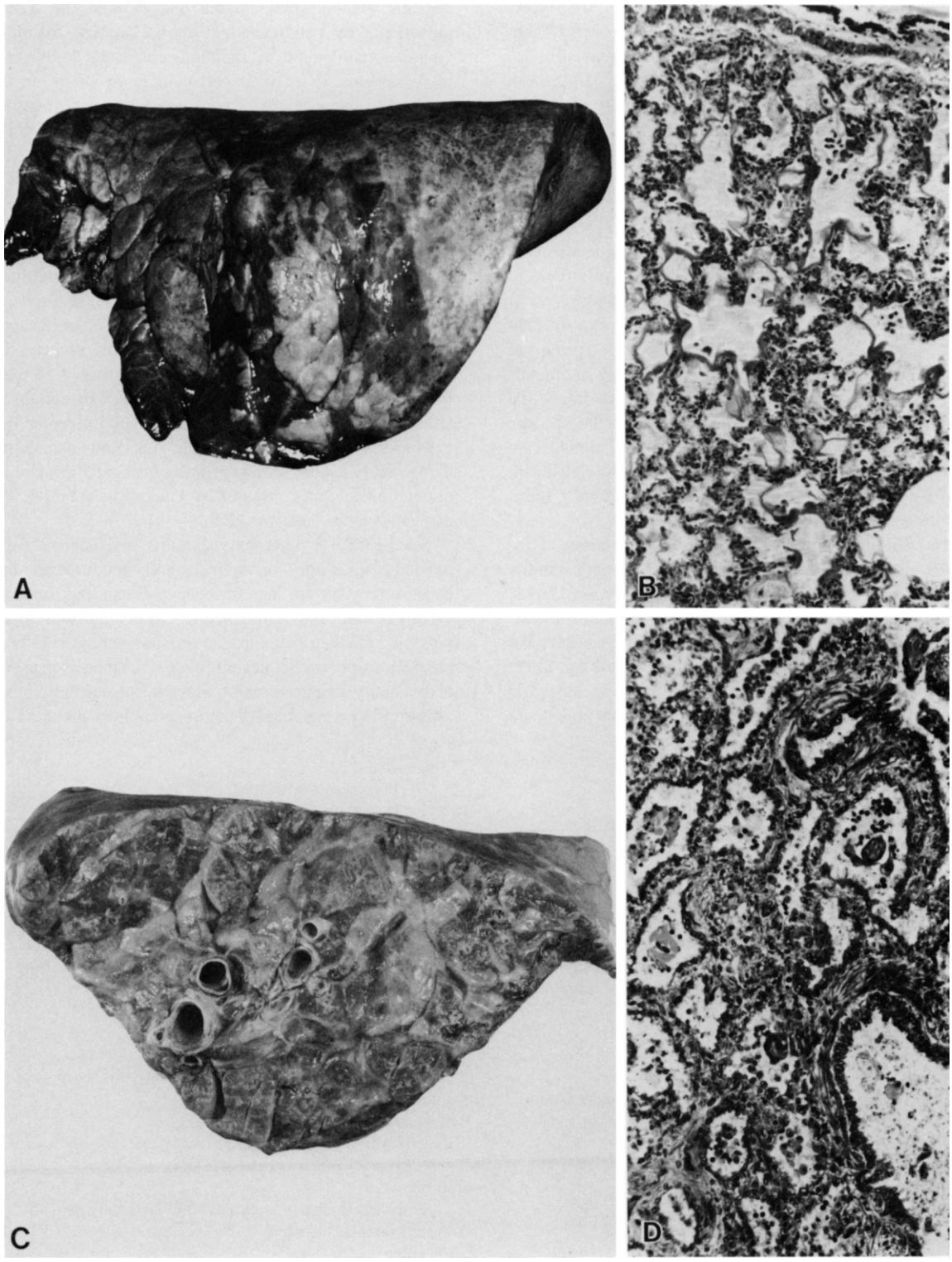

Fig. 6.18. (**A**) Acute interstitial pneumonia. Ox. The lung has failed to collapse. Subpleural and interstitial emphysema is present. (**B**) Acute interstitial pneumonia caused by *Zieria arborescens* poisoning. Ox. Diffuse alveolar wall damage, with edema and hyaline membrane formation. (**C**) Acute interstitial pneumonia. Ox. Cross section of caudal lobe. Emphysema and edema in interlobular septa and around vessels and airways. (**D**) Acute interstitial pneumonia. Ox. Note prominent epithelialization of thickened alveolar walls.

probably the most common chronic form (Fig. 6.20). Hyperplasia of smooth muscle and distortion of airspaces ("honeycombing") are sometimes present in more advanced cases, not necessarily in proportion to one another. Hyperplasia of smooth muscle, for instance, is a prominent feature of chronic progressive pneumonia (maedi) in sheep (Fig. 6.27C).

A large variety of agents representing all major etiologic categories of disease can cause interstitial pneumonia. The list of recognized causes or associations is much larger for humans than for animals. Most of the recognized interstitial pneumonias in animals are caused either by infectious or parasitic agents or by toxins entering via the digestive tract. Hypersensitivity pneumonitis (extrinsic allergic alveolitis) and pneumoconiosis occur occasionally, as described later. Occupational exposure to dusts, gases, fumes, and vapors, which are the largest groups of causative agents in humans, are essentially lacking in animals for obvious reasons. Other important categories of interstitial pneumonia in humans for which there is little or no specific information concerning analogous conditions in animals are those caused by adverse drug reactions and those associated with collagen–vascular disorders such as systemic lupus erythematosus and rheumatoid arthritis.

Most interstitial pneumonias in animals are infectious in origin and are caused by viral, bacterial, fungal, or parasitic diseases (Table 6.1). Many different agents are involved; most produce pulmonary lesions as the result of systemic or bloodborne infection, for example, toxoplasmosis (Fig. 6.21A,B).

Most **inhaled viruses**, particularly myxoviruses, can infect both airway and alveolar epithelium. When uncomplicated viral pneumonia occurs, the lesion is centered on bronchioles and adjacent alveolar parenchyma and is therefore a bronchopneumonia by pathogenetic pattern. Because interstitial accumulation of leukocytes rapidly becomes the dominant feature of the lesions, these viral pneumonias are often termed "interstitial." Since the interstitial response in most instances is clearly associated with bronchioles and adjacent alveoli, such cases can be distinguished from the more characteristic interstitial pneumonias not orientated on bronchioles. For these viral bronchopneumonias a combined morphologic designation of **bronchointerstitial pneumonia** is preferable.

The pattern of viral pneumonia resulting from aerogenous exposure is affected by the extent to which viral proliferation is limited by the immune system and by the cell tropism of the virus. With influenza virus infection in mice, for instance, limitation of viral proliferation to airways is an important determinant in minimizing the severity of the disease. Cell tropism is important in pneumonia such as that caused by certain virulent strains of feline calicivirus, in which type I alveolar epithelial cells are principally affected following aerosol infection. Although early lesions are in regions adjacent to bronchioles, this orientation becomes obscured by 4 days postinfection, when the damage is more widespread.

Severe diffuse pulmonary parenchymal damage caused by inhaled gases, fumes, or vapors is rarely encountered in animals because they do not have the occupational exposures that are usually responsible in humans. Occasional poisoning of cattle, pigs, and chickens by nitrogen dioxide generated in corn silos has been suspected but never proven. Acute pulmonary injury is occasionally seen in animals trapped in burning buildings. When asphyxiation is not immediate, the combined chemical and heat

TABLE 6.1

Causes of Interstitial Pneumonia in Animals

Acute	Chronic
Infections	Infections
Principally systemic viral, bacterial, or parasitic involvement, e.g., canine distemper, feline infectious peritonitis, septicemic salmonellosis in calves and pigs, toxoplasmosis, and acute parasitism by lungworm or migrating ascarid larvae	Principally systemic viral, bacterial, fungal, or parasitic involvement, e.g., ovine progressive pneumonia, chronic African swine fever, tuberculosis, pneumocystosis, histoplasmosis, and some verminous pneumonias
Inhaled chemicals	Inhaled inorganic dusts (pneumoconioses)
Oxygen (>50% concentration)	Silicosis in horses
Smoke	Ingested toxins or precursors
Ingested toxins or precursors	Pyrrolizidine alkaloids in horses, pigs, cattle, and sheep; Crofton weed toxicity in horses
L-Tryptophan, *Perilla* mint ketone, and furanoterpenoid from moldy sweet potatoes in cattle; paraquat and kerosene in dogs	Hypersensitivity
Adverse drug reactions	Hypersensitivity pneumonitis in cattle and horses; microfilariae of *Dirofilaria immitis* in dogs
Uncertain	Irradiation
Hypersensitivity	Experimental studies in dogs and other laboratory animals
Acute hypersensitivity pneumonitis	Collagen–vascular disorders
Endogenous metabolic/toxic conditions	Uncertain
Shock (particularly endotoxic)	Possibly canine systemic lupus erythematosus
Disseminated intravascular coagulation	Unknown
Uremia, pancreatitis	Occasionally in all species
Unknown	Diffuse fibrosing alveolitis in cattle
Acute/subacute interstitial pneumonia in a variety of species, particularly dogs	

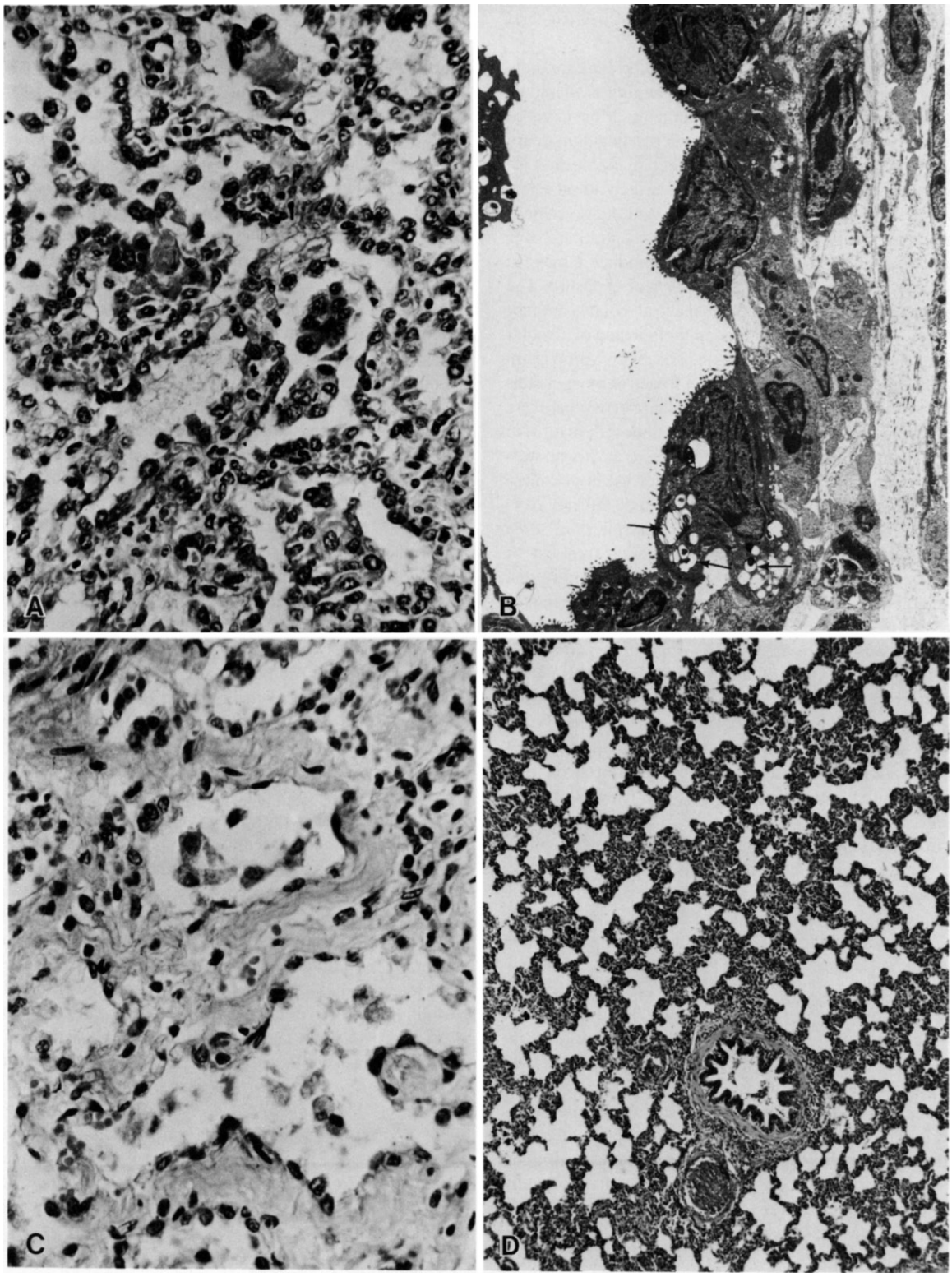

Fig. 6.19. (**A**) Acute interstitial pneumonia. Ox. Proliferation of alveolar type II epithelial cells forming partial cuboidal lining of alveoli 4 or 5 days after onset of damage. (**B**) Ultrastructure of (**A**), showing lining of alveolus by type II cells, some of which contain characteristic lamellar inclusions (arrows). (**C**) Aftermath of acute interstitial pneumonia. Ox. Fibrosis of alveolar walls and persistence of type II cells. (**D**) Acute interstitial pneumonia in salmonellosis. Pig. Thickening of alveolar walls by leukocytes.

effect of smoke can cause widespread epithelial necrosis and exudation, and death within a few days.

With the advent of increased attention to intensive care units in veterinary hospitals, oxygen toxicity is emerging as an important form of inhaled chemical injury in animals. Most cases of oxygen toxicity are superimposed on the preexisting pulmonary abnormality, which necessitates oxygen therapy in the first instance. Susceptibility to oxygen toxicity varies with species, previous exposure history, metabolic state, and the severity of preexisting pulmonary damage, if any. Concentrations over 50%, particularly in the range 80–100%, can produce damage in already compromised lungs after 2 or 3 days of exposure. The lesion is nonspecific, consisting of damage to alveolar–capillary endothelium, necrosis of bronchiolar epithelium and of alveolar type I cells, and serofibrinous exudation. The relative proportion of these changes also varies with species. Reactive oxygen radicals (superoxide, hydroxyl, and excited singlet oxygen) are favored as the active metabolites. These are believed, in turn, to damage cell membranes by lipid peroxidation, to inactivate sulfhydryl-containing enzymes, and to damage a variety of macromolecules, including DNA. The enhanced toxic effect of oxygen in the period shortly after acute pulmonary injury of some other cause has important implications for therapeutic use of high oxygen concentrations. It also raises the possibility that alveolar epithelial cells exert some controlling influence on proliferating fibroblasts.

Ingested toxins or precursors are second in importance to infections as causes of interstitial pneumonia in animals generally. In cattle, they are probably the most important cause. Several plant or feed-related substances can cause a nonspecific **acute interstitial pneumonia** in **cattle**. L-Tryptophan and 3-methylindole are implicated in causing the pasture-related form in cattle (commonly referred to as "acute bovine pulmonary emphysema and edema" or "fog fever"). Similar pulmonary damage in cattle is caused by *Perilla* mint, moldy sweet potato, and stinkwood (*Zieria arborescens*) poisoning. Pulmonary lesions are also produced in horses, pigs, sheep, and cattle by pyrrolizidine alkaloids from a variety of plants (mostly *Crotalaria, Trichodesma,* and *Senecio*). Crofton weed (*Eupatorium adenophorum*) is another poisonous plant that produces chronic interstitial pneumonia in horses. Toxicity is associated with ingestion of the flowering plant, but the nature of the toxin is not known. The lungs have a multifocal chronic interstitial pneumonia in which proliferation and metaplasia of alveolar epithelial cells and fibroplasia are the prominent features.

Pneumotoxins produce different patterns of pulmonary response according to the specific toxin and the species of animal affected. This appears to be due at least in part to the distribution of monooxygenase enzymes among pulmonary cells potentially at risk, because the actual damage often requires production of reactive metabolites from parent toxins by the action of the monooxygenase system.

Poisoning of dogs and cats by the herbicide paraquat is another common toxic cause of acute interstitial pneumonia in animals. As with most other pneumotoxins, paraquat produces a nonspecific, acute to subacute lesion. Cases of malicious poisoning are more likely to cause fulminating pulmonary edema and hemorrhage because of the high dosage, whereas in accidental poisonings there is more often time for hyperplasia of alveolar type II cells and fibroplasia to be superimposed on the earlier exudative changes. Affected animals are often placed on oxygen therapy, but it is difficult or impossible to determine whether oxygen might have exacerbated the lesions because of the severity of the preexisting damage caused by paraquat. Poisoning by the rodenticide α-naphthylthiourea (ANTU) also causes respiratory distress, but it causes pulmonary edema and pleural effusion without the tendency to epithelial hyperplasia and fibroplasia if the animal survives. There is insufficient damage to components of the alveolar wall for it to be included in the interstitial pneumonias as defined here.

Little is known concerning pulmonary damage caused by therapeutic use of drugs in animals. Development of acute pulmonary edema as part of the anaphylactic or anaphylactoid shock caused by drugs such as penicillin is widely recognized but not well documented.

Inhaled inorganic dusts (**pneumoconioses**) are uncommon in animals because they lack occupational exposures to dusts, which are the basis for pneumoconioses in humans. There are old reports of asbestosis in animals with industrially related exposure. A very mild form of pneumoconiosis was found in ponies used in coal mines. There were multiple compact aggregates of coal dust, particularly around small vessels adjacent to terminal and respiratory bronchioles. The amount of fibrosis was minimal. More recently, there have been reports of silicate pneumoconiosis or diatomaceous pneumoconiosis in animals kept in zoos. The minimal to mild, clinically insignificant lesions mostly consist of focal dust granulomas associated with lymphatics in perivascular, peribronchiolar, and other interstitial sites. Similar foci can be seen in the lungs of many animals living in a dusty environment, but the amount of dust retention appears to be greater in birds.

Silicate pneumoconiosis in horses is the only reported clinically important pneumoconiosis in animals. Multifocal granulomatous interstitial pneumonia with interstitial fibrosis (Fig. 6.21C) is associated with exercise intolerance of various degrees. Necrosis and mineralization are frequently present in the centers of granulomas in the most severely affected lungs (Fig. 6.21D). Small crystalline particles are difficult to detect in the macrophages by light microscopy but are plentiful when examined electron microscopically. The type of silicate responsible is cristobalite, one of the highly fibrogenic species.

In its most specific sense, **hypersensitivity pneumonitis** (**extrinsic allergic alveolitis**) refers to pulmonary disease caused by inhalation of organic antigens. Naturally occurring hypersensitivity pneumonitis in animals occurs in cattle and, to a lesser extent, horses. Lesions are those of a lymphocytic interstitial pneumonia. Noncaseating granulomas can be found in the farmer's lung analog in cattle, caused by spores of thermophilic actinomycetes (especially *Micropolyspora faeni*) from moldy hay. A lymphocytic and plasmacytic bronchitis and bronchiolitis is frequently a prominent feature of the disease in cattle and horses.

There is probably some degree of mixed immediate and delayed-type hypersensitivity in many infectious and parasitic conditions. An example of the latter is the interstitial pneumonia associated with microfilaria of *Dirofilaria immitis* in dogs with

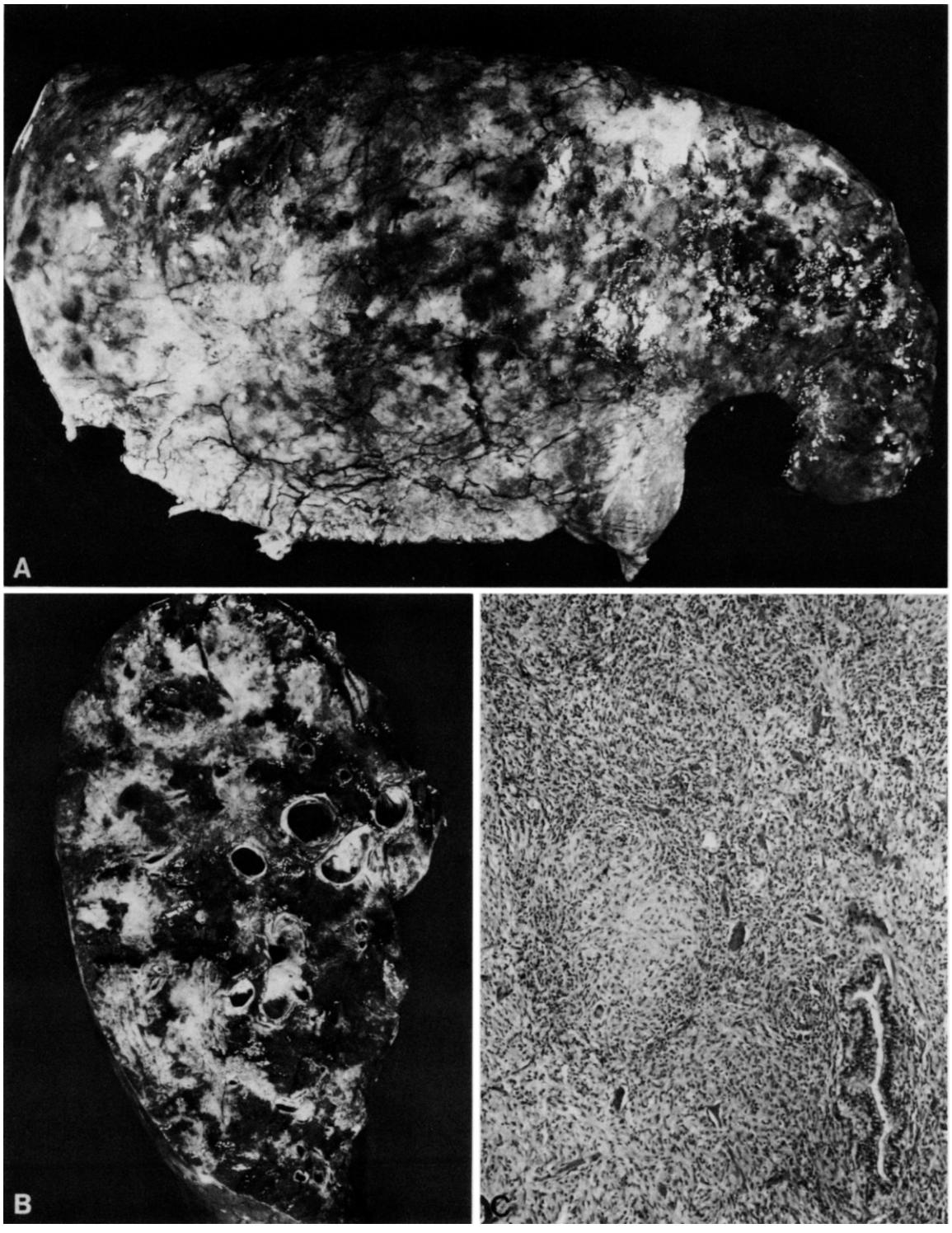

Fig. 6.20. (**A**) Chronic granulomatous interstitial pneumonia of undetermined cause. Horse. (**B**) Section of caudal lobe of (**A**), showing multiple, confluent foci of consolidation. (**A** and **B** courtesy of T. E. Dorr.) (**C**) Effacement of pulmonary parenchyma by granulomatous inflammation.

both occult and nonoccult heartworm disease. Immunologic mechanisms will undoubtedly be found to play some part in the pathogenesis of virtually all chronic interstitial pneumonias.

This is a convenient place to consider **eosinophilic syndromes** involving the lung. As would be expected of any set of diseases grouped on the basis of the presence of a particular inflammatory cell, these represent an ill-defined, poorly understood mixture. Little is known of the range of eosinophilic involvement of animal lungs, though their presence in helminth infections and presumed allergic bronchitis is well recognized. The term "pulmonary infiltrates with eosinophilia" has come into use to include all cases in which, as the name implies, there is radiologic evidence of interstitial pulmonary infiltrates together with a blood eosinophilia. Eosinophils may be present in bronchoalveolar lavage fluid, with or without the blood eosinophilia. Since affected animals usually recover with corticosteroid treatment, the precise nature of the pulmonary lesion and the etiology often remain uncertain. The best known causes of pulmonary infiltrates with eosinophilia are dirofilariasis in dogs and migrating helminth larvae in many species. Involvement in hypersensitivity pneumonitis, allergic bronchitis, and "asthmatic" states is more often suggested than clearly proven. Whether pulmonary infiltrates with eosinophilia can be part of adverse drug responses or immune-mediated disorders can only be determined by extensive, careful studies. "Pulmonary infiltrates with eosinophilia" is not a diagnosis, and there should be concerted efforts to make the term redundant by identification of the specific disease responsible in each case.

A variety of **endogenous metabolic** and **toxic conditions** can cause acute pulmonary injury leading to inflammatory edema or more severe alveolar wall damage and serofibrinous exudation, as described for acute interstitial pneumonia. Acute uremia frequently causes severe pulmonary edema. Acute pancreatitis in dogs is occasionally associated with radiologic evidence of pulmonary edema. Shocklike states, massive burns and trauma, and prolonged surgery can also produce acute pulmonary injury, and these are also a major cause of the acute respiratory distress syndrome in humans. Endotoxin is suspected to play an important role in many instances, for example, shock associated with severe enteric diseases in horses. But the situation is extremely complex because essentially all mediators implicated in any form of acute inflammation have to be considered. Involvement of clotting factors starting with activation of Hageman factor, the alternate pathway of complement activation, and arachidonic acid metabolites are all likely, but most attention is on derivatives of the arachidonic acid cascade. A summary of current understanding of the endotoxin-induced pulmonary injury is that there is an early transient severe pulmonary hypertension followed several hours later by an increased vascular and alveolar-wall permeability phase lasting up to 36 hr. The initial hypertension appears to be due mainly to release of thromboxane and prostaglandin $F_{2\alpha}$, which are derived from the cyclooxygenase pathway of arachidonic acid metabolism. Their effect is to some extent counteracted by prostacyclin, another endoperoxide derived from the cyclooxygenase pathway. The subsequent increased permeability phase is associated with aggregation of leukocytes, mostly neutrophils, in pulmonary capillaries. Exactly how this is brought about is less clear, but hydroperoxides (hydroperoxyeicosatetraenoic acids, hydroxyeicosatetraenoic acids, and leukotrienes) derived from the lipoxygenase pathway of arachidonic acid metabolism appear to be involved.

Acute and chronic interstitial pneumonias of unknown cause are encountered in all species, but the sporadic reports do not enable assessment of their prevalence. Since the clinicopathologic picture of interstitial pneumonias is often nonspecific, many are not identified by a specific cause and go unreported. In cattle, acute interstitial pneumonia occurs in calves and feedlot cattle. Chronic interstitial pneumonia (diffuse fibrosing alveolitis) of adult cattle has been described. In pet animals, particularly dogs, acute interstitial pneumonia is occasionally seen where there is no evidence of access to a pneumotoxin such as paraquat. There seems sometimes to be an association with cardiac insufficiency. An acute shocklike pulmonary injury occurs in terminal cardiovascular collapse. Similar lesions, often with superimposed oxygen toxicity, are seen in animals that have been treated in intensive care units.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome is a term used to refer to the clinical signs associated with acute pulmonary injury of diverse causes. Clinically, there is acute onset of respiratory distress, with rapid death, or there might be temporary recovery followed by progressive worsening of respiratory function and death in one to several weeks. Functionally, there is hypoxemia caused by intrapulmonary shunting of blood or mismatching of ventilation and perfusion. There are also reduced compliance and decreased functional residual capacity. Radiographically, there are widespread alveolar infiltrates or mixed alveolar and interstitial patterns. Lesions in affected lungs are usually of a nonspecific, acute to subacute interstitial pneumonia. The causes of acute respiratory distress are the following:

Acute viral and bacterial pneumonias
Septicemia and endotoxemia
Shock, massive burns or trauma, and prolonged surgery
Aspiration of liquids
Chemical or drug toxicity
Uremia and pancreatitis
Disseminated intravascular coagulation
Oxygen toxicity

Bronchointerstitial Pneumonia

The most important attribute of a classification scheme in pathology is that it provides an effective framework for diagnosing, interpreting, and conveying information about disease processes. From this point of view the designation of certain pneumonias as bronchointerstitial is justified. As referred to previously under Interstitial Pneumonia, bronchointerstitial pneumonia is caused commonly by aerogenous viral infections, particularly myxoviruses. The essential features of the lesion are that it is centered on bronchioles and that interstitial accumulation of lymphocytes is a prominent feature. Sequential studies reveal that the early lesion is one of bronchiolar epithelial necrosis and accumulation of acute inflammatory components in the bronchioles and adjacent alveoli. Pathogenetically, the lesion is therefore a bronchopneumonia. Because of the mainly cell-me-

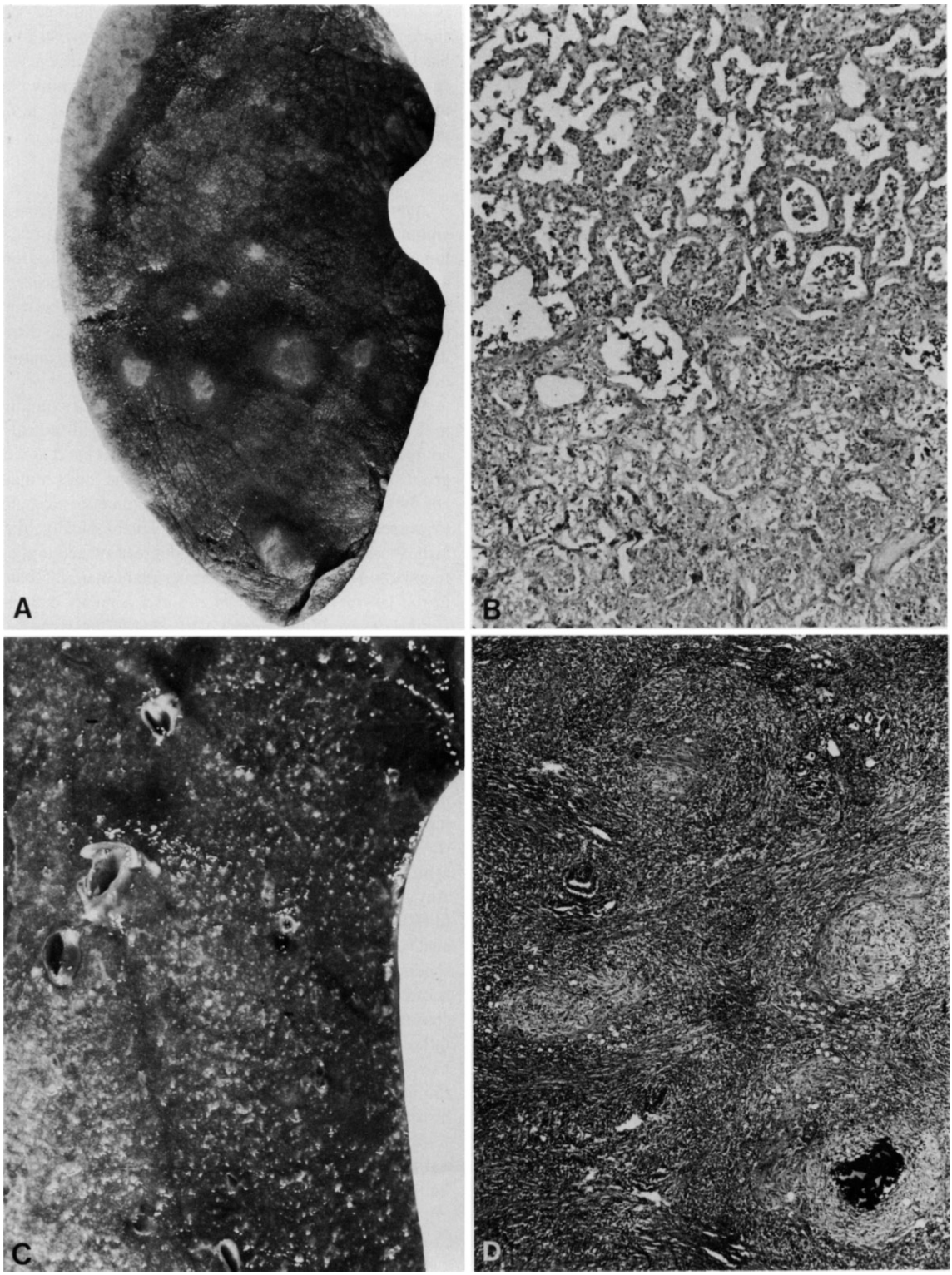

Fig. 6.21. (**A**) Multifocal necrotizing interstitial pneumonia. Toxoplasmosis. Cat. (**B**) Histology of periphery of a necrotic focus in (**A**). (**C**) Multifocal granulomatous pneumonia of silicate pneumoconiosis. Horse. (**D**) Details of granulomas in (**C**). Some have central necrosis or mineralization.

diated immune responses that develop, however, accumulation of lymphocytes in the peribronchiolar and adjacent alveolar interstitium becomes the dominant feature (Fig. 6.22A). This has resulted in the lesions being referred to as interstitial pneumonia. It is important, however, from the standpoint of pattern recognition and interpretation, that this type of response, which is orientated on bronchioles, be differentiated from the interstitial pneumonias that do not have a bronchiolar orientation. Hence the special designation bronchointerstitial pneumonia. This is not merely an academic exercise, because careful analysis of whether parenchymal abnormalities are centered on bronchioles is one of the most important criteria in the histologic diagnosis and interpretation of pneumonias. In ruminants and swine, *Mycoplasma* infection is the most common cause of bronchointerstitial pneumonia (Fig. 6.22B).

Abscesses of the Lung and Embolic Pneumonia

Pulmonary abscesses usually arise either from foci of severe, suppurative lobar or bronchopneumonia, or from septic emboli lodging in the pulmonary vascular bed (Fig. 6.22C). Craniоventral location and associated scarring or bronchiectasis are evidence of origin from a suppurative pneumonia. Multiple, widely distributed abscesses indicate hematogenous origin and are usually associated with an obvious source of septic emboli elsewhere in the body, for example, septic thrombosis of the posterior vena cava in cattle. Isolated abscesses in dorsocaudal regions are more likely to have arisen from septic emboli, but in the absence of a pattern of abscesses in other organs, the origin remains uncertain. Difficulty is encountered in interpreting the pathogenesis of pulmonary abscesses in horses; they are relatively frequent and can arise by either major route. It is often impossible to determine with certainty the pathogenesis of isolated old abscesses.

Two less common causes of pulmonary abscesses are aspirated foreign bodies, such as plant awns, or direct traumatic penetration of the lung. Complications of abscessation include pleural fistulation and empyema, hemorrhage from a ruptured blood vessel, and fulminating suppurative bronchopneumonia subsequent to rupture into a bronchus.

The term embolic pneumonia could be extended to include pneumonias caused by any circulating particulates, including bacteria and parasites, but it is preferable to consider pneumonia caused by hematogenous infectious agents under the general heading Interstitial Pneumonia. Embolic pneumonias can be considered as a special category of interstitial pneumonia in which there are focally discrete lesions. In addition to the abscesses caused by septic emboli mentioned previously, other examples are the hematogenous abscesses, which are an integral part of specific diseases such as caseous lymphadenitis and melioidosis.

Special Forms of Pneumonia

Gangrenous Pneumonia

Gangrene can be a complication of other forms of pneumonia in which there is extensive necrosis of pulmonary parenchyma. It is occasionally seen in cattle as a result of penetration of a foreign body from the reticulum, but mostly it is a result of aspiration of foreign material and associated saprophytic, putrefactive bacteria. The yellowish to greenish black color and foul odor are characteristic. Extensive ragged cavitation rapidly develops. If a gangrenous cavity extends to the pleura, a foul empyema results, with putrefactive pneumothorax.

Aspiration Pneumonia

Aspiration pneumonia refers to pneumonia caused by large amounts of foreign material, often in liquid form, reaching the lungs through the airways. This distinguishes it from pneumonias caused by inhalation of small respirable particles, which includes the bulk of aerogenous pneumonias. The response to the aspirated material depends on three factors: the nature of the material, the bacteria carried with it, and the distribution of the material in the lungs.

Widespread distribution of inhaled milk or combination of milk and gruel is observed occasionally in pail-fed calves. The course of the disease in these cases can be as short as 1 day. The gross appearance is not characteristic. The lungs remain inflated; they are hyperemic, and small amounts of exudate can be expressed from the small airways. Histologically, there is an acute bronchiolitis with various degrees of acute alveolar inflammation. Lipids, and sometimes plant material, can be seen in the lesions. Aspiration of ruminal contents can produce a similar picture in recumbent cattle, but in these cases the aspirated material is usually obvious, and there is hemorrhagic tracheobronchitis.

When the distribution of foreign material is more localized, either discrete foreign-body granulomas, bronchopneumonia (Fig. 6.22D), lobar pneumonia, or gangrene of the lungs occurs. Cattle and lambs frequently aspirate inflammatory exudate from necrobacillary laryngitis. Lambs with nutritional myopathy affecting the muscles of deglutition aspirate milk and plant material, including whole grain. Pigs in dry, dusty environments can aspirate starch granules and particles of plants from the feed. Any cause of dysphagia, pharyngeal paralysis in particular, is likely to lead to aspiration pneumonia. It is also a hazard of anesthesia. Aspiration of vomitus and medications occurs in all species. The aspiration of vomitus in a simple-stomached animal is often rapidly disastrous, and death can occur from laryngeal spasm or acute pulmonary edema before there is time for much inflammation to develop. The possibility of aspirated material's being responsible must always be considered in any case of fulminating lobar or bronchopneumonia, especially one with a history of one of the predisposing conditions just mentioned. Careful search will usually reveal evidence of foreign material, but this is not the case when the material is largely or entirely liquid.

Lipid (Lipoid) Pneumonia

Lipid (lipoid) pneumonia is a special form of aspiration pneumonia in which large droplets of oil are inhaled. It used to be fairly common in cats but occurs in all species in which animals are subjected to the forced administration of mineral oil (liquid paraffin), as a laxative, or cod-liver oil, for its antirachitic properties. The reaction is typically macrophagic and proliferative, with some qualitative differences depending on the nature of the

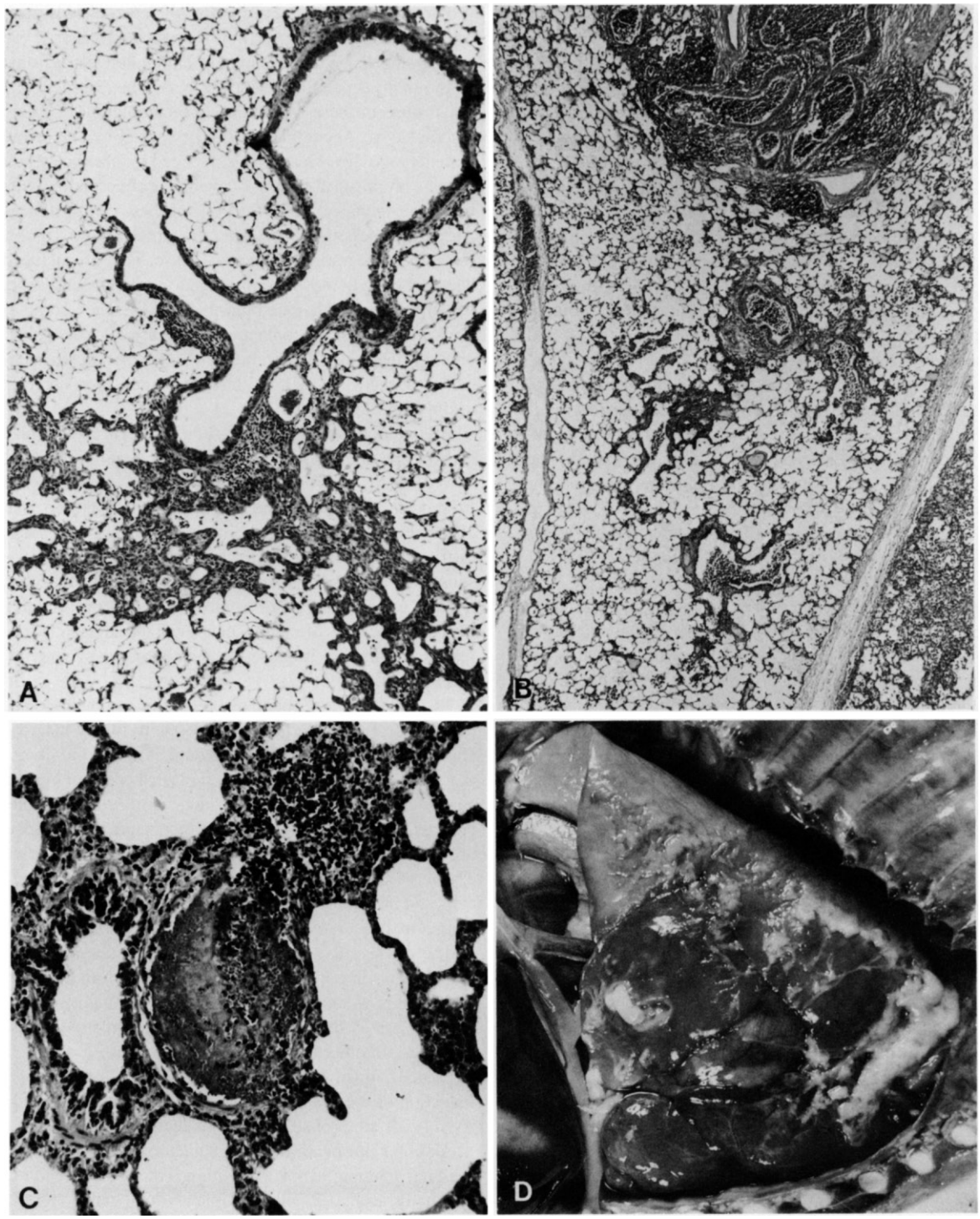

Fig. 6.22. (**A**) Bronchointerstitial pneumonia caused by myxoviruses. Parainfluenza type 1 (Sendai) virus. Mouse. (Courtesy of D. G. Brownstein). (**B**) Bronchointerstitial pneumonia of mycoplasmosis. Calf. (**C**) Thromboembolic suppurative pneumonia. Ox. Early lesion associated with septic thrombus. (**D**) Aspiration pneumonia. Cat. There is confluent bronchopneumonia and fibrinopurulent pleuritis.

oil. In general, vegetable oils, such as olive oil, are not irritating, and they are eventually resorbed with little reaction or fibrosis. Oils of animal origin are irritants and provoke an early exudation of serofibrinous fluid and leukocytes. This is replaced later principally by macrophges, among which giant cells can be numerous. Foamy macrophages fill the alveoli, and the alveolar walls are thickened by infiltrated mononuclear cells and fibrosis. The oil is ultimately resorbed. The purest cellular response occurs to mineral oil, which is the usual offender in animals. The nature of the oil can be distinguished by its permanence and its failure to stain with osmic acid. The lipid is both extracellular and intracellular. Lipid-laden macrophages tend to fill the alveoli, and in time they accumulate in the lymphatics that surround the bronchi and blood vessels (Fig. 6.23B). Fibrosis of alveolar walls and proliferation of alveolar type II epithelial cells are conspicuous, and the foamy macrophages tend to be incorporated into the alveolar septa by extension of the fibroplasia. Unless complicated by secondary bacterial infection, the lesions have a characteristic yellowish, homogeneous or finely mottled appearance (Fig. 6.23A). They vary from multiple small nodules to complete consolidation of a lobe. Involvement is usually bilateral and tends to be in ventral regions. The bronchial lymph nodes are grossly normal, but histologically often contain droplets of oil.

Pneumonias caused by aspiration of foreign (exogenous) lipid must be differentiated from the so-called endogenous-lipid pneumonias, described below. Accumulation of lipid-filled macrophages and various amounts of interstitial response are common to both conditions. The most important distinguishing feature is that in lipid-aspiration pneumonias there are large, discrete extracellular globules of lipid. In paraffin-embedded sections these appear as clear, spherical spaces with distinct borders formed by the compressed cytoplasm of macrophages and giant cells.

Uremic Pneumonopathy

Severe uremia causes increased permeability of the alveolar air–blood barrier and is therefore a cause of pulmonary edema. The usual form of uremic pneumonopathy occurs in dogs with chronic uremia, where the principal lesion is degeneration and calcification of smooth muscle and connective tissue fibers (see the Urinary System, this volume). This occurs mainly in the walls of respiratory bronchioles and alveolar ducts in mild cases. Severe involvement results in extensive mineralization of alveolar septa, which can be recognized grossly by the gritty, porous texture of the lung. Inflammatory cell components are not usually a significant feature of uremic pneumonopathy in dogs, and although the condition is sometimes referred to as uremic pneumonitis, this is not appropriate.

Alveolar Filling Disorders

Alveolar filling disorders is a convenient term for lumping together an ill-defined group of conditions with overlapping morphologic features. They are usually found as incidental lesions in which alveoli are filled by one or more of the following: collections of large, foamy, lipid-filled macrophages with lipofuscin pigment and, possibly, cholesterol crystals (endogenous-lipid pneumonia); amorphous acidophilic material (alveolar lipoproteinosis); or clusters of macrophages and giant cells containing hyaline or faintly laminated material (pulmonary hyalinosis). The amount of inflammation varies from minimal to mild, depending on the variety of the disorder. The central feature in these conditions is accumulation of lipid-filled macrophages. Accumulation can be caused by one or more of three factors: their clearance is impeded by obstructed airways, they are produced in excess, or metabolic abnormalities interfere with their mobility. More than one of these circumstances may coexist. These conditions could be regarded as forms of lipidosis rather than pneumonia in the usual sense. They are included here because some do have an inflammatory component, especially the so-called endogenous-lipid pneumonia. The various conditions are grouped for convenience because of overlapping morphologic features. Clarification of the range of causes and pathogenic mechanisms will eventually enable more precise and useful classification.

Endogenous-lipid pneumonia (foam-cell pneumonia, cholesterol pneumonia) is characterized by large, focal accumulations of foamy macrophages. The disease is encountered mostly in laboratory rodents and furbearing animals. It is seen occasionally in cats, rarely in dogs. Grossly, the lungs have irregularly distributed, yellowish white, firm foci. Most of the foci are subpleural and appear as sharply defined small flecks or bulging nodules up to a centimeter or more in width (Fig. 6.23C). The overlying pleura is often thickened, and the adjacent lymphatics may be prominent because of accumulations of macrophages and lipid.

Histologically, the bulk of the lesion in many instances is composed of distended alveoli filled with foamy macrophages (Fig. 6.23D). There is a small amount of interstitial fibrosis and accumulation of lymphocytes and plasma cells. In more severe cases, there are intracellular and extracellular cholesterol crystals, more severe interstitial fibrosis and mononuclear-cell accumulation, and regions of alveolar type II cell proliferation. The large cholesterol crystals stimulate development of giant cells and intraalveolar fibroplasia. Extensive fibrosis is accompanied by obliterative periarteritis and endarteritis.

The causes of endogenous lipid pneumonia are not clearly defined. In some instances, the accumulation of alveolar macrophages is associated with localized bronchitis and bronchiolitis and is therefore attributed to obstruction of alveolar clearance. In other instances, there is no evident obstruction of clearance pathways. Excessive production of macrophages and reduction of their mobility by ingested surfactant or serum-derived lipids are probable causes of accumulation in such cases.

Alveolar lipoproteinosis is characterized by accumulation of acellular acidophilic material within alveoli. The predominantly mucopolysaccharide–lipid complex is homogeneous or granular by light microscopy and is strongly PAS (periodic acid–Schiff) positive. Ultrastructurally, the material consists mostly of lamellar and tubular arrays of surfactant phospholipid. Because of the predominance of lipid, the condition is also referred to as pulmonary lipidosis. Alveoli are lined by type II epithelial cells, but inflammatory and fibrotic changes in alveolar walls are usually minimal. Alveolar lipoproteinosis has been produced experimentally in animals by exposing them intratracheally to massive concentrations of silica or coal dust, or by parenteral

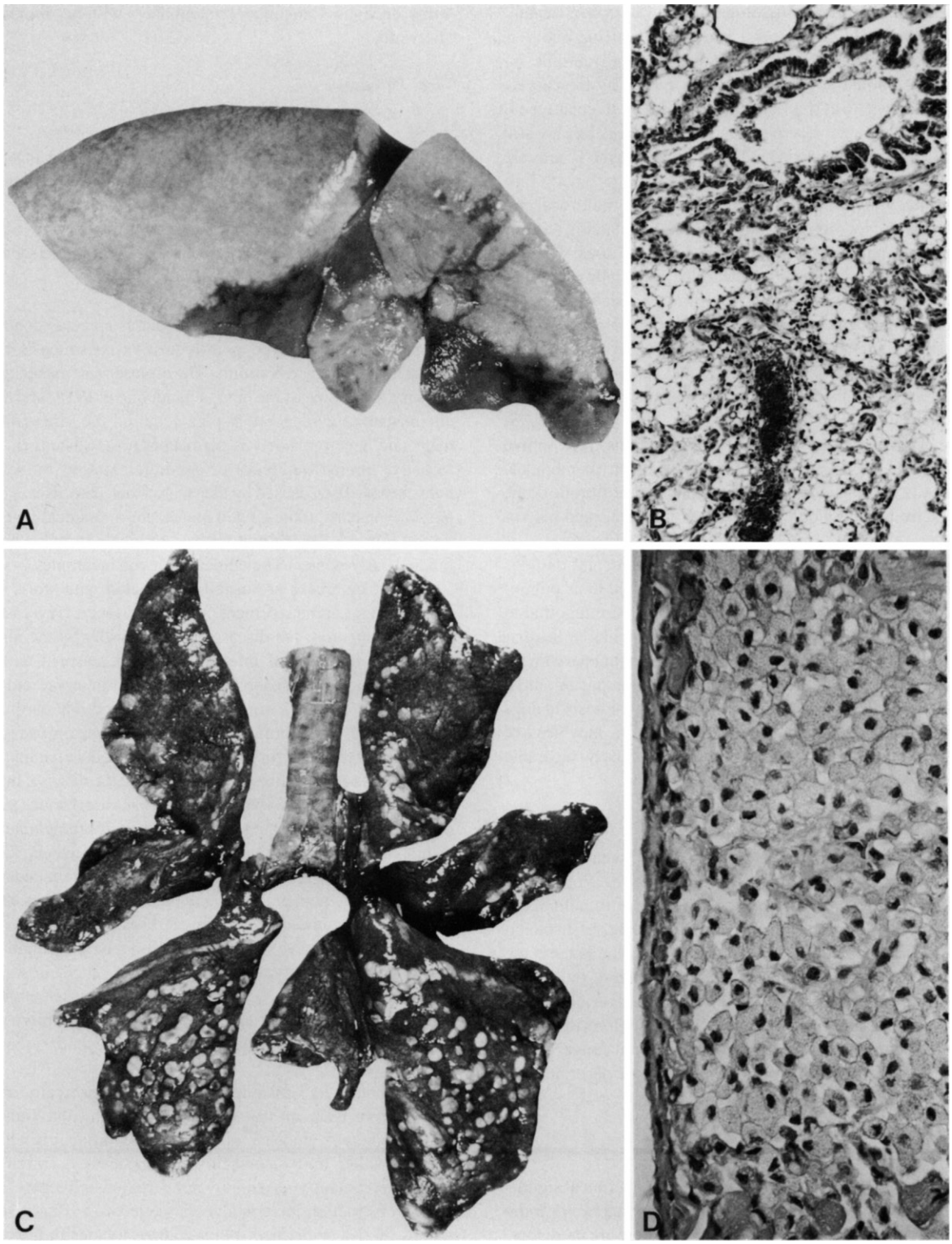

Fig. 6.23. (**A**) Lipid aspiration pneumonia. Cat. Bronchopneumonia with atelectasis in darker areas. (**B**) Lipid-laden macrophages in alveoli and perivascular lymphatics of (**A**). (**C**) Endogenous lipid pneumonia. Cat. Multiple, discrete, pale subpleural nodules. (**D**) Histology of (**C**), showing accumulations of foamy macrophages.

administration of amphiphilic drugs such as chlorphentermine. It has not been recognized as a naturally occurring entity in domestic animals other than in association with chronic interstitial pneumonia in goats, such as is caused by the caprine arthritis–encephalitis virus. The relative roles of alveolar type II cells and macrophages in producing the acellular debris are still in dispute, but most evidence indicates alveolar type II cells are more important.

Pulmonary hyalinosis, which consists of multifocal accumulations of macrophages and giant cells containing hyaline or laminated material, is seen in the lungs of dogs. Grossly detectable foci occur mainly subpleurally, especially at the narrow ventral margins of the lungs. They are grayish white to tan, nodular or confluent, and firm to gritty. Histologically, the cytoplasm of macrophages and giant cells is greatly distended and disrupted by amorphous or sometimes laminated material. The material is amphophilic, often staining with a pronounced bluish tinge with hematoxylin and eosin. It is strongly PAS-positive, and limited ultrastructural observations have shown that it consists of packed segments of cytoplasmic membranes. Plasma cells, lymphocytes, and small amounts of fibrous tissue usually surround individual or clustered giant cells and macrophages.

The lesions can be found occasionally as incidental findings in the lungs of old dogs. They have been referred to as pulmonary granulomas with PAS-positive bodies and are reported to occur mostly in brachycephalic breeds, particularly boxers. They are usually found accompanying chronic pulmonary injury such as pneumoconiosis or experimental radiation pneumonitis. Although the lesions described as pulmonary hyalinosis in dogs have some differences from pulmonary corpora amylacea of humans, the extent to which they represent clearly separable responses remains to be established.

Granulomatous Pneumonia

Granulomatous or pyogranulomatous pneumonia may occasionally be caused by *Actinobacillus, Actinomyces,* or *Nocardia.* In these cases there is usually local damage to pulmonary tissue, such as by trauma or aspirated foreign body, or suspicion of systemic immunodeficiency. An example of the latter is the occasional finding of systemic nocardiosis, including multifocal pulmonary pyogranulomas, in dogs with distemper or in Arabian foals with combined immunodeficiency. More important granulomatous pneumonias are tuberculosis and fungal infections of the lung (pneumonomycoses), which are described under the appropriate headings.

The Specific Infectious Pneumonias

Naturally occurring infectious pneumonias of clinical significance usually have complex causes. Interaction of two or more organisms is commonly involved, and often there are predisposing environmental factors. The relatively nonspecific nature of many pneumonic lesions compounds the difficulty of attributing them to specific causes. In the following discussion, features of pneumonias caused by, or strongly associated with, individual infectious agents will be presented first. The variety of agents implicated in causing conditions grouped under epidemiologic terms such as "enzootic pneumonia" will be summarized afterward.

Viral Diseases

Myxovirus Infections

Myxoviruses typically cause inapparent to mild infections, mainly of the upper respiratory tract, unless they are unusually virulent or the affected animals unduly susceptible. This is the pattern of human influenza. Where severe disease does occur, it is mostly due to the viral infection's predisposing to secondary bacterial involvement.

SWINE INFLUENZA. Swine influenza is an acute contagious disease caused by a type A influenza virus, which is closely related to human type A strains. The disease was first recognized in swine at the time of the human pandemic in 1918, and there is circumstantial evidence that pigs acquired the virus from humans and have remained as permanent hosts since then. More recently, limited outbreaks or sporadic cases of influenza in humans have been caused by the swine virus. The disease occurs regularly in parts of the United States, and sporadically in Canada and Europe. Typically it appears suddenly in swine herds in fall and early winter. The epidemiology is incompletely understood, but outbreaks are usually associated with stress of climatic changes or management procedures. Once a few cases in a herd are triggered, the disease spreads rapidly by the airborne route. The reservoir of infection between seasonal outbreaks appears to be either carrier swine or lungworm larvae and earthworms. The classical work of Shope showed that earthworms that ingested lungworm larvae from influenza-infected pigs could harbor the virus for long periods. Subsquent feeding of the earthworms to susceptible pigs reproduced the disease, but only if the virus was "activated" by a provoking factor, such as repeated intramuscular injection of killed *Haemophilus* organisms. Migrating ascarid larvae can also precipitate the disease. Lungworm larvae and earthworms are not important under most current management practices, but predisposing factors are necessary for infection to cause clinical disease.

Affected herds have sudden onset of coughing and high fever, which rapidly spreads to pigs of all ages. There is stiffness, weakness, and serous oculonasal discharge. The virus itself causes a mild illness lasting no more than a week; more severe illness and deaths are usually because of secondary bacterial pneumonia.

Uncomplicated viral infection rarely causes death, and the lesions have been mostly studied in experimental situations. Grossly, there is evidence of acute tracheobronchitis with reddened, swollen mucosa and filling of the airways by tenacious mucus, particularly in cranioventral regions. Because of the airway obstruction there is alveolar atelectasis. This is seen as groups of clearly defined, plum-colored lobules in the cranioventral lung regions. The overall extent of the atelectasis depends on the severity of the viral bronchitis and bronchiolitis. In fatal cases, in addition to atelectasis, there is diffuse hyperemia and edema of the lungs, and the interlobular septa are widened by edema fluid. The airways contain bloodstained foam as well as thick mucus, and as a result there can be terminal air trapping

in nonatelectatic regions of the lung. Tbe pleura is normal or covered by a small amount of serous or serofibrinous exudate, and there is excess fluid in the pleural cavity. The pulmonary lymph nodes are enlarged by hyperemia and edema. There is usually a nonspecific severe congestion of the gastric mucosa along the greater curvature. In the more common instances where pigs die of secondary bacterial pneumonia, usually involving *Haemophilus, Pasteurella multocida,* or both, the lesions are characteristic of an acute bacterial bronchopneumonia.

Microscopically, there is patchy, acute inflammation of oculonasal membranes and mucosa of the tracheobronchial tree. The severity of infection is correlated with the extent of involvement of the respiratory tract. In mild cases, viral replication and the lesions it causes are limited to the upper respiratory tract. In severe infection, viral involvement extends to the bronchioles and alveolar parenchyma. Viral replication begins in epithelial cells by 2 hr after infection, and by 8 hr there is loss of cilia, extrusion of mucus, and vacuolar degeneration of epithelial cells. Within 24 hr there is epithelial necrosis and sloughing with emigration of leukocytes, chiefly neutrophils, into the airway lumen. The net effect in severe infections is an acute bronchiolitis and bronchitis in which plugs of neutrophilic exudate are responsible for alveolar atelectasis. Extension of virus infection to alveolar epithelial cells causes alveolar flooding by serofibrinous exudate and neutrophils. The response after the first 24 to 48 hr becomes increasingly mononuclear. There is extensive infiltration of lymphocytes and smaller numbers of other leukocytes into the walls of airways and into the peribronchiolar and adjacent alveolar interstitium. Macrophages become the predominant cell in alveolar lumina. Epithelial proliferation and repair are easily detected histologically by the third to fourth days and lead to hyperplastic cells, which by light microscopy have an undifferentiated appearance. Return to ciliated and secretory cells occurs more slowly. The bronchial and bronchiolar epithelium frequently consists of several layers of stratified cells, with the superficial ones degenerating and desquamating into the residual luminal exudate.

The lesion likely to be seen in the few animals dying primarily of the pure viral infection is one in which there is severe involvement of the bronchiolar–alveolar regions. The acute inflammatory exudate and associated interstitial accumulation of mononuclear cells gives the characteristic bronchointerstitial pattern of pneumonia defined earlier. In pigs dying of secondary bacterial infection, the exudative bacterial pneumonia obscures the earlier viral lesion. In addition to the constitutional signs associated with severe infection, swine influenza in pregnant sows may cause abortion or weakness of the newborn.

EQUINE INFLUENZA. Equine influenza is caused by either of two strains of type A virus (A/Equi–1/Prague and A/Equi–2/Miami). A role for type B virus is unconfirmed. The clinical syndrome caused by the influenza viruses overlaps those caused by equine herpes (rhinopneumonitis) virus, equine arteritis virus (see the Cardiovascular System, Volume 3), and perhaps equine parainfluenza type 3 virus, rhinovirus, and reovirus. Only virologic techniques establish the diagnosis with certainty.

In common with other influenza infections, the disease spreads rapidly among susceptible horses. All ages in a previously unexposed population are susceptible, but the disease is seen most often in young animals brought together or mixed with older animals. Main clinical signs are cough, serous to purulent oculonasal discharge, fever, and weakness. Most horses have a mild illness that resolves within 1 to 2 weeks, but death can occur either from secondary bacterial bronchopneumonia or from severe viral infection involving damage to heart, gastrointestinal tract, kidney, and other parenchymal organs, as well as severe ocular and pulmonary lesions. Edematous swelling of subcutaneous tissues of legs and, less commonly, ventral trunk might also be present.

Respiratory lesions are those of hyperemia, edema, exudation, desquamation, and focal erosions in the upper respiratory tract. In severe cases there is an acute bronchointerstitial pneumonia accompanied by more widespread pulmonary edema, as described for swine influenza, and a tendency for secondary bronchopneumonia caused mostly by streptococci, but occasionally by *Escherichia coli, Pasteurella multocida,* or various other organisms normally resident on the nasopharyngeal mucosa.

Parainfluenza Virus Infections

Parainfluenza viruses are best established as a cause of pneumonia in cattle. They can cause pneumonia by themselves but more commonly are part of the etiologic complex of enzootic pneumonia in calves or more acute episodes of the "shipping fever" type. Uncomplicated **parainfluenza-3 virus** infection in **cattle** has been studied mainly in natural or experimental infections of calves. The disease is either clinically inapparent or causes coughing, moderate fever, tachypnea, and slight mucoid or mucopurulent nasal discharge. Signs are most evident from about 4 to 12 days after infection. Disease caused by the virus alone is more likely to be encountered in calves from 2 weeks to a few months of age, depending on management practices. Uncomplicated infection does not appear to be an important cause of death.

Lesions caused by the virus are basically similar to those caused by influenza viruses, that is to say, the pattern is of a bronchointerstitial pneumonia. Grossly, there is usually evidence of mild mucopurulent inflammation of nasal passages and upper airways. Early macroscopic lung lesions are limited to irregular lobular foci of atelectasis or slightly consolidated purple-red foci in cranioventral regions. In more developed lesions, some 4 to 12 days after experimental infection, there is more confluent consolidation. Thereafter, affected regions are less frequent and more atelectatic as they undergo resolution.

Histologically, in the more severe viral infections there is initially an acute bronchitis and a more obvious bronchiolitis, with extension to adjacent alveoli. The bronchiolar and alveolar exudate is predominantly neutrophilic, although edema and hemorrhage might be present in the alveoli. From about 2 to 4 days after infection, bronchiolar epithelium is variously hyperplastic or vacuolated and necrotic. Acidophilic intracytoplasmic inclusions can be found at this stage in vacuolated bronchiolar epithelium and, to a lesser extent, bronchial epithelium. They are usually in a basal location relative to the nucleus. Intranuclear inclusions are rare. Intracytoplasmic inclusions are pre-

sent infrequently in alveolar epithelial cells. The exudate in bronchioles and alveoli contains macrophages and lymphocytes mixed with neutrophils. Many alveoli are atelectatic because of bronchiolar obstruction. Lymphocytes and plasma cells also accumulate around vessels, bronchioles, and within alveolar septa. Lesions are of maximum cellularity somewhere between 6 and 12 days after infection and are dominated by hyperplasia of bronchiolar epithelium and alveolar type II epithelial cells. Squamous metaplasia may be present. Many alveoli are "epithelialized." Occasional binucleate or multinucleate cells are present. Exudate in bronchioles and alveoli is mixed cell debris, macrophages, and serofibrinous exudate. Intracytoplasmic inclusions are seldom found after 7 days, which is the height of the epithelial proliferative response. Early obliterative bronchiolitis (bronchiolitis fibrosa obliterans) can be seen in severely affected bronchioles at the peak of the pneumonic involvement but is more prominent in later, incompletely resolved lesions.

Several points need emphasizing relative to the range of lesions reported in naturally occurring or experimental disease. The severity of alveolar damage depends on the extent to which virus reaches the alveolar epithelium and replicates, thus causing necrosis. This in turn is governed by the virulence of the strain of virus, the mode of infection, and the resistance of the calf. In general, experimental infections deliver more virus to deep regions of the lung and hence cause more alveolar damage. In natural infection, viral replication seems usually to be limited more to airways and hence is characterized more by bronchiolitis than pneumonia. In severe experimental infections, the amount of alveolar epithelial damage can be pronounced. The degree of alveolar exudation and subsequent proliferation of alveolar type II epithelial cells (epithelialization) is correspondingly more dramatic. The extent to which syncytial or multinucleated giant cells are seen on the alveolar walls or in the bronchiolar epithelium varies. They are not usually a notable feature. Occasional multinucleated cells are seen in the active proliferative phase of alveolar and bronchiolar epithelium following severe damage by a wide variety of infectious and noninfectious agents, particularly in cattle. It therefore appears that no specificity can be attributed to occasional giant cells in the absence of viral inclusions or ultrastructural or immunochemical demonstration of virus. The same holds true for occasional macrophage-derived giant cells. Finally, although intracytoplasmic inclusion bodies tend to be present as the viral lesion approaches its peak, they are rarely encountered in calves that die, because secondary bacterial damage usually obscures possible earlier viral lesions or causes death after the stage at which inclusion bodies are detectable.

The role of parainfluenza-3 virus in **sheep** is similar to its role in cattle in that it acts mostly to pave the way for severe pasteurella pneumonia. The experimental lesions in lambs are essentially the same as those produced in calves. The situation in goats might well be the same, but there has been less study in this species. The pathogenic role of the equine parainfluenza 3 virus is also uncertain.

Parainfluenza-2 virus infection in dogs, formerly referred to as parainfluenza SV-5, has been discussed in its role as one of the causative agents of infectious tracheobronchitis. Lesions are those of a mild tracheobronchitis and bronchiolitis.

CANINE DISTEMPER. Canine distemper is the most ubiquitous and serious of the diseases of dogs. In spite of the development of effective vaccines, the disease remains endemic in most parts of the world. All members of the Canidae (e.g., dog, dingo, fox, coyote, wolf, jackal), Procyonidae (e.g., raccoon, coati, kinkajou, panda), and Mustelidae (e.g., ferret, mink, badger, weasel, otter) are thought to be susceptible, but cases have not been proven in some species of these families. The ferret is remarkably susceptible and for this reason was used extensively in investigation of the disease. Carré first demonstrated that the causative agent is a filterable virus. This virus is now identified as a paramyxovirus, a large RNA virus closely related to measles virus of humans and to rinderpest virus of cattle. Various isolates of the virus cannot be distinguished serologically, but they differ in the type and severity of the disease they produce.

Infection by canine distemper virus is pantropic, and the manifestations protean. The disease is described here because respiratory signs and lesions, although variable in severity, are relatively constant in occurrence. Effective antibacterial therapy has greatly reduced the incidence of secondary bronchopneumonia, but it is still frequently seen in neglected cases. Intestinal disease is also common in dogs with distemper.

The disease is a summation of the effects of the virus and of secondary infections with other organisms. These secondary infections are particularly important in this disease because one of the primary sites of action of the virus is the lymphoid tissue. This causes suppression of immune function. Secondary bacterial infections in the alimentary tract are nonspecific, but in the respiratory tract, *Bordetella bronchiseptica* is frequently associated with suppurative bronchopneumonia. Activated toxoplasmosis develops in dogs whose immune systems have been damaged by the distemper virus, and in fact, toxoplasmosis as a clinical disease seldom occurs in dogs other than in association with canine distemper or other diseases that cause immunodeficiency.

The virus is shed in all the excretions from infected animals during the systemic phase of the infection, and natural transmission is usually by inhalation. The pathogenesis of the infection has been followed in dogs, and the distribution of the virus monitored by the use of immunofluorescence. After aerosol exposure, the virus appears in macrophages of the bronchial lymph nodes and tonsils during the first 24 hr. The virus proliferates in the bronchial lymph nodes, and 2 to 5 days after exposure is distributed throughout the lymphatic tissue, including bone marrow, thymus, and spleen. The animals become febrile and viremic at this stage, and cells of the buffy coat contain virus. The infection is primarily confined to the lymphoid tissues until 8 or 9 days after exposure. In some infections, the virus spreads no further, and the disease is mild or inapparent. The control of the infection at this stage is correlated with the development of neutralizing antibody. If protective titers develop within the first 2 weeks of infection, spread of virus does not occur, and virus disappears from lymphatic tissues. If protective levels of antibody are not reached, the infection persists in lymphatic tissues and spreads to the epithelium of the alimentary, respiratory, and urogenital tracts as well as to the skin and endocrine glands and may reach the brain. In the central nervous system, the virus

appears first in perivascular and meningeal macrophages, but infection of the choroid plexus epithelium occurs early, and the cerebrospinal fluid contains large amounts of virus. The critical timing involved in the rise of neutralizing antibody titer, and its role in influencing the pattern of disease, appears to offer a partial explanation for the variability in the severity of the disease produced by the canine distemper virus. The disease is more severe in young animals, in which the immune system is less well developed, but even among littermates infected by the same strain of virus, the disease is unpredictable in severity.

The incubation period of canine distemper, as indicated by the onset of acute fever, is rather constant at ~5 days. The febrile reaction is typically diphasic, with a second peak occurring at ~11 days, but this diphasic response is seldom observed clinically. The fever is continuous for the course of the systemic infection, which may be some weeks. The clinical signs are variable in their severity and in their emphasis on particular systems. A syndrome consisting of catarrhal oculonasal discharge, pharyngitis, and bronchitis is common but may be so mild as to be missed. Signs of pulmonary involvement accompany moderate to severe damage, whether purely viral with edema and interstitial inflammation, or mainly bacterial with bronchopneumonia. The alimentary disturbance is usually expressed as diarrhea, which becomes more severe as the disease advances. The feces become semifluid, slimy, foul, and occasionally streaked with blood. The animals lose weight, and dehydration results. Vesicles and pustules develop in the skin in some cases. These cutaneous lesions are confined to the epidermis beginning in the deeper layers and are particularly to be found on the thin skin of the abdomen and inner aspects of the thighs. They are bacterial complications usually produced by staphylococci and streptococci. Cutaneous hyper- and parakeratosis also occur, but these never reach the degree of development seen in ferrets and mink, except on the footpads (Fig. 6.24A) and nose. In dogs, there is at most a generalized scurfiness of the skin. Small zones of moist alopecia are common on the palpebral margins and oral commissures.

Blindness, or some loss of vision, is common. Keratitis developing as an extension of conjunctivitis is rare. Few if any dogs, however, escape completely from a retinitis if the disease becomes generalized, and in many there are degenerative and inflammatory changes in the optic nerves and pathways. There may be complete or focal retinal degeneration, patchy edema of the retina with focal detachments, and retinal ischemia with pallor and contraction of the papilla that can be recognized ophthalmoscopically. Proliferations of the pigmented epithelium are visible in the tapetal fundus.

The onset of neurologic signs is usually sudden and follows the systemic signs by 1 to 5 weeks, but it can be longer, and in some cases only neurologic signs are recognized. Certain patterns of signs can be identified: generalized convulsions of cerebral cortical origin; ataxia, the result of cerebellar or vestibular dysfunction; and posterior paralysis due to cord damage. But the neurologic signs of distemper are usually progressive and the result of multifocal damage. Convulsions, depression, paralysis, and rhythmic motor movements (myoclonus) are the most common. Myoclonus may persist as a residual sign of the diseases in animals that recover from the infection.

The gross lesions seen in canine distemper will depend on the phase of the disease when the animal dies or is killed. When death occurs early in the course of the disease and systemic effects are still prominent, as is usual in pups, gross lesions can be expected. But in the majority of cases, which die or are killed because of the encephalitic effect of the virus, there may be little to be seen grossly.

Visceral lesions of canine distemper are common in the respiratory system, but they may be subtle. Inflammation of the nasopharynx is serous in initial stages, and in the course of 3 or more weeks becomes catarrhal and sometimes purulent. The mucosal vessels of the larynx and trachea are congested. The bronchi contain a small amount of foamy, serous fluid from the edematous lungs, and they may contain a mucopurulent exudate in complicating bacterial pneumonia. The lungs are edematous, and when this is severe, there is also serous effusion in the pleural sacs. The specific lesion is an interstitial pneumonia (see Anatomic Patterns of Pneumonia). To a variable extent, the lungs may reveal the smooth, liver-like appearance associated with extensive serofibrinous filling of alveoli, but the more usual lesions are reddish tan patches immediately beneath the pleura, and grayish zones of firmer consistency along the sharp margins of the lobes. Deflation is incomplete in such lungs.

Lesions are regularly present in the lymphoid organs, but except for the thymus, these changes are difficult to recognize grossly. If the animal dies or is killed during the acute systemic phase of the disease, the lymph nodes may be variable in size. Some are large and edematous, others small and atrophic. In the large, edematous nodes, cortical and medullary distinction may be lost. The thymuses of affected animals at this stage are greatly reduced and in some cases are difficult to identify. Later in the course of the disease, lymphoid tissue of lymph nodes and thymuses can regenerate and may be of normal size in animals dying in the chronic neurologic phase of the disease.

Many animals dying of canine distemper are severely emaciated and their muscles wasted. The lobular pattern of the liver is sometimes prominent because of mild fatty change and centrilobular congestion. Large, irregular, whitish areas of necrosis and mineralization are often seen in the myocardium of very young suckling pups, which are most apt to die during the acute early phase of the disease.

The histologic changes in canine distemper, when present, are fairly specific; specificity depends on the demonstration of the viral inclusion bodies or, better yet, detection of viral antigen by immunofluorescence.

The number and distribution of inclusion bodies vary from case to case and with the phase of the disease. Their appearance coincides with, or follows shortly after, the appearance of systemic signs of illness. This is from about 10 to 14 days after infection. By about the fifth or sixth week, their numbers diminish rapidly in most tissues and disappear. Of the nonneural tissues, they persist longest in the lung. Inclusion bodies can be found in the central nervous system before changes of encephalomyelitis are present, and they persist in the neural tissue when they have disappeared from all extraneural sites, provided that infection of the brain has occurred.

The inclusion bodies are acidophilic and occur in either the nucleus or cytoplasm, or both, depending on the tissue. They are

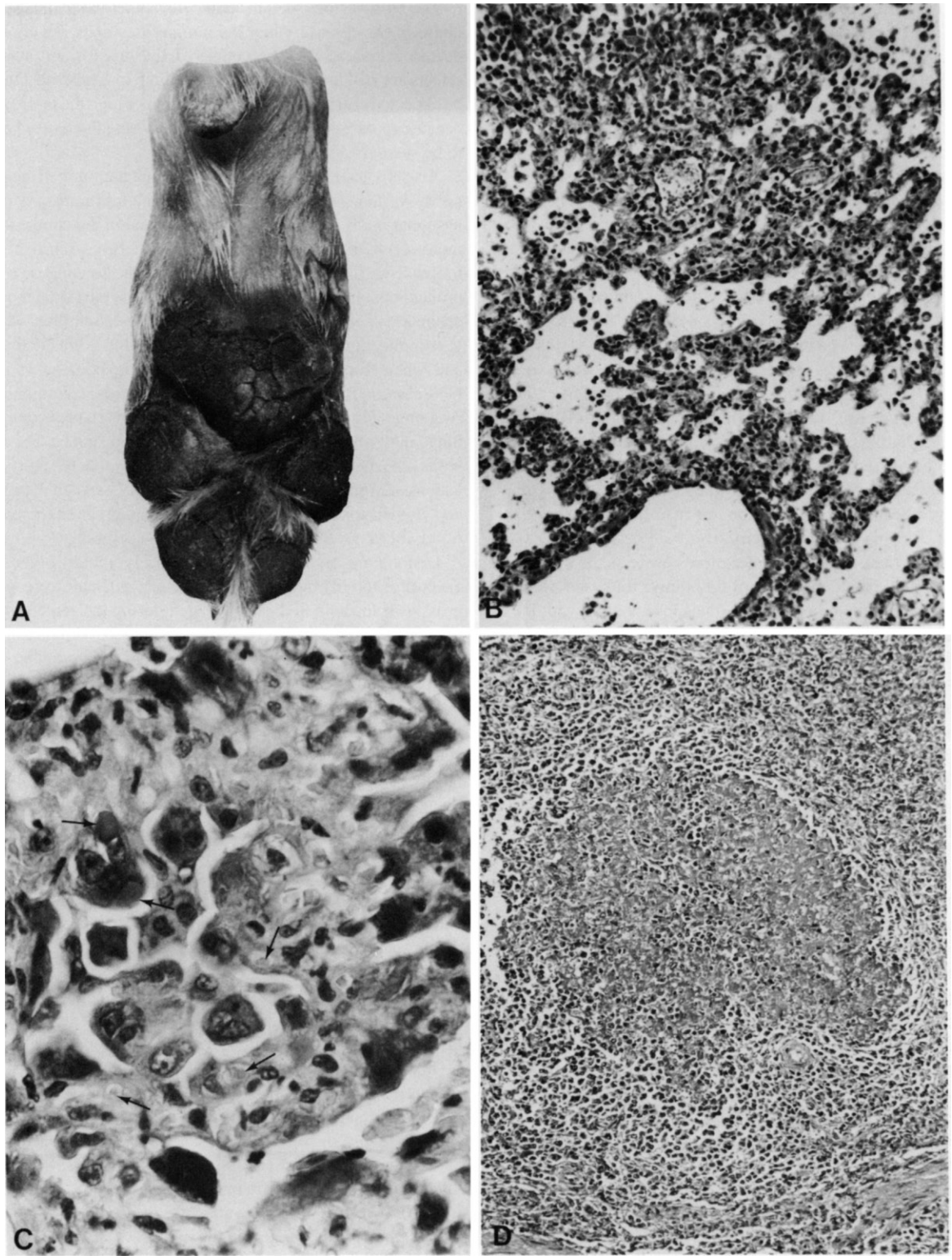

Fig. 6.24. Canine distemper. (**A**) Hyperkeratosis of foot pads. (**B**) Acute interstitial pneumonia with predominance of mononuclear cells in alveolar walls. (**C**) Giant cells in alveoli with intracytoplasmic inclusions (arrows). (**D**) Necrotic focus. Spleen.

usually easier to find and recognize with confidence in brain and epithelial tissues. In lymph nodes they can be very easily confused with eosinophilic debris unless their specificity can be proven by fluorescent antibody.

The earliest lesions of canine distemper are those affecting the lymphatic tissues. These are rarely seen in clinical cases, as dogs only rarely die during this period, but in experimental series it has been shown that as early as the sixth day after exposure there is a depletion of lymphocytes in the cortical zone of the lymph nodes. By the ninth day the lymph nodes are largely depleted of lymphocytes, and the cortical zones are reduced to thin rims. Individual lymphocytes undergo necrosis, and the sinusoids and cords are infiltrated by neutrophils. Similar lesions develop in the spleen, and small foci of necrosis may be scattered throughout the white pulp (Fig. 6.24D). Large multinucleated syncytial cells form in the nodes; often these cells contain acidophilic inclusion bodies. Approximately 2 weeks after exposure, hyperplasia of the reticulum cells develops, focally at first, and later as diffuse sheets of cells. In some fatally infected animals, the nodes are not repopulated by lymphocytes. The nodes are of normal size but filled only with proliferating large mononuclear cells when the animal dies 25–35 days after infection. Repopulation of the node by both B and T cells can occur in convalescent dogs. The recovery is not complete in some of these dogs, and some die with neurologic signs. The thymus also undergoes a severe lymphocytic depletion in parallel with the lymph nodes. The thymic atrophy is due to loss of cortical thymocytes as well as great reduction in the medulla. In some animals that die, the thymuses show no tendency to regenerate, but regeneration, if it is to occur, commences at the same time as it does in the nodes.

Severe leukopenia is a characteristic feature of canine distemper. It is due chiefly to a lymphopenia. The lymphopenia develops at the time the initial necrosis of lymphatic tissue occurs and is most likely the result of viral multiplication and destruction of the lymphoid tissues. The lymphopenia persists in the acute disease until death or recovery, but some animals die of encephalitis after the circulating lymphocyte levels have returned to normal. Lymphopenia coincides with the onset of the leukocyte-associated viremia but persists long after viral antigen can no longer be demonstrated in the buffy coat.

The characteristic changes in the lung produced by the virus of canine distemper are those of interstitial pneumonia, as described above (Fig. 6.24B), but the lesion found at autopsy may be complicated by secondary bacterial bronchopneumonia. The change is diffuse in the lungs, although more severe in some areas than in others. Syncytial giant cells formed by alveolar type II epithelial cells are a characteristic feature of the interstitial pneumonia caused by the virus. Many contain the acidophilic intracytoplasmic viral inclusions (Fig. 6.24C). As the systemic phase is overcome in the chronic disease, residual changes tend to persist in patches beneath the pleura and about venules and small bronchioles as areas of thickened alveolar septa with epithelialization or accumulation of alveolar macrophages. Specific inclusion bodies can sometimes still be found in the cytoplasm of altered alveolar epithelium and in the bronchial mucosa. Among nonneural tissues, they are most likely to be found in the alveolar epithelium because they persist longest in these cells in terms of the disease process, and these cells are not as subject to postmortem lysis and sloughing as most epithelial cells.

Intracytoplasmic inclusion bodies are regularly found in the transitional epithelium of the urinary tract in the acute systemic disease. Intranuclear inclusions are less common. In some cases, inclusions are found in the epithelium of the collecting tubules. The epithelial cells are often swollen and hydropic, and in the absence of these degenerative changes, inclusion bodies are unlikely to be found. Mild interstitial epididymitis and orchitis are common in canine distemper; inclusion bodies are found in the epididymal epithelium, and the interstitium is mildly infiltrated with mononuclear cells. Inclusion bodies can occasionally be found in the epithelium of the biliary and pancreatic ducts, and in the pancreatic exocrine tissue. Inclusions are common in the gastric epithelium but uncommon in the intestine. In the stomach, they are found in superficial epithelium as well as in chief and parietal cells. The latter frequently show acute degenerative changes.

Necrosis and cystic degeneration of ameloblastic epithelium of the developing tooth give rise to the defective enamel seen in animals that have recovered from infection. The defects may consist of small, focal depressions to large areas lacking enamel. The boundaries of the defects are discrete.

Intraocular lesions occur in most cases of canine distemper. Ulcerative keratitis may complicate a purulent conjunctivitis, but this is uncommon, and otherwise the anterior segment is not significantly changed, except for leukocytic infiltrations in the ciliary body. Distinctive retinal lesions of variable severity and extent are present, and nuclear and cytoplasmic inclusions may be found in the retinal ganglion cells and glia, as well as in glia of the optic nerve. The retinal changes may be predominantly exudative in the acute cases, but in those of longer duration they are predominantly degenerative (Fig. 6.25A); in all cases, there is prominent proliferation of the pigmented epithelium. The earliest changes include severe degeneration of the retinal ganglion cells, revealed as dispersion of the Nissl substance and migration of the nucleus to the margin of the cell. The degenerative changes in the ganglion cells are diffuse, but these cells tend to persist until the layered organization of the retina is lost. In acute retinitis, there is congestion and cuffing of the blood vessels in the optic nerve and ganglion cell layers. Patchy edema often separates the fibers of the optic nerve layer and the reticular layers and produces focal retinal detachments. Atrophy of the retina may be patchy, or spare none of it. In some cases, the atrophy is limited to the layer of rods and cones, the outer limbs of which shorten and disappear concurrently with pyknosis of the nuclei. In other foci or cases, the atrophy results in disorganization of the layers, and when the ganglion cell layer disappears also, the retina in such areas consists of disorganized remnants of the layer of bipolar cells. Swelling and proliferation of the cells of the pigment epithelium are common and more marked in the ventral than in the tapetal fundus. It is also common in the pars ciliaris retinae. Associated with the reactive changes in the pigmented epithelium is a migration of pigment into the retina. Pigmentation of the retina is rather common in old dogs, but in these it tends to be restricted to the periphery of the retina and is not obviously associated with reactive changes

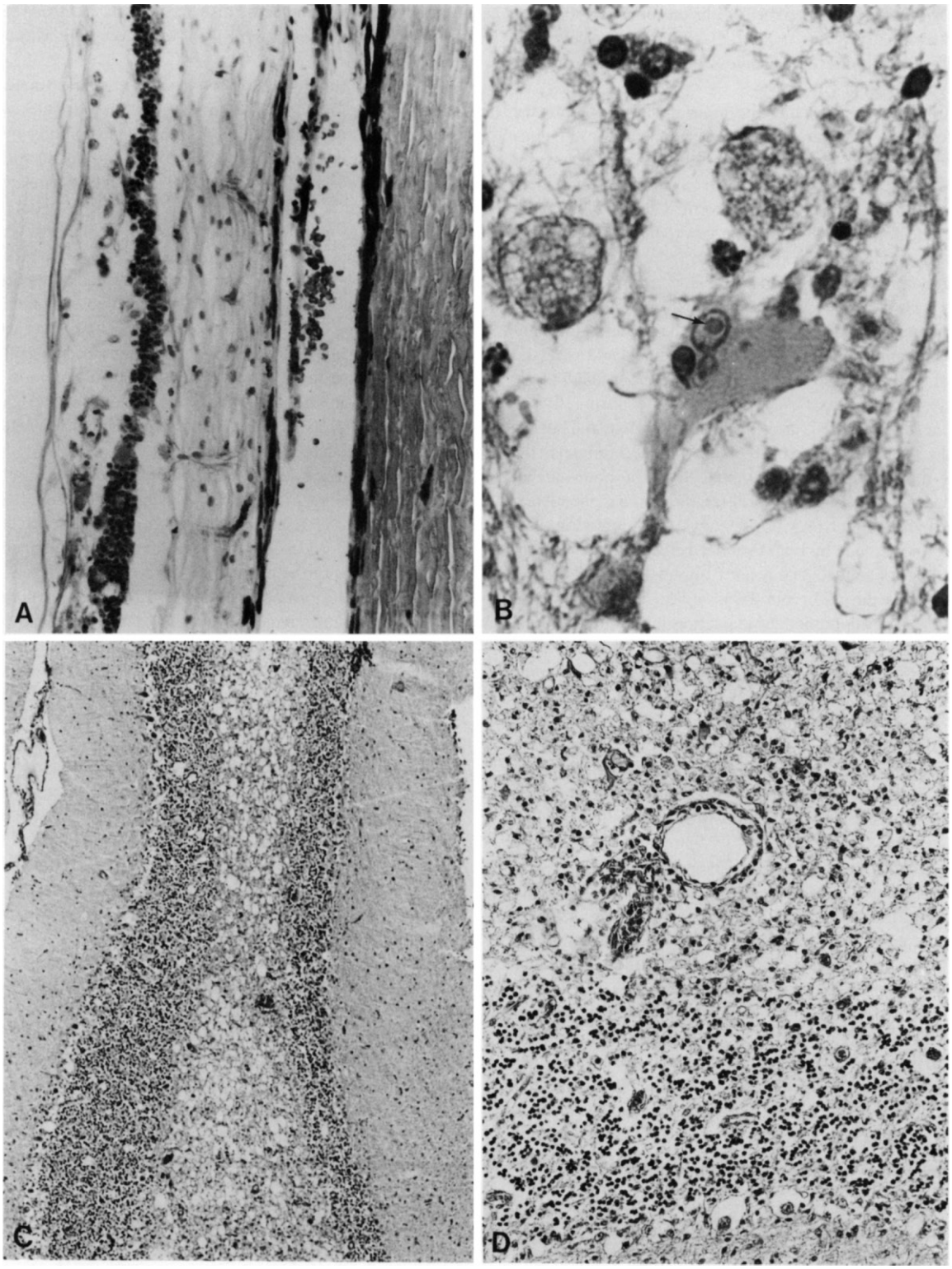

Fig. 6.25. Canine distemper. (**A**) Severe retinal degeneration. Only a few ganglion cells and remnants of outer nuclear layer persist. (**B**) Myelin vacuoles, *Gitter* cells, and one swollen astrocyte containing an intranuclear inclusion body (arrow). (**C**) Demyelination in cerebellar folium. (**D**) Perivascular cuffing and demyelination in cerebellar folium.

in the epithelium. In canine distemper, the pigmentation occurs centrally as well as peripherally, and activity of the epithelium may be sufficient to cause focal detachments of the retina. Changes in the optic nerve are not constantly present, but papilledema may be observed in acute cases, and gliosis of the nerve head or demyelinating neuritis in chronic ones.

Demyelination is the salient feature of the encephalomyelitis of distemper. The lesions are widespread, but correlation with the clinical signs is often not apparent. The lesions have a pattern of development with regional differences in quality and severity. They are most severe and obvious in the cerebellum (Fig. 6.25C,D), surrounding the fourth ventricle and in the optic tracts. Meningitis is always present but is usually mild and consists of accumulation of mononuclear cells, mainly lymphocytes, most obvious on the ventral surface of the brain. Inclusion bodies can be demonstrated in meningeal macrophages in both nuclei and cytoplasm.

Acute degenerative changes in the neurons occur extensively in the brain but are modest in the spinal cord. Experimental studies, both immunofluorescent and ultrastructural, associate this degeneration with viral infection of the neurons. The cells most susceptible to this viral-induced injury are the small pyramidal cells of the motor cortex and Purkinje cells of the cerebellum. More widespread neuronal degeneration occurs in subacute or chronic cases, particularly in the pyriform cortex, Ammon's horn, and deep structures in the temporal lobes. The degenerating neurons have eosinophilic, granular cytoplasm and are often shrunken. The nuclei are pyknotic and may be eccentric. The surrounding neuropil is edematous, and the endothelial cells of the capillaries are swollen and proliferating. The malacic lesion remains viral associated in these cases, and inclusion bodies can be seen in the neurons and astrocytes, but the neuronal injury may be indirect and caused by immune mechanisms, ischemia, or anoxia.

Patchy demyelination is very common in dogs that come to autopsy. Early in the course of the cerebral involvement (this may be difficult to judge in clinical material because of the great variation in the onset in neurologic signs) there is vacuolation of the white matter. This vacuolation may be widely spaced or in foci, giving the lesion a spongy appearance. In some foci there is only a reduction in the intensity of myelin staining, which can be best demonstrated by myelin stains. At this stage there is no perivascular infiltration and little or no astrocytic reaction, although viral inclusion bodies can be frequently seen in their nuclei. There appears to be no special affinity of the demyelinating process for particular tracts, but it is usually more severe in some locations than others. The commonly involved sites are the anterior medullary velum, the cerebellar peduncles and arbor vitae, and the periphery of the optic chiasm and tracts. Demyelination is also common in subpial areas of the brain stem, either patchily or encircling it completely. Large foci of acute demyelination are uncommon in other parts of the brain.

Later stages of demyelination are characterized by reactive changes of astrocytes, consisting of diffuse proliferations of astrocytes and some microglia. Occasionally, proliferating astrocytes form multinucleated syncytial cells. Inclusion bodies can be found in both types of astrocytes. The demyelination becomes more obvious, but it is usual for the original framework of the tissue to remain and produce a lacelike appearance. Occasionally, especially in the folia of the cerebellum, there are foci of colliquative necrosis in which nothing remains except a few vessels and cells surrounded by fluid. These colliquative foci in the cerebellum may involve the granular layer but, as is usual for the lesions of canine distemper, spare the molecular layer. The demyelination reaction can progress to this stage with only very minor perivascular cuffing developing.

In canine distemper, perivascular cuffing is a late development and follows the demyelination. At the margins of larger foci in the chronic stage of the demyelination, thick perivascular cuffs of mononuclear cells form. At this stage the lesions have a distinctly "moth-eaten" appearance. Macrophages are prominent in the lesion, and astrocytic proliferation and fusion continue. The astroglia have abundant, glassy cytoplasm and plump processes. Viral inclusion bodies in the astrocytic nuclei may be common (Fig 6.25B). Animals that survive the encephalomyelitis of canine distemper may be left with old sclerotic astrocytic foci and myelin loss.

The role of the canine distemper virus in old-dog encephalitis remains unclear. **Old-dog encephalitis** (see the Nervous System, Volume 1) is a disease of mature dogs, characterized clinically by progressive motor and mental deterioration and pathologically by encephalitis with widely scattered perivascular infiltrations of lymphocytes and plasma cells and by intranuclear inclusions in the astrocytes and neurons. The inclusion bodies have been shown to contain paramyxovirus nucleocapsids and the viral antigen of canine distemper, but most investigators have been unable to recover the distemper virus from affected dogs or to transmit the disease to either dogs or distemper-susceptible ferrets. The nature of the lesions and the localization are distinct between old-dog encephalitis and the demyelinating encephalitis of canine distemper. The cerebellum, which is regularly involved in canine distemper encephalitis, is usually spared in old-dog encephalitis, and clinical signs of the two entities are different. If the canine distemper virus is the cause of old-dog encephalitis, the pathogenetic mechanisms must differ from those that operate to produce the conventional disease.

BOVINE RESPIRATORY SYNCYTIAL VIRUS INFECTION. Bovine respiratory syncytial virus belongs to the genus *Pneumovirus* of the Paramyxoviridae. Although serologic evidence of widespread infection in cattle populations has been recognized since 1975, only more recently has the virus been widely accepted as an important respiratory pathogen. Current evidence indicates that virulent strains of the virus are one of the synergistic agents involved in bovine respiratory disease, but they are also capable of causing outbreaks of respiratory disease and occasional deaths independently, most often in animals less than 1 year of age. Outbreaks usually occur in fall or early winter, generally within a few weeks of the animals' being housed. Late-weaned calves seem to be most susceptible to the disease. Prominent clinical signs are coughing and tachypnea, and in the most severely affected animals there is respiratory distress with open-mouthed breathing and forced, grunting expiration.

Gross lesions in animals dying of the naturally occurring disease are irregular lobular or confluent regions of atelectasis

and consolidation in cranioventral portions of the lungs. Interstitial emphysema is frequently present and is particularly evident in more caudal regions, where there sometimes are large bullae within interlobular septa. There is often mucopus within bronchi of pneumonic and atelectatic regions. The exudate may be foamy in major bronchi. Histologically, as with other myxoviruses, an acute bronchiolitis is a major component of the disease. A special characteristic of the bronchiolar response is the frequent prominance of syncytial giant cells formed by proliferating bronchiolar epithelial cells, some of which may contain acidophilic intracytoplasmic inclusion bodies. Alveoli are either atelectatic, because of bronchiolar obstruction, or contain a mixed cellular exudate in their lumina and mononuclear thickening of their septa. When alveoli are directly involved, alveolar epithelial proliferation with a tendency to form large syncytial giant cells is even more prominent than in bronchioles, and here also acidophilic intracytoplasmic inclusion bodies are sometimes seen. There is moderate accumulation of lymphocytes and plasma cells in the peribronchiolar and associated connective tissues.

Experimental infections with virulent strains produce a bronchointerstitial pneumonia with peak involvement about 5–8 days after infection. Syncytial giant cells of bronchiolar and alveolar epithelium are an outstanding feature during this period, and many contain intracytoplasmic inclusions. Both natural and experimental infections can lead to obliterative bronchiolitis in surviving animals.

In comparing bovine respiratory syncytial virus and parainfluenza-3 infections, it appears that bovine respiratory syncytial virus is more likely to cause severe respiratory disease by itself and that in fatal cases there is a reasonable chance of finding intracytoplasmic inclusion bodies in the exaggerated syncytial giant-cell formations. Once the giant-cell and inclusion-body stage has passed, it is not possible to distinguish the lesions.

A feature of the respiratory syncytial virus infection that has not been fully explained is its association with lesions of acute (atypical) interstitial pneumonia. This usually occurs during the fall in newly weaned, well-fed calves. After signs of an initial viral infection there is sometimes a period of 2 or 3 days during which partial recovery takes place, and then some of the calves develop severe respiratory distress, which often leads to death. In such cases, the most dramatic findings are those of widespread interstitial edema and emphysema accompanying acute interstitial pneumonia. Lesions of cranioventral bronchopneumonia may also be detected. The role played by the syncytial virus in causing the diffuse alveolar damage and its sequelae is not known. The diffuse damage has not been produced experimentally. It has been suggested that a hypersensitivity mechanism is involved, such as is believed to occur in children with antibodies to human respiratory syncytial virus who are reinfected with the virus, but there is no supporting evidence. Other alternatives are that the viral infection predisposes the calves to acute interstitial pneumonia of dietary or other origin, or that in some cases the infection is merely coincidental.

Antibodies to bovine respiratory syncytial virus have been detected in sheep, and mild pulmonary disease has been produced experimentally in young, colostrum-deprived lambs using a bovine strain.

Picornavirus Infections

Two serotypes of rhinovirus are widespread among cattle populations. **Bovine rhinovirus** is generally believed to be of minor importance as a cause of respiratory disease in cattle. Viral isolation and serologic responses occasionally provide circumstantial evidence that it is involved in causing upper respiratory disease. Experimental production of disease is inconsistent, but there have not been recent attempts to confirm earlier indications that the virus might be able to produce a bronchointerstitial pneumonia. It seems most probable that the viral replication and damage are limited to the upper respiratory tract in natural infections. The same holds true for **equine rhinovirus**, which is incriminated as a minor cause of acute upper respiratory disease in horses.

Calicivirus Infections

Caliciviruses are closely related to picornaviruses, and originally, feline caliciviruses, which are the important members of the genus causing respiratory disease, were considered feline picornaviruses. **Feline calicivirus** infection is commonly manifest as an upper respiratory tract disease (see Rhinitis). Feline caliciviruses can replicate in a variety of tissues, but their pathogenic effects are usually limited to the oral and respiratory mucosa and, to a lesser extent, the conjunctiva. Clinical signs are principally fever, oral ulceration, rhinitis, conjunctivitis, and possibly pneumonia. The range and severity of lesions depends on the virulence and tropism of the particular strain of calicivirus and on the mode of infection. Ulceration of oral epithelium is a common finding in both natural and experimental infections and reveals the close relationship of feline caliciviruses to vesicular exanthema virus of swine. The ulcers, which occasionally are detected in the earlier transient vesicular stage, are most often present on the dorsal surface or lateral margins of the tongue and on the hard palate and external nares. Serous or mucous rhinitis and conjunctivitis are less consistent findings but are more common in natural infections, or in experimental infections if the virus is administered intranasally rather than by aerosol exposure. Clinical signs of pneumonia may be present in natural infections, but affected cats usually recover within 7 to 10 days unless bacterial complications ensue.

Most information on the pneumonia caused by feline caliciviruses is derived from experiments using heavy exposure to aerosolized pneumotropic strains. This produces an exaggerated picture of lung lesions compared to natural infections. Nevertheless, certain strains of the virus have a strong tropism for alveolar type I epithelial cells. The resulting lesion is an acute to subacute interstitial pneumonia with little of the bronchiolitis produced by the viral infections described previously. Grossly, the pneumonia involves cranioventral margins of the lungs, and possibly irregular foci elsewhere. Early lesions are bright red and become gray-red at the peak of consolidation (7–10 days) and thereafter become gray-tan as resolution occurs. Histologically, the lesion is an interstitial pneumonia initiated by virus-induced necrosis of alveolar type I epithelial cells. The epithelial necrosis is extensive from $\frac{1}{2}$ day to 4 days after infection and is accompanied by exudation of serofibrinous fluid and large numbers of neutrophils. Hyaline membranes may be present. As the viral replication, necrosis and acute inflammation

subside, type II epithelial cells proliferate to line denuded alveolar walls, and the inflammatory cells become increasingly mononuclear. Between 7 and 10 days after infection, alveoli are epithelialized by type II cells; lumina contain mostly macrophages, and alveolar septa are thickened by accumulation of lymphocytes, plasma cells, and sometimes, fibroblasts. Few residual lesions are present after 30 days, other than scarring as the result of necrosis of alveolar walls and hemorrhage that occurred during the acute phase. The upper respiratory tract involvement in feline herpesvirus infections compared to the oral and pulmonary distribution of lesions in calicivirus infections are useful differential features, especially so in cats reaching the pathologist. Specific diagnosis, however, requires demonstration of virus in tissues by immunofluorescence.

Adenovirus Infections

Adenoviruses have been isolated from most species of animals. They have differing virulence and tissue tropisms, but more often cause respiratory and enteric disease than other manifestations. The most pronounced feature of the pneumotropic strains is a necrotizing and proliferative bronchiolitis. Severe, naturally occurring disease usually requires an immunodeficiency state.

Canine adenovirus type 1 is the cause of **infectious canine hepatitis** and is described with diseases of the liver (in the Liver and Biliary System, this volume). **Canine adenovirus-2** is more strictly associated with respiratory disease, but strain differences within both serotypes makes the distinction between them not as clear-cut as once thought. Naturally occurring respiratory disease caused by adenovirus in dogs is mostly found in conjunction with canine distemper or other conditions causing immunologic impairment. The salient features are necrotizing bronchiolitis and the presence of large, amphophilic, intranuclear inclusions in swollen nuclei of degenerating bronchiolar epithelial cells. Intranuclear inclusions are usually less common in alveolar and bronchial epithelial cells and alveolar macrophages. The inclusions either fill the nuclei or are separated by a narrow clear zone from the thickened nuclear membrane (Cowdry type A inclusion). Affected bronchioles are filled with debris of sloughed epithelium and neutrophils. When viral infection of alveolar cells is extensive, there is an accompanying exudate of serofibrinous material, neutrophils, erythrocytes, and macrophages. Alveolar epithelialization can be prominent after viral replication has peaked (~10 days). Interstitial thickening by mononuclear cells and neutrophils occurs but is not an impressive feature.

Equine adenovirus infection is widespread in horses but mainly causes disease in young Arabian foals with congenital, combined or selective immunodeficiency disease. Pulmonary lesions are a combination of coalesced atelectatic and consolidated lobules in cranioventral regions; large amounts of lung may be affected. Mucopurulent exudate is frequently present in the airways. Histologically, the main lesion is a severe bronchiolitis, which varies from necrotizing to proliferative, depending on the age of the lesions and the proportion of epithelial cells infected with virus. In the early stage of severe infection, there is extensive necrosis and sloughing of bronchiolar epithelium (Fig. 6.26A). Later, bronchiolar epithelium is hyperplastic, and swollen superficial epithelial cells contain amphophilic intranuclear inclusion bodies. Large, indistinct, blue inclusions are present in nuclei of dead cells that have been sloughed into the lumen (Fig. 6.26B). The combination of sloughed or hyperplastic epithelium and luminal filling by cell debris and neutrophils causes bronchiolar obstruction, which is responsible for the widespread alveolar atelectasis. The uncomplicated adenoviral lesion is sometimes limited to airways, without direct alveolar involvement. In other instances there are intranuclear inclusions in alveolar epithelial cells and an alveolitis mainly characterized by accumulations of macrophages and a variety of leukocytes. Epithelial lesions and inclusions may also be present in conjunctival and upper respiratory epithelium during the height of the disease. They can also occur in epithelium of the renal pelvis, ureters, urinary bladder, urethra, lacrimal and salivary glands, and pancreas. The viral bronchiolitis or bronchopneumonia and the associated immunodeficiency state may combine to lead to secondary bacterial pneumonia or pneumocystis pneumonia (Fig. 6.26C,D).

A variety of epitheliotropic and endotheliotropic **bovine** and **ovine adenoviruses** has been isolated from ruminants. Circumstantial evidence indicates that certain serotypes can cause mild respiratory or enteric disease or a combination of both. They are not generally considered to be important pathogens, however. Experimental infection of calves with epitheliotropic strains can cause necrotizing and proliferative bronchiolitis, with intranuclear inclusions similar to the lesions occurring in foals. Only rarely are the characteristic lesions found in naturally occurring disease, usually in very young calves that lack colostral antibody or in which environmental stress or intercurrent diseases have impaired immune responses. A similar situation seems to exist in sheep. A noteworthy feature of the lesions caused by at least one strain of adenovirus from sheep is the exaggerated enlargement of both nucleus and cytoplasm of inclusion-bearing bronchiolar and alveolar epithelial cells. The pronounced cytomegaly can cause confusion with the cellular enlargement associated with cytomegalovirus infections.

Porcine adenoviruses studied so far appear to have less affinity for pulmonary epithelium than those from the species already mentioned. Limited experimental information indicates that pulmonary lesions are probably more of a true interstitial pneumonia, with alveolar septa thickened by proliferation of alveolar epithelial cells and accumulation of macrophages, lymphocytes, and plasma cells. Cells within alveolar septa, some possibly capillary endothelial cells, contain bluish intranuclear inclusions. Bronchiolar epithelial necrosis or hyperplasia is not a significant feature. Porcine adenoviruses have been associated with field cases of encephalitis or diarrhea but have not been established as an important cause of respiratory disease.

Herpesvirus Infections

Members of the family Herpesviridae are important causes of respiratory disease. Three of them are discussed under Rhinitis: inclusion-body rhinitis of swine, infectious bovine rhinotracheitis, and feline viral rhinotracheitis. Another described elsewhere is malignant catarrhal fever (see the Alimentary System, this volume). Pseudorabies (Aujeszky's disease) mainly causes disease of the nervous system (see the Nervous System, Volume 1), but certain strains of the virus can also cause rhinitis

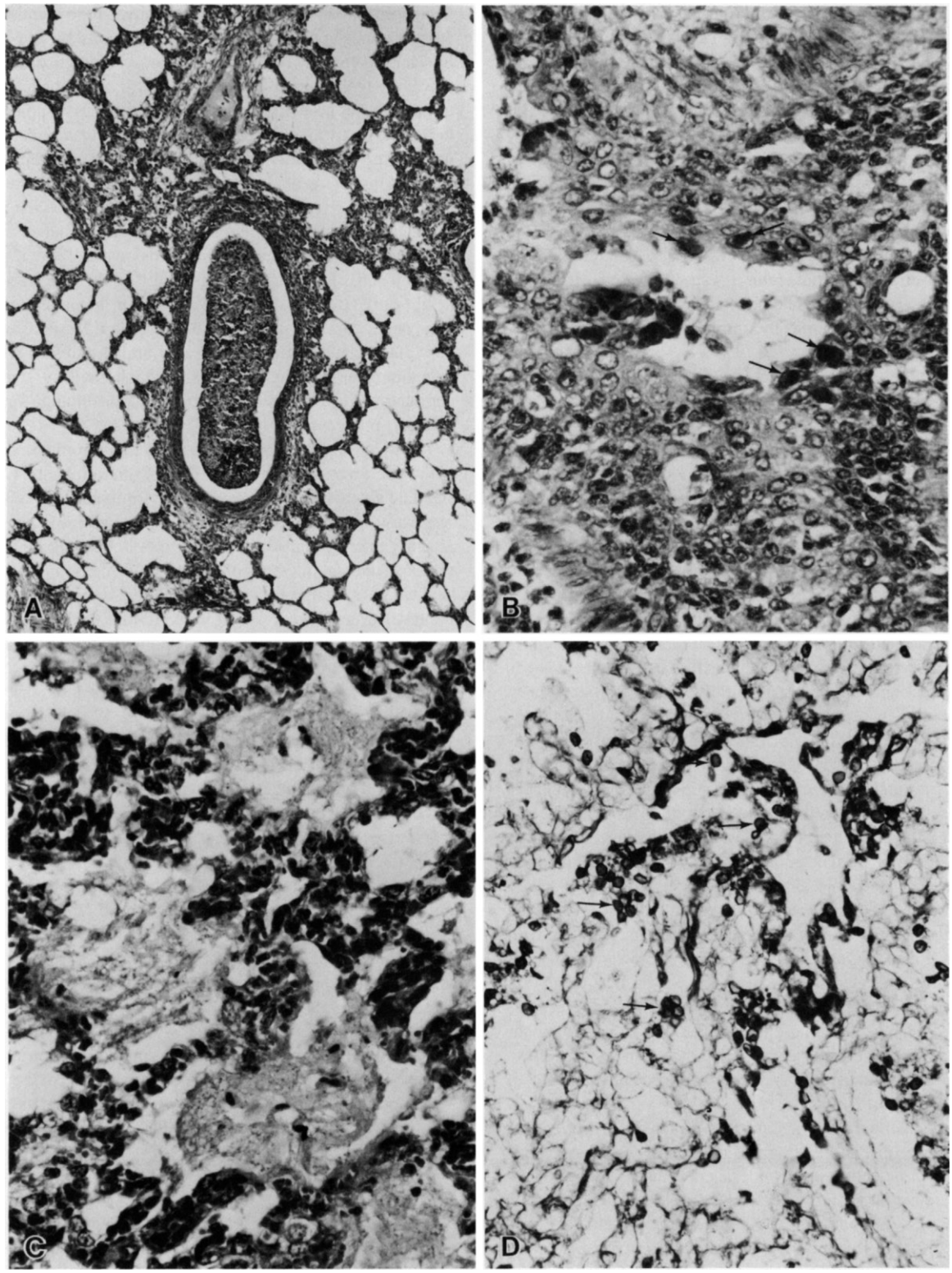

Fig. 6.26. Adenovirus infection in Arabian foal with combined immunodeficiency. (**A**) Acute necrotizing bronchiolitis. (**B**) Intranuclear inclusions (arrows) in superficial hyperplastic bronchiolar epithelium. (**C**) Pneumocystis pneumonia complicating adenovirus infection. Alveoli contain abundant foamy and granular acidophilic material. (**D**) *Pneumocystis carinii* organisms revealed by methenamine–silver stain (arrows).

and pneumonia in swine. The severe acute lesion is hemorrhagic consolidation of cranioventral regions of the lung, which histologically has necrotizing lesions in bronchioles and adjacent alveoli as the principal features. Acidophilic or amphophilic intranuclear inclusions might be found in bronchiolar and alveolar epithelial cells early in the infection.

Canine herpesvirus is most important as a cause of fatal, generalized infection in neonatal puppies (see the Female Genital System, Volume 3). It can occasionally be associated with usually nonfatal respiratory infection in older animals, either alone or with other infectious agents. The respiratory lesions are those to be expected from herpesviruses, namely, a necrotizing rhinotracheitis and, possibly, bronchopneumonia. Acidophilic intranuclear inclusions can sometimes be found in epithelial cells in early lesions, more commonly in nasal and turbinate mucosa.

Equine herpesvirus (rhinopneumonitis virus) is an important respiratory tract pathogen, and even when herpesviruses cause abortion, they appear to affect mostly full-term foals and cause predominantly pulmonary lesions. The respiratory disease often occurs independently of abortions, and it appears likely that different strains of equine herpesvirus are specifically associated with each syndrome. Currently, strains causing rhinopneumonitis and abortion are grouped together as equine herpesvirus-1, but eventually they will probably be separated. For the role of equine herpesviruses in causing genital lesions and abortion, see the Female Genital System (Volume 3). A syndrome of paresis or ataxia is occasionally seen in mares (see the Nervous System, Volume 1).

The clinical respiratory disease is seen mostly in weanling foals during the fall. It is characterized by slight fever, and serous or catarrhal rhinitis and conjunctivitis. Rarely, there is diarrhea and edema of the extremities. Recovery occurs in ~1 week but may be delayed when secondary bacterial infections supervene and cause mucopurulent or suppurative rhinitis and pharyngitis, or possibly pneumonia. The uncomplicated viral infection is not fatal, even when severe, as it can be in young horses crowded in stockyards or stables. When fatalities occur, they are usually due to secondary suppurative bacterial bronchopneumonias. Intranuclear inclusions are extremely rare in postnatal respiratory infections.

Parvovirus Infections

Canine parvovirus is mainly a cause of enteritis and myocardial necrosis [see the Alimentary (this volume) and Cardiovascular (Volume 3) Systems]. Pulmonary lesions are usually those of severe acute to subacute pulmonary congestion and edema, secondary to the myocardial damage. A true viral interstitial pneumonia is generally limited to very young pups (<2 weeks of age) in which there is generalized parvovirus infection. In such cases, basophilic intranuclear inclusions can be found in the vascular endothelium of many organs, including the lung. In the lung, viral infection of capillary endothelium, and perhaps alveolar epithelium, causes necrosis and accumulation of mixed inflammatory cells, mostly lymphocytes and monocytes. Alveolar edema is partly the result of local alveolar septal inflammation, and partly cardiac failure.

Reovirus Infections

Of the three serotypes of reovirus, one or more have been isolated from cattle, horses, dogs, and cats. They are associated with inapparent infection or a mild upper respiratory disease. Their role as significant causes of, or predisposers to, pneumonia is not established.

Retrovirus Infections

OVINE PROGRESSIVE PNEUMONIA. Chronic progressive pneumonia of sheep (maedi) is a slow virus infection of the ovine lung, characterized by a gradually progressive interstitial pneumonia. It is caused by identical or very closely related strains of maedi–visna virus. Maedi–visna virus belongs to the lentivirus subfamily of retroviruses and therefore resembles the type C oncornaviruses and the virus causing pulmonary adenomatosis (*jaagsiekte*) of sheep (see Neoplastic Diseases of the Lungs). The name of the maedi–visna virus is derived from the fact that investigators in Iceland were the first to isolate the virus and demonstrate that the progressive pneumonia they referred to clinically as maedi ("shortness of breath") and the meningoencephalitis they designated clinically as visna ("wasting") were different manifestations of the same slow virus infection. For descriptions of visna, see the Nervous System (Volume 1).

The pulmonary disease caused by the maedi–visna virus occurs widely throughout Europe, North America, Africa, and Asia, and until the development and use of serologic tests for detecting infected animals, was being spread further by importation of affected sheep. In addition to the terms ovine progressive pneumonia and maedi, the condition is known as **Graaff–Reinet disease** in the Republic of South Africa, ***zwoegerziekete*** in the Netherlands, and ***la bouhite*** in France.

The virus is spread by close contact among sheep, and in milk from ewe to lamb. *In utero* infection can also occur. Infection of sheep is common in regions where the disease is endemic, but many go to slaughter without developing clinical signs. Because of the slow rate of progression of pulmonary lesions, clinical signs are uncommon until sheep reach 2 years of age. Evidence of disease is most frequent among sheep 5 to 10 years of age. The early signs are loss of weight and increased respiratory rate on exertion. Once signs begin, death usually occurs within about 6 to 8 months because of continuing deterioration in condition and increasing respiratory difficulty.

The specific lesions of ovine progressive pneumonia occur in the lungs and their associated lymph nodes. Grossly, the lungs of severely affected sheep do not collapse fully when the thorax is opened, and sometimes the impressions of the ribs are retained. In cases uncomplicated by bronchopneumonia or abscessation, the lungs are mottled gray to grayish tan, and the pleura is smooth and glistening (Fig. 6.27A). Lungs are much heavier than usual, often two or more times the normal weight. Close examination of the lung reveals that although the lesions are widespread, there is relative sparing of the cranioventral regions in the absence of secondary bronchopneumonia. Least involved regions have an irregular grayish speckling against a light tan background. More involvement results in a reticular pattern, and in most severely affected regions there is homogeneous grayish consolidation. The lungs have a soft rubbery consistency or are

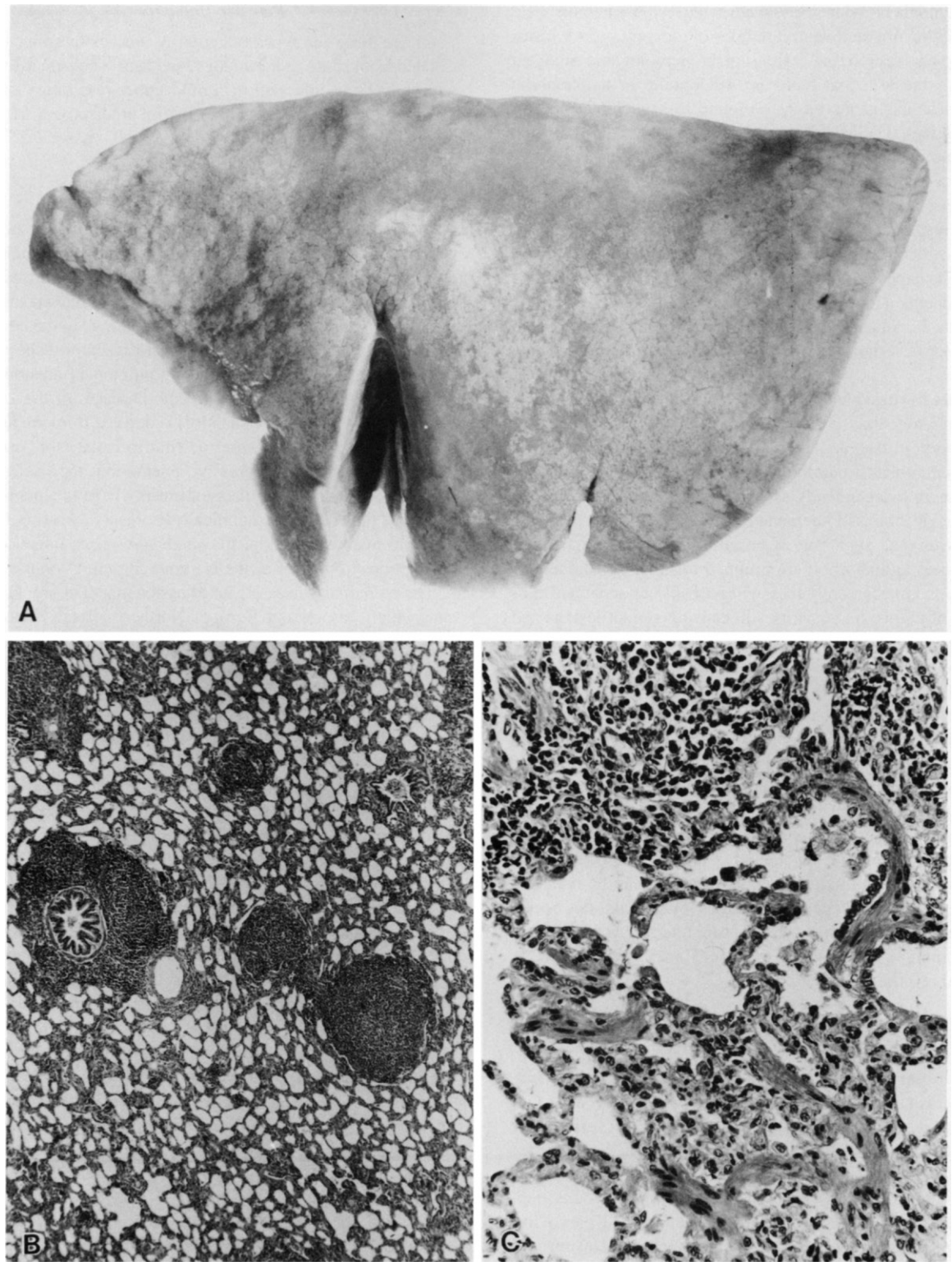

Fig. 6.27. Chronic progressive pneumonia (maedi). Sheep. (**A**) Lungs fail to collapse and have widespread, grayish mottling. (**B**) Diffuse thickening of alveolar walls and lymphofollicular accumulations around vessels and airways. (**C**) Hyperplasia of smooth muscle of terminal bronchioles and alveolar ducts, with adjacent interstitial accumulation of lymphoid cells.

moderately firm, depending on the degree of confluence of the lesions. The cut surface is moist, but without oozing of free fluid. When complicated by bronchopneumonia, there are the typical cranioventral consolidations, with pus-filled airways. There can also be coexistent lungworm lesions. A consistent gross finding in ovine progressive pneumonia is enlargement of bronchial and mediastinal lymph nodes, with soft, grayish white, homogeneous thickening of cortical regions on cut section.

Histologically, the most characteristic feature of ovine progressive pneumonia is the extensive lymphofollicular proliferations that occur predominantly in the perivascular, peribronchial, and peribronchiolar sheaths in association with the pulmonary lymphatics. The most consistent association is with pulmonary veins. Many of the lymphoid follicles contain germinal centers (Fig. 6.27B). The next most striking feature is hyperplasia of smooth muscle, which is most evident in the walls of terminal bronchioles and alveolar ducts but also extends into the walls of neighboring alveoli (Fig. 6.27C). Alveolar septa are thickened by infiltrations of lymphocytes and macrophages, especially at the peripheries of the lymphoid nodules. The amount of interstitial fibrosis is usually slight but tends to be exaggerated by collapse of small clusters of alveoli and apposition of their walls (microatelectasis). Hyperplasia of alveolar type II epithelial cells is not a prominent feature of ovine progressive pneumonia, in striking contrast to ovine pulmonary adenomatosis (see Neoplastic Diseases of the lungs). Partial or complete lining of alveoli by cuboidal type II cells does occur, but usually only in alveoli adjacent to the large interstitial lymphoid follicles or occasionally lining large, cystlike spaces. Bronchiolar epithelial hyperplasia is also not a prominent feature of uncomplicated ovine progressive pneumonia, although collapsed airways have pleated epithelium that can be mistaken for hyperplasia or that leads to exaggerated interpretation of it. The alveolar exudate in the uncomplicated disease is usually sparse and consists mainly of alveolar macrophages and small amounts of debris. Multinucleated macrophages are a variable feature. Suppurative lesions oriented around bronchioles indicate a secondary bacterial bronchopneumonia. Bronchial and mediastinal lymph nodes have a chronic hyperplastic lymphadenitis in which the main feature is pronounced follicular hyperplasia.

In infected flocks, there is usually serologic evidence of infection of many animals, and the maedi–visna virus can be isolated from both normal and diseased lungs. The diagnosis of ovine progressive pneumonia depends mainly on the presence of the characteristic lymphofollicular interstitial pneumonia.

Progressive pneumonia is the most common manifestation of disease in sheep infected by the maedi–visna virus. Meningoencephalitis (visna) is less common and occurs separately or, occasionally, in the same sheep. It is now recognized that the virus also causes a chronic proliferative arthritis about as frequently as the meningoencephalitis. Lymphofollicular lesions sometimes occur in mammary glands of infected sheep. In these respects, the range of lesions caused by maedi–visna virus closely resembles those produced by the caprine arthritis–encephalitis virus described below. The extensive lymphoid proliferations in ovine progressive pneumonia and the similarities of the maedi–visna virus to the oncornaviruses have given rise to the speculation that the proliferations are neoplastic in nature. The proliferative lymphoid elements do not resemble any of the forms of lymphoma, however, and the cells do not exhibit malignant cytologic or behavioral characteristics.

Caprine arthritis–encephalitis is a disease complex in goats caused by a retrovirus antigenically related to the maedi–visna virus but separable on the basis of the large differences in nucleic acid sequences. The caprine virus has mainly been studied in reference to its ability to cause encephalitis and arthritis, as the name indicates (see the Nervous System, and Bones and Joints, Volume 1). An alternative term for the disease is viral leukoencephalomyelitis–arthritis. There are brief descriptions of a chronic interstitial pneumonia produced by the virus, but there has not been a detailed study of the pulmonary lesions. Naturally occurring chronic pneumonia in older goats often has two prominent features lacking in ovine progressive pneumonia. One is extensive alveolar filling mainly by a dense, acidophilic, proteinaceous (lipoproteinaceous) material. The other is widespread lining of alveolar septa by alveolar type II epithelial cells. The pathogenesis of these components and their relationship to infection with the caprine arthritis–encephalitis virus remain to be determined.

Other Virus Infections

A variety of viruses, particularly those of enteric origin, such as enteroviruses, coronaviruses, and bovine virus diarrhea virus, have occasionally been isolated from cases of respiratory disease. Significant primary roles have not been established for such agents, although the immunosuppressive effects of viruses like bovine virus diarrhea virus could be important in predisposing infected cattle to respiratory infection.

Bacterial Diseases

Pasteurellosis

The pasteurellae are strict parasites of animals, their usual habitat the mucous membranes of the nasopharyngeal and oral regions. The type species is *Pasteurella multocida.* The other species of major importance for respiratory disease in domestic animals is *P. haemolytica.* A third, *P. pneumotropica,* can frequently be isolated from the pharynx of cats and may contaminate bite wounds made by cats.

The collective term pasteurellosis will be used here for infections by either *Pasteurella multocida* or *P. haemolytica.* Pasteurellosis may be manifested as a peracute or acute septicemia, or be slightly less acute and cause signs according to the organ in which the infection is localized. Thus, in the various species, pasteurellosis can take a variety of forms. It may be a primary infection, a contaminant of cutaneous or mucosal injuries, or a secondary infection, especially following viral disease of the respiratory tract.

Pasteurella multocida can be isolated from pathologic conditions in cattle, sheep, buffalo, deer, pigs, rabbits, and other animals, and from a variety of birds in which it causes fowl cholera. The different strains had been named for the species of host in which they were found, but it is current practice to regard these as types of the one species *P. multocida.* Mammalian

isolates of *P. multocida* are typed by biologic characteristics (biotype), and serologically (serotype). The important strains form smooth colonies and are assigned on the basis of capsular antigens to one of four serotypes: A, B, D, and E. Further characterization can be made on the basis of somatic O antigens. Types B and E are the cause of epidemic pasteurellosis, the classical hemorrhagic septicemia of cattle, sheep, goats, deer, and buffalos. Type B is widespread in tropical Asia and Africa and in southern Europe. Type E occurs mainly in central Africa. Type A is ubiquitous and responsible for sporadic infections in many species; strains of this serotype are the ones usually isolated from pneumonia of cattle and fowl cholera and are sometimes found in pneumonia of swine. Type D is ubiquitous but has been found particularly in association with atrophic rhinitis and pneumonia in swine. It is also occasionally isolated from pneumonia in sheep.

Strains of *Pasteurella haemolytica* are also classified by biotype and serotype. The organism is weakly hemolytic, and as a rule is nonpathogenic for rodents. The two main biotypes are A (arabinose fermenters) and T (trehalose fermenters). There are 15 currently recognized serotypes based on analysis of capsular antigens. Of these, 3, 4, 10, and 15 belong to biotype T, and the remainder to biotype A. Type A1 is the usual cause of severe pneumonic pasteurellosis ("shipping fever") of cattle. Type A strains are associated with pneumonia in sheep and septicemia in lambs before weaning. Type T strains cause septicemia in lambs past weaning age.

Pasteurella multocida and *P. haemolytica* are both members of the bacterial flora of normal nasopharyngeal and oral mucous membranes, with the former usually predominating. Outbreaks of disease caused by the organisms occur when local and systemic defense mechanisms are impaired and virulent strains of pasteurellae undergo massive proliferation prior to invading the nasopharyngeal mucosa or being inhaled in large numbers into the lung. Predisposing factors, such as the stress induced by shipping, crowding, climatic changes, and poor management, or the damaging effects of respiratory viral infections, were mentioned previously (see Bronchopneumonia). Many of the effects of stress are mediated by adrenocorticosteroid release.

CATTLE. The major pasteurelloses of cattle are hemorrhagic septicemia and pneumonic pasteurellosis. Two other forms of pasteurellosis, meningitis in calves and mastitis in cows, occasionally are important in local situations. Meningeal pasteurellosis of calves is caused by *Pasteurella multocida,* and it is usually a disease of housed calves 2–4 months of age. The reaction is fibrinopurulent and is sometimes accompanied by polyarthritis of the same type. Bovine mastitis is caused by either *P. multocida* or *P. haemolytica*. Sporadic, peracute, fatal mammary infections occur that are caused by *P. haemolytica;* these infections are characterized by severe hemorrhagic inflammation of the parenchyma and a fibrinous and necrotizing inflammation of the ducts, quite similar to the peracute inflammation produced by coliform organisms. The pathway of infection is via the duct system. *Pasteurella multocida* can be responsible for outbreaks of mastitis in a herd. If the mastitis is acute, it may be progressive and result in fibrosis and atrophy. The route of infection is assumed to be through the ducts, and the source of infection, in some cases at least, is assumed to be the suckling calf. *Pasteurella haemolytica* is sometimes responsible for outbreaks of abortion in cattle in which there are no premonitory signs.

The classical form of bovine pasteurellosis is **hemorrhagic septicemia**, which is caused by *Pasteurella multocida* types B or E. This disease was originally recognized in western Europe in the last century as a severe epidemic in deer that later spread to cattle, wild and domestic pigs, and horses. It has been observed as an epidemic disease of cattle, sheep, and horses in Argentina, in bison in the western United States, and it is the disease known as *el guedda* of Syrian camels, and *barbone* of Italian buffalo. Hemorrhagic septicemia is now limited largely to tropical lands from Egypt to the Philippine Islands and in these regions is primarily a disease of buffalo.

The most detailed descriptions are of the disease as it occurs in Asia. There outbreaks occur particularly during the rainy season. In intervening periods, the organism is apparently maintained in the nasopharyngeal regions of carrier cattle or buffalo. The start of an outbreak depends on some stress disturbing the balance in a carrier animal. This results in extensive proliferation and dissemination of the organisms to susceptible contact animals.

Approximately 10% of animals survive subclinical infections and become immune, but once the infection is established clinically, the mortality is 100%, even though the bacteria may be killed by chemotherapy. This, together with the immense proliferation of organisms in the clinical disease, indicates that toxins, particularly endotoxins, are important in causing the fatal outcome.

Hemorrhagic septicemia is almost by definition a peracute disease, with death often so early that few signs are observed. When observed clinically, there is high fever and rapid prostration, with profuse salivation. The saliva and feces contain large numbers of pasteurellae. The postmortem picture is characterized by petechial hemorrhages on the serous membranes and in the various organs, especially the lungs and muscles. Severe endotoxemia may cause an acute fibrinohemorrhagic interstitial pneumonia. The lymph nodes are swollen and hemorrhagic, and there may be bloodstained fluid in the serous cavities. Acute gastroenteritis, which can be hemorrhagic, is often present. The spleen is not greatly enlarged, which is a point of differentiation from anthrax.

There is an edematous form of hemorrhagic septicemia, which may also be peracute. Actually, edema of the throat is a regular part of hemorrhagic septicemia, but in some cases it can be unusually pronounced. It is characterized by extensive swelling of the subcutaneous tissues, especially of the throat, but it might affect the whole head, the tongue, or some other part of the body, such as the brisket or a limb. The swellings are produced by a copious, clotted, straw-colored exudate. The additional lesions in this form of pasteurellosis are those of hemorrhagic septicemia, although death may be caused by asphyxiation.

Pneumonic pasteurellosis refers to forms of pneumonia in which the predominant pulmonary damage is caused by pasteurellae. The most important form is the fulminating fibrinous lobar pneumonia caused, usually, by *Pasteurella haemolytica.* The

frequent occurrence of this form of the disease in the period soon after shipping and crowding of beef cattle led to the widespread use of the term "shipping fever." This term emphasizes the major circumstances under which pneumonic pasteurellosis occurs but cannot be used with precision as a synonym. Acute fibrinous lobar pneumonia can also occur in very young calves, in older calves as an infection superimposed on enzootic pneumonia, and sporadically in cattle of any age. The fulminating fibrinous pneumonia is principally the result of rapid and massive proliferation of organisms. Although this is mostly associated with pathogenic strains of *P. haemolytica* in animals whose pulmonary defense has been compromised by various environmental stresses, and often a predisposing viral infection, it can also be caused by *P. multocida*. Occasionally, *Haemophilus somnus* causes an indistinguishable lesion. Of the various viruses that have been incriminated as predisposing to the severe *Pasteurella* pneumonia, parainfluenza-3 virus appears to be the most common. It has also been the virus used in most of the successful attempts to reproduce the characteristic pneumonia. When specific-pathogen-free calves or lambs are exposed to parainfluenza-3 virus, and 4–7 days later to aerosolized pathogenic strains of *P. haemolytica*, a severe pneumonia can be produced. Infectious bovine rhinotracheitis virus and, possibly, bovine respiratory syncytial virus and others appear to play a similar role.

The general features of fibrinous lobar pneumonia are described under Lobar Pneumonia. In addition to the extensive reddish black to grayish brown cranioventral regions of consolidation with prominent gelatinous thickening of interlobular septa and fibrinous pleuritis, areas of coagulation necrosis are a characteristic feature. At their most prominent, they appear as irregular but sharply demarcated regions with thick, white boundaries and sunken, deep red, central zones. Histologically, the necrotic regions are frequently seen to supervene in previously pneumonic tissue. They usually contain very large numbers of bacteria, particularly at their peripheries adjacent to the compacted debris of inflammatory cells that form the white boundary zones seen grossly. The cause of the necrosis is not fully determined. Although it has been attributed to thrombosis (infarction), the occurrence of thrombosed vessels is not consistent enough to be a satisfctory explanation, nor would it account for the necrosis sometimes cutting across interlobular septa into neighboring lobules (Fig. 6.29A). In view of the massive numbers of bacteria present, it is much more likely that the necrosis is caused by the necrotizing effect of the large amounts of bacterial endotoxins and cytotoxins released locally and by the associated capillary thrombosis. Another characteristic histologic feature is the presence of clustered inflammatory cells with elongated or streaming nuclei. These are commonly referred to as "oat cells." They seem to be an effect of bacterial toxins on leukocytes accumulating within inflamed alveoli. The extent to which they are derived from blood monocytes or neutrophils is not firmly established.

Also properly included in the general term "pneumonic pasteurellosis" is the less fulminating, fibrinous or fibrinopurulent bronchopneumonia (Fig. 6.28). This is more commonly caused by *Pasteurella multocida* but can be caused by *P. haemolytica*. The nature of the pneumonia caused by pasteurellae depends on the rate and extent of bacterial proliferation and the amount of toxins released, which in turn depend on the virulence of the strain of organism and the degree to which the defenses of the host are impaired. Although there is a tendency for *P. haemolytica* to be the cause of fulminating fibrinous lobar pneumonias, and *P. multocida* the cause of fibrinopurulent bronchopneumonias, this can change with local circumstances, and intermediate lesions (Fig. 6.29B) may be found among cases in the same outbreak.

SHEEP. There are several syndromes in sheep associated with *Pasteurella haemolytica* or *P. multocida*. Mastitis in ewes caused by *Pasteurella* spp. is discussed with the Female Genital System (Volume 3). The principal forms of pasteurellosis in sheep are septicemia caused by *P. haemolytica*, and sporadic or enzootic pneumonia, which is associated more often with *P. haemolytica* than *P. multocida*.

Septicemia caused by *Pasteurella haemolytica*, biotype T, occurs mainly in weaned lambs during the fall months, but it can occur in other age groups and at other times of the year. Deaths, which seldom exceed 5% of the sheep at risk, usually follow within a few days of changes in pasture, feed, or other management practices.

The clinical syndrome is not specific. Signs of illness are vague, and the usual course is short, with sudden death reminiscent of clostridial enterotoxemia. At necropsy, petechial and ecchymotic hemorrhages are usually present but sometimes difficult to detect. They occur in subcutaneous tissues, particularly of the neck and thorax, in intermuscular fascia, and in the pleura, epicardium, and mesentery. The lymph nodes are mainly affected in the throat and mesenteric regions, where they are hemorrhagic and edematous. Yellow plaques of necrotizing pharyngitis are common, especially around tonsillar crypts, and ulcers may involve the esophageal mucosa. The abomasal and colonic mucosae sometimes have shallow ulcers. The lungs have diffuse, severe congestion and edema with abundant white or bloodstained foam in the airways. Discrete hemorrhagic foci (infarcts) can sometimes be seen scattered throughout the lungs. The liver is usually congested, and in some cases there are many yellowish necrotic foci disseminated through the parenchyma. These are usually of miliary size but can be up to 1.0 cm in diameter and surrounded by a narrow red border. Occasionally there is inflammation of many joints, the pericardium, meninges, and choroid plexus, but the development of these lesions requires that the course be a little longer than it normally is. These additional lesions are observed more frequently in the experimental disease, which is less fulminating than the natural one.

Microscopic examination of tissues reveals a widespread bacterial embolism. The pale hepatic foci consist of colonies of bacteria with a surrounding ischemic zone. There may be thrombosis of the adjacent tributaries of the portal vein, and small amounts of parenchymal necrosis, but generally there is little or no leukocytic response. This is probably related to the short course of the disease, and partly the effects of bacterial toxin on the leukocytes. The pulmonary lesions are a combination of the effect of multiple bacterial emboli and the severe diffuse pulmonary congestion and edema found in sheep dying suddenly of

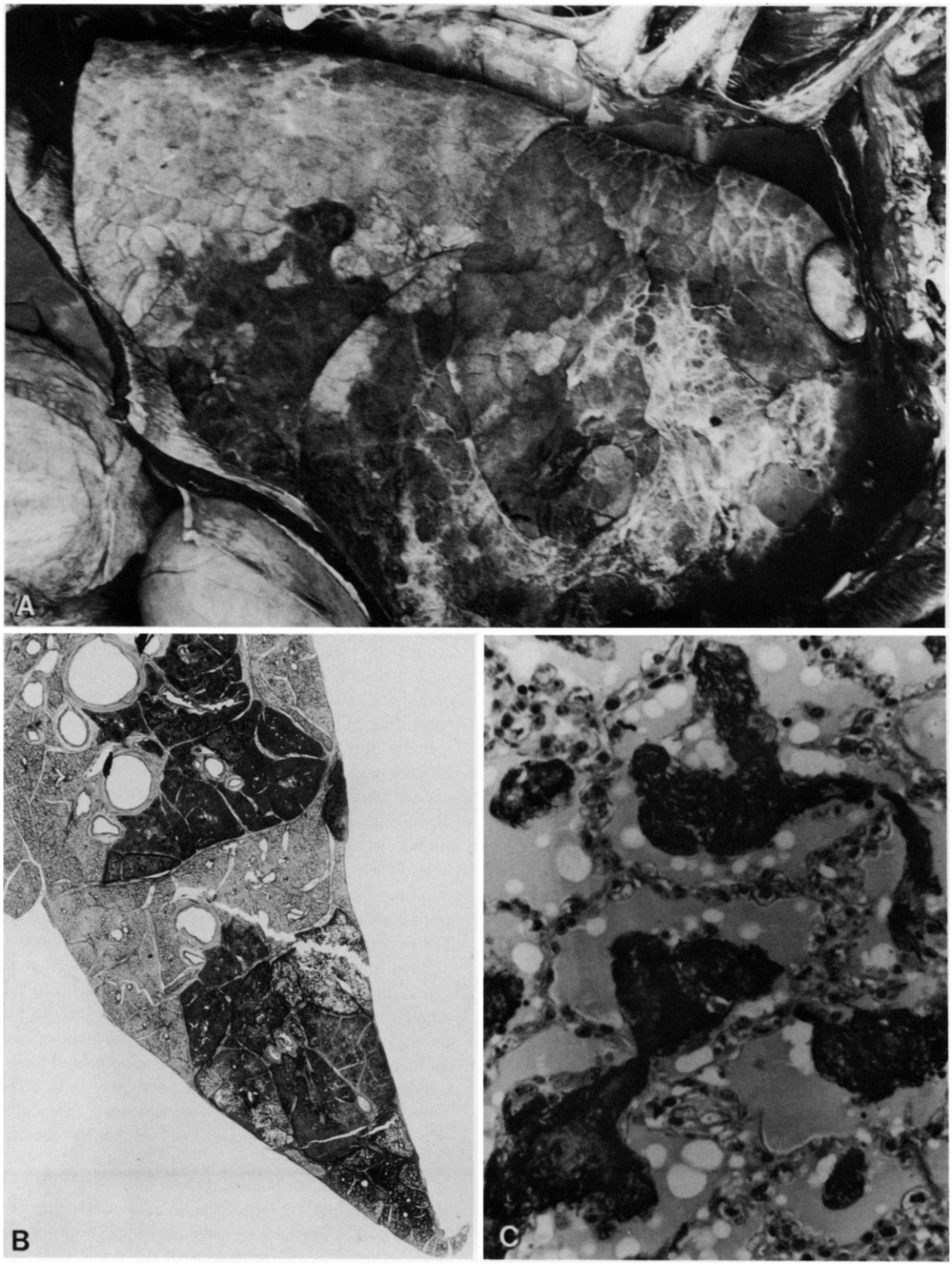

Fig. 6.28. (**A**) Fibrinous bronchopneumonia and pleuritis of pneumonic pasteurellosis. Ox. (**B**) Section of middle lobe in pasteurellosis. Ox. Irregular lobular involvement. (**C**) Intraalveolar fibrin clumps connecting through pores of Kohn in alveolar septa. Fibrinous pneumonia. Ox.

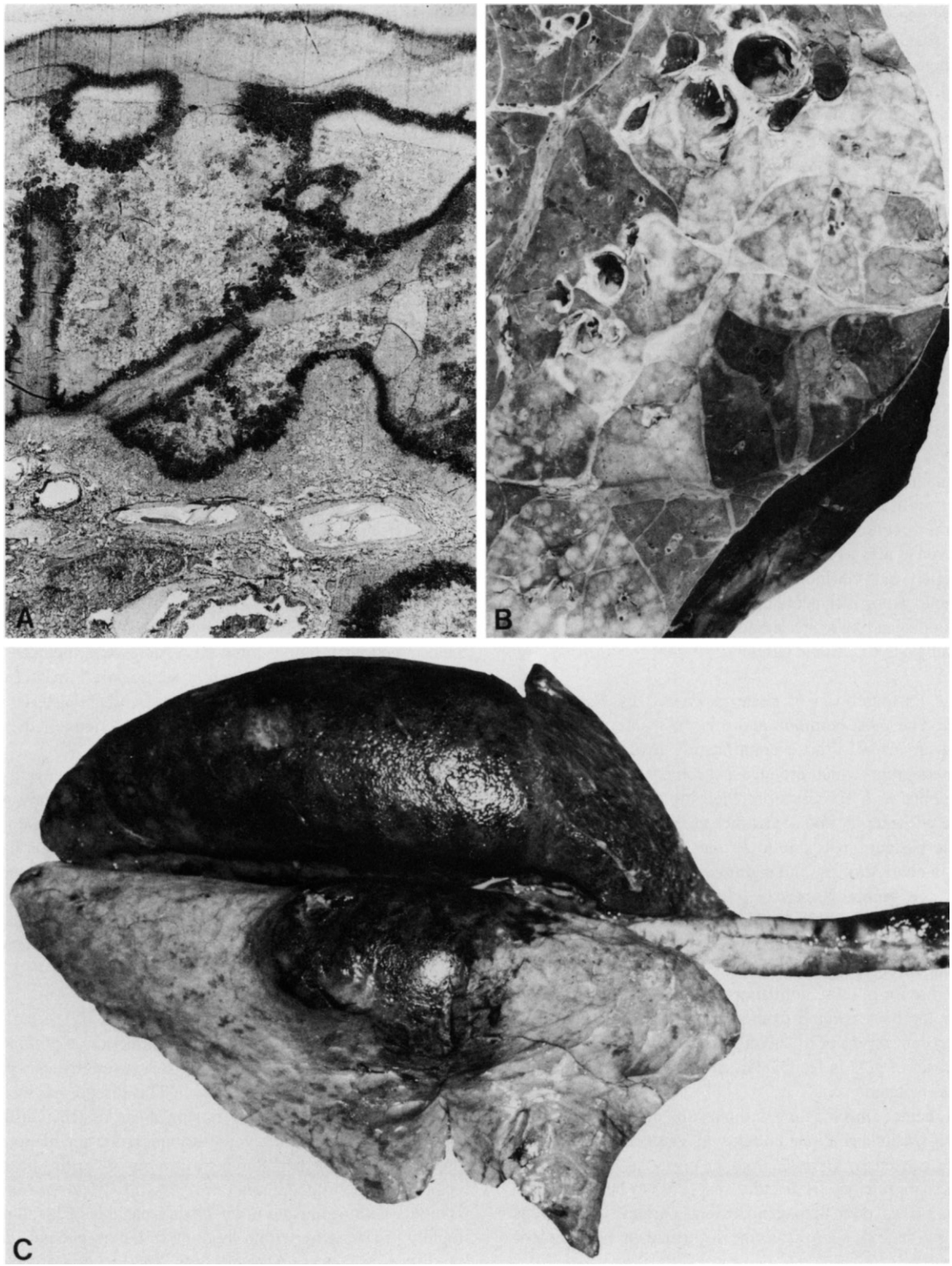

Fig. 6.29. (**A** and **B**) Fibrinonecrotic pneumonia of pneumonic pasteurellosis. Ox. (**A**) Large areas of pneumonic lung are necrotic and marginated by densely packed leukocytes. (**B**) "Marbled" pattern produced by differing degrees and stages of consolidation. (**C**) Porcine contagious pleuropneumonia (*Haemophilus pleuropneumoniae*). Hemorrhagic consolidation and necrosis in dorsal and hilar regions with fibrinous pleuritis. (Courtesy of B. W. Fenwick.)

almost any cause. In the focal hemorrhagic lesions, masses of bacteria occluding capillaries are accompanied by hemorrhagic and fibrinous exudate into the alveoli and sometimes with a peripheral zone of necrosis and degenerating, spindle-shaped leukocytes. Occlusive bacterial emboli are regularly found in the spleen and adrenals, and occasionally kidney, but are rare in other organs. Masses of bacteria adhere to the surface of the pharyngeal ulcerations and occlude underlying blood vessels and lymphatics. Peripheral and intermediate sinuses of the local lymph nodes also contain huge numbers of bacteria within the hemorrhagic and edematous exudate. The principal site of bacterial proliferation and subsequent systemic invasion is believed to be the pharyngeal lesion.

Pneumonic pasteurellosis in sheep is usually caused by *Pasteurella haemolytica*, biotype A. The same biotype can also cause septicemia in the absence of pneumonia in lambs less than 2 months of age. The generalizations regarding circumstances giving rise to pneumonic pasteurellosis in cattle hold true for sheep. Most outbreaks occur in lambs during late spring and early summer. Sudden climatic changes, gathering, and handling are the most commonly recognized predisposing situations. Viral infection, particularly by parainfluenza-3 virus, is also believed to play a role. The lesions tend to be those of acute hemorrhagic or fibrinonecrotic lobar pneumonia and serofibrinous pleuritis in acute cases, and fibrinopurulent bronchopneumonia leading to abscessation and fibrous pleural adhesions in subacute to chronic cases.

SWINE. Pasteurellosis of swine is caused by *Pasteurella multocida*. The most common and important infections by *P. multocida* are usually those complicating mycoplasmal (enzootic) pneumonia, which produce a chronic suppurative bronchopneumonia with abscessation. Pleuritis frequently accompanies the pneumonia, and sometimes pericarditis also occurs. Septicemic pasteurellosis due to *P. multocida* is occasionally observed in neonatal pigs, and meningitis can also be present in the same age group. *Pasteurella haemolytica* rarely affects swine but has been recovered from aborted fetuses.

Septicemic disease without localization or distinctive lesions is seen in adult pigs, especially those that are specific pathogen free. The disease in these animals is peracute, and *Pasteurella multocida* can be recovered from all organs in large numbers. The only recent report of a "hemorrhagic septicemia" type of pasteurellosis in pigs is from India, from which *P. multocida* type B was isolated.

Severe, acute, fibrinous pneumonias analogous to the more fulminating *Pasteurella* pneumonias in cattle and sheep are sometimes caused by *P. multocida* in pigs. As in cattle and sheep, stressing factors are usually suspected to be important. These are usually poor management, and perhaps intercurrent infection by viruses such as swine influenza or hog cholera (swine fever).

The acute fibrinous or fibrinonecrotic pneumonia is similar in many respects to the lesion in cattle. The extensive gelatinous thickening of interlobular and subpleural tissues and the severe serofibrinous pleuritis lead to the term "pleuropneumonia" being used on occasion. In this connection, although epidemiologic patterns indicate that most severe pneumonias of the "pleuropneumonia" variety are caused by *Haemophilus pleuropneumoniae (H. parahaemolyticus)*, there is no clear separation between the severe pneumonia caused by the two organisms. Massive proliferation of a Gram-negative organism releasing abundant endotoxins and cytotoxins is common to both infections, hence a common pulmonary response.

In addition to the severe thoracic lesions in pneumonic pasteurellosis, there is often acute pharyngitis and inflammatory edema of the throat, and yellow, jaundice-like discoloration of the carcass of unknown cause. Severe pharyngitis can be necrotizing and ulcerative. A fibrinohemorrhagic polyarthritis may be present, and there is intense congestion of the gastric and intestinal mucosa. Complete recovery from pneumonic pasteurellosis seldom occurs in pigs. Animals that survive the acute disease tend to develop chronic lesions that are usually fatal in due course. In these, most obvious findings are polyarthritis, adhesive pericarditis and pleuritis, and extensive areas of fibrotic lung which contain numerous abscesses or fibrous capsules enclosing sequestra or caseous detritus. As usual in the fibrinous pneumonias caused by *Pasteurella* spp., the bacterium can often be cultured from the blood and other organs as well as the lung. The septicemic or bacteremic nature of the infection is revealed also by the recovery of the bacterium from aborted fetuses from pregnant sows that survive the acute disease.

OTHER SPECIES. *Pasteurella multocida* has been reported in fatal infections in horses, and this species was included in the earliest reports of "hemorrhagic septicemia" from Europe. Pasteurellae may be found along with other bacteria in the fibrinous pneumonias that complicate infections of the upper respiratory tract in horses.

Pasteurella species are common inhabitants of the oral cavity of cats and dogs. They are important as infections in bite wounds. Pulmonary infections with pasteurellae are uncommon in dogs, and when present are usually found with other bacteria as complications of canine distemper and aspiration pneumonia. *Pasteurella multocida* causes meningitis and otitis media in cats. It is also commonly associated with pyothorax, often together with other bacteria, and probably results in many instances from penetration of the pleural cavity by a foreign body.

Haemophilus Infections

The most important *Haemophilus* infection is porcine contagious pleuropneumonia, which is caused by *H. pleuropneumoniae (H. parahaemolyticus)*. This disease has increased dramatically in major swine-raising areas of the world. The characteristic lesion is a severe fibrinonecrotic and hemorrhagic pneumonia with accompanying fibrinous pleuritis, hence the designation pleuropneumonia. *Haemophilus pleuropneumoniae* is highly pathogenic and often appears capable of invading and rapidly proliferating within the lung in the absence of obvious predisposing factors. All aspects of pathogenesis of field outbreaks of the disease, however, are not understood.

Contagious pleuropneumonia can affect pigs of any age but is more common from about 6 weeks to 6 months of age. The severe form of the disease occurs mostly in later stages of fattening with a mortality rate of 20 to 80%. Peracute, acute, and subacute to chronic forms are recognized. Deaths in the peracute

and acute forms occur suddenly or after a short period of depression, fever, and possibly, hemorrhage from nose and mouth. The main gross lesions are bloody nasal discharge, bloodstained foam in trachea and bronchi, and large regions of hemorrhagic or fibrinonecrotic pneumonia accompanied by fibrinous pleuritis. Since the tissue damage is caused by massive bacterial proliferation and release of toxins, the essential features are those already described for fulminating pneumonic pasteurellosis in cattle. There is less tendency for the pneumonic foci caused by *Haemophilus pleuropneumoniae* to be limited to the cranioventral lung regions, however, presumably because of the greater virulence of the organism. Irregular, well-circumscribed regions of hemorrhagic consolidation or necrosis are commonly found in more dorsocaudal regions, especially surrounding major bronchi near the hilus of the lung (Fig. 6.29C). The foci of consolidation are also particularly prone to undergo sequestration, with the result that in subacute cases there may be large foci of caseous or cavitating yellow-gray or tan necrotic debris surrounded by fibroblastic zones. Many of these can subsequently become abscesses through secondary contamination by *Corynebacterium pyogenes, Pasteurella multocida, Bordetella bronchiseptica,* Gram-negative enteric organisms, streptococci, or others. The end result can be a severely scarred, abscessed lung tightly bound to the thoracic wall by fibrous adhesions.

Extrapulmonary vascular lesions sometimes occur in acutely affected pigs, particularly in the kidneys. Hyaline thrombosis and fibrinoid necrosis of glomerular capillaries, afferent arterioles, and interlobular arteries indicate the probable effect of severe endotoxemia.

Other *Haemophilus* species can cause lung lesions. *Haemophilus parasuis* is a common synergistic infection with swine influenza virus. It causes a nonspecific suppurative bronchopneumonia. For its involvement in polyserositis and arthritis of swine, see Bones and Joints (Volume 1). *Haemophilus somnus* is discussed with diseases of the Nervous System (Volume 1). Its occasional production in cattle of a severe lesion indistinguishable from the fibrinous lobar pneumonia of pneumonic pasteurellosis was mentioned earlier.

Bordetellosis

Bordetella bronchiseptica is an obligate parasite of the upper respiratory tract of rodents, dogs, and pigs and can occasionally be found in various other species. In dogs, it is involved in the causation of kennel cough and chronic bronchitis, as discussed previously. It is also frequently associated with the development of suppurative bronchopneumonia in dogs with interstitial pneumonia caused by the distemper virus. *Bordetella bronchiseptica* can also cause secondary bronchopneumonia in association with other diseases leading to reduced pulmonary defenses.

In swine, the role of *Bordetella bronchiseptica* in the production of atrophic rhinitis has been dealt with under Atrophic Rhinitis of Swine. As a pulmonary pathogen, *B. bronchiseptica* is most important as the occasional cause of septicemia or severe bronchopneumonia in suckling pigs usually less than 3 weeks of age. Mortality can be high in these outbreaks. The bronchopneumonia is predominantly suppurative. Typically, it is associated with acute arteritis and rapid onset of fibrosis, most evident in peribronchiolar sites. Fibrosis may extend to other interstitial regions when the amount of inflammation and exudation is severe. *Bordetella bronchiseptica* may also be a cause of suppurative bronchopneumonia in older pigs, mostly as a complication of mycoplasmal pneumonia in fattening animals.

Bordetella bronchiseptica has also been recorded as an occasional cause of suppurative bronchopneumonia in cats and foals.

Tuberculosis

Tuberculosis is typically a chronic infectious disease caused by bacteria of the genus *Mycobacterium.* Various forms of the disease have many features in common, but the exact pattern differs according to the species of *Mycobacterium* involved and the species of animal affected.

Tuberculosis is an ancient disease and is still widespread in some parts of the world. In many areas, however, the incidence of classical tuberculosis in humans and animals has been reduced to the point where mycobacterial disease is more often caused by atypical (nonmammalian) acid-fast bacilli. Infection and disease caused by these atypical mycobacteria are probably more widely recognized because they are no longer overshadowed by the classical disease and have been revealed for more detailed investigation. Changing environments and a susceptible population no longer provided with the cross-protection afforded by infection with the classical mycobacteria probably also play some role. The emergence of a wide range of mycobacteria as agents capable of causing disease has resulted in both diagnostic and taxonomic confusion. This is compounded by the large number of saprophytic mycobacteria now recognized and the lack of clear-cut separation between saprophytic and potentially pathogenic species. Assessment of the etiologic role of a mycobacterium isolated or identified in a particular case therefore needs to be made on the basis of specific evidence available for that case rather than on the basis of generalizations.

Mycobacteria are widely distributed in nature. Many are saprophytes, and some of these are opportunistic pathogens. Others, as far as known, are strictly parasitic. Some of the pathogenic types cannot be cultivated *in vitro,* and those that can be cultivated generally grow slowly. For these reasons taxonomic classification has been difficult. Currently, a variety of cultural and biologic characteristics, including serotyping, lipoprotein analyses, and phage typing, are used in numerical classification schemes. More than 100 properties of new isolates can be subjected to computer analysis. A high degree of matching (>80% of characteristics) is used to group organisms together as the same species. Mycobacterial classification is still incomplete, however, so in the meantime the following categorization puts the organisms into useful perspective. The listing is incomplete, and not all are of known veterinary significance.

The classical tubercle bacilli are *Mycobacterium tuberculosis* (human), *M. bovis* (bovine), and *M. avium* (avian). *Mycobacterium tuberculosis* and *M. bovis* are the principal, closely related mammalian pathogens. Two other closely related species are *M. microti* from voles and *M. africanum.* Differing strains of *M. avium* are now commonly included with strains of the very closely related *M. intracellulare* as the *M. avium–intracellulare* complex. To avoid confusion surrounding the term "tuberculosis," a convention that has been adopted is to limit it to diseases caused by *M. tuberculosis* or *M. bovis.* Other condi-

tions are referred to as **mycobacteriosis**, qualified with the specific agent where known (e.g., avian mycobacteriosis when caused by *M. avium).* Atypical mycobacteriosis is sometimes used as a general term to cover all the diseases other than those caused by *M. tuberculosis* and *M. bovis.* In most veterinary literature, however, disease caused by *M. avium* is still included as one of the classical forms of tuberculosis, and this usage will be continued in this chapter.

Mycobacteria, which can have an independent saprophytic existence in nature, are widespread in soil and water, on vegetation, and in mucous membranes of the oropharynx. There are a large number of species whose taxonomic status is not fully established. When these organisms cause disease, it is usually in immunologically compromised hosts, and the manifestations are either cervical lymphadenitis, pulmonary lesions similar to tuberculosis, or cutaneous lesions associated with local penetration of organisms through wounds or abrasions of the skin. An example is *Mycobacterium marinum,* which is abundant in pools in regions with temperate climates and causes tuberculous disease in fish and cutaneous ulcers in humans. This organism is grouped with the photochromogens (Runyon's group I) together with *M. kansasii.* The latter produces cervical lymphadenitis and pulmonary disease in humans, and has been isolated from cow's milk and from cattle in the United States and the Republic of South Africa. Scotochromagens produce pigment without photoactivation (Runyon's group II) and include *M. scrofulaceum,* which is closely related to the *M. avium–intracellulare* complex. These organisms have been isolated from disease in cattle and tuberculous-type lesions in dogs. Another member of the group, *M. aquae,* has been isolated from nodular lesions on the teats of cows. Nonphotochromagens (Runyon's group III) have organisms in the *M. avium–intracellulare* complex as the most important members. Organisms belonging to this complex have been isolated from tuberculin-sensitive cattle and pigs, and their pathogenicity has been assessed experimentally in calves and pigs. Some strains are virtually nonpathogenic, and others produce generalized disease.

Mycobacteria of group IV are rapid growers at room temperature, are usually nonpigmented, and include many saprophytes. Within this group, *Mycobacterium smegmatis* is one of the organisms isolated from tubercle-like lesions in lymph nodes of swine. *Mycobacterium smegmatis* has also been associated with development of bovine mastitis following its injection into the udder in oily infusions of penicillin. Another member, *M. fortuitum,* was initially isolated from lesions in bovine lymph nodes and is an occasional cause of mastitis in cattle. Members of this group, particularly *M. fortuitum* and *M. chelonei,* are the usual causes of cutaneous mycobacteriosis in cats and dogs. Further discussion of cutaneous lesions caused by mycobacteria, including those associated with *M. lepraemurium,* will be found with bacterial diseases of the skin (in the Skin and Appendages, Volume 1).

Other important distinct species of mycobacteria are *Mycobacterium leprae* (human leprosy), *M. lepraemurium* (rat leprosy), and *M. paratuberculosis* (*M. johnei*). The last named causes Johne's disease in ruminants (see the Alimentary System, this volume).

It will be evident that the pathogenic mycobacteria present a wide range of specializations, from saprophytes to the extremes of parasitism represented by *Mycobacterium leprae,* and from a wide host range to infectivity for only specific hosts. As parasites, they are principally intracellular. They are mostly within macrophages in an association that does not necessarily cause their death or the death of the host cell. The lesions produced tend to be similar and of granulomatous type, characterized by collections of macrophages, epithelioid cells, and giant cells. Additional components of inflammation and necrosis depend on the degree of cell-mediated response of the host against living bacilli, with the corresponding production of lymphokines and other inflammatory mediators. The phenomena of chronicity and latency are common to the mycobacterial infections. Both are related to the resistance of the organisms to phagocytic killing, to the slow growth of the organisms, and to the complex interactions between the organisms and the host's cellular immune system.

The three main species of tubercle bacilli (*Mycobacterium tuberculosis, M. bovis,* and *M. avium*) occur most frequently in their respective hosts, but cross-infections do occur, and various other species of animals are affected. Under natural conditions, the bovine type of the bacillus causes disease chiefly in cattle, humans, swine, and occasionally, horses, dogs, cats, and sheep; the avian type causes disease chiefly in birds and occasionally is found in cattle, swine, horses, sheep, and captive monkeys; the human-type bacillus is chiefly responsible for tuberculosis in humans and occasionally infects pigs, captive monkeys, dogs, cats, cattle, and psittacine birds. The expression of tuberculosis in the different hosts usually differs somewhat according to the type of bacilli involved as well as other factors. Although the human and bovine bacilli can produce disease in a wide range of species under conditions of special exposure, they are each naturally maintained in only one species, the human bacillus in people and the bovine in cattle. Thus, in the absence of infection from cattle, the bovine type disappears from the human and porcine populations. The situation with the *M. avium–intracellulare* complex is not so clear because of saprophytic members.

In addition to the hosts just mentioned, others of almost unlimited variety can be infected experimentally with one or more species of the tubercle bacilli. The differential pathogenicity of the organisms for guinea pigs, rabbits, and fowls was the original basis of the biologic classification of organisms as to type in diagnostic laboratories. Fowls are highly susceptible to the avian types, but highly resistant to the mammalian types. The avian type will, with the usual test doses, produce progressive infection in rabbits, but only localized lesions in guinea pigs. For the differentiation of mammalian strains, the rabbit is usually used. In rabbits, the bovine bacillus, in the standard dose for the test, produces progressive infection that is fatal in up to 3 months; the human type does not kill rabbits, although isolated tubercles can be found in various organs. The guinea pig is highly susceptible to both mammalian types and therefore useful for isolating the organisms.

The mycobacteria are nonmotile, non-spore-forming pleomorphic coccobacilli. They are Gram-positive but almost

unstainable by the simpler bacterial stains because of their high content of lipids. They are routinely stained with hot carbol dyes, usually carbolfuchsin, and then resist decoloration by inorganic acids. This property of acid fastness, or acid–alcohol fastness, of the stained bacilli depends on the amount and spatial arrangement of mycolic acids in the bacterial wall. Sometimes, in cultures or in old lesions, the organisms have a beaded or granulated appearance. This beading is partly caused by presence of lipid droplets within the bacteria and is an indication of an unfavorable environment for organisms in the postexponential growth phase. Staining of the bacilli can be facilitated by incorporating a surface-active wetting agent, such as Tween 80, in the dyes. They are also demonstrable by fluorescence microscopy when stained by a fluorescent dye such as auramine.

Much attention has been given to the chemical composition of the mycobacteria, particularly the cell walls, in the interests of clarifying the pathogenesis of the lesions, perfecting diagnostic techniques, and developing vaccines. The chemical composition of the cell wall is dominated by complex lipids, which include glycolipids, peptidoglycolipids, lipopolysaccharides, lipoproteins, and waxes. The mycolic acids, on which acid fastness depends, are among them. The precise role of the various lipids in contributing to the virulence and immunogenicity of the organisms is still unclear. The waxes, which are themselves composed of various proportions of lipids, glycolipids, and peptidoglycolipids, depending on the species of *Mycobacterium*, are important in the initial "foreign body" type of macrophage response. Waxes, together with peptidoglycan (muramyl dipeptide) and various glycolipids, are responsible for most of the adjuvant activity of mycobacteria. Attraction of antigen-processing cells (macrophages) and presentation of antigen in appropriate surface configuration are major attributes of adjuvant activity. The relative importance of purified components is still under investigation. Increased glycolipid content of mycobacterial cell walls is associated with increased virulence. A close parallel is with the amount of "cord factor" (virulent mycobacteria form cordlike aggregates when trehalose dimycolate is in the culture medium). This correlates with the fact that, in general, the more acid fast strains are more virulent. Other glycolipids (mycosides) appear to form a barrier against lysosomal digestion and partly explain the ability of the organisms to survive after phagocytosis by macrophages. Intracellular survival is also facilitated by the bacteria preventing fusion of phagosomes and lysosomes, possibly by secretion of cyclic AMP. The differing effectiveness of such mechanisms determines the relative ability of various mycobacteria to resist intracellular degradation.

Tuberculoproteins are the otber major category of immunoreactive substances in mycobacteria. They provide most of the antigenic determinants, but in order for an animal to produce an immunologic response to these determinants, the adjuvant activity of the lipids and polysaccharides in the mycobacterial cell wall is needed. Purified protein derivatives from mycobacteria are capable of eliciting the delayed type of hypersensitivity once the animal is sensitized, however, and this is the basis of tuberculin testing. Both tuberculoproteins and the adjuvant lipids are present in infection, and the result is the development of both humoral and cell-mediated immune responses. The humoral antibodies can be demonstrated by serologic techniques but do not participate in the pathogenesis of the characteristic lesions or in the production of immunity. Cell-mediated responses are responsible for both aspects of the disease.

Cell-mediated immunity and delayed-type hypersensitivity are expressions of immune responses mediated by lymphocytes, mostly T cells. Both manifestations usually develop simultaneously. They do not have identical mechanisms, however, because sometimes one is present without the other, and there is no quantitative relationship between them when both are present. Since both are mediated by T lymphocytes, the dissociation between the two responses will perhaps eventually be explained on the basis of involvement by different subpopulations of T cells.

Cell-mediated immunity is effected by the enhanced ability of activated macrophages to phagocytose and kill bacilli. Macrophages are activated by lymphokines secreted by specifically sensitized T lymphocytes, which respond to processed antigens released by previously infected macrophages. Most activated macrophages are derived from blood monocytes. Immunity to tuberculosis therefore is principally determined by the ability of macrophages to inhibit the growth of intracellular bacilli. Both innate (genetic) and acquired resistance are involved. Macrophages, for unexplained reasons, can also respond differently in organs such as the liver and kidney in the same animal. Since the balance between the virulence of the myobacteria and the ability of macrophages to kill them is often a precarious one, any compromise of the host's immune system is prone to precipitate or exacerbate the disease. This is revealed by the frequent clinical association of tuberculosis with immunosuppression caused by diseases, drugs, hormones, or malnutrition.

Delayed-type hypersensitivity is also mediated by lymphokines released mainly from sensitized T cells in response to antigenic materials from the tubercle bacilli. The lymphokines cause further accumulation of macrophages and lymphocytes. Release of cytotoxic lymphokines and hydrolytic enzymes from macrophages is principally responsible for the caseation necrosis characteristic of many tuberculous lesions.

Functionally heterogeneous populations of lymphocytes and macrophages are present in tuberculous lesions. Relative numbers of the various subpopulations of these cells partly determine whether activation of macrophages and inhibition of bacterial growth (cell-mediated immunity) or a severe, delayed-type hypersensitivity response is the dominant feature.

The importance of hypersensitivity in the pathogenesis of lesions of tuberculosis was first demonstrated by Koch in what is now known as the Koch phenomenon. If a normal guinea pig is inoculated subcutaneously with a culture of tubercle bacilli, generalization of the infection causes death in 2 to 3 months. At the site of inoculation, a hard nodule, or tubercle, develops in 10 to 14 days. This nodule soon breaks down to form an ulcer that persists until the animal dies. If the inoculation is made into a tuberculous guinea pig, however, the events are quite different. An acute response characterized by exudation and necrosis develops at the site of inoculation. The necrotic tissue soon

sloughs, the lesion heals permanently and quickly, and the infection is not disseminated from it, even to the regional lymph node. The injected organisms that provoke the hypersensitivity reaction in the skin are fairly rapidly destroyed, but those in the primary lesions of the disease are not destroyed, and their persistence and proliferation might eventually kill the animal. Whether the hypersensitivity reaction is beneficial or harmful to the host depends on the circumstances. In common with most complex inflammatory conditions, there is a balance between inhibitory and amplifying factors. On the one hand, hypersensitivity to relatively small numbers of bacilli causes accelerated tubercle formation, which enhances the killing of the organisms and helps prevent reinfection or dissemination from the initial site of infection. On the other hand, the hypersensitivity response to large amounts of mycobacterial antigen causes extensive cell necrosis and tissue destruction, which is seriously detrimental. Liquefaction, which is brought about by hydrolytic enzymes of macrophages, and possibly neutrophils, is the most harmful response. The bacilli multiply extracellularly in the liquefied material and are available in large numbers for dissemination through cavities, vessels, and airways. In summary, the final determinants of the nature and intensity of lesions are the mass of bacterial antigen presented to specifically reactive lymphocytes and the modifying influences of the structure of the tissue involved.

The lesions of tuberculosis are the prototype of a granulomatous inflammation. The tuberculous granuloma (tubercle) is mainly cellular, and its development is frequently designated as "productive" or "proliferative" in contrast to the more exudative type of lesion it occasionally causes.

When tubercle bacilli are initially implanted in tissue, they behave as relatively bland, lipid-rich foreign particles would be expected to do and incite a "foreign body" macrophage response. Bacilli are phagocytosed by macrophages, and if the resistance of the macrophages is adequate, the bacilli are eventually killed. If the balance tips the other way, however, the bacilli proliferate and are released from killed macrophages together with antigenic materials that sensitize attracted T lymphocytes. By the tenth day or so after exposure, by which time hypersensitivity is developing, many bacilli are present, and the tempo of events begins to quicken. Lymphokines secreted by the sensitized T lymphocytes cause the attraction, proliferation, and activation of macrophages, which are derived mostly from blood monocytes. In the infected foci, macrophages assume a distinctive appearance, causing them to be designated as epithelioid cells because of a vague histologic similarity to sheets of large epithelial cells. The epithelioid cells have large, vesicular nuclei, and extensive pale cytoplasm with ill-defined borders. The epithelioid cells ultrastructurally are characterized by abundant organelles and extensive interdigitations of their plasma membranes. They contain ingested bacilli within their cytoplasm, and the structural changes indicate a heightened bactericidal activity. Mixed in with the epithelioid cells are variable numbers of giant cells of the Langhans type (Fig. 6.30B). These are large cells with several eccentric nuclei and are formed by the fusion of macrophages. This admixture of epithelioid and giant cells forms the center of young tubercles. At the periphery is a narrow zone of lymphocytes, plasma cells, and unaltered monocytes. As the lesion progresses, the classical tubercle develops peripheral fibroplasia and central necrosis (Fig. 6.31C). These two features are not present in all tuberculous infections; there are both species and individual variations. Encapsulating fibroplasia is more conspicuous in those individuals that have considerable powers of resistance, and it might, as tuberculous granulation tissue, overgrow and dominate the lesions. It is the development of central necrosis that gives the tubercle its high degree of histologic specificity. The necrosis is a product of the cell-mediated hypersensitivity and is of caseous character. The necrotic material is most commonly inspissated into a yellowish, cheesy mass, but may liquefy or calcify. Calcification is a characteristic development in some species of animals, but seldom observed in others.

The exudative type of lesion in tuberculosis usually develops acutely. The exudate is relatively voluminous and consists of fibrin and neutrophils as well as the usual mononuclear cells. Eventually, the exudate clots, and it too caseates. A combination of factors is usually regarded as responsible for the exudative lesions. Chief among them are rapid bacterial proliferation, presence of abundant reactive lymphocytes, and a site of localization in easily distensible or space-lining tissues.

There are various portals of entry available to the tubercle bacilli. Infection can occur congenitally by way of the umbilical veins, or postnatally through alimentary, respiratory, genital, or cutaneous routes. Growth of the original tubercle takes place by centrifugal expansion and by the development of satellite tubercles formed by spread of bacilli from the initial focus. The new tubercles may coalesce to produce large lesions. In a susceptible, unsensitized animal, the bacilli spread rapidly, either free or in macrophages, along the lymphatics (Fig. 6.30C) to the regional lymph nodes, where further tubercles develop. The combination of lesions in the initial focus and in the regional lymph node is known as the *primary complex* of Ranke. It is always present with first infection in animals, but both components may not be detectable, because when infection occurs across a mucous membrane, such as of the pharynx or intestine, the initial lesion in the membrane might not be visible when the nodal lesions are present. The decision as to which lesions in a case of generalized tuberculosis constitute the primary complex is often impossible to make. The relative age of the lesions is an indication, as is their localization, because the site must be intimately related to one of the portals of entry.

As lesions develop in the regional lymph node, the infection passes successively from one node to another, and can eventually reach the blood, for potential widespread dissemination. Extensive hematogenous dissemination, however, is most frequently the result of breakdown of a blood vessel by an expanding, caseating tubercle or cavitating lesion. The number of bacilli then released into the blood can be very large, and when these are removed by phagocytes in the various organs, a large number of small tubercles develop. The course of the disease after massive generalization is short, and the disease is then referred to as miliary tuberculosis because of the large number of tubercles the size of millet seeds observed. Hematogenous dissemination is, however, not always massive; the

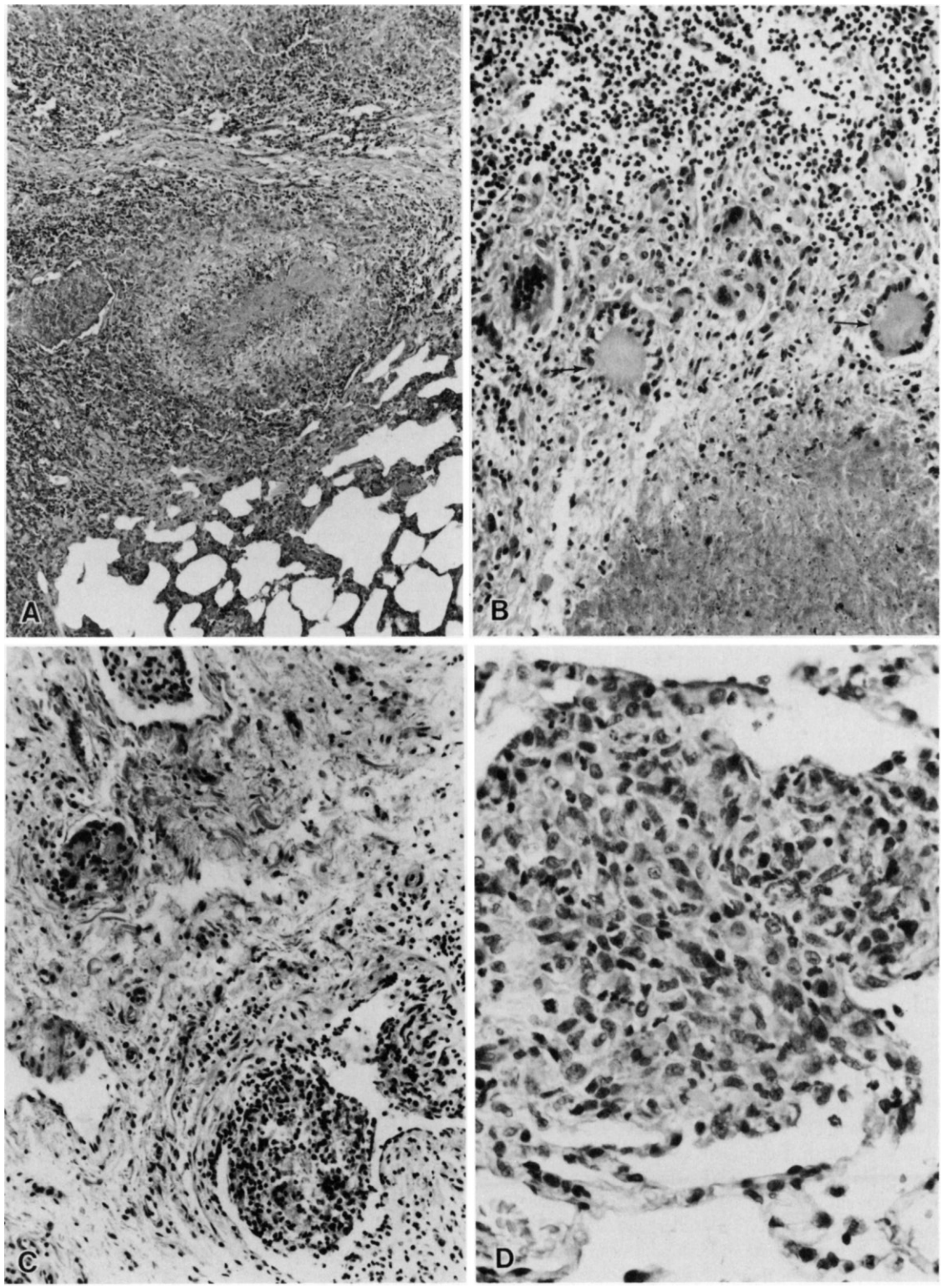

Fig. 6.30. Tuberculosis. (**A**) Pulmonary tuberculosis. Ox. Effacement of pulmonary tissue by granulomas. (Courtesy of D. M. Gillette.) (**B**) Periphery of tubercle with Langhans' giant cells (arrows) and epithelioid cells bordering caseation necrosis. Ox. (**C**) Tuberculous lymphangitis. Liver. Pig. (**D**) Nonspecific appearance of pulmonary granuloma in disseminated (miliary) tuberculosis. Dog.

course then is much longer, and the metastatic foci are large and few or solitary. Some organs, such as muscle, thyroid, and pancreas, seldom develop lesions of hematogenous origin.

Spread can occur via natural passages. Common examples are spread from the kidney along the ureter to the bladder, from one bronchus to another by coughing and aspiration, or from the lungs to the intestine when infected sputum is swallowed. Rapid spread is possible in cavities such as the meningeal space and serous cavities of the trunk. Involvement of a serous membrane is usually by direct extension from an underlying lymph node or viscus. When the bacilli are freed on the serous surfaces, they are readily distributed by movements such as respiration and peristalsis.

CATTLE. Bovine tuberculosis has been, and in some areas remains, one of the most important diseases of cattle. In areas where the incidence is high, the disease is caused almost exclusively by *Mycobacterium bovis*. But when bovine tuberculosis is brought under control by eradication programs, the patterns of infection change, and the proportion of infections caused by the *M. avium–intracellulare* complex increases. Infections with *M. avium* usually have a benign, self-limiting course. Often no lesions are detectable. If lesions develop, they are usually found in the mesenteric and retropharyngeal lymph nodes and are seldom larger than 2 cm in diameter. They are usually caseous and encapsulated and might be either calcified or liquefied. There is commonly no spread from these sites, but sometimes initial lesions in intestinal mucosa are detected as focal thickenings. When extension of the avian type infection occurs in cattle, the serous surfaces are most often involved. Occasionally, lesions may be found in the udder, lungs, liver, kidney, and spleen. The uterus is the most frequently involved organ in pregnant cows and abortion or congenital disseminated tuberculosis in newborn calves can result. Large numbers of epithelioid cells are a regular feature of the histologic response and pleomorphic acid-fast bacilli are abundant. The human bacilli, at most, cause small nonprogressive lesions in the lymph nodes of the pharynx, thorax, and mesentery.

The usual routes of infection by *Mycobacterium bovis* are respiratory and alimentary. The unusual routes, which will be considered first, are cutaneous, congenital, and genital. Infection via the **skin** is rather rare. It requires that other primary cutaneous lesions be contaminated with the tubercle bacillus. The infection is limited to the initial site or may spread to the local lymph node. In **congenital tuberculosis**, the infection spreads via the umbilical vessels to the fetus. This route of infection is of some importance where the disease is common in cattle, and where as many as 0.5% of newborn calves have been found to have tuberculosis. This route is of little significance in other species, because only in cows is tuberculous endometritis common. When the primary complex is present in congenital infection of calves, it is in the liver and portal lymph nodes. But, as elsewhere, the complex might be apparently incomplete, and the lesions are found only in the nodes. In a fetus or calf of a few days of age, lesions in the portal node are assumed to be evidence of congenital infection; this is not necessarily the case in older calves because the portal node is also the regional node of the duodenum. Congenital tuberculosis in calves progresses quite rapidly, and the animals usually die in a few weeks or months. By that time, the disease has generalized, and lesions can be found especially in the lungs and regional lymph nodes, and in the spleen. Tuberculous lesions rarely occur in the spleen of adult cattle, and when present, irrespective of the age of the animal, they are regarded as indicative of congenital infection. For congenital tuberculosis to occur, infection must be present in the uterus. Small tubercles can be found in the endometrium. Typical placental lesions are a slimy exudate separating the placenta from the endometrium, and caseonecrotic foci in the cotyledons. Extensive areas of tuberculosis in the uterus result in repeated abortions. **Genital infection** occurs in cattle but is not common; its development requires that the sexual organs of either the female (usually uterus) or male (usually epididymis) be tuberculous. Mammary infusions used in the treatment of mastitis and contaminated with tubercle bacilli are responsible for occasional, but epidemiologically important, cases of tuberculosis of mammary gland.

Most bovine tuberculosis is acquired by inhalation or ingestion. Management factors and age at which the disease is contracted are major determinants of which route is the more probable. Search for whether the primary complex is alimentary or respiratory can be helpful, but the evidence is sometimes not clear.

The incidence of respiratory versus alimentary infection in postnatal calves is difficult to determine precisely, especially in very young calves, because it depends on whether involvement of the portal nodes, in the absence of intestinal or hepatic lesions, is taken to indicate alimentary or congenital infection. Primary complexes in the intestine are common in calves, particularly those that have been allowed to suck tuberculous udders or that have been given tuberculous milk to drink. Pulmonary complexes are also common in calves more than a few weeks of age. Pulmonary infections may well be more important than alimentary infections under crowded conditions. Tuberculosis of the anterior cervical nodes occurs with both aerogenous and alimentary routes of infection and is not, therefore, an indication of the route of infection.

Most cattle obtain their infections when they are older than 6 months. In these adult infections, the majority of lesions are in the retropharyngeal, mediastinal, and bronchial lymph nodes. When the lesions are limited to the retropharyngeal nodes, infection could be by either oral or nasal routes. Lesions have seldom been found in the lungs with a frequency equal to their occurrence in the thoracic lymph nodes. This is probably because primary lesions in the pulmonary parenchyma can be very small and difficult to detect. In the very few series in which the examination has been thorough, the preponderance of primary complexes in the lung has been revealed. Intestinal infections do occur, and lesions in the mesenteric lymph nodes are common; a significant proportion of these, perhaps most, are secondary infections, which are established when sputum is swallowed.

In adult cattle, therefore, primary infection is usually in the lungs and is caused by inhalation of infected droplet nuclei. The primary lesions may be single or multiple and may occur in any lobe, but they occur predominantly in a subpleural location in

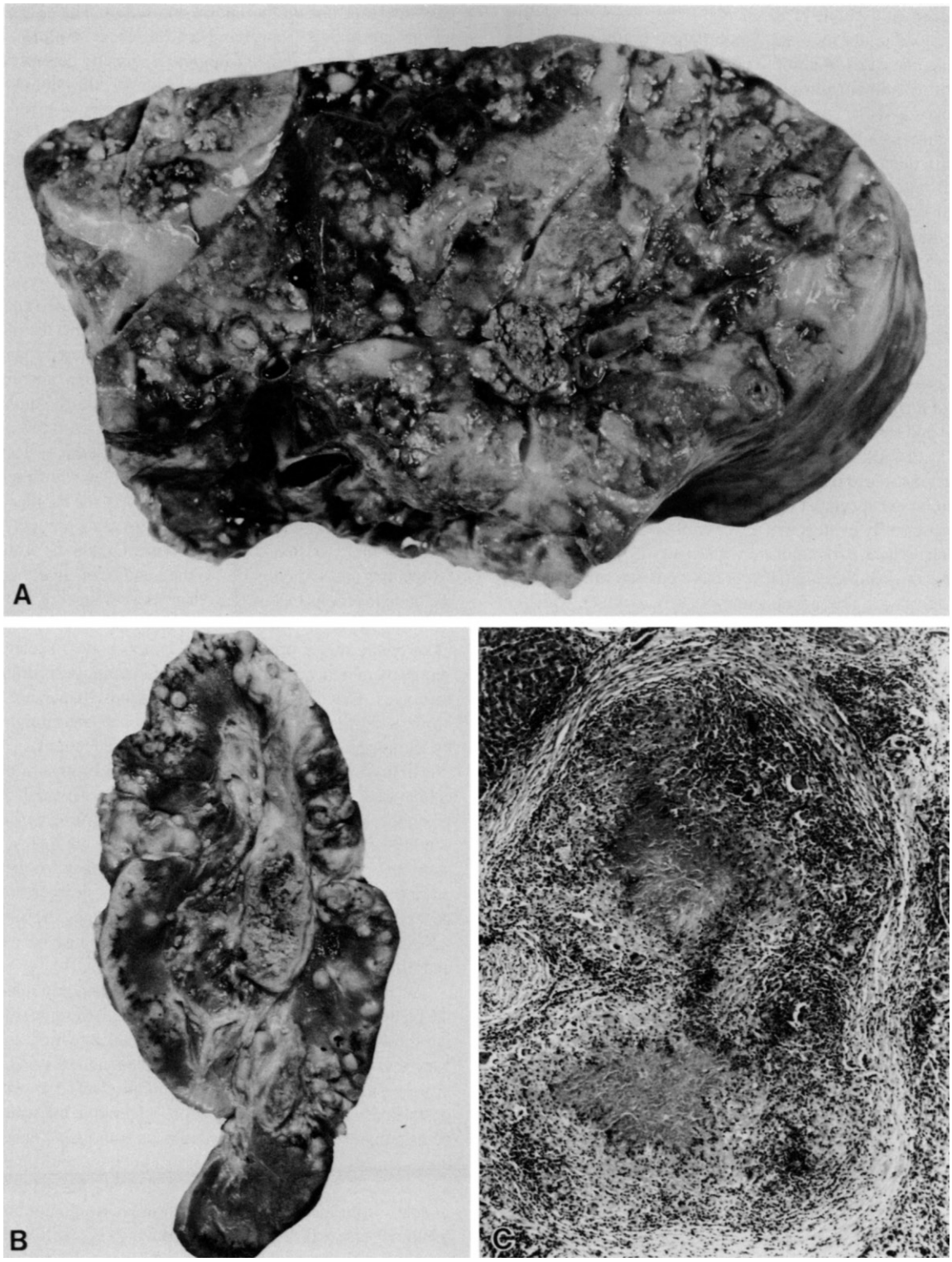

Fig. 6.31. Tuberculosis. (**A**) Tuberculous bronchopneumonia. Ox. Larger granulomas (tubercles) have crumbly caseonecrotic centers (arrows). (**B**) Tuberculous lymphadenitis. Ox. (**C**) Caseous tubercles with encapsulation. Liver. Sheep.

the dorsocaudal portions of the caudal lobes. There are almost always lesions in the regional lymph nodes, but they might be absent in some cases of chronic tuberculous pneumonia.

The **tuberculous pulmonary process** usually starts at the bronchiolar–alveolar junction and extends into the alveoli, so that it is initially sublobular or lobular. The histologic structure is typically tuberculous (Fig. 6.30A). There may be more than one focus within a lobule, giving a cloverleaf appearance, and more than one lobule can be involved (Fig. 6.31A).

The initial lesions and their secondaries in the lymph nodes can heal completely, persist without progression, or progress. It is generally believed, on good but not certain grounds, that bovine tuberculosis most often progresses, with acquired cellular resistance slowing the progress considerably but not halting it.

The appearance of the pulmonary lesions varies with their age and rate of progress. The earliest lesions are not encapsulated but are small and surrounded by condensed alveolar tissue. Even in these early lesions, the yellowish caseation and the calcification so characteristic of bovine tubercles can be seen. Caseated lesions can be encapsulated and heavily calcified. The capsules are not necessarily evidence of successful containment because many such nodules communicate with an airway and allow local dissemination. Multiple initial foci can coalesce to form large regions of caseating bronchopneumonia (Fig. 6.31A), which in due course are usually encapsulated and calcified. Cavitations may form in any of these lesions, but they are never large because of the limitations imposed by the interlobular septa.

Dissemination of the infection within the lung can be by way of an intrapulmonary tuberculous lymphangitis but is mainly through the airways. The bronchogenic extension may be by direct contiguity, or it might be by aspiration of exudates, but in either case what is initially a lobular type of lesion comes to involve much or all of a bronchopulmonary segment, or even most of a lobe. The reaction is the same as that in the primary lesion, although often more severely caseating. Depending on the rapidity and extent of spread, the lesions form a pattern of irregular caseous bronchopneumonia or more confluent caseous lobar pneumonia.

In association with chronic progressive pulmonary tuberculosis, it is common to find ulcers in the trachea and bronchi. These can arise by implantation of bacilli coughed up in the sputum or by progression of tuberculous lymphangitis. They begin as typical tubercles in the mucous membrane, especially near the bifurcation of the trachea, and are followed shortly by ulceration. Similar ulcers develop on the larynx by implantation of bacilli.

A feature of tuberculosis in cattle is the tendency to spread to the serous membranes (Fig. 6.32A). This can take place by direct expansion of the original lesion, by lymphogenous extension from the lungs, by direct hematogenous dissemination, or by local expansion from a hematogenous focus in an adjacent organ. Once the tuberculous process breaches the serosa, the bacilli are distributed by respiratory movements and may be widely implanted. **Pleural tuberculosis** may be largely nodular, diffusely caseous, or with transitions between the two. The affected areas of pleura, both visceral and parietal, are thickened by fibrous granulation tissue, and as a rule the tuberculous process does not invade the underlying tissue. The characteristic lesions are nodular, and these tend to occur in clusters. They may be sessile or pedunculated, and frequently coalesce to form cauliflower-like masses. In the early stages, they consist of reddish tags of granulation tissue containing typical tubercles and may be soft. Later, heavy calcification is usual and largely responsible for the term "pearl disease." Caseous tuberculous pleuritis consists of large plaques of caseous exudate beneath which the pleura is uniformly thickened. Fibrin may be deposited on and between the plaques.

Generalization of the infection (dissemination to other organs) can occur early in the course of the disease (postprimary generalization) or late in the course of the disease (late generalization). In late generalization, it is assumed that the immunity the animal has acquired has broken down, thereby permitting wide spread. Generalization might be sudden and massive, when large numbers of the bacilli enter the bloodstream (miliary tuberculosis), or it may be more protracted, with fewer bacilli entering the circulation. The latter, whether early or late, is the more usual, and the lesions are larger and often of different ages.

In the respiratory pattern being described, the bacilli can enter the bloodstream in the lungs when the caseating process erodes a vessel, usually a small vein, or they might pass through the lymphatics and lymph nodes to the vena cava. In either event, the hematogenous metastases occur more frequently in the lung than elsewhere. Hematogenous metastases can also occur in most of the major organs and in lymph nodes, skeleton, and serous membranes, including the peritoneum, pericardium, and meninges. Organs such as salivary glands, pancreas, spleen, brain, and muscles, including myocardium, are rarely affected by hematogenous metastases in postnatal infections.

Miliary lesions in the lungs are associated with a fulminating course of the disease. The lesions are typical, small, grayish tubercles, translucent at first but soon becoming caseous and centrally calcified. Hematogenous tubercles are diffusely scattered in both lungs, although there is a tendency for them to be more numerous in the cranial portions. In slow or protracted generalization, which is the more usual type, the metastatic tubercles tend to be few in number, large, caseated and calcified, and often surrounded by a heavy capsule.

Tuberculosis of the **peritoneum** is less common than that of the pleura. It can arise in a number of ways. Peritonitis surrounding the liver is common in the congenital infection and is regarded as being of local and lymphatic spread. Peritonitis might also be hematogenous in the congenital disease as well as in postprimary and late generalization. Ulcerative intestinal tuberculosis that extends to the serosa is an important route of peritoneal infection in postnatal life. In adults, the intestinal lesions are usually secondary to respiratory lesions. Spread to the peritoneum from the uterus via the uterine tubes no doubt occurs, but the reverse is probably more common. The peritoneal lesions are similar to those of the pleura but are usually not so clearly nodular or "pearly." They tend to be softer and more diffuse and to consist of extensive granulation tissue in which the tubercles are embedded (Fig. 6.32A).

Hepatic lesions are hematogenous in origin. Infection arrives either through umbilical veins, as in congenital infections, through arteries as part of hematogenous dissemination, or

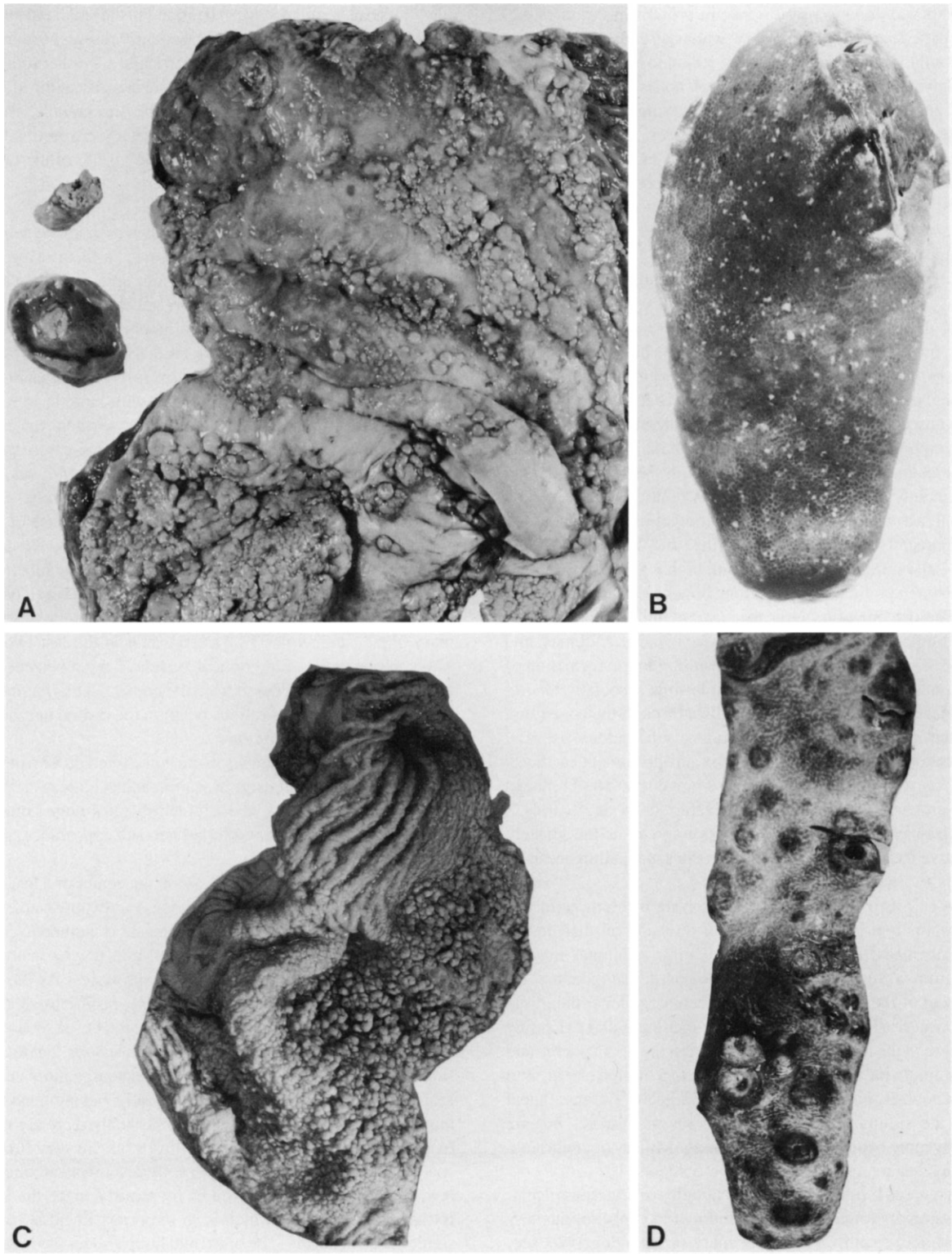

Fig. 6.32. Tuberculosis. (**A**) Tuberculous peritonitis. Ox. (**B**) Miliary tuberculosis of avian type in liver. Pig. (**C**) Hypertrophic tuberculous gastritis caused by *Mycobacterium bovis*. Pig. (**D**) Multiple tuberculous granulomas caused by *M. bovis* in spleen. Pig.

through portal veins when lesions are present in the intestine. The hepatic foci might be miliary, but as elsewhere, it is more usual for the coarse, nodular type of lesion to be present, sometimes only in one lobe. The portal lymph nodes are affected. The coarse, nodular types of lesion occur in varying numbers and can be quite small or up to 10 cm in diameter. They tend to be rounded and often project hemispherically above the surface. When sectioned, the nodules are seen to be enclosed by a heavy capsule, and the contents are bright yellow and caseous; the exudate might be inspissated and calcified or, sometimes, liquefied.

The **renal lesions** resemble in structure and type those of the liver. Miliary lesions are limited to the cortex, the initial development of the tubercles occurring in the interstitial tissue. The coarse, nodular lesions might be multiple, but often they are limited to one or two adjacent lobules of the kidney. The caseating tubercles can be very large and might erode into the pelvis to cause a descending infection of the urinary tract. Frequently, the renal lymph nodes are concurrently involved.

Tuberculosis of the **skeleton** is usually hematogenous and occurs mainly in young animals. Its distribution is governed by the usual factors in hematogenous osteomyelitis. The lesions are most frequently in the vertebrae, ribs, and flat bones of the pelvis—all bones that are spongy and highly vascular. The epiphyseal–metaphyseal regions of long bones are also predilection sites. The osteomyelitis is in the form of miliary tubercles or large granulomas. Caseation is extensive in the granulomas, and there is a tendency to liquefaction, resulting in the formation of tuberculous abscesses. The liquefied lesions especially tend to be progressive. They erode and fistulate through the cortex and erode the articular cartilages to produce tuberculous arthritis. Regenerative osteophyte formation is not prominent in tuberculosis, as it is, for example, in actinomycosis. The predominantly erosive type of process is referred to as "caries." Through the cortical fistulae the infection spreads to the adjacent connective tissues and muscle. This is the usual pathogenesis of tuberculous myositis.

Tuberculosis in the **central nervous system** begins mainly as a meningitis and is more common in the cerebral than in the spinal meninges. Involvement of the spinal meninges may be direct from a vertebral osteomyelitis, or hematogenous. Involvement of the cranial meninges is hematogenous, the initial lesions occurring usually in the basilar meninges and extending from there in the arachnoid spaces between the hemispheres and cerebellum, to the choroid plexuses and, to a limited extent, into the Virchow–Robin spaces and the brain itself. The meningeal lesions are similar to those of the serous membranes but are generally more exudative and necrotizing. Miliary or conglomerate tubercles are an uncommon development.

Tuberculous lesions, either small nodules or craterous ulcers, are occasionally found in the epithelium of the upper alimentary tract and abomasum. Whether primary or as endogenous secondaries, however, lesions in the alimentary lining membranes are uncommon. In contrast, the regional nodes, particularly of the retropharynx (Fig. 6.31B) and mesentery, are often severely involved. In young calves, round or oval ulcers of small size may be found, especially in the ileum. These probably begin as small tubercles in the Peyer's patches or solitary lymphoid nodules. Tubercles and ulcers can be found in the small intestine and cecum in adults, in which they frequently represent reinfection from the lungs. The ulcers vary in size and are either rounded or elongate in the axis of the intestine. The margins of the ulcers are distinct, firm, and raised. The bases are firm granulation tissue speckled with tiny hemorrhages and usually covered with dry, caseous exudate. Granulomas might be visible in the draining lymphatics.

HORSES. Horses apparently possess a high innate resistance to tubercle bacilli, and the disease is rare in them. Most infections involve *Mycobacterium bovis*, but both *M. avium* and *M. tuberculosis* can produce localized or generalized disease. Many of the bovine strains recovered from horses are of lowered virulence when tested in laboratory animals.

The route of infection is almost exclusively alimentary. The primary complex is often incomplete, with large lesions in the retropharyngeal or mesenteric nodes, but without an obvious primary focus in the related mucosa. In some cases, primary ulcers are present in the intestine. Bacilli of the *Mycobacterium avium–intracellulare* complex sometimes produce a proliferative enteritis closely resembling Johne's disease of cattle. Lesions might be limited to the alimentary tract, but in fatal cases there is generalization with either miliary tubercles or scattered coarse, nodular lesions. Secondary lesions have been described in the lungs, liver, spleen, serous membranes, mammary gland, and skin. They are unusual in the last two sites. Tuberculous changes in cervical vertebrae are repeatedly cited as being common in the disease in the horse, but this has not been thoroughly explored. If lesions occur in the central nervous system or genitalia, they are rare.

The lesions of tuberculosis in the horse often differ from those in cattle. Whereas extensive caseation and calcification are typical of bovine tubercles, the equine tubercles more commonly have a uniform, gray, smooth (lardaceous) appearance, grossly resembling a sarcoma.

Caseation does occur sometimes in the center of a lesion, but it is of minor degree, and calcification is rarely observable by the naked eye. Histologically, the early lesion is a tubercle consisting of macrophages, epithelioid cells, and few or many giant cells, without a peripheral zone of lymphocytes. As the lesion progresses, it develops more and more proliferative fibrous tissue in which ill-defined tubercles are scattered. It is sometimes very difficult to find bacilli in these lesions, but the occasional tubercle that liquefies contains very large numbers. Pulmonary tuberculosis in horses is usually hematogenous and might be miliary or coarsely nodular. Usually there are miliary foci, which appear like glassy dewdrops but are very firm. The coarse, nodular lesions, which grossly resemble sarcomas, are fewer and larger. Progression is by expansion of the lesion. Intrabronchial spread, which is so important in cattle, is of no significance in horses. The bronchial lymph nodes are invariably involved when the lung is; their appearance is that of a firm sarcoma, and corticomedullary distinction is lost.

When the primary lesions are found in the intestine, they take the form of tuberculous ulcers, which are more common in the large than in the small intestine. Tubercles in the liver and spleen are usually nodular rather than miliary. They can be extremely

large, and the organs correspondingly so; the spleen is more frequently affected than the liver. The lesions are of the usual lardaceous type. The serosal lesions, which are relatively common, are nodular and sometimes accompanied by much effusion into the cavity.

SHEEP AND GOATS. Sheep and goats appear not to have any special resistance to tubercle bacilli, except possibly the human type, but tuberculosis in them is rare. It is usually caused by either *Mycobacterium bovis* or *M. avium*. The main route of infection in goats, and possibly in sheep, is thought to be respiratory, because lesions are more common in the thorax than elsewhere. In general, tuberculosis in the small ruminants is similar in most respects to the disease in cattle.

SWINE. Pigs are susceptible to all three major species of mycobacteria. The incidence of a particular species in any population of pigs depends largely on the species to which they are exposed and is, therefore, a reflection of the incidence of tuberculosis in associated cattle, poultry, or humans. *Mycobacterium bovis* is more capable of producing generalized disease than the *M. avium–intracellulare* complex. *Mycobacterium tuberculosis* rarely spreads past the nodes local to the point of entry. Tuberculosis is seldom observed in pigs except at meat inspection, and because these animals are usually young, a local lymphadenitis is the extent of the disease usually observed.

Tuberculous infections of wounds, castration wounds especially, occur in swine, and occasionally the primary infection is respiratory. As a general rule, however, the route of infection is alimentary (Fig. 6.32C). The primary complex in swine is seldom complete by gross inspection, but tubercles can usually be found microscopically in the mucosa of the pharynx or small intestine when gross lesions are present in the retropharyngeal, portal, or mesenteric nodes. Ulceration of a primary focus in a mucous membrane is rare.

There are certain differences between the lesions produced by the bovine and avian types of bacilli. The bovine bacilli produce caseocalcareous tubercles similar to those that occur in cattle, and the lesions are often surrounded by a fibrous capsule. In the liver, there is a tendency for the caseous centers to liquefy. The avian bacilli produce lesions that are proliferative in nature and consist of tuberculous granulation tissue resembling the lardaceous or sarcomatous lesions described in equine tuberculosis. Caseation is not a feature of these lesions, although it might occur as minute foci, especially in the hepatic tubercles. There is little tendency for these caseous foci either to calcify or to liquefy, or for the lesions to be encapsulated. Affected lymph nodes are only slightly enlarged, and on cut surface they have a lardaceous appearance. The histologic appearance is of diffuse accumulations of macrophages, epithelioid cells, and Langhans' giant cells accompanied by extensive fibroplasia. The bacilli are numerous in these lesions, and they may also be recovered from nodes that appear grossly to be normal.

Pulmonary tuberculosis in swine is hematogenous and usually of the miliary pattern. In some infections with the bovine bacillus, there is extensive consolidation of the cranial lobes, resembling grossly the caseous bronchopneumonia of cattle, but histologically seen to be a confluence of numerous hematogenous tubercles. In this form of the pulmonary disease, there might be a tuberculous tracheitis. Miliary lesions in the lungs produced by the avian bacilli resemble dewdrops, and there appears to be a characteristic tendency for these to spread along the subpleural and septal lymphatics, which are beaded by small tubercles.

The hepatic lesions produced by the bovine bacilli take the form of miliary or, more usually, coarse nodules. Those produced in the liver by the avian bacilli (Fig. 6.32B) are quite different. The early lesions are scattered and miliary and are not discrete but blend peripherally with the interlobular septa. The later lesions are merely an extension of this and, although softer, closely resemble the lesions of parasitic hepatitis produced by *Ascaris suum* and *Stephanurus dentatus*. Hepatic tuberculosis of avian type also cannot be distinguished grossly from the infiltrates of myeloid or lymphoid leukemia. Tuberculous granulation tissue spreads along the portal triads, surrounding and obliterating lobules, and at the periphery unites with the expansions of adjacent lesions. Typical tubercles do not occur.

Splenic lesions regularly occur in the generalized disease (Fig. 6.32D). They project hemispherically above the surface, and their appearance, as indicated above, depends on the type of bacilli present. Tuberculosis of the serous membranes is seldom observed in swine. Skeletal lesions, often confined to individual bones of the axial skeleton, are common. Tuberculous meningitis, primarily basilar in location, is relatively frequent in generalized infections by the bovine bacilli. The meningeal lesions in swine are more nodular than those in cattle, in which there tends to be diffuse exudation. Tubercles may also be found in the genital organs, skin, and eye.

CATS AND DOGS. Cats appear to be more susceptible to *Mycobacterium bovis* than to *M. tuberculosis* or *M. avium*. The route of infection in cats is usually by ingestion of contaminated milk or, possibly, diseased wildlife. Dogs are susceptible to *M. bovis* and *M. tuberculosis*, and less so to *M. avium*. Dogs are more prone than cats to contract tuberculosis, usually by inhalation, in households with tuberculous persons. Exposure of dogs to tuberculous cattle usually results in the alimentary form of the disease, by ingestion of milk or other contaminated food.

The lesions of tuberculosis in carnivores differ from those in other species. Typical tubercles are not as common, and when they occur, caseation necrosis is not a prominent gross feature. More often there is a nonspecific granulation tissue in which macrophages are scattered at random and giant cells are rare (Fig. 6.30D). The discrete tuberculous granulomas that do occur are composed principally of epithelioid cells surrounded by narrow zones of fibrous tissue in which are scattered small collections of lymphocytes and plasma cells. Necrosis is often present in the centers of larger granulomas. Giant cells are rare or absent. The presence of central necrosis and fairly small numbers of acid-fast bacilli in lesions of cats helps to distinguish lesions of tuberculosis from those of feline leprosy.

The frequently sarcomatous gross appearance of the lesions can easily lead to misdiagnosis. This is particularly the case in cats. The pattern of pale homogeneous tissue causing enlargement and effacement of lymph nodes, and present as diffuse or

nodular lesions in the intestine and possibly other viscera, can readily be mistaken grossly for lymphoma.

The primary foci in the lungs of dogs develop in most cases in the dorsal part of the caudal lobes. They appear as firm, pale, bulging nodules about 1–3 cm in size. The cut surface can be uniform, but frequently there is central liquefaction and a tendency to fistulation onto the pleura to produce serofibrinous or serohemorrhagic pleuritis. Metastatic nodules in the lung are usually few in number, with an appearance similar to that of the primary foci. The bronchial lymph nodes are regularly involved. They might be only moderately enlarged with softened necrotic areas on cut surfaces, or they might be very large and centrally liquefied. Dissemination within the lungs occurs quite rapidly and is predominantly intrabronchial, with the production of a tuberculous bronchitis and bronchiolitis rather than a bronchopneumonia. The granulation tissue involves and destroys segments of the bronchial walls, and cavitation occurs by liquefaction and evacuation of exudate.

Pleuritis is particularly common in tuberculosis of dogs, and ascites is also likely to be present when the abdominal viscera are affected. The serosal lesions are not at all like those in cattle. Instead, there is diffuse or finely nodular pleural thickening by nonspecific granulation tissue. A large amount of serofibrinous exudate accumulates in the pleural cavity; this is often blood-stained. The pleural lesions may be unilateral or bilateral. Peritoneal tuberculosis accompanies lesions in the mesenteric nodes and liver and is accompanied by ascites. Large or small nodules of granulation tissue or a diffuse thickening occur on the visceral layers especially, and the omentum is often converted to a partially necrotic, ropy mass in which there are very large numbers of bacilli. Tuberculous processes are seldom found in other organs, although involvement of the meninges, uveal tract of the eye, genitalia, bones, and skin have all been reported. Hypertrophic osteopathy is a possible sequel to pulmonary tuberculosis (see Bones and Joints, Volume 1).

CORYNEBACTERIUM EQUI INFECTION. *Corynebacterium (Rhodococcus) equi* is an important cause of pneumonia in foals. It can also cause intestinal lesions, and occasionally produce more widespread involvement. Bacteria of the genera *Corynebacterium, Mycobacterium,* and *Nocardia* share the property of having cell walls containing complex lipids. *Corynebacterium equi* therefore has pathogenic features resembling those of mycobacteria. It is a facultative intracellular parasite of macrophages and causes a predominantly pyogranulomatous response characterized by abundant caseation necrosis. *Corynebacterium equi* is an inhabitant of both soil and the equine intestinal tract. Whether it is a true soil saprophyte is still uncertain. Buildup of organisms in soil and dust occurs principally in association with the presence of carrier horses. This emphasizes the importance of its commensal status in the horse.

Pneumonia caused by *Corynebacterium equi* generally causes clinical signs in foals 2–6 months of age, but the subacute to chronic nature of the lesion indicates that infection occurs well before clinical signs in most cases. Signs of the disease are fever, cough, nasal discharge, and increased respiratory rate. Because lesions are usually well advanced by the time the pneumonia is clinically apparent, mortality is commonly 40–80%.

Characteristic gross lesions are multiple firm nodules of various sizes separated by congested and partly atelectatic lung. A typical feature is the very large size of many of the foci. Evidence of their origin by coalescence of clustered small nodules is sometimes evident. There is a tendency for more rapidly progressive lesions to be distributed widely throughout the lungs, and occasionally an acute clinical form in foals is associated with miliary pyogranulomatous foci. Lesions of slower, more insidious onset occupy cranioventral regions of the lungs, usually bilaterally, and therefore have the distribution pattern of a bronchopneumonia (Fig. 6.33A). The nodular lesions are often referred to as abscesses if circumscribed, or as areas of suppurative bronchopneumonia if irregular and less well defined. They are, in fact, usually regions of caseation necrosis with either a slimy, homogeneous texture or a moist crumbly consistency with fluid-filled fissures. In most instances there is no distinct fibrous tissue capsule surrounding the necrotic tissue (Fig. 6.33B).

Histologically, the lesions produced by *Corynebacterium equi* are predominantly pyogranulomatous. Alveoli are filled with masses of macrophages containing many organisms (Fig. 6.33D). Giant cells containing organisms are common; neutrophils are less numerous. Lymphocytes and plasma cells are present in moderate numbers, mostly in alveolar septa and other interstitial zones. Necrosis of bacteria-laden macrophages and other cells involves local alveolar septa. Necrosis spreads gradually to affect large amounts of pulmonary parenchyma and produce the caseonecrotic foci seen macroscopically.

The bronchial lymph nodes are swollen and edematous. Sometimes they contain soft caseonecrotic foci. Histologically there is a pyogranulomatous lymphadenitis, with components similar to the pneumonia. Pleuritis is uncommon, even when pulmonary involvement is extensive.

After the lungs, the next most frequent sites of lesions caused by *Corynebacterium equi* in foals are the intestinal tract and mesenteric lymph nodes. These sites can be affected with or without accompanying lung lesions. The intestinal lesion is an ulcerative enterocolitis (Fig. 6.33C) that mainly involves the cecum and colon. The mucosa has numerous irregular but well-defined ulcers with fibrinonecrotic surfaces, red bases, and raised borders. They can be recognized as based on lymphoid tissues, Peyer's patches in the ileum, and solitary nodules of the large intestine. Mesenteric lymph nodes are swollen and edematous. Those of the large intestine frequently contain caseonecrotic foci. Histologically, the main intestinal lesions are pyogranulomatous inflammation of lymphoid tissue and fibrinonecrotic ulceration of the overlying epithelium. Inflammatory cellular components are the same as those in the pulmonary lesions.

More widespread dissemination of infection in foals can occasionally give rise to suppurative arthritis, hepatic or splenic "abscesses," vertebral abscesses, and hypopyon. *Corynebacterium equi* may also be a cause of ulcerative lymphangitis.

The pathogenesis of *Corynebacterium equi* infection in foals is incompletely understood. The abundance of the organism in dusty environments where foals contract pneumonia, together with the predominant bronchopneumonic pattern of the disease, indicate that aerosol infection is the usual route of pulmonary involvement. It also appears that the alimentary route of infec-

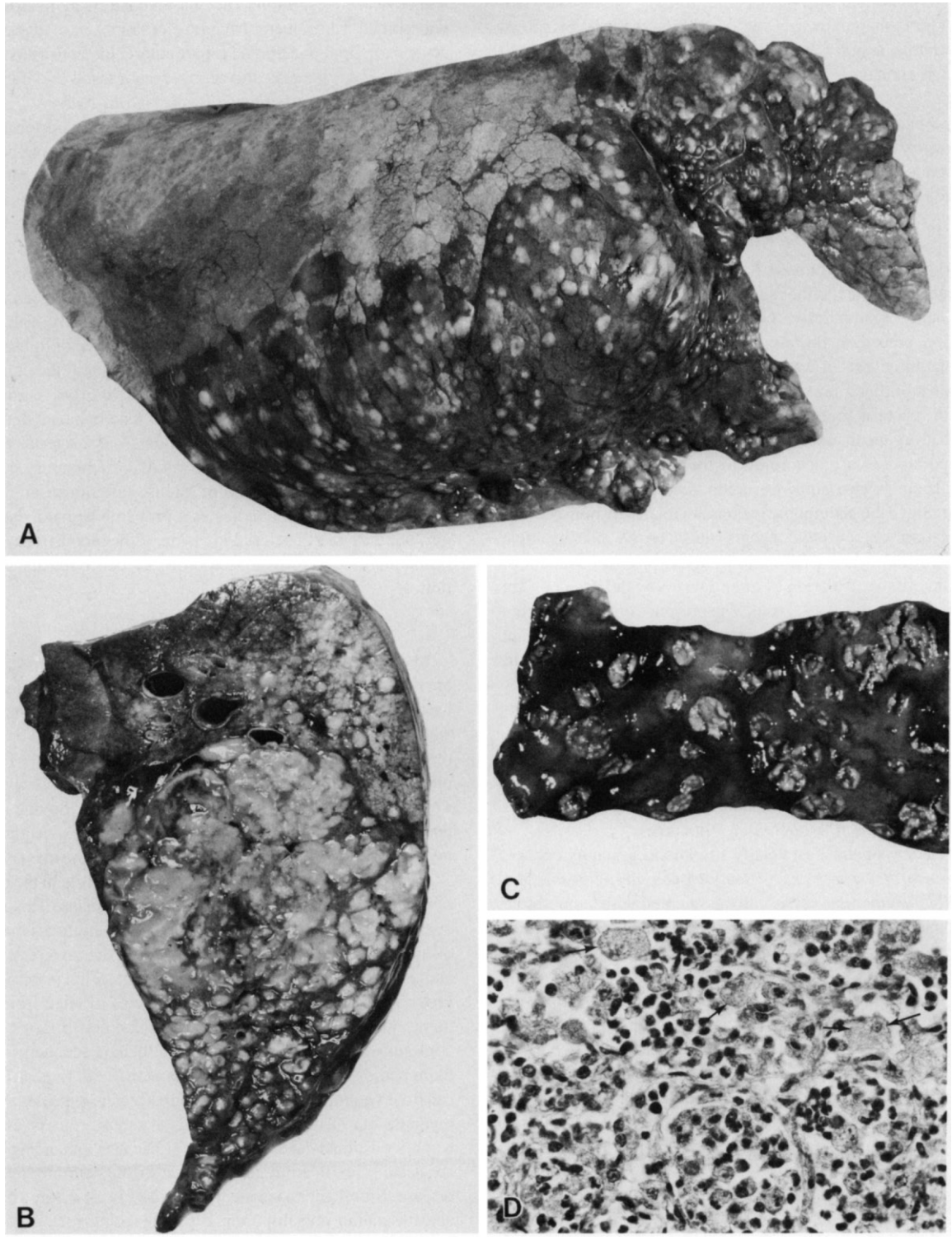

Fig. 6.33. *Corynebacterium equi* infection. Foal. (**A**) Extensive bronchopneumonia with multiple pyogranulomatous foci (''abscesses''). (**B**) Cross section of (**A**), showing variation in size and consistency of foci and absence of distinct capsules. (**C**) Multiple discrete ulcers in colon (Courtesy of J. A. Johnson and *Veterinary Pathology*.) (**D**) Alveoli filled by macrophages, which contain large numbers of *C. equi* (arrows).

tion is the usual one for the intestinal form of the disease. Isolated pyogranulomatous foci can develop in the lung by spread from intestinal lesions. Infection of foals *in utero,* during birth, or through neonatal umbilical contamination is probably unimportant.

Corynebacterium equi has also been associated with metritis and abortion in mares, metritis in cows, pneumonia in calves, and tubercle-like lesions in lymph nodes of pigs and cattle. Its etiologic role in some of these instances is still questionable.

Other Bacterial Infections

A large variety of Gram-positive and Gram-negative bacteria can cause pneumonia, either singly or in mixed infections. They mostly cause a suppurative bronchopneumonia in lungs damaged by a preceding disease process such as a viral or mycoplasmal infection, or when pulmonary defenses are impaired for reasons outlined previously. There is considerable overlap among the bacteria found in the different species of animals, but the sets of organisms most commonly involved, and their relative importance, vary according to the species of animals affected. There is also some variation according to geographic location. Since the pneumonic lesions are relatively nonspecific, identification of causative agents must be by bacteriologic means. But because bacteria can be opportunistic invaders of pneumonic tissue, isolation of an organism by culture does not necessarily indicate a causal role. The presence of large numbers of a bacterial species in pure culture, or as the predominant agent, provides presumptive evidence of its importance in causing the pneumonic process. Difficulty in fulfilling Koch's postulates often leaves a measure of uncertainty even after considerable study. This was formerly the case for pneumonic pasteurellosis and still holds true for many of the mycoplasmal infections, as will be discussed later. A further example of a bacterium whose pathogenic capability is not fully established is *Streptobacillus (Bacillus) actinoides* in calves.

Pyogenic organisms, especially streptococci, staphylococci, *Corynebacterium pyogenes, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae,* are usually associated with suppurative bronchopneumonias that may progress to abscessation. Either more virulent organisms or more severely compromised host defenses can lead to fibrinonecrotic or hemorrhagic pneumonias, such as the pneumonia caused by *Salmonella choleraesuis* in swine. This pneumonia can have the same appearance as pneumonic pasteurellosis in swine. In contrast, *S. typhisuis* characteristically causes a chronic suppurative bronchopneumonia in which, grossly, there are large, confluent regions of swollen, creamy tan consolidation. On cut section these appear smooth and homogeneous, except where there are granular or friable foci of necrosis.

In addition to the bronchopneumonias, various bacteria cause interstitial pneumonia as part of a pyemia or septicemia. These are usually in very young animals and are most commonly caused by streptococci, *Escherichia coli,* and in foals and pigs, by *Actinobacillus* spp. *Actinobacillus (Shigella) equuli* in foals is typically associated with multifocal purulonecrotic foci, often recognizably involving small vessels. Fulminating systemic bacterial infections causing septicemias may be accompanied by little evidence of direct pulmonary involvement, or there may be a severe, diffuse, acute interstitial pneumonia with intravascular leukocyte sequestration, foci of alveolar wall necrosis, and widespread fibrinohemorrhagic exudation into alveoli. The acute interstitial pneumonia is particularly likely to be associated with the endotoxemias and septicemias caused by Gram-negative organisms like *Salmonella* spp. and *E. coli.*

Finally, it is convenient to mention here that bacteria resembling *Pseudomonas mallei* and *Pasteurella* spp. have been isolated from multifocal interstitial pneumonia in several cats, a dog, and a tiger cub, representing regions as far apart as California, Australia, and Northern Ireland. The bacteria are of uncertain taxonomic status and are currently referred to as Eugonic Fermenter-4. These organisms are present in the oral and nasopharyngeal flora of dogs and cats, and have been isolated from infected bite wounds in humans and animals. The pulmonary lesions are numerous, firm, cream-colored or light tan nodules up to 1 cm in diameter scattered throughout the pulmonary parenchyma. Histologically, they are foci of massive accumulations of neutrophils, monocytes, and macrophages that efface alveolar architecture and contain numerous bacterial colonies interspersed among them. Necrosis of inflammatory cells and alveolar walls occurs in foci of intense inflammation. The distribution of the lesions indicates a probable hematogenous origin, but the site of bacterial invasion of the bloodstream has not been identified to provide supporting evidence for this speculation.

Mycoplasmal Diseases

Mycoplasmas are the smallest, free-living prokaryotes. They are placed in a class separate from other bacteria, mainly on the basis of their lacking the genetic capability to synthesize a cell wall (class Mollicutes, "soft skinned"). Lack of a cell wall results in extreme pleomorphism of the organisms. The taxonomic type of *Mycoplasma* is *M. mycoides* subsp. *mycoides.* This organism was isolated from contagious bovine pleuropneumonia and therefore gave rise to the former designation of mycoplasmas as pleuropneumonia-like organisms (PPLOs).

It is difficult to prove a definite pathogenic role in the production of pneumonia for many infectious organisms. This is especially true for the mycoplasmas. They are ubiquitous inhabitants of moist mucosal surfaces, particularly of the respiratory tract, and are common opportunistic inhabitants of pneumonic lung. Proving the etiologic role of mycoplasmas isolated from pneumonic lung is complicated by several factors. Species of mycoplasmas vary in pathogenicity, and there is a tendency for the more pathogenic strains to be the most difficult to culture. This can divert attention to relatively nonpathogenic species. When a mycoplasma suspected of having a causal role is cultured, Koch's postulates are hard to fulfill because enhancing factors are usually involved in development of the naturally occurring disease. Simultaneous evaluation of the role of the mycoplasma and the nature and importance of enhancing factors, whether they are additional damaging agents or act by reducing pulmonary defenses in other ways, causes difficulty in designing experimental protocols that can convincingly demonstrate the mycoplasma's pathogenic importance. The degree of uncertainty regarding the significance of a species or strain of *Mycoplasma* is inversely proportional to its pathogenicity. Since establishment of a relatively highly pathogenic organism, *M. mycoides* subsp. *mycoides,* as the causal agent of contagious bovine

pleuropneumonia was difficult, it is easy to understand why considerable uncertainty still exists concerning the importance of many much less virulent species. A further source of uncertainty is the lack of understanding of the mechanisms by which mycoplasmas cause injury to tissues. The relative importance of a direct effect on cilia, toxic effects on ciliated and other cells, macrophage–neutrophil interactions, and various immune-mediated responses are under investigation. The set of pathogenetic mechanisms appears to vary from one species of *Mycoplasma* to another.

Respiratory Mycoplasmosis of Cattle

There are two types of pneumonia associated with mycoplasmal infection in cattle. One is contagious bovine pleuropneumonia. The other is mycoplasmal bronchitis, bronchiolitis, and pneumonia of calves, which is an important component of enzootic pneumonia.

CONTAGIOUS BOVINE PLEUROPNEUMONIA. Contagious bovine pleuropneumonia is caused by *Mycoplasma mycoides* subsp. *mycoides* (small-colony type). The small-colony designation is currently used to distinguish the organism causing bovine pleuropneumonia from *M. mycoides* subsp. *mycoides* (large-colony type), which is a cause of disease in goats. Contagious bovine pleuropneumonia is characterized by a fibrinonecrotic pneumonia (Fig. 6.34C,D) with abundant serofibrinous pleuritis. Presence of necrotic material sequestered by fibrous capsules is a usual finding in subacute or chronic cases (Fig. 6.34A,B). The pattern of pneumonia is usually that of a lobar or bronchopneumonia (see Anatomic Patterns of Pneumonia). The lungs of cattle dying in the more acute stages of the disease typically have a "marbled" appearance in which relatively normal lobules are intermixed with lobules showing red or gray consolidation or necrosis. The marbled effect is heightened by the distension of interlobular septa, and interstitium surrounding vessels and airways by broad bands of fibrinous exudate. It is also enhanced by the dense, yellow-gray zones of packed inflammatory cells surrounding the necrotic areas. The fibrinonecrotic pneumonia and accompanying pleuritis of contagious bovine pleuropneumonia have features similar to the fibrinonecrotic pneumonia of acute pneumonic pasteurellosis. The marbled effect is more pronounced in contagious bovine pleuropneumonia, however, and the lesions are more prone to involve the caudal lobes. There is also a much greater frequency of development of sequestra in the mycoplasmal disease.

It appears that the disease originated in central Europe and remained endemic there until spread by the movement of cattle during the Napoleonic wars, and later by the growth in international commerce. Toward the end of the nineteenth century it had become almost worldwide in distribution. It was eradicated from North America and much of Europe before the turn of the century, and more recently appears to have been eradicated from Australia. It now occurs mostly in portions of Asia, central Africa, Spain, and Portugal. Enormous losses were reported from this disease in the last century, and in endemic areas the mortality rate among indigenous breeds of cattle is reported still to be more than 40%; in improved European breeds, the mortality in an unrestricted outbreak is not expected to exceed 10% of the animals. Species such as the buffalo, reindeer, and yak are susceptible to the disease but are seldom affected. Sheep and goats do not contract the natural disease caused by *Mycoplasma mycoides* subsp. *mycoides* (small-colony type) and do not appear to develop the pulmonary disease after experimental infection, but they do develop a severe local reaction and septicemia if the organism is inoculated.

The transmission of infection requires close contact between infected and susceptible animals. It seems probable that the disease is transmitted by the inhalation of infected droplets exhaled by affected animals, because the most reliable means of reproducing the disease experimentally is by endobronchial or aerosol exposure of susceptible cattle with suspensions of infected lung or organisms obtained from early subcultures. Factors other than the administration of the organism are evidently involved in determining whether cattle develop the disease, but exactly what these are is not known. Variations in innate susceptibility, interaction with other microorganisms or preexisting pneumonic lesions, and the state of pulmonary defenses have all been suggested as being important. It appears necessary for the organisms to reach the alveolar parenchyma, but the subsequent chain of pathogenetic events is still uncertain. It has been suggested that the acute vasculitis, fibrinous exudation, thrombosis, and necrosis are due in part to an Arthus-type or mixed hypersensitivity in animals with circulating antibodies capable of reacting with surface antigens on the mycoplasmas. Whatever the pathogenesis of the vasculitis, the thrombosis it can cause is to a large extent responsible for the infarction and sequestrum formation.

The disease that can be produced in a percentage of animals following the aerosolization or endobronchial instillation of cultured organisms is similar to the natural disease, but the lesions are frequently small and multifocal and are not as likely to cause confluent consolidation of large regions of lung, such as occurs in field outbreaks. Use of a suspension of infected lung is a more reliable method of reproducing the disease. Transmission experiments have confirmed that in an exposed population, 10–30% of the animals are refractory to infection. This resistance is native and not acquired by prior exposure to the organism. The natural incubation period is quite variable, but usually it is longer than 1 month. The clinical signs are those of a febrile pleuropneumonia, with a course of 2 to 8 weeks, ending in death or slow recovery. Peracute cases that die in less than 1 week do occur. On the other hand, there are mild cases, and some that are subclinical. Mortality can range from 10 to 70% in outbreaks. Slaughter of affected herds of cattle on occasion reveals frequency of pulmonary lesions approaching 90% even though clinical signs might be obvious in only 30% of the animals at the time killing starts. There is no particular age distribution. Evidence of extrapulmonary localization may be observed in young calves as a polyarthritis, and in pregnant cows as abortion. Up to a third of cases that recover from the acute disease harbor residual infection in pulmonary sequestra. The organisms may remain viable in a sequestrum for several years. Cattle with sequestra that break down and discharge liquefied or caseous debris containing viable mycoplasmas into the airways are frequently the source of new outbreaks of the disease.

MYCOPLASMAL BRONCHIOLITIS AND PNEUMONIA OF CALVES. Mycoplasmal bronchitis and bronchiolitis or bronchointerstitial

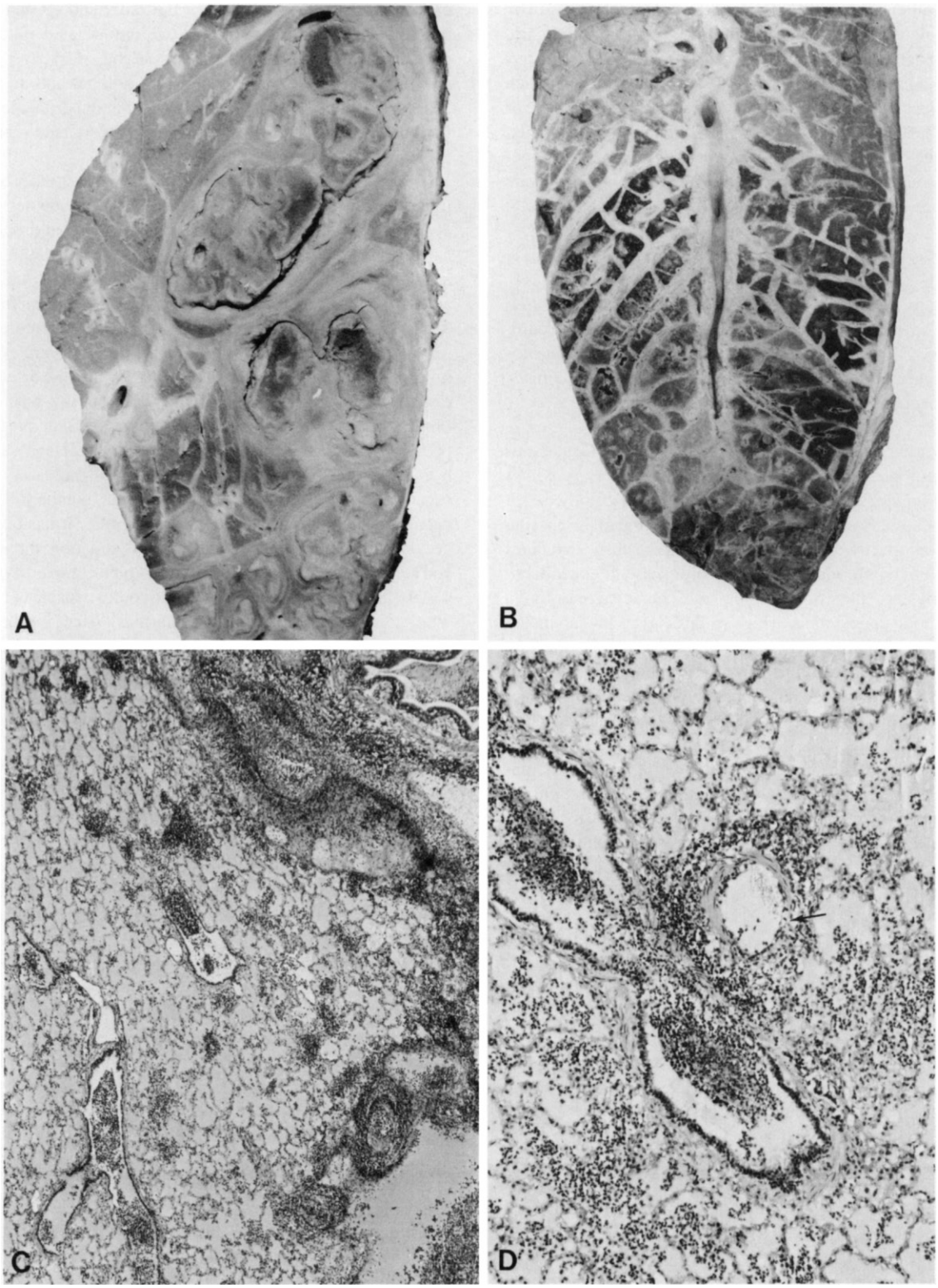

Fig. 6.34. Contagious bovine pleuropneumonia. (**A**) Encapsulation of necrotic tissue (sequestra). (**B**) Scarring of distended interlobular septa in chronic disease. (**C**) Acute fibrinonecrotic pneumonia with inflammation and necrosis within interlobular septa and peribronchial interstitium. (**D**) Acute arteritis (arrow) affecting portion of the wall of peribronchial artery.

pneumonia is an important component of enzootic pneumonia of calves, involving synergistic action of several infectious agents. Enzootic pneumonia will be discussed subsequently, but the pulmonary lesions attributable to mycoplasmas will be considered here. More than a dozen species of mycoplasmas can be isolated from bovine lungs. The difficulties in proving pathogenetic significance for mycoplasmas recovered from pneumonic lung was referred to earlier. Nevertheless, on the basis of both field and experimental studies, *Mycoplasma dispar, M. bovis,* and *Ureaplasma* spp. are generally accepted as being capable of producing subclinical bronchiolitis or pneumonia. A fourth species, *M. bovigenitalium,* is experimentally pathogenic for lung but is rarely isolated from the respiratory tract. *Mycoplasma dispar* appears to be the most important mycoplasmal pathogen in lungs of calves.

The mycoplasmas colonize the upper respiratory tract of calves soon after birth and extend to various depths of airways. They attach to the ciliated epithelial cells, and when present in large numbers can be seen by electron microscopy to be packed two or three layers deep on and between the microvilli and base of the cilia. Their characteristic effect is to cause a chronic catarrhal bronchitis and bronchiolitis that over the course of several months leads to the development of prominent lymphofollicular sheaths around tbe airways. The term "cuffing pneumonia" is sometimes applied to lungs in which this is the predominant finding (Fig. 6.35C).

The uncomplicated mycoplasmal lesion is usually inconspicuous. Grossly, there are patchy, purple-red atelectatic foci in cranioventral regions of the lungs (Fig. 6.35A). More confluent, meaty consolidation is an indication of probable involvement by additional organisms. Microscopically, the lesion for the first several weeks after infection is a catarrhal bronchitis and bronchiolitis. There are accumulations of neutrophils and mucus in the lumina of the airways, and increased prominence of bronchial submucosal glands and epithelial goblet cells. There are moderate accumulations of lymphocytes and lesser numbers of plasma cells in the walls of the airways and around accompanying blood vessels. There is loss of cilia, and many ciliated cells have degenerative changes. Inflammation of alveoli adjacent to terminal bronchioles occurs in heavy experimental infections in colostrum-deprived, specific-pathogen-free calves and can probably occur in heavy natural infection. The alveolitis is nonspecific. There is a mixed intraluminal accumulation of neutrophils and alveolar macrophages, with occasional plasma cells and giant cells. The alveolar septa appear thickened. This is partly because of accumulation of mononuclear cells within the septa but often has a large artifactual component because of microatelectasis. Hyperplasia of alveolar type II cells can occur but is usually minimal in uncomplicated infections. More commonly, alveolar regions distal to occluded bronchioles are atelectatic rather than directly inflamed, and this correlates with the usual gross finding of atelectasis. The composite picture is of a bronchointerstitial pneumonia and partial atelectasis (Fig. 6.35B).

Widespread lymphofollicular accumulations containing germinal centers develop slowly and are not usually present in calves less than 3 months of age. The follicular or ensheathing collars of lymphocytes extend into the lamina propria, often obliterate the bronchiolar smooth muscle, and cause narrowing of the bronchiolar lumina. This is the hallmark of cuffing pneumonia (Fig. 6.35C). There is associated epithelial hyperplasia, including goblet cells in bronchi and large bronchioles, and hypertrophy of bronchial submucosal glands. Alveolar regions are principally atelectatic because of bronchiolar occlusion by lymphofollicular accumulations and intraluminal exudate, but might have an alveolitis as described for the earlier stages. The epithelium covering large lymphofollicular nodules in the submucosa of bronchi tends to assume the flattened appearance characteristic of lymphoepithelium.

Because the uncomplicated mycoplasmal lesion is rarely lethal, if ever, it is usually detected as a cuffing type of pneumonia in slaughtered veal calves or in calves dying for other reasons. It can also be a component of other pneumonias of calves. Other than the designation cuffing pneumonia, various morphologic terms have been used. The most appropriate one for the airway lesion is chronic catarrhal bronchitis and bronchiolitis with lymphofollicular cuffing. When the inflammation extends to peribronchiolar alveoli, the general term bronchointerstitial pneumonia is applicable. Although the lesion is a chronic one, examination of the lungs of cattle older than 9 to 12 months of age indicates that it does gradually regress in most instances.

Respiratory Mycoplasmosis of Goats

Mycoplasmas are an important cause of disease in goats. A variety of species are responsible for pneumonia, mastitis, polyarthritis, keratoconjunctivitis, or a combination of these. Septicemic forms can also occur, mostly in young kids. Manifestations of mycoplasmosis vary according to prevalence of the various species and strains of *Mycoplasma,* the husbandry practices, and the presence of environmental influences or intercurrent diseases that act as predisposing factors.

CONTAGIOUS CAPRINE PLEUROPNEUMONIA. Contagious caprine pleuropneumonia is the most important form of respiratory mycoplasmosis in goats. The disease occurs mainly in Africa, the Middle East, and western Asia. The prominent lesions are a severe fibrinous or fibrinonecrotic pneumonia and a profuse serofibrinous pleuritis. Fibrinous pericarditis is also common. Three taxa of *Mycoplasma* are associated with severe outbreaks of caprine pleuropneumonia: *M. mycoides* subsp. *capri, M. mycoides* subsp. *mycoides* (large-colony type), and an unclassified organism referred to as strain F38. The relative importance of these organisms in the various geographic regions is not clearly established. Strain F38, which was isolated in Kenya, has been reported to be the cause of a pleuropneumonia most resembling the classical caprine contagious pleuropneumonia reported from South Africa at the end of the nineteenth century. The points of resemblance are a high degree of contagiousness for goats but not sheep or cattle, a fibrinous pleuropneumonia lacking conspicuous serofibrinous widening of interlobular septa, and absence of local inflammation when the organism is inoculated subcutaneously. *Mycoplasma mycoides* subsp. *capri* and *M. mycoides* subsp. *mycoides* (large-colony type) appear to cause a form of caprine pleuropneumonia resembling the disease in cattle in that there is often extensive widening of interlobular septa and peribronchial interstitium by serofibrinous exudate. They

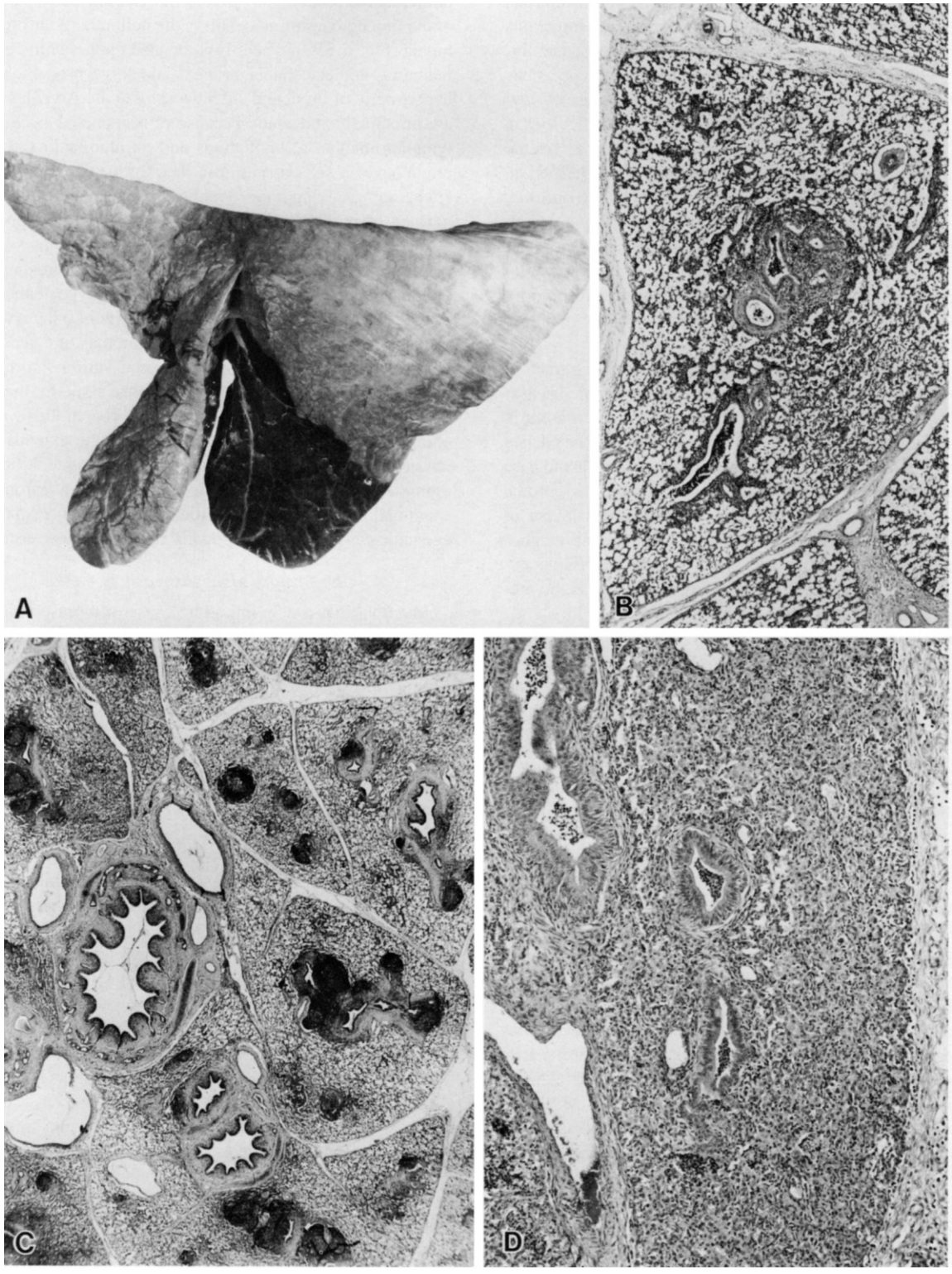

Fig. 6.35. (**A**) Atelectasis and consolidation of enzootic pneumonia. Calf. (**B**) Bronchointerstitial pneumonia and atelectasis associated with *Mycoplasma* infection. Calf. (Courtesy of M. L. Anderson.) (**C**) Prominent lymphofollicular sheaths around bronchioles and vessels in chronic enzootic (''cuffing'') pneumonia. Calf. (**D**) Bronchointerstitial pneumonia caused by *Chlamydia psittaci*, with epithelial hyperplasia of bronchioles and increased cellularity of atelectatic alveoli. Goat.

also seem to be less readily transmitted from goat to goat by contact. Necrotic sequestra are present in chronic stages of disease caused by all three mycoplasmas but are not as conspicuous a feature as in contagious bovine pleuropneumonia. The distinction between the pleuropneumonia caused by F38 and related strains on the one hand and *M. mycoides* subsp. *capri* or *M. mycoides* subsp. *mycoides* (large-colony type) on the other is not firmly established. There is a positive correlation, however, between the profuse interstitial pulmonary exudation produced by the *M. mycoides* subspecies and their ability to cause an intense local reaction when inoculated subcutaneously.

Mycoplasma mycoides subsp. *capri* and *M. mycoides* subsp. *mycoides* (large-colony type) are also found in areas of the world where explosive outbreaks of caprine contagious pleuropneumonia do not occur. Both organisms have been isolated in Australia, and *M. mycoides* subsp. *mycoides* (large-colony type) is widespread in North America. Syndromes caused by *M. mycoides* subsp. *mycoides* (large-colony type) vary. In North America and France, it causes severe disease with high mortality in kids. The predominant lesion is fibrinopurulent polyarthritis, but fibrinous pleuritis and pericarditis, acute interstitial pneumonia, and meningitis frequently accompany the severe mycoplasmemia. In older goats, less fulminating cases of mastitis, pneumonia, or arthritis are more usual. Peritonitis and abortion are occasional complications.

Various other mycoplasmas have been isolated from the lung. *Mycoplasma capricolum* is principally a cause of fibrinopurulent polyarthritis in kids. A mild, acute interstitial pneumonia, such as occurs in other septicemias, occurs in the septicemia associated with acute polyarthritis in young kids. Mastitis can occur in milking females.

Other mycoplasmas, particularly *Mycoplasma ovipneumoniae* and *M. bovis*, have been isolated from pneumonic lungs of goats. Their significance is uncertain. It is probable that they play a role similar to that of *M. bovis* in calves and *M. ovipneumoniae* in sheep by causing a mild, subacute to chronic catarrhal bronchiolitis or bronchointerstitial pneumonia and perhaps acting synergistically with other infectious agents to produce an enzootic type of pneumonia.

Respiratory Mycoplasmosis of Sheep

The mycoplasma most frequently isolated from lungs of sheep is *Mycoplasma ovipneumoniae*. Most of the evidence indicates that it is one of the combined etiologic factors causing enzootic pneumonia of sheep, usually in association with *Pasteurella haemolytica*. Experimental studies using *M. ovipneumoniae* alone have been inconsistent and often difficult to interpret. There is sufficient evidence, however, to show that at least some strains of the organism can cause mild, subclinical lesions in some infected sheep. Lesions are principally chronic catarrhal bronchitis and bronchiolitis, with development of lymphofollicular collars around the airways. The affected alveoli are mostly atelectatic because of bronchiolar obstruction, although a mild chronic alveolitis might be present. The role of *M. ovipneumoniae* therefore appears to be analogous to that of *M. dispar* in calves.

Mycoplasma mycoides subspecies of caprine origin experimentally cause fibrinous pneumonia and pleuritis in sheep. They are isolated only on rare occasions from naturally occurring outbreaks of pneumonia in sheep, and even in these instances their etiologic importance is open to question because of the presence of *Pasteurella haemolytica*.

Respiratory Mycoplasmosis of Swine

Mycoplasmas are by far the most important cause of enzootic pneumonia of pigs. In the absence of other proven etiologic agents, there is a tendency to regard mycoplasmas as the sole cause. It remains to be determined whether this is too sweeping a generalization. It is safe to say, however, that mycoplasmal pneumonia is the overwhelmingly preponderant form of enzootic pneumonia in pigs. Now that mycoplasmas are established as the main causative agents, the term **mycoplasmal pneumonia** replaces the earlier one, virus pneumonia of pigs (enzootic virus pneumonia).

Mycoplasma hyopneumoniae (*M. suipneumoniae*) and *M. hyorhinis* are both established respiratory pathogens, *M. hyopneumoniae* the more important. A variety of other mycoplasmas, such as *M. flocculare* and *Ureaplasma* spp., can also be isolated occasionally from enzootic pneumonia. Their relative importance in causing the disease is still under investigation.

ENZOOTIC MYCOPLASMAL PNEUMONIA OF SWINE. Enzootic mycoplasmal pneumonia is a chronic, usually nonfatal disease of young pigs. It is widespread throughout the world, and in its most severe form can affect from 70 to 100% of pigs in a herd. Clinical expressions of the uncomplicated disease are coughing, unthriftiness, poor weight gain, and reduced food conversion ratio. Because there is usually low mortality associated with mycoplasmal pneumonia, the lesions are generally seen in slaughtered animals or those dying from other diseases. When deaths do occur because of pneumonia, it is due mainly to superimposed bacterial infections. *Pasteurella multocida* is the most common secondary invader, but *Corynebacterium pyogenes*, *Haemophilus* spp., streptococci, staphylococci, *Klebsiella* spp., and *Bordetella bronchiseptica* can be involved singly or in combination.

The characteristic gross feature of mycoplasmal pneumonia is confluent consolidation of cranioventral regions of the lungs (Fig. 6.36A). When the amount of consolidation is small, it tends to affect portions of the right middle and right cranial lobes and the caudal portion of the left cranial lobe, but frequently there is bilateral involvement of more than 50% of cranial and middle lobes together with the accessory lobe and cranioventral portions of caudal lobes. The consolidated lung ranges from dark red through grayish pink to more homogeneous gray, according to the age of the lesion. This change occurs over the several-month course of disease. Even though there is often extensive confluent consolidation, careful examination reveals a regular pattern of small grayish nodules against a red background. This denotes the bronchiolar orientation of the inflammation. The cut surface of consolidated lung is moist and meaty, and mucopus is present in the airways. Minor mycoplasmal lesions are less characteristic and have a mosaic pattern of intermixed consolidated, atelectatic, hyperinflated, and more normal lobules. Occasional atelectatic lobules represent the minimal

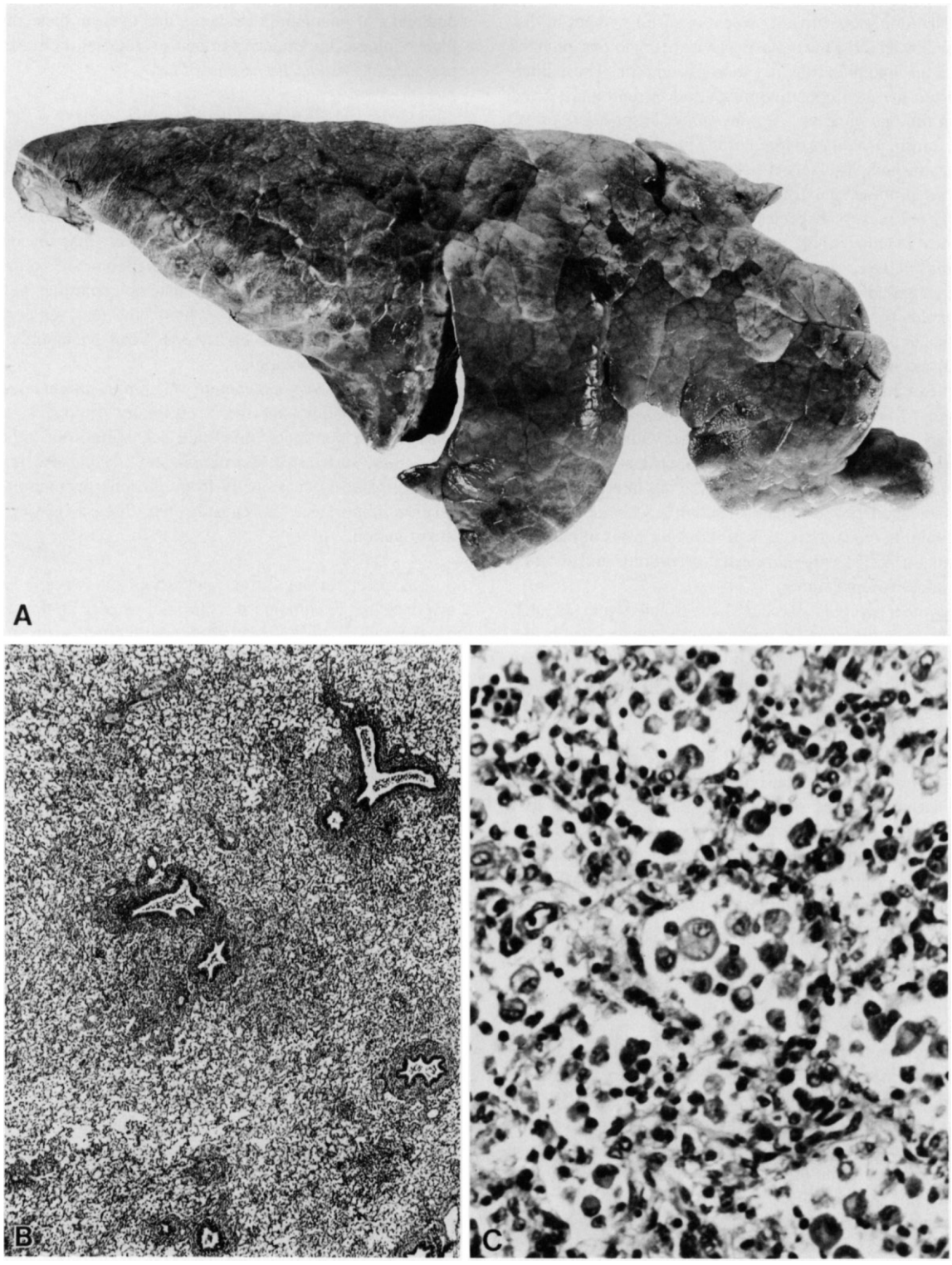

Fig. 6.36. Enzootic mycoplasmal pneumonia of swine. (**A**) Confluent consolidation of cranioventral lobes. Multiple pale foci within affected lobules, indicating bronchiolar orientation of the pneumonia. (**B**) Bronchointerstitial pattern of early lesion. (**C**) Peribronchiolar alveoli in (**B**), showing thickening of septa by lymphoid cells and macrophages within lumina.

gross lesion. Sometimes, pale nodules indicating the presence of peribronchiolar lymphoid tissue can be detected in the centers of atelectatic lobules. Lesions of severe exudative bronchopneumonia or lobar pneumonia, especially with necrosis or abscessation, indicate secondary bacterial infection.

Mycoplasma hyopneumoniae can cause fibrinous or serofibrinous pleuritis and inflammation of other serous surfaces. When pleuritis is present, however, it is more probably associated with *M. hyorhinis* or infections complicated by *Pasteurella multocida* or *Haemophilus* spp. Pulmonary lymph nodes are enlarged by nonspecific hyperplastic lymphadenitis to a degree corresponding to the extent and activity of pulmonary consolidation. On cut surface they are moist, usually bulging, and sometimes hyperemic.

Histologically, mycoplasmal pneumonia in swine has the morphologic pattern of a catarrhal bronchointerstitial pneumonia (Fig. 6.36B), with development of prominent peribronchial and peribronchiolar accumulations of lymphoid tissue in the chronic stages. Thus there is a resemblance to the lesions caused by mycoplasmas associated with enzootic pneumonias in calves and lambs. The mycoplasmas of swine appear to be much more capable of eliciting chronic inflammation of the alveolar parenchyma without the assistance of other organisms, however, even though they mainly colonize the surface of ciliated cells in the airways, as do the mycoplasmas of calves and lambs.

In the fully developed mycoplasmal pneumonia, there is extensive lymphoid hyperplasia around airways and their associated vessels. In severe cases, the lymphoid nodules or sheaths efface the muscularis mucosae and cause narrowing of the lumina of airways. Germinal centers may be present. The epithelium over prominent nodules is often degenerated or ulcerated. Elsewhere, there is epithelial hyperplasia, particularly in bronchioles. Cilia are absent from many surface regions. There is hyperplasia of goblet cells in the bronchi and larger bronchioles, and the bronchial submucosal glands are increased in size and number. The increased activity of mucus-secreting cells is responsible for the presence of large amounts of mucus or mucopus. The alveolitis component of the bronchointerstitial pneumonia consists of wide thickening of the septa of alveoli adjacent to bronchioles, and accumulation of exudate in their lumina. The alveolar septa are thickened by accumulations of various-sized lymphocytes and small numbers of plasma cells. The intraalveolar exudate consists predominantly of macrophages (Fig. 6.36C), but plasma cells, lymphocytes, and neutrophils are present to various degrees. There is hyperplasia of type II alveolar epithelial cells of inflamed alveoli in established lesions. This can be difficult to detect histologically when alveolar architecture is obscured by absence of detectable demarcation between thickened alveolar septa and atelectatic or exudate-filled lumina.

Experimental studies of the pathogenesis of mycoplasmal pneumonia indicate that typical gross lesions do not occur until 2 to 4 weeks after infection. The rate of development of lesions is dependent on factors relating to the dose and strain of *Mycoplasma,* method of administration, and susceptibility of the pigs exposed. Inoculation of suspensions of lung containing mycoplasmas is a more reliable way of reproducing the disease, as is also the case with experimental production of respiratory mycoplasmosis in cattle, sheep, and goats. Young pigs naturally exposed to infectious aerosols soon after birth can also develop lesions by the time they are 3–5 weeks of age. Initial lesions caused by the mycoplasma, that is, within a week after infection, are a neutrophilic bronchitis and bronchiolitis, and a mixed neutrophil and macrophage accumulation in adjacent alveoli. The numbers of neutrophils diminish, and the lymphoid cells increase over the subsequent several weeks to reach the fully developed stage of consolidation described earlier. There is conflicting evidence concerning persistence of the pneumonia after it has reached its peak some 5–6 weeks after infection. Estimations range from essentially complete resolution of uncomplicated mycoplasmal pneumonia within 2 months to no appreciable reduction in its extent even after 3 months. In view of the large number of variables in experimental and especially in field situations, the wide range in persistence is to be expected.

Respiratory Mycoplasmosis of Horses

Although several mycoplasmas have been isolated from the respiratory tract of horses, particularly *Mycoplasma equirhinis* and *M. felis,* there have been no studies to determine whether any of them is capable of causing a subclinical bronchiolitis or bronchointerstitial pneumonia. *Mycoplasma felis* has been implicated as a possible cause of pleuritis in the horse.

Respiratory Mycoplasmosis of Dogs and Cats

Of the various mycoplasmas isolated from canine pneumonia, *Mycoplasma cynos* experimentally is capable of causing a mild bronchointerstitial pneumonia similar to that produced by mycoplasmas in other species. *Mycoplasma bovigenitalium* is also pathogenic, but to a lesser extent. The clinical significance of these mycoplasmas is doubtful, however, because they are usually isolated from severe exudative lesions in which pathogenic bacteria are also present, often in dogs with distemper.

Mycoplasma felis is an opportunistic pathogen of the conjunctiva in cats. Neither it nor the other mycoplasmas isolated from the respiratory tract of cats are recognized as significant respiratory tract pathogens.

Chlamydial Diseases

Indigenous strains of *Chlamydia psittaci* have been associated with respiratory disease in cats, cattle, sheep, goats, and horses. Feline *C. psittaci* was the first agent isolated from cats with conjunctivitis and respiratory disease, and therefore became known rather misleadingly as the feline pneumonitis agent. It is now recognized to be mainly a cause of chronic conjunctivitis, although it can cause transient rhinitis and subclinical bronchointerstitial pneumonia. Strains of *C. psittaci* can occasionally be isolated from pneumonia in cattle, sheep, and goats. The pneumonias are usually of the enzootic type and are sometimes accompanied by enteritis. Since the intestine is a major carrier site for chlamydiae, and they can readily be isolated from feces of ruminants, inhalation of dust contaminated with feces is assumed to be a source of respiratory infection.

In all the domestic animals studied, experimental pulmonary infection by indigenous strains of *Chlamydia psittaci* causes a

mild, acute bronchointerstitial pneumonia that resolves within 3 to 4 weeks unless secondary bacterial invasion occurs. The extent of the pneumonia varies according to the amount of inoculum and whether it is delivered by aerosol, intranasal, or intratracheal routes, but the course of the disease remains the same. There is an initial neutrophilic bronchiolitis and alveolitis, but by 5 days after infection there is predominance of macrophages in the alveolar exudate and extensive hyperplasia of alveolar type II epithelial cells. Moderate-sized cuffs of lymphoid cells are present around bronchioles and small blood vessels at the height of the lesion, and alveolar septa are thickened by a mixed infiltrate of mononuclear cells with a few neutrophils. A similar lesion, in which chlamydiae can be detected by immunofluorescence, is occasionally encountered in naturally occurring pneumonia in ruminants (Fig. 6.35D). The chlamydiae are mostly destroyed during the acute phase of inflammation, which then subsides and resolution can be complete within 3 to 4 weeks after experimental infection.

In assessing the importance of chlamydial infections in ruminants, it is important to note that they are usually only capable of inducing a transient inflammation. This is in contrast to mycoplasmas, which tend to persist on ciliated epithelium and cause chronic lesions. The part chlamydiae play in contributing to the cause of chronic enzootic pneumonia is therefore probably a relatively minor one.

Rickettsial Diseases

Several rickettsial diseases can cause interstitial pneumonia as one of the manifestations of their systemic involvement. This is particularly true for rickettsias affecting vascular endothelium. The important organism of this type in animals is *Cowdria ruminantium*, which causes heartwater in cattle, sheep, and goats (see the Cardiovascular System, Volume 3). A mild interstitial pneumonia can be present in salmon poisoning of dogs caused by *Neorickettsia helminthoeca* (see the Alimentary System, this volume).

Pulmonary Mycoses

Aspergillosis

Fungi of the genus *Aspergillus* are ubiquitous, and exposure to the spores is an everyday matter. Nonetheless, established infections that produce disease are uncommon in mammals, although of great importance in birds. *Aspergillus fumigatus* is responsible for most infections in mammals, birds, and humans. Other species, including *A. flavus*, *A. niger*, and *A. nidulans*, occasionally act as pathogens.

Aspergillosis in animals is most often a respiratory infection initiated by inhaled spores. Moldy litter and feeds, especially hay and grain that have been damp and heated during storage, support an enormous growth of fungi among which *Aspergillus fumigatus* can predominate. In view of the high rate of exposure that takes place among housed animals, it is perhaps surprising that more progressive infections are not detected. Very little is known concerning the pathogenesis of aspergillosis. Questions concerning the susceptibility of hosts, the number of spores necessary to initiate infection, toxigenicity of the organisms, and the role of immunity and hypersensitivity still have to be resolved.

Aspergillosis can be a respiratory or placental disease in animals. Infections of either the upper or lower respiratory tract are sporadic in all species, but thus far infection of the pregnant uterus and fetus has been found mainly in cattle. The latter, which is described with diseases of the pregnant uterus (in the Female Genital System, Volume 3), is the more economically important of the two.

Aspergillosis of the respiratory tract appears often to be a complication of some other debilitating disease, but there are cases in which no clear predisposition can be found. The infection may develop as an implantation on the mucous membrane of the nasal cavity, sinuses, guttural pouches, and tracheobronchial airways, or it may be in the form of a nodular bronchopneumonia. Secondary intestinal infections have been observed in cattle. When the fungi grow on a mucous membrane, they may be visible to the naked eye, first as a whitish growth and later as a powdery, feltlike growth with a typical blue-green color produced by the conidia. These superficial colonies may develop after death, and the presence of colonies of the fungus on a mucosa is not significant unless there is a tissue reaction. The usual reaction is caseating necrosis surrounded by a zone of hemorrhagic inflammation. Breakdown of these lesions in the walls of bronchi can result in bronchiectatic cavities.

The pulmonary lesions typically occur as one or many discrete gray-white nodules about 1–10 mm in diameter, with a narrow hyperemic rim. They may be obscured, especially in young animals, by severe pulmonary congestion. The nodules develop around fungal colonies that proliferate in the terminal bronchioles (Fig. 6.37B) and adjacent alveoli. The fungal colony consists of long, branching, septate hyphae (Fig. 6.37A) and is surrounded by a zone of neutrophils, macrophages, and debris. The focus expands and compresses adjacent alveoli. The affected bronchioles contain plugs of purulent exudate. As is common in invasive fungal lesions of this type, occasional blood vessels are invaded, inflamed, and thrombosed. The nodules may become cavitated if they evacuate into airways. Chronic lesions are granulomatous. Macrophages and epithelioid cells predominate in the nodules and extensively infiltrate the septal tissues, and encapsulating fibroplasia is evident. Giant cells are not a significant part of the lesion, although they may be present later when the focus is being obliterated by fibrosis. Perhaps as an indication of host resistance, the form of the colonies changes in chronic infection. Instead of stretching out freely as long hyphae in all directions, as they do in early and progressive infections, the colonies become composed of shorter, radiating hyphae that branch freely near their outer ends—the so-called actinomycotic forms of the fungus. Sometimes "asteroid" bodies can be found in the nodules being obliterated. These consist of small tangled remnants of the colony, surrounded by radiating acidophilic clubs quite similar to those of the granules of actinomycosis (Fig. 6.37C). Dissemination of the infection from the pulmonary lesions can occur. Of the many organs in which metastases develop, including the meninges, the kidney seems to be the most prone.

Mortierellosis

Acute fatal mycotic pneumonia may be associated with placental infection by *Mortierella wolfii*, the most important cause of mycotic abortion of cattle in New Zealand. An acute fibrino-

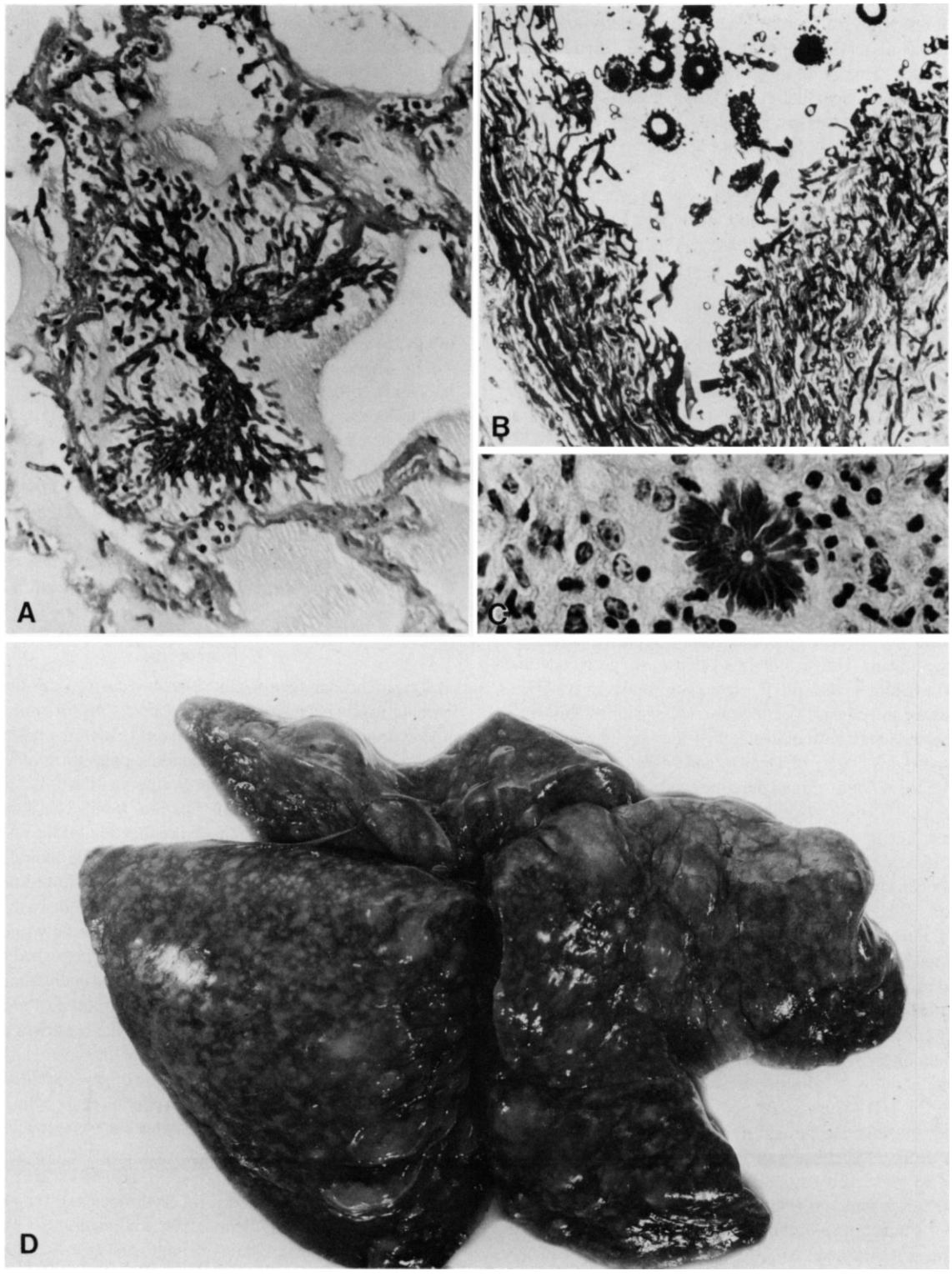

Fig. 6.37. (**A**) Branching septate hyphae of *Aspergillus fumigatus* in lung. Ox. (**B**) Mycelium invading bronchiolar wall and fruiting bodies in lumen. Pulmonary aspergillosis. Ox. (**C**) Chronic pulmonary aspergillosis. Ox. Clubs surrounding fungus in epithelioid-cell granuloma. (**D**) Disseminated granulomatous foci of severe pulmonary blastomycosis. Dog.

necrotic pneumonia can occur in infected cows at or within a few days of abortion or parturition. There is apparently extensive hematogenous dissemination of fungal elements when the placenta separates. This is followed by widespread vegetation of hyphae in pulmonary capillaries and larger vessels, with resulting inflammation, thrombosis, and necrosis. Less severe pulmonary involvement leads to chronic, focal, granulomatous lesions.

Other fungi within the class Phycomycetes, such as *Mucor* and *Rhizopus*, are occasional opportunistic invaders of lung and are usually associated with the nodular caseonecrotic or granulomatous lesions.

Blastomycosis

Blastomycosis is a disseminated or localized mycotic infection caused by *Blastomyces dermatitidis*. It is chiefly a disease of humans and dogs in North America and Africa. It is sometimes referred to as North American blastomycosis, to distinguish it from South American blastomycosis (*B. brasiliensis*) and European "blastomycosis" (*Cryptococcus neoformans*). The lesions are typically granulomatous or pyogranulomatous.

Blastomyces dermatitidis is a dimorphic fungus; in cultures at room temperature it produces a mycelial growth, whereas in tissues or culture at 37°C it is yeastlike, 8–25 μm in diameter with a thick, double-contoured wall, and reproduces by budding. The epidemiology of blastomycosis is obscure. The infection appears not to be contagious from animal to animal or animal to human. The available evidence suggests that the source of infection is the soil or related site. In North America, most cases of the disease occur in the Mississippi–Ohio river basins and the central Atlantic states of the United States, and near the northern border of Ontario and Manitoba in Canada.

The disease in dogs is found predominantly in young males of large breeds. The lung is the most frequent site of primary involvement, but primary cutaneous infections are also found. Systemic dissemination often occurs and is particularly prone to cause clinical signs associated with lesions in lymph nodes, eyes, skin, subcutaneous tissue, bones and joints, and the urogenital tract. The pulmonary form of the disease is insidious in onset and has a chronic course that may last many months. The usual syndrome is one of a chronic debilitating disease with cough, exercise intolerance, and terminal respiratory distress. The other clinical signs depend on the pattern of dissemination.

The pulmonary lesions of fatal blastomycosis are multiple, gray-white nodules of various sizes distributed throughout all lobes (Fig. 6.37D). Superficial nodules produce elevations of the pleura, but it is exceptional for there to be pleuritis. When this does occur, it is because of fistulation from a mycotic abscess. Most pulmonary nodules are of firm granulomatous tissue, but some undergo central abscessation or caseation and then may fistulate into a bronchus or onto the pleura. Calcification is minimal or absent. Microscopically, the high frequency with which small lesions affect bronchioles and adjacent alveoli can be taken as evidence of aerogenous infection, although intrabronchial spread of organisms confuses the picture. The regional lymph nodes are consistently involved and contain granulomas, abscesses, or caseous foci. It is usual for the pulmonary nodules to be more or less of equivalent age, but it is sometimes possible to locate larger, older caseous lesions in the lung and lymph node, which together are probably comparable to the primary complex of tuberculosis.

Disseminated lesions take the same form as those in the lungs and have been observed in peripheral lymph nodes, eyes, skin, subcutaneous tissues, bones, and joints. Testes, prostate, brain, heart, liver, spleen, kidneys, intestines, and other organs are less commonly affected. The lesions are either typical granulomas with abundant epithelioid and giant cells, or pyogranulomatous foci with central accumulation and necrosis of neutrophils and macrophages. The yeastlike fungi are plentiful and readily detected in the lesions, either free or in the cytoplasm of macrophages and giant cells. Identification of the organism, and its characteristically broadbased, single-budding forms, is aided by use of PAS or methenamine–silver stains.

The cutaneous lesions begin as papules, which soon develop into small abscesses with a surrounding inflammatory reaction. The lesions expand, with new small abscesses forming in the expanding margin of the papules while the central areas undergo some cicatrization.

Microscopically, the abscesses and granulomas found within the skin and subcutis are structurally similar to the pulmonary lesions.

Pulmonary, cutaneous, or systemic blastomycosis occasionally occurs in cats, particularly in the Siamese breed. It has also been found in other species.

Cryptococcosis

Cryptococcosis (European "blastomycosis") is a subacute or chronic mycosis caused by *Cryptococcus neoformans* (*Torula histolytica*). *Cryptococcus neoformans* is monomorphic, yeastlike, reproduces by single buds, and is approximately 5–10 μm in diameter, not including the large amount of capsular material. The disease has worldwide distribution. It may be a localized or disseminated disease, but it has a predilection for the respiratory system, particularly the nasal region, and for the central nervous system. All species of animals appear to be affected occasionally. Most attention has been focused on the disease in cats.

There are several species in the genus, but only one, *Cryptococcus neoformans*, is a pathogen. It is distinguished from the nonpathogens by producing disease in experimental mice. The yeast is surrounded by a wide capsule composed of mucopolysaccharides, and although cultivation of the organism is necessary for proper identification, a confident diagnosis can be made on pathologic material by identification of the capsule. The capsular material is sometimes copious enough to give the lesions a grossly mucinous texture, and it stains well with mucicarmine, the PAS reaction, or Alcian blue. The capsule is wider in hydrated than in dehydrated sections. The organisms in wet mounts are not easily distinguished from erythrocytes or lymphocytes, but they are clearly evident by negative staining of the wide capsular zones with India ink or nigrosin.

The source of infection is generally believed to be soil, especially when enriched with pigeon or other bird droppings. Cases are sporadic, and as usually true for the deep mycoses, the infection is not contagious. Cryptococci are natural saprophytes and only accidentally act as pathogens in animals with impaired local or systemic immunity. Debility, malnutrition, prolonged

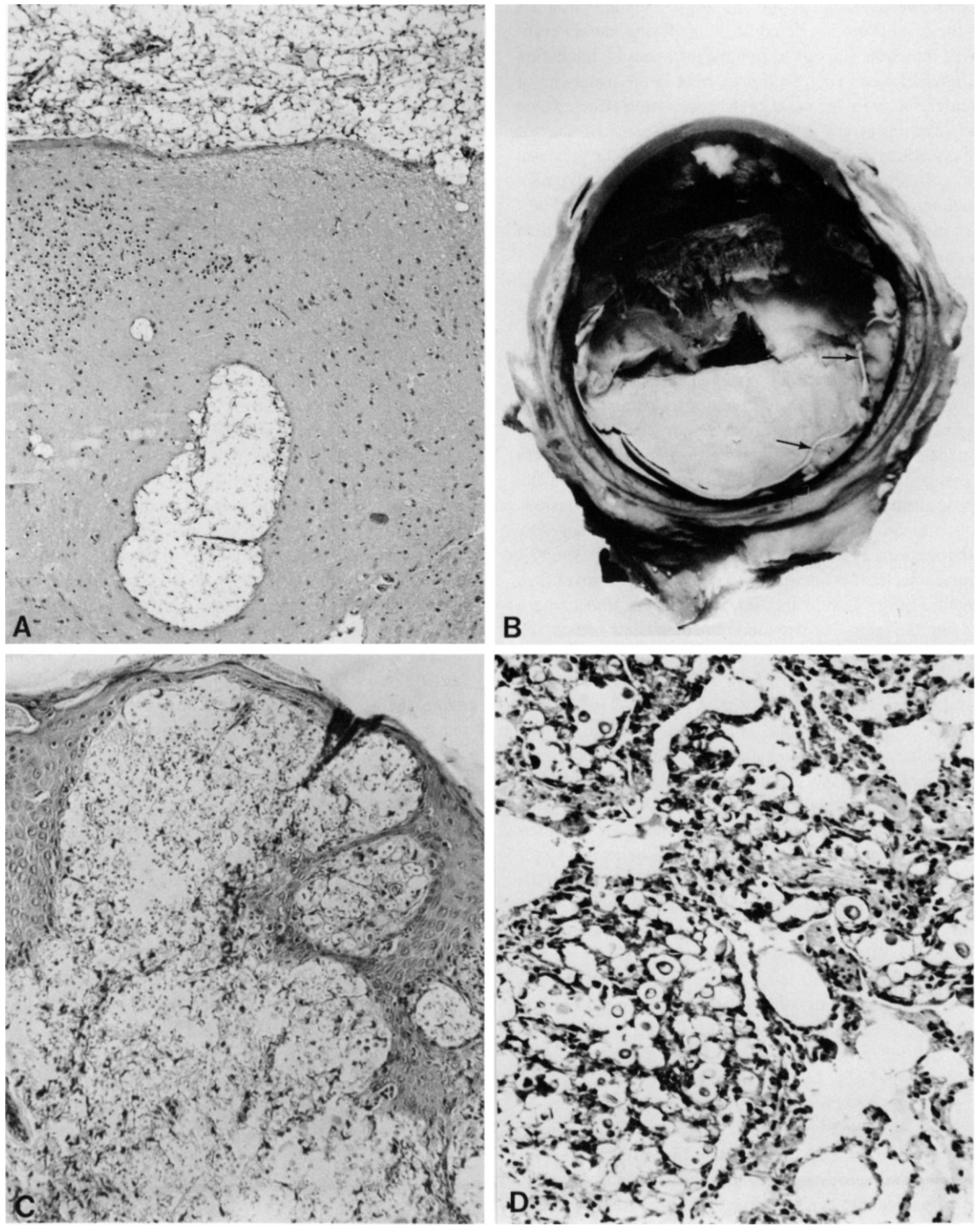

Fig. 6.38. Cryptococcosis. (**A**) Granulomatous meningitis with extension along Virchow–Robin space of penetrating vessel. Cat. Note characteristic "soap bubble" appearance. (**B**) Cryptococcal choroiditis with exudative detachment of retina (arrows). Dog. (**C**) Cutaneous lesion. Dog. (**D**) Yeastlike *Cryptococcus neoformans* in pulmonary alveoli. Dog.

use of corticosteroids, and feline leukemia virus infection are some of the conditions suspected of predisposing cats to cryptococcosis. Infection is acquired in most instances by inhalation of contaminated dust. The respiratory tract is the usual site of primary infection, with the nasal cavity more often affected than the lungs. The lungs are often stated to be the usual site for systemic dissemination of cryptococcal organisms, but the nasal region is probably the more important because its involvement leads much more frequently to dissemination to the central nervous system, eyes, lymph nodes, skin, and other organs than does pulmonary involvement. There is also the possibility of local spread to the meninges and brain from nasal lesions. Local inoculation of the organism does not appear to be of general significance, although it has resulted in outbreaks of cryptococcal mastitis in cows (see the Female Genital System, Volume 3). The cutaneous lesions, which are observed occasionally, may be primary or metastases following hematogenous dissemination from respiratory infection. The infection has a predilection for the central nervous system (Fig. 6.38A). Lesions can occur there without being grossly apparent in any other organ, but it is usual in the disseminated infection to find gross or microscopic lesions in some combination of the respiratory tract and other organs. Intraocular metastases may occur (Fig. 6.38B).

The cutaneous lesions of cryptococcosis take the form of firm small nodules (Fig. 6.38C) that tend to ulcerate, discharge a small amount of serous exudate, and may then heal. In cats, the skin of the head is most commonly affected, but sometimes the lesions are distributed widely over the body. Nasal involvement was described earlier with granulomatous rhinitis. In the parenchymatous organs, the lesions are discrete, whitish, gelatinous foci and may not be more than a few millimeters in diameter. Lesions in the meninges, brain, and spinal cord also have a discrete, gelatinous character when they are visible, but often there are no significant gross changes. There may be some gelatinous areas in arachnoid spaces, especially around the larger vessels and in the cisterns, but the opacity of bacterial meningitis is seldom observed. The parenchymal lesions are chiefly in the peripheral gray matter and probably develop by extension of the lesions along the Virchow–Robin spaces (Fig. 6.38A).

The usual cryptococcal lesions are characterized histologically as having a "soap bubble" appearance because of the unstained capsules of massed organisms. A profound cellular reaction is not typical, in contrast to other mycotic infections, and usually consists of a few macrophages, lymphocytes, and plasma cells (Fig. 6.38D). Vacuolated and degenerating macrophages may occasionally dominate the picture. Sometimes, particularly in lungs, the lesions become more typically granulomatous, with numerous epithelioid and some giant cells. The changes in organisms and cell-mediated responses that modulate the differences in host response are not understood. Caseation may occur in lesions in lymph nodes, but otherwise necrosis is not part of the reaction to these organisms.

When examined in sections stained by hematoxylin and eosin, the fungi appear as typical yeasts surrounded by a clear halo produced by unstained capsular substance. The capsular substance immediately around the organism is often condensed into an acidophilic rim. The free-lying organisms may calcify and stain intensely with hematoxylin.

Coccidioidomycosis

Coccidioidomycosis, which is caused by *Coccidioides immitis*, is important in humans but also occurs in animals in areas in which the infection is endemic. Most cases of coccidioidomycosis occur in the endemic area of the United States, which includes the arid parts of California, Arizona, and Texas. The disease is also endemic in portions of South and Central America. In arid regions there is an association between the feces of desert rodents and high concentrations of the fungus. It is not clear to what extent numbers of organisms are increased by spherules excreted in the feces of the rodents, as compared to the fecal matter's enhancing vegetative growth of the organism in the soil. Vegetative growth of the fungus occurs in soil after rains, and subsequently large numbers of infective arthroconidia (spores) are disseminated widely in windblown dust after the soil dries. It is estimated that most animals living in endemic areas eventually become infected, but relatively few become clinically diseased.

The fungus is dimorphic. In tissues, the distinctive form is a spherule (sporangium) measuring about 10–70 μm in diameter, with a thick, double-contoured wall (Fig. 6.39B). It is called a sporangium because reproduction in tissues is by endosporulation; the endospores are globose, 2–5 μm in diameter, and are released into the tissues in large numbers when a spherule ruptures. Mycelia are rare in animal tissues. On most artificial media, however, growth is mycelial. Reproduction in mycelial growth is by arthroconidia, produced in very large numbers along the hyphae. These arthroconidia are highly infective and easily detached from the mycelial growth.

Coccidioidomycosis is a primary respiratory infection. Local traumatic inoculation can occur and result in a fluctuating abscess, but dissemination from such a focus is unusual. The high susceptibility of the lungs to the establishment of infection can be demonstrated experimentally by intranasal insufflation of spores. The great majority of respiratory infections are benign and nonprogressive. This form in humans is known as San Joaquin Valley fever. A small percentage of the infections disseminate from the lung, and the generalized disease is known as coccidioidal granuloma, with secondary lesions anywhere in the body. Among domestic animals, the disseminated disease has been observed mostly in dogs, and occasionally in horses, sheep, and cats. In these species, the lesions may be limited to the lungs and associated lymph nodes. In cattle and swine, lesions have so far only been observed in the lungs and their lymph nodes. The disease is common in cattle in endemic areas. As many as 20% of slaughtered cattle from feedlots in Arizona have lesions of the disease, but they are observed only in slaughtered animals. There is either a complete pulmonary complex, or an incomplete complex with lesions only in the bronchial and mediastinal lymph nodes.

Dissemination is common only in dogs, and in this species there is reported to be a predisposition for boxers and Doberman pinschers. The clinical signs frequently lack specificity and depend on the sites of active lesions. Persistent fever with one or more of respiratory abnormalities, shifting lameness, and the development of cutaneous nodules suggest the diagnosis in chronically ill dogs in endemic areas. The lameness is ephemeral

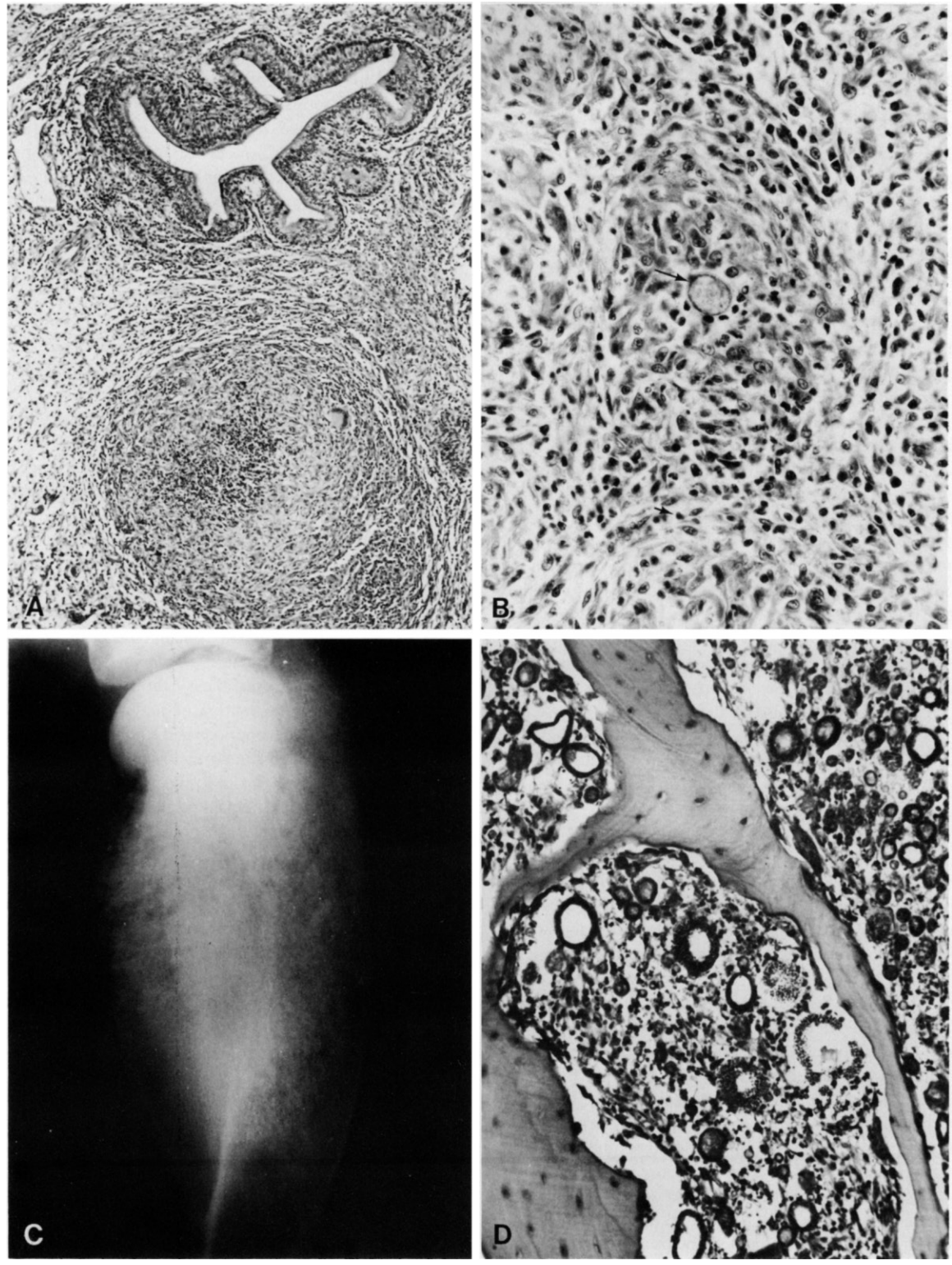

Fig. 6.39. Coccidioidomycosis. (**A**) Pyogranuloma adjacent to bronchiole. Lung. Horse. (**B**) Granulomatous pneumonia. Dog. Spherule (arrow) in center of small granuloma. (**C**) Radiograph of coccidioidal osteomyelitis. Dog. (**D**) Granulomatous osteomyelitis from (**C**). There are spherules in various stages of their developmental cycle.

when first seen, and radiographic evidence of the underlying osteomyelitis (Fig. 6.39C,D) is obvious only late in the course of disease. Usually the progressive debility leads to cachexia and eventual death, although recoveries do occur.

The lesions of coccidioidomycosis are granulomas or pyogranulomas (Fig. 6.39A,B). The granulomas are grayish white and usually nodular. There may be central caseation necrosis or liquefaction, but calcification is unusual. A common finding, particularly in the dog, is that large granulomatous nodules are composed of collections of discretely unitized small granulomas separated by fibrous tissue (Fig. 6.39B). The cellular reaction on the part of the host depends on the phase of the organism against which it is directed. Spores, whether endospores or the initial arthroconidia, provoke an acute exudative reaction in which neutrophils predominate. The larger spherules are usually surrounded by a wide zone of epithelioid cells mixed with a few giant cells, lymphocytes, and neutrophils. Because the organisms in any large focus are often in different phases of growth, there can be variations in the proportions of suppurative and granulomatous responses. In contained infections, however, the granulomatous response predominates, and it may then be difficult to find organisms. In such cases they are most likely to be found in the cytoplasm of giant cells as large spherules that are either evacuated and crenated or contain endospores. Often in cattle, and occasionally in other species, the spherules become surrounded by a corona of acidophilic clubs similar to those that form around colonies of *Actinomyces bovis* and some other microorganisms. This is an indication of high host resistance.

A variety of other fungal diseases can affect the lung, the most important being histoplasmosis (see the Hematopoietic System, Volume 3). Among the occasional opportunistic infections are sporotrichosis (*Sporothrix schenkii*), adiaspiromycosis (*Emmonsia* spp.), and geotrichosis (*Geotrichum candidum*).

Parasitic Diseases of the Lungs

The lungs are at the crossroads of parasitic migrations, and the many parasites that pass through them cause various degrees of damage according to the nature and intensity of the host–parasite interaction. Usually the lesions produced by transient parasites are of slight significance and are resolvable. There are exceptions, however. Severe and possibly fatal pulmonary lesions may develop if the migrating parasites are large in number, or large in size, or especially when the host has a hypersensitivity reaction to them. Hypersensitivity occurs because of previous exposure of a natural host or because of infection of an unnatural host. *Ascaris suum,* because of its tremendous biotic potential, may migrate in huge numbers and sometimes kill pigs, which are its natural hosts. It can also cause death of cattle, which are its frequent unnatural hosts. The lesion is an acute, diffuse, eosinophilic, interstitial pneumonia associated with the presence of large numbers of larvae. The trematodes *Fasciola gigantica* and *F. hepatica* invade the lungs accidentally from the liver. Since they are large parasites that wander extensively, a small number of them in the lungs can produce extensive cavitations. In other instances, lesions caused by parasites may be of some importance for differential diagnosis even though not of much clinical significance. In this category are the "worm nodules," such as those caused by migrating *Parascaris equorum* larvae in horses. Although distinctive when young by virtue of the mass of eosinophils present, when scarified and calcified they need to be differentiated from residual lesions of small abscesses or infectious granulomas, such as occur in glanders.

The transient parasites with principal habitats in other organs are discussed elsewhere. Here we are mainly concerned with "lungworms," whose final habitat is the airways or, less commonly, the parenchyma of the lungs.

Dictyocaulus

Dictyocaulus contains the most important lungworms. There are three species: *D. filaria* is parasitic in sheep, goats, and other small ruminants; *D. viviparus* is parasitic in cattle; and *D. arnfieldi* is parasitic in the horse and its relatives. The three species are similar morphologically and in the details of their life cycles. *Dictyocaulus filaria* will serve as the type for discussion.

Dictyocaulus filaria, the large lungworm of sheep and goats, is a slender, whitish worm 3–10 cm long. The adults live mainly in the small bronchi. The life cycle is direct. The eggs are embryonated when laid, and some of them hatch in the lungs. The eggs and larvae are expelled from the lung by coughing; most are subsequently swallowed. The eggs that have not hatched in the air passages hatch in the alimentary canal, and first-stage larvae are passed in the feces. Further development occurs on the ground and requires moisture and moderate to low temperatures. This explains why verminous pneumonia is predominantly a disease of cool, moist climates. The larvae can develop at temperatures as low as 5°C, and their viability is prolonged at these temperatures. The combination of long survival at low temperatures and long patent periods in the host endow these worms with the ability to persist in northern, cold latitudes.

The larvae undergo two molts on pasture in ~1 week. The third stage is infective, and infestation can occur only if the third-stage larvae are ingested by the final host. The infective larvae penetrate the wall of the intestine and migrate via the lymphatics to the lungs. In the abdominal nodes, they undergo the third molt. Some larvae accidentally take the portal route and are destroyed in the liver. Some, on reaching the lungs, continue into the systemic circulation and are lost, except for those rare ones that pass the placenta and produce intrauterine infections in the fetus. The worms take ~1 month to reach maturity, and it is then that clinical signs are most common because of the development of parasitic bronchitis. Adult worms persist for ~3 months.

The life cycle of *Dictyocaulus viviparus* in cattle is a little shorter than that of *D. filaria* but is otherwise comparable. Adult worms can continue to lay eggs for 6 months, but most are expelled within 3 months. *Dictyocaulus arnfieldi* is mostly a patent infection in donkeys, but the worms can develop to maturity if horses or ponies are infected as young foals.

The lesions produced by *Dictyocaulus* depend on the susceptibility of the host and on the number of invading larvae. Cattle and sheep are most susceptible to infection when they are first exposed to contaminated pastures, and therefore severe lesions and the clinical disease they cause are most commonly seen in animals less than a year of age where infection is endemic. Minor reaction occurs along the pathway of larval migration, but

the important lesions are found in the lungs. The lesions in the pulmonary tissues can be considered in two main phases, the first when the larvae reach the lung and break out into the alveoli, and the second when the mature parasites are located in the bronchi. In natural infections, these two phases overlap and are associated with hyperplastic lymphadenitis in the related nodes. The larvae arrive in the lungs from about 5 to 7 days after ingestion. Where they emerge from pulmonary capillaries, they cause microscopic foci of necrosis or rupture of alveolar walls with an infiltrate of eosinophils, neutrophils, macrophages, and a few giant cells. With more severe larval invasion, these foci become more numerous and larger. Mononuclear cells thicken the alveolar walls, and there is focal exudation of fibrin into alveoli together with the inflammatory cells. Eosinophils are a prominent feature of the reaction. Various degrees of hyperplasia of alveolar type II epithelial cells also occur. The larvae, some of them dead, can be found in the alveoli. When the number of larvae is large, the foci of acute interstitial pneumonia may be visible grossly as small, lobular or sublobular areas, slightly depressed, purplish, and distributed widely throughout the lungs.

By about the tenth day, many of the larvae have gained the terminal bronchioles. Frothy fluid is present in the bronchi, and in very heavy infestations there is often edema and emphysema of the interlobular septa. Eosinophils invade the septal tissues in large numbers and follow the larvae into the bronchioles. Most of the bronchioles contain plugs of exudate composed largely of eosinophils. Neutrophils, lymphocytes, and macrophages are present in smaller numbers in both the lumina and walls of the bronchioles. The early bronchiolar epithelial response is of degeneration and sloughing, but subsequently hyperplasia and metaplasia also occur. As the worms reach maturity, beginning ~4 weeks after infection, emphasis shifts to the bronchial lesion, and some resolution of the initial alveolar lesion occurs. The mature, threadlike worms in the bronchi and perhaps caudal trachea are easy to see in moderate to severe infections. Although the early development of lungworms takes place in all lobules, the mature worms are most numerous in the dorsocaudal bronchi of the caudal lobes, and in light infections may be found only in these regions. The worms are usually bathed in mucinous, foamy bronchial exudate. In some cases there may be no superficial indications of the worms, except for failure of the lungs to collapse. It is usual for gross lesions to be present in patent infections, however. Typically, there are large, wedge-shaped areas of dark red or grayish consolidated lung at the posterior border of the caudal lobes (Fig. 6.40A). These consolidated areas have firm consistency and are slightly depressed below the surface of surrounding inflated or sometimes hyperinflated lung. The patchy consolidations may also occur in other dorsocaudal regions, and with severe involvement they can be found on cut section to occupy much of the pulmonary tissue surrounding larger bronchi. There is no pleuritis.

The adult worms cause chronic catarrhal bronchitis and bronchiolitis, with a large component of eosinophils. The epithelium of bronchi is thickened and hyperplastic. Increase in the proportion of mucus-producing cells is a prominent feature. Elsewhere there might be ulceration or, occasionally, squamous metaplasia. The epithelium and lamina propria are infiltrated by mixed leukocytes, with a preponderance of eosinophils, and there is hyperplastic bronchus-associated lymphoid tissue. The lumina contain adult worms, plugs of mucus, numerous leukocytes, eggs, and larvae. Components of the verminous bronchiolitis are similar, but there is also a tendency for obliterative bronchiolitis to occur. The hyperplasia of bronchiolar smooth muscle, the increase in peribronchiolar fibrous tissue, and proliferation of lymphoid cells in bronchiolar walls also assume relatively greater prominence (Fig. 6.41A).

The parenchymal lesions that accompany the bronchitis caused by the adult worms are compounded mostly of atelectasis secondary to the bronchiolitis, and of pneumonia, which is provoked by aspirated eggs and newly hatched larvae. It is complicated in some cases by bacteria. Granulomas are frequently present around fragments of discarded cuticle, eggs, or dead larvae. The alveoli, which are partially collapsed, contain many giant cells and vacuolated macrophages. Their walls are thickened by cellular infiltration and slight fibroplasia and may be more or less completely covered by low cuboidal epithelium. Toward the end of the patent period the alveolar reaction subsides and resolution begins, especially in the periphery of the lobules. Around the bronchioles, however, many of the alveoli are permanently obliterated by the organizing peribronchiolar reaction. The lymphoid nodules that develop in the walls of bronchi and bronchioles are not generally as conspicuous as those occurring in chronic mycoplasmal infection. In resolving lesions, however, when worms are no longer present, there is no clear morphologic distinction. A useful clue to separate these two major causes of lymphoid proliferation is that the airways mainly affected by mycoplasmas are in cranioventral regions, whereas those affected by lungworms in ruminants are dorsocaudal.

Two features of the lesions caused by *Dictyocaulus viviparus* in cattle deserve special mention. The first is that extremely severe damage is associated with pulmonary edema and interstitial emphysema. In fatal cases, these may be the most obvious gross finding and therefore lead to confusion with the edema and interstitial emphysema accompanying acute interstitial pneumonia of toxic origin. This is particularly likely where the pulmonary damage is caused by massive invasion of larvae, and mature worms are not yet present for gross detection. Microscopic detection of larvae and immature worms usually provides the diagnosis. The second feature is the presence in the lungs of older animals of scattered lymphocytic nodules 2–4 mm in diameter. The nodules are homogeneously gray, or gray with a greenish center. The gray tissue represents dense accumulations of lymphocytes, and the greenish center the degenerating larval or adult worm surrounded by eosinophils. The nodules are an indication of reinfection of an immune animal, vaccination with X-irradiated larvae, or anthelmintic treatment.

Dictyocaulus arnfieldi is mainly a lungworm of donkeys and survives for long periods without causing undue clinical signs. The gross lesions are scattered, discrete foci of hyperinflated pulmonary parenchyma, mostly in caudal lobes. In the center of the lesions are small bronchi packed with coiled adult worms. Histologically, the worms are associated with a chronic catarrhal bronchitis. Goblet-cell hyperplasia and extensive lymphoid-cell infiltration of the walls are the main features. Adult worms cause

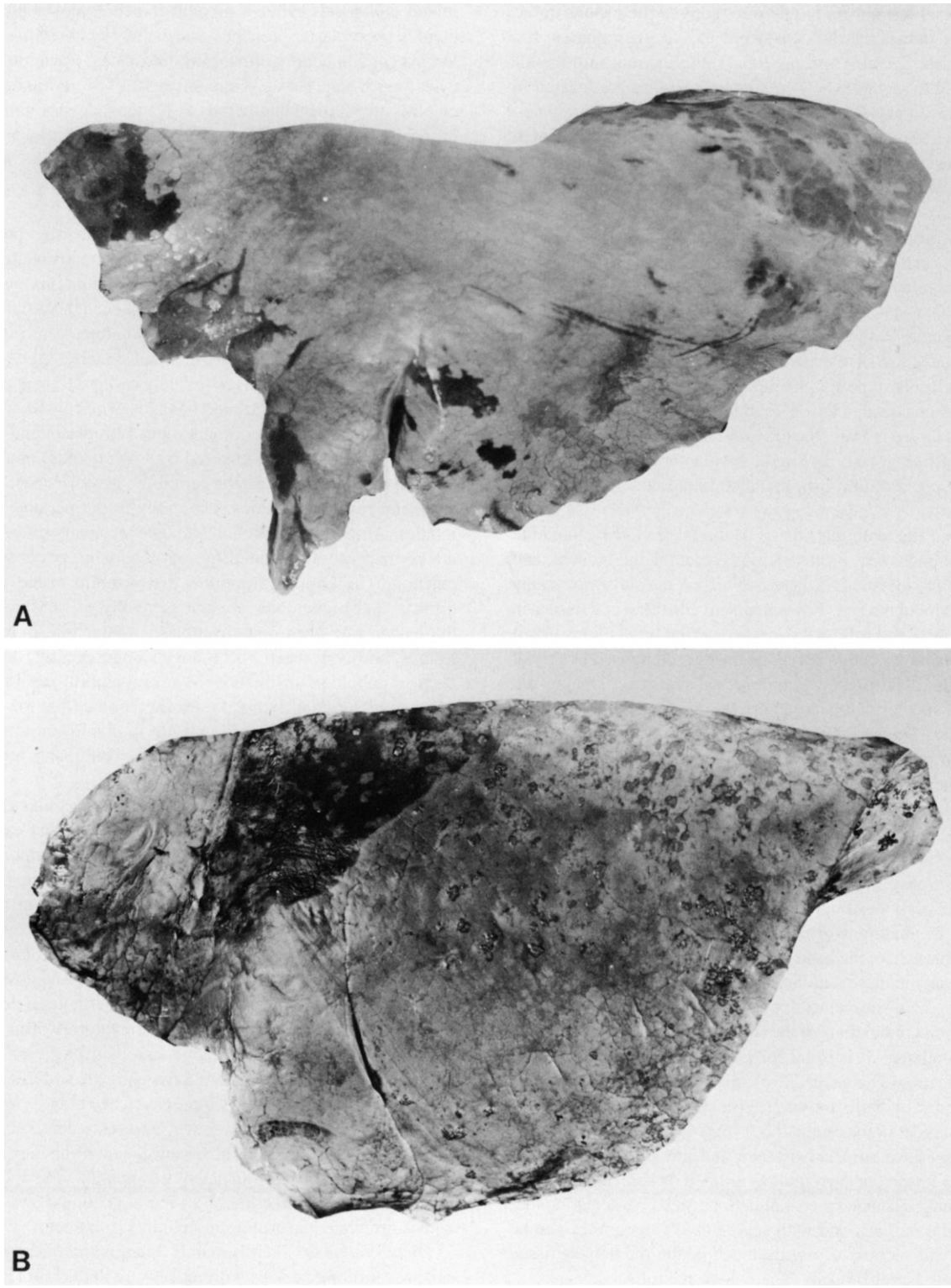

Fig. 6.40. Verminous pneumonia. (**A**) Bronchopneumonia caused by *Dictyocaulus filaria* in dorsocaudal region of caudal lobe. Unrelated areas of atelectasis and enzootic pneumonia in cranioventral regions. Sheep. (**B**) Multifocal subpleural nodules of interstitial pneumonia produced by *Muellerius capillaris*. Sheep.

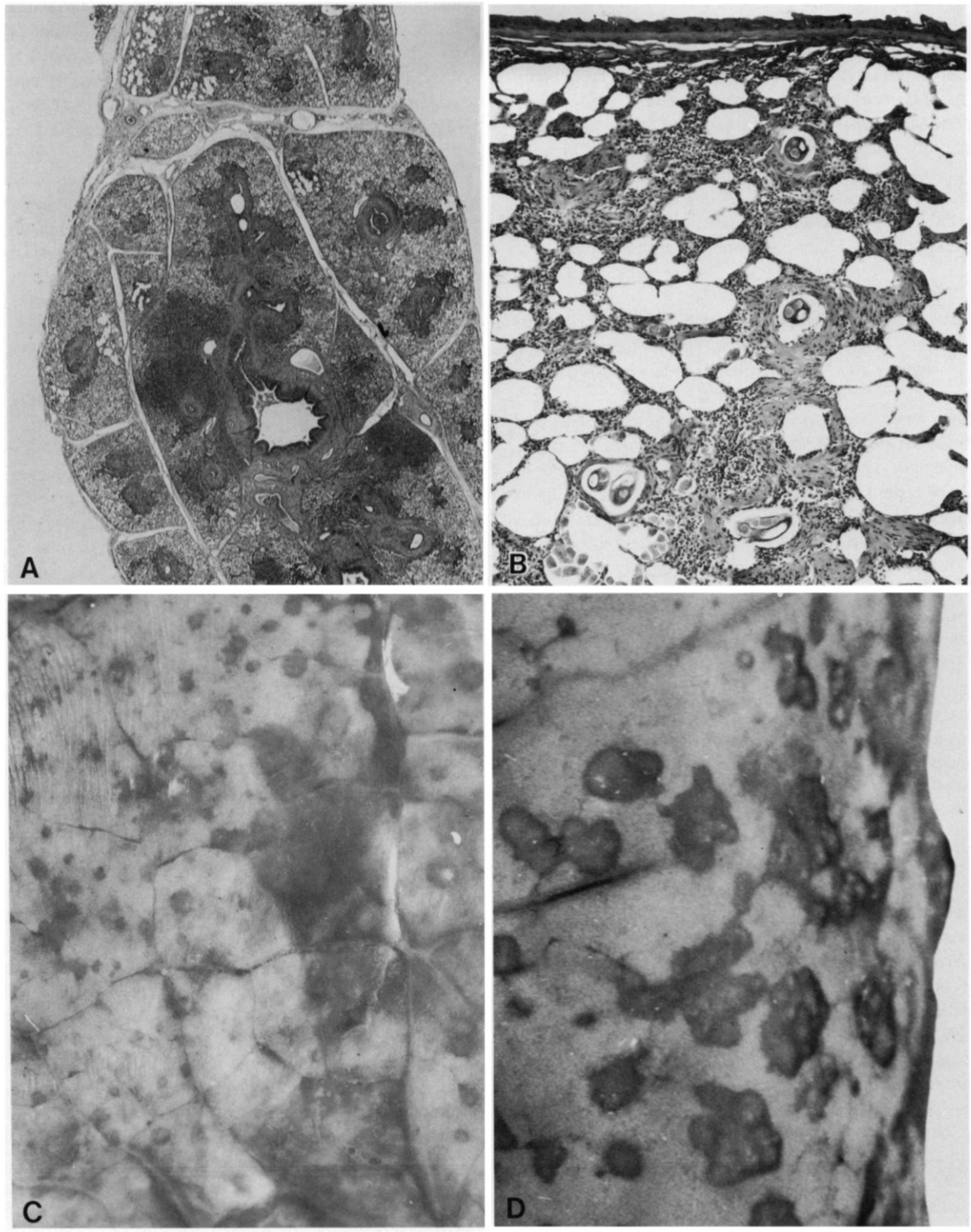

Fig. 6.41. Verminous pneumonia. (**A**) Residual lesions caused by *Dictyocaulus filaria*. Sheep. Note the obliterative bronchiolitis and prominent hyperplasia of bronchiolar smooth muscle with lymphofollicular cuffing. (**B**) Moderate reactions to *Muellerius capillaris*. Sheep. Adults lie in bronchioles and alveolar ducts and are associated with muscular hyperplasia. Eggs and first-stage larvae have provoked a chronic interstitial pneumonia. (**C**) Multiple subpleural nodules produced by *Metastrongylus* sp. Pig. (**D**) Subpleural nodules produced by *M. capillaris*. Sheep.

relatively little luminal response, whereas first-stage larvae stimulate an intense mucopurulent reaction. There is also a chronic catarrhal and eosinophilic bronchiolitis of bronchioles distal to affected bronchi. Alveoli are reported to be hyperinflated, but it is uncertain to what extent this reflects true *in vivo* hyperinflation as opposed to air trapping and failure to collapse when the lungs are examined after death. Infection of adult horses with *D. arnfieldi* usually results in failure of the worm to develop to sexual maturity. The lesions are similar to those described for the donkey and are occasionally associated with chronic coughing and abnormal sounds on auscultation.

Protostrongylus

The most common and important member of *Protostrongylus* is *P. rufescens*. Whereas *Dictyocaulus* species have direct life cycles, *P. rufescens* and the other worms to be discussed below have indirect life cycles.

Protostrongylus rufescens is parasitic in sheep, goats, and deer. The adults are smaller than *Dictyocaulus filaria*, being 16–35 mm in length. They are reddish and mainly inhabit the bronchioles. The lesions that accompany the infection are similar to those produced by *D. filaria* but are quantitatively less, lobular in size, and located chiefly in the periphery of the caudal lobes. The lesions are not readily distinguished grossly from those produced by *Muellerius capillaris*. The first-stage larvae are passed in the feces and enter the intermediate hosts, which are various genera of land snails, by boring through the foot. Two molts occur in the snail, and the infective third-stage larvae develop in 2 weeks. Sheep and goats obtain the parasites by eating the snails.

Neostrongylus linearis is a species comparable to *Protostrongylus rufescens*. It is common in western Europe and probably elsewhere but is confused with other small lungworms of sheep.

Muellerius and Cystocaulus

Cystocaulus ocreatus (*C. nigrescens*) is little studied, but it is stated to resemble *Muellerius* in the details of life cycle and pathogenicity.

Muellerius capillaris, which is parasitic in sheep and goats, is the most common and ubiquitous of the lungworms. The species is sometimes referred to as the nodular lungworm because the adults live in the alveolar parenchyma and almost always provoke an enveloping, granulomatous response. The adult worms are found on rare occasions in the bronchioles. There is usually no clinical evidence of respiratory disease in sheep, even when the number of nodules is large. Sometimes they become confluent. Diminished weight gains have been recorded in heavily infested lambs, and it has been postulated that the worms might predispose to pulmonary bacterial and viral infections.

The eggs are laid and hatch in the nodules. This requires that the sexes be paired in the nodules. Often this does not occur, and therefore the examination of feces for larvae may give no indication of the degree of pulmonary parasitism. The first-stage larvae break out of tissues into the airways and are eventually passed with feces or mucus. The intermediate hosts are various slugs and snails. The infective stage is reached after two molts in the intermediate host, and the life cycle is completed when sheep and goats swallow the intermediate hosts. The larvae migrate to the lungs, presumably via the lymphatic pathway, and break out into the alveoli. As a consequence of this type of life cycle, infections are acquired gradually, and large worm burdens are seldom observed in animals less than 6 months of age. On the other hand, heavy infections are not common in old sheep and goats.

The nodules produced by these parasites represent lesions of multifocal interstitial pneumonia. They may occur anywhere in the lung, but most of them are located beneath the pleura of the dorsal region of the caudal lobes (Figs. 6.40B and 6.41D), so the severity of infestation can be assessed quite accurately by superficial inspection. Why there should be this predilection for the subpleural tissues is not known. The nodules range in size from 1 mm to several centimeters. They are soft and hemorrhagic early in an infection. Later they are greenish gray and project above the pleural surface of adjacent lung at necropsy. Some of them become calcified. Similar nodules are present in various numbers in the bronchial and mesenteric lymph nodes. Sheep are rather tolerant of initial exposure and readily develop patent infections. With repeated exposure, sheep become resistant and inhibit fourth-stage larval migration or development. Immature adults may have their development checked, or mature worms may cease reproduction in a resistant animal. The cellular reaction reflects the stage of the parasite present and resistance of the host. The earliest form of nodule is produced by the fourth-stage larvae when they enter the lungs, and usually consists of little more than groups of alveoli that are mechanically disrupted. There may be little cellular reaction to these larvae of the first infestation, but an eosinophilic infiltration may accompany later ones. The adult worms also disrupt the alveolar septa. The eggs and first-stage larvae lie in the alveolar spaces and provoke little inflammatory response, although there is a mild fibrous thickening of the alveolar septa with infiltrated lymphocytes in the septa and around the blood vessels and bronchioles. In older animals, presumably as a result of a developing resistance, the cellular reaction is more marked, especially to the first-stage larvae and the adults (Fig. 6.41B). There are intense foci of infiltrated eosinophils around the larvae; the alveolar spaces become crowded with macrophages and some giant cells, and the distorted alveolar walls are thickened by fibrous tissue. The larvae that escape into small bronchioles are enclosed in plugs of mucus and cellular debris. The epithelium of the bronchioles is hyperplastic, and the muscularis much thickened. When the larvae leave the nodules, the cellular reaction subsides, but the thickening of the alveolar septa persists because of patchy or diffuse fibromuscular hyperplasia. An intense reaction also occurs to the adult worms. There are large numbers of eosinophils, a narrow zone of epithelioid and giant cells, and a periphery of fibroblastic tissue. The cellular debris becomes calcified, particularly when the worms die, and these calcified nodules persist indefinitely as spherical masses of calcium salts surrounded by a fibrous capsule. Not all the calcification, however, occurs about adult worms. Some is precipitated in the inspissated mucus that collects in obstructed bronchial glands, and some in mucus and debris that accumulate in the bronchioles.

An extensive diffuse interstitial pneumonia has been reported to be associated with *Muellerius* infection in goats, but in such

cases it is often impossible to assess the possible role of concurrent infection with *Mycoplasma* or the caprine arthritis–encephalomyelitis virus.

Metastrongylus

There are three important species of *Metastrongylus, M. elongatus* (*M. apri*), *M. pudendotectus,* and *M. salmi,* and they are all parasitic in the bronchi and bronchioles of pigs. They are believed to be responsible for the occasional transmission of the virus of swine influenza. The adult worms are white, threadlike, and 14–60 mm in length, depending on species and sex. In heavy infections, which are mostly in young pigs, they may be found in all lobes of the lung. But when there are fewer worms, particularly as occurs in older animals, the worms may be restricted to airways along the ventrocaudal borders of the caudal lobes. These apparently are areas of predilection or residual infestation. The eggs are laid in the bronchi, and a few of them hatch there, but most hatch after passing to the exterior in the feces. The first-stage larvae are inactive and are capable of prolonged survival in moist conditions. Their further development depends on ingestion by earthworms, which are the intermediate hosts. The larvae develop to the third, infective stage in ~10 days and then remain quiescent unless the earthworm is eaten by a pig. The larvae may survive for as long as 18 months in the earthworms, and by that time, some thousands of them may be accumulated by a single worm without doing it any harm. Migration within the pig is through the lymphatics from the intestine to the lungs. Some larvae pass through the liver and produce a focal hepatitis for which the larvae of *Ascaris suum* are, however, more usually responsible.

Even with heavy adult infestations, gross lesions are inconspicuous and seldom as extensive as those produced in ruminants by *Dictyocaulus*. In light infections the worms live in the smallest airways, and on superficial examination of the lungs the presence of the parasites frequently is indicated only by grayish nodules 1–3 mm in diameter, and by hyperinflated lobules along the ventrocaudal margins of the caudal lobes (Fig. 6.41C).

Histologically, the lesions are basically the same as those produced by *Dictyocaulus*. The initial lesions are multiple foci of intense accumulations of eosinophils surrounding larvae in alveoli. Subsequently, when reproduction is active, a granulomatous alveolar response occurs to the eggs and larvae. The prepatent period for *Metastrongylus* is ~25 days, after which the rate of egg production rapidly reaches a peak and then subsides to a low level. At this later stage, the adults persist mainly in the bronchioles and small bronchi and provoke a chronic catarrhal and eosinophilic bronchiolitis and bronchitis with the features as described for *Dictyocaulus* infection in ruminants. Large, lymphofollicular nodules are mainly responsible for the grayish nodules visible grossly (Fig. 6.41C).

CRENOSOMA VULPIS. *Crenosoma vulpis* is a common lungworm of foxes, but it also occurs in other Canidae. It is occasionally found in dogs that have access to the snails and slugs that are intermediate hosts. The adult worms live in bronchioles and small bronchi. The gross lesions usually observed in dogs are grayish consolidations in dorsal regions of the caudal lobes. Histologically, the lesions caused by adult worms are catarrhal, eosinophilic bronchitis and bronchiolitis closely resembling those caused by *Dictyocaulus* in ruminants.

FILAROIDES ROSTRATUS. *Filaroides (Anafilaroides) rostratus* is a parasite of cats that appears to have very limited distribution since it has been recorded mainly from Sri Lanka. In that its final habitat is the walls of large airways it resembles *F. osleri* of dogs (see Parasitic Diseases of the Larynx and Trachea). It does not form nodules, however, but causes sinuous thickenings of the bronchial walls. When the infective larvae invade the bronchial walls, they provoke only slight cellular response. The adults develop in cystic spaces that are probably dilated lymphatics and that cause displacement of the surrounding tissues. The worms are viviparous, and the larvae escape to the bronchiolar lumen where they provoke a catarrhal bronchitis. The adults remain alive for ~1 year, and possibly for much longer. When they die, they provoke an intense infiltration of neutrophils and may calcify. There is residual fibrosis in the bronchial wall. The larvae are passed in the feces and develop to the infective stage in a variety of molluscs. They can probably survive for a long time in the intermediate hosts, and the capacity for survival and dissemination is increased by the fortuitous use of transport hosts, such as mice and chickens.

There are other species of lungworms in cats, which are probably similar to *Filaroides rostratus,* but virtually the only details concerning them are taxonomic. *Vogeloides massinoi (Osleroides massinoi)* lives in the bronchial wall. *Vogeloides ramanujacharii* occurs in cats in India. *Troglostrongylus brevior* occurs in cats in the Middle East and is known to use snails as intermediate hosts.

FILAROIDES HIRTHI. Two similar filarid worms have been recorded as inhabiting the pulmonary parenchyma of dogs, *Filaroides hirthi* and *F. milksi.* Original reports were of *F. milksi,* but more recent descriptions have been of a worm that, although it closely resembles *F. milksi,* has been assigned to a separate species, *F. hirthi.* This description summarizes the current knowledge concerning *F. hirthi,* leaving the taxonomic and pathogenic uncertainties surrounding *F. milksi* for resolution in the future.

Adult *Filaroides hirthi* worms, which are 6–10 mm in length, live in alveoli and respiratory bronchioles. Clinical signs of infection are rare, and evidence of the worms' presence is usually limited to the incidental finding at necropsy of tan, green, or gray subpleural nodules 1–5 mm in diameter. The nodules are widely scattered over subpleural regions, the numbers varying with the severity of infection. Histologically, there is little response to living adult worms (Fig. 6.42A), but a severe granulomatous response featuring many eosinophils occurs around dead or degenerating worms (Fig. 6.42B). Larvae provoke a more acute neutrophilic reaction. Foci of granulomatous interstitial pneumonia can often be found in which worm remnants may no longer be identified. Killing the worms with anthelmintic is particularly prone to cause the severe response.

Filaroides hirthi has a direct life cycle, like *F. osleri.* Infective first-stage larvae are passed in the feces, and usually the infection is passed from dam to pups. Infection is reported to occur mostly in colonies of beagles reared for experimental stud-

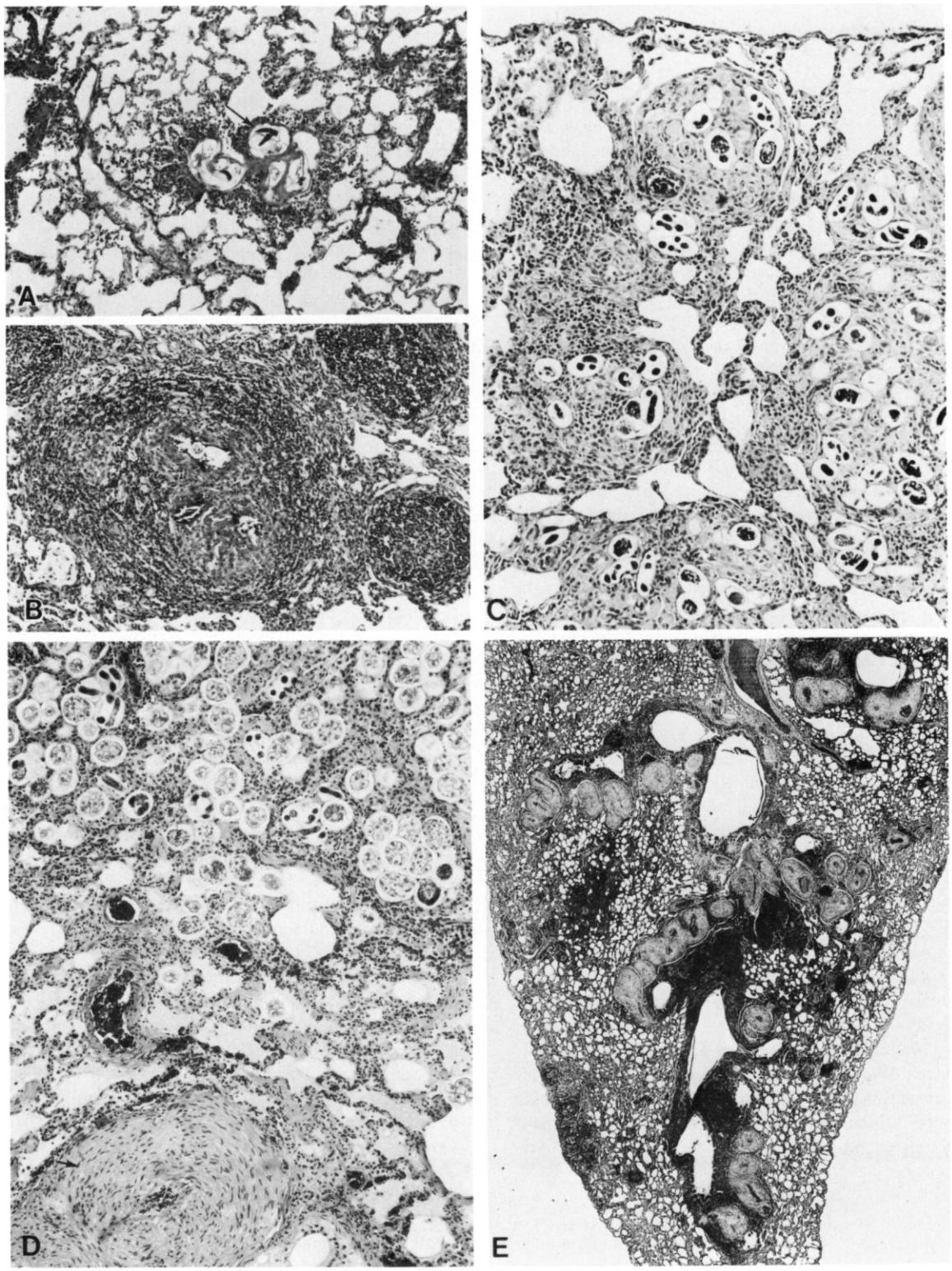

Fig. 6.42. Verminous pneumonia. (**A**) Eosinophilic and lymphocytic interstitial reaction to adult *Filaroides hirthi* (arrow). Dog. (**B**) Severe granulomatous response surrounding dead *F. hirthi*. Dog. (**C**) Chronic interstitial pneumonia with prominent fibrosis surrounding eggs and larvae of *Angiostrongylus vasorum*. Dog. (**D**) Granulomatous interstitial pneumonia provoked by eggs and larvae of *Aelurostrongylus abstrusus*. Cat. Note hyperplasia of smooth muscle of pulmonary artery (arrow). (**E**) Residual lesions of *Aelurostrongylus abstrusus*. Tortuous hypertrophied arteries have infiltration of walls by eosinophils. Cat.

ies in which lungs are routinely given thorough examinations. The incidence of *F. hirthi* in the canine population at large is not known. There are a few single-case reports of dogs with lethal infection, however, so it is probably more widespread than realized. The fatalities have been caused by severe miliary granulomatous pneumonia with a superimposed acute exudative component associated with huge numbers of worms and larvae. This type of hyperinfection and probable autoinfection seems to occur in dogs with drug or disease-induced immunosuppression.

AELUROSTRONGYLUS ABSTRUSUS. *Aelurostrongylus abstrusus* is a widespread lungworm of the cat. The adults live in the respiratory bronchioles and alveolar ducts. The eggs form nodular deposits in alveoli and hatch to give first-stage larvae that reach the airways and are eventually passed in the feces. The indirect life cycle involves various snails and slugs as intermediate hosts, and birds, rodents, frogs, and lizards as transport hosts. The life cycle can be completed if a cat eats either an intermediate host or a transport host.

The extent to which infective larvae reach the lungs in the blood or by migration through peritoneal and pleural cavities is not certain. Worms reach maturity about 5–6 weeks after ingestion of the third-stage larvae. The pulmonary lesions are quite characteristic, usually being in the form of nodules 1–10 mm in diameter that represent nests of eggs and larvae (Fig. 6.42D). These nodules, which are yellowish and firm, are scattered throughout the parenchyma but are more common in the peripheral parts of the lungs and usually project from the surface of the deflated lung. A small amount of creamy exudate containing numerous eggs and larvae can be expressed from the cut surface of incised nodules. Severe, confluent consolidation caused by heavy infections of *Aelurostrongylus abstrusus* can produce clinical signs of chronic coughing, and perhaps progressive loss of weight. Occasionally, death occurs when there is secondary infection.

Microscopically, the eggs and larvae are visible in the alveolar spaces, with some disruption of alveolar septa. They are surrounded by dense collections of mixed mononuclear cells with some giant cells. The latter are more numerous around dead or disintegrating larvae. Eosinophils and neutrophils are mostly a feature of early infection. Lymphocytic nodules form around vessels and airways (Fig. 6.42E). Necrosis and calcification seldom occur. In older lesions from which eggs and larvae have disappeared, the alveoli remain epithelialized for a time and the septa are persistently thickened by fibrous tissue and smooth muscle. This fibromuscular hyperplasia is often focal and barely appreciable, but in some cases is diffuse and rigid enough to produce a rubbery consistency.

Hypertrophy and hyperplasia of the smooth muscle in the walls of the bronchioles and alveolar ducts occur early in the course of the infestation and are progressive, but are not so well developed as the increase in smooth muscle in the media of small pulmonary arteries and arterioles. The presence of one or more of adult worms, eggs, or larvae in the bronchioles is associated with a chronic catarrhal and eosinophilic bronchiolitis similar to that caused by *Dictyocaulus* in ruminants. A prominent component is the hyperplasia of submucosal glands, which is a usual but generally inconspicuous feature of small airways of cats.

The most active phase of the parasite is 6–12 weeks after infection, and this is associated with the peak pulmonary response. Adult worms can persist up to 9 months. Although the granulomatous alveolitis and catarrhal bronchiolitis gradually regress, the hypertrophy and hyperplasia of smooth muscle in arteries, bronchioles, and alveolar ducts persist. The association between *Aelurostrongylus* infection and the dramatic muscular thickening of the walls of pulmonary arteries has been the subject of controversy. The current evidence indicates that hyperplasia and hypertrophy of smooth muscle in pulmonary arteries are a common finding in cats of all ages for reasons that are obscure. Infection with *Aelurostrongylus abstrusus* appears to be the major recognized cause of enhancement of this inherent tendency.

ANGIOSTRONGYLUS VASORUM. *Angiostrongylus vasorum* is a parasite of the pulmonary arteries and the right ventricle of dogs and foxes. The adult worms are 15–25 mm in length. They cause a proliferative endarteritis, but the more severe damage is caused by eggs that lodge in arterioles and capillaries. They and the larvae that hatch from them provoke a chronic inflammation in which fibroplasia predominates (Fig. 6.42C). The larvae break into the alveoli, migrate in the respiratory passages, and are eliminated in the feces. Various snails and slugs serve as intermediate hosts.

In the acute form of the disease, with heavy infestations of larvae in alveoli, the fatal outcome is in large part attributable to pulmonary edema and pneumonia. The chronic expression of the disease is largely one of congestive cardiac failure secondary to obliterative and thrombotic vasculitis, organizing infarcts, and progressive granulomatous response to eggs and larvae. Inflammation and scarring of alveolar walls leads to distortion and enlargement of remaining airspaces, which can result in a "foam rubber" appearance. This is sometimes referred to as emphysema but is more a form of "honeycombing" than emphysema in the conventional sense.

Because of their similar location, there is overlap in the types of abnormalities caused by *Angiostrongylus vasorum* and *Dirofilaria immitis* (see the Cardiovascular System, Volume 3).

PARAGONIMUS. Of the trematodes, the only genus that has its final habitat in the lungs is *Paragonimus*. A number of species have been described for the genus. The important ones are *P. westermanii* (the oriental lung fluke) in the Far East, and *P. kellicotti* in America. For the latter species, mink and other fish-eating carnivores are regarded as the usual hosts. The fluke is not selective in its final hosts, however, and has also been found in humans, swine, and ruminants. Among domestic animals, it is most commonly found in cats. Its natural habitat is the lung, but aberrant localizations have included the nervous system.

The life cycle of the parasite is typical of the cycles of the trematodes. The first intermediate hosts are small aquatic snails. The second intermediate host is a freshwater crab or crayfish. When the crayfish is eaten by the final host, the metacercariae are liberated in the intestine and migrate across the peritoneal and pleural cavities to the lungs. Their passage through the pleura is marked by multiple small hemorrhages and foci of

eosinophilic and fibrinous pleuritis, which heal as small umbilicate scars (Fig. 6.43A). The adult flukes are ovoid, reddish brown, and up to 7 mm in length. They are found, usually in pairs, in inflammatory cysts in the pulmonary parenchyma (Fig. 6.43B) and, occasionally, the bronchi. The cysts are more common in the caudal lobes, particularly the right side. They are spherical, approximately 10–15 mm in diameter, and dark red-brown. Their size and the fact that surrounding lung is frequently atelectatic give them a distinctive appearance. The cysts frequently communicate with bronchioles. Rupture of cysts on the pleural surface and resulting pneumothorax is a rare complication. The cysts become progressively surrounded by fibrous tissue and partially lined by bronchiolar epithelium. Eosinophilic granulomatous pneumonia develops around degenerating eggs adjacent to the cysts containing flukes (Fig. 6.43C). There is also a chronic catarrhal eosinophilic bronchiolitis with smooth muscle hyperplasia. Clusters of eggs, which occasionally are visible grossly as yellowish brown streaks, occur in subpleural and mediastinal lymphatics and cause a granulomatous pleuritis and lymphangitis. The large operculate eggs are quite distinctive (Fig. 6.43C); in old lesions only fractured shells may remain.

PNEUMOCYSTIS CARINII. *Pneumocystis carinii* is an organism of uncertain taxonomic status that is widespread as a latent infection in the lungs of animals. It has been considered in the past to be either a fungus in the class Ascomycetes or a protozoan. Currently it is generally held to be a form of protozoan, possibly within the class Sporozoa.

Pneumocystis carinii is an important cause of pneumonia in various forms of congenital or acquired immunodeficiency states in humans. Latent infection in rats can be regularly converted to the active disease by administration of corticosteroids. *Pneumocystis* pneumonia has been recorded occasionally in young dogs, foals, goats, and pigs as well as in laboratory animals. In horses, it appears mainly in Arabian foals with known or suspect congenital immunodeficiency, sometimes as a complication of adenovirus or other infectious pneumonia. Most of the reported canine cases have been in miniature dachshunds ranging from about 8 to 24 months in age. Clinical signs are gradually increasing exercise intolerance, respiratory difficulties, and progressive loss of weight. The unusual frequency of involvement of miniature dachshunds raises the possibility of a heritable immunodeficiency in this breed.

Gross lesions associated with pneumocystis pneumonia are diffuse or patchy, red to yellow-brown regions of rubbery firmness or consolidation. The appearance may be modified by coexisting viral or bacterial pneumonia. Histologically, *Pneumocystis carinii* causes a diffuse interstitial pneumonia in which the characteristic feature is prominent filling of alveoli by a foamy, pale, acidophilic material (Fig. 6.26C). The amount of interstitial inflammation varies from minimal to moderate accumulation of lymphocytes, plasma cells, and macrophages. There are various degrees of hyperplasia of alveolar type II epithelial cells (epithelialization), and accumulation of macrophages within alveolar lumina. Fibrosis accompanies intense cellular inflammation within alveolar septa.

Pneumocystis carinii stains poorly with hematoxylin and eosin and is therefore easily overlooked. Its presence should be suspected when alveoli contain abundant, foamy, pale, eosinophilic material. This is particularly important in young animals where there might be congenital, drug-induced, or disease-induced immunodeficiency. The foamy acidophilic material consists mainly of trophozoite and cyst forms of the organism. These might be seen as indistinct outlines of erythrocyte-sized structures, possibly with the presence of pale, basophilic dots. The organism is best demonstrated histologically by methenamine–silver staining. This reveals the argyrophilic capsules of the cysts as round, distorted, or crescentic structures from 3 to 8 μm in width (Fig. 6.26D). The PAS stain is not as satisfactory for demonstration of the organism.

Current evidence indicates that *Pneumocystis carinii* is mainly kept in check by alveolar macrophages in normal animals, but that this process fails in immunodeficient states. Progressive colonization of alveolar type I epithelial cells by *P. carinii* causes their necrosis and replacement by type II cells, with eventual filling of alveoli by the organisms and acellular material rich in alveolar surfactant lipid.

Various protozoa are capable of causing interstitial pneumonia, most notably *Toxoplasma gondii* (see the Alimentary System, this volume). *Sarcocystis* species also produce a multifocal interstitial pneumonia as part of the widespread multiplication of tachyzoites in vascular endothelium during acute sarcocystosis in herbivores (see Muscles and Tendons, Volume 1).

Enzootic Pneumonia

Enzootic pneumonia refers to pneumonia prevalent in groups of young animals maintained in close contact. It is mainly of importance in calves, lambs, and young pigs. Since it is an epidemiologic term, it allows considerable latitude in the morphologic and etiologic types of pneumonia it embraces. Both acute exudative bronchopneumonias and more chronic bronchointerstitial pneumonias have been included under the general designation enzootic pneumonia, but the emphasis has differed according to the species of animal concerned, as will be evident from the following discussion.

Enzootic pneumonia of **calves** is a disease complex in intensively managed calves, caused by the synergistic action of two or more of a wide variety of viruses, mycoplasmas, and bacteria. The morphologic appearance of the pneumonia varies according to the mix of agents and the age of lesions encountered. The disease mainly affects calves less than 6 months of age and is of most importance as a cause of unthriftiness. Mortality is low unless there is a coincidence of highly pathogenic agents and predisposing factors associated with poor husbandry and, possibly, intercurrent disease.

Evidence to date indicates that the acute pneumonia is usually initiated by viral infection. More than one species of virus may be involved in an outbreak or even in a single calf. The relative importance of the 10 or so candidate viruses varies geographically to some extent. In general, respiratory syncytial and parainfluenza-3 viruses are considered to be most important. Infectious bovine rhinotracheitis virus, adenovirus, and the bovine virus diarrhea virus are the next most commonly mentioned. The lesions caused by those and the other viral respiratory pathogens were described earlier in this chapter. Although calves can die because of acute, uncomplicated viral lesions, most fatal cases have a superimposed acute bacterial bronchopneumonia or lobar pneumonia. These have the acute fibrinonecrotic to suppurative

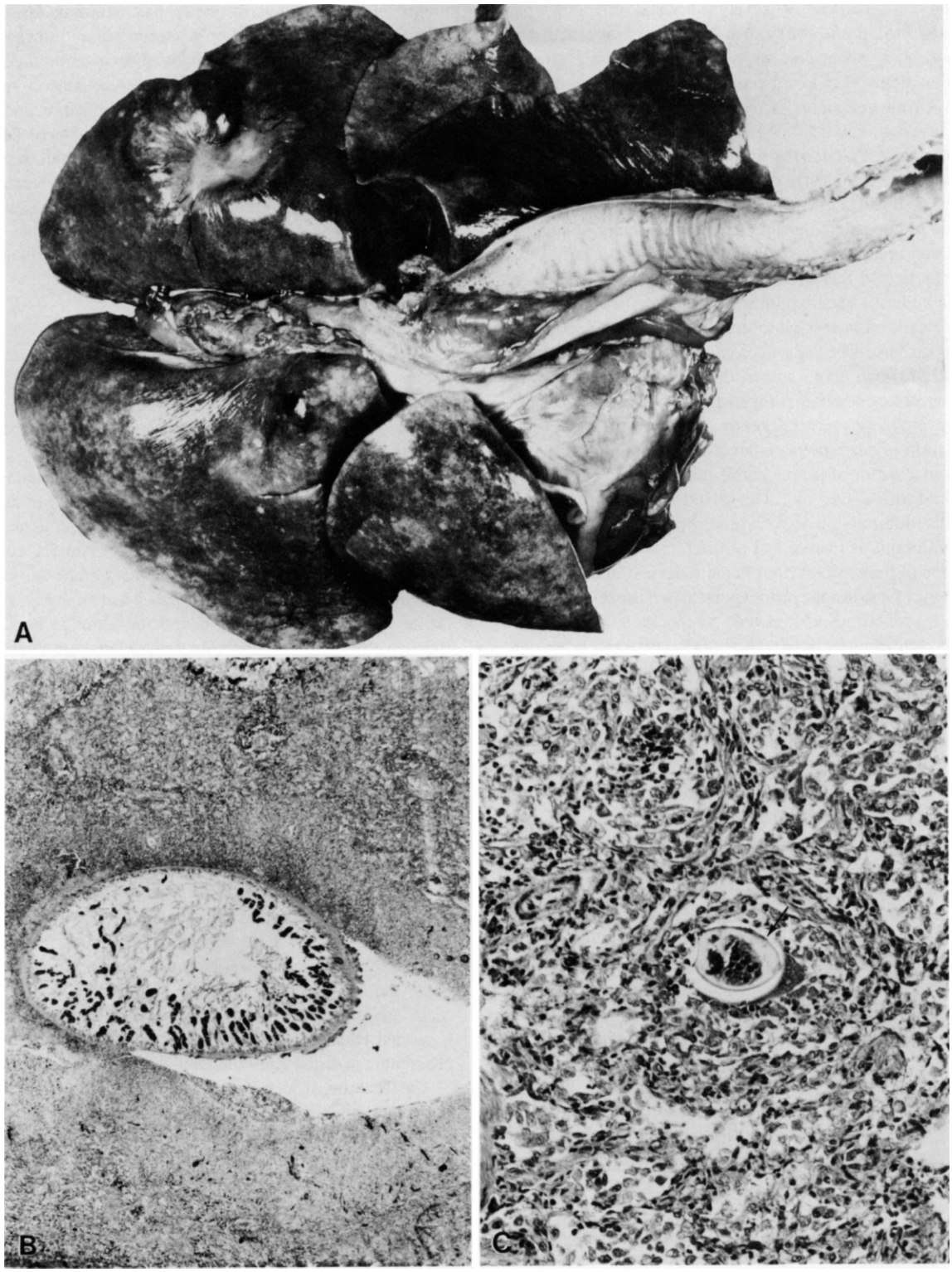

Fig. 6.43. Paragonimiasis. Dog. (**A**) Residual scar on surface of left caudal lobe. (**B**) *Paragonimus kellicotti* in inflammatory cyst in pulmonary parenchyma. (**C**) Granulomatous pneumonia surrounding distinctive operculate egg (arrow).

exudation characteristic of severe bacterial infection, particularly by *Pasteurella*. More than 20 different species of bacteria have been isolated at various times however, often in mixed infection. Next to *Pasteurella*, the most common are *Streptobacillus actinoides*, *Corynebacterium pyogenes*, and *Escherichia coli*. Chlamydiae may also be involved occasionally. Since most fatal pneumonias are predominantly the result of bacterial activity, clearly establishing the initial role of viral infection can be difficult and requires attempts to isolate viruses by culture, demonstrate their presence by immunofluorescence and electron microscopy, and obtain serologic evidence of an active infection in the affected groups. Histologic search for inclusion bodies is usually unrewarding in fatal field cases but pays dividends often enough to make the attempt necessary.

Mycoplasmas, especially *Mycoplasma dispar*, *Ureaplasma* spp., and *M. bovis*, are implicated in helping cause the acute form of enzootic pneumonias together with viruses and bacteria. They are probably more important, however, in causing the chronic form of enzootic pneumonia. This is the grayish pink, meaty consolidation of cranioventral regions of the lung found in slaughtered veal calves or calves dying because of other diseases. Histologically, it is a chronic bronchointerstitial pneumonia with both exudative and proliferative components (see Mycoplasmal Bronchiolitis and Pneumonia of Calves).

This type of lesion appears to represent persistent infection by both the mycoplasmas and bacteria of species similar to those found in more acute lesions. The usual course of chronic enzootic pneumonia is that of a low-grade inflammatory lesion that resolves in several months to a year. The term "cuffing pneumonia" has been used for chronic enzootic pneumonia in which a dramatic feature is sheathing of small airways by lymphofollicular proliferations. Acute exudative bacterial pneumonia can supervene at any time and cause severe clinical disease or death if the calf's pulmonary defenses are impaired or there is additional infection by virulent pathogens. An alternative sequel is chronic abscessation and scarring.

Enzootic pneumonia of **lambs** has many similarities to enzootic pneumonia of calves. The acute form is manifest as pneumonic pasteurellosis and has been described under Pasteurellosis. The chronic, enzootic bronchointerstitial pneumonia (Fig. 6.44) has features essentially the same as in enzootic mycoplasmal pneumonia of swine mentioned previously. Because the term enzootic pneumonia was used initially only for acute pneumonic pasteurellosis in sheep, various descriptive terms have been used for the chronic form. The most frequent ones are proliferative interstitial, proliferative exudative, atypical, and chronic nonprogressive. To avoid confusion, however, the chronic bronchointerstitial pneumonia of lambs should also be referred to as an enzootic pneumonia, just as it is in calves and pigs.

The causes of chronic enzootic pneumonia in lambs are not completely established. The disease can be regularly produced by intratracheal inoculation of a suspension of pneumonic lung. Attempts to produce the disease using various combinations of cultured microorganisms isolated from pneumonic lung have indicated that intratracheal or endobronchial inoculation of mixed strains of *Mycoplasma ovipneumoniae* and *Pasteurella haemolytica* is the most successful.

It therefore seems that most cases of chronic enzootic pneumonia in lambs involve the synergistic action of *Mycoplasma ovipneumoniae* and *Pasteurella haemolytica*. Either of these agents alone or in combination with other infectious agents may occasionally be responsible. The active pneumonic consolidation persists for about 3 to 12 weeks after infection and largely resolves within a few months unless acute bacterial exacerbations occur. Since the disease is not usually fatal, the characteristic cranioventral consolidations (Fig. 6.44A) are mostly seen in slaughtered lambs or those dying of other diseases.

Enzootic pneumonia of **swine** is generally held to be synonymous with enzootic mycoplasmal pneumonia (see Respiratory Mycoplasmosis of Swine).

Interstitial Pneumonia of Cattle

The general features and wide range of causes of interstitial pneumonia were discussed under Interstitial Pneumonia. The condition in cattle is deserving of further mention, however, because of its frequency and the confusion concerning its causes.

Acute interstitial pneumonia is the result of acute diffuse damage to alveolar septa. Characteristic features in cattle are pulmonary hyperemia, alveolar edema and hyaline membrane formation, hyperplasia of alveolar type II epithelial cells, and interstitial emphysema and edema. Other components may be present, such as larvae and eosinophils when migrating helminth larvae are the cause, but in general the lesion is nonspecific. Extensive interstitial emphysema and edema are usually only found in cows dying after a bout of severe, labored respiration. When this is prolonged, the interstitial emphysema can dissect through the mediastinum and reach subcutaneous regions of the back. Since the structure of the bovine lung predisposes it to the development of interstitial emphysema when there is severe pulmonary insufficiency and labored respiration for any cause, the diagnosis of acute interstitial pneumonia cannot be made solely on the basis of air in the pulmonary interstitium.

Various terms have been used for acute interstitial pneumonia in cattle, the most general one being "atypical" interstitial pneumonia, in recognition of the acute exudative nature of the process. Other terms have been used in certain geographic regions and have emphasized epidemiologic or morphologic features, the latter usually misleadingly. Examples of common usage are "fog fever" and "acute bovine pulmonary emphysema and edema" for the pasture-associated acute interstitial pneumonia in Britain and the United States, respectively.

The pasture-associated condition usually occurs in adult, beef-type cattle soon after a change from sparse summer range or pasture to relatively lush pastures containing regrowth following removal of a crop for hay or silage. Cows dying of the disease have gross lesions dominated by interstitial emphysema and edema. Major airways contain abundant white foam. The pulmonary parenchyma is purplish to brownish red, depending on the acuteness of the disease, and affected lobules have a homogeneous, moist cut section and a soft, rubbery texture (Fig. 6.18A,C). Irregular lobular or sublobular distribution of the lesions occurs to some extent. There is a tendency for most diffuse involvement to be found in dorsocaudal regions of the lungs. Histologically, the main features are as outlined previously, but hyperplasia of alveolar type II epithelial cells is not a pronounced feature until 4 to 6 days after the onset of the

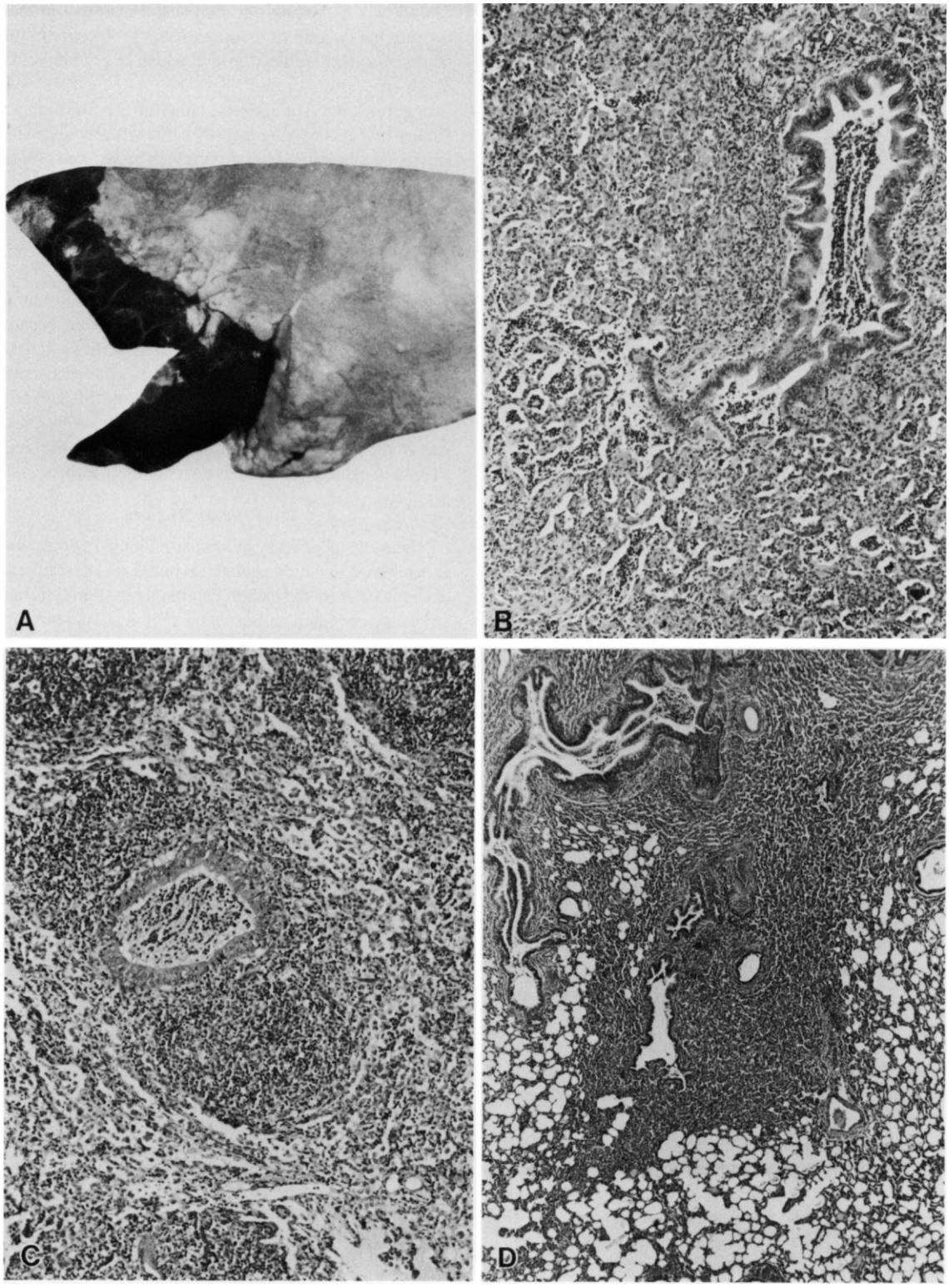

Fig. 6.44. Chronic enzootic pneumonia. Lamb. (**A**) Confluent cranioventral consolidation. (**B**) Histology of (**A**), showing bronchointerstitial pneumonia with mixed exudative and proliferative components. (**C**) Prominent peribronchiolar lymphofollicular nodules in chronic lesion. (**D**) Residual atelectasis in resolving pneumonia.

alveolar damage (Fig. 6.18B,D). Cows that survive the acute episode usually have residual interstitial fibrosis and some persistence of alveolar type II epithelial cells (Fig. 6.19C).

Current evidence indicates that the pasture-associated form of acute interstitial pneumonia is related to increased amounts of L-tryptophan in the ingested feed; the quantity of L-tryptophan can be sufficient to provide toxic levels of 3-methylindole under the special conditions of rumen fermentation occurring at the time of change in pasture. Acute interstitial pneumonia can also be caused by the pneumotoxic activity of 4-ipomeanol and related furanoterpenoids from moldy sweet potatoes, *Perilla* ketone from purple mint (*P. frutescens*), and an unidentified toxin from stinkwood (*Zieria arborescens*). Apart from chemical toxins, a similar lesion can be caused by massive invasion of the lungs by larvae of *Dictyocaulus viviparus* or, less commonly, *Ascaris suum* (see Parasitic Diseases of the Lungs).

Acute interstitial pneumonia also occurs occasionally in housed or feedlot cattle. There is frequently an associated, more chronic, cranioventral bronchopneumonia. The factor or factors involved in the pathogenesis of the acute interstitial pneumonia occurring under these circumstances are not understood, however. The association of severe infection with bovine respiratory syncytial virus and acute interstitial pneumonia, particularly in newly weaned calves in the fall, has given rise to the suggestion that the respiratory syncytial virus alone can cause the interstitial pneumonia under certain circumstances. This is not proven (see Bovine Respiratory Syncytial Virus Infection). An acute interstitial pneumonia also occurs in weanling foals in the early fall. Affected foals are usually those in best condition that eat more of the feed supplementation. The relative roles of dietary-related toxic factors and infection have not been explored.

Chronic interstitial pneumonia in cattle occurs chiefly as a manifestation of **hypersensitivity pneumonitis**. This condition is also referred to as bovine farmer's lung or extrinsic allergic alveolitis and is caused by inhalation of dust from moldy hay that contains spores of *Micropolyspora faeni* and other thermophilic actinomycetes. The disease is primarily one that develops in the winter in housed dairy animals. Death does not usually result from lesions occurring early in the disease. If lungs are available for examination, careful search reveals multiple, small, gray, subpleural foci and many pulmonary lobules with slightly pale, hyperinflated peripheral zones. Characteristic histologic lesions are a lymphocytic and plasmacytic bronchitis and bronchiolitis, often with severe obliterative bronchiolitis, the presence of scattered granulomas composed of epithelioid and giant cells, and thickening of alveolar septa by infiltration of lymphocytes, plasma cells, and macrophages. Eosinophils, globule leukocytes, and increased mast cells are usually present. Cattle are more likely to die as the result of severe, chronic disease. Additional features of severe interstitial fibrosis, accumulation of alveolar macrophages, and hyperplasia of alveolar type II epithelial cells are present in such cases. There can also be metaplasia of type II cells to ciliated or mucus-secreting cells. Vascular compromise can lead to pulmonary hypertension and cor pulmonale in a small proportion of cases. In these advanced cases, epithelioid granulomas are inconspicuous or absent. The lungs grossly are pale and heavy. Most severely affected lobules are yellow-white and fibrous or may show evidence of distortion and enlargement of airspaces by the scarring ("honeycombing"). "Asteroids" caused by *Aspergillus* spp. may also be present in these lungs because the conditions leading to heavy exposure to dusts containing *M. faeni* are also those in which large numbers of spores of *Aspergillus* are present.

A chronic interstitial pneumonia (diffuse fibrosing alveolitis) similar to that occurring in dairy cattle with advanced hypersensitivity pneumonitis is sometimes seen in pastured beef cattle. Its cause remains undetermined.

Neoplastic Diseases of the Lungs

Primary pulmonary tumors are rare in domestic animals. Metastatic lesions are relatively common, however, because of the vulnerability of the lungs to tumor emboli. In view of the much greater frequency of metastatic tumors, and because their gross and microscopic patterns can sometimes be difficult or impossible to distinguish from those of a primary tumor, an important part of the diagnosis of a primary lung tumor is thorough examination to exclude possible primary sites elsewhere in the body.

Primary Tumors

The rarity of primary pulmonary tumors in domestic animals is in contrast to their frequency in humans. This can probably be accounted for by the lack of carcinogenic stimuli from cigarette smoke or occupationally related chemicals in animals, and by the absence of large numbers of aged individuals. Primary tumors are encountered more often in dogs and cats than in other species. Reported incidence for the dog is about 4 or 5 per 100,000 animals in the population per year. The frequency based on postmortem examination varies with the population sampled, but up to 1% of dogs necropsied have been recorded as having primary tumors of the lung. Comparable statistics for the cat indicate a frequency approximately half that for the dog.

Neoplasms can arise from any of the tissues present in the lung, but with few exceptions the significant ones arise from pulmonary epithelium. Classification of epithelial tumors of the lung is complicated by the recognition that what were once looked on as specific cell types can undergo metaplasia (transdifferentiation) in both inflammatory and neoplastic lesions. The histologic appearance of cells in a tumor is therefore not certain evidence of histogenetic origin. Thus there can be no absolutely rigid histogenetic classification. With this in mind, the following classification provides a useful working basis for categorization:

Primary Epithelial Tumors of the Lung

- Bronchial papilloma
- Bronchial gland adenoma
- Bronchogenic carcinoma
  - Squamous-cell (epidermoid) carcinoma
  - Adenocarcinoma
  - Adenosquamous carcinoma
  - Undifferentiated (anaplastic) carcinoma
    - Small-cell type
    - Large-cell type
- Bronchioloalveolar tumor
  - Adenoma
  - Carcinoma
- Carcinoid

Most pulmonary tumors in animals are adenocarcinomas of bronchogenic or bronchioloalveolar origin. Squamous-cell carcinomas are occasionally found, mostly in the dog, and the other varieties are extremely rare. Affected animals are usually middle-aged to old, with the mean age in dogs and cats around 10 to 12 years.

Bronchogenic carcinomas are conventionally subdivided into squamous-cell (epidermoid), adenocarcinoma, and undifferentiated forms. There is a strong tendency, however, for both glandular and squamous components to occur in the same tumor (Fig. 6.45B). Sometimes these are mixed with more anaplastic regions. It is more useful to classify these pleomorphic tumors according to the predominant invasive and destructive component, rather than to put them in the adenosquamous category. Squamous-cell and undifferentiated carcinomas are especially prone to arise from major airways and therefore have a more central (hilar) location in the lung. The bronchogenic carcinoma is typically a large, irregular, pale, fleshy mass with ill-defined border and, possibly, satellite nodules. More distant intrapulmonary metastasis can occur in the same or opposite lung. Consistency ranges from firm to soft and friable. Mucinous, cystic, or hemorrhagic and necrotic regions are sometimes present in the center of large, bulky masses. Occasionally, highly malignant infiltrative tumors cause more diffuse, discolored, rubbery, or solid regions that cannot be distinguished grossly from pneumonia. Squamous-cell carcinomas have a preponderance of large cells with vesicular nuclei and abundant faintly granular acidophilic cytoplasm. Intercellular bridges can often be detected, but keratinization is usually limited to individual cells with intracytoplasmic clumps of keratin. Bronchogenic adenocarcinomas are invasive and destructive. They have disordered acinar, papillary, solid, or mixed patterns (Fig. 6.45A), and intermixed squamous components are frequently present (Fig. 6.45B). Differentiation from metastatic adenocarcinomas is often difficult.

Undifferentiated (anaplastic) carcinomas are the rarest variety in animals. Those recorded have mainly been of the small-cell type. This type can be further subdivided into round (oat cell), fusiform, and polygonal forms, according to the appearance of the component cells. The so-called oat-cell carcinoma has ill-defined clusters of small, round or oval cells resembling lymphocytes because of their hyperchromatic nuclei and small amounts of cytoplasm. In humans, the small-cell anaplastic tumors mostly arise from solitary neuroendocrine cells or organized neuroepithelial bodies, as do carcinoids. They are therefore particularly likely to be associated with paraneoplastic syndromes caused by secretion of polypeptide hormones (e.g., adrenocorticotropin, antidiuretic hormone, calcitonin) or biogenic amines (e.g., serotonin). Paraneoplastic syndromes accompanying primary pulmonary tumors do not appear to have been identified in animals.

In general, squamous-cell and undifferentiated carcinomas are more malignant than adenocarcinomas, but all have a strong predilection for spread through intrapulmonary lymphatics. Dissemination through airways to alveoli also occurs. Metastasis can also take place to thoracic lymph nodes, abdominal nodes and kidneys, liver, brain, heart and bones.

Bronchioloalveolar tumors originate from either secretory bronchiolar (Clara) cells or alveolar type II epithelial cells. Because of the close phenotypic relationship between these two cell types, it is not surprising that histologic and ultrastructural examination sometimes reveals both cell types in the same tumor. Bronchioloalveolar tumors are found most often in dogs, occasionally as an incidental finding at necropsy. They comprise over half the tumors found in some surveys of primary pulmonary tumors of dogs. Typically, they occur as solitary nodules in the periphery of the lung (Fig. 6.46B). Occasionally there are multiple nodules. The more benign tumors (adenomas) grow slowly by peripheral expansion and compression of surrounding parenchyma. Centers of large nodules frequently become necrotic. Other tumors, in which the neoplastic cells spread peripherally over alveolar walls, have the characteristics of low-grade adenocarcinomas. Less frequently, there is a rapidly spreading diffuse or disseminated multifocal type (Fig. 6.46A). Histologically, the special feature of bronchioloalveolar tumors is the regular alveolar pattern and preservation of pulmonary architecture (Fig. 6.46C). The preexisting alveolar stroma becomes lined by cuboidal or columnar epithelium, often with small, papillary projections into the alveolar lumina. As with many tumors, there is difficulty in clearly separating benign and malignant bronchioloalveolar tumors. Because there seems to be potential for eventual development of malignant behavior, there is often no attempt to categorize them as adenomas or carcinomas, but to regard them all as low-grade carcinomas unless there is clear evidence of highly aggressive behavior.

There are two major pitfalls in the diagnosis of bronchioloalveolar tumors. One is that the hyperplasia of bronchiolar and alveolar type II epithelial cells frequently caused by chronic inflammation of the bronchioloalveolar junction can be mistaken for neoplastic proliferation. The other is that rapidly invasive spread of neoplastic cells from either a bronchogenic adenocarcinoma or a metastasis from elsewhere in tbe body can sometimes mimic the regular pattern of a bronchioloalveolar carcinoma. Exclusion of alternative primary sites is therefore an integral part of the diagnosis of bronchioloalveolar tumors, especially the multinodular or diffuse varieties.

PULMONARY ADENOMATOSIS. Pulmonary adenomatosis (*jaagsiekte*) of sheep is an infectious form of bronchioloalveolar tumor that has the behavioral characteristic of a low-grade carcinoma. For this reason it is sometimes referred to as pulmonary carcinoma. The cause is now established as a retrovirus, probably type B or D. The term *jaagsiekte* appeared in original descriptions of the disease from South Africa, *jaagsiekte* being the Afrikaans word for "driving sickness."

Pulmonary adenomatosis occurs in many sheep-raising areas of the world. It is most important under conditions of intensive management, which favor aerosol transmission of the causative virus. The disease is less common where populations of sheep are dispersed, and it can escape detection for a time, as happened in the United States. The condition belongs in the category of slow virus diseases. Lesions develop slowly, with the result that the disease has an insidious onset. Clinical signs are not apparent for several months to several years and therefore are seen only in adult sheep. Early signs of the disease are coughing and exercise intolerance. Later there are also crackles and wheezes associated with the production of abundant watery exudate. The exudate is

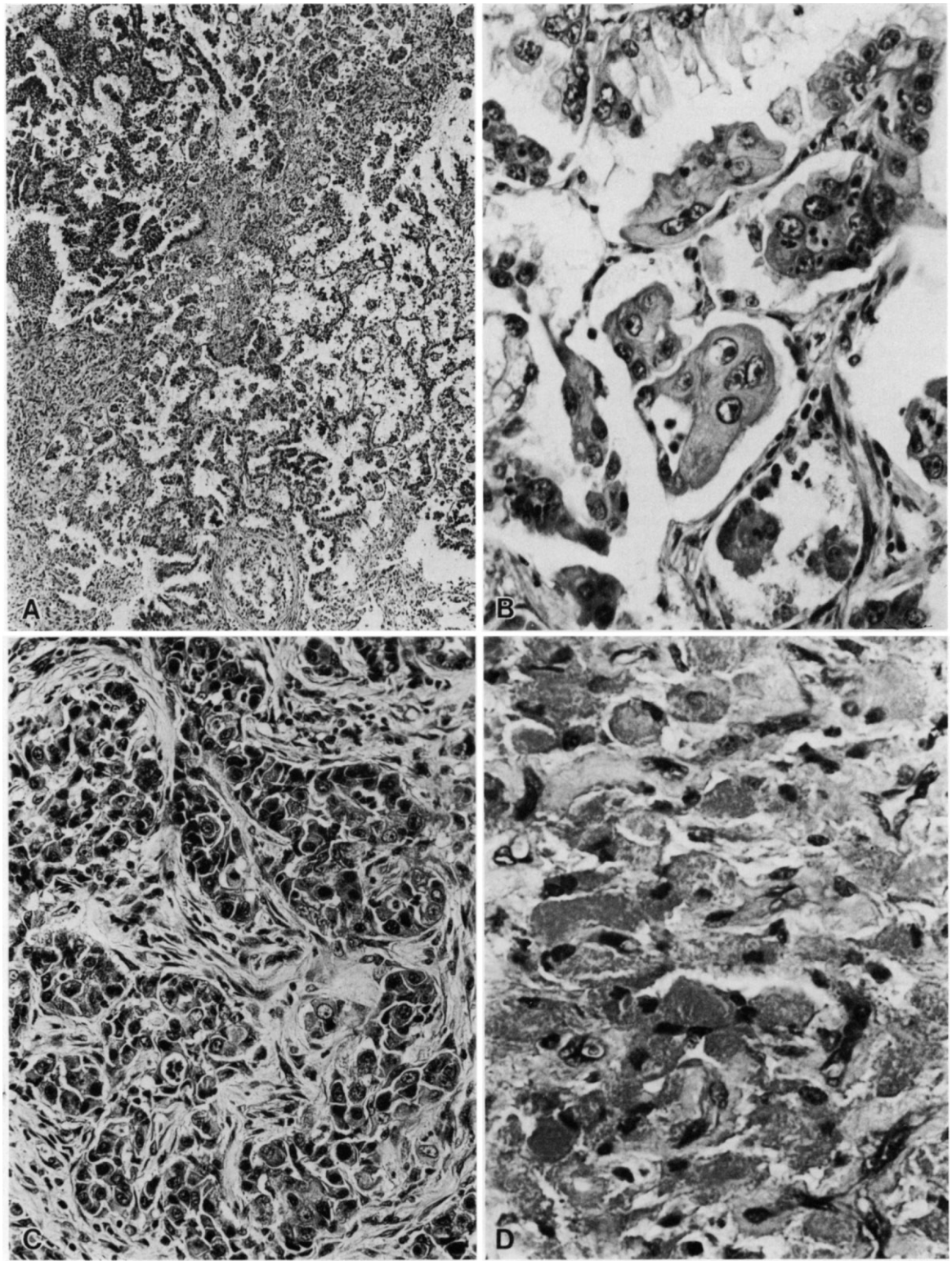

Fig. 6.45. (**A**) Invasive and destructive pattern of bronchogenic adenocarcinoma. Cat. (**B**) Mixed glandular and squamous elements in bronchogenic carcinoma. Dog. (**C**) Granular-cell tumor of the lung. Horse. (**D**) Higher magnification of (**C**), showing cells with abundant acidophilic granular cytoplasm.

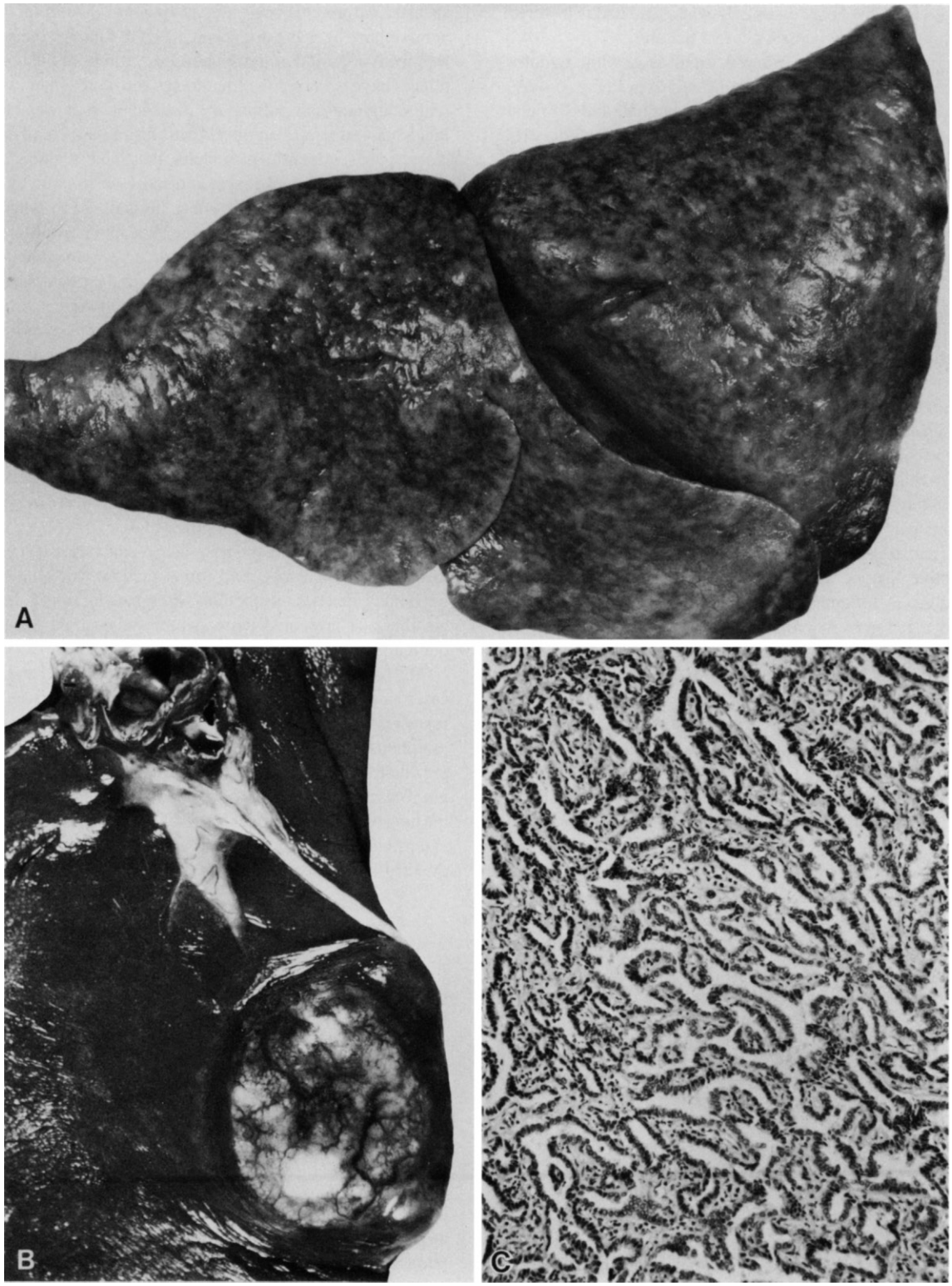

Fig. 6.46. (**A**) Widespread multifocal involvement in bronchioloalveolar carcinoma. Dog. (**B**) Solitary, peripheral bronchioloalveolar tumor. Dog. (Courtesy of S. W. Nielsen.) (**C**) Histology of bronchioloalveolar tumor, showing regular pattern of spaces lined by cuboidal to low columnar epithelium. Dog.

discharged from the nose, especially when the head is lowered, and is an important diagnostic clinical feature.

Early gross lesions are scattered, small gray-white nodules, sometimes with surrounding hyperinflated zones (Fig. 6.47A). Sheep with clinical signs have extensive nodular and confluent firm gray lesions affecting much of the pulmonary tissue. The lungs are heavy and fail to collapse. The cut surface is moist and reveals the basic nodularity of the lesion, even in regions where they coalesce. The centers of advanced lesions lose their friability and become fibrotic. There can be coexisting bronchopneumonia, verminous pneumonia, chronic progressive pneumonia (maedi), or combinations of these. This has been a source of considerable confusion in the past, particularly where the viruses causing chronic progressive pneumonia and pulmonary adenomatosis were both present in the same flock. The lesions of chronic progressive pneumonia and pulmonary adenomatosis are quite different histologically.

The characteristic histologic lesion of pulmonary adenomatosis consists of multiple proliferative foci of cuboidal or columnar cells that line alveoli and form papillary projections into their lumina (Fig. 6.47B,C). Continued proliferation obscures this pattern, and fibroplasia often occurs in more disorganized and degenerative regions. Early and uncomplicated proliferative lesions are not associated with significant accumulations of inflammatory cells, although there is usually some aggregation of macrophages in alveolar lumina. The papillary proliferation of cuboidal or columnar epithelium in the absence of significant interstitial inflammation is in marked contrast to the lymphofollicular interstitial pneumonia of chronic progressive pneumonia (maedi), in which alveolar epithelial hyperplasia is an inconstant and relatively minor feature.

The papillary proliferations involve both alveoli and bronchioles in many nodules. Ultrastructurally, the cuboidal cells usually have lamellar bodies characteristic of alveolar type II cells, whereas the columnar cells have secretory granules and glycogen compatible with origin from secretory bronchiolar epithelial (Clara) cells. The potentially carcinomatous nature of the lesions of pulmonary adenomatosis is confirmed by the occasional finding of metastatic foci in the bronchial or mediastinal lymph nodes.

Carcinoids have been reported to occur in lungs of animals but have not yet been adequately documented. Carcinoids in humans originate from neuroendocrine components of major airways. They have an endocrine pattern of nests or ribbons of uniform cells separated by well-vascularized stroma. The cells are round to polygonal. They have relatively small nuclei and abundant, pale, acidophilic cytoplasm. Ultrastructurally, their neuroendocrine derivation is revealed by large numbers of small, dense, secretory granules. It is probable that carcinoids occur in animals, albeit extremely rarely.

GRANULAR-CELL TUMORS. Granular-cell tumors (myoblastomas) are the only neoplasm of mesenchymal origin deserving of special mention. These are tumors that were originally thought to be derived from myoblasts but are now believed to originate from a fibroblast-like cell related to the progenitor of Schwann cells. Although granular-cell tumors can occur in various tissues, there is a difference in predilection sites among species. All granular-cell tumors found to date in the lungs of animals have been in horses, and in fact this has become the most frequently reported primary pulmonary tumor of the horse. The tumors have occurred in older horses and were either associated with coughing and pulmonary insufficiency or were found as incidental lesions at slaughter. Gross lesions are usually multiple discrete or semiconfluent nodules that have a tendency to be associated with major bronchi and cause obstruction by bulging into their lumina. The lesions are limited to one lung in most instances, more often the right one. The main histologic feature of the tumor is lobular aggregation of large, round to polyhedral cells with abundant acidophilic granular cytoplasm (Fig. 6.45C,D). The lobules are surrounded and dissected by fibrovascular stroma. The cytoplasmic granules in the tumor cells are PAS-positive and have characteristic ultrastructural features.

LYMPHOMATOID GRANULOMATOSIS. Lymphomatoid granulomatosis refers to a rare condition of dogs in which there is extensive infiltration of one or more lobes of the lung by accumulations of mixed atypical lymphoreticular cells. The cells have a pronounced tendency to invade the walls of vessels (Fig. 6.47D) and airways. The few reported cases have been in young dogs. Cells comprising the neoplasm are of various types. Large histocytic and plasmacytoid forms predominate (Fig. 6.47E), but binucleate cells, eosinophils, lymphocytes, and plasma cells are often also present. A network of fibrous stroma runs throughout the tumor. Mitotic figures are plentiful.

The exact nature of the condition is not known, and too few cases have been described for a clear pattern to emerge. It might represent primary pulmonary involvement by a form of polymorphous lymphoma similar to that occasionally found affecting other viscera or the skin of the dog. It is important, however, not to use this diagnosis for generally unclassifiable tumors of the lung or for those typical forms of lymphoma in which there is extensive invasion of perivascular and peribronchial regions of the lung by the neoplastic lymphoids cells.

Metastatic Tumors

Many types of malignant tumors can metastasize to the lungs. Among the most frequent are mammary carcinomas in dogs and cats, uterine adenocarcinomas in cattle (Fig. 6.48B), and malignant melanoma in the horse. Carcinomas originating in endocrine gland or skin are also a common source. Osteosarcomas, hemangiosarcomas, and fibrosarcomas are frequent varieties of sarcoma. The most easily recognizable pattern of metastatic tumors is of multiple nodules scattered throughout the pulmonary parenchyma, without great variation in size range (Fig. 6.48A). The presence of a few gross lesions, especially if there is great discrepancy in size, requires careful analysis of all gross and microscopic findings to provide the best chance of making an unequivocal distinction between metastatic foci and primary pulmonary tumor. The probability of neoplastic foci in the lungs being metastases is increased if the animal is a young one. Sometimes, microscopic examination is needed to differentiate between neoplastic nodules and multifocal granulomas.

Microscopically, metastatic tumors usually resemble the primary lesions, although they may be either better or less differentiated. Presence of tumor cells within arteries is an important

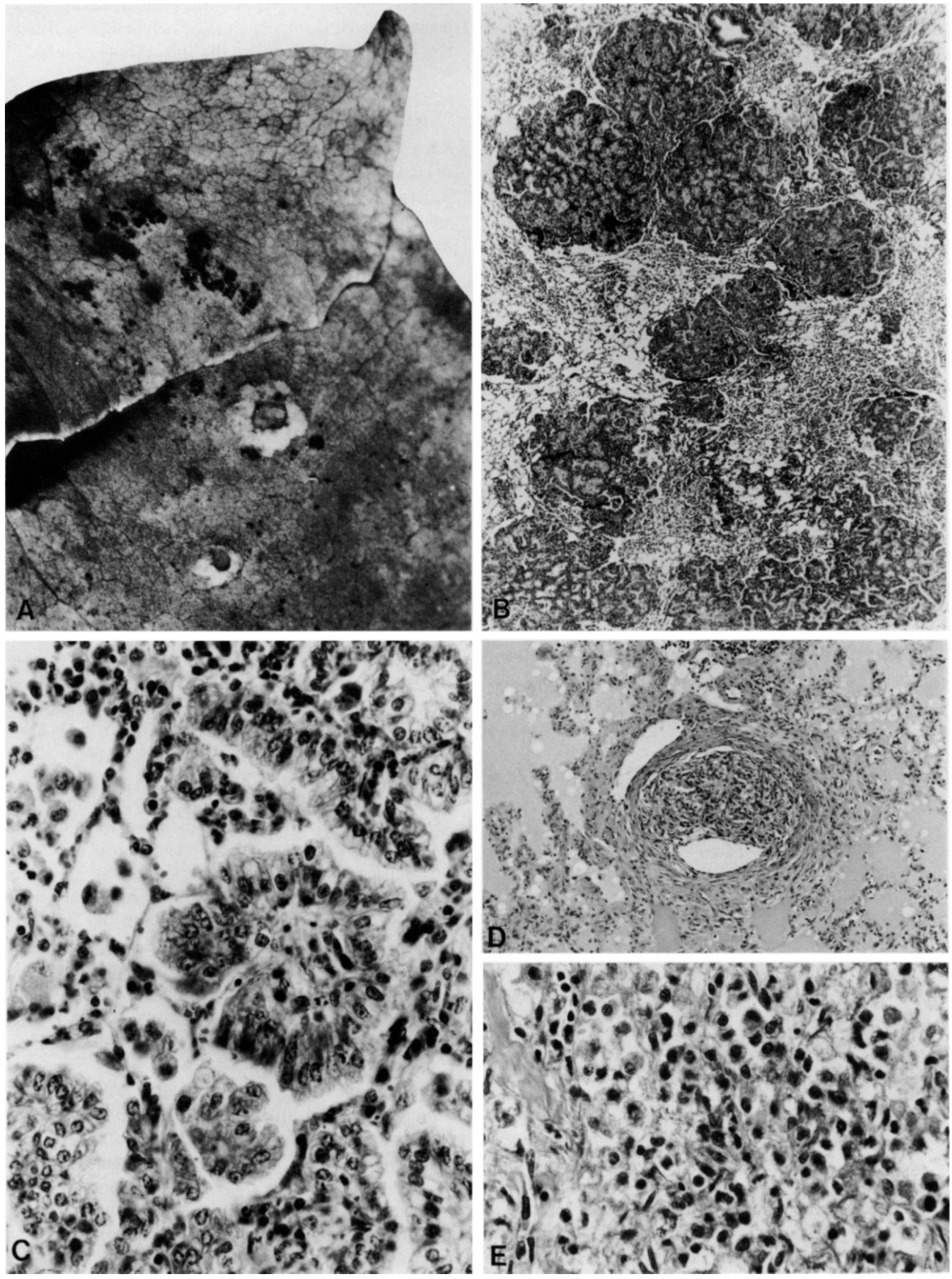

Fig. 6.47. (**A**) Isolated subpleural nodules present in early case of pulmonary adenomatosis (*jaagsiekte*). Sheep. (**B**) Multiple discrete tumor nodules with acinar and papillary patterns in pulmonary adenomatosis. Sheep. (**C**) Higher magnification of (**B**), showing columnar cells lining alveolar walls and forming papillae within lumina. (**B** and **C** courtesy of K. Perk and *Advances in Veterinary Science*.) (**D**) Eccentric invasion of intima of small artery in lymphomatoid granulomatosis. Dog. (**E**) Predominance of histiocytic and plasmacytoid cells in lymphomatoid granulomatosis. Dog.

indicator of metastatic origin, although this can be difficult to identify in some instances. This is particularly so where scirrhous response around invaded lymphatics gives them a superficial resemblance to thick-walled blood vessels.

In some cases where there is fulminating metastasis, there is no gross evidence of solid neoplastic infiltrations, merely tan discoloration of the lung and slightly increased firmness. Microscopically, however, widespread vascular embolization by anaplastic cells is seen (Fig. 6.48C), with early invasion of alveoli and lymphatics. Regardless of source or initial pattern of pulmonary involvement, highly malignant tumors have a predilection for widespread dissemination through intrapulmonary lymphatics.

Pleura and Mediastinum

Pleural abnormalities are usually secondary to lesions in tissues or organs forming the pleural cavity, especially the lung, or are part of more generalized disorders.

Congenital anomalies of the pleura and mediastinum are of little significance unless associated with a condition such as congenital diaphragmatic hernia. Congenital cysts may occasionally be found in the anterior mediastinum, mostly of brachycephalic dogs, and are presumed to be vestiges of the branchial pouches. Usually they are detected microscopically as cystic spaces lined by a single layer of cuboidal epithelium, often in close association with thymic tissues. Cysts of ~1 cm or more in diameter can be seen grossly as thin-walled structures containing clear, light yellow fluid. Air- or fluid-filled cysts in the caudal mediastinum are more likely to be of bronchogenic origin and can be large enough to cause pulmonary insufficiency.

Degenerative changes in the pleura occur in some cases of uremia in dogs (see the Urinary System, this volume). They are most evident in parietal pleura of the intercostal spaces, particularly the second, third, and fourth. Calcification centered on degenerated subpleural elastin and collagen fibers is visible as white horizontal striations.

Pneumothorax refers to the presence of air or gas in the pleural cavities. Air in the cavities allows the lungs to collapse to a degree proportional to the amount of air present. A normal subatmospheric pressure can be assumed to have been present at necropsy if the diaphragm moves caudally when the thorax is pierced and air allowed to enter. In small animals, pneumothorax can be detected by opening the chest under water and observing the escape of air bubbles.

Pneumothorax can be spontaneous or traumatic. Spontaneous pneumothorax is rare. It may complicate any pulmonary disease that leads to rupture of pulmonary parenchyma at the pleural surface. It is most often associated with rupture of emphysematous bullae. Less commonly it follows rupture of a parasitic cyst such as can occur in paragonimiasis. Traumatic pneumothorax is usually the result of accidental perforation of the thoracic wall or rupture of lung and visceral pleura. Air that tracks through the pulmonary interstitium to the mediastinum (pneumomediastinum) does not usually escape into the pleural cavities unless there is traumatic rupture of the mediastinum.

Traumatic pneumothorax can also be a complication of cardiac resuscitation or biopsy of the lung. Whatever the cause of pneumothorax, if entry of air stops before there is critical reduction of pulmonary function, the air is slowly resorbed.

Noninflammatory Pleural Effusions

Hydrothorax is the accumulation of edema fluid in the thoracic cavities. It is usually bilateral and has the same wide range of causes as edema of the lung or elsewhere. The fluid is clear, watery, and ranges from almost colorless to light yellow. Large amounts of it are present when there is widespread neoplastic involvement of pleural surfaces or when lymphatic drainage is impeded by neoplastic enlargement of the thymus or cranial mediastinal lymph nodes.

Hydrothorax may be present in cases of congestive heart failure, particularly in dogs, cats, and cattle. It is also present in severe anemias or in hypoproteinemias associated with the nephrotic syndrome, hepatopathy, protein-losing enteropathy, or malnutrition. Hydrothorax is also a feature of disease syndromes such as mulberry-heart disease in swine, black disease in sheep, African horsesickness, and ANTU poisoning. Chronic hydrothorax causes pleural opacity because of reactive hyperplasia of mesothelial cells and fibrous thickening of the underlying pleural connective tissue.

Chylothorax refers to the accumulation of milky fluid in the thorax (Fig. 6.49B). The fluid is lipid-rich lymph, which can be distinguished from other turbid effusions by extraction of the fat with ether or by staining the droplets with a Sudanophilic dye. Occasionally the source of the chylothorax is traced to rupture of the thoracic or right lymphatic duct. This is presumed to be the case in the many instances where the origin is not found. The most common association of chylothorax is with a traumatic event, bouts of severe coughing, or tumors in the cranial mediastinum.

Hemothorax is the presence of blood in the pleural cavities. It is most often the result of traumatic rupture of blood vessels, but it can also be caused by erosion of the wall of a vessel by an inflammatory or neoplastic process. Less common causes are diseases in which there is a clotting disorder. Hemorrhage may also arise from highly vascularized tumors (e.g., hemangiosarcoma) or inflammatory processes, such as pleural tuberculosis in dogs. Chronic hydrothorax may lead to the development of well-vascularized papillae on the pleura, and rupture of these might cause the effusion to resemble blood.

Pleuritis

Inflammation of the pleura (pleuritis) is the most commonly encountered abnormality. It is usually secondary to pneumonia (see Anatomic Patterns of Pneumonia). Other pathways by which inflammatory agents reach the pleura are the bloodstream, lymphatic permeation from the peritoneal cavity, traumatic penetration from outside the chest or from the esophagus or abdominal viscus (such as the bovine reticulum), or direct extension from a mediastinal abscess or esophagitis. The agents causing pleuritis as part of blood-borne infections vary with species of animal affected. *Haemophilus* species are commonly the cause in swine, as are mycoplasmas in swine and goats. *Chlamydia psittaci* is occasionally involved in ruminants. The virus of feline infectious peritonitis is the most common cause in

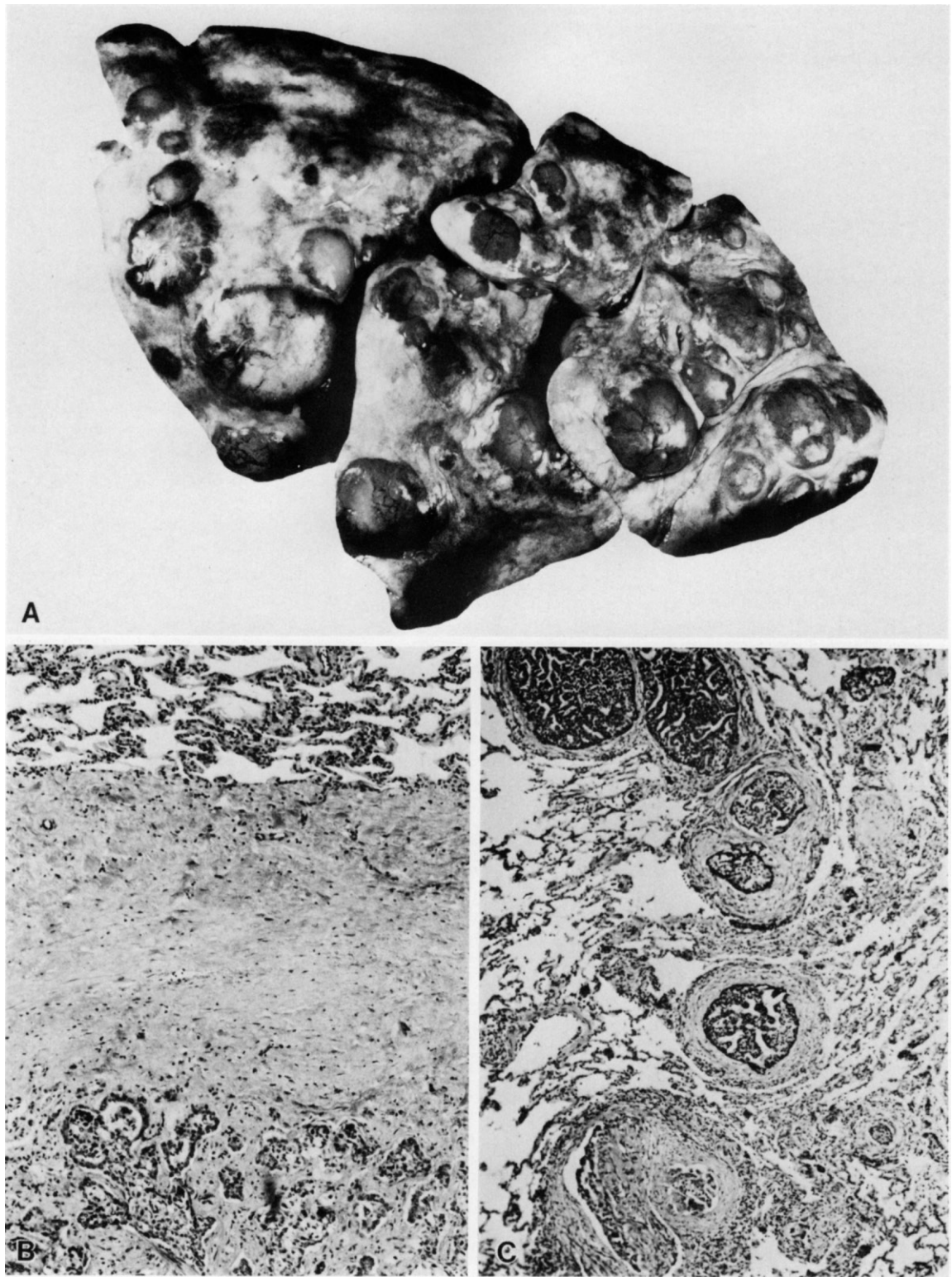

Fig. 6.48. (**A**) Metastatic nodules of mammary adenocarcinoma. Dog. (**B**) Metastatic uterine adenocarcinoma with extensive scirrhous response. Cow. (**C**) Multiple foci of malignant mammary adenocarcinoma resulting from neoplastic embolization of pulmonary vessels. Dog.

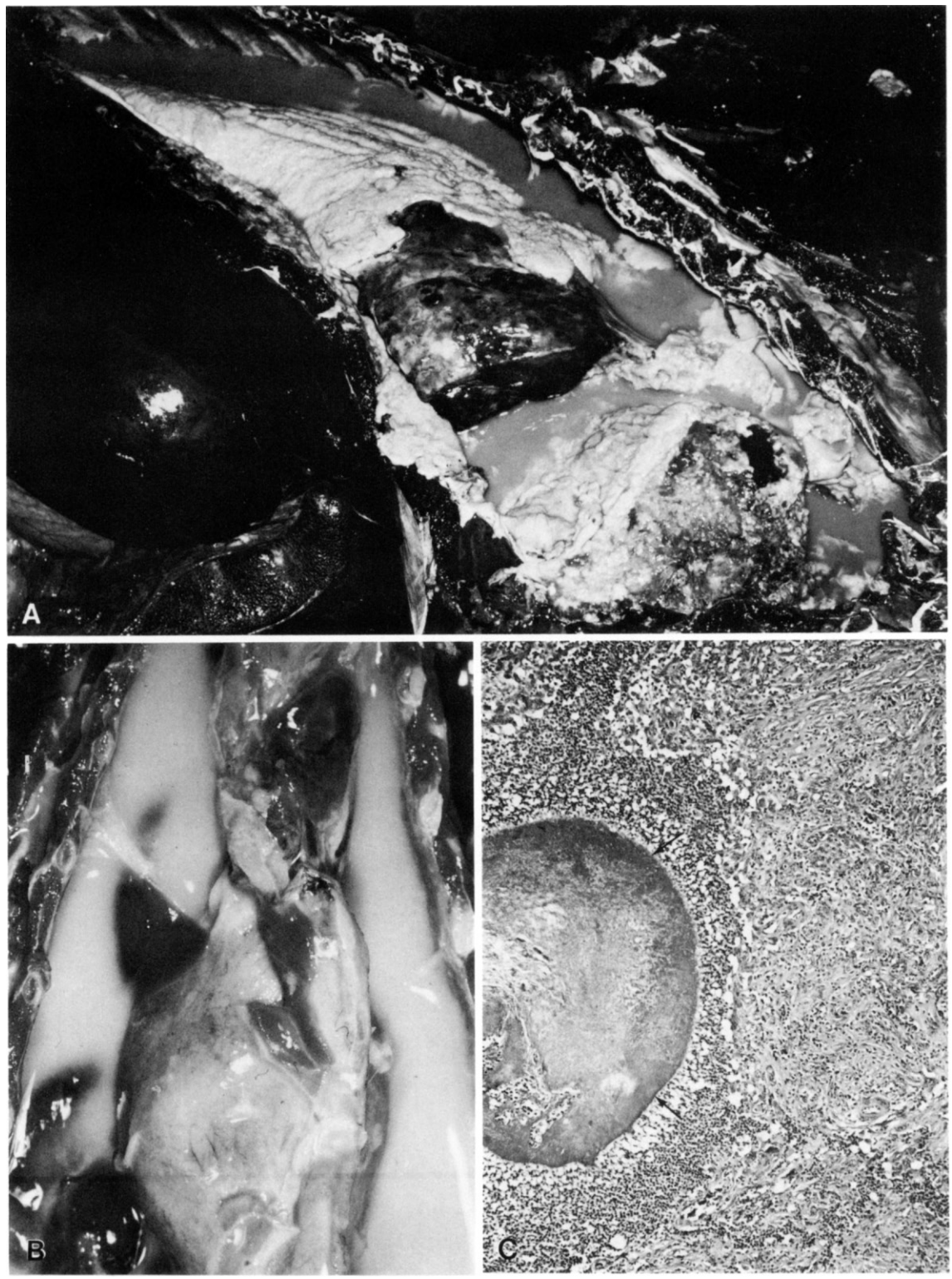

Fig. 6.49. (**A**) Severe fibrinopurulent pleuritis and pyothorax. Horse. (**B**) Chylothorax. Cat. (**C**) Pyogranulomatous pleuritis caused by *Actinomyces* sp. Dog. Note the large bacterial colony (arrows).

cats. Pleural defenses against microorganisms are much less effective than those of the lung. Even a few organisms reaching the pleural surfaces are therefore apt to have serious consequences in contrast to the result of a similar exposure in the lungs. The reactions of the pleura to inflammation are the same as those of the pericardium (see the Cardiovascular System, Volume 3).

Abundant purulent effusion into the pleural sacs is designated as **pyothorax** or **thoracic empyema**. The condition can occur in any animal but is of most clinical significance in horses, dogs, and cats. It can be caused by pyogenic organisms reaching the pleural cavities by any of the pathways mentioned previously, but the relative importance of the pathways and the mix of organisms involved varies with the species of animal. The majority of cases of serofibrinous effusion or pyothorax in the horse are secondary to either pneumonia or pulmonary abscessation. The exudate is usually thin and dirty yellow in color (Fig. 6.49A) and may be either unilateral or bilateral. Streptococci are the organisms most consistently isolated, sometimes in mixed infections with *Escherichia coli, Klebsiella, Pasteurella, Pseudomonas,* or staphylococci. *Pasteurella,* staphylococci, and *Bacteroides* are isolated in pure culture on occasion. *Mycoplasma felis* has been added to the list of possible agents. There is failure to culture organisms from the pleural effusion in as many as 50% of cases, however. In horses, exudative pleuritis occurs most often in racehorses and in many cases the onset is associated with stress of traveling, training, or racing.

Pyothorax unassociated with significant pneumonia occurs in dogs, mostly in sporting breeds with access to rural environments. It particularly affects dogs used for hunting or those in training. The exudate is unilateral or bilateral, more commonly the latter. It is usually bloodstained and viscous or flocculent, but may be creamy or darkly serofibrinous. Yellowish "sulfur granules" may be present in the bloodstained pus. The pleural surfaces are thickened and velvety red or grayish yellow and fibrotic, depending on age and nature of the lesion. The cranial mediastinum is the main site of thickening. *Actinomyces, Nocardia,* and *Bacteroides* are the most frequently recovered organisms, and these are commonly associated with the presence of sulfur granules and a characteristic pyogranulomatous pleuritis and mediastinitis (Fig. 6.49C). Mixed infections are common, however, and a variety of other organisms can be present, including *Corynebacterium, Pasteurella, E. coli, Fusobacterium necrophorum, Pseudomonas,* and streptococci. The pathogenesis of the lesion is uncertain, but the circumstantial evidence supports the belief that infection reaches the pleural cavity in most instances by way of migrating grass awns or florets. It is next to impossible to find plant material in the copious pleural exudate, but there is sometimes an association with subcutaneous abscesses or fistulous tracts compatible with migration of grass awns, and affected dogs are those with greatest exposure to the species of grasses responsible for invasion of bodily orifices and subcutis. The damage caused by the migrating grass awns also seems particularly favorable for growth of the actinomycetes. Pyothorax is fairly common in cats. The pus is usually creamy yellow or a grayish brown. As in dogs, it is more often bilateral than unilateral. A variety of bacteria are responsible, often in mixed infection. *Pasteurella multocida,* various Gram-negative enteric bacteria, streptococci, and staphylococci have been isolated. *Actinomyces, Nocardia,* and *Bacteroides* are recovered on occasion, but much less consistently than in dogs. There are few pointers regarding the pathogenesis of the condition in cats. Although it is speculated that infection could gain access by penetration of a foreign body from the external surface or esophagus, or by a penetrating bite wound, there are few concrete data available.

Neoplastic Diseases of the Pleura

Primary pleural tumors are rare. The specific type is the pleural mesothelioma, which has been found in the cow, dog, cat, horse, and goat. Mesotheliomas arise from the pericardial and peritoneal surfaces as well as from the pleura; details of their appearance are given with diseases of the peritoneum (in the Peritoneum, Retroperitoneum, and Mesentery, this volume). There is one report of ferruginous bodies being present in significantly large numbers in the lungs of a small series of dogs with mesotheliomas. Ferruginous bodies are fine fibers irregularly coated by ferritin and amorphous protein. The cores are most commonly asbestos fibers, and therefore the numbers of ferruginous bodies are usually accepted as an index of exposure to asbestos. The finding of large numbers in the lungs of dogs with mesotheliomas suggests that inhalation of asbestos fibers could be related to the development of mesotheliomas in this species, as it is in humans.

Primary tumors can also arise from the chest wall and mediastinal tissues. Tumors of bone and cartilage, nerve sheaths, thymus, lymph nodes, and ectopic glandular tissue are discussed elsewhere.

Secondary tumors of the pleura are also uncommon, but transpleural dissemination of carcinomas and sarcomas occasionally occurs by extension from the lungs, chest wall, or mediastinum. Carcinomas from the abdominal cavity can reach the pleura by penetrating diaphragmatic lymphatics.

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