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# CHAPTER 1

# The Alimentary System

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## Oral Cavity

Examination of the oral cavity should be standard procedure during any postmortem examination. To obtain a clear view of the mucous membranes, teeth, tongue, gums, and tonsils, it is essential to split the mandibular symphysis and separate the mandibles as far as possible. A thorough examination of all structures will reveal not only local lesions but often those that may be due to systemic disease. Lesions may be associated with congenital anomalies, trauma (physical and chemical), bacterial, mycotic, viral, and parasitic infections, metabolic and toxic diseases, and dysplastic and neoplastic disease. The poor nutritional state of an animal may be directly related to oral lesions that result in difficulties of prehension, mastication, or swallowing of food.

### *Congenital Anomalies*

The development of normal facies and the oral cavity depends on the integrated development of a large number of embryonic processes. The complexity and protracted period of this development may lead to a great variety of aberrations. These are usually expressed in the newborn in the form of clefts resulting from failures of integrated growth and fusion. A common failure of fusion is that of the maxillary processes to the frontonasal process. This may leave facial fissures, uni- or bilateral primary cleft palate (formerly called harelip), or secondary cleft palate (formerly called cleft palate).

**Facial clefts** may involve the skin only or the deeper tissues as well. They are variously located, and not all are obviously related to normal lines of fusion. All are rare. The least uncommon is a complete cleft from one angle of the mouth to the ear of that side. This results from failure of fusion of the lateral portions of the maxillary and mandibular processes. A defect extending from a harelip to the eye results from failure of fusion of the maxillary and frontonasal processes; its least expression is superficial and a failure of closure of the nasolacrimal duct.

**Primary cleft palate** (harelip) includes developmental anomalies of the lips anterior to the nasal septum, columella, and premaxilla. They may be uni- or bilateral and superficial or extend into the nostril. The defect arises from incomplete fusion of the frontonasal process with the maxillary processes.

**Secondary cleft palate** (cleft palate, palatoschisis) (Fig. 1.1B) is often associated with primary cleft palate. The hard palate is formed, except for a small anterior contribution from the frontonasal process, by the bilateral ingrowth of the palatine shelves from the maxillary processes. At the midline, they fuse with each other and the nasal septum, except in their posterior part, which becomes the soft palate. Inadequate growth of either palatine shelf leaves a central defect that communicates between the oral and nasal cavities.

Cleft palates have been reported in most species of domestic animals. Secondary cleft palate and arthrogryposis frequently occur together in Charolais calves and appear to be hereditary (probably simple autosomal recessive). In calves, cleft palate is one of the most common anomalies. The defect is uncommon in lambs, in which it may be genetic in origin (possibly simple recessive) or associated with ingestion of *Veratrum californicum*. In swine, primary cleft palate is less common than secondary cleft palate, although the two anomalies often occur together. The defects are probably polygenic or multifactorial

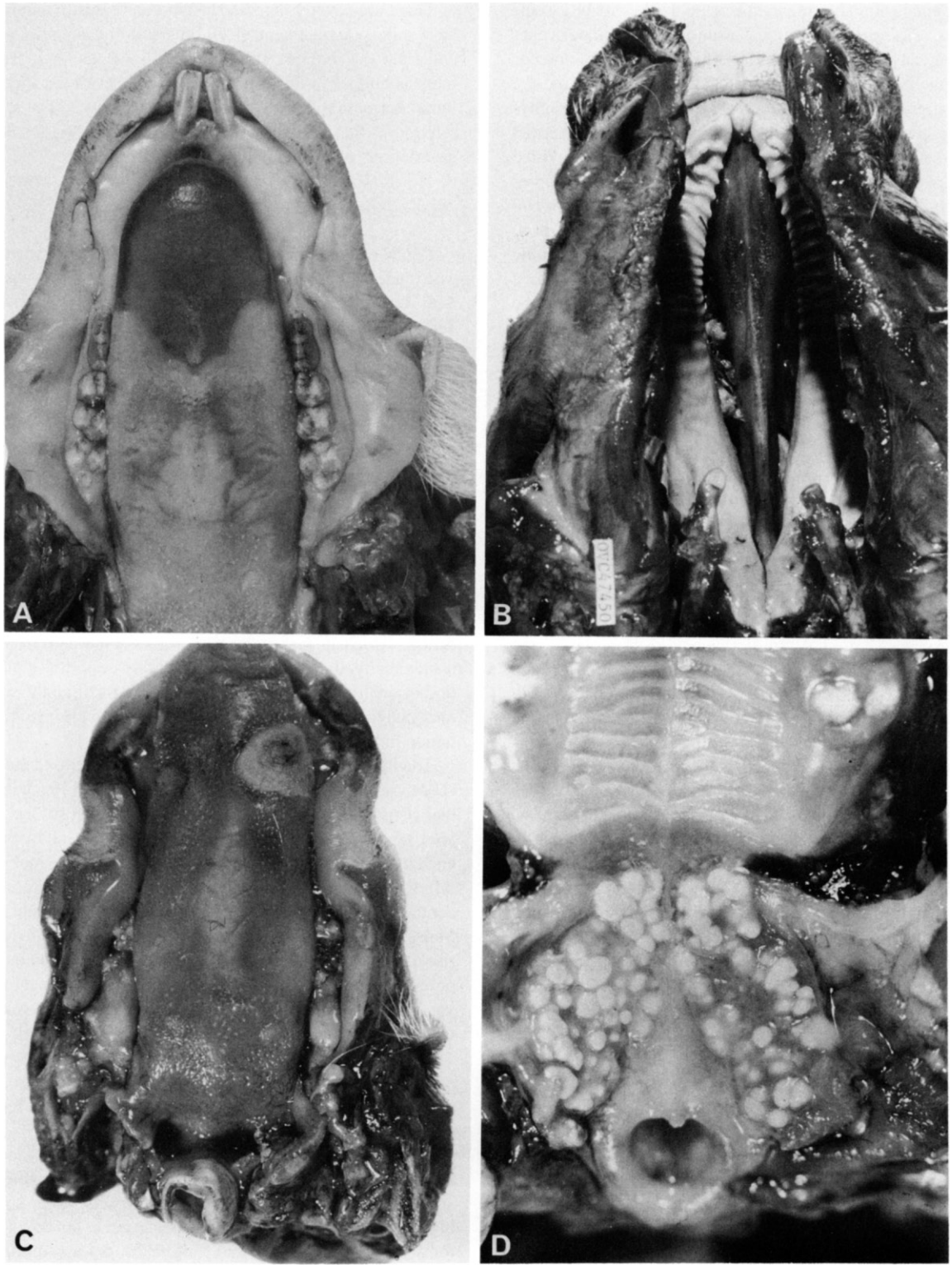


**Fig. 1.1.** (**A**) Epitheliogenesis imperfecta. Tongue. Pig. (**B**) Secondary cleft palate exposing the nasal cavity. Pig. (**C**) Necrotic glossitis and stomatitis. Pig. *Fusobacterium necrophorum* infection associated with trauma by needle teeth. (**D**) Suppurative tonsillitis. Piglet. Streptococci and *Escherichia coli*.

developmental anomalies in this species and also may be associated with *Crotalaria* intoxication. Secondary cleft palate occurs in Siamese cats and is thought to be hereditary in this breed, although the mode of inheritance has not been determined.

Anomalies of the growth of jaws are quite common. **Brachygnathia superior**, shortness of the maxillae, is an inherited breed characteristic among dogs and swine. It has been reported in the Large White or Yorkshire breed. The condition is progressive with age, resulting in malapposition of the incisor and cheek teeth, which interferes with prehension and mastication. In swine, brachygnathia superior may be confused with atrophic rhinitis. In Jersey cattle, brachygnathia superior occurs as a simple autosomal recessive trait. It may, in any species, be associated with chondrodysplasia.

**Brachygnathia inferior** or micrognathia, shortness of the mandibles, may be a mild to lethal defect in cattle and sheep and is a breed characteristic of long-nosed dogs. Micrognathia is a common defect in calves. It is inherited, probably as a simple autosomal recessive trait. There is a higher incidence in males. In Aberdeen Angus calves the defect may occur concurrently with cerebellar hypoplasia, and with osteopetrosis in this and other breeds (see Bones and Joints, Volume 1). Mild brachygnathia inferior, termed "parrot mouth," is a common conformational defect in horses.

**Prognathism** refers to an abnormal prolongation of the mandibles. It too is rather common especially in sheep. It may develop with recovery from calcium deficiency in this species (see Bones and Joints, Volume 1). The malformation is relative, and it is not always easy to determine whether the jaw is absolutely long or merely apparently so, relative to a mild brachygnathia superior.

**Agnathia** is a mandibulofacial malformation characterized by absence of the lower jaw, due to failure of development of the first branchial arch and associated structures. The defect is one of the most common anomalies in lambs but is rare in cattle. Associated malformations in lambs may include ateloprosopia (incomplete development of the face), microglossia or aglossia, and atresia of the oral pharynx. Concurrent anomalies affecting other body systems may also be evident.

**Epitheliogenesis imperfecta** is an anomaly causing widespread defects in cutaneous epithelium that also affects the epithelial lining of the oral cavity, especially the tongue (Fig. 1.1A) (see diseases of Skin and Appendages, Volume 1). The condition is characterized by irregular, well-demarcated, red, ulcerated areas in the oral mucosa. Histologically, these consist of abruptly ulcerated areas in the squamous mucosa with inflammation of the submucosal connective tissues. The anomaly occurs in most species and is inherited as a simple autosomal recessive character in cattle, horses, and pigs; the mode of inheritance is unknown in the other species.

A lethal glossopharyngeal hereditary defect, termed "bird tongue" and caused by a simple recessive autosomal gene has been reported in dogs. The breed in which the condition occurred was not revealed. The affected pups have a narrow tongue, especially the anterior half where the margins are folded medially onto the dorsal surface. The pups are unable to swallow. The muscle fibers of the affected tongues are normal histologically.

There are several hereditary skin conditions in animals that have minor involvement of the lips and oral mucosa, such as epidermolysis bullosa simplex in collie dogs, ovine epidermolysis bullosa in Suffolk and South Dorset Down sheep, and familial acantholysis of Aberdeen Angus calves. The reader is referred to the Skin and Appendages (Volume 1) for detailed descriptions of these conditions.

### *Diseases of Teeth and Dental Tissues*

Dental examinations in animals are usually cursory, except to assess age, but dental disease is common and often is the factor that limits the useful life span, especially of sheep. The "borderland of embryology and pathology" is never more nebulous than it is for teeth, and the comments on dental development and anatomy given below are intended to assist the understanding of dental disease.

Teeth develop from horseshoe-shaped thickenings in the oral ectoderm called dental laminae. Neural crest cells beneath the laminae induce formation of tooth buds, which generate the enamel organs. These epithelial structures grow into the underlying ectomesenchyme and organize it to form dental papillae, which they enclose like a cap. Surrounding both is another mesenchymal condensation, the dental sac. The inner enamel epithelium of the enamel organ induces differentiation of odontoblasts from the mesenchyme of the papilla. They produce dentin, which in turn induces enamel formation by the inner enamel epithelium. Formation of dentin is essential for formation of enamel. These inductive interactions of epithelium and mesenchyme are considered to be important in the histodifferentiation of some tumors of dental tissues.

The free edge of the enamel organ extends beyond the enamel–dentin junction, and this extension is called Hertwig's epithelial root sheath. It molds dental papilla to form the root or apex of the tooth. Subsequently it fragments, allowing mesenchymal cells from the dental sac to contact the root dentin, differentiate into cementoblasts, and deposit cementum on the dentin. Remnants of the root sheath are called epithelial rests of Malassez. They persist in the periodontal ligament and may give rise to tumors or cysts. They may be important in the induction or repair of cementum, and in periodontal reattachment following injury. If cells of the root sheath adhere to the dentin, they may produce enamel pearls.

Once the dental lamina has produced the buds of the permanent teeth, it degenerates. Epithelial remnants persist as epithelial pearls or islands in the gingiva and jaws. These remnants also may give rise to tumors and cysts.

There are important differences between the brachydont teeth of humans, carnivores, and swine, in which the enamel is restricted to the tooth crown, and the hypsodont teeth of herbivores. In hypsodont teeth, enamel extends far down on the roots and is invaginated into the dentin to form infundibula. Also, the hypsodont teeth of herbivores, except the mandibular premolars of ruminants, are covered by cementum that more or less fills the infundibula. Exceptions to these rules are provided by the tusks of boars, which are hypsodont but not covered by cementum, and by ruminant incisors, which are brachydont but do have enamel covering part of the root dentin.

The three hard tissues of teeth are dentin, enamel, and cementum. **Dentin** is light yellow and constitutes most of the tooth. It consists of about 35% organic matter and 65% mineral. Thus its composition is similar to bone, and like bone it contains type I collagen. Dentin is produced by columnar cells with basal nuclei called odontoblasts, which differentiate from mesenchyme of the dental papilla. Initially it is unmineralized (predentin), but later mineralized. The odontoblasts move away from the dentin–enamel junction, gradually encroaching on the pulp cavity as they produce dentin. Each odontoblast has a process extending into the dentin, encased in a dentinal tubule, that arborizes at the dentin–enamel junction. The process also anastomoses with the processes of other odontoblasts. Dentinal tubules are visible in histologic sections, but the anastomoses are not. Except for the processes, and nerve endings in the dentin near the pulp, dentin is acellular.

Normal dentin contains incremental or imbrication lines of von Ebner, which are fine basophilic lines running at right angles to the dentinal tubules. They represent normal variations in the structure and mineralization of dentin. Sublethal injury caused by certain infections, metabolic stresses, or toxic states may injure the odontoblasts, which then produce accentuated incremental lines known as the contour lines of Owen. Sometimes, irregular zones of unmineralized or poorly mineralized dentin form between foci of normal mineralization. These are zones of interglobular dentin, which may be caused by hypophosphatemia.

Odontoblasts normally are active throughout life, producing layers of secondary dentin that often contain fewer dentinal tubules than primary dentin. Reparative dentin is produced locally in response to injury and contains a limited number of twisted tubules and sometimes a few odontoblasts, which soon die. Sclerotic (transparent) dentin is formed when dentinal tubules are occluded by calcium salts. The junctions between primary, secondary, and reparative dentin are usually demarcated by basophilic lines.

**Enamel** has about 5% organic matter and 95% mineral. It is produced by the tall, columnar ameloblasts of the inner enamel epithelium. Enamel is produced in the form of prisms or rods, cemented together by a matrix. Mineralization begins as soon as it is formed and is a two-stage process, somewhat similar to that in bone but much more rapid. The cells of the inner enamel epithelium also move away from the dentin–enamel junction as the tooth is formed, but unlike odontoblasts, they do not have processes. Enamel is hard, dense, brittle, and permeable and is translucent and white. Mature enamel is not present in demineralized sections, but some of the matrix of immature enamel may be visible near ameloblasts of developing teeth.

Ameloblasts are very sensitive to environmental changes. Normal enamel contains incremental lines of Retzius, which are analagous to the incremental lines of von Ebner in dentin and also reflect variations in structure and mineralization. The incremental lines are accentuated during periods of metabolic stress. More severe injury, in fluorosis or infections by some viruses (Fig. 1.2A,B), can produce focal hypoplasia or aplasia of enamel.

Formation of enamel ends before tooth eruption. The inner enamel epithelium then merges with the cells of the underlying stratum intermedium and the outer enamel epithelium to form the reduced enamel epithelium. It protects the enamel of the formed tooth prior to eruption and digests the connective tissue separating it from the gingival epithelium. Fusion of the two epithelia is necessary for eruption to occur. Degeneration of this protective layer permits connective tissue to contact the enamel, and there may be resorption of enamel or deposition of a layer of cementum on it. This normally occurs during odontogenesis in horses.

**Cementum** is an avascular, bonelike substance, produced by cementoblasts; it contains about 55% organic and 45% inorganic matter. In general, the dentin of brachydont teeth is covered by cementum wherever it is not covered by enamel. When dentin formation has begun in the root, degeneration of Hertwig's epithelial root sheath begins and permits mesenchymal cells from the dental sac to contact dentin. They differentiate into cementoblasts, which produce cementoid and later mineralize it. Some layers of cementum do not contain cells (acellular cementum), but in other layers cementocytes are enclosed in lacunae. Sharpey's fibers from alveolar bone are embedded in the cementum. Cementum is more resistant to resorption than bone, and unlike bone, normally is not resorbed and replaced as it ages; instead, a new layer of cementum is deposited on top of the old layer. In some pathologic conditions cementum is resorbed; subsequently, cellular or acellular cementum is deposited, more or less repairing the defect.

Hypercementosis is abnormal thickening of cementum and may involve part or all of one or many teeth. When extra cementum improves the functional properties of teeth, it is called cementum hypertrophy; if not, it is called cementum hyperplasia. Extensive hyperplasia often is associated with chronic inflammation of the dental root.

The periodontal ligament is a very cellular, well-vascularized connective tissue that develops from the dental sac. The **periodontium** comprises the periodontal ligament, gingival lamina propria, cementum, and alveolar bone. The ligament supports the tooth and adjusts to its movement during growth. It is well supplied with nerves and lymphatics, which drain into alveolar bone. The periodontal ligament also is a source of the cells that remodel alveolar bone and, in disease, cementum.

Epithelial rests of Malassez are present in the periodontal ligament and are particularly numerous in the incisor region of sheep. In all species, they may proliferate and become cystic when there is inflammation of the periodontium. The periodontium is also a site of origin of tumors. The periodontal ligament normally is visible in radiographs as a radiolucent line between tooth and alveolar bone. In prolonged hyperparathyroidism, alveolar bone is resorbed and the ligament is no longer outlined radiographically, a change referred to as "loss of the lamina dura."

### *Developmental Anomalies of Teeth*

**Anodontia**, absence of teeth, is inherited in calves, probably as a sex-linked recessive trait in males, and is associated with skin defects. **Oligodontia**, fewer teeth than normal, occurs sporadically in horses, cats, and dogs, and also as an inherited trait in dogs. In brachycephalic breeds, the cheek teeth are deficient; in toy breeds, the incisors are deficient. **Pseudooligodontia** and

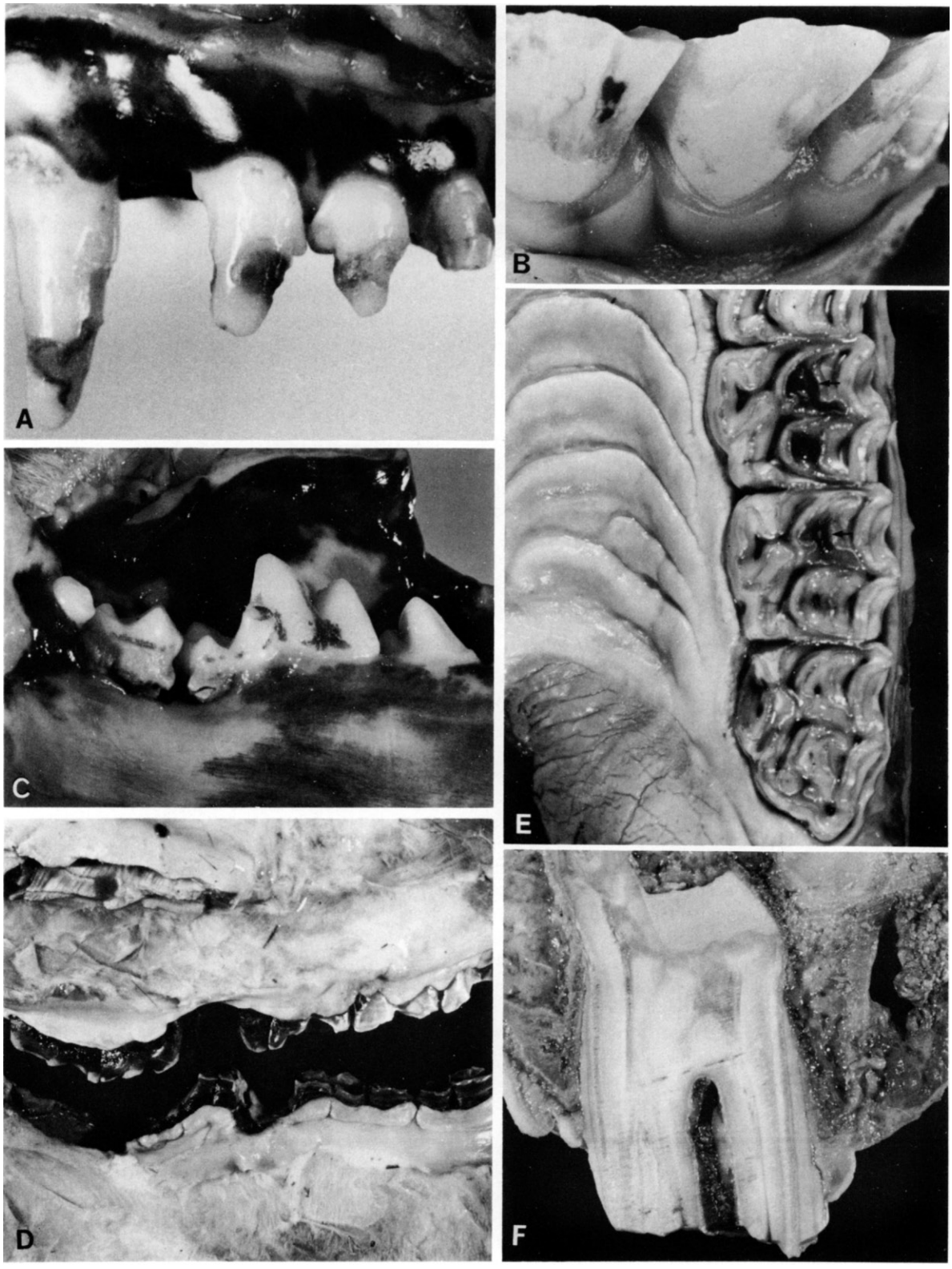


**Fig. 1.2.** (**A**) Focal enamel hypoplasia, sequel to canine distemper. Dog. (**B**) Enamel hypoplasia. Calf. Sequel to intrauterine infection by bovine virus diarrhea virus. (Courtesy of R. B. Miller.) (**C**) Periodontal disease. Dog. Marked gingival recession with exposure of roots of the molar teeth. (**D**) Irregular wear of teeth. Horse. (**E**) Infundibular necrosis of first and second maxillary molars (arrows). Horse. Necrosis confined to cement lakes. (**F**) Section through (**E**), showing black discoloration of infundibulum.

**pseudoanodontia** result from failed eruption. These defects may be associated with bone modeling defects in *grey* lethal mice with osteopetrosis. Delayed eruption of permanent teeth occurs in Lhasa Apso and Shih Tsu dogs. **Polyodontia**, excessive teeth, occurs in brachycephalic dogs; the incisors are involved, and the defect is probably related to breeding for broad muzzles. A high incidence of canine polyodontia, involving particularly an extra maxillary premolar, has been reported from the Netherlands. Polyodontia also occurs in horses and cats, involving either incisors or cheek teeth. **Pseudopolyodontia** is retention of deciduous teeth after eruption of the permanent dentition. It occurs in horses, cats, and dogs, especially in the miniature breeds.

**Heterotopic polyodontia** is an extra tooth, or teeth, outside the dental arcades. The best known example is the "ear tooth" of horses, which develops in a branchiogenic cyst. The cysts originate from failure of closure of the first branchial cleft, or from the inclusion of cellular rests in this area. They are lined by a stratified mucous- or cutaneous-type epithelium and may contain one or more teeth, either loosely attached in the cyst wall or deeply embedded in the petrous temporal bone. The tooth is derived from misplaced tooth germ of the first branchial arch, which is displaced toward the ear with the first branchial cleft. The cysts form in the parotid region and may fistulate to the exterior. They are occasionally bilateral, and rarely the tooth may form a pedunculated mass enclosed by skin and attached by a pedicle to the skin of the head. Heterotopic polyodontia also occurs in cattle, dogs, pigs, and sheep.

Malformation and malpositioning of teeth accompany abnormalities of the jaw bones. Aberdeen Angus and Hereford calves with congenital osteopetrosis have brachygnathia inferior, malformed mandibles, and impacted cheek teeth (see Bones and Joints, Volume 1). Impacted molars occur as an inherited lethal in shorthorns; an association with osteopetrosis apparently has not been investigated in this breed.

**Odontogenic cysts** are epithelium-lined cysts derived from cell rests of Malassez, cell rests of dental laminae, reduced enamel epithelium, or malformed enamel organs. **Dentigerous cysts** are, by definition, cysts that contain part or all of a tooth, which often is malformed. Of the odontogenic cysts just listed, all except those derived from cell rests of Malassez are potentially dentigerous. (The rests of Malassez are the probable source of periodontal cysts.) Dentigerous cysts originating in malformed enamel organs should include malformed teeth, since development of enamel is incomplete until the organ degenerates. Those teeth in cysts of reduced enamel epithelium or rests of dental laminae are not necessarily abnormal. The affected teeth probably "erupt" into the preformed cysts. Dentigerous cysts enclose at least the crown of the tooth, but may include it all. The most common form of odontogenic dentigerous cysts in animals are those involving the vestigial wolf teeth of horses and the vestigial canines, especially of mares. The smaller cysts appear as tumors of the gums, while some of the larger ones may cause swelling of the jaw or adjacent maxillary sinus. Dentigerous cysts of animals are not as destructive as those in humans, in which they are regarded as the most common benign destructive lesion of the skeleton.

The ear tooth of horses is probably the most common nonodontogenic dentigerous cyst (see heterotopic polyodontia, above). Occasionally, true dentigerous cysts form when a tumor prevents normal eruption or when there is maleruption due to odontodystrophy.

Cystic dental inclusions about vestigial supernumerary teeth also occur in the juxtamolar positions in cattle but are insignificant. These too may be dentigerous, or they may be primordial cysts developed before the stage of enamel formation, and hence containing no mineralized tooth structures. Either type of cyst may give rise to ameloblastomas.

A high incidence of dentigerous cysts involving incisors occurs in some sheep flocks in Scotland and New Zealand.

Permanent teeth are unique in that their development continues for a long time after birth. Thus inflammatory and metabolic disease of postnatal life can produce hypoplasia of dentin and enamel. Hypoplasia of enamel of deciduous teeth occurs in some calves with intrauterine bovine virus diarrhea infection. Extreme fragility of deciduous teeth is a feature of bovine osteogenesis imperfecta, but the variety of inherited dentinal dysplasias and enamel anomalies that occur in humans is not recognized in domestic animals.

### *Degenerative Conditions of Teeth and Dental Tissue*

PIGMENTATION OF TEETH. Normal enamel is white and shiny, but normal cementum is off-white to light yellow and normal dentin is slightly darker yellow. Depending on the tooth, or the part of the tooth being examined, the normal color may be any one of these. Normal enamel is never discolored. Hypoplastic enamel of chronic fluorosis is discolored yellow through brown to almost black. Discoloration of brachydont teeth results from pigmentation of dentin, which is then visible through the semitransparent enamel, or pigmentation of the cementum of the root. Dentin may be colored red-brown by pulpal hemorrhages or inflammation, gray-green in putrid pulpitis, and yellow in icterus. Congenital erythropoietic porphyrias of calves, cats, and swine discolor the dentin red in young animals (pink tooth) and darker brown in adults, although in swine the discoloration may disappear with aging. Transient porphyria with pink discoloration of teeth has been reported in a dog.

Yellow to brown discoloration of teeth, and bright yellow fluorescence in ultraviolet light, due to deposition of tetracycline antibiotics in mineralizing dentin, enamel, and probably cementum, occurs in all species. Treatment of the pregnant dam may cause staining of deciduous teeth in the offspring. Tetracyclines are toxic to ameloblasts in the late differentiation and early secretion stages and, at high dose rate, may produce enamel hypoplasia.

Black discoloration of ruminant cheek teeth is extremely common and is caused by impregnation of mineral salts with chlorophyll and porphyrin pigments from herbage.

DENTAL ATTRITION. The mature conformation of teeth is largely the outcome of opposed growth and wear, and the degree of wear depends on the type of tooth, the species of animal, and the matter chewed. Wear is most evident in herbivores, and irregularities of wear are perhaps the most common dental ab-

normalities. In general, with normal occlusion and use, the extraalveolar portion of the tooth does not shorten; instead, its length is maintained initially by growth (the period of growth depending on the species) then by hypertrophy of the root cementum and proliferation of alveolar bone (which serves to push the tooth out), and finally by senile atrophy of the alveolar processes. Cementum hypertrophy and alveolar atrophy may result in loss of teeth in senility, or if combined with subnormal wear, produce teeth that in old age are excessively long. Normal wear of the complicated cheek teeth of horses and cattle causes smoothing of the occlusal surfaces. As soon as wear of enamel exposes the dentin, which being softer wears more rapidly, secondary dentin is deposited to protect the pulp. In time, this may fill the pulp cavity and cause death of the tooth.

Abnormalities of wearing are most common in herbivores (Fig. 1.2D). Subnormal wear, due to loss of the opposing tooth, occurs in oligodontia, abnormal spacing of adjacent teeth, and acquired loss of teeth; it results in abnormal lengthening. Such elongated teeth may grow against the opposing gum or, if deviated, into an adjacent soft structure such as cheek or lip. These teeth usually wear in abnormal places because complete loss of antagonism is unusual, because the upper and lower arcades do not coincide exactly, and the coincidence is further reduced by the displacement of chewing. Incomplete longitudinal coincidence of the molar arcades allows irregular wear and hook formation on the first and last cheek teeth. Abnormal wear due to abnormal chewing is caused by voluntary, as in painful conditions, or mechanical impairment of jaw movement. Lateral movements of the jaws without the normal rotary grinding movements allow the ridges of the teeth of herbivores to become accentuated. Steep angulation of the occlusal surfaces results from inadequate lateral movement of the jaws, and sharp edges form on the buccal aspect of the maxillary teeth and the lingual aspect of the mandibular teeth. This may be unilateral when the animal chews with only one side of its mouth, the other side then being affected. The teeth wear progressively sharper and pass each other like shear blades, hence the term "shear mouth." Subnormal resistance to wear on the part of the molar teeth is common and results in "weave mouth" or "step mouth," in which successive teeth in an arcade wear at different rates. The weave or step form of the antagonistic arcade is reversed so that the teeth of the two arcades interdigitate. This pattern of attrition is caused by variation in the hardness of opposing teeth, and usually is caused by intermittent odontodystrophy. Opposing teeth of the upper and lower jaws do not develop at the same time, thus discontinuous nutritional deficiencies often result in unequal wear. Certain vices, such as crib biting, also produce abnormal wear. In severely worn ruminant incisors a central black core may be visible, which is secondary dentin deposited in the pulp cavity. It is not carious but stains darker than the surrounding primary dentin.

ODONTODYSTROPHIES. Odontodystrophies are diseases of teeth caused by nutritional, metabolic, and toxic insults. They are manifest by changes in the hard tissues of the teeth and their supporting structures. Lesions of enamel and dentin are emphasized here. The most prominent affects of odontodystrophies appear in enamel, and lesions of enamel are most significant because they are irreparable.

Formation of enamel occurs in a set pattern. It begins at the occlusal surface and progresses toward the root. Mineral maturation occurs in the same sequence, but for each level it begins at the dentin–enamel junction and moves toward the ameloblast. Deleterious influences have their most severe affects on those ameloblasts that are forming and mineralizing enamel. Depending of the severity of the insult, ameloblasts may produce no enamel, a little enamel, or poorly mineralized enamel. Removal of the insult permits those ameloblasts not yet active to begin making normal enamel. Thus enamel defects vary in severity from isolated opaque spots or pits on the surface to deep and irregular, horizontal indentations. These defects are most clearly seen on the incisor teeth and canine teeth and are usually bilaterally symmetric. Similar lesions are also produced by infectious agents that injure ameloblasts, such as the viruses of canine distemper and bovine virus diarrhea (Fig. 1.2A,B).

Odontoblasts are susceptible to many of the same influences as ameloblasts, but they can be replenished from the undifferentiated cells of the dental pulp. Thus lesions in actively forming dentin may be repaired, while those in enamel are permanent.

Because of their close anatomic association with the jaws, teeth are very susceptible to disruption in the harmony of growth. This harmonious arrangement often is upset in the odontodystrophies and osteodystrophies and leads to malocclusion and anomalous development of teeth.

There are several nutritional and toxic conditions that produce odontodystrophy. Fluorine poisoning is exemplary (see metabolic diseases of bone, in Bones and Joints, Volume 1). In vitamin A deficiency, ameloblasts do not differentiate normally, and their organizing ability is disturbed. As a result, odontoblastic differentiation is abnormal. Several lesions develop, including enamel hypoplasia and hypomineralization, cellular, vascularized dentin (osteodentin), and retarded or obviated eruption.

Calcium deficiency retards eruption and causes enamel hypoplasia and mild dentin hypoplasia. Teeth formed during the period of deficiency are very susceptible to wear. Recovery from prolonged calcium deficiency results in malocclusion due to inferior prognathia in sheep. This reflects inadequate maxillary, but normal mandibular repair during the recovery phase.

Phosphorus deficiency, combined with vitamin D deficiency, depresses dentin formation slightly but has virtually no effect on enamel, at least not in sheep. Hypophosphatemia is associated with formation of interglobular dentin in humans. Malocclusion and abnormalities of bite in rachitic sheep are secondary to mandibular deformity.

Severe, experimental malnutrition also produces malocclusion. Recovery from malnutrition does not correct the lesion and in addition is associated with misshapen, malformed teeth, oligodontia, and polyodontia.

The major effects of odontodystrophies in herbivores are malocclusion and/or accelerated attrition. Sometimes a high incidence of these abnormalities is attributable to one of the causes discussed above, but often they are idiopathic. Most of the lesions described in experimental odontodystrophies also occur in natural diseases. A syndrome of dental abnormalities of sheep on the North Island of New Zealand is characterized by excessive wear of deciduous teeth, maleruption and excessive wear of permanent teeth, periodontal disease involving permanent teeth,

and development of dentigerous cysts involving permanent incisors. Mandibular osteopathy is also present. All animals more than 5 years old are culled for dental problems. The odontodystrophy (and osteodystrophy) possibly is caused by deficiencies of calcium and copper, and perhaps other nutrients such as protein and energy. Sheep from an affected flock, pastured elsewhere, have minimal lesions.

This syndrome exemplifies the naturally occurring odontodystrophies in that it probably has a complex pathogenesis and is associated with an osteodystrophy. The latter association is to be expected since bones and teeth usually are susceptible to the same insults.

### *Infectious and Inflammatory Diseases of Teeth and Periodontium*

The role of viruses in enamel hypoplasia is mentioned above. Bacterial plaque is discussed below along with other tooth-accumulated materials.

Tooth enamel is covered by a translucent pellicle, which is formed by selective adsorption of salivary constituents and which is essential to the development of plaque. **Dental plaque** is a dense, nonmineralized, bacterial mass, firmly adherent to tooth surfaces, that resists removal by salivary flow. Formation of plaque involves adhesion of bacteria to the pellicle and adhesion of bacteria to each other. Only organisms with the ability to adhere to pellicle can initiate the formation of plaque; those that cannot are removed by oral secretions and mechanical action.

The bacteria in plaque are usually Gram-positive. Most are streptococci and *Actinomyces* spp., which form an organized array on the tooth surface. Some plaque-forming bacteria synthesize extracellular polymers that constitute the matrix of the plaque and permit adhesion between organisms of the same species. Some utilize polymers derived from host secretions to adhere to the pellicle, while others attach to bacteria of a different species already fixed to the tooth. Plaque increases in mass with time, and its composition becomes more complex as Gram-negative bacteria join the streptococci and actinomycetes that initiated plaque formation.

Plaque is metabolically active. It utilizes dietary carbohydrates to produce the adhesive polymers and, as energy sources, for maintenance and the production of various enzymes and mediators of inflammation. Dental plaque is important because it initiates the development of dental caries and periodontal disease. Enamel may harbor extensive deposits of supragingival plaque that are virtually invisible unless treated with a disclosing solution.

**Dental calculus** (tartar) is mineralized plaque. The mineral mainly comes from saliva. In horses, it is predominantly calcium carbonate; in dogs, calcium phosphate. Calculus is often found in old dogs and cats, occasionally in horses and sheep, and rarely in other species. The distribution is often uneven, but it is most abundant next to the orifices of salivary ducts. Calculus on horses' teeth is chalky and easily removed. In dogs, it is hard, firmly attached, and often discolored. Red-brown to black calculus with a metallic sheen develops in pastured sheep and goats. It usually involves all the incisors, principally on the neck of the buccal surface. Minor amounts are common along the gum–tooth junction of the molar teeth, but occasionally, larger (up to 2.0 cm), hard, black, rounded concretions may protrude from between opposed surfaces of the premolars.

Materia alba is a mixture of salivary proteins, desquamated epithelial cells, disintegrating leukocytes, and bacteria that adheres to teeth. The bacteria are not organized, and materia alba is easily removed. It is distinct from dental plaque, and from food debris, which also accumulates between uncleaned teeth.

DENTAL CARIES. Dental caries is a disease of the hard tissues of teeth, characterized by demineralization of the inorganic part and enzymatic degradation of the organic matrix. This definition permits the inclusion of equine infundibular necrosis as a form of caries (see below).

Dental caries is the principal disease of teeth in humans up to about the age of 30 years. It is then superseded by periodontal disease. Caries is common in horses and sheep but rare in dogs and cats.

There are two types of caries, "pit" or "fissure" caries and smooth-surface caries. The first type develops in irregularities or indentations, usually on the occlusal surface of the tooth, which trap food and bacteria. Plaque is not essential for initiation of this form of caries, of which equine infundibular necrosis is an example. Smooth-surface caries usually occurs on proximal (adjacent) surfaces of teeth, typically just below contact points or around the neck, and requires dental plaque for its initiation.

The organic acids, principally lactic, that initiate demineralization are produced by bacterial fermentation of dietary carbohydrates. In smooth-surface caries, plaque produces the acid and maintains a low pH on the surface of the tooth. Progression of lesions depends on various factors such as salivary pH and hardness and resistance to demineralization of enamel. The enzymes that lyse the organic matrix probably are produced by plaque but may be derived from leukocytes, for which plaque is chemotactic. Carious enamel loses its sheen and becomes dull, white, and pocked. When dentin is exposed, it becomes brown or black. Dentin is softer and more readily demineralized than enamel, and a pinpoint lesion in enamel may lead to a large defect when the carious process reaches the dentin.

In horses and dogs, caries develops most often on the occlusal surface of the maxillary first molar. In sheep, the proximal surfaces of mandibular teeth are usually affected, and caries is commonly accompanied by periodontitis. Cats, whose teeth do not have retaining centers where food can collect, sometimes develop caries-like lesions of the neck region of cheek teeth. In some cases they are associated with hypervitaminosis A. These lesions seem to be distinct from conventional caries, but their pathogenesis is not known.

The enamel invaginations (infundibula) in the cheek teeth of horses normally are filled with cementum before the teeth erupt. Filling proceeds from the occlusal surface toward the apex, but often is not completed before eruption. At this time the blood supply is cut off, and ischemic necrosis of any residual cementogenic tissue in the infundibula occurs. The deficiency of cementum is called hypoplasia. Anterior infundibula are affected more frequently than posterior, and the first molar more often than other teeth (Fig. 1.2E,F).

Teeth with incompletely filled infundibula may accumulate food material and bacteria, and in some animals the necrotic area expands to involve all the cementum and the adjacent enamel

and dentin. Decay of the mineralized tissues sometimes progresses to coalescence of the cement lakes, fracture of the tooth, root abscess, and empyema of the paranasal sinuses. The incidence of infundibular necrosis increases with age, and 80–100% of horses more than 12 years old may have the lesion. Most are without signs, and in most the lesion does not progress. Inflammation of the dental pulp, in horses and in other species, may result from direct expansion of caries, or from penetration of bacteria and bacterial degradation products along the dentinal tubules. Production of reparative dentin in the pulp cavity is expected.

PULPITIS. The dental pulp is derived from the dental papilla. It is surrounded by odontoblasts and dentin, except at the apical foramen, through which vessels and nerves pass. Pulp is a loose syncytium of stellate fibrocytes and contains histiocytes and undifferentiated mesenchymal cells. The latter are odontoblastic precursors.

The apical foramen is narrow, and this predisposes to vascular occlusion, ischemic necrosis of the pulp, and death of the tooth in pathologic processes. Production of abundant secondary dentin and reparative dentin can do this, but the usual cause is inflammation. Pulp is the only vascular tissue of the tooth, and along with the periodontium, the only site of conventional inflammation. Pulpitis is always related to infection, the effector bacteria or their products entering through fractures; carious perforations, especially in teeth with enamel defects; perforations resulting from abnormal wear; periodontitis; and possibly hematogenously. In herbivores the pulp is divided by enamel foldings, inflammation usually is limited to one division and is usually purulent. Very mild pulpitis may heal, but usually it terminates in necrosis, suppuration, or gangrene.

Inflammation of the pulp may extend to the periodontium and the jaws. Osteomyelitis of the jaws is a complication of clipping the tusks of piglets. Some chronic inflammations are confined to the periodontium and become slowly expansive, spherical granulomas about the root apex (root granulomas). Occasionally these granulomas are enclosed by an epithelial cyst (periodontal cyst) derived from cell rests of Malassez. The epithelium contains plasma cells, and the combination may have a protective role in periapical sepsis.

PERIODONTAL DISEASE. Periodontal disease is the most common chronic disease of humans, the most common dental disease of sheep and dogs, and an important problem in horses, ruminants, and cats. Although there are minor differences between species, in general, periodontal disease begins as plaque-associated gingivitis and may progress through gingival recession and loss of alveolar bone to chronic periodontitis and exfoliation of teeth.

The gingival sulcus or crevice is an invagination formed by the gingiva as it joins with the tooth surface at the time of eruption. Clinically normal animals have a few lymphocytes, plasma cells, and macrophages under the crevicular epithelium of the gingiva, which forms the outer wall of the crevice, and under the junctional epithelium, which is apposed to the enamel of the tooth.

Clinical gingivitis usually is initiated by accumulation of plaque in the crevice, but may be associated with impaction of feed, especially seeds, between teeth. The gingivitis initially is characterized by increased leukocytes and fluid in the gingival crevice, then by acute exudative inflammation and accumulation of plasma cells, lymphocytes, macrophages, and neutrophils in the marginal gingiva. Marked loss of gingival collagen occurs in a few days due to the activity of enzymes from neutrophil lysosomes, or possibly from plaque. Grossly, the gingiva is red. Acute gingivitis may become quiescent, with lymphocyte aggregations beneath the junctional epithelium.

Continuation and exacerbations of the inflammation cause apical recession of the tooth–gingiva attachment, and resorption of alveolar bone. If gingival recession precedes bone loss, the sulcus is deepened to form a periodontal pocket, which is the site of chronic active inflammation (Fig. 1.2C). When gingival recession is accompanied by concomitant loss of alveolar bone and gingival collagen, pockets do not form. In either case, destruction of the periodontium and resorption of alveolar bone, cementum, and root dentin leads to exfoliation of teeth. In dogs, pocket formation is quite unpredictable and may be present on one root of a tooth and absent on the other. Gingivitis in dogs is unusually proliferative, the gingiva being replaced by collagen-poor, highly vascular granulation tissue, which appears as a red, rolled edge next to the tooth. Bone loss in dogs is often more severe at the bifurcation of two-rooted teeth than in interproximal areas. Resorption of bone is associated with osteitis as the inflammation extends from the periodontium into alveolar bone. In dogs, the premolars and, to a lesser extent, the first molars and central incisors are most severely affected, while the second molars and mandibular canines are quite resistant.

In sheep, periodontal disease may involve all teeth, but the effects are most severe on the incisors, and periodontal disease is a major cause of premature exfoliation. Sheep develop acute gingivitis during tooth eruption, in association with accumulation of subgingival plaque around the tooth. Chronic gingivitis ensues, and on farms with a high incidence of "broken mouth," this progresses to chronic active periodontal disease.

A major part of chronic periodontal disease is resorption of alveolar bone, which modifies the attachment site of the periodontal ligament. Evidence that periodontal disease in humans and other animals is primarily a nutritional disease, and that the bone resorption is caused by hyperparathyroidism, has been presented but is not generally accepted. It seems reasonable, however, that the less bone that is present when the disease is initiated, the more rapid the progression of this aspect of the disease.

The sequelae of suppurative periodontitis are many, being variations on a theme of osteomyelitis. The osteomyelitis frequently leads to the development of a fistula. If the mandible is involved, the fistula usually develops on the ventral margin. If the maxillary molars are involved, fistulation may occur into the maxillary sinus. If the premolars are involved, fistulation may develop into the nasal cavity or externally. In dogs, involvement of the canine teeth may produce internal or external fistulas, and involvement of the maxillary carnassials usually produces a fistula beneath the eye, and orbital inflammation. Fistulation may be prevented for some time or permanently by ossifying periostitis over the involved bone. Fistulas in the upper jaw tend

to be persistent. In the lower jaw, they may heal, usually with extensive deposition of new bone. Occasionally, especially in horses, chronic mild periodontitis may be confined by the periodontium, which is, however, expanded by granulation tissue to form a root granuloma. Under the same circumstances there may be hyperplastic exostosis of the cementum.

### *Diseases of the Buccal Cavity and Mucosa*

#### *Pigmentation*

Melanotic pigmentation is normal and common in most breeds of animals and increases with age. It may be irregular, or the mucosa may be entirely pigmented. Diffuse, yellow discoloration may be seen in icterus.

#### *Circulatory Disturbances*

Examination of the mucous membranes is an essential detail in any clinical or autopsy examination. Pallor may indicate anemia but is misleading in a cadaver. In cyanosis, the mucosa is a dark reddish blue color. The mucosae are muddy in methemoglobinemia. Congestion and edematous swelling of the tongue and buccal mucosa are specific lesions of bluetongue of sheep. An acute congestion and cyanosis associated with ulceration is common in dogs and sometimes in cats in chronic uremia. Hemorrhages are indicative of septicemia, and larger ones may accompany local inflammation, trauma, and the hemorrhagic diatheses. Petechiae on the ventral surface of the tongue and frenulum in horses are consistent with equine infectious anemia or other thrombocytopenic or purpuric conditions. The active hyperemia that gives the diffuse, pink coloration to the mucosa in diffuse stomatitis disappears immediately at death, so that at autopsy the inflamed mucosa is disappointingly blanched.

#### *Foreign Bodies in the Oral Cavity*

The presence of feed in the mouth of a cadaver is abnormal. In most cases it is attributable to disease that results in paralysis of deglutition or semiconsciousness. It is common in horses with encephalitis, leukoencephalomalacia, and hepatic encephalopathy. The food in such cases is usually poorly masticated and readily differentiated from that refluxed postmortem. Bones or other large foreign bodies lodged in the pharynx of cattle suggest pica of phosphorus deficiency. They may cause asphyxiation or pressure necrosis in the wall of the pharynx. Large portions of root crops may also lodge in the pharynx. In dogs, bones, sticks, or balls may be found. The bones and sticks tend to be wedged across the mouth behind the carnassial teeth. In this species, too, a foreign-body glossitis occurs, caused by plant fibers, burrs, or quills that become deeply embedded and provoke exuberant granulomas. These must be differentiated from neoplasms.

Sharp foreign bodies that cause laceration of the mucosa predispose to necrotic and deep stomatitis. Grass grains and awns frequently impact between the retracted gingival margin and teeth in periodontitis of ruminants and exacerbate the local initial lesion, perhaps predisposing to the development of osteomyelitis. Swine have a diverticulum of the pharynx in the posterior wall immediately above the esophagus, and barley awns and other rough plant fibers occasionally lodge here and penetrate the pharynx. This occurs mainly in young pigs, and death follows pharyngeal cellulitis. Similar problems occur in sheep, following improper use of drenching guns.

### *Inflammations of the Oral Cavity*

Inflammatory processes of the oral cavity may be diffuse (stomatitis) or localized predominantly in certain regions to produce, if the pharynx is involved, pharyngitis; the tongue, glossitis; the gums, gingivitis; the tonsils, tonsillitis (Fig. 1.1D); and the soft palate, angina. Lesions limited to the mucosa of the oral cavity are termed superficial stomatitides. Processes seated in connective tissues of the mouth, the deep stomatitides, are usually sequelae to transient superficial lesions.

#### *Superficial Stomatitis*

Inflammatory changes may be associated with ingestion of irritating chemicals such as caustic or toxic compounds. An example is paraquat, a herbicide, which may cause a severe erosive stomatitis in dogs. Electrical burns are occasionally seen in puppies or kittens that chew through electrical wires. It is often not possible to differentiate the cause of diffuse stomatitides, but an attempt to do so is important because it may indicate a systemic disease state. Viral diseases causing stomatitis will be considered in detail under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Inflammatory disease, localized to the buccal cavity and not part of systemic viral disease, is also common and important. It is generally due to the indigenous bacterial flora. The oral microbiota ordinarily contains many microbial species, mainly anaerobes, such as *Actinomyces, Fusobacterium,* and spirochetes, which exist in balance with each other and in harmony with the host. The oral mucosa is quite resistant to microbial invasion for several reasons. These include the squamous mucosal lining, antibacterial constituents of saliva (e.g., lysozyme), immunoglobulins (especially IgA) in oral secretions, and the presence of submucosal inflammatory cells. Factors altering the balance of indigenous organisms are not well delineated. Systemic illness, stress, and nutritional and hormonal imbalances may alter the microbial population by altering the amount, composition, and pH of saliva. The integrity of the oral epithelium depends on a high rate of epithelial regeneration to balance loss due to a high rate of abrasion and desquamation. Rapid epithelial replication promotes quick healing of superficial lesions.

The lamina propria of the oral epithelium is well vascularized, but generally dense and relatively inelastic. For this reason, there is little distention of lymphatics and tissue spaces with fluid exudate, and therefore, swelling due to edema is not a significant part of stomatitis involving gums and hard palate.

CATARRHAL STOMATITIS. Catarrhal stomatitis is a superficial inflammation of the oral mucosa that usually involves the posterior fauces and may be associated with mild gingivitis. It is a common nonspecific lesion that often develops in the course of debilitating diseases. The mucosae are hyperemic, and the loose texture of the submucosa in the fauces permits development of edema. The swelling is aggravated by edema and hyperplasia of the abundant lymphoid tissues of the soft palate, tonsil, and pharyngeal mucosa. The epithelium accumulates, producing a

dull, gray mucosal surface. There is excessive mucus production by palatine glands. Catarrhal stomatitis resolves with the return of normal oral function.

Thrush, or oral candidiasis, occurs most commonly in foals, pigs, and dogs. It involves the proliferation of yeasts and hyphae in the parakeratotic superficial layers of the oral epithelium. It appears grossly as patchy, pale pseudomembranous material on the oral mucosa and back of the tongue and probably reflects alterations in epithelial turnover and oral flora. It is considered more fully under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

VESICULAR STOMATITIDES. Stomatitis, characterized by the formation of vesicles, occurs in most species of domestic animals. The vesicles develop as accumulations of serous fluid within the epithelium or between the epithelium and the lamina propria. These may coalesce to form bullae, and the elevated epithelium is easily rubbed off during chewing to leave raw eroded patches with bits of epithelium still adherent. The transition from vesicle to erosion occurs rapidly so that in individual animals, vesicles may not be seen. This is especially so in dogs and cats because the oral mucosa is very thin. Because the basal epithelium or basement membrane remains intact, regeneration and healing are complete in a few days unless the local lesions are complicated by bacterial or mycotic infections. However, foci of previous erosion may be identifiable for some months by their slight depression and lack of pigmentation.

Vesicular stomatitides in animals have been associated with viral infections, and these are still the most common causes. In horses, cattle, and swine, oral vesicles should be regarded as indicating foot and mouth disease, vesicular stomatitis, swine vesicular disease, or vesicular exanthema until proven otherwise. These conditions are described in detail under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Since the early 1970s, the bullous immune skin diseases have been reported with increased frequency, especially in dogs, and some of these have severe oral lesions, which will be described in detail here; the reader is also referred to the Skin and Appendages (Volume 1).

**Pemphigus vulgaris** is a severe chronic, vesicular, bullous autoimmune disease. It is characterized by acantholysis of the epidermis, which results in formation of flaccid bullae and erosions involving mainly mucocutaneous junctions, oral mucosa, and to a lesser extent, skin. The disease is similar, if not identical, to pemphigus vulgaris in humans. Clinically, affected dogs and cats show excessive salivation, halitosis, and erosions and ulcerations of the oral mucosa. The oral lesions are generally more prominent than, and precede, the skin lesions. They are most obvious on the dorsal surface of the tongue, which is bright red with a few scattered pink raised areas representing islands of normal mucosa. The lesions vary greatly in severity and distribution, although the hard palate is often severely ulcerated. Bullae are rarely seen in the oral cavity because they ulcerate rapidly.

Microscopically, the earliest lesion consists of suprabasilar acantholysis, which is followed by the formation of clefts. These lead to ulceration of the mucosa. The basal cells of the epidermis remain attached to the basement membrane and form a so-called row of tombstones. A few neutrophils and eosinophils may infiltrate the epithelium. There is a variable lymphocytic and plasmacytic lichenoid reaction in the propria.

The presence of suprabasilar clefts and bullae due to acantholysis are considered to be diagnostic of pemphigus vulgaris. However, extensive erosion and ulceration of the mucosa and secondary bacterial infections frequently obscure these clefts and bullae. Several biopsies from different areas of the oral mucosa may be required to demonstrate the characteristic lesions. A presumptive histologic diagnosis should be supported by direct immunofluorescence tests showing autoantibodies (usually IgG) and complement in the intercellular spaces of stratified squamous epithelium.

**Bullous pemphigoid** is characterized by mucocutaneous, superficial vesicobullous or ulcerative disease of mucous membranes (including the oral mucosa) and skin. Clinically, the disease is often impossible to distinguish from pemphigus vulgaris. Bullous pemphigoid has been reported in humans and dogs. The characteristic microscopic lesions are subepidermal blisters, which may contain fibrinocellular exudate. Direct immunofluorescence of lesions shows autoantibody (IgG) and complement deposits along the basement membrane.

The oral lesions of pemphigus vulgaris and bullous pemphigoid must be differentiated from lesions due to trauma, toxic epidermal necrolysis, drug eruptions, chronic uremia, mucocutaneous candidiasis, and lymphoreticular malignancies, which are described in other sections of this chapter and with diseases of skin (in the Skin and Appendages, Volume 1).

**Feline calicivirus** belongs to the Picornaviridae and causes mainly a respiratory infection in cats. The disease is complicated by lingual and oropharyngeal ulcers, which start out as vesicles. They are 5–10 mm in diameter, smooth, and well demarcated from the surrounding normal mucosa. They occur mainly on the anterodorsal and lateral surfaces of the tongue and each side of the midline of the hard palate. The palatine lesions are apparently more severe in cats fed dry food. Microscopically, the earliest lesions consist of foci of pyknotic cells in the stratum corneum and superficial stratum spinosum. They progress to foci of necrosis with vesicle formation and subsequent erosion and ulceration of the mucosa. Regeneration of the oral mucosa in the ulcerated areas generally occurs within 10 to 12 days. A single layer of squamous epithelial cells extends from the margins of the ulcer beneath a layer of exudate. Active viral replication also takes place in the tonsillar crypt epithelial cells, and virus may be recovered from these areas for weeks postinfection. Inclusions have not been observed in oral epithelial cells.

EROSIVE AND ULCERATIVE STOMATITIDES. Erosive and ulcerative stomatitides are characterized by local epithelial defects of the oral mucosa and nasolabium and usually associated with acute diffuse stomatitis and pharyngitis. Erosions are circumscribed areas of loss of epithelium that leave the stratum germinativum and basement membrane more or less intact. They are usually associated with acute inflammation in the underlying propria. The erosions vary in size and shape, and although they are often a nonspecific development in a wide variety of condi-

tions, they are also an essential part of a number of important diseases. They heal cleanly and quickly, but if secondarily infected or complicated, may develop into ulcers.

Ulcers, in contrast to erosions, are deeper deficiencies that extend into the substantia propria. They too vary greatly in size and shape, the edges tend to be elevated and ragged, and when they heal it is with scar formation.

The causes of ulcerative stomatitis are in general those of erosive stomatitis. There are, however, a number of recognized syndromes and specific diseases in which the predominant change is ulcerative. Viral diseases causing erosive–ulcerative stomatitis in ungulates are described under Infectious and Parasitic Diseases of the Gastrointestinal Tract. Erosive–ulcerative conditions in other species are discussed below.

**Ulcerative stomatitis** and **glossitis** in **cats** is an ulcerative and chronic inflammation of the mucosa of the fauces, the angle of the jaws, and less commonly, the hard palate, gingiva, and tongue, occurring particularly in older cats. These lesions may comprise the largest group of feline oral clinical conditions. The cause is unknown but is probably multifactorial, involving imbalance in the oral microbial flora, with predominance of spirochetes.

**Eosinophilic ulcer** (eosinophilic granuloma, lick granuloma, labial ulcer, "rodent ulcer") is a chronic, superficial ulcerative lesion of the mucocutaneous junctions of the lips and to a lesser extent the oral mucosa and skin, in cats of all ages. The cause is unknown, but the lesions may respond to corticosteroid or radiation therapy, although recurrences are common.

Typically, well-demarcated, red-brown, shallow ulcers, often with elevated margins, occur on the upper lip on either side of the midline. They are usually a few millimeters wide and several centimeters long. Occasionally, ulcers are present elsewhere in the mouth, such as the gums, palate, pharynx, and tongue. Skin lesions are located in those areas that are frequently licked, such as the neck, lumbar area, and abdomen. Microscopically, eosinophilic ulcer is characterized by ulceration of the squamous mucosa, with large areas of necrosis of the underlying connective tissues, accompanied by a marked inflammatory cell reaction. The cellular reaction consists predominantly of neutrophils at the periphery of the ulcers, with a mainly mononuclear-cell reaction (plasma cells and mast cells) in the propria. Eosinophils and histiocytes may be seen occasionally. In our experience, the eosinophils and mast cells may predominate, but this difference may be only a reflection of the evolution of the lesion.

Eosinophilic ulcer is considered to be one of the three different types of lesion that have been associated with the so-called eosinophilic granuloma complex. The other two conditions, eosinophilic plaque and linear granuloma, cause mainly skin lesions, which are different clinically and morphologically from eosinophilic ulcer. The differences are discussed in the Skin and Appendages (Volume 1).

**Oral eosinophilic granuloma** (linear granuloma) in dogs occurs as a familial disease in young Siberian huskies. Affected dogs have single or multiple, firm, often ulcerated, raised plaques, which are covered by a yellow-brown exudate, on the lateral or ventral surfaces of the tongue. Lesions on the soft palate are less common, and there they tend to be oval to circular ulcers that have slightly elevated borders. Cytologic preparations made from scrapings of the oral lesions show many eosinophils, a few neutrophils, occasional macrophages, and epithelial cells.

Microscopically, the lesions are characterized by foci of collagen degeneration (necrobiosis), in the mid and deep zones of the lingual submucosa, surrounded by a granulomatous inflammatory reaction. The reaction consists mainly of histiocytes, including epithelioid macrophages, with fewer lymphocytes, plasma cells, and mast cells. Eosinophils are a constant feature, but their numbers vary from few to many. Multinucleated giant cells may also be present.

The lesions are identical to those seen in linear granuloma of cats. The cause is unknown, although the morphology of the lesion and the response to corticosteroid therapy are suggestive of hypersensitivity reaction. The familial tendency may indicate that hereditary factors are involved. Eosinophilic granuloma must be differentiated from oral mast-cell tumors, which also affect the tongue in dogs. Necrobiosis of collagen fibers is often a feature of mast-cell tumors; however, the characteristic mixture of mast cells and eosinophils infiltrate the tongue and connective tissues more diffusely. The mast cells may be in various stages of degranulation, and inflammation is minimal or absent in mast-cell tumors.

**Feline viral rhinotracheitis** is a common upper respiratory tract infection of cats caused by feline herpesvirus-1 (see the Respiratory System, this volume). This virus may cause ulcerative lesions in the mouth, especially on the tongue. Rarely, oral and skin ulcers may occur, without evidence of concurrent respiratory tract infection. Microscopic lesions are characterized by foci of cytoplasmic vacuolation in squamous epithelium that evolve into areas of necrosis and ulceration. The ulcers are often covered by a layer of fibrinocellular exudate. Herpetic inclusions may be present in epithelial cells at the periphery of the ulcers.

**Ulcerative stomatitis** in **uremia** occurs commonly in dogs and less commonly in cats; a fetid ulcerative stomatitis develops in the course of chronic renal disease. The buccal cavity, and especially the tongue, are deeply cyanotic. Dirty grayish brown ulcers occur on the gums, lateral surface and margin of the tongue (Fig. 1.3D), and inner surface of the lips and cheeks. The margins of the ulcers are swollen and hyperemic.

The pathogenesis of the oral lesions in uremia is still poorly understood. Urease-producing bacteria, normally present in the oral microflora, generate ammonia from salivary urea. Ammonia has a caustic effect on the oral mucous membranes. This may explain why the lesions are mainly located where salivary ducts enter the oral cavity. There is apparently a poor correlation between the levels of blood urea nitrogen and the development of uremic stomatitis, suggesting that other factors are involved in its pathogenesis.

**Ulcerative glossitis** and **stomatitis** in **swine** is commonly part of exudative epidermitis ("greasy-pig disease") of preweaning pigs (see bacterial diseases of skin, in the Skin and Appendages, Volume 1). In addition to the characteristic skin lesions, about a third of the piglets may develop ulcers on the

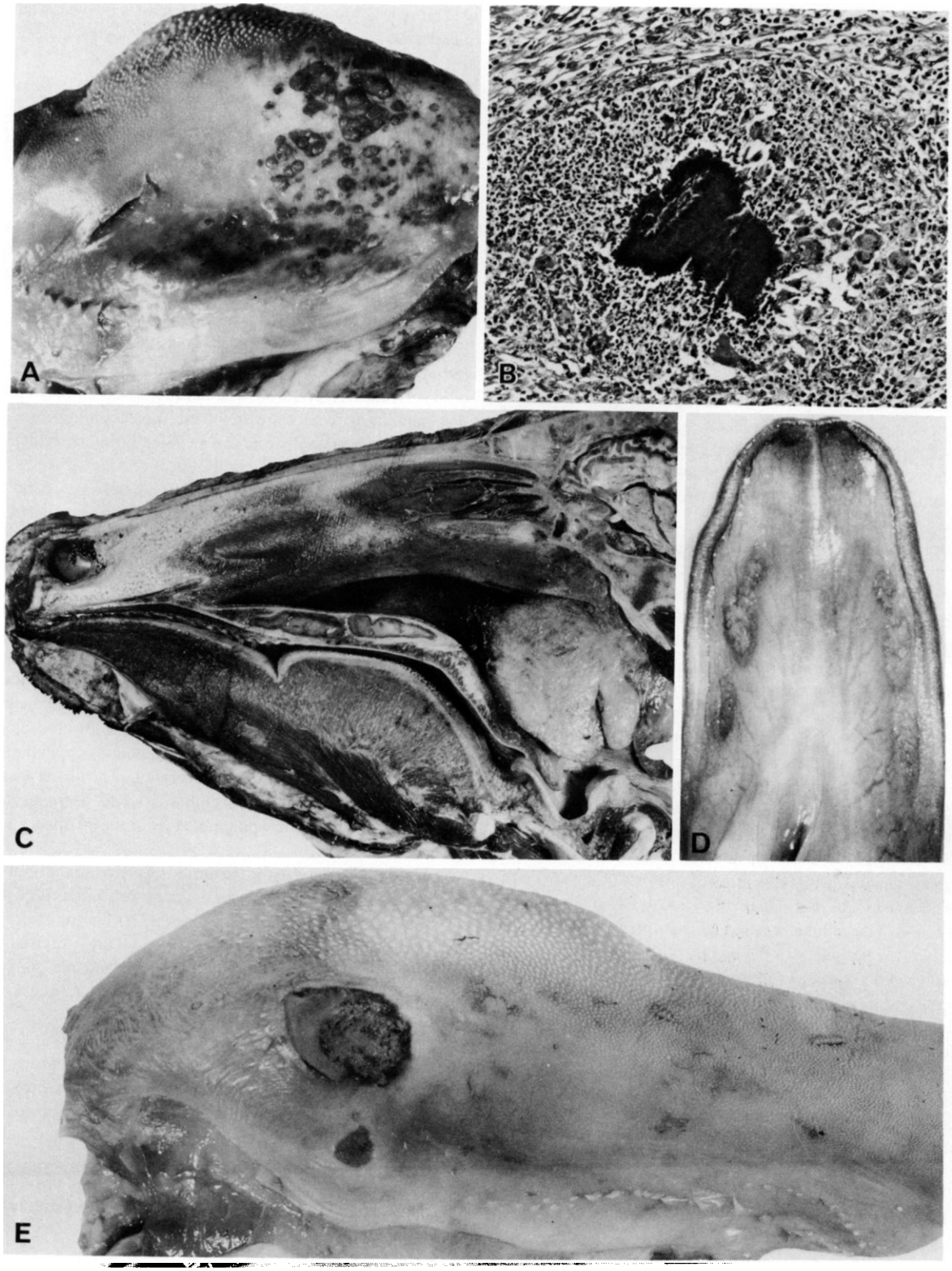


**Fig. 1.3.** (**A** and **B**) Actinobacillosis. Cow. (**A**) Granulomas bulging on lateral surface of tongue. (**B**) Pyogranulomatous focus containing club colony of *Actinobacillus lignieresi*. (**C**) Pharyngeal actinomycosis. Cow. Fleshy mass in pharynx, which resembles actinobacillosis. (**D**) Superficial necrotic lesions on the ventral aspect of the tongue. Dog with uremic stomatitis. (**E**) Oral necrobacillosis. Calf.

dorsum of the tongue. Erosions and ulcers of the hard palate occur in a small number of piglets. Microscopically, there is ulceration of the squamous mucosa with coagulation necrosis, and vesicle and pustule formation in the superficial epithelium of the rete pegs. A pleocellular inflammatory reaction is evident in the connective tissue below the ulcers.

### *Deep Stomatitides*

Lesions of the oral mucosa may permit the entry of pyogenic bacteria, often normal oral flora, into the connective tissues of the submucosa and muscle. Purulent inflammation or cellulitis may develop in the lips, tongue, cheek, soft palate, and pharynx. Abscesses may form and may fistulate through the mucosa or skin. Abscesses in the wall of the pharynx may result from necrosis of retropharyngeal lymph nodes. Necrotic stomatitis with simple necrosis of the epithelium and lamina propria may be produced by thermal or chemical agencies, but in animals, it is usually caused by *Fusobacterium necrophorum* and other anaerobes.

ORAL NECROBACILLOSIS. *Fusobacterium necrophorum* is the principal cause of necrotic stomatitis in animals. It is also associated with necrotizing lesions elsewhere in the upper and lower alimentary tract and liver. Wherever it occurs, it is usually a secondary invader following previous mucosal damage. The organism produces a variety of exo- and endotoxins, whose exact role in the pathogenesis of the lesions has yet to be determined. The exotoxins include leukocidins, hemolysins, and a cytoplasmic toxin, all of which probably enhance the necrotizing ability of the organism. Once established in a suitable focus, *F. necrophorum* proliferates, causing extensive coagulation necrosis.

The best known form of necrobacillary stomatitis is **calf diphtheria**, an acute necrotizing ulcerative inflammation of the buccal and pharyngeal mucosa. The predisposing lesions may include trauma, infectious bovine rhinotracheitis, and papular stomatitis. Necrosis of palatine and pharyngeal tonsils may be seen. The incidence of diphtheria in slaughtered beef cattle may be as high as 1.4%. The same syndrome is rather common in housed lambs as a complication of contagious ecthyma. The infection also may be initiated in the gums about erupting teeth in any species, and by the trauma produced in baby pigs by removing the needle teeth. It is frequently fatal in young animals, in which extension often occurs to other organs. In adults, oral necrobacillosis tends to remain localized to the oral cavity, where it may complicate vesicular and ulcerative stomatitides. It is not unusual, however, for the infection to spread down the alimentary tract. In the lower alimentary tract, the Peyer's patches especially are involved, perhaps as a complication of bovine virus diarrhea.

The early lesions are large, well-demarcated, yellowish gray, dry areas of necrosis, surrounded by a zone of hyperemia (Fig. 1.1C and 1.3E). They are found on the sides or dorsal groove of the tongue and on the cheeks, gums, palate, and pharynx, especially the recesses beside the larynx. Primary foci may occur in the laryngeal ventricles. Death may be associated with asphyxia. The necrotic tissue projects slightly above the normal surface and is friable but adherent and is not easily detached. In time it may slough and leave deep ulcers, which may heal by granulation. The necrotic tissues are histologically structureless and are surrounded at first by a zone of vascular reaction, later by a dense but narrow rim of leukocytes, and later still by thick, encapsulating granulation tissue. The bacteria are arranged in long filaments, particularly at the advancing edge of the lesions. The submucosal extension of the lesions may take them deeply into the underlying soft tissues and bone.

Spread from the oral foci occurs down the trachea (causing aspiration pneumonia), down the esophagus, and via blood vessels. Death may occur acutely in septicemia with only multiple small serosal hemorrhages as evidence, or metastases may occur in other tissue. Venous drainage from the face to the vascular sinuses of the meninges may lead to pituitary and cerebral abscessation.

More recently, *Fusobacterium necrophorum* has been associated with a syndrome of necrotic stomatitis, enteritis, and granulocytopenia in calves. Affected calves have a nonregenerative anemia, leukopenia, absolute neutropenia, hypoproteinemia, and increased fibrinogen levels. In addition to the characteristic oral lesions, there is marked depletion of lymphoid tissues and necrotic enteritis. *Fusobacterium*-like organisms are present in large numbers in a variety of organs, including the bone marrow. Possibly, very virulent strains of *F. necrophorum* produce enough leukotoxins, especially in immunodeficient calves, to suppress bone marrow activity.

A gross diagnosis of oral necrobacillosis is ordinarily possible but may be confirmed by a smear from the margin of the lesion. The organism is difficult to cultivate due to its strict anaerobiasis.

NOMA. Noma is a rapidly spreading pseudomembranous or gangrenous stomatitis; it is not caused by a specific pathogen but is associated with tissue invasion by the normal oral flora, particularly spirochetes and fusiforms. The predisposing factors are unknown, but they are probably nonspecific and associated with mucosal trauma and debility. The disease, which is observed occasionally in horses, dogs, and monkeys, is in many respects similar to oral necrobacillosis. In the lesions, the spirochetes can be found in large numbers at the advancing margins as well as in peripheral viable tissue. In the deep layers of necrosis, fusiforms predominate, and toward the surface there is a variety of other organisms, chiefly cocci.

The initial lesion is a small, tattered ulcer of the cheek or gum, which spreads rapidly and may involve much of the buccal surface of the gums and the mucosa of the cheek. It is intensely fetid and consists of a dirty necrotic pseudomembrane surrounded by a zone of acute inflammation. The necrotic tissue may slough to leave deep ulcers; the cheek may be perforated to leave a gaping defect, or gangrene may supervene.

ACTINOBACILLOSIS. Actinobacillosis is a deep stomatitis caused in cattle by *Actinobacillus lignieresi*, a member of the normal oral flora. When introduced into the submucosa it causes pyogranulomatous inflammatory foci centered on club colonies containing Gram-negative coccobacilli. Morphologically similar lesions may be caused by a variety of organisms (Fig. 1.3C). *Actinomyces bovis*, a Gram-positive filamentous organism,

causes pyogranulomatous mandibular and maxillary osteomyelitis in cattle (see inflammatory diseases of bones, in Bones and Joints, Volume 1) and mastitis in sows. Staphylococci may cause pyogranulomatous lesions (botryomycosis) in any species, especially mastitis in sows (see the Skin and Appendages, Volume 1, and the Female Genital System, Volume 3). Less common causes of similar microscopic lesions include *Nocardia* and the various agents associated with mycetomas (see the Skin and Appendages).

Actinobacillosis is typically a disease of soft tissue, spreading as a lymphangitis and usually involving the regional lymph nodes. This distinguishes it from actinomycosis, which causes bone lesions. The tongue is often involved in actinobacillosis, and the chronic condition produces clinical "wooden tongue."

Entry of actinobacilli to the tongue may be gained through traumatic erosions along its sides, but often the primary lesion is in the lingual groove. Here, trapped grass grains and awns may provoke the initial trauma. Lesions elsewhere in the soft tissue of the mouth may be attributed to disruption of the mucosa by similar types of insults and eruption of, or abrasion by, teeth.

Microscopically, the lesion is a pyogranuloma, centered on a mass of coccobacilli, surrounded by radiating eosinophilic "clubs," probably made up of immune complexes (Fig. 1.3B). The club colonies, in turn, are surrounded by variable numbers of neutrophils and are invested by macrophages or giant cells. Lymphocytic and plasmacytic infiltrates are present in the surrounding reactive fibrous stroma or granulation tissue. An individual inflammatory focus appears grossly as a nodular, firm, pale, fibrous mass a few millimeters to 1.0 cm in diameter, containing in the center minute yellow "sulfur granules," which are the club colonies.

Actinobacillosis causes a lymphangitis, and lymphogenous spread is common. Affected lymphatics are thickened, and nodules are distributed along their course. This distribution is best seen beneath the mucosa of the dorsum and the lateral surface of the tongue and can often be traced through to the pharyngeal lymphoid tissue (Fig. 1.3A). Some of these more superficial nodules erode the overlying epithelium, and coalescence may produce quite large ulcers. The most common form of lingual actinobacillosis consists of granulation tissue in which are embedded many small abscesses surrounded by a dense connective-tissue capsule. The epithelium overlying these large granulomas may be intact or ulcerated. Diffuse sclerosing actinobacillosis of the tongue (wooden tongue) is characterized by firmness, the result of extensive proliferation of connective tissue that replaces the muscle fibers. Granulomatous nodules are sparsely scattered in the fibrous stroma.

Although actinobacillosis in cattle is best known as a disease of the tongue, the infection may occur in any of the exposed soft tissues, especially those of mouth and neck; occasionally it involves the wall of the forestomachs, any portion of skin, and the lungs. Lesions in these sites resemble those described for the tongue.

Actinobacillosis causes regional lymphadenitis. The cut surface of the node reveals small, soft yellow or orange granulomatous masses that project somewhat above the capsular contour and contain "sulfur granules." There is also sclerosing inflammation of the surrounding tissues, which may cause adhesion to overlying skin or mucous membranes. The retropharyngeal and submaxillary nodes are most often affected, as well as the lymphoid tissues of the submucosa of the soft palate and pharynx. Involvement of the pharynx and the retropharyngeal lymph nodes may cause dyspnea and dysphagia.

Oral actinobacillosis in swine causes lesions similar to those in cattle, including glossitis. Actinobacillosis may also occur sporadically or as outbreaks in sheep, but in this species the tongue seems to be exempt. The characteristic lesions in sheep occur in the subcutaneous tissue of the head, especially of the cheeks, nose, lips, submaxillary and throat regions, and on the nasal turbinates. They may also occur on the soft palate and pharynx as complications of wounds received at drenching.

ORAL DERMATOPHILOSIS IN CATS. *Dermatophilus congolensis* is a bacterium that commonly causes an exudative dermatitis in a wide variety of species (see bacterial diseases of skin, in the Skin and Appendages, Volume 1). In cats, the organism is uncommonly associated with oral granulomas affecting especially the tongue and tonsillar crypt. Large numbers of Gram-positive, filamentous, branching organisms, with longitudinal and transverse divisions, may be demonstrated in the necrotic centers of submucosal granulomas. The organisms most likely enter through damaged mucosa. The lesion must be differentiated from the more common squamous-cell carcinomas of the tongue. In cattle, cutaneous streptothricosis involving the muzzle may extend into the oral cavity.

### *Parasitic Diseases of the Oral Cavity*

Parasitic disease of the oral cavity are of minor significance. Sarcosporidiosis and cysticercosis occur in the striated muscles of the tongue and produce the same lesions as they do elsewhere (see parasitic diseases of muscle, in Muscles and Tendons, Volume 1). *Trichinella spiralis* may be found in muscles of the tongue and mastication. *Gongylonema* spp. are found in the mucosal lining of the tongue, especially in swine allowed to graze, and less commonly in cattle and sheep. They evoke little or no inflammation of the mucosa, but a mild to moderate lymphocytic and eosinophilic reaction may be evident in the underlying lamina propria. The larvae of *Gasterophilus* spp. in the horse and of *Oestrus ovis* in sheep are found attached to the pharyngeal mucosa, where they may cause focal ulceration and excite mild inflammation. The larvae of *Gasterophilus nasalis* migrate from the lips and invade the gums around and between the teeth and behind the alveolar processes to cause small, suppurating pockets.

## Tonsils

The tonsils are normally prominent and protrude slightly from the tonsillar fossa in the dog and cat. In swine, tonsillar lymphoid tissue is concentrated in the posterior soft palate. In other species, the tonsils are diffuse. They are subject to the usual conditions of lymphoid tissue and undergo progressive atrophy with age.

By virtue of their function in immune surveillance in the oropharynx, tonsils are constantly exposed to antigenic stimuli.

As a result, they are a usual site of functional lymphoid hyperplasia and physiologic inflammation. Many bacteria native to the oropharyngeal mucosa probably inhabit the tonsillar crypts. A significant percentage of swine may carry *Erysipelothrix rhusiopathiae* and *Salmonella* spp. in the tonsils. They consequently may serve as portal of entry for a variety of bacterial agents, including *Streptococcus suis* and intracellular organisms, and for viruses that are lymphotropic.

Desquamated epithelium, bacteria, necrotic debris, and neutrophils may normally be present to moderate degree in tonsillar crypts. This reaction is exaggerated and may be associated with ulceration of the crypt and suppuration of involuted tonsillar lymphoid tissue, in certain bacterial infections, causing the formation of visible yellowish nodules. Conditions in which such bacterial tonsillitis may occur include pasteurellosis in sheep and pigs, and necrobacillosis in all species. In porcine anthrax, hemorrhagic necrotizing tonsillitis is reported.

Involution of B-dependent tonsillar lymphoid follicles due to viral lymphocytolysis may occur during the early phase of a number of lymphotropic diseases such as feline panleukopenia, canine parvovirus infection, canine distemper, bovine virus diarrhea, rinderpest, and swine vesicular disease. Numerous karyorrhexic nuclei, lymphocyte depletion, and prominent histiocytes signal such damage. In distemper, involuted tonsils are susceptible to secondary bacterial invasion and suppuration. Compensatory lymphoid hyperplasia may occur during the postviremic phase of parvoviral infections and distemper.

### *Neoplastic and Like Lesions of the Oral Cavity*

Many of the lumps, bumps, and cysts that develop in and around the oral cavity are malformations, hyperplasias, and neoplasias originating in tooth germs or teeth. The classification of these masses, especially those containing more than one tissue, is not established and must be arbitrary. Malformations of dental origin have been considered previously under Developmental Anomalies of Teeth. Gingival masses of all types, many of which are of tooth germ origin, are common in dogs and rarely occur in other species. The oral and pharyngeal mucosa is the fourth most common site of malignant tumors in the dog. It is also a common site of malignant tumors in cats; large domestic animals have a low prevalence of such tumors. When they do occur in ungulates, they usually are nonaggressive.

Regional geographic differences exist in the prevalence of certain oral tumors, especially in dogs and cattle. These differences may be related to types and levels of carcinogens in the environment and warrant further investigation from the point of view of comparative oncology.

The most common types of malignant oral tumors in dogs and cats are, in order of their frequency, squamous-cell carcinomas, malignant melanomas (in dogs only), and fibrosarcomas. They vary considerably in their behavior, depending on species and location. Dogs and cats 7 years of age or older are mainly affected. Typical clinical signs associated with these tumors are excessive salivation, halitosis, pain, dysphagia, loose teeth, oral bleeding, coughing, and a change in voice. All of these signs are determined by the location of the tumor. All malignant oral tumors in dogs and cats tend to follow a rapid course, and regardless of the type of malignancy, the prognosis is poor. Radiography and exfoliative cytology are useful diagnostic aids in concert with histopathologic examination.

ORAL PAPILLOMATOSIS. Oral papillomas, benign epithelial tumors ("warts") in dogs and cattle, are caused by papovaviruses. In dogs, they occur mainly in young animals, but older dogs in close contact may become infected. The virus is host and site specific. It can be transmitted only to the scarified oral mucosa and not to other mucous membranes. The incubation period is generally 1 month. Spontaneous recovery, followed by solid immunity usually occurs within 2 to 3 months. The warts first develop on the lips as single, smooth, papular elevations that are pale or the color of the mucosa. These lesions progress to multiple, proliferative, cauliflower-like, firm, white to gray growths (Fig. 1.4F). Similar lesions develop on the inside of the cheeks and on the tongue, palate, and walls of the pharynx. The gingiva are usually not affected. The esophagus may be involved.

The microscopic structure is typically papillomatous with a very thick squamous epithelium covering thin, branching, often pedunculated cores of proprial papillae. Individual or small groups of epithelial cells in the upper areas of the stratum spinosum undergo hydropic or acidophilic degeneration with loss of intercellular bridges. There is also marked acanthosis. Intranuclear basophilic inclusions may be found in the cells in the outer spinose layers.

Oral papillomas, due to bovine papillomavirus type 4, occur commonly in cattle. Their morphology and distribution are similar to the papillomas of dogs, and they are considered more fully under Neoplasia of the Esophagus and Forestomachs.

PYOGENIC GRANULOMAS. Pyogenic granuloma is a bright red or blue mass on the gums. It is composed of extremely vascular chronic granulation tissue and ulcerates and bleeds easily. Pyogenic granuloma is probably an exaggerated response to local irritation.

GINGIVAL HYPERTROPHY. Hypertrophy of the gums is common in dogs and is either generalized or localized to one or more teeth. When localized, it is a discrete tumor-like mass and, whether local or general, may cover part of the crown (Fig. 1.4A). Local enlargement is caused by chronic, probably painless, inflammation. It may be associated with periodontal disease.

Diffuse gingival hypertrophy is familial in boxer dogs, and a more severe overgrowth, termed hyperplastic gingivitis, occurs as a recessive inherited disease in Swedish silver foxes. In the foxes, both jaws are affected and the hypertrophy causes displacement and malalignment of teeth, eventually reaching such proportions that the mouth cannot be closed. Diffuse gingival hypertrophy sometimes is associated with prolonged anticonvulsant therapy in humans.

EPULIDES. Epulis is the generic and clinical term for tumor-like masses on the gingiva. By common usage, however, it refers to the epulides of periodontal origin that are so numerous in dogs and develop occasionally in cats.

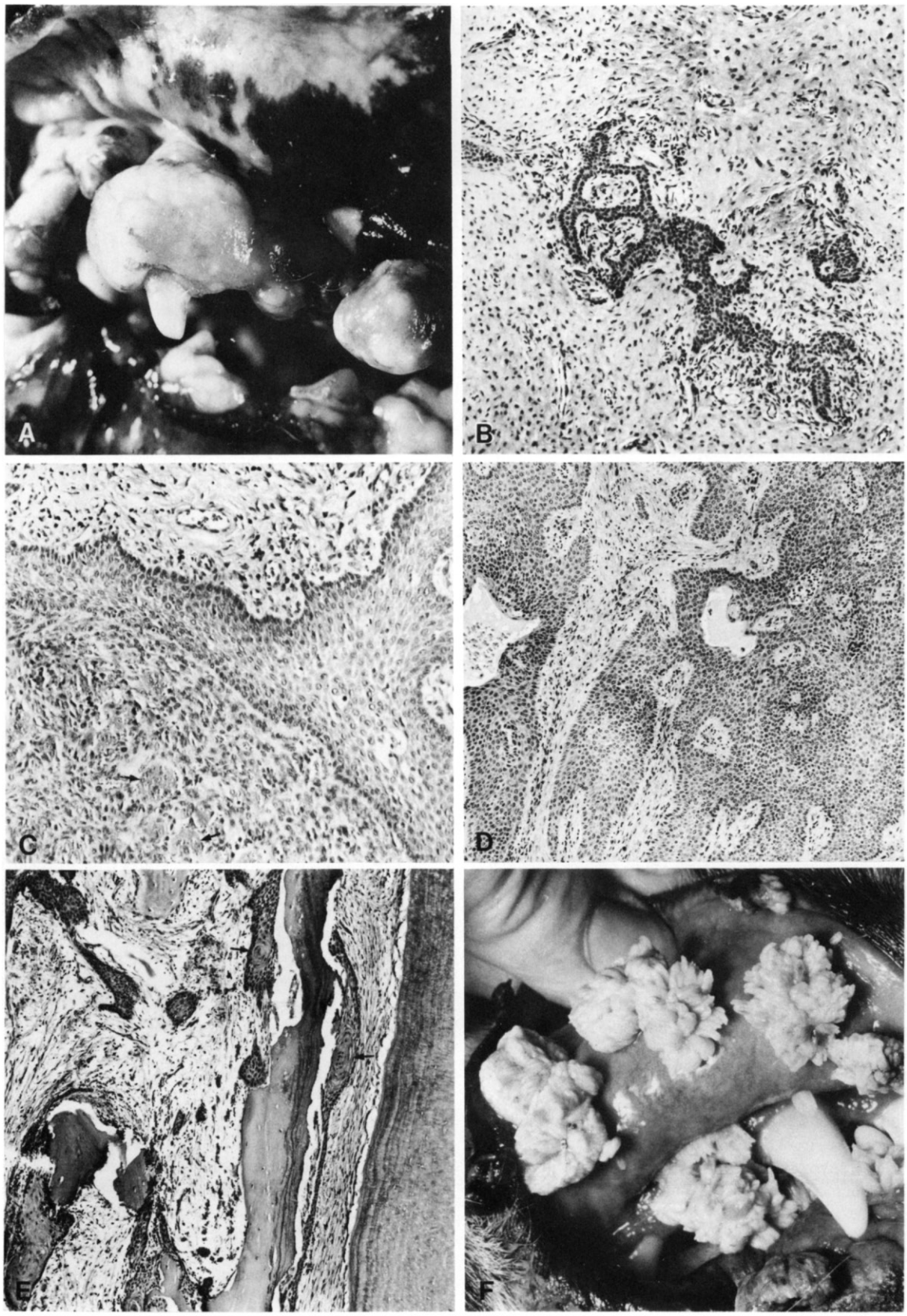


**Fig. 1.4.** (**A**) Epulis (gingival hypertrophy). Boxer dog. (**B**) Branching cords of epithelium in mesenchymal stroma. Epulis. Dog. (**C**) Acanthomatous epithelium in canine epulis with giant cells in stroma (arrows). (**D**) Acanthomatous epulis. Dog. (**E**) Acanthomatous epulis invading bone (arrows). Cementum (right), alveolar bone (center). (**F**) Oral papillomatosis. Dog. (Courtesy of W. R. Kelly.)

Epulides are firm to hard, gray-pink neoplasms, often projecting from between the teeth or from the hard palate near the teeth. They are most common around the carnassial and canine teeth of brachycephalic breeds (Fig. 1.4A). Often they are mushroom-shaped and have an irregular, smooth surface.

Epulides are stromal tumors, and the stromal tissue occasionally resembles periodontal membrane, comprising well-vascularized, interwoven bundles of cellular fibrous tissue; usually the stroma is mature, dense collagen. About 60% contain branching cords or islands of epithelium that usually are continuous with the gingiva. The epithelium is bordered by a row of cuboidal cells somewhat resembling odontogenic epithelium (Fig. 1.4B,C). Epulides sometimes are divided into fibromatous and ossifying types, depending on the abundance of hard tissue (osteoid, bone, cementum, etc.) that develops by stromal metaplasia in ~ 60% of affected dogs. There is no prognostic value in this distinction since these are all benign tumors that are cured by excision. Indeed, some authorities believe them to be hyperplasias.

Easily confused with these benign epulides is the epithelial tumor variously called oral adamantinoma and acanthomatous epulis. Clinically, these initially resemble epulis, but in many dogs recurrence and local invasion of alveolar bone (Fig. 1.4E) with loss of teeth follow conservative treatment. Histologically, the tumor is composed of sheets and anastomosing cords of epithelium bordered by a row of cuboidal to columnar cells. Prominent intercellular bridges are present between many of the central polyhedral cells. In some tumors there are intraepithelial cysts containing vacuolated, otherwise structureless, eosinophilic material and cellular debris (Fig. 1.4D). These cysts probably form from degenerate epithelium. Small areas of hard tissue may develop by metaplasia in the stroma between the epithelium.

Some of these neoplasms transform to squamous-cell carcinoma when they invade bone. Others have reported development of squamous-cell carcinoma at the site of irradiated acanthomatous epulis. The characteristic appearance of these tumors, and of the epithelial component of benign epulides, is probably a function of epithelial–mesenchymal interaction between tissues of dental origin.

The naming of these tumors is unsettled. "Adamantinoma" is an obsolete synonym for ameloblastoma and is therefore unsatisfactory. "Acanthomatous epulis" is morphologically more accurate for the superficial lesion and is used widely but does not disclose the behavioral characteristics of the tumor. Indeed, it is confusing, since epulis is widely recognized in veterinary medicine as a nonneoplastic or benign oral tumor. Nevertheless, until more of the invasive tumors have been studied and a suitable alternative established, "acanthomatous epulis" is likely to persist. Squamous-cell carcinoma, acanthomatous type, may prove to be more appropriate.

TUMORS OF DENTAL TISSUES. Tumors of dental tissues are classified as epithelial tumors, with or without inductive effects, and mesodermal tumors. The latter are very rare in animals. Some of the former are neoplasms, and others are probably malformations. Tooth development provides the classic example of epithelial–mesenchymal interactions, and it is generally accepted that inductive influences are active in certain mixed tumors. Familiarity with dental embryology assists an understanding of the origin, appearance, and classification of the tumors discussed below.

Most tumors of dental tissues are rare, nonmalignant, and infiltrative or expansive. Their location involves destruction of bone, however, and they are difficult to remove.

**Ameloblastoma** is an invasive tumor consisting of proliferating odontogenic epithelium in a fibrous stroma. The proportions of epithelium and stroma vary widely. *Ameloblastoma* is preferable to the synonyms adamantinoma and enameloblastoma. These tumors are more common in dogs and cattle than in cats and horses, and seem to occur more often in the mandible than the maxilla.

Ameloblastomas occur at any age and originate from the dental lamina, the outer enamel epithelium, the dental follicle around retained unerupted teeth, the oral epithelium, or odontogenic epithelium in extraoral locations. Because of their predominantly intraosseous location, they may destroy large amounts of bone and extend into the oral cavity or sinuses. Large tumors undergo central degeneration and become cystic.

The odontogenic epithelium, which is the criterion for diagnosis of ameloblastoma, may form any one of several patterns (Fig. 1.5D). Follicular and plexiform patterns are most common, consisting of discrete islands or irregular masses and strands of epithelium, respectively. Many tumors contain both patterns. In both, central masses of cells, often resembling the stellate reticulum of the enamel organ, but sometimes with an acanthomatous appearance, are surrounded by a single layer of cuboidal or columnar cells that resemble inner enamel epithelium. Cysts originate from degeneration of the centers of epithelial islands, or from stromal degeneration. Small cysts may coalesce to form gross cavities. Ameloblastomas occasionally undergo keratinization. In some there is stromal osteoid and bone. Stromal ossification may be an epithelial inductive effect.

**Ameloblastic fibroma** (fibroameloblastoma) is a rare tumor in calves and in the maxilla of young cats. It consists of cords of epithelium resembling dental lamina, intimately associated with spindle cells resembling dental pulp. It behaves like an ameloblastoma.

Ameloblastic fibroma corresponds to that stage of odontogenesis when dental epithelium invests the dental papilla but odontoblasts have not yet differentiated.

**Ameloblastic odontoma** (ameloblastic fibro-odontoma) resembles ameloblastic fibroma but contains dentin and enamel, and the epithelium is more typical of the enamel organ. It occurs in horses, cows, and dogs, often in immature animals.

**Complex** and **compound odontomas** are malformations in which all of the dental tissues are represented. In complex odontomas the tissues are disorganized, while in compound odontomas toothlike structures (denticles) are present, each one containing enamel, dentin, cementum, and pulp, arranged as in a normal tooth. Separation of the two may be arbitrary. Separate areas of ameloblastic epithelium are not present in complex and compound odontomas. A tumor that contains areas of ameloblastic epithelium and areas of complex or compound odontoma is an odontoameloblastoma.

Odontomas are usually located in the mandibular or maxillary

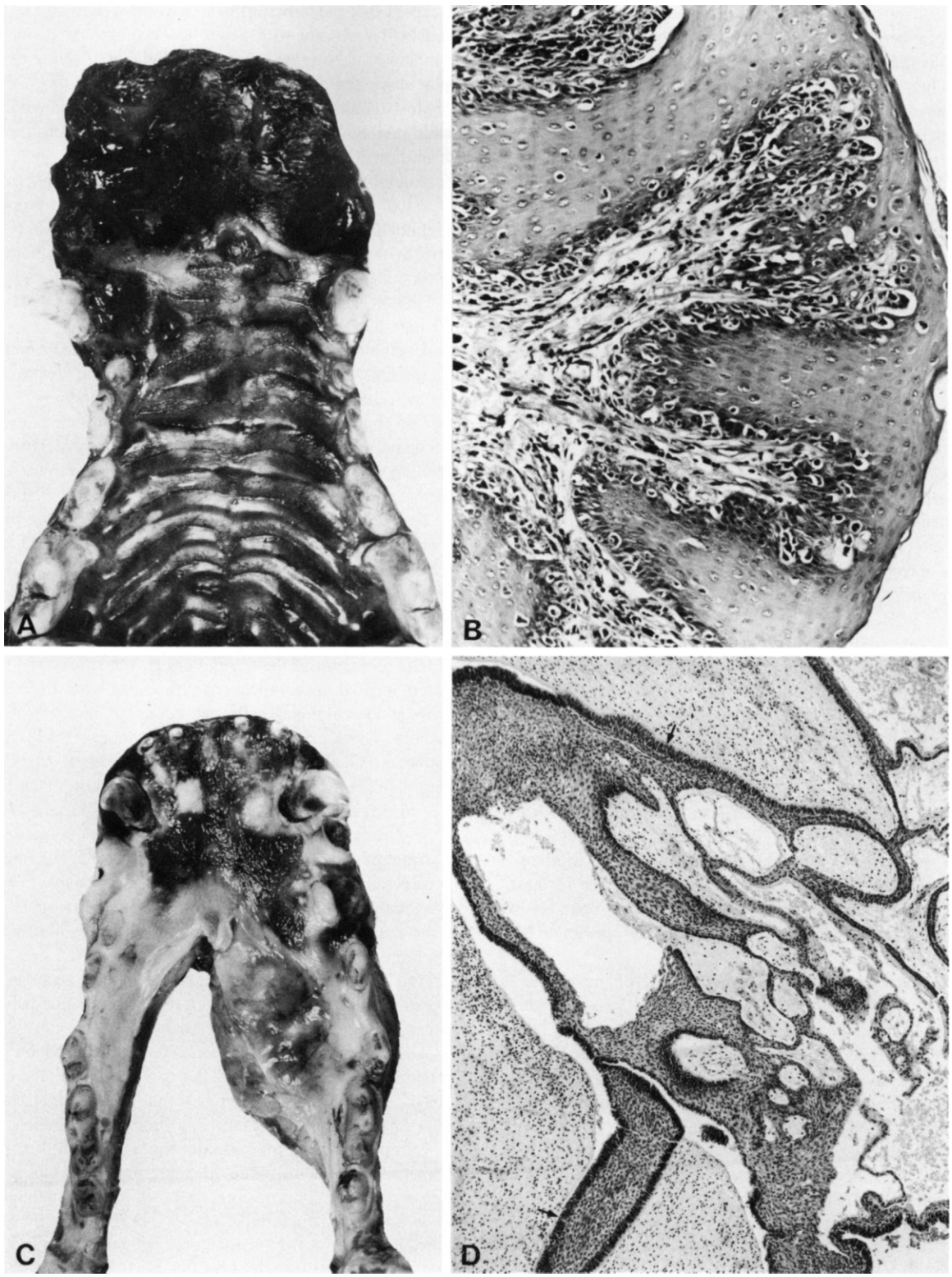


**Fig. 1.5.** (**A**) Malignant melanoma of palate. Dog. (**B**) Junctional activity in oral mucosa adjacent to melanoma. (**C**) Squamous carcinoma arising from alveolus of right canine tooth and invading mandible. Dog. (**D**) Ameloblastoma. Cow. Tall, enamel-type epithelium (arrows) and cyst formation.

arch and are less rare in cattle and horses than in other species. They are connected with existing dental alveoli and are detected when they bulge the contour of the host bone or interfere with other teeth. They may originate from normally or abnormally placed dental anlagen as well as from supernumerary dental anlagen.

SQUAMOUS-CELL CARCINOMA. Squamous-cell carcinoma is the most common oral malignancy of cats. It is most frequently located on the ventral lateral surface of the body of the tongue. The tonsils and gingiva are less common sites. Microscopically, the tumor is conventional in appearance. It is locally invasive and metastatic to regional lymph nodes and distant organs.

In the dog, this tumor is second to melanoma in prevalence in the oral cavity. It usually involves the tonsils, although the gingivae are common sites. Squamous-cell carcinoma is apparently more common in male than female dogs.

Grossly, tonsillar carcinoma usually appears unilateral. The earliest lesion appears as a small, slightly elevated, granular plaque on the mucosal surface. In the advanced stages, the affected tonsil is two to three times normal size, nodular, firm, and white, and the surface may be ulcerated. There is often extensive infiltration of the surrounding tissues. Histologic examination of the grossly unaffected tonsil frequently also shows early carcinoma. Squamous-cell carcinomas originating in the tongue and tonsils often metastasize to the regional nodes, with distant metastases to visceral organs, especially the lungs, in dogs. Tonsillar carcinoma must be differentiated from involvement of the tonsil in lymphosarcoma.

Gingival squamous-cell carcinomas may be associated with chronic periodontitis in dogs. It is not always clear whether they have predisposed to periodontitis or have resulted from chronic irritation of the gingiva. Their appearance is conventional, though often obscured by chronic active inflammation. They are most common about the incisor and canine teeth and are locally invasive, and may invade bone (Fig. 1.5C). However, they are less likely to metastasize than squamous-cell carcinoma of the tonsil. It is assumed that some originate in the gingiva and others in subgingival or periodontal epithelium (see also acanthomatous epulis, above).

In horses, squamous-cell carcinomas are rarely found on the gums and hard palate, possibly arising in chronically irritated hyperplastic alveolar epithelium in cases of chronic periodonitis. They are slow growing, exceedingly destructive, and metastatic only to the regional lymph nodes. Such tumors are large when first observed and may project from the palate or gums as grayish, extensively ulcerated masses, or appear as craterous ulcers. The large ones are extensively necrotic and putrid, and the teeth are lost or loosely embedded in the tumor. These tumors of the maxilla rapidly fill the adjacent sinuses and cause bulging of the face and may extend further into the nasal, orbital, and cranial cavities.

In cattle, oral squamous-cell carcinomas are very rare, with the exception of a few geographic foci where they are associated with oral papillomatosis and ingestion of bracken fern. A similar association is made in the etiology of squamous carcinomas of the esophagus and forestomachs in cattle and is considered more fully under Neoplasia of the Esophagus and Forestomachs.

MELANOMA. In contrast to cutaneous melanomas in the dog, which are usually benign, melanomas of the oral mucosa are almost always malignant. Melanomas are the most common malignant oral tumor in dogs. They are usually located on the gums, buccal mucosa, lips, and palate (Fig. 1.5A,B). The prevalence is higher in males than females. The degree of pigmentation of these tumors varies considerably, and there appears to be no relationship between the amount of pigment and biologic behavior, although the information supporting this last observation is quite controversial. They grow rapidly; necrosis and ulceration are common, and 70–90% metastasize to the regional lymph nodes, mainly the submandibular nodes. They may spread via hematogenous and lymphatic routes to more distant sites.

The histologic appearance of melanomas varies greatly from a fairly well differentiated, heavily pigmented type to a highly anaplastic amelanotic type. The diagnosis of the latter is often difficult. However, there are certain features that are evident in most of these tumors. Anaplastic melanocytes, which have large oval or elongated nuclei with distinct nucleoli and abundant cytoplasm, show junctional activity, infiltrating the junction between the basilar epithelial cells and the submucosa. Frequently there is a characteristic mixture of epithelial-like and spindle-shaped cells, which have a marked tendency to form nests extending deep into the submucosa. Multinucleated giant cells may also be present. About 75% of melanomas have melanin pigment, but detection of this pigment often requires careful examination of individual tumor cells.

Melanin, free and in macrophages, is often found in superficial areas of the submucosa in a variety of nonneoplastic lesions resulting from irritation to the mucosa. This so-called pigmentary incontinence must be differentiated from malignant melanoma.

Although cutaneous melanomas are common in horses and certain breeds of swine, these species have no tendency to develop oral melanomas. These tumors are also rare in cats.

FIBROSARCOMA. Fibrosarcoma is the most common sarcoma of the oral cavity in dogs. It occurs mainly on the gums of the upper molars and adjacent soft palate, and the anterior half of the lower mandible. Infiltration of maxillary and mandibular bone is common. It grows rapidly and frequently recurs after surgical removal. About 35% metastasize to regional nodes, and pulmonary metastases occur early in its course.

MAST-CELL TUMOR. Mast-cell tumor occurs occasionally in the oral cavity of the dog. It may be an extension of cutaneous tumors in the lip, or it may arise in submucosal areas, especially of the tongue. The tumor should be considered potentially malignant, with metastasis to regional lymph nodes a likely possibility. Mast-cell tumor should be considered in the differential diagnosis of oral lesions resembling granulation tissue or eosinophilic granuloma in dogs.

GRANULAR-CELL MYOBLASTOMA. Granular-cell myoblastoma, a rare tumor or tumor-like lesion probably of Schwann-cell origin, occurs mainly in the base of the tongue in the dog. It is

elevated, red, and granular or smooth on the mucosal surface. The cut surface is white and firm. Microscopically, the mass consists of large, polyhedral to round, epithelioid cells that have abundant acidophilic granular cytoplasm. The cytoplasmic granules are strongly periodic acid–Schiff (PAS) positive. The nuclei are round to oval, centrally located, and have one or two nucleoli. Mitotic figures are rare. The tumor cells have a marked tendency to form nests, which are separated by a delicate network of reticulin fibers. None of these tumors in dogs has recurred after excision, nor has any metastasized. Similar tumors occur in humans, where they are most common in the skin but may occur in a variety of organs.

## Salivary Glands

The most common affections of the salivary glands are functional, ptyalism being an increased secretion of saliva and aptyalism a reduced or ceased secretion. Ptyalism (to be differentiated from failure to swallow) is seen as abnormal accumulation of saliva in the mouth. It occurs in a variety of conditions, including heavy-metal poisoning, poisoning with organophosphates, encephalitis, and most often, stomatitis. Decreased secretion of saliva is less common but accompanies fever, dehydration, and salivary gland disease.

Ptyalism in cattle and horses may be an expression of a mycotoxicosis. *Rhizoctonia leguminicola,* which causes "black patch" disease of several legumes, is the offensive fungus. On well-cured legume hay, the mycelial growth is not visible grossly. The fungus has a wide geographic distribution. The toxic principle is a parasympathomimetic alkaloid called slaframine, which literally means "an amine that causes an animal to salivate." In addition to excessive salivation, other signs include anorexia, excessive lacrimation, diarrhea, frequent urination, and bloat. Milk production is reduced, and there is loss of body weight. No specific lesions have been associated with slaframine toxicosis. Guinea pigs are extremely sensitive to the toxin. Presumptive diagnosis may be based on feeding trials in that species, if chromatographic analysis for slaframine is not readily accessible.

**Foreign bodies** occasionally are present in the ducts, usually the parotid duct but sometimes the submaxillary. They are usually of plant origin, being awns or fiber. They invariably cause some degree of inflammation with secondary infection; if the duct epithelium is destroyed, a local cellulitis occurs. **Salivary calculi** (sialoliths) may also cause obstruction and inflammation. They are more common in horses than other species. Calculi are composed largely of calcium carbonate, possibly centered on a small foreign body and whitish, hard, and laminated. Calculi are usually single and cylindric, and they may be quite large. Most of them lodge at the orifice and cause some degree of salivary retention, glandular atrophy, and a predisposition to infection and further inflammation.

**Dilations** of the duct are due to stagnation of flow, and this in turn is a result of obstruction by foreign bodies, calculi, and inflammatory strictures. The dilated ducts appear as fluctuating cords, sometimes with local diverticula. Ranula is the term applied to a cystic distension of the duct in the floor of the mouth. These present as a smooth, rounded prominence with a bluish tinge and fluctuations. The contents may be serous or of thick, tenacious mucus. Rupture of a duct or a gland to an epithelial surface results in permanent fistulas as the continued flow of saliva prevents normal restoration, the duct epithelium fusing with that of the surface.

While ranula by definition is a dilation of a duct with its lining epithelium more or less intact, accumulation of salivary secretions in single or multiloculated cavities adjacent to ducts is now referred to as **salivary mucocele**. These cystic formations do not have an epithelial lining. Small mucoceles, seldom exceeding 0.5 cm in size, are occasionally observed on the side of the bovine tongue. Their origin is presumably from rupture of the fine tortuous ducts of the dorsal part of the sublingual gland.

Mucoceles in dogs are well known because they are large enough to be a surgical problem. They occur in dogs of any breed. There may be a history of an antecedent ranula-like swelling in the mouth. Many mucoceles are probably the result of trauma to the duct. They may be located anywhere, from the mandibular symphysis to the middle of the neck, the latter due to gravitational displacement. Most are ventrolateral, sometimes bilateral or midline, at the angle of the mandible. It appears that they arise most commonly from the sublingual salivary gland, either from individual units of the polystomatic portion or from the duct of the monostomatic portion. Zygomatic salivary mucoceles also occur, associated with local swelling and exophthalmos. Most mucoceles are subcutaneous and are up to 10 cm in diameter, the larger ones being pendulous. The wall is of soft, pliable connective tissue, well vascularized, with a glistening lining. The contents are brown and mucinous, becoming progressively inspissated and tenacious with time.

The histologic appearance of mucoceles varies greatly, apparently depending on the stage of development. Initially, the wall consists of an outer, highly vascularized layer of immature connective tissue and an inner zone of loosely arranged fibroblasts. A pleocellular inflammatory reaction is evident in the central area, which also contains much amorphous acidophilic or amphophilic debris. Collagenous connective tissue forms the wall in later stages. The inflammatory cells are mainly mononuclear, and plasma cells often predominate. The debris in the center becomes progressively more basophilic.

Cysts of other origins do occur in this region. Cysts of the thyroglossal duct are midline and distinguishable readily when they contain thyroid follicles. Cystic salivary adenomas are rare. Branchial cleft cysts may be located ventrolaterally, as are the salivary cysts, or dorsolaterally on the neck. Their distinction is probably valid when no demonstrable connection occurs with a salivary duct and a pseudostratified columnar or stratified squamous lining epithelium is present.

**Sialoadenitis**, inflammation of the salivary glands, is uncommon in animals though inflammation of the zygomatic gland in dogs is a cause of retrobulbar abscess. The infection usually gains entrance via the excretory duct, although the infection may be hematogenous or develops by local trauma. Inflammation of the duct results in its obstruction by exudate, desquamated epithelial cells, and mucus. Some of this may be expressed from the ductal orifice as pus; the orifice is usually acutely inflamed. Obstruction of the duct, whether partial or complete, produces secondary atrophic changes in the glands, although there is initial enlargement due to the combined effects of retained secretion and inflammation. The ducts throughout the gland dilate,

and leukocytes infiltrate the lumen and stroma. The acini undergo compression atrophy or swell and rupture from retained secretion. In acute infections this often leads to suppuration, and in chronic ones only remnants of atrophic epithelium remain in a mass of inflamed scar tissue.

Specific inflammations of the salivary glands in domestic animals are unusual, although sialoadenitis does occur in rabies and malignant catarrhal fever. In rabies there is often focal lysis of acinar cells, a mononuclear infiltration, and uncommonly, Negri bodies in the ganglionic neurons. The lesions of malignant catarrhal fever, also specific in type, are described under Infectious and Parasitic Diseases of the Gastrointestinal Tract. Probably the most common associations with sialoadenitis in animals are strangles in horses and distemper in dogs. It is suggested that mumps virus may infect dogs. Sialoadenitis also occurs in vitamin A deficiency in calves and pigs and in cattle poisoned with highly chlorinated naphthalenes. In these latter conditions, the inflammations, often purulent, are secondary to squamous metaplasia of the ducts, with stasis of flow and secondary infection; squamous metaplasia of interlobular ducts is an early and rather specific lesion of vitamin A deficiency.

**Neoplasms** of the salivary glands are rare in all species but have been reported in cattle, sheep, pigs, horses, and cats. Local invasion by tumors originating in adjacent tissue is more common than primary neoplasia. Only in dogs do salivary tumors occur often enough to permit a general statement. They may arise from either the major or the minor salivary glands, involvement of the major glands being twice as frequent; of these the most susceptible is the parotid. The tumors develop almost exclusively in aged animals; the majority grow rapidly, become fixed to the overlying skin, and are painful.

Salivary tumors have two main sites of origin within the gland: the ducts and the glandular tissue. In most cases, the histogenesis can be recognized, the duct neoplasms being papillomatous if benign, and carcinomas squamous or mucoepidermoid if malignant. Tumors arising in the glandular tissue are usually adenomatous. Their malignant potential may be manifest only by carcinomatous areas at the periphery of the neoplasm.

The histologic structure of salivary tumors in animals is as diverse as in humans, and the accepted classifications apply. The most frequent variety in dogs is of acinar-cell origin, and although there are various structural patterns, an acinar arrangement is usually evident. This arrangement is emphasized by the common occurrence of pseudocystic dissolution, in which tumor cells with clear vesicular cytoplasm rupture, the secretion forming cystlike spaces. Mixed tumors, comparable to those of the mammary gland, occur. The mesenchymal component probably originates from myoepithelial cells. It is similar to that in mammary tumors, with areas of myoepithelial cells embedded in a mucinous matrix that also contains neoplastic epithelial cells. Bone and cartilage form in these areas.

## Esophagus

The esophagus merits particular attention during the examination of animals with inadequate growth rate, cachexia, ptyalism, dysphagia, regurgitation, vomition, and aspiration pneumonia. In the ruminant, tympany may be a sequel to esophageal disease. The presence of a "bloat line" in the esophagus at the thoracic inlet may indicate a condition causing increased intraabdominal pressure, such as gastric dilatation or ruminal tympany. The squamous mucosa is frequently eroded or ulcerated in viral diseases, with similar lesions elsewhere in the upper alimentary tract. Conditions of striated muscle such as nutritional myodegeneration and eosinophilic myositis will occur in the esophageal muscle of the ruminant.

### *Anomalies, Epithelial Metaplasia, and Similar Lesions*

Congenital anomalies of the esophagus are very rarely recorded, and their interpretation as such can be difficult, since some similar defects may develop as sequelae of esophageal trauma or inflammation.

Rare **segmental aplasia** of the proximal esophagus may be apparent in the neonate. A short, blind pouch communicates with the pharynx, and a thin, fibrous band connects it to the distal patent limb of the esophagus, which follows a normal course to the stomach. Esophageal aplasia and congenital esophagorespiratory communications result from anomalies occurring when the respiratory primordium buds from the embryonic foregut. **Esophagorespiratory fistulas** without esophageal atresia are more commonly recognized in animals, and in calves and dogs strong circumstantial evidence suggests that some of these are congenital. Short, fibrous bands with a narrow, mucosa-lined lumen connecting an esophagus of normal diameter with trachea or bronchus are reported, as are small apertures connecting the lining of esophageal diverticula with the respiratory tree. The lining of such defects changes from stratified squamous to columnar respiratory epithelium in the fistula or wall of the diverticulum. Gastric distention by air in calves, and pneumonia due to aspiration, have been associated with esophagorespiratory fistulas.

The diagnosis of esophagorespiratory fistulas and diverticula as congenital anomalies is best based on recognition early in life, since both may be acquired following esophageal obstruction. Gradual-pressure necrosis caused by an intraluminal mass and adhesion of esophagus to underlying trachea, or lung, with development of a fistula into the adjacent airway, creates the acquired communication. This may be lined eventually by epithelium of esophageal or respiratory origin.

**Esophageal diverticula** are irregular outpouchings or herniations of the esophageal mucosa through the muscularis, with a thin, fibrous wall. They communicate with the esophagus by variously sized, often slitlike apertures. Most are probably acquired. Increased intraluminal pressure associated with foreign bodies, obstruction, or stenosis is considered the cause of "pulsion" diverticula, in which the mucosa is forced out through the distended or ruptured muscularis. Such diverticula may be large in the horse and dog, where they are most common. Traction diverticulum is the result of maturation of a periesophageal fibrous adhesion, following perforation and inflammation, drawing with it a pouch of esophageal mucosa that is usually small and inconsequential. Ingesta and foreign bodies may accumulate in diverticula, causing gradual enlargement, with the potential for local esophagitis, ulceration, and perforation or fistula formation.

Rare **anomalies** of the **mucosa** include epithelial inclusion cysts, the presence of papillae resembling those of the rumen in the distal esophagus of cattle, and gastric heterotopia. The presence of gastric glands of the cardiac mucous type in the distal esophagus of dogs and cats is uncommon, and whether it is a developmental anomaly or a metaplastic response to mucosal injury, perhaps gastric reflux, is unclear. Hyperkeratosis and thickening of the epithelium may be signs of vitamin A deficiency or chlorinated naphthalene toxicity. Squamous metaplasia in the ducts of submucosal esophageal mucous glands and in ducts and glands elsewhere should be sought. Mild hyperkeratosis may be difficult to assess since in herbivores some degree of keratinization may be normal, and anorexia or failure to swallow results in loss of the abrasive effect of food passage, with accumulation of keratinized squames. Parakeratotic thickening and basal hyperplasia of the epithelium should be considered indicative of response to epithelial injury, and in the distal esophagus of pigs it is a concomitant of ulceration of the pars esophagea of the stomach. Parakeratosis of the esophagus occurs in pigs with cutaneous parakeratosis of zinc deficiency.

### *Esophagitis*

Erosive and ulcerative esophagitis is a common finding associated with viral diseases causing similar lesions in the oropharynx or reticulorumen. Bovine virus diarrhea, rinderpest, and malignant catarrhal fever tend to produce longitudinal epithelial defects in cattle; bovine papular stomatitis, infectious bovine rhinotracheitis, the herpesviruses of small ruminants and calicivirus in cats may on occasion produce focal necrotizing esophageal lesions, which tend to be punctate or round, perhaps with a raised periphery. Healing focal esophageal ulcers repair by granulation. Local epithelial proliferation and thickening produce an opaque, pearly appearance of the edge of the lesion or surface of the scar.

Caustic or irritant chemicals, ionizing radiation, or hot ingesta may cause mucosal injury, the severity of which depends on the nature of the insult and duration of exposure. Mild acute insult may result in diffuse or local reddening of the mucosa. Deep sloughing of the mucosa, liquefactive necrosis associated with alkalis, and coagulation necrosis following acid and toxins such as paraquat reflect more severe insult and may result in ulceration extending to deeper layers of the esophagus. Superficial epithelial damage heals uneventfully, though repeated insult may cause thickening of the epithelium, with the development of prominent rete pegs. Ulcerated mucosa will granulate, and raised islands of surviving pearly proliferative epithelium may be present over the surface. The inflammatory reaction in ulceration frequently involves muscularis and adventitia. The ultimate development of a contracted fibrous scar causes stricture or stenosis if the original mucosal defect involved a significant portion of the esophageal circumference.

**Reflux esophagitis** results from the action on the esophageal mucosa of gastric acid, pepsin, probably regurgitated bile salts, and possibly pancreatic enzymes. Stratified squamous epithelium appears more susceptible to the corrosive effects of gastric secretion than other types of mucosa in the lower gastrointestinal tract. Relatively short duration of exposure to refluxed gastric content is required to induce epithelial damage, signaled by hyperemia or linear erosions and ulcers, perhaps with superficial fibrinonecrotic debris, and erythematous margins. Such damage is most common in the distal esophagus but may extend well forward, in some instances to the esophageal origin. The expected microscopic basal epithelial activation, rete-peg elongation, and epithelial transmigration of neutrophils occur in response to mild superficial epithelial necrosis. A thinned epithelium following recent moderate insult or granulation of an ulcerated surface may be evident. Reepithelialization with a columnar mucous cell type may occur in distal esophagus adjacent to the cardia. Papillomatous esophagitis of unknown etiology has been reported in the distal esophagus of the cat, which normally has a somewhat corrugated mucosa.

Functional integrity of the lower esophageal sphincter may be compromised or overwhelmed by airway occlusion and increased intraabdominal pressure, the pharmacologic effects of preanesthetic agents, or abnormality of the hiatus. Reflux esophagitis is thus most common in dogs and cats as a sequel to surgery involving general anesthesia, though it may follow chronic gastric regurgitation or vomition for any cause (Fig. 1.6D). In swine and horses, it may be associated with ulceration of the squamous esophageal portion of the stomach (Fig. 1.6E). In dogs, it is associated with rare hiatus herniation. Hiatus hernia usually involves sliding herniation of all or part of the abdominal esophagus, cardia, and stomach into the thoracic esophagus, rather than periesophageal herniation. It is usually self-reducing and associated with lower esophageal sphincter failure and reflux rather than gastric herniation and obstruction. Gastroesophageal intussusception is a very rare event, most reported in puppies of large breeds of dogs, and may be associated with congenital megaesophagus. The entire stomach everts into the esophagus, and occasionally the spleen and pancreas may be involved.

**Thrush**, or mycotic esophagitis caused by *Candida albicans*, is seen in piglets and weaner swine, where the lesions may involve squamous mucosa of the entire upper alimentary canal. The condition is probably secondary to other intercurrent problems, including antibiotic therapy, inanition, and possibly esophageal gastric reflux and is considered more fully under Mycotic Diseases of the Gastrointestinal Tract. Similarly, secondary zygomycotic granulomatous involvement of the esophagus is a rarely recorded complication of debilitating systemic disease states and heavy use of glucocorticoids and antibiotics.

### *Esophageal Obstruction, Stenosis, and Perforation*

"Choke," obstruction, or impaction of the esophagus occurs when large or inadequately chewed and lubricated foods such as beets, potatoes, corncobs, apples, bones, or masses of grain or fibrous ingesta lodge in the lumen of the esophagus (Fig. 1.6C). Sites of lodgment are often where the esophagus deviates or is slightly restricted normally, and include the area over the larynx, the thoracic inlet, at the base of the heart, and immediately anterior to the diaphragmatic hiatus. Complications of obstruction include pressure necrosis and ulceration of the mucosa, which may progress to perforation. Usually, fatal cellulitis of the

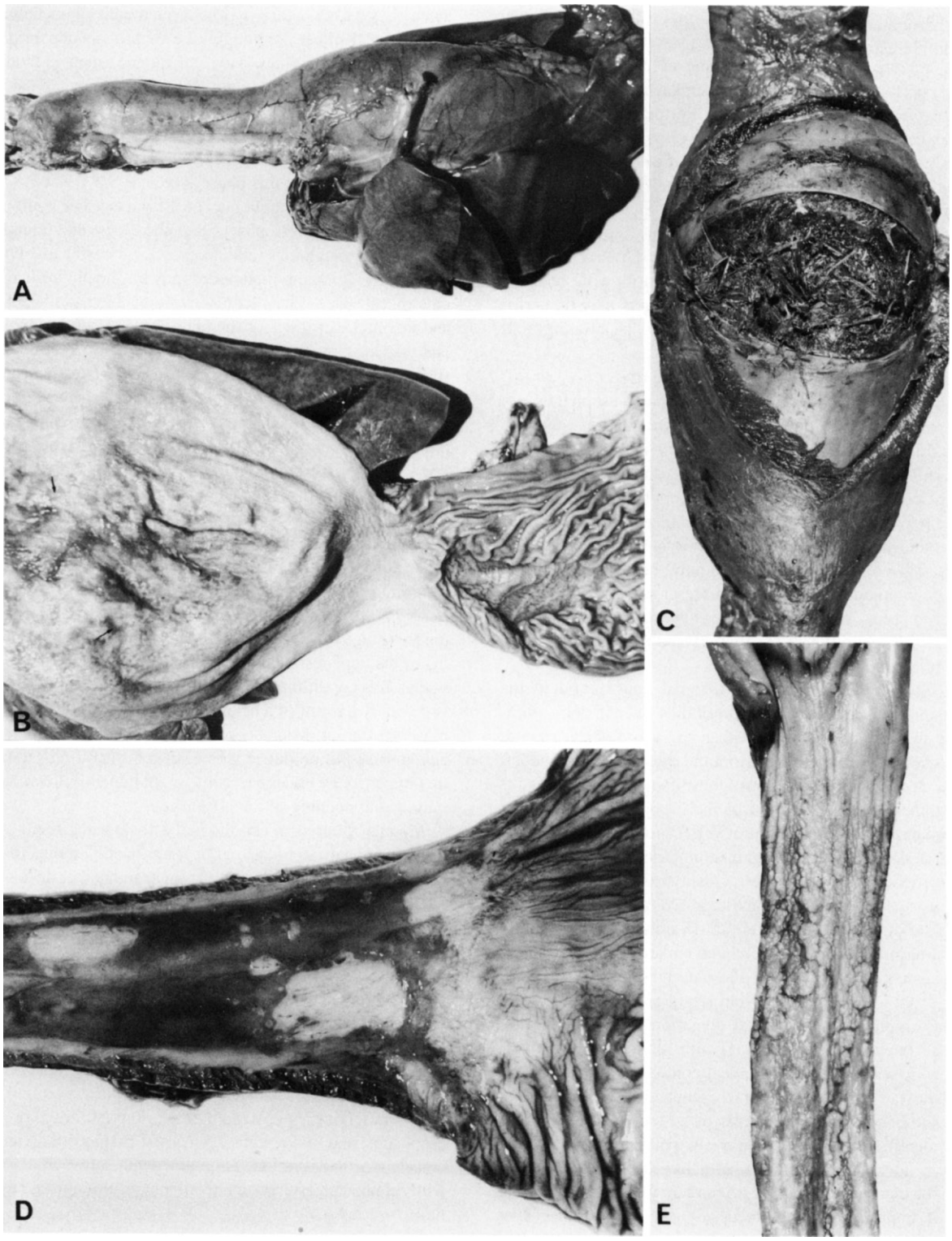


**Fig. 1.6.** (**A**) Megaesophagus. Dog. Congenital esophageal dilatation. Thoracic esophagus is particularly distended. (**B**) Congenital esophageal dilatation. Dog. Mucosal erosions (arrows). Capacity of distal esophagus exceeds that of stomach. (**C**) Impaction of esophagus with rupture of muscularis. Horse. (**D**) Reflux esophagitis following chronic vomition. Dog. Islands of squamous epithelium remain, surrounded by ulcerated mucosa. (**E**) Reflux esophagitis associated with esophagogastric ulceration. Pig.

periesophageal tissue ensues, which may involve the mediastinum directly or by extension along fascial planes from the cervical region, depending on the site of perforation. Alternatively, perforation of the thoracic esophagus may lead to sepsis of the pleural space, and pleuritis. Perforations of the pharyngoesophageal diverticulum above the cricoid cartilage, due to injuries caused by administration of medication by balling or drenching guns, or by passage of a stomach tube, probang, or endoscope may have similar consequences. Sharp objects, such as needles, quills, grass grains (seeds), awns, etc., may penetrate and track from the esophagus. Diverticulum or esophagorespiratory fistula may also ensue following obstruction by foreign bodies. The cervical esophagus may be perforated by sharp objects such as wire or needles, penetrating from the external surface of the skin.

Removal or dissolution of an obstructing object may be followed by scarring of the segmentally ulcerated esophagus, resulting in a narrowing of the lumen, stricture or stenosis. Esophagitis, especially due to gastric reflux, may have a similar sequel. Although hypertrophy of internal and external muscle layers is seen occasionally in the distal esophagus of cattle and horses (in which species the distal esophageal muscle is normally somewhat thickened), obstruction is not apparent. Stenosis may also result from rare intramural or intraluminal neoplasia, or commonly by external compression. Among causes of external compression may be enlarged hyperplastic or neoplastic thyroids, and neoplasia of the thymus and cervical and mediastinal lymph nodes.

The most common causes of external constriction of the esophagus are "**vascular ring**" **anomalies**, seen in dogs, occasionally in cats, and rarely in other species. Dextraaorta, or development of the aortic arch from the right instead of the left fourth arch, is the most common of these anomalies. This results in entrapment and constriction of the esophagus between the heart and pulmonary artery ventrally, the anomalous right-sided aortic arch dorsally, and the ligamentum arteriosum or remnant of the ductus arteriosus on the left. Other vascular anomalies that may constrict the esophagus, and reported only in the dog, are persistence of both right and left aortic arches; persistent right ductus arteriosus; aberrant left subclavian artery, in association with persistent right aortic arch; aberrant right subclavian artery, arising distal to the left subclavian artery and passing dorsally over the esophagus. Esophageal deviation and stenosis have been associated in English bulldogs with "thoracic shortening" due to hemivertebra and esophageal compression between the left subclavian artery and the brachiocephalic artery.

The site of stricture, with its narrowed esophageal lumen, is readily identified at autopsy. Constricting mural fibrosis or other causative internal or external obstructive lesions will be obvious. The mucosa at the site of stricture may be ulcerated, as the result of impaction of ingesta or as a sequel to antecedent esophagitis, pressure necrosis, or neoplasia. The esophagus anterior to the stenotic area is dilated, may contain retained ingesta, and itself may have evidence of esophagitis.

### *Dysphagia*

Dysphagia, or disorder of swallowing, is a major sign of esophageal disease. Swallowing is a complex and highly coordinated physical act, which may be conveniently divided into three phases. **Oral-phase dysphagias** are the product of painful physical lesions of the oral cavity and tongue, such as stomatitis, glossitis, gingivitis, or lesions that limit movement of the tongue or delivery of the bolus to the pharynx. Loss of hypoglossal nerve function associated with hydrocephalus, trauma, or myasthenia gravis impairs lingual function. Cleft palate results in nasal regurgitation at this phase.

**Pharyngeal dysphagia** may be associated with painful pharyngitis, tonsillitis, retropharyngeal abscesses, and granulomas. Abscesses, granulomas, and neoplastic processes involving the tonsils and regional lymph nodes may physically intrude on the pharyngeal space. Encephalitis involving the medulla oblongata and the nuclei or tracts of the major cranial nerves involved in pharyngeal contraction and lingual function (V, IX, X, XII) should be sought in pharyngeal dysphagia, unexplained on physical grounds. Rabies and brain abscess in all species, infectious bovine rhinotracheitis, and listeriosis in cattle are candidate central causes of pharyngeal paralysis. Retropharyngeal abscesses and lesions of the equine guttural pouch may cause peripheral nerve damage and paralysis. Idiopathic myodegeneration and myasthenia gravis have been reported as causes of impaired pharyngeal muscle function. Bluetongue and Ibaraki disease cause necrosis of lingual, pharyngeal, and esophageal muscle, resulting in dysphagia and aspiration of ingesta.

**Cricoesophageal incoordination** or **achalasia** may impede the first stage of the esophageal phase of swallowing, the opening of the upper esophageal sphincter to accept the approaching bolus. This condition is recognized in the dog, but not the cat. It is probably a result of a neurologic rather than local physical or muscular deficit. Microscopic examination of the cricopharyngeal muscle has produced inconsistent observations, though either hypertrophy or degeneration might impede relaxation of the muscle and opening of the esophagus.

**Megaesophagus** or **esophageal ectasia** is the result of atony of the esophageal muscle, flaccidity, and luminal dilatation (Fig. 1.6A,B). This is the product of segmental or diffuse motor dysfunction of the body of the esophagus. This results in failure of peristaltic propulsion of the food bolus to, and through, the lower esophageal sphincter, or high-pressure zone, to the stomach. Ingesta accumulates in the esophageal lumen, with eventual regurgitation of undigested food. Retention of some ingesta in the esophagus may lead to putrefaction and esophagitis in dilated or dependent areas. The volume of the dilated thoracic and cervical esophagus may greatly exceed that of the stomach, and the intrathoracic trachea and heart may be displaced ventrally. Animals presenting with esophageal hypomotility or megaesophagus may have signs of marked malnutrition, including emaciation, dehydration, and osteopenia, often in association with rhinitis and aspiration pneumonia resulting from regurgitation.

**Idiopathic megaesophagus** is a relatively common congenital disease in dogs. It is considered to be a neuromuscular developmental disorder or immaturity, which may improve functionally to some extent with time. Megaesophagus in this manifestation is not secondary to physical obstruction or failure to open by the lower esophageal sphincter. Hence it is not comparable to esophageal achalasia in humans. No consistent reduction in number of ganglia in the esophageal myenteric plexus has

been recognized. The functional defect in the dog has no basis in the vagal dorsal motor nucleus, since the external muscle layers of the entire esophagus are striated and are innervated directly by fibers arising from lower motor neurons in the nucleus ambiguus. These fibers are not parasympathetic, despite being carried in the vagus nerve. The striated esophageal muscle does not show consistent signs of neurogenic atrophy in idiopathic megaesophagus, and vagal stimulation causes contraction. Hence it is inferred that the lower motor unit is intact. The functional lesion may reside in the upper motor neurons of the central swallowing center or in the afferent sensory arm of the reflex controlling peristalsis, which arises in the esophagus. The pathogenesis of the lesion in megaesophagus in unknown.

Congenital idiopathic megaesophagus in dogs has its highest prevalence in Great Danes, followed by German shepherds, and Irish setters. The condition appears to be heritable, with a pattern in miniature schnauzers compatible with a simple autosomal dominant, or a 60% penetrance autosomal recessive mode of inheritance. Analagous idiopathic functional and morphologic defects may also develop in mature dogs. In addition, megaesophagus in older dogs may be secondary to myasthenia gravis, hypoadrenocorticism, canine giant axonal neuropathy, immune-mediated polymyositis and systemic lupus erythematosus, and Chagas' disease.

Megaesophagus in the cat may be congenital, with signs appearing about weaning time, and is associated particularly with Siamese breeding. The pathogenesis is unclear. Since the esophageal muscle of the cat is smooth in the distal half , dependent on the myenteric plexus for motor control and the vagus for coordination of peristalsis, the pathogenesis probably differs from that in the dog. One report associates megaesophagus in cats with functional pyloric stenosis. Neuronal degeneration or denervation atrophy of muscles are not recognized in the esophageal wall.

Several foals have been reported with esophageal dilatation or ectasia, apparently congenital. Dilation of the anterior portion, with a normal or thickened caudal thoracic esophagus, was found in two cases. Examination of the wall, which is smooth muscle in the caudal half, revealed equivocal muscle abnormalities, and no anomalies of the autonomic ganglia.

### *Parasitic Diseases of the Esophagus*

**Sarcosporidiasis** occurs in the striated esophageal muscle of sheep. Esophageal sarcocysts appear as ovoid, white, thin-walled nodules ~1.0 cm long projecting from the esophageal muscle (Fig. 1.7A). The species producing large esophageal cysts and similar large cysts in skeletal muscle is spread by cats, where gametogony and sporogony occur in the lamina propria of the small intestine. Other species of microscopic sarcocysts also may be encountered in esophageal striated muscle. Sarcocysts in esophageal muscle normally incite little or no local inflammatory reaction and are of significance only in meat inspection, though lesions of eosinophilic myositis, possibly associated with rupture of cysts, are found in the esophageal muscle.

Larvae of *Gasterophilus* may be temporarily attached to the caudal pharyngeal and cranial esophageal mucosa, and to the mucosa cranial to the cardia, in horses. Insignificant focal ulceration may occur at the sites of attachment.

The larvae of the warble fly (*Hypoderma lineatum*) migrate to the dermis of the back following a period of residence in the submucosa or adventitia of the bovine esophagus. The easily overlooked translucent larvae may be only 2–4 mm in length, but they instigate local hemorrhage and neutrophil infiltration. *Hypoderma* assumes significance in a small proportion of animals treated with systemic organophosphate insecticides while larvae reside in the esophageal wall. An acute inflammatory reaction, probably an allergic response to products of dead larvae, develops in the esophageal submucosa. This leads to swelling, hemorrhage, and necrosis, causing usually fatal esophageal obstruction, tympany, and esophageal perforation.

Spirurid nematodes of the genus *Gongylonema* may be encountered in the stratified squamous mucosa of the upper alimentary tract, including the esophagus, in ruminants and swine. White, threadlike worms up to 10 to 15 cm long, they burrow in the epithelium, and occasionally the propria of the esophageal wall. They usually produce white or red, blood-filled zigzag tracks in the mucosa (Fig. 1.7B). Their presence is inconsequential to the host.

*Spirocera lupi* is a spirurid nematode that parasitizes the esophageal wall of Canidae and some other carnivores. It is most common in warm climatic zones where appropriate species of dung beetles are found to act as intermediate hosts and where the opportunity for dogs to obtain access to larvae in vertebrate transport hosts is high. The normal site for the adult nematode is in large, thick-walled cystic granulomas in the submucosa of the caudal portion of the esophagus, where one or more pink worms surrounded by purulent exudate are found (Fig. 1.7C,D). A fistulous tract to the esophageal lumen is usually present, through which the tail of the female worm may protrude, and which provides the outlet for ova to the gastrointestinal tract. Third-stage larvae, ingested with dung beetles or encysted in the insectivorous transport hosts, penetrate the gastric mucosa and migrate along arteries to the aorta. Here they migrate, often subintimally, forward to the caudal thoracic area, which they attain within several weeks of infection. Following 2–4 months in an inflammatory granuloma in the aortic adventitia, worms migrate to the subjacent esophagus, where they develop to adulthood in the submucosa and perforate the epithelium. Larvae that adopt aberrant migratory pathways may be found in granulomas in sites such as the subcutis, bladder, and kidney as well as stomach and intrathoracic locations.

Aortic lesions associated with *Spirocerca* are detailed under diseases of the Cardiovascular System (Volume 3) but include subintimal and medial hemorrhage and necrosis with eosinophilic inflammation, intimal roughening with thrombosis, aneurysm with rare aortic rupture, and subintimal and medial mineralization and heterotopic bone deposition. The presence of persistent aortic lesions in the dog, even in the absence of esophageal granuloma, is evidence for prior infection with *S. lupi*. Spondylosis of the ventral aspects of thoracic vertebral bodies 5–10 occurs in some cases. Exostoses or bony spurs arise from one or both ends of the vertebral bodies and presumably are instigated by the local irritant effects of migrating worms.

In some animals with *Spirocerca lupi*, mesenchymal neoplasms develop in the wall of the esophageal granuloma (Fig. 1.7E), and there is a report of a pulmonary fibrosarcoma associated with an ectopic worm. The granulomas around *Spirocerca*

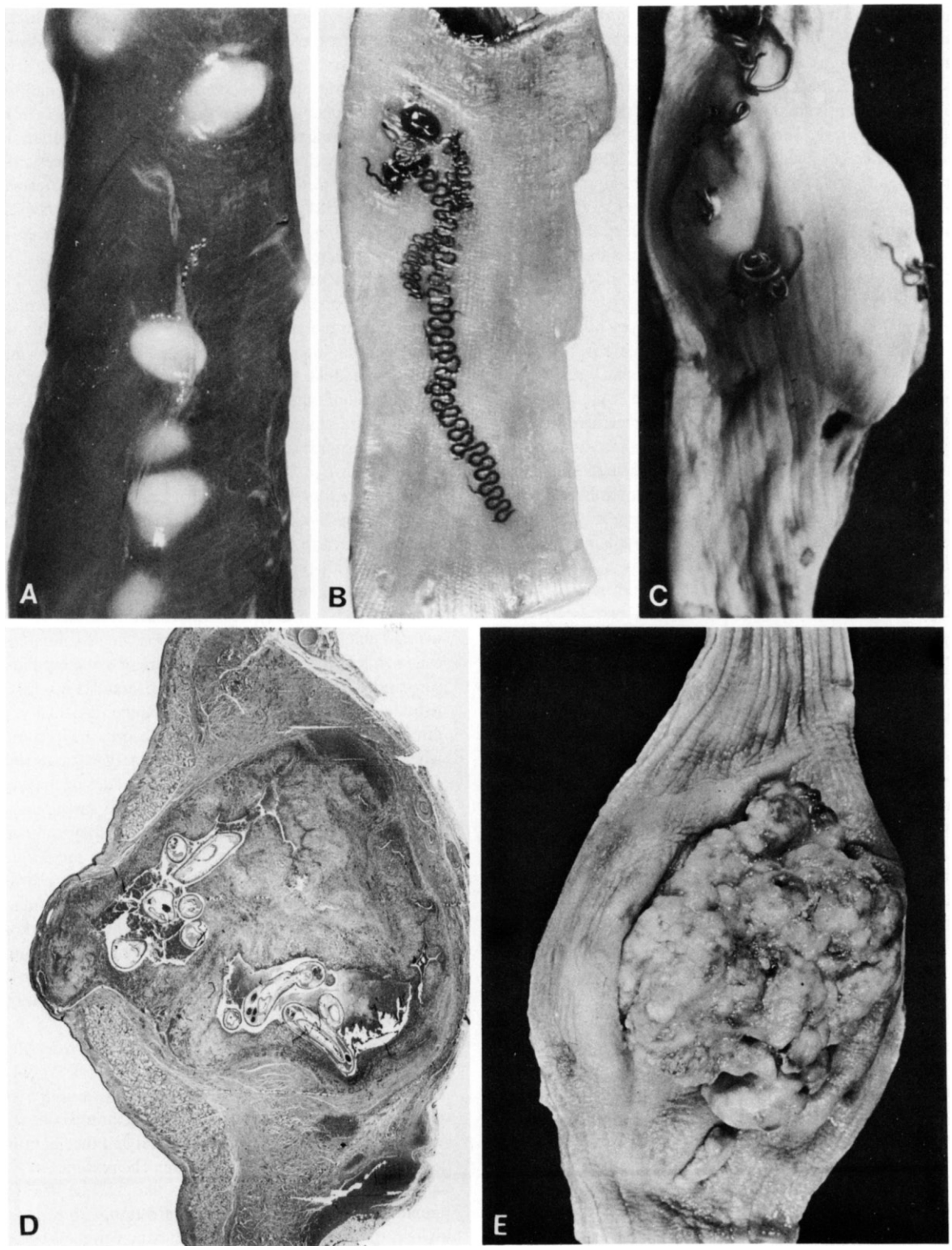


**Fig. 1.7.** (**A**) Cysts of *Sarcocystis* sp. in esophageal muscle. Sheep. (**B**) Blood-filled tracks and small hematoma in esophageal mucosa. *Gongylonema pulchrum*. Cow. (**C**) *Spirocerca lupi* nodules in distal esophagus. Dog. Worms protrude through fistulas into esophageal lumen. (Courtesy of R. G. Thomson.) (**D**) Section through esophageal nodule containing *Spirocerca lupi*. Dog. (**E**) Ulcerating fibrosarcoma associated with *Spirocerca* granuloma. Distal esophagus. Dog. (Courtesy of R. G. Thomson.)

contain highly reactive pleomorphic fibroblasts with large, open nuclei and numerous mitotic figures. Neoplasms arising from such lesions have cytologic characteristics typical of fibrosarcoma and osteosarcoma with local tissue invasion and, in many cases, pulmonary metastasis. The carcinogenic stimuli associated with the development of these tumors are unknown. Hypertrophic pulmonary osteopathy is a concomitant lesion found in animals with *Spirocerca*-associated sarcoma and, rarely, granuloma. Clinical disease, exclusive of that associated with neoplasia, is uncommon in animals with *S. lupi* and is restricted to aortic thrombosis, aneurysmal rupture, or occasionally, partial esophageal obstruction.

## Forestomachs

The importance of closely examining the rumen contents is often overlooked during routine autopsy. The first, and sometimes only, indication of the presence of certain toxic substances may be provided by the odor and appearance of the rumen content. Urea toxicity may be indicated by an ammoniacal odor and alkaline pH. Organophosphates have a characteristic pungent insecticidal smell reminiscent of cooked turnip. *Taxus* toxicity is signified by an aromatic odor like cedar oil, and the presence of needles in the ingesta. In other suspected plant poisonings, characteristic foliage should be sought in rumen contents. The presence of paint flakes, pieces of metallic lead, and oily content and odor (from used crankcase oil) point to lead poisoning. Frothy voluminous rumen content will support a diagnosis of primary tympany. Porridge-like content with a fermentative odor and perhaps acid pH (<5.0) suggests grain overload.

### *Dystrophic Changes in the Ruminal Mucosa*

The ruminal papillae in the newborn are rudimentary, which gives the mucosa a relatively smooth and pale appearance. Subsequent development of the ruminal papillae depends mainly on the type of diet fed. Little or no growth of papillae occurs in animals as long as they are fed milk. Animals on rations containing adequate levels of roughage develop long, slender, regular, white to gray, ruminal papillae. The ruminal pillars normally lack papillae. Microscopically, the normal papilli are covered by a thin layer of keratinized squamous epithelial cells.

Rations high in concentrate give rise to black, club- and tongue-shaped papillae that have a tendency to form clumps, nodules, and rosettes. They are distributed over the entire mucosa, except for a small area in the dorsal sac where the gas cap would be located. The most prominent changes are mainly in the atrium ruminis and ventral caudal sac, depending somewhat on the age of the animal and the type of concentrate. Microscopically, there is marked acanthosis, hyper- and parakeratosis, and hyperpigmentation of the papillary epithelial cells. Hyperplasia of secondary papillae is also prominent, which may explain the formation of clumps and rosettes seen grossly. The wall is thickened due to fibroplasia of the lamina propria and submucosa. Rumens in animals fed barley rations have similar changes. In addition, animal and vegetable hairs, from the rachillas of barley, adhere to the mucosa, especially in the interpapillary areas, giving it a distinct matted appearance (Fig. 1.8F). Large numbers of hairs are seen in sections of the mucosa. They penetrate the mucosa and lamina propria, where they evoke a leukocytic inflammatory reaction, often causing microabscesses. A diffuse pleocellular reaction is evident in the thickened fibrotic wall.

The pathogenesis of morphologic variations in the ruminal papillae depends on several factors. These include the level, type, and proportion of volatile fatty acids evolved in the ruminal contents, the pH, and the proportion and coarseness of the roughage fed. Other factors are probably involved. High concentrate rations result in increased levels of propionic and butyric acids and lower concentrations of acetic acid. The pH is also lowered, but not enough to cause chemical rumenitis. Hyper- and parakeratosis do not occur when ruminants are fed rations containing adequate levels (~15%) of coarse roughage. The dystrophic changes in the mucosa are reversible when high concentrates are replaced by such levels of roughage. Such a change in the ratio of roughage to concentrate in the diet results in a rise in pH and a shift in the proportions of fatty acids; acetic acid levels increase, and propionic and butyric acids decrease. Roughage is also thought to remove keratinaceous debris and food particles from the mucosal surface. The animal and vegetable hairs in barley rations may provide the portal of entry for bacteria that cause the mild rumenitis and microabscesses in the ruminal wall. Hyperkeratosis of the ruminal epithelium also occurs in calves deficient in vitamin A.

### *Postmortem Change*

The ruminal mucosa usually sloughs within a few hours after death. It separates from the lamina propria in large gray patches, which cover the ingesta when the rumen is opened.

Persistent firm attachment of epithelium is abnormal. This undue adhesion occurs in dystrophic changes, described earlier, in acute rumenitis, especially if caused by fungi, and about healed lesions of necrobacillary rumenitis. Adhesion may not occur in the early stages of ruminal acidosis.

## *Dilation of the Rumen (Tympany, Hoven, Bloat)*

Tympanitic distension of the forestomachs may be acute, or chronic and recurrent, and there is a basic distinction between the two. The acute tympany of cattle fed legumes is characterized by foaming of the rumen contents, whereas in chronic or recurrent tympany the gas is free but retained because of some physical or functional defect of eructation.

**Primary tympany** is also called frothy bloat. Foam production in ruminal contents occurs normally. The amount of foam produced is small, however, and it is also unstable. There is apparently a delicate balance between pro- and antifoaming factors. These factors are multiple, and there is considerable controversy as to the extent each one influences the production of the foamy, viscous ruminal content so characteristic of frothy bloat.

The formation of foam is primarily dependent on soluble proteins, which are present in high levels (up to 4.5%) in bloat-inducing legumes. Legumes that are not associated with bloat, such as bird's-foot trefoil, have low levels of soluble protein, generally less than 1.0%. These soluble proteins are released

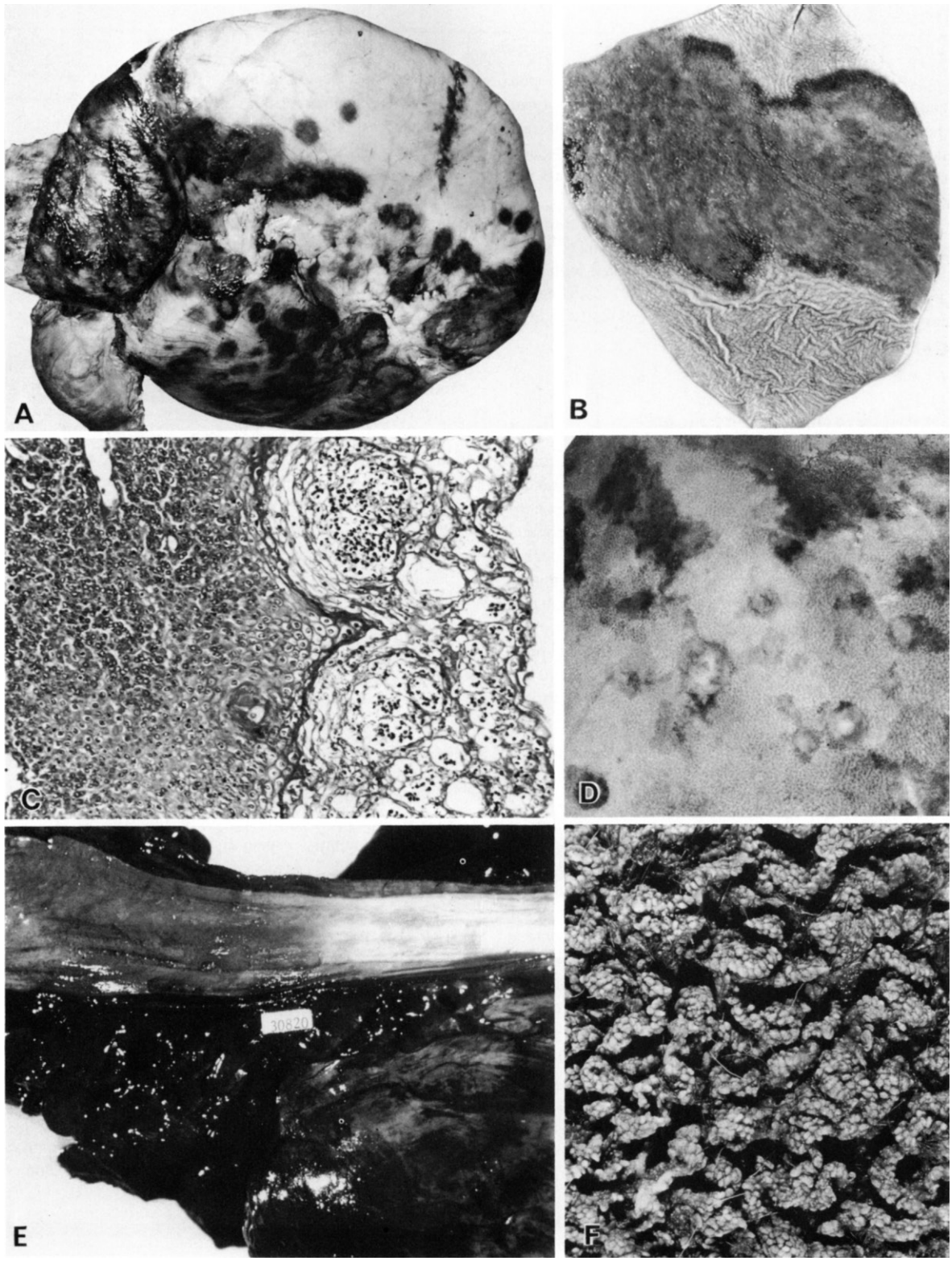


**Fig. 1.8.** (**A** and **B**) Mycotic rumenitis following acidosis. Cow. (**A**) Dark areas of infarction involving rumen and reticulum. *Aspergillus* and *Rhizopus*. (**B**) Appearance of mucosal surface of rumen. (**C**) Vacuolation and neutrophil infiltration into superficial epithelium of rumen papilla. Chemical rumenitis (ruminal acidosis) due to excess carbohydrate intake. (**D**) Necrosis in liver due to metastasis of fungi via portal circulation from primary foci of zygomycotic rumenitis. (**E**) "Bloat line." Cow. Ruminal tympany. Congestion of esophagus and connective tissue cranial to thoracic inlet and blanching of esophagus caudal to thoracic inlet. (**F**) Clubbing and adhesion of rumen papillae with parakeratotic epithelium, associated with feeding a ration high in barley. Plant fibers and hairs are among the matted papillae.

from chloroplasts. When they are degraded by the rumen microflora, they rise to the surface, where they are denatured, become insoluble, and stabilize the foam. The optimum pH (isoelectric point) for foam production by soluble proteins ranges from 5.4 to 6.0. Pectins are considered to increase viscosity of ruminal fluid and may act as foam-stabilizing agents. Plant lipids may act as antifoaming agents by competing for metal ions with the soluble proteins, thus inhibiting the denaturation of these proteins and resulting in decreased foam production.

Animal factors that may contribute to bloat are less accessible to study, and rather little is known of them. Excessive foam production causes distension of the rumen because the animals are unable to eructate foam. Frothy ruminal contents prevents the clearing of the cardia, which is essential for normal eructation to take place. When foam enters the esophagus, it stimulates the swallowing reflex, which also interferes with normal eructation. There is a genetic predisposition to bloating in cattle. Certain sires are known to produce cows that have a high susceptibility to bloating. Monozygotic twins may have similar bloating tendencies.

The variation among animals in their susceptibility to bloat may be determined in part by variations in the amount and composition of saliva secreted. Saliva apparently has properties that may promote or prevent foaming in the rumen. When secretion of saliva decreases, the viscosity of ruminal contents increases, which in turn promotes foaming. Cows that have a high susceptibility to bloating produce less saliva than cows that have a low susceptibility. Succulent and high-concentrate feeds reduce salivary secretion, thus increasing viscosity of rumen contents. The composition of saliva affects foam production in several ways. Combination of salivary bicarbonate with organic acids such as citric, malonic, and succinic acids, which are present in high levels in legumes, results in the production of large amounts of carbon dioxide, enhancing bubble formation. Carbon dioxide accounts for 40 to 70% of the total gas produced in the rumen.

Salivary mucoproteins increase viscosity, while mucins reduce viscosity. The levels of the various pro- and antifoaming compounds in saliva are dependent on the gland of origin. The parotid and submaxillary glands produce saliva with a high concentration of mucins. These glands actively secrete saliva when the animal is eating and when ruminal pressure is high. The buffering action of saliva may raise the pH of the ruminal contents above the range at which soluble proteins are most likely to produce stable foam. The knowledge of the full role played by saliva in bloat is still incomplete, and more research in this area may show that other factors are involved.

Rations high in concentrate and low in roughage not only reduce saliva secretion, they also change the ruminal microflora. They promote the growth of large numbers of encapsulated bacteria, which increase the concentration of polysaccharides, and these in turn increase the viscosity. These bacteria are also often mucinolytic and may destroy the salivary mucins. Perhaps this explains the more gradual onset of feedlot bloat, since it takes time for the ruminal flora to change.

The cause of death in bloat is probably due to the combined effects of increased intraabdominal pressure on the diaphragm, inhibiting respiration, and the shunting of a large volume of blood away from the abdominal viscera. Anoxia may be caused by respiratory embarrassment. Increased intraabdominal pressure also has a marked effect on the hemodynamics of the abdominal viscera. There is compression of the posterior vena cava, which results in a redirection of blood flow from the caudal areas of the animal. The blood is shunted through the lumbar veins, into the longitudinal vertebral sinuses, from there to the intercostal veins, and into the hemiazygos or costocervical vein. There is considerable variation among animals, and in individual animals from day to day, in the ruminal pressures that can be tolerated.

The bloated animal is often found dead and distended with gas; blood exudes from the orifices, and because of the gaseous distension, the carcass often rolls on its back. The blood is dark and clots poorly; both features are indicative of death due to anoxia. Subcutaneous hemorrhages are prominent in the neck and trunk. There is marked edema, congestion, and hemorrhage of the cervical muscles and of the lymph nodes of the head and neck. An inconsistent, but significant, finding is the so-called bloat line in the esophageal mucosa (Fig. 1.8E). This lesion is formed due to congestion with petechial and ecchymotic hemorrhages in the mucosa of the cervical esophagus, which changes abruptly or gradually to a pale mucosa at the level of the thoracic inlet. The tracheal mucosa is hemorrhagic, especially anterior to the thoracic inlet. Blood clots are frequently seen in the bronchi and paranasal and frontal sinuses. The lungs are compressed into the anterior thorax by the bulging diaphragm. There is pressure ischemia of the abdominal viscera, especially the liver. The extreme margins of the hepatic lobes may be congested. Lymph nodes and the muscles of the hind legs are pale. There may be marked subcutaneous edema, particularly of the vulva and perineum. If the autopsy is done soon after death, the ruminal contents are bulky and foamy. The foam gradually disappears after death and is usually absent if the autopsy is delayed for 10 to 12 hr. Inguinal hernia and diaphragmatic rupture may occur after death.

**Secondary tympany**, or secondary bloat, may be acute but is usually chronic, with periods of acute exacerbation. It is usually the result of a physical or functional defect in eructation of gas produced by normal rumen fermentation. The more common physical problems include obstructions of the esophagus or esophageal groove by tumor, papilloma, or foreign body; reticular adhesions; and esophageal stenosis of any cause. Functional causes of secondary tympany include organophosphate intoxication and vagal damage due to adhesion or lymphosarcomatous infiltrates. It is a component of the syndromes collectively termed "vagus indigestion." Secondary tympany, sometimes fatal, occurs in bucket-fed calves. A diagnosis of secondary bloat at autopsy is based on physical findings like those described in primary bloat, but without frothy rumen content, and with the addition of any physical cause of impaired eructation.

Bloat must be differentiated from other causes of sudden death. These include hypomagnesemia, blackleg, malignant edema, anthrax, lightning stroke, and accidental electrocution. None of these conditions has lesions associated with the redistribution of abdominal blood flow, nor are the rumen contents foamy. The bacterial infections are characterized by typical muscle lesions in the case of blackleg and malignant edema, and

there are septicemic lesions including an enlarged raspberry-like spleen in anthrax. Ruminal distention occurs with grain overload; however, the contents are watery and have a fermentative odor.

Postmortem distention of the rumen must not be mistaken for antemortem tympany. Extraruminal lesions must be present to establish a diagnosis of bloat.

### *Foreign Bodies in the Forestomachs*

Cattle are notoriously lacking in alimentary finesse, a deficiency that allows an amazing variety of foreign bodies, prehended with the food, to be deposited in the forestomachs. Sheep are largely immune because of their more selective eating habits. Foreign bodies are rarely found in the rumen of goats, despite their reputation for indiscriminate feeding habits. In consequence, a large proportion of adult cattle, and very few goats or sheep, have foreign bodies in the rumen and reticulum but rarely in the omasum. It is possible that many of the lighter and smaller foreign bodies are regurgitated.

Foreign bodies consisting largely of hair or wool (**trichobezoars**), or plant fibers (**phytobezoars**) may also form in these compartments. Hair balls are most common in younger ruminants, the hair being swallowed after licking, particularly by animals deprived of dietary fiber. They may have some other foreign body as a nucleus and contain a proportion of plant fibers, the whole mass concreted by organic substances and inorganic salts. The same general comments apply to phytobezoars. Being smooth, neither are important unless regurgitated to lodge in the esophagus or passed on to obstruct the pylorus or intestine.

The important foreign bodies are those, such as lead, that when dissolved cause intoxication, and those that being abrasive or sharp, penetrate the mucosa. In calves on diets low in roughage, ingestion of wood shavings or straw may lead to diffuse cellulitis of the forestomachs and sometimes the abomasum. A mixed bacterial flora containing clostridia is responsible, presumably following mucosal trauma. The sequel to penetration by sharp objects in adult cattle is traumatic reticuloperitonitis.

TRAUMATIC RETICULOPERITONITIS AND ITS COMPLICATIONS. Perforation of the forestomachs by foreign bodies virtually always is a penetration of the reticular wall by a sharp foreign body, usually a piece of wire or a nail. Incomplete perforation of the wall is usually without significant effect, although in some cases a suppurative or granulomatous inflammation develops in the wall of the reticulum, with minor overlying peritonitis. There are no adequate answers as to why perforation occurs or why it is so frequently in the anteroventral direction. It is probably caused by forceful contraction of the reticulum, and many cases seem to be precipitated by the increased intraabdominal pressure of late pregnancy and parturition.

There is a rather uniform train of events when complete perforation occurs, but variations of the pattern are common. The perforation is usually in the anteroventral direction and is followed immediately by an acute local peritonitis. If the foreign body is short or bent, it may progress no further, and some foreign bodies are apparently withdrawn with the reticular movement; in such instances a chronic local peritonitis with adhesions develops. The foreign body may advance to perforate the diaphragm and pericardium, resulting in traumatic pericarditis, but this advancement may be delayed.

A ventral penetration may result in subperitoneal and subcutaneous abscess near the xiphoid. Rare perforation of one of the larger regional arteries may result in sudden death from hemorrhage, and sudden death may also occur if there is penetration of the myocardium or rupture of a coronary artery. Penetration of the thoracic cavity may occur without perforation of the pericardium and cause pneumonia and pleuritis. Right lateral deviation of the penetrating agent causes involvement of the wall of the abomasum. It is unusual for the liver or spleen to be penetrated, but metastatic abscesses in the liver are common.

As soon as the foreign body penetrates the serosa, a local fibrinous peritonitis develops, leading later to dense adhesion of variable extent between the reticulum and adjacent structures. Further progression of the foreign body is ordinarily slow and produces a canal surrounded by chronic granulation tissue and containing, besides the foreign body, ingesta, purulent exudate, and detritus. The bacteria commonly active in the tract are *Corynebacterium pyogenes, Fusobacterium necrophorum,* and a variety of putrefactive types. In many cases, a foreign body cannot be found, perhaps because it has rusted away or been withdrawn into the reticulum.

**Traumatic pericarditis** is a less common sequel now, perhaps because so many of the initial penetrations are diagnosed and the foreign body removed surgically. The pericardial reaction is copious, fibrinopurulent, and putrid. There are usually additional lesions of traumatic pneumonia and pleurisy, with emphysema from rupture of the lung.

The prophylactic use of magnets has become common practice in many herds, and this probably contributes to the marked decrease in fatal cases. Frequently, these magnets are found incidentally in the reticulum, completely covered with metal foreign bodies, including nails and wires, which might otherwise have penetrated the reticular wall. The replacement of baling wire with binder twine is another reason for the apparent decline in the prevalence of this disease.

One of the variants in the usual pattern of migration of the foreign body is penetration of the side of the reticulum, leading to a suppurative inflammation in the grooves between the reticulum, omasum, and abomasum. Although the acute local peritonitis causes immediate cessation of ruminal movements, a persistent ruminal atony or inactivity may ensue. Clinically, this is referred to as "vagus indigestion," and at autopsy there are very characteristic changes in the stomachs.

In "**vagus indigestion**," the abomasum may be distended and impacted with dry ingesta presumably due to functional pyloric stenosis or abomasal stasis. The omasum in this condition can be very large and impacted with dehydrated ingesta. The rumen is distended with enough fluid to cause sloshing if the carcass is jolted. There is no ruminal fermentation or odor, and bits of unmacerated straw and food particles float on the watery fluid. The more normal ingesta has sedimented.

The question of the importance of vagal nerve damage in the pathogenesis of so-called vagus indigestion remains unresolved. The rumen and reticulum are dependent on intact vagi for normal

movement, and a minority of cases of "vagus indigestion" appear to be associated with damaged nerves. Vagal lesions may be intrathoracic, such as in lymphosarcomatous infiltration, or abdominal. The latter are usually investment of the nerve in adhesions following reticular perforation, or trauma following abomasal volvulus. In other cases, degeneration of the vagus is not evident, and the dysfunction and lesions are more likely to be due to peritonitis and the subsequent abscessation or adhesions that interfere with normal motility of the forestomachs and the abomasum. A diagnosis of vagal indigestion at autopsy is orinarily dependent on evidence of abnormal abomasal, omasal, or reticuloruminal motility, in association with morphologic lesions of the vagus nerves, or adhesion involving the forestomachs and abomasum.

### *Rumenitis*

Inflammatory lesions in the forestomachs occur in a number of viral diseases of the alimentary mucosae in ruminants. In neonatal calves, necrosis of ruminal mucosa is an important sequel to infectious bovine rhinotracheitis infection. Bovine papular stomatitis and contagious ecthyma will rarely cause rumen lesions. Rumenal erosions and ulcers are present in some cattle with bovine virus diarrhea; they are reportedly less frequently found in rinderpest. Extensive hemorrhage and ulceration of the reticuloruminal mucosa may be seen in bluetongue in sheep. Adenovirus infection occasionally causes a multifocal fibrinohemorrhagic rumenitis. Focal or diffuse rumenitis may be present in cattle with malignant catarrhal fever. These conditions are described under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

A mild inflammation of the forestomachs occurs in some young calves fed milk from a pail, when, because of laxity of the esophageal groove reflex, the milk spills into the rumen and reticulum in large quantity. A similar problem occurs with feeding by stomach tube. Putrefaction in these compartments leads to mild rumenitis.

Accidental consumption of excessive quantitites of urea, in the form of nonprotein nitrogen supplement, or fertilizer, in liquid or powder form, results in the production of ammonia in the rumen. The toxic effect is accelerated by urease in soy-based rations and is based on the production of high blood levels of ammonia. A history of abdominal pain and central nervous signs such as incoordination and violent struggling may be available. Rumen contents smell ammoniacal when the organ is opened, the content is alkaline, and there may be congestion or coagulation necrosis of the anteroventral wall of the rumen.

A more common form of acute chemical rumenitis develops after overeating on rapidly fermentable carbohydrate, usually grain.

RUMENITIS AND ACIDOSIS CAUSED BY OVEREATING GRAIN. Ruminal acidosis and rumenitis associated with ingestion of excess carbohydrate is a problem mainly of intensive beef and dairy production. Sheep and, especially, goats are also susceptible to this problem. Its importance lies partly in loss of production and partly in mortality due to the acute disease, in which the rumenitis is of minor significance, and the lactic acidosis is the major cause of morbidity and mortality. Rumenitis assumes significance in subclinical disease or in survivors of acute episodes by providing a portal for the entry for fungi and *Fusobacterium necrophorum*. These complications are discussed below. There are other complications. Primary tympany (frothy bloat) may coexist and be the fatal partner of grain overload in feedlot cattle.

Ruminal acidosis usually follows the ingestion of excess carbohydrate in the form of grain or other fermentable feedstuffs occasionally used, such as bread, brewer's waste, and apples. There is a wide variation in the amount of carbohydrate necessary to kill an animal, because tolerance to rations high in starch does develop. Sudden increments in the amount of carbohydrate ingested are of more importance than the actual amount, provided this increases slowly. In sheep, for which some information is available, ~60 g of wheat per kilogram of body weight must be ingested to cause death; probably this figure is generally applicable to cattle also. Lesser amounts than this may cause illness but permit eventual recovery. Even after cattle are accustomed to high concentrate rations, they may still develop ruminal acidosis. Sudden changes from concentrates with lower energy values to those with higher values may predispose to acidosis. Extreme environmental temperature changes, either hotter or cooler, may result in temporary reductions in feed consumption, and acidosis may develop once animals return to full feed.

Shortly after the ingestion of a toxic amount of carbohydrate, the ruminal pH begins to fall. The decrease in pH during the first 8 hr is mainly due to an increase in dissociated volatile fatty acids, not lactic acid. The production of the latter increases after there has been a marked change in the ruminal flora, which is very responsive to the substrate available for fermentation. The normal pH of ruminal fluid in cattle and sheep varies between 5.5 and 7.5, depending on the diet fed.

The Gram-negative bacteria that predominate in the normal flora and the protozoa are very sensitive to changes in the pH. Most of these organisms die at a pH of 5.0 or less. Once the pH of the ruminal contents starts to fall, there is a rapid proliferation of streptococci, mainly *Streptococcus bovis*, and these bacteria are the main source of lactic acid. When the pH reaches 5.0–4.5, the numbers of streptococci decrease, with a concomitant increase in lactobacilli. The pH of rumen content may fall as low as 4.5 to 4.0 in fatal cases.

As the ruminal pH drops, ruminal atony develops, mainly as the result of an increase in the concentration of dissociated fatty acids, rather than of lactic acid, as was once thought. There is also a cessation of salivary secretion so that the buffering effect of saliva is absent. The increase in ruminal organic acids, mainly lactate, causes an increase in ruminal osmotic pressure. This results in movement of fluid from the blood into the rumen, producing bulky and liquid ruminal contents and severe dehydration. There is a reduction in plasma volume; hemoconcentration, anuria, and circulatory collapse follow. Serum protein levels, urea, inorganic phosphorus, lactate, pyruvate, and liver enzymes are all elevated. The osmotic pressure of the intestinal contents also increases when the ingesta with the high lactate concentration arrives there. Loss of fluid at this level probably contributes further to the dehydration, and it may also play a significant role in the development of the diarrhea that is commonly seen clinically.

In those animals that survive the acute phase of ruminal acidosis, complete recovery is delayed until a normal ruminal flora is reestablished through contact with other animals. A temporary recovery may be followed by what appears clinically to be a relapse in acidosis, but which is a developing mycotic rumenitis. If treatment of the initial fluid imbalance is delayed, death may occur in a week or so from ischemic renal cortical necrosis.

In addition to the osmotic effects, there is acidosis due to the absorption of lactate from the rumen, and possibly from the intestine. Almost equal concentrations of D and L isomers of lactic acid are produced in the rumen. However, the D isomer of lactic acid is poorly metabolized by the host and hence accumulates eventually to a much higher concentration in plasma than the L isomer. This is probably reinforced by endogenous lactate produced in the state of relative anaerobiosis of peripheral circulatory failure. The blood pH may drop as low as 7.0, which causes a marked depletion of alkali reserves. Absorption of D-lactate exceeds the rate of metabolic breakdown, and further aggravation of the acidosis may occur when the excretion of this isomer is impaired due to reduced renal function. Such a reduction in the plasma clearance of lactic acid occurs only after the blood pH drops to 7.14 or less and lactic acid levels have risen to ~25 ml/liter or higher. There are other toxic factors, including histamine, produced in this disease, but the amounts absorbed from an acid rumen are probably too low to have any effect.

The low ruminal pH that develops is lethal to much of the normal flora and fauna. The protozoa appear to be particularly sensitive, but many types of bacteria are also lost. Therefore, in animals that show signs of immediate recovery, with or without therapeutic aid, the reestablishment of normal fermentation reactions may be delayed.

The morbid anatomy of this metabolic disease is not specific, and a practical diagnosis requires knowledge of access to fermentable carbohydrate and a clinically observed circulatory failure. At autopsy, the eyes are sunken and the blood may be thick and dark due to dehydration and hypoxia, and there is general venous congestion. The appearance of the ruminal contents varies with the time interval between ingestion of the carbohydrate and the autopsy. In the early stages, there is a copious amount of porridge-like rumen contents, which has a distinct fermentative odor. The amount of grain or corn varies considerably and is an unreliable indication of acidosis, and the presence of finely ground concentrate may be overlooked. Ruminal pH is helpful only when it is low (<5.0), since it may rise in later stages of acidosis. Although the ruminal contents may appear relatively normal in more advanced cases of acidosis, the intestinal contents tend to remain very watery. Absence of protozoa is consistent with chemical rumenitis but is also influenced by the interval between death and the postmortem examination.

The diagnosis of ruminal acidosis at autopsy can be difficult. The most suggestive abnormality is the rumenitis. It is probably chemical and dependent on the low pH, and is not readily discerned grossly. There may be a slight, poorly defined bluish coloration in the ventral sac of the rumen and reticulum and in the omasum, visible through the serosa. When the epithelium is detached, the lamina propria is seen to be hyperemic in patches.

Microscopic examination of the ruminal mucosa is the most reliable way to confirm a diagnosis of chemical rumenitis. The ruminal papillae appear enlarged. There is marked cytoplasmic vacuolation of the epithelial cells, often leading to vesiculation. A mild to marked neutrophilic reaction is evident in the mucosa and submucosa (Fig. 1.8C). Focal areas of erosion and ulceration may or may not be present.

*Fusobacterium necrophorum* is a normal inhabitant of the anaerobic ruminal environment. This bacterium is usually responsible for the infective complications of ruminal acidosis, and it produces characteristic lesions in the forestomachs (Fig. 1.9A–C) and metastases in the liver. Invasion of the wall of the rumen probably does not occur with significant frequency unless a foothold is provided by the superficial necrosis and inflammation of acidosis. Necrobacillary rumenitis is common in feedlot cattle, probably a product of mild acidosis following a too rapid introduction to a high-concentrate ration. It is also an observed complication in other cattle, especially dairy cows, which gain access to unusual amounts of grain, and in sheep under the same circumstances.

Necrobacillary rumenitis affects the papillated areas of the ventral sac and occasionally the pillars. On the inner surface, the early lesions are visible as multiple, irregular patches from 2 to 15 cm across, in which the villi are swollen, dark, slightly mushy, and matted together by fibrinocellular inflammatory exudate. The affected villi are necrotic, but ulceration may be delayed if there is ruminal atony and stasis. If the animal recovers from the immediate effects of overeating, the necrotic epithelium sloughs, the ulcer contracts, and epithelial regeneration begins from the margins. The regenerated epithelium is flat and white, and the specialized villi do not completely return. A stellate scar remains, but many of the smaller lesions may disappear completely (Fig. 1.9C). Hepatic metastases are initially typical of necrobacillosis, consisting of coagulative necrosis, but in time they liquefy to form typical abscesses and these often persist long after the initial ruminal lesions have healed, cicatrized, and disappeared.

It is unusual for ruminal necrobacillosis in cattle to be more than a superficial infection, and although the muscle layers are involved in the inflammation, they are not ordinarily invaded by the organism. Infection of the omasum differs in that perforation of the omasal leaves is common. In sheep, the infection is more progressive than in cattle.

When inflammation in the wall of the forestomachs extends to the serosa and is hemorrhagic, mycotic infection should be suspected. The fungi, which are opportunists like *Fusobacterium necrophorum*, are usually members of the genera *Mucor*, *Rhizopus*, and *Absidia*, and these cannot be differentiated from each other in histologic sections. In the few cases cultured, the incriminated organism was *Rhizopus*.

Mycotic rumenitis is much more severe and extensive than necrobacillary rumenitis and is often fatal. The inflammation extends to the peritoneum, causing a hemorrhagic and fibrinous peritonitis that mats the omentum to the rumen. In fatal cases, most of the ventral sac and parts of the omasum are involved. The lesions are very striking and suggest on initial inspection that the walls have been massively infarcted, which in part they have (Fig. 1.8A,B). The margins are well demarcated, usually by a narrow zone of congestive swelling. The affected areas are red to black in color, thickened to a centimeter or more, firm,

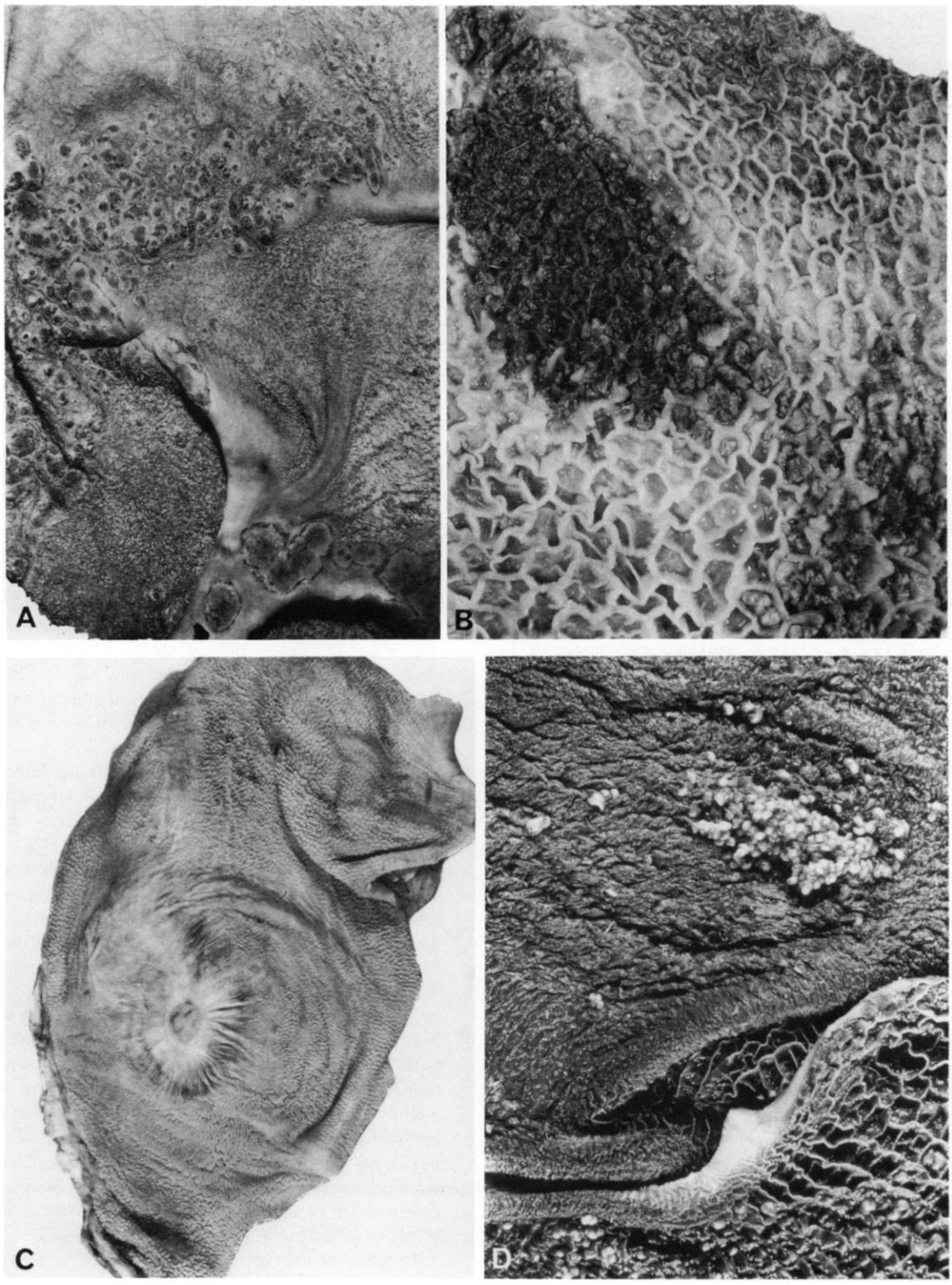


**Fig. 1.9.** (**A** and **B**) Acute necrobacillosis in rumen and reticulum. Cow. (**C**) Stellate scarring of incompletely healed ulcer in rumen mucosa in fusobacterial rumenitis. (**D**) *Paramphistomum* sp. flukes on the mucosa of the reticulorumen.

and leathery. There is acute fibrinohemorrhagic inflammation of the overlying peritoneum, and beneath it in the grooves there is a bloodstained, inflammatory edema. Thrombosis, as the result of vasculitis due to the invasion of the vessels by the fungus, is the basis for this lesion.

On the inner surface of the rumen, the lesions are more hemorrhagic than those of necrobacillosis, and often more irregular in outline, and the necrotic epithelium is difficult to detach. Histologically, the rumenitis is characterized by hemorrhagic necrosis of all structures in the wall, by copious fibrinous exudate, and by rather scant leukocytic reaction. A severely necrotizing vasculitis is characteristic, the fungus being readily visible in the necrotic tissues and the lumina of the blood vessels.

Metastases sometimes occur in the liver and cause a necrotizing thrombophlebitis of the portal radicles, visible as small irregular, tan areas of infarction surrounded by a deep red margin (Fig. 1.8D).

Other conditions that have been associated with ruminal acidosis are laminitis and an encephalopathy that morphologically resembles the lesions of early polioencephalomalacia. The pathogenesis of laminitis are discussed in the Skin and Appendages (Volume 1). The encephalopathy has been observed in experimental acidosis in sheep. Grossly, the brain is swollen due to edema. The cerebellar vermis prolapses into the fourth ventricle, and there is coning of the cerebellum into the foramen magnum. Microscopically, there is neuronal degeneration of the middle laminae of the cerebral cortex and perivascular edema. These lesions may be due to an induced thiamine deficiency. There is no storage of thiamine. In the normal ruminal flora, thiamine production depends on a delicate balance between thiamine and thiaminase-producing bacteria. In ruminal acidosis this balance may be disturbed by the proliferation of *Streptococcus bovis*, which is known to consume thiamine. In addition, the acid medium may be favorable for thiaminase-producing organisms such as *Clostridium sporogenes* and *Bacillus thiaminolyticus*. The prevalence of the cerebral lesions in spontaneous cases of ruminal acidosis is not known but warrants further investigation.

### *Parasitic Diseases of the Forestomachs*

*Gongylonema* species occur in the epithelium of the rumen. They appear as described for the esophagus. They are insignificant as pathogens.

More important parasites are the conical flukes belonging to the family Paramphistomatidae. They are found in cattle and sheep in warm temperate, subtropical, and tropical regions. These reddish, plump, droplet-shaped flukes are about the size of the papillae between which they reside in the rumen, where they are nonpathogenic (Fig. 1.9D). Their significance lies in the potential for larval paramphistomes in the duodenum to cause disease. The biology and pathogenicity of paramphistomes is discussed under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Myiasis of the rumen caused by larvae of the "screwworm" fly *Cochliomyia hominivorax* is occasionally a cause of mortality in young calves in South America. The larvae are presumed to be licked from cutaneous wounds and swallowed. They lodge in the rumen and perforate it.

### *Neoplasia of the Esophagus and Forestomachs*

Neoplasia of the esophagus and reticulorumen is, with the exception of papilloma, uncommon in domestic animals.

**Papillomas** of the esophagus in dogs are uncommon and may be associated with oral papilloma. In cattle, papillomas of the esophagus and reticulorumen may be common in some areas. They are caused by bovine papillomavirus type 4, which infects only squamous mucosa of the mouth, pharynx, and upper alimentary tract. Bovine alimentary papillomas are usually solitary, though a minority of infected animals may have multiple lesions. Most are small (<1.0 cm), broadly pedunculate, tapering, acuminate masses. They are composed of a number of closely packed fronds of squamous epithelium, each supported by a light core of fibrous stroma and arising from a common fibrous base. Some form flattened sessile hyperplastic epithelial plaques, while others, usually limited to the esophagus, form fibropapillomas. The latter are smooth, nodular masses comprised of acanthotic epithelium supported by a fibromatous stroma, occasionally found in close physical association with a more typical papilloma. In a low proportion of typical alimentary papillomas in cattle, but not in fibropapillomas, eosinophilic intranuclear inclusion bodies may be present in keratinizing cells. In these, and in vacuolate nuclei containing amphophilic material, papovaviruses may be found by electron microscopy. Papillomas are normally asymptomatic, though large lesions of the reticular groove and esophagus may interfere with eructation and deglutition.

**Malignant neoplasms** of the **esophagus** and **forestomachs** in ruminants are ordinarily extremely rare. In several localities, however, squamous-cell carcinoma is relatively commonly found in association with papilloma. It has been suggested that an interaction between viral papillomas and ingestion of carcinogens in bracken fern predisposes to the development of squamous-cell carcinomas of the esophagus and forestomachs in the hill country of Scotland and northern England. In Brazil a similar association is made with carcinomas of the oropharynx. A high prevalence of carcinoma of the esophagus and forestomachs also has been reported from a single valley in Kenya, in association with papillomas, not confirmed as viral, and with a carcinogen apparently ingested with or derived from native forest plants. Esophageal and ruminal carcinomas are associated with dysphagia or difficult deglutition, rumen tympany, and apparent abdominal pain with progressive cachexia. Concurrent papillomas, carcinomas, and hemangiomas of the bladder like those causing enzootic hematuria are often found in cattle with esophageal or ruminal cancer. In Scotland, intestinal adenomas or adenocarcinomas were also found in many cases.

**Esophageal** and **ruminal carcinoma** may be seen developing from recognizable papillomas, as brownish, irregular, roughened hyperplastic epithelium, or as ulcerated or irregular proliferative fungating lesions. The distal esophagus, reticular groove, and adjacent ruminal wall are the sites most commonly affected with carcinoma. Microscopically, they are typical

squamous-cell carcinomas and invade locally, causing induration of the wall of the organ. They may metastasize to local lymph nodes and to distant sites such as liver and lung.

**Squamous-cell carcinomas** may also be encountered rarely in the esophagus of cats, where they develop in the distal portion, forming proliferative plaques of neoplastic cells that eventually ulcerate and invade the wall of the esophagus and adjacent mediastinum. In horses, squamous-cell carcinomas of the stomach may also involve the adjacent terminal esophagus.

**Mesenchymal tumors** of the esophagus, with the exception of the *Spirocerca*-associated fibrosarcomas and osteosarcomas in dogs, referred to previously, are very rare. Connective-tissue tumors of the rumen are similarly rare. Occasional involvement of the omasum and reticulum by direct extension from adjacent affected abomasum may occur in cattle with lymphosarcoma. Invasion of or metastasis to the canine esophagus by thyroid, respiratory, and gastric carcinomas is also reported.

## Stomach and Abomasum

### *Normal Form and Function*

Particular attention should be paid to the stomach in the examination of animals of any species with a history of inappetence or anorexia, cachexia, hypoproteinemia, diarrhea, regurgitation, or vomition. Abdominal distention may be associated with gastric dilatation or displacement. Hematemesis, melena, or anemia may signify gastric bleeding. Many infectious diseases with major systemic or alimentary tract signs elsewhere produce gastric lesions. Systemic states such as uremia and toxemia cause characteristic gastric lesions in some species.

In the horse and pig, an obvious smooth, white or yellowish **esophageal region** is present. It is covered by stratified squamous epithelium, with susceptibility to insult and reparative capacity similar to that of the esophageal lining. This area is most extensive in the horse, incorporating the cranial third of the stomach, including the saccus cecus. The pars esophagea of the stomach of the pig is a rectangular area around the cardia. Chronic inflammatory infiltrates and lymphoid follicles are normally present in the lamina propria and submucosa of the **cardiac gland mucosa** abutting the esophageal region, especially in the pig. The cardiac gland zone has a grayish color and is particularly well developed in this species, lining the gastric diverticulum, fundus, and about half the body of the stomach. In the dog, cat, and ruminant, cardiac glands are limited to a narrow zone at the cardia or omasal opening. Cardiac glands are branched tubular structures, lined almost exclusively by columnar mucous cells with a few endocrine cells interspersed, though chief cells may be present in the pig. These glands open into gastric pits or foveolae, which are lined by tall columnar mucous cells continuous with the covering of the gastric surface. The anterior portions of the equine and porcine stomach are so modified to permit bacterial fermentation and evolution of volatile fatty acids in an environment of relatively high pH (>5), buffered by saliva and cardiac gland secretions.

The **fundic** or **oxyntic gland** acid-secretory mucosa in the horse and pig is reddish brown and slightly irregular but not highly folded. More prominent longitudinally oriented rugae or plicae are present in the dog and cat, and in the abomasum. Gastric secretion undiluted by ingesta in the dog or cat normally should have a pH less than 4. Abomasal content should have a pH of 3.5 to 4.0. Tall columnar mucous cells cover the gastric surface and line pits or foveolae in this region of the stomach as well. Fundic glands contain several classes of cells. The junction of the base of the foveolus and the upper portion of the gland proper is termed the isthmus. Here the proliferative compartment of the gland is found. Cuboidal, or low columnar mucous neck cells in a narrow zone in this area undergo mitosis. Some daughter cells differentiate into foveolar mucous cells, migrating up onto the gastric surface, where they are lost, probably in about 4 to 6 days. The neck of the oxyntic gland below the isthmus is lined by pyramidal, peripherally located, acid- and intrinsic-factor-producing parietal cells. Interspersed are inconspicuous mucous neck cells, mainly in the upper neck, and scattered endocrine cells. In the base of the gland, pepsinogen-producing zymogen or chief cells are concentrated.

Mucous neck cells, like foveolar and surface mucous cells, stain PAS-positive. The cytoplasm of these cells contains, in addition to mucous granules, many polyribosomes and rough endoplasmic reticulum, suggesting poor specialization. Parietal cells differentiate from mucous neck cells proliferating at the isthmus and appear to be relatively long-lived, that is, of the order of weeks to months in the species studied. They contain many mitochondria, hence staining well with eosin. A complex tubulovesicular–canalicular structure opens at the luminal apex of the cell in the secretory state. A number of long-lived endocrine cells, probably derived from proliferative elements at the isthmus, are recognized in the oxyntic gland: ECL cells (histamine, serotonin), EC cells (serotonin, peptides), D cells (somatostatin), and A, $D_1$, and X cells (function unclear). Endocrine cells usually abut the basement membrane of the gland, lack exposure to the gland lumen, and have characteristic basal granules visible in thin, plastic-embedded sections. The chief cells are apparently long-lived cells, probably derived from stem cells at the isthmus, but possibly autonomously replicative at a slow rate. Ultrastructurally, they have extensive rough endoplasmic reticulum, a prominent Golgi zone, and numerous zymogen granules.

Under normal circumstances, mitotic figures are not commonly encountered in cells at the isthmus of fundic glands, and virtually never at any distance from the isthmus. The fundic mucosa of newborn ruminants and, especially, piglets may be relatively poorly differentiated and proliferative. The proliferative compartment is sensitive to radiomimetic insults. This is reflected in attenuation of the lining epithelium and narrowing of the isthmus and upper neck of oxyntic glands in dogs with parvovirus infection (Fig. 1.32A) and in animals treated with cytotoxic agents such as cyclophosphamide. *Spirillum*-like bacteria are considered normal in the fundic glands of dogs and cats. *Chlamydia* has been recognized in surface mucous cells of otherwise normal fundic mucosa in cats, with no specific signs of disease.

The **pyloric mucosa** is also covered by columnar mucous cells, which form a slightly pitted or irregular surface in the

distal portion of the stomach, including the pyloric antrum. It extends further cranially along the lesser, compared to the greater, curvature. The knoblike torus pyloricus at the pylorus of the pig is a normal structure. The tubular glands of the pyloric mucosa open into deep gastric pits, which may extend half the thickness of the mucosa. The glands are lined by pale mucous cells, with interspersed endocrine elements, mainly G (gastrin) and D (somatostatin) cells. Scattered parietal cells may be present, especially in glands in the zone intergrading with fundic mucosa.

The stromal elements of the gastric lamina propria are relatively inconspicuous, in the fundic mucosa in particular. Normally, relatively few lymphocytes and plasma cells and scattered mast cells are present, mainly deep between glands. Occasional lymphocytic nodules or follicles may be present, usually near the muscularis mucosae. Lymphoid infiltrates are more common in the antral mucosa.

### *Regulation of Gastric Secretion*

The major function of the stomach, hydrolysis of protein in preparation for subsequent intestinal digestion and absorption, is accomplished by acid and pepsin, activated by autocatalysis from pepsinogen at low pH. Secretion of acid (and intrinsic factor) is the function of the oxyntic or parietal cells, about one billion of which are present in the stomach of a 20-kg dog. Regulation of the volume and acidity of gastric secretion is physiologically complex and highly integrated, involving neurocrine, endocrine, and paracrine mechanisms.

The parietal cell secretes hydrochloric acid in response to stimulation by histamine, acetylcholine, and gastrin. Studies on isolated parietal cells suggest that receptors specific for each of these secretagogues are present on the cell membrane. All three agonists are probably continuously present and involved in basal acid secretion. However, the effects of acetylcholine and gastrin are largely dependent on concurrent stimulation by histamine. Potentiation or synergism of effect occurs when histamine–acetylcholine, histamine–gastrin, or all three agents together act on the cell. The mechanism of this synergism is unclear, but it involves intracellular metabolic events beyond the receptor, and probably beyond the second messenger.

**Histamine**, probably derived from mast cells in the lamina propria, and possibly from local enteroendocrine cells, is a paracrine permissive stimulant, continuously present in the environment of the oxyntic cells. Evidence for a stimulus causing a phasic increase in histamine effects on parietal cells is not available, though it is suggested that gastrin may promote histamine release in some species. The oxyntic cell has an $H_2$ histamine receptor, which, when occupied, causes, through the mediation of adenylcyclase, enhanced generation of the second messenger, cyclic adenosine monophosphate. This in turn stimulates, via poorly understood mechanisms, intracellular metabolic events culminating in acid secretion.

**Acetylcholine**, the neurocrine agonist, is released near the oxyntic cell from processes of parasympathetic postganglionic neurons. Its release is both background and phasic, being enhanced by vagal activity during the central stimulation of the cephalic phase—the Pavlovian response. Gastric distention also stimulates the parietal cell via vagovagal and short intramural reflex pathways. The effect of acetylcholine is associated with calcium-ion influx as second messenger.

**Gastrin** is a hormone released into the bloodstream by G cells, located mainly in the pyloric antrum. Stimuli for gastrin release are of two types. Direct action of calcium, amino acids, and peptides in ingesta, impinging on G cells, may stimulate gastrin release. In addition, vagal stimulation during the cephalic phase, and fundic–pyloric vagovagal reflexes, in concert with pyloric vagovagal and local intramural antral reflexes, initiated by distention, cause G cells to release gastrin. This stimulus is probably the product of removal of paracrine somatostatin inhibition of the G cell, coupled with neurocrine stimulatory effects of bombesin on the G cell. Gastrin alone appears to be a weak calcium-ion-dependent stimulator of acid production by isolated cells, but it contributes to the synergistic effects on secretion seen in cells exposed to histamine and acetylcholine. This probably explains its contribution to phasic acid secretion in the intact animal. In addition, gastrin has an important trophic effect on parietal cell mass, stimulating synthesis of nucleic acid and protein and increasing the number of parietal cells in fundic mucosa.

Inhibition of acid production during the gastric phase of secretion occurs as the result of the negative-feedback effect of acid in the antrum, possibly by paracrine somatostatin influence on the G cell, inhibiting gastrin release below pH 3. In addition, the presence of acid, fat, and hyperosmolal solutions in the proximal small intestine inhibit acid secretion, perhaps in part by the mediation of neural reflexes and secretin, gastric inhibitory polypeptide, or other enterogastrones. The effects of histamine on the parietal cell are central to its basal secretion and its susceptibility to the synergistic effects of cholinergic and gastrin stimulation.

The chief cell is probably susceptible to the same general stimuli for secretion as the parietal cell, with the exception that secretin stimulates, rather than inhibits, pepsinogen release.

### *Gastric Mucosal Barrier*

The gastric mucosal barrier to acid back diffusion and autodigestion presumably resides largely in the single layer of foveolar and surface mucous cells, and their secretion. Gastric mucus is freely permeable to hydrogen ions and has little innate buffering capacity. Cardiac gland mucosa in the pig, and pyloric mucosa in several species, secretes bicarbonate in considerable quantities and normally resists acid attack. Fundic surface mucous cells also may actively secrete bicarbonate into a thin, unstirred layer of surface mucus. Here a sharp pH gradient is maintained, neutral on the cell-surface side, acid on the luminal side. By this means, bicarbonate secretion of relatively small magnitude in relation to total acid secretion may hypothetically protect the mucosa against attack by acid. Mucus is itself susceptible to enzymatic proteolysis but provides a good barrier to diffusion by these large molecules. Continual mucus secretion on the cell side of the layer presumably balances hydrolysis and loss on the luminal side.

Bicarbonate secretion by surface mucous cells is stimulated by $PGE_2$ and $PGF_2$ at low concentration in amphibians and similar phenomena may occur in mammals. Prostaglandins, ubiquitous in gastric mucosal lamina propria, may have protec-

tive effects other than by stimulation of bicarbonate secretion by mucous cells and by inhibition of histamine-stimulated acid secretion by parietal cells. In some species, prostacyclin ($PGI_2$) and prostaglandins of the E and A series cause vasodilation and increased blood flow in addition to inhibiting acid secretion. The high metabolic rate of the gastric mucosa requires a high blood flow to maintain an intact surface epithelium and experimentally, increased perfusion is protective against a number of significant mucosal insults.

### *Response of the Gastric Mucosa to Insult*

Repair of acute erosive physical or chemical trauma to the mucosal surface, such as that caused by aspirin and, presumably, by abrasive foreign bodies, is by proliferation of cells in the isthmus, if the erosive lesion is superficial, and spares the progenitor cells. An acute inflammatory reaction demarcates eroded or superficially necrotic mucosa. Mitoses become common in the upper gland. During the early phase of repair, cells lining shallow foveolae and covering the surface are basophilic, poorly differentiated, and flattened, cuboidal, or low columnar. Sites of epithelial exfoliation and neutrophil transmigration or effusion into the lumen may be evident. Congestion, edema, mild neutrophilia, and fibroplasia are seen in the superficial lamina propria. The evolution and repair of gastric ulceration, to which erosion may be antecedent, is discussed later. The progenitor cells of the fundic mucosa have the potential to produce tall columnar mucous cells of the foveolar or surface type, to produce mucous neck cells, and presumably by further differentiation, to evolve parietal cells. **Atrophy** of **parietal cell mass** without extensive mucous-cell hyperplasia occurs in animals, particularly ruminants, that have signs of gastrointestinal disease including inappetence. The change is not evident grossly. Microscopically, fewer parietal cells are seen in the upper neck of fundic glands, and apparently, in the depth of the gland. This is accompanied by epithelial proliferation, indicated by moderate numbers of mitotic figures at the isthmus and in the neck of the gland. The PAS stain demonstrates the encroachment of increased numbers of such cells into the deeper portion of fundic glands. In extreme cases, mucous neck cells are present to the base of glands, and achlorhydria occurs.

The cause of this change is unclear. It has been demonstrated in sheep infected with intestinal nematodes, but similar findings occur in animals with a wide variety of syndromes involving loss of appetite. Starvation of moderate duration does not produce comparable lesions. Reduction in, or interference with, the trophic effect of gastrin on parietal cell mass, might be the mechanism in parietal-cell atrophy of this type.

Inflammatory infiltrates are unusual and mild in normal fundic mucosa. Chronic inflammation in the fundic stomach in all species is associated with the development of **mucous metaplasia** and **hyperplasia** of glands in the vicinity of inflammatory foci. As the lesion evolves, parietal cells are present only in the basal portion of the glands, and they appear to be progressively displaced by hyperplastic mucous cells.

Mitotic figures may be numerous throughout the neck of the gland, which elongates. The epithelium in early lesions tends to resemble mucous neck cells. In established lesions, columnar mucous cells with regular nuclear polarity, similar to foveolar mucous cells, may be present. When inflammatory infiltrates are local, the mucous change is limited to a few surrounding glands. More diffuse inflammation is associated with the development of widespread epithelial mucous metaplasia.

Mucous metaplasia and hyperplasia may be mediated in part by immune events or inflammation in the lamina propria. Interactions between immune processes in the stomach and epithelial differentiation are poorly explored. Secretion of lysozyme, and of secretory piece and IgA, are properties of mucous neck cells in gastritis in humans. Cell-mediated immune events in the lamina propria of the small intestine are increasingly implicated in altered proliferation and differentiation of enteric epithelium by as yet undefined mechanisms. It may be that similar phenomena in the stomach await recognition and investigation.

Such atrophy of the parietal cells and mucous metaplasia and hyperplasia apparently do not result from withdrawal of the trophic stimulus of gastrin. At least in *Ostertagia*-induced gastritis, it occurs in the face of gastrin concentrations many times above normal levels, which are not simply the result of achlorhydria and failure of suppression of G-cell secretion by antral acidification. Mucous metaplasia and hyperplasia are associated with focal or diffuse, superficial or mucosal, proprial infiltrates of plasma cells and lymphocytes. Often, neutrophils, eosinophils, and Russell-body cells will be present in the lamina propria, and lymphocytes may be between epithelial cells in glands. Globule leukocytes are present in the epithelium of glands, especially in the parasitized abomasum.

This mucous metaplasia, hyperplasia, and chronic inflammation are associated with a variety of causes, including chronic traumatic insults, such as those due to implanted foreign bodies, which may render the mucosa permeable to antigen present in the lumen. Abomasal involvement in bovine virus diarrhea or herpes rhinotracheitis is associated with mucosal lesions of this type. The specific agency most commonly recognized is gastric parasitism by nematodes such as *Ostertagia* spp., *Trichostrongylus axei*, and *Hyostrongylus rubidus*, where the distribution of the lesion is closely related to the physical presence of nematodes and to the interstitial inflammatory reaction they incite. Mucous metaplasia and hyperplasia are also typically present around the healing margins of chronic ulcers, perhaps in response to local inflammation.

The mucosa affected in these circumstances is grossly thickened, as on the overhanging margin of an ulcer or in an *Ostertagia* "nodule," with a pebbled or convoluted surface if the lesion is widespread. Gastric rugae or plicae are thickened, partially as a result of mucosal hypertrophy, perhaps with submucosal edema. The surface of the stomach is usually paler than normal in affected areas; however, local congestion or hyperemia may be evident. Though the surface may be glistening, profuse mucus secretion is not usually obvious. Achlorhydria is the consequence of widespread change of this type. Mucous metaplasia and hyperplasia are differentiated on the basis of the degree of mucous-cell hyperplasia and differentiation, and the presence of inflammatory cells, from fundic atrophy associated with loss of appetite.

Antral mucosa also undergoes hyperplasia and thickening in

antritis. Some chronic inflammatory infiltrate between antral glands and at the base of the mucosa is usual, and lymphoid follicles may be present in the lamina propria. Expansion of the proliferative compartment in the antral glands is recognized as mitotic figures scattered in the neck of the gland. Foveolar and glandular mucous cells increase in number, and the antral mucosa is thickened and superficially rugose, perhaps with local congestion or erythema. The stimulus for antritis is often unclear. Gastric reflux of duodenal contents containing bile may be of some significance in the dog. In ruminants, the pyloric mucosa may be colonized by abomasal nematodes, and by a few worms of species normally found in the small intestine if enteric populations are high.

The functional significance of gastric mucous metaplasia is unclear. Presumably, hyperplasia of cells is partly a response to soluble local immune-mediated stimuli or products of inflammation. Replacement of parietal cells by mucous neck cells, or an apparently more fully differentiated mucous cell in chronic gastritis, may be a protective response. It may eliminate the threat of local acid corrosion and promote the transfer into the lumen of protective soluble factors such as lysozyme and IgA or its analogs.

Achlorhydria ensues in severe chronic gastritis and mucous metaplasia. The pH of gastric secretion approaches or exceeds neutrality under some circumstances, as sodium ion replaces hydrogen ion in gastric content and bicarbonate is secreted. With diminished gastric acid concentration, progressive microbial colonization of the stomach and upper intestine ensues. Parietal-cell atrophy and replacement by mucous neck cells in ruminants with anorexia due to enteric disease may predispose to mycotic invasion of the mucosa. Mucous metaplasia and hyperplasia, as seen in chronic gastritis or conditions like ostertagiosis, does not seem to render the mucosa prone to mycosis. Loss of the hydrolytic effects of acid and pepsin, in achlorhydria, seems to have little effect on digestion of protein and uptake of nitrogen, at least in animals with ostertagiosis, and effects of atrophic gastritis in humans on protein digestion appear to be minimal.

### *Pyloric Stenosis*

Pyloric stenosis is a functional and sometimes anatomic problem that, in part, represents probably the only anomaly of the stomach recognized in animals. It is apparently common in dogs and rare in cats and horses. It appears as a presumably congenital problem in many instances. Recurrent vomition and poor growth in recently weaned animals suggest the clinical diagnosis of a congenital lesion. Signs beginning later in life indicate an acquired problem. Contrast radiographic studies will confirm delayed gastric emptying. There is limited critical information on this problem. Clinical reports indicate that in some dogs there may be hypertrophy of pyloric muscle, which appears grossly thickened. Tonic stenosis of the pyloric sphincter may occur in dogs, perhaps due to unconfirmed lesions of the myenteric plexus or due to gastrin excess. In cats, no gross alteration in the diameter of the pylorus or the thickness of its muscle is recognized. An association with esophageal dilatation has been made in the cat. Congenital pyloric stenosis in a foal was associated with signs of abdominal pain and reluctance to consume solid feed. In all species the clinical problem is usually abolished by pyloromyotomy.

Acquired pyloric stenosis or obstruction occurs following ulceration and stricture of the pyloric canal in any species, due to hypertrophic antritis in dogs, and as a complication of polyps and tumors in the area.

### *Gastric Dilatation and Displacement*

**Gastric dilatation** in the **horse** is often a secondary effect of obstruction of the small bowel or of colic with ileus and is also part of the syndrome "grass sickness," discussed elsewhere. Primary gastric dilation, and sometimes rupture, in horses is a sequel to consumption of excess fermentable carbohydrate or sudden access to lush pasture. The pathogenesis is analogous to that of grain overload in cattle. Ingesta may swell through absorption of saliva and gastric secretion. Evolution of gas and organic acids, including lactic acid, by bacterial fermentation of carbohydrate occurs in the cranial portion of the stomach. An influx of water follows as the result of increased osmotic pressure in the stomach, contributing to increased distention and systemic dehydration. Animals surviving for any time with acute gastric dilatation of this type may develop laminitis. The contents of the stomach in gastric dilation may be fluid, especially in secondary dilatation, and can smell fermented in primary dilation. Gastric rupture may ensue. Rupture usually occurs along the greater curvature parallel to the omental attachment, releasing gastric content into the omental bursa or the abdominal cavity. Death ensues acutely as the result of shock and peritonitis. The margins of the gastric laceration, which may be 10–15 cm long, show evidence of antemortem hemorrhage. Postmortem rupture of the dilated stomach is common and must be differentiated. There may be congestion of the cervical esophagus and blanching of the thoracic esophagus, producing a prominent "bloat line." This, and compression atelectasis of the lungs in some cases, attests to the tremendous increase in intraabdominal and intrathoracic pressure exerted by the dilated stomach prior to rupture. Congestion of cervical and cranial soft tissues and blanching of the abdominal organs also are found. Perforation, as distinct from rupture, of the stomach in the horse is rare and is associated with parasitism, peptic ulcer, or neoplasia.

**Gastric dilatation** and **volvulus** occur relatively commonly in the dog (Fig. 1.11D), and the condition has been reported in swine and a cat. In dogs, gastric dilatation and volvulus is usually a problem associated with overeating and probably aerophagia, especially in the deep-chested breeds such as Great Danes, St. Bernards, Irish setters, wolfhounds, borzois, and bloodhounds. Beyond that, hereditary factors, management, behavior, and type of feed may contribute in obscure ways to the development of dilation. The gas, which appears to play a large part in the development of dilation, is probably the result of aerophagia and evolution of carbon dioxide by physiologic mechanisms, rather than the product of intragastric clostridial fermentation. Inability to relieve the accumulation of food, fluid, and gas in the stomach causes the organ to dilate and alter its intraabdominal position, so that its long axis rotates from a transverse left–right orientation to one paralleling that of the

abdomen. In simple dilation, the esophagus is not physically completely occluded, the spleen remains on the left side, and the duodenum is only slightly displaced dorsally and toward the midline. The gastric mucosa at this stage is usually not infarcted, though the effects of dilation on venous return from the abdomen and on the systemic circulation may be substantial.

For reasons that are unclear, gastric dilatation may be converted to gastric volvulus. Perhaps this is related to laxity or laceration of the gastrohepatic ligament, or to the development of violent antiperistalsis and abdominal contraction in vain attempts by the dog to vomit against a functionally or physically obstructed cardia. The stomach rotates about the esophagus in a clockwise direction, as viewed from the ventrocaudal aspect. The greater curvature of the distended organ moves ventrally and caudally, and then rotates dorsally and to the right. This forces the pylorus and terminal duodenum cranially to the right and clockwise around the esophagus. Ultimately, they lie to the left of midline across and ventral to the esophagus, compressed between the esophagus and the dilated stomach. Depending on the degree of volvulus, the spleen, which follows the gastrosplenic ligament, usually ends up lying in a right ventral position, between the stomach and liver or diaphragm. It is bent into a V shape by tension on its ligaments, becomes extremely congested, and may undergo torsion, infarction, and rupture. The esophagus becomes completely occluded in volvulus, which may involve rotation of up to 270 to 360°. Venous infarction of the gastric mucosa ensues as volvulus progressively constricts venous outflow from the stomach. The mucosa and, usually, the full thickness of the gastric wall are edematous and dark red to black, and there is bloody content in the lumen of the stomach. Necrosis of ischemic mucosa occurs, and the stomach may rupture.

Obstruction of veins by volvulus and pressure exerted by the distended stomach result in decreased venous return via the portal vein and posterior vena cava, causing reduced cardiac output and circulatory shock. Endotoxemia is implicated speculatively in disseminated intravascular coagulation and may contribute to shock. A variety of acid–base and electrolyte abnormalities ensue in dogs with gastric dilatation and volvulus, contributing to the physiologically precarious state. Cardiac arrhythmias as a sequel to gastric dilatation and volvulus have been associated with putative release of "myocardial depressant factor" from an ischemic pancreas, and with myocardial necrosis, possibly the result of ischemia. Death is inevitable in dogs not treated early.

**Abomasal displacement** and **volvulus** is a common clinical problem in high-producing, intensively managed, dairy cattle, particularly around the time of parturition. The displacement usually is ventrally and to the left of the rumen. Many affected animals have concurrent problems, including ketosis, hypocalcemia, metritis, and retained placenta. Abomasal atony and increased gas production are believed to be prerequisites for displacement of the organ. Influx of high concentrations of volatile fatty acids from the rumen, and hypocalcemia, may play a part in instigating hypomotility, while evolution of gas in the abomasum is directly related to the amount of concentrate in the ration. Left displacement of the gas-filled abomasum is amenable to treatment and is rarely encountered at autopsy. Handling of an affected animal postmortem may correct displacements in any case. Other than possible scarring of the lesser omentum, the abomasum may be unremarkable. Simple right displacement, which accounts for 9 to 15% of abomasal displacements, is probably caused by similar agencies. But right displacement may be complicated in about a fifth of cases by progression to abomasal volvulus, which is clinically serious.

**Abomasal volvulus** is probably the sequel to rotation of a loop formed by a distended abomasum and attached omasum and duodenum, counterclockwise about a transverse axis through the lesser omentum when viewed from the right side. Rotation, buoyed by the gas-filled body of the abomasum, may be in the sagittal plane. With a 360° volvulus, the pylorus ends in the anterior right portion of the abdomen dorsal to the twisted omasum, with the duodenum trapped medial to the omasum and lateral to the partially rotated reticulum. Alternative modes of displacement and rotation are possible, but all may end in this relationship. Obstruction of duodenal outflow in volvulus results in sequestration of chloride in the abomasal content and the development of metabolic alkalosis. Severe volvulus causes obstruction of blood vessels at the neck of the omasum, as well as causing trauma to the vagus nerves in the region. The abomasum becomes distended with bloodstained fluid and gas. Infarction of the deeply congested mucosa may result in ultimate abomasal rupture, often near the omaso–abomasal orifice, and peritonitis. Damage to the vagal branches may prohibit return of normal abomasal motility in animals successfully withstanding surgery.

### *Gastric Foreign Bodies and Impaction*

A variety of foreign bodies may be encountered in the stomach and, rarely, in the abomasum. Most are incidental findings, or at worst, associated with vomition, mild acute or chronic gastritis, or occasionally ulceration. Rarely, obstruction of the pyloric outlet ensues. Hair balls are often found in the stomach of longhaired cats, and in calves reared on diets low in roughage, where most are in the rumen, with a few in the abomasum. Accumulation of considerable amounts of fine sand may occur in the abomasum, apparently with little ill effect.

Gastric impaction by inspissated content is reported in the horse as a clinical problem of unknown cause. It causes severe abdominal pain and is to be differentiated clinically and at autopsy from gastric dilation secondary to intestinal obstruction, and from primary gastric dilation due to ingestion of excess fermentable carbohydrate.

Primary abomasal impaction is the product of a regime of restricted water intake and coarse, high-roughage feed, such as wheat stubble or straw, as may occur in winter feeding of cattle in northern prairie areas. Secondary abomasal impaction may follow pyloric stenosis, physical or functional, of any cause. Rarely, foreign bodies such as ingested placenta or hair balls block the pylorus. It is perhaps most common as a functional abomasal stasis in one of the manifestations of "vagus indigestion," which is discussed more fully under Traumatic Reticuloperitonitis and Its Complications. Loss of abomasal motility may be the product of intrathoracic inflammatory or neoplastic vagal lesions, vagal involvement in adhesions following traumatic reticuloperitonitis, vagal trauma in surgically cor-

rected abomasal volvulus, or adhesions of the abomasum and omasum, which may physically impair motility. The abomasum is impacted with inspissated coarse ingesta, despite an apparently patent pylorus. Metabolic derangement due to sequestration of chloride in the rumen following regurgitation from the obstructed abomasum, and hypokalemia due to decreased intake in feed in the face of continued normal renal excretion, place these animals in perilous physiologic circumstances before inanition becomes a significant factor.

### *Circulatory Disturbances*

Hyperemia of the gastric mucosa is a concomitant of the ingestion of chemicals such as arsenic, thallium, and aspirin. It usually coexists in these circumstances with superficial erosion, which is discussed later with gastric ulcer. Focal hyperemia may be related to local irritation of the mucosa by foreign bodies, and with focal acute viral lesions of the abomasum in cattle. Congestion of the mucosa can occur in conditions causing portal hypertension, including cirrhosis and shock in the dog.

**Uremic "gastritis"** presents as severe congestion of the body of the stomach, associated with signs of hematemesis and melena, is found in some dogs with chronic renal disease. In such animals, the mucosa is thickened and deep red-black. Lesions vary in severity from case to case, and premonitory changes without severe hemorrhage and necrosis are present in animals euthanized earlier in the course of disease. In such dogs there may be no gross gastric lesion, or variable edema and thickening of rugal mucosa, perhaps with focal ulceration.

Microscopically, the lamina propria between glands is edematous, and there are increased numbers of mast cells. Deposits of basophilic ground substance and mineral are found, especially on the basement membrane of vessels and glands, or on collagen fibrils and in degenerative smooth muscle. These changes occur particularly in the middle and deeper portions of the mucosa. Parietal cells in this area are usually mineralized as well. Such mineral deposits may be appreciated at autopsy in gross cross sections of mucosa. More extensive mineral deposition also involves arterioles of the submucosa and serosa. Such vessels also show evidence of endothelial damage, medial necrosis, and in some cases, thrombosis. Severe mucosal congestion, edema, and necrosis are possibly related to ischemia secondary to the vascular lesions, though perhaps not directly associated with arterial thrombosis and obstruction, which is often not readily found. Microvascular lesions in the lamina propria and systemic states in uremia may be contributory. Impaired renal degradation and excretion of gastrin may promote hyperchlorhydria and exacerbate mucosal damage.

The cause of the vascular lesions may be a poorly characterized circulating toxic peptide associated with uremia. Mineral deposition is probably the product of altered systemic metabolism of calcium in renal failure, perhaps coupled with the local microenvironment resulting from bicarbonate moving across the basal border of secreting parietal cells. Membrane lesions in metabolically compromised parietal cells may also act as foci of mineral deposition (see the Urinary System, this volume, for discussion of uremia).

**Gastric venous infarction** is a common lesion in swine and is also encountered in ruminants and horses. It is related to endothelial damage and thrombosis in venules, usually associated with endotoxemia or other bacterial or toxic damage. Salmonellosis and *Escherichia coli* septicemia in all species and, in addition, in swine, postweaning coliform gastroenteritis, erysipelas, swine dysentery, Glasser's disease, and hog cholera are associated with the lesion. The fundic mucosa is bright red or deep red-black and may have some excess mucus or perhaps fibrin on the surface (Fig. 1.34D). Occasionally, the superficial mucosa is obviously necrotic and may lift off with the ingesta. In section there is thrombosis of venules in the mucosa and often at the mucosal–submucosal junction, usually with prominent fibrin plugs. Thrombosed capillaries and venules may be present at any level of the mucosa, along the base of the ischemic zone of superficial coagulation necrosis, with local hemorrhage and edema. There may be an acute inflammatory reaction delineating the necrotic area in the mucosa. Sometimes the full thickness of the gastric mucosa, focally or diffusely, may be necrotic.

**Edema** of the gastric rugae occurs with hypoproteinemia in any species and is found in the abomasum of cattle poisoned by arsenic. Edema fluid collects in the submucosa of the folds and is particularly obvious in the normally thin abomasal plicae. Edema may contribute to the thickening of rugae seen in gastritis. Edema of the submucosa of the stomach is a common and important lesion in gut edema of swine (Fig. 1.34C). It is best appreciated by making several slices through the serosa and external muscle to the submucosa over the body of the stomach. Gut edema is considered fully under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

### *Gastritis*

Gastritis is a poorly defined term often applied to acute gastric injury with grossly visible hemorrhage or erosion, when inflammatory processes, strictly speaking, are scarcely present. The differential considerations in diffuse gastric hemorrhage, and the etiopathogenesis of mucosal erosion will be considered later, with ulcer. Microscopic acute inflammatory infiltrates in the gastric wall are usually associated with subacute superficial erosion, the floor of a stable gastric ulcer, gastric venous infarction, clostridial and mycotic gastritis, chronic active interstitial inflammation, and some acute systemic viral infections.

Chronic gastritis, as it is seen in humans, is rarely recognized in domestic animals. **Chronic superficial gastritis** is a term applied in humans to a lesion with a chronic inflammatory infiltrate confined to the interfoveolar propria; normal gastric glands with minimal interstitial infiltrate are present. Such an entity might occur in animals sporadically, with no etiologic connotation. Chronic atrophic gastritis, as it is defined in human beings, is very rarely encountered. Atrophy of parietal cell mass, associated with autoimmune phenomena and the development of pernicious anemia, does not occur spontaneously in animals, though it can be induced in dogs by immunization with gastric juice. Chronic antritis with reduced gastrin secretion theoretically might result in atrophy of parietal cell mass. Duodenal reflux in dogs has been associated with a syndrome of vomition and gastric hyposecretion. Mononuclear-cell infiltrates and follicle formation in the lamina propria of the antrum and fundus are found, with subjective atrophy of parietal cell mass.

Intestinal metaplasia of the gastric mucosa, considered to be a

sequel to chronic gastritis in humans, is rarely, if ever, found in domestic animals. The stomach in dogs is involved very uncommonly in eosinophilic gastroenteritis. Eosinophils may infiltrate the mucosa and submucosa in large numbers, in association with a syndrome of protein loss, eosinophilia, and eosinophilic infiltrates in more distal gut (see diseases of the intestine, below). Even rarer cases of scirrhous eosinophilic gastritis and arteritis, and of histiocytic gastritis in association with amyloidosis in dogs, are on record.

**Chronic hypertrophic gastritis**, similar to Menetrier's disease of humans, occurs in dogs. Vomition and weight loss, in some cases associated with inappetence or diarrhea, are described in the history. The characteristic lesion is marked gastric rugal hypertrophy involving part or most of the fundic mucosa in the greater curvature. Grossly thickened folds of gastric mucosa over an area 4–10 or 12 cm in diameter are thrown up in a convoluted pattern that may resemble cerebral gyri. Microscopically, these areas are composed of hyperplastic mucosa, which may or may not include secondary folds of muscularis mucosa and submucosa. Findings are variable in the few cases reported. There may be foveolar and glandular hyperplasia with progressive or total loss of parietal cells, which are replaced by mucous cells of varying degrees of differentiation. Cystic dilatation of mucous glands may occur. Mononuclear cells infiltrate the lamina propria between glands and near the muscularis mucosa, and the propria may be edematous.

The lesion is to be differentiated from adenomatous polyps, Zollinger–Ellison syndrome, and infiltrating lymphoid tumors. Its cause is unknown. The condition in humans is associated with protein-losing gastropathy. Perhaps significantly, chronic gastritis and chronic hypertrophic gastritis have been reported a number of times in the basenji, a breed in which a syndrome of protein-losing gastroenteritis and diarrhea is well recognized. This syndrome, and the enteric lesions associated with it, will be discussed with diseases of the intestine. Hypertrophic antritis, producing a thickened, sometimes convoluted mucosa in the antrum, has been associated with pyloric stenosis in dogs, considered earlier. Its cause is unknown but may be related to chronic irritation by duodenal reflux.

**Braxy**, or bradsot, is an acute abomasitis of sheep and, rarely, cattle, due to infection with *Clostridium septicum* (Fig. 1.41B). It is a sporadic disease of young animals, usually occurring in cooler climates. It is reported from Iceland, Scandinavia, Scotland, Canada, the northern United States, and Tasmania. The factors initiating bacterial invasion are unknown. Cold weather is usually associated with the disease, but it is difficult to imagine feed being cold enough, by the time it attains the abomasum, for significant mucosal hypothermia and necrosis to occur. Evolution of exotoxin by *C. septicum* causes the signs and death, which usually ensues acutely.

At autopsy there may be blood-tinged abdominal fluid, and the serosa of the abomasum may be congested or fibrin covered. Mucosal lesions may be diffuse or involve demarcated foci of variable size and shape. Abomasal folds may be thickened, reddened, occasionally hemorrhagic, or necrotic. Most notable is the presence of extensive gelatinous edema and emphysema in the submucosa. Diffuse edema, and extensive areas of suppurative infiltrate demarcating areas of coagulation necrosis, with prominent pockets of emphysema, are evident in tissue sections. These involve mainly submucosa and extend into adjacent mucosa and external muscle. There may be venous thrombosis and hemorrhage. Gram-positive bacilli are usually evident as individuals or colonies in affected tissue. They may be identified as *Clostridium septicum* by fluorescent antibody reaction or culture. Such lesions are occasionally complicated by other clostridia. Braxy must be differentiated from cellulitis of the abomasal wall due to mixed anaerobic flora without *C. septicum*.

**Abomasitis** associated with **viral infection** occurs in a number of the systemic viral diseases affecting the gastrointestinal tract, including infectious bovine rhinotracheitis in calves and, rarely, older animals, herpesvirus infections of small ruminants, bovine virus diarrhea, rinderpest, malignant catarrhal fever, and bluetongue. Abomasal lesions are rarely the sole manifestation of these diseases but form part of a picture at autopsy that may suggest an etiologic diagnosis. The appearance and pathogenesis of abomasitis in these diseases varies with the conditions, which are discussed in detail under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

**Mycotic gastritis** is a sporadic problem almost invariably secondary to insults that cause achlorhydria (or focal atrophy), necrosis, or ulceration under conditions where mycotic colonization can occur. Compromised resistance, perhaps associated with neoplasia, endogenous or exogenous steroids, lympholytic viral disease, and altered gastrointestinal flora due to antiobiotic therapy, may further promote mycosis. Fungal hyphae attaining the submucosa typically invade venules and arterioles, causing thrombosis and a hemorrhagic infarct. The agents involved are usually zygomycetes (phycomycetes) such as *Rhizopus, Absidia,* or *Mucor;* rarely, *Aspergillus* may be implicated.

Mycotic abomasitis in calves is secondary to gastrointestinal infectious bovine rhinotracheitis and to venous infarction of the mucosa in endotoxemia or septicemia with *E. coli* or *Salmonella*. Bovine virus diarrhea and, occasionally, gastric ulcer provide conditions for mycotic invasion of the abomasum in older cattle. The lesions are areas of necrosis, with an intensely congested or hemorrhagic periphery, ranging in diameter from 1 to 2 cm, to confluence over much of the body of the stomach (Fig. 1.11A). Affected mucosa is thickened, red or pale in the necrotic zone, and may be covered by hemorrhage. Edema and hemorrhage are evident in the submucosa. The lesion may penetrate to the serosa, where it is typically seen as a roughly circular area of hemorrhage in the external muscle and subserosa. Hyphae, usually broad and nonseptate zygomycotic in type, are present in sections of the necrotic mucosa, submucosa, and invading vessels, where they initiate thrombosis (Fig. 1.11B,C). The associated inflammatory infiltrate is usually consistent with acute or subacute insult.

In dogs, rare cases of acute multifocal **infarctive** or **granulomatous gastritis** are reported, associated with zygomycetes. **Mycosis** of the glandular stomach of horses and pigs is virtually unknown. **Candidiasis** of the pars esophagea may occur in swine, often in association with preulcerative epithelial hyperplasia and parakeratosis. An overview of mycosis of the digestive system, and its sequelae, is provided under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Parasitic gastritis is generally of little significance in small animals. Members of the genera *Physaloptera* and *Gnathostoma*

are found in dogs, where the former cause focal ulceration and the latter are the cause of submucosal inflammatory cysts containing suppurative exudate and worms. In cats, *Physaloptera* spp. may attach to mucosal ulcers, while *Gnathostoma* spp. and *Cylicospirura felineus* are found in nodules in the gastric wall. *Ollulanus tricuspis* is found on the mucosa of the stomach in cats, where it may cause mild to, rarely, severe chronic gastritis.

In the horse, *Draschia megastoma* is found in inflammatory nodules in the submucosa of the cardiac zone, especially along the margo plicatus. *Habronema muscae* and *H. majus* (formerly *microstoma*) are found on the mucosa and have been associated with mild ulceration. *Trichostrongylus axei* may cause chronic gastritis in the horse. Bots of the genus *Gasterophilus* are found attached to small erosions and ulcers in the esophageal and glandular mucosa.

In swine, the spirurids *Ascarops* spp., *Physocephalus* spp., and *Simondsia* spp. are associated with mild gastritis in heavy infections. *Gnathostoma* may be embedded in inflammatory cysts in the submucosa. *Ollulanus tricuspis* may be encountered. *Hyostrongylus rubidus* can cause chronic gastritis and wasting in pigs.

In cattle, sheep, and goats, members of the genera *Haemonchus* and *Mecistocirrus* are large, abomasal, bloodsucking trichostrongyles, capable of causing severe anemia and hypoproteinemia. *Ostertagia* spp. and related genera, including *Camelostrongylus, Teladorsagia, Marshallagia,* and *Trichostrongylus axei* in various ruminants cause chronic abomasitis with mucous metaplasia, achlorhydria, diarrhea, and plasma protein loss. Large schizonts of undetermined coccidia in sheep produce harmless, pinpoint, pale foci in the abomasal mucosa; formerly the obsolete name *Globidium gilruthi* was applied. The pathology and pathogenesis of the significant gastric parasitisms is considered in greater detail under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

### *Gastroduodenal Ulceration*

Gastroduodenal ulcer produces signs of disease much less often in animals than in humans. The pathogenesis of peptic ulcer in humans or animals is by no means clear. It resolves into a relative imbalance between the necrotizing effects of gastric acid and pepsin on one hand, and the ability of the mucosa to maintain its integrity on the other. Hypersecretion of acid, or impairment of mucosal integrity in the face of normal acid secretion, may be invoked as general mechanisms. Some suggest that peptic ulceration of the duodenum, pylorus, or combined gastric and duodenal ulcers in humans reflect mainly hypersecretion, while ulcers in the body of the stomach mainly are a result of deficient mucosal resistance.

Factors implicated in hypersecretion of acid include abnormally high basal secretion, possibly associated with an expanded parietal cell mass, perhaps the result of increased trophic stimulation by gastrin. Gastrinomas cause the Zollinger–Ellison syndrome, characterized by elevated gastric acid secretion and severe gastroduodenal ulceration. Increased histamine levels associated with mastocytosis or mastocytoma also cause acid hypersecretion and ulceration.

Ulceration due to compromise of mucosal protective mechanisms is attributed to nonsteroidal antiinflammatory agents such as aspirin, phenylbutazone, and indomethacin. The therapeutic and ulcerogenic properties of these drugs reside largely in their effects on prostaglandin metabolism. This they block by interfering with the cyclooxygenase-catalyzed conversion of arachidonic acid to the prostaglandin endoperoxides $PGG_2$ and $PGH_2$. In the stomach, prostaglandin-mediated vasodilatation, modulation of histamine-induced acid secretion, and stimulation of bicarbonate secretion by mucous cells may be impaired. In addition to the effect of ionized aspirin on prostaglandin synthesis, in the acid gastric environment un-ionized, lipid-soluble acetylsalicylic acid readily crosses the surface-cell membrane. It damages the cell metabolically, permitting back-diffusion of acid and incipient ulceration.

Reflux of duodenal contents containing bile salts has been implicated in the induction of gastritis and gastric ulcer. Under some experimental conditions, acid back diffusion into the gastric mucosa, and morphologic damage, have been caused by application of bile salts. The effects are dependent on the $pK_a$ of the bile salt, which must be soluble at acid pH, and on the concentration of hydrogen ion. Lipid solubility of bile salts, and associated damage to surface-cell membranes, may mediate these effects. Alcohols, also lipid-soluble compounds, alter permeability of gastric mucosa and permit back diffusion of acid. Lysolecithin, formed when pancreatic lipase hydrolyzes lecithin in bile, increases gastric mucosal permeability too.

Glucocorticoids and "stress" have been implicated in the genesis of ulcer, though the role of steroids is controversial. Experimentally, gastroduodenal hemorrhage and ulceration occur in some species of animals stressed by restraint or social factors, and they are a feature of "trap-death syndrome" in small mammals. Severe gastric hemorrhage or ulceration may occur following neurosurgery, trauma to the spinal cord, and burns, and it is considered by some to be stress related. Administration of steroids may cause increased gastrin and acid secretion. Steroids decrease reparative gastric epithelial-cell turnover and, by stabilizing membranes, decrease the availability of arachidonic acid for prostaglandin synthesis. These effects may predispose to development of ulcer when combined with other insults.

Reduced mucosal perfusion or ischemia may be a principal factor interacting in stress-associated ulceration, and in that initiated by other modalities discussed previously. Reduced blood flow to the mucosa in local areas has been suspected, under a number of circumstances, to precede mucosal hemorrhage or erosion. Ischemia will result in hypoxemic compromise of surface cells. In combination with the effects of other insults, this may cause reduced bicarbonate secretion and initiate mucosal permeability and back diffusion of acid. Mechanisms of mucosal ischemia are obscure. Reduction in local prostaglandin concentration may contribute, as may local or systemic hypotension. Following mucosal damage and back diffusion of hydrogen ions, vasodilatation and hyperemia develop, perhaps the result of liberation of mucosal histamine. Microvascular disruption then results in hemorrhage.

Whatever the cause, the results of a breach of the gastric mucosa have the potential to follow a **common pathway** to **ulceration** in all species. Acute superficial lesions such as those associated with stress or following administration of aspirin are

often seen as areas of reddening and hemorrhage, especially along the margins of rugae in the fundic mucosa. Acid treatment of hemoglobin gives blood on the surface or in the gastric lumen a red-brown or black color. In some species, severe "stress-associated" gastric hemorrhage may occur diffusely over the entire congested gastric mucosa, resulting in hypovolemic shock and anemia, with melena. In some instances, melena, presumably the result of a recent episode of gastric bleeding, may be present in the lower intestine, with minimal gross evidence of hemorrhage or ulceration in the stomach. The microscopic lesion associated with hemorrhage of this type is often subtle, bleeding seemingly resulting from diapedesis, with minimal mucosal damage. Usually there is superficial erosion of the mucosa, often difficult to differentiate from autolysis, with granules of brown, acid hematin in debris on the surface. Inflammation is usually absent. Evidence for healing mild gastric erosion is the presence of basophilic, poorly differentiated, flattened, cuboidal or low columnar cells on the mucosal surface, with mitotic cells in the upper neck of the glands.

Lesions of any genesis proceeding to gastric ulcer do so by progressive coagulation necrosis of the gastric wall. Ulcers vary in microscopic appearance depending on their aggression, and the point in their development at which they are intercepted. Acute gastric lesions appear as erosions with superficial eosinophilic necrotic debris and loss of mucosal architecture to the depths of the foveolae, or as a depression in the mucosal surface with necrotic debris at the base. Necrosis usually extends rapidly to the muscularis mucosa, causing ulceration. Once the superficial portion of the mucosa is destroyed, natural local buffering by surface cells is lost, and the proliferative compartment of the gland, which is near the surface, is obliterated, preventing a local epithelial reparative response. Ulcers attaining the submucosa impinge on arterioles of increasing diameter, multiplying the risk of significant gastric hemorrhage. The ulcer may progress through the muscularis and serosa, culminating in perforation of the gastric wall. Severe gastric hemorrhage and perforation are relatively common sequelae of gastroduodenal ulceration in domestic animals.

Ulcers that come into equilibrium with reparative processes may do so at any level of the gastric wall below the mucosa, but usually at the submucosa. Subacute to chronic ulcers are typified by a base and sides composed of granulation tissue of varying thickness and maturity, infiltrated by a mixed inflammatory cell population, and overlain by a usually thin layer of necrotic debris. Chronic ulcers wax and wane. Depending on the relative dominance of reparative processes and aggressive ulceration, the layer of granulation tissue may be thick and mature, or thinner, less mature, and with superficial evidence of recent necrosis. There is mucous metaplasia and hyperplasia in glands at the periphery of the ulcer, which, with time, overhang the edge of the lesion. Under favorable conditions they gradually fill in the mucosal defect from the margins. Healed ulcers are usually depressed and may be somewhat puckered, with a scirrhous submucosa on cut section. The mucosa of healed ulcers, even in the fundic zone, is comprised of mucous glands. Excessive scarring of healed ulcers strategically located near the pylorus may lead to pyloric obstruction in any species.

Duodenal ulcers, which usually occur proximal to the opening of the pancreatic and bile ducts, resemble gastric ulcer in their pathogenesis, microscopic appearance (allowing for their intestinal location), evolution, and sequelae.

Peptic ulcer occurs commonly in cattle, uncommonly in dogs, rarely in cats, and is unusual in horses and swine, where ulceration of the esophageal, rather than glandular, gastric mucosa is the rule. In most species the prevalence of ulcer is probably underestimated, since only lesions producing severe signs associated with pain, hemorrhage, or perforation come to attention.

**Peptic ulcer** in **dogs** is relatively infrequently reported in the literature but is seen on a regular basis in university clinics, usually in adult animals. Signs associated with peptic ulcer include variable appetite, abdominal pain, vomition, melena, and anemia. Ulcers, a few millimeters to 3 to 4 cm in diameter, are found most commonly in the pyloric antrum or proximal duodenum. The gross and microscopic appearance of ulcers vary with their aggressiveness and duration, as previously described. Thrombosed arterioles and venules cut by the ulcerative process are often seen and should be sought in the bed of gastric and duodenal lesions associated with anemia or obvious hemorrhage.

**Perforation** of **gastric** or **duodenal ulcers** may lead to massive hemorrhage or release of gastric contents into the abdomen. Perforating duodenal ulcer may instigate pancreatitis. Some ulcers perforate silently, the serosal lesion healing by granulation, or adhesion by, and fibroplasia in, the omentum. The irritant nature of gastric contents released in these circumstances may lead to chronic inflammation, granulation, and thickening of the serosa, even when previous perforation cannot be appreciated. A search for microscopic particles of food such as plant material or muscle fibers in the serosal inflammatory response confirms perforation in this circumstance. Chronic peptic ulcers with thickened mucosal margins, scirrhous bases, and perhaps serosal thickening associated with perforation or near perforation must be differentiated from gastric adenocarcinoma in the dog.

Syndromes clearly the result of **hypersecretion** of **acid** occur in dogs. Mastocytoma has been associated with peptic ulcer, presumably due to histamine-stimulated acid hypersecretion and microvascular effects. The tumor and mastocytosis do not involve the stomach directly, and ulcers may occur in animals with solitary skin tumors. In one series of 24 dogs with recurrent or metastatic mastocytoma, gastric and duodenal erosions or ulcers, frequently multiple, were present in 20. In many cases such lesions are clinically silent, and they should be sought at autopsy in animals with mastocytoma. Mast-cell tumors have been associated rarely with gastric ulceration in the cow, and in the cat, where gastric ulcer is very uncommon.

**Zollinger–Ellison syndrome**, peptic ulcer due to gastrin-secreting pancreatic islet-cell tumors or gastrinomas, has been reported in a few dogs. The history usually includes inappetence, vomition, weight loss, and possibly diarrhea or melena. Reflux esophagitis and gastric or duodenal ulcer are present in most cases. Small, nodular masses histologically confirmed as islet-cell tumors may be found in the pancreas with, in most animals, metastases to the liver or hepatic lymph nodes. Hypertrophy of the fundic mucosa has been associated with a subjec-

tive increase in parietal cell mass. Peptic ulcer and reflux esophagitis in such cases result from gastrin-stimulated acid hypersecretion. Firm diagnosis rests on demonstration of elevated serum gastrin levels by radioimmunoassay, by identification of gastrin-bearing cells in fixed or frozen tumor tissue by immunocytochemistry, or by demonstration of gastrin in extracts of frozen tumor. Other peptide hormones may also be present. The microscopic appearance of these islet-cell tumors is not diagnostic for gastrinoma, nor is the ultrastructural appearance of tumor cells necessarily characteristic of the G cell. Pancreatic islet-cell neoplasms may be difficult to find and should be sought assiduously in suspect cases. In humans, some gastrinomas arise in the wall of the stomach or duodenum. The usual therapy in humans is removal of the target tissue, the fundic mucosa, by gastric resection, rather than attempted ablation of often occult and disseminated islet-cell tumor.

The cause in dogs of gastroduodenal ulcer possibly associated with decreased resistance to back diffusion of acid is less clear. Hepatic disease is often present in dogs with gastric ulcer, but the basis for a causal association is obscure. Some ulcers are obviously associated with administration of glucocorticoids in high doses as antiinflammatory, immunosuppressive, or antineoplastic therapy. Nonsteroidal antiinflammatory drugs such as aspirin, naproxen, or indomethacin, sometimes given by the owner in excessive quantity, are also associated with spontaneous ulcers. Gastric hemorrhage and gastroduodenal ulceration are occasionally seen in dogs following trauma or major surgery. A syndrome of gastric hemorrhage, pancreatitis, and colonic ulceration and perforation is recognized in dogs following spinal trauma. The pathogenesis of this problem is obscure and undoubtedly complex. Endogenous and exogenous hyperglucocorticoidism appear to be implicated, in association with the stress of trauma and surgery and putative neurogenic influences initiated by damage to the spinal cord. In dogs, diffuse gastric hemorrhage due to reduced mucosal resistance to acid must be differentiated from the effects of heavy-metal ingestion, uremic gastritis, coagulopathy (especially due to warfarin or disseminated intravascular coagulation), and canine hemorrhagic gastroenteritis, among others.

**Peptic ulcer** in **cattle** is confined largely to the abomasum, where it is common (Fig. 1.10C); duodenal ulcer is rarely encountered in this species. Acute ulcers or erosions considered to be the result of stress are frequently seen incidentally in animals, of any age, dying of a variety of causes. They are present usually as linear areas of brown or black hemorrhage or erosion along the margins of abomasal rugae, or as punctate hemorrhages and erosions scattered over the mucosa, especially of the fundus. Such lesions must be differentiated from foci of acute necrosis and ulceration due to systemic viral infections.

In feedlot animals in one study, a prevalence of abomasal ulcer of about 3 to 4% was described, with about half the cases having clinical signs. Bleeding abomasal ulcer or perforation and septic peritonitis are the usual cause of death due to abomasal ulcers. Most ulcers are in the pyloric region in feedlot cattle, and it is in this area that perforations commonly occur. Frequently more than one ulcer is present. Most are 2–4 cm in diameter and approximately circular, though some may be irregular and up to 15 cm in size. Active ulcers may have a dirty brown or gray necrotic floor with some fibrin. Arteries may be visible in the base of bleeding lesions. Older ulcers are puckered, with an overhanging periphery. Abomasal rugae or plicae may be scalloped along their margins or perforated by active or healed ulcers, and in a study of pastured dairy cattle most ulcers and scars were found in the fundic area.

The causes of abomasal ulcer are usually unclear. Some appear to occur under stressful circumstances, as in weaned calves or after transportation. Lactic acid and histamine entering the abomasum from the forestomachs in animals poorly adapted to high-concentrate rations may contribute to mucosal damage. Abomasal stasis may play a part in animals with physical or physiologic abomasal obstruction. Ulceration of the abomasal mucosa infiltrated by lymphosarcoma will occur.

Bleeding abomasal ulcer should be sought in cattle with melena or anemia, and perforating abomasal ulcer in animals presenting with septic peritonitis, especially if digesta is in the abdominal cavity. Some points of perforation will be adherent to the abdominal wall or occluded by superficially adherent omentum.

Abomasal "stress" ulcer in calves must be differentiated from lesions associated with infectious bovine rhinotracheitis, and mycotic abomasitis must be differentiated from ulcer in calves and older animals. Mycosis is a rare complication of peptic ulcer. In juvenile and adult cattle, focal abomasal lesions due to bovine virus diarrhea must be differentiated.

**Gastric ulcer** in **swine** is usually restricted to the pars esophagea (Fig. 1.10D–F); in a small proportion of affected pigs lesions extend into the contiguous esophagus. Rarely are significant ulcers of the cardiac, fundic, or pyloric mucosa encountered in swine, sometimes in association with ulcer of the pars esophagea, occasionally with gastric parasitism or systemic disease. Venous infarcts in the body of the stomach in swine are not to be confused with gastric ulcer. There is little disagreement over the pathology of ulceration of the pars esophagea; its etiopathogenesis remains unresolved.

Under conditions of modern pig husbandry, the prevalence of ulcer and associated abnormalities of the pars esophagea is high. Weaned growers and feeders are commonly affected. Most lesions are subclinical; however, some prove fatal. Pigs die without premonition, or with a short history that may include anemia, weakness, inappetence, vomition, and melena. Other animals are affected chronically, with signs of anorexia, intermittent melena, and weight loss, which may culminate in death or slow recovery with runting. Despite its high subclinical prevalence, and occasional outbreaks of clinical disease or loss of individual valuable pigs, most studies indicate that the economic significance of gastric ulceration is marginal. Little or no effect on growth rate or feed efficiency is evident in most subclinically affected animals.

Lesions of the pars esophagea may involve only a small part, or virtually all, of the gastric squamous mucosa. The lesion evolves through parakeratosis, to fissuring and erosion, with ultimate ulceration in severe cases. All stages in this progression will be encountered at autopsy in pigs. The milder lesions are incidental findings. The epithelium of the pars esophagea often appears yellowish and is thickened, irregular, roughened, and may flake or peel off readily. This gross change is the result of

microscopic thickening and parakeratosis, with nucleated cells present at the irregular mucosal surface. *Candida* may be present over the epithelial surface, with hyphae invading the parakeratotic epithelium, perhaps due to favorable cystine or glycogen levels. Rete pegs and proprial papillae are elongate. Neutrophils and eosinophils may be present at the tips of proprial papillae, infiltrating into the epithelium, which appears hydropic and may erode over the tips of papillae.

Erosion of the epithelium progresses to ulceration and exposure of papillae and deeper propria, which bleed as small vessels are disrupted. Such lesions begin as fissures in the hyperplastic parakeratotic epithelium but advance to ulcerate the entire pars esophagea. They usually spare only a microscopically visible margin of squamous epithelium adjacent to the cardiac gland mucosa. Ulcers of the pars esophagea, like peptic ulcer, have a floor or necrotic debris overlying exposed connective tissue (Fig. 1.10F). Depending on the stage and aggression of the ulcer, there may be a well-developed inflammatory margin to the necrosis and a bed of granulation tissue. Fatal gastric hemorrhage often occurs, and thrombosed arterioles and venules cut by ulceration are exposed in the floor of the acute ulcer, which is often overlain by a blood clot. Ulcers of the pars esophagea usually involve only the submucosa, but they may advance to the muscularis externa and occasionally to the serosa. They rarely perforate.

Grossly, fully developed ulceration of the pars esophagea is apparent as a punched-out lesion with elevated rolled edges, obliterating the entire pars esophagea and obscuring the esophageal opening (Fig. 1.10D). Pigs with gastric ulcer at any stage of evolution tend to have fluid content in the stomach. Those with hemorrhagic ulcer may have red-brown gastric content, or massive hemorrhage into the stomach with large blood clots in the lumen, and thrombosed blood adherent to the base of the ulcer and its exposed bleeding points. Melenic content will often be in the intestine, and the colon may contain firm, black, pelleted feces. The carcasses of animals that bleed out with gastric ulcer are very pale. Blood in the intestine associated with gastric ulcer in pigs must be differentiated from mesenteric torsion and proliferative hemorrhagic enteropathy due to *Campylobacter*. A few pigs with parakeratosis, erosion, and ulceration of the pars esophagea have esophageal lesions suggestive of gastric reflux.

Gastric ulcers in some pigs resolve by granulation, and they may become reepithelialized. Such lesions usually become scirrhous, puckered, and contracted as the ulcer closes from the periphery, and scarring may be visible from the serosa (Fig. 1.10E). In these circumstances occlusion of the esophageal opening into the stomach may occur, and pigs with this problem can develop muscular hypertrophy of the distal esophagus. Swine that have suffered chronic gastric hemorrhage may have an enlarged spleen due to extramedullary hematopoiesis.

Factors implicated in the etiology of ulceration of the pars esophagea are many, and their mode of involvement, if any, is usually obscure. Stressful husbandry practices have been considered to contribute to development of ulcer, though glucocorticoid administration causes lesions of the fundus, not pars esophagea, in pigs. High dietary copper levels, feeding of whey, starchy diets low in protein, and high levels of dietary unsaturated fatty acids have been associated. Experimental infection with *Ascaris suum* has been implicated with ulcer, but natural infection is not considered causally associated. Experimentally, factors stimulating acid secretion, especially histamine, consistently cause ulcers of the pars esophagea, suggesting that gastric acidity may play an etiologic role. Repeatedly, finely ground rations have been found to be ulcerogenic and are the single most important contributing factor.

Squamous epithelium has no innate buffering capacity, and it is highly susceptible to attack by gastric acid, as occurs in reflux esophagitis. Similar events may initiate ulceration of the pars esophagea. Swine with gastric ulcer often have abnormally fluid stomach contents. In experimental studies there is slow gastric emptying with progressive declines in pH with time. Feeding of finely divided rations is associated experimentally with increased water in stomach content. There is loss of partitioning of gastric content, and the pH gradient from esophagus to pylorus that occurs in the normal porcine stomach is not established. Relatively low pH occurs at the esophageal end of the stomach, while the pH at the pylorus is higher than normal. Under these conditions of prolonged gastric distention and relatively high antral pH, gastrin-stimulated acid secretion may be excessive. Fluidity and increased mixing of content may expose the pars esophagea, which should normally be in contact with material buffered to pH 5 or greater, to excess acid. This may initiate the epithelial changes described, which culminate in ulceration. Whey may in itself be acid, and would presumably cause an abnormally fluid gastric environment. This could explain its association with ulcer in swine. How other factors mentioned above might be implicated in ulcerogenesis is less clear.

In **horses**, **ulcers** in the **stomach** of foals and adults are often found at autopsy incidental to some other disease process. Gastric ulcer as a clinical entity is less commonly recognized, though a syndrome of abdominal pain, in some cases associated with gastric reflux, has been described. Ulcers in horses are most common in foals more than 2 weeks of age, are often multiple, and can simultaneously involve all four mucosal zones of the stomach and the duodenum.

Ulcers of the esophageal zone are common. They are frequently most severe at or adjacent to the margo plicatus, sometimes involving the edge of the squamous epithelium. They are often large and irregular in shape. There may be extensive fissuring, erosion, and ulceration of the bulk of the squamous mucosa. Often, islands of thickened white proliferative mucosa are scattered as plaques on a predominantly ulcerated mucosa (Fig. 1.10A,B). Ulcers in the secretory stomach are also often large and multiple, though a full range from focal punctate to extensive deep lesions may be seen. Microscopically, gastric ulcers in horses follow the typical pattern previously described. *Candida* may colonize hyperkeratotic squamous mucosa of the esophageal portion of the stomach in some horses with ulcers.

Perforation may occur at any site of ulceration and in one series represented 1% of 600 autopsies on foals. Pyloric and duodenal stenosis have been associated with healing ulcers in horses. Severe esophagitis occurs in foals with ulcer and gastric reflux. Lesions of the margo plicatus have been reported as a site colonized with *Clostridium botulinum* type B, implicated in toxicoinfectious botulism of horses.

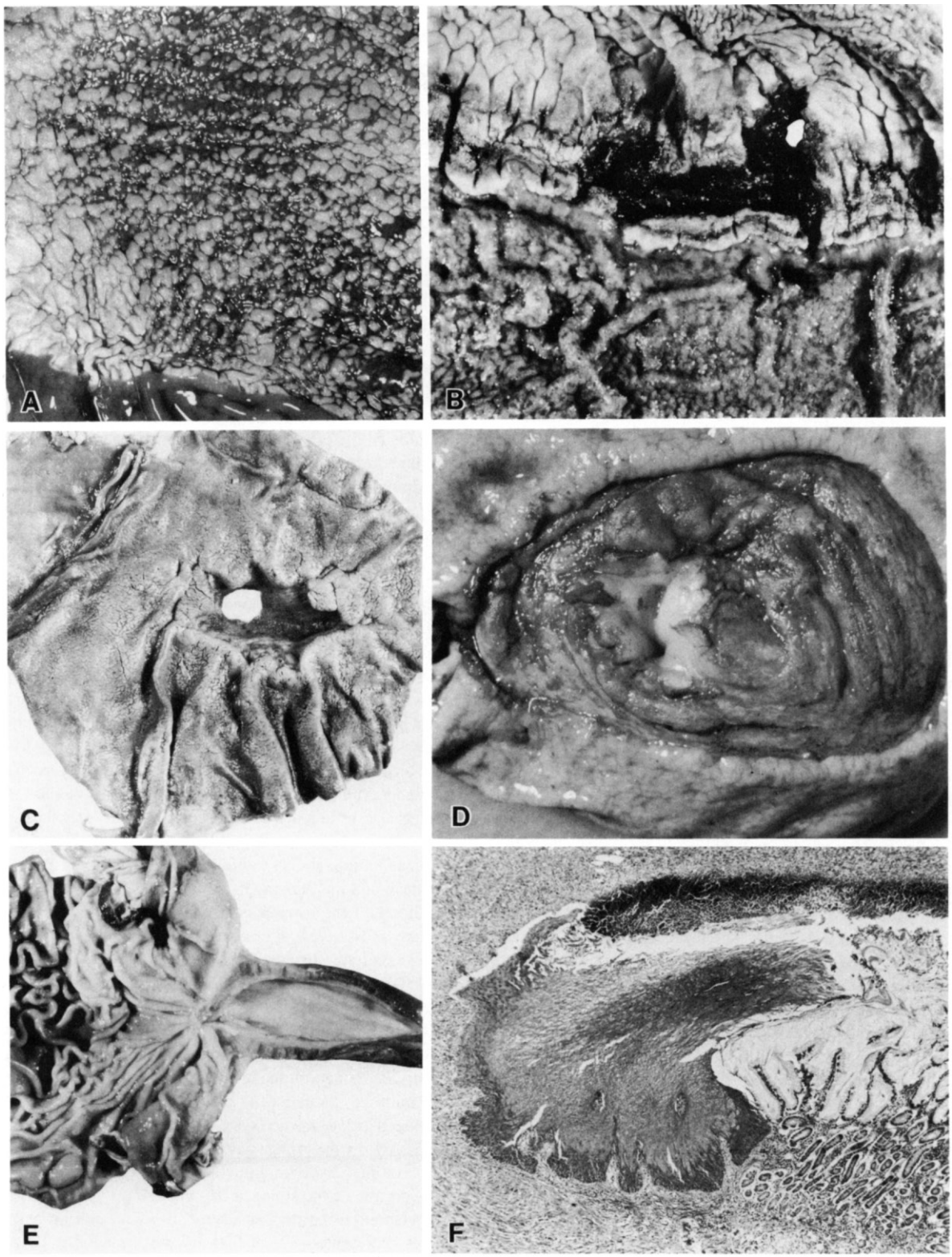


**Fig. 1.10.** (**A**) Stomach. Foal. Multiple confluent areas of ulceration of the squamous mucosa. Smooth nodular islands of surviving hyperplastic mucosa are scattered over the ulcerated area. (**B**) Ulceration with perforation of squamous gastric mucosa. Foal. (**C**) Perforated abomasal ulcer. Calf. (**D**) Ulceration of the pars esophagea. Pig. Squamous mucosa is ulcerated, but adjacent cardiac glandular mucosa is unscathed. (**E**) Scarring of distal esophagus and pars esophagea following ulceration. Pig. (**F**) Margin of ulcer. Pars esophagea. Pig. Cardiac glandular mucosa and normal remnant of squamous mucosa overhang margin of ulcer.

The pathogenesis of gastric ulcers in horses is unclear. Many cases are associated with enteric disease, ileus, surgery, or other circumstances that can be considered stressful. Administration of steroids and analgesics such as flunixin meglamine and phenylbutazone is commonly associated. *Candida* is considered contributory to ulceration by some, but it is often not present. Esophageal reflux and the severity of lesions in the esophageal portion of the stomach suggest that altered partitioning of abnormally fluid gastric content, and access of acid to squamous mucosa, may explain lesions in the nonglandular gastric mucosa and esophagus. Hypersecretion of acid has not been confirmed, but some cases show subjective clinical response to the histamine-receptor-blocking agent, cimetidine.

### *Gastric Neoplasia*

Gastric neoplasms are uncommon in all species and are very rare in some.

**Adenocarcinoma** of the **stomach** is most frequently reported in dogs, usually in animals less than 10 years of age, and it comprises the majority of the gastric neoplasms found in that species. Males predominate in the population with gastric cancer, and more than half of gastric adenocarcinomas in dogs occur in the pyloric region. Grossly, some gastric neoplasms appear as nonulcerating, firm thickenings involving most of the gastric wall and causing loss of the normal rugal pattern on the mucosal surface. Others are more localized, plaquelike thickenings, which tend to obliterate rugae and ulcerate centrally. Ulceration is expected in more than half of canine gastric adenocarcinomas. Surface proliferation or irregularity other than ulceration is very uncommon in gastric carcinoma in dogs. Cut sections through the stomach wall invaded by carcinoma reveal edema and pale, firm, fibrous tissue. Induration or plaquelike pale masses may be evident on the serosa, where the outline of infiltrated lymphatics may be prominent. Widespread gastric mural fibrosis and thickening causes "linitis plastica" or the so-called leather-bottle appearance. The scirrhous nature of most gastric carcinomas in the dog is the result of desmoplasia induced by the malignant epithelium.

These tumors adopt two basic microscopic forms. Most gastric adenocarcinomas in dogs are of the diffuse type. Most of these consist of widespread random infiltrates of neoplastic cells in small clusters or dispersed singly between supporting stromal elements. The cell type is usually relatively uniform within a single neoplasm, commonly consisting of poorly differentiated, round or angular, mucus-secreting epithelial cells. In many of these tumors, some cells adopt the hollow, mucus-filled "signet ring" appearance, and extracellular mucin may be present. Occasional tumors of this type have a more variable cell population, with some cells containing little cytoplasm, others with extensive eosinophilic cytoplasm, and large atypical nuclei. Other tumors will have scattered, irregular, glandlike structures. Desmoplasia is typically heavy in diffuse gastric carcinomas.

Adenocarcinomas of the tubular or intestinal type are encountered less commonly in the canine stomach. They are characterized by tubular glandular structure, with a lumen, and a relatively well differentiated and polarized lining epithelium. They retain this form with some variation as they infiltrate and metastasize, and they are relatively less scirrhous than the diffuse type. There may be papilliform infoldings of the epithelium of tubular adenocarcinomas; some form smaller acinar structures; others rarely adopt a more solid form of growth, with occasional acinar structures and a more anaplastic cytologic appearance. Cells may have eosinophilic cytoplasm, and many contain mucin. The better differentiated tubular tumors resemble pyloric glands. Infiltrates of lymphocytes and plasma cells, sometimes with follicle formation, may occur in the primary site of all types of gastric carcinoma.

A single squamous-cell carcinoma has been reported arising from the pyloric gland mucosa in a dog, and carcinoids develop, very rarely, in the gastric mucosa.

Gastric carcinomas in dogs infiltrate the stomach wall aggressively, invading lymphatics, and they have usually metastasized to the local lymph nodes, and often to distant organs, particularly lung, liver, and adrenal, by the time they are diagnosed.

**Benign "adenomatous" polyps** or sessile proliferative lesions occur uncommonly in the pyloric stomach in dogs. These have been alluded to previously as a potential cause of pyloric stenosis or obstruction and as a possible hyperplastic sequel to chronic antritis. Their exact status, whether inflammatory hyperplasia or benign neoplasia, is unclear. Although there are reports of malignant polypoid adenocarcinoma, it seems, on the basis of the relative frequency of "adenomas" *vis-à-vis* adenocarcinoma, that they are unlikely to be common precursors of gastric cancer. Grossly, these lesions appear as solitary or multiple, raised, convoluted, nodular, sessile or sometimes pedunculate, polypoid masses, usually 1–2 cm in size. Microscopically, there is foveolar and glandular hyperplasia, with well-differentiated columnar mucous cells on the surface and in glands. Some mucus-filled glandular cysts may be present, and mononuclear-cell infiltrates are often in the mucosal propria.

**Mesenchymal tumors** of the stomach in dogs are less common than adenocarcinomas. Most are typical leiomyomas, which may produce nodular, sometimes polypoid, masses several centimeters in size that project into the gastric lumen or protrude from the serosa. Leiomyosarcomas, lymphosarcomas, and rare anaplastic sarcomas are also found in the canine stomach. These tumors may ulcerate the mucosa and, to that extent, mimic the behavior of adenocarcinoma. Their microscopic appearance is typical.

Tumors other than lymphosarcoma are rarely encountered in the stomach of cats, and even that is uncommon. Several cases of gastric adenocarcinoma have been described, adopting tubular and diffuse patterns.

**Gastric adenocarcinoma** in **cattle** is exceptionally uncommon, but when it occurs it resembles patterns adopted by similar tumors in other species, being scirrhous, invading the wall, and capable of ulceration. Much more important in cattle is **lymphosarcoma** of the abomasum. Involvement of this organ is common in adult cattle, Diffuse submucosal and mucosal lymphocytic infiltrates or nodular proliferations may occur. Strategically placed pyloric tumor may cause obstruction. Diffuse lesions, thickening the gastric wall, frequently ulcerate and hemorrhage from such ulcers, producing melena. The lymphoid infiltrates are recognizable as firm, gray-white tissue in the submucosa and mucosa. Involvement of abomasal lymph nodes is dispropor-

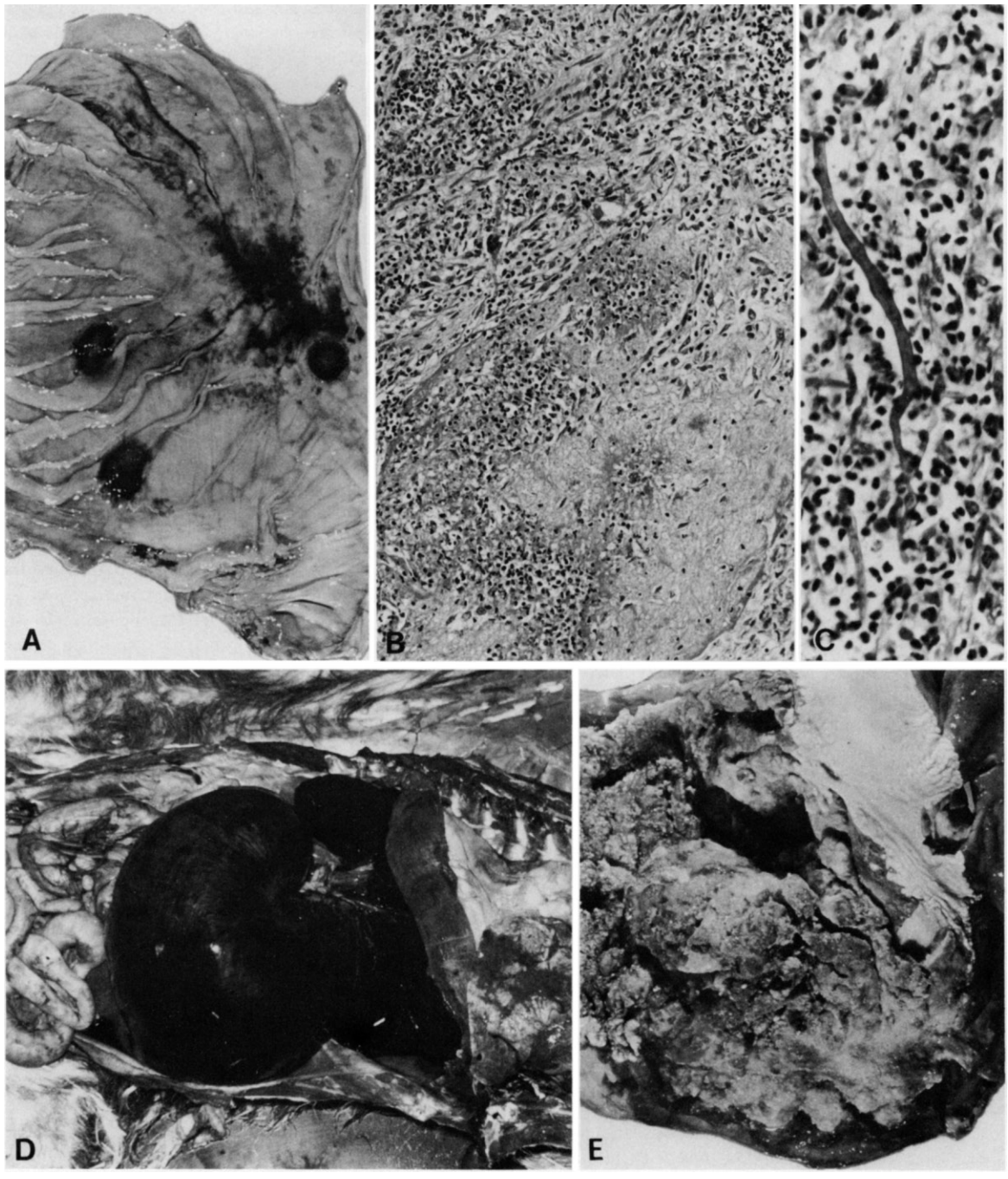


**Fig. 1.11.** (**A–C**) Mycotic abomasitis. Calf. (**A**) Focal lesions surrounded by deep red areas of infarction and hemorrhage due to thrombosis of mucosal and submucosal vessels. (**B**) Thrombosis of a venule in submucosa of abomasum due to hyphal invasion. (**C**) Nonseptate hyphae of zygomycete invading the submucosa. (**D**) Gastric volvulus in a dog. The stomach has undergone venous infarction due to strangulation of its vascular outflow and is extremely distended and congested. (**E**) Fungating and ulcerative squamous-cell carcinoma arising from the gastric squamous mucosa. Horse.

tionately slight. Gastric lymphosarcoma also occurs in swine, where it is usually diffuse. The wall of the stomach is thickened by submucosal lymphocytic infiltrates, which sometimes invade the mucosa locally in many areas, producing nodular elevations that may ulcerate.

In the horse, most gastric neoplasms are **squamous-cell carcinomas** derived from the esophageal mucosa; occasional adenocarcinomas, originating in glandular epithelium, and leiomyomas are also reported. Squamous-cell carcinomas occur in middle-aged horses. They usually present in an advanced

state, with a history of unexplained anorexia, occasionally dysphagia, and weight loss sometimes progressing rapidly to emaciation. At autopsy there may be peritoneal effusion, and there is usually evidence of the neoplasm on the serosa of the stomach. There also may be peritoneal implants, especially on intestine, testes, omentum, parietal abdominal surfaces, and diaphragm; direct extension to adjacent organs, including liver, spleen, and diaphragm, with progression to the pleural space; and sometimes distant metastases, usually in liver and lung. The appearance of the tumor on serosal surfaces resembles mesothelioma, with smooth, creamy plaques or nodules up to 2 to 4 cm in diameter.

The origin of these lesions is in a fungating, cauliflower-like mass 10–40 cm in diameter, with superficial fissures, usually projecting above the surface of the pars esophagea (Fig. 1.11E). Sometimes these lesions are superficially more ulcerative than proliferative. Necrosis and hemorrhage are evident in the tumor mass, which is usually well demarcated from adjacent normal squamous mucosa. Occasionally the tumor extends into the distal esophagus and may obstruct it. Microscopically, these neoplasms are typical squamous-cell carcinomas, invading in cords or nests of cells through the gastric wall. They induce desmoplasia, imparting a scirrhous, firm texture and appearance to the thickened gastric wall and to the peritoneal and pleural implants. One such tumor has been reported as a cause of pseudohyperparathyroidism in a horse.

## Intestine

### *Normal Form and Function*

#### *Small Intestine*

The microtopography of the small bowel is extensively modified, to increase its surface area, by spiral mucosal folds in some species, and by villi projecting into the lumen. The villi, projections of lamina propria covered by a layer of epithelium one cell thick, are calculated to expand the absorptive surface of the small bowel 7- to 14-fold. In most species, villi are tallest in the duodenum and decline somewhat in height toward the ileum. The length and shape of villi in "normal" animals varies with the species, age, intestinal microflora, and immune status. In general, villi in dogs, cats, and neonatal piglets and ruminants tend to be tall and cylindric; those in horses and young ruminants tend to be moderately tall and cylindric; villi in weaned ruminants and swine may be cylindric, leaf- or tongue-shaped or, rarely, ridgelike, with their broad surface at right angles to the long axis of the gut.

Opening onto the mucosal surface around the base of each villus are several crypts of Lieberkühn. These are straight or somewhat coiled (depending on the species and the proliferative status), glandlike structures, lined by a single layer of epithelium. The progenitor compartment of the enteric epithelium resides here, producing cells that differentiate and move up onto the surface of villi, mainly as absorptive enterocytes, ultimately to be extruded as effete cells from the tips of villi.

**Primordial stem cells** are present at the base of the crypts, and they divide to produce cells of four main types. Poorly differentiated cuboidal or low columnar cells with relatively few, short microvilli are the predominant type of cell lining crypts; especially in the lower half of crypts, these cells form a population that cycles rapidly, undergoing amplification division. One of the ensuing daughter cells usually differentiates and moves into the functional compartment of absorptive enterocytes on the villus.

**Oligomucous cells**, derived by mitosis from the basal stem cells, are also a population undergoing amplification division. They contain mucous granules and are intermediate in structure between undifferentiated crypt epithelium and goblet cells, into which they mature. Well-differentiated goblet cells are present in crypts and on the surface of villi, with varying prevalence and distribution at various levels of the intestine, and in the different species. They have basal nuclei and secrete mucus, apparently by exocytosis, from the luminal border of the cell. The precise function of intestinal mucus, which stains strongly for neutral and sialic acid–rich mucosubstances, is uncertain. It probably serves to "insulate" the surface from organisms, which it may entrap or immobilize. It contains lysozyme, and IgA secreted into it by epithelium. Mucus secretion appears to be promoted by a variety of noxious stimuli and by immune events in the gut.

**Paneth cells**, a population of cells turning over slowly in the base of crypts, are not found in dogs, cats, or swine, and they are not prominent in the intestine of ruminants. Among domestic animals they are most obvious in horses. Eosinophilic secretory granules are present in the apical cytoplasm of Paneth cells; though the function of the granules is unclear, it seems that they may be lysozyme, which could have an antimicrobial function in the crypt and in mucus.

The fourth type of cell found in intestinal crypts is the **enteroendocrine cell**. They too are derived from crypt stem cells and comprise a heterogenous population of about a dozen amine- or peptide-secreting endocrine/paracrine cells. These are the cells variously recognized as enterochromaffin, argentaffin, or argyrophil; the specific cell type is defined by immunocytochemistry and the ultrastructure of secretory granules. Enteroendocrine cells are scattered singly among other cells on villi and, more commonly, in crypts. They tend to be located peripherally in the epithelial layer, with little luminal exposure, and contain scattered small secretory granules in the basal cytoplasm. Hormones with relatively clearly understood functions, such as secretin and cholecystokinin, as well as peptides or amines, whose endocrine or paracrine implications are less certain, are secreted. Some probably integrate in function with similar neurohormones secreted by the submucosal nervous plexus. With the exception of carcinoid tumors of serotonin-secreting cell origin, and rare functional neoplasms of other enteroendocrine cells in humans, the pathologic implications of this class of cells are still very poorly defined.

Scattered among the cells of the crypt and villus are specialized **caveolated** or "**tuft**" **cells**. These are flask-shaped cells tapering toward the luminal border, also found in other gastrointestinal and respiratory epithelial surfaces. They are characterized by the presence of an apical tubulovesicular system, from which they derive their name, but the function of these cells is not known. Specialized "cup" epithelial cells, of unknown function also, have been described on villi in the ileum of several species.

The **enterocytes**, which are responsible for the final digestion and absorption of nutrients, electrolytes, and water, are by far the predominant cells on intestinal villi. They are normally tall columnar cells, hexagonal in cross section, with a regular basal nuclear polarity. A tight junction, which is nevertheless "leaky" to small ions and water, joins the apical margins of adjacent cells. Basal to the tight junction, the lateral cell membranes interdigitate loosely, and a long, narrow potential space exists between enterocytes. The basolateral cell membrane is the site of $(Na^+,K^+)$-ATPase activity, driving the sodium pump, and of carrier systems exporting monosaccharides from the cell. Absorptive epithelial cells lie on a basal lamina, which they may produce.

The apical surface of normal enterocytes is highly modified into microvilli, about 0.5–1.5 μm long and 0.1 μm wide, which are regularly arrayed in close apposition to each other at right angles to the surface of the cell. They are visible as the "brush border" by conventional microscopy. Microvilli increase the surface area of absorptive epithelium by a factor of about 15 to 40. The plasmalemma of microvilli is studded with massive numbers of enzyme molecules, including aminopeptidases and disaccharidases involved in terminal digestion of peptides and carbohydrates. These protrude as minute knoblike structures into the glycoprotein "glycocalyx," which coats the surface of microvilli. Proteins binding calcium ions, vitamin $B_{12}$ and water-soluble vitamins, and proteins involved in the transport into the cell of peptides, amino acids, glucose, galactose, and triglyceride, coupled with transport of sodium ion, are also embedded in the plasmalemma of microvilli. Clines in the distribution of microvillus-associated functions are present along the small intestine. The activities of alkaline phosphatase and most disaccharidases are greater in the anterior small bowel, while the receptor for vitamin $B_{12}$:intrinsic factor is concentrated in the ileum.

In neonatal swine and ruminants, vacuolation of absorptive enterocytes is normal, and the nucleus is often also displaced into the apical cytoplasm. In piglets, vacuolation is usual in the ileum (Fig. 1.34B), not in the duodenum, and seems to be a function of cell age. Such vacuolation should be differentiated from the presence of eosinophilic colostrum present in cytoplasmic vacuoles in the epithelial cells of neonates (Fig. 1.14A). The cytoplasm of absorptive enterocytes is stabilized at the apical border by the filaments of the terminal web. Smooth endoplasmic reticulum is most prominent in the upper half of cells, while cisternal elements of rough endoplasmic reticulum are more uniformly distributed. The Golgi zone lies above the nucleus. Free ribosomes and polyribosomes are numerous in differentiating cells of the upper crypt and lower villus and are relatively fewer in mature absorptive enterocytes.

The complex of endoplasmic membranes and Golgi apparatus is active particularly in handling absorbed lipid, which diffuses from micelles at the cell surface, through the apical membrane, in the form of long-chain fatty acids or monoglyceride. These are reesterified to triglyceride, appearing in the smooth endoplasmic reticulum, and are complexed with apoproteins produced in the rough endoplasmic reticulum, to be excreted via the Golgi apparatus through the basolateral cell membrane as chylomicrons. Chylomicrons enter the extracellular space and leave the villus via the lacteal. Mitochondria are numerous in the metabolically active absorptive enterocyte. Vacuoles formed by endocytosis of macromolecules at the base of microvilli fuse with lysosomes in the subapical cytoplasm, and by this process of heterophagia, potentially noxious material is destroyed. In addition to lysosomes, acid phosphatase–containing vesicular bodies, and peroxisomes containing catalase but of uncertain function, are also found in intestinal epithelium.

The epithelium of the small intestinal mucosa is supported by a highly plastic mesenchymal stroma, the **lamina propria**. This is composed of loose, fibrous tissue, through which course blood vessels and in which smooth muscle, inflammatory, and immune-active cells are interspersed. Surrounding the crypt of Lieberkühn and underlying the basal lamina of the epithelium of the villi is a fibroblast sheath. Proliferation of elements of this sheath has been demonstrated around the crypt, and [$^3$H]thymidine-labeled mesenchymal cells appear to move in concert with overlying epithelium up onto villi, ultimately undergoing degeneration in the lamina propria at the villus tip. There, histiocytes containing nuclear fragments may be found, presumably phagocytosing effete sheath cells.

Scattered in the lamina propria of villi and between crypts are lymphocytes, neutrophils, and eosinophils. The latter are particularly common in the intestine of ruminants and horses, with no specific pathologic connotation. Intraepithelial lymphocytes (theliolymphcytes) are frequently found between epithelial cells on villi and, less commonly, in crypt lining. Globule leukocytes may be found in the epithelium of crypts and low on villi, or sometimes in the lamina propria between crypts. Plasma cells normally are not numerous in villi but are concentrated in the lamina propria between the upper portions of crypts. Few attempts at quantitative assessment of the distribution of the various cell types in the lamina propria of "normal" animals have been undertaken in domestic species.

The **vascular supply** to the **mucosa** arises in submucosal arteries, which give off arterioles at right angles, some of which send branches to a capillary plexus around crypts of Lieberkühn. The majority pass up the centers of villi, arborizing near the villus tip into a dense capillary plexus that lies immediately beneath the basal lamina of the epithelium. Capillaries in villi have fenestrations facing the basal lamina, which may be more permeable than the remainder of the endothelium. One or more venules drain blood from the capillaries in villi and between crypts and flow into larger veins in the submucosa, which drain into mesenteric veins and the hepatic portal circulation. At least in swine there appear to be anastamoses between the capillary plexi of villus and crypt. The lacteal, or central lymphatic vessel of the villus is sufficiently permeable to permit the entry of macromolecules and chylomicrons and is the main route of lipid transport from the villus.

It is suggested that the juxtaposition of arteriole and venule in the villus may result in a countercurrent multiplier system in the villus, establishing an increasing gradient of sodium concentration and a decreasing oxygen gradient toward the tip of the villus. Anastomoses between capillary plexuses surrounding the villi and crypts might provide a mechanism for shunting electrolytes and water, just absorbed in the villi, into the vicinity of crypts, where secretion is occurring. Thus a putative crypt–villus fluid and electrolyte circuit would be provided with a direct vascular arm.

*Large Intestine*

The anatomy and size of the cecum and colon vary widely among domestic animals, depending largely on the significance of microbial fermentation of carbohydrate in the hindgut. Production of volatile fatty acid from carbohydrate by colonic flora occurs in all species. In the horse, this is a primary source of energy, and it is significant in swine and ruminants as well. Extensive movement of electrolytes and water occurs across the colonic wall. In the horse, a volume of fluid up to one-third that of the extracellular fluid space of the animal may be in the large bowel, which must maintain a fluid medium for microbial fermentation; daily fluid absorption from the hindgut may equal the extracellular fluid volume. Absorption of electrolytes and water, an electrolyte-conserving mechanism, is probably the major function of the colon in dogs and cats, and of the distal colon of herbivores.

The mucosa of the cecum and colon in all domestic species lacks villi, though there are ridges or folds on the mucosal surface. The surface of the hindgut is lined by a single layer of tall columnar absorptive epithelial cells with basal nuclei. These cells have sparser and fewer regular microvilli in comparison with absorptive cells of the small bowel, and numerous glycoprotein-laden vesicles are in the apical cytoplasm. Typical goblet cells are also interspersed on the colonic surface in variable numbers, depending on the species and a variety of other factors.

Colonic crypts or glands are straight, tubular structures. The architecture of colonic glands and their cell population resemble somewhat those of small intestinal crypts. Stem cells are present in the base of the gland, and poorly differentiated mitotic columnar epithelium may be present in the basal two-thirds of the gland, though its extent may vary considerably. These cells differentiate progressively toward absorptive epithelium as they approach the surface. Oligomucous cells, derived from basal stem cells, form a second proliferative population in the lower half of the colonic gland. Well-differentiated goblet cells are usually present in the upper half of glands in the large bowel as well as on the surface. Spirochetes have been found in colonic goblet cells in apparently normal dogs and cats and in some laboratory animals. Enteroendocrine cells of about a half dozen types have been recognized, scattered in the cell column lining glands in the large bowel.

The lamina propria of the colon is minimal between closely packed glands. It contains a cell population similar to that in the small bowel. A fibroblast sheath encloses the colonic glands and appears to migrate with the epithelium. Normally, relatively few inflammatory and immune-active cells are present in the superficial mucosa; most plasma cells and lymphocytes are between deeper portions of glands.

*Electrolyte and Water Transport in the Intestine*

The small intestinal mucosa is highly permeable to the passive movement of small ions and water and is therefore considered "leaky," despite the presence of "tight" junctions at the apical margins of absorptive enterocytes. Epithelia of this type, which also include gallbladder and renal proximal tubule, are specialized for the absorption of large volumes of salts and water in isotonic concentrations and for separating compartments similar in osmolality and ion composition. The leakiness of the epithelium of the small bowel ensures that the intestinal content is approximately isosmolal with the interstitial fluid space. The leaks in the small intestinal epithelium are paracellular, at the tight junctions, and act as water-filled spaces 0.4–0.8 nm in diameter. The permeability of junctional complexes appears to be sensitive to Starling forces, influenced by intravascular hydrostatic and oncotic pressure, so that fluid and solute actively absorbed may leak back into the lumen, thus modulating net absorption by the mucosa.

Sodium absorption takes place by three active transcellular mechanisms. Chloride ion moves independently via a paracellular route, or coupled with sodium by a transcellular route. Fundamentally, sodium absorption depends on electrochemical forces established by the ATP-dependent sodium pump on the basolateral cell membrane of the enterocyte. This pump moves $Na^+$ up a concentration gradient from the cell in the lateral intercellular space. The first mechanism involves independent, or uncoupled, electrogenic $Na^+$ absorption. Sodium ion enters the cell from the luminal solution down an electrostatic and concentration gradient established by the sodium pump, which exchanges $K^+$ for $Na^+$, but not at an equal rate. Absorption of $Na^+$ is also coupled to that of organic solutes such as amino acids and glucose. Sodium moves into the cell down the electrochemical gradient established by the sodium pump, but it does so coupled to movement of the organic solute. Sodium is then pumped out across the basolateral membrane, while the organic solute moves via carrier-mediated facilitated diffusion out of the cell. Most sodium and chloride is probably absorbed together by a neutral process, involving transcellular route for both ions. Sodium ion moving into the cell at the apical margin, as a result of the gradient established by the sodium pump, is coupled with $Cl^-$, carrying it "uphill" into the cell, whence it moves passively to the interstitium, while $Na^+$ is pumped out. An alternate hypothesis suggests that $Na^+$ and $Cl^-$ are absorbed into the epithelium by processes that exchange them for $H^+$ and $HCO_3^-$, which enter the gut lumen.

The concentration by these mechanisms of solute, especially sodium and chloride ion, in the lateral intercellular space, causes water to follow from the intestinal lumen down an osmotic gradient. Since cell membranes and junctional complexes are highly permeable to water, movement is rapid via both transcellular and paracellular routes, and differences in osmotic pressure between lumen and lateral intercellular space are small. Absorbed solute and water in isotonic proportions move into the interstitium of the villus, where within a few micrometers, they encounter a subepithelial capillary or lacteal. The dilated lateral intercellular space is readily seen in sections of villus epithelium in mucosa that was actively absorbing when fixed.

The colon of carnivores, the spiral colon of ruminants and swine, and the small colon of horses are charged with the task of reducing the volume of electrolyte and water lost to the animal in the feces. This process is relatively poorly understood. In contrast to the small intestine, the colonic epithelium is moderately restrictive to the free movement of sodium and chloride, though not potassium. Therefore it is capable of maintaining differences is osmotic pressure, ionic composition, and electrical potential between luminal and proprial surfaces, which make it more efficient than the small bowel in absorbing some electrolytes and water. Ultimately, fecal water may be hypotonic with respect to plasma. Absorption of volatile fatty acids also accounts for con-

siderable water absorption from the colon. Potassium increases in concentration in colonic content as sodium concentration declines; this may be due to an active secretory process, or involve mainly paracellular flux down an electrochemical gradient. Colonic sodium, chloride, and water absorption and potassium secretion are stimulated significantly by aldosterone.

In pathologic states, both the small intestinal mucosa and that of the large bowel secrete sodium chloride and water. There is accumulating evidence that this process, which appears to be a function mainly of the crypts, also may be physiologic and perhaps segmental, involved in maintaining the fluidity of the intestinal content. Intestinal secretion will be considered more fully later as part of the pathogenesis of diarrhea.

*Immune Elements of the Gastrointestinal Tract*

The gastrointestinal tract is continually presented with food antigens, ingested toxins, viruses, bacteria and their products, and parasites and their excretions and secretions. The epithelial barrier of the gut is but one cell thick and has enormous surface area. Therefore, it is not surprising that the epithelium and associated lymphoid and inflammatory cells in the mucosa and submucosa have evolved a complex system for sampling, blocking, neutralizing, and eliminating antigens. Lymphoid tissue has been estimated to constitute 25% of the intestinal mucosal mass and to exceed that of the spleen in volume.

The epithelial cell of the neonate is capable of uptake and transport of macromolecules from the intestinal lumen to the basolateral cell surface. In all species of domestic animals, **colostral transfer** of **immunoglobulins** by this route provides the neonate with passive humoral immunity during the early postnatal period. The selectivity of macromolecular transfer varies with the species, being least specific in neonatal ruminants, piglets, and foals, which take up most macromolecules contacting the epithelium. Permeability of the gut to macromolecules is the result of energy-dependent pinocytosis by the apical cell membrane at the base of microvilli. Colostral protein is transferred in membrane-bound vacuoles in the cytoplasm to the basolateral membrane, where, by exocytosis, the contents are extruded, to find their way via the lacteal and lymphatics to the general circulation. The period of active uptake of macromolecules is short, usually only 24–48 hr in ungulates, and "closure" precludes further bulk transport of macromolecules. Closure is probably at least partly related to "maturity" of the epithelium and involves failure of intracellular transport or exocytosis, possibly due to replacement of surface enterocytes by cells incapable of export of proteins. Cells containing eosinophilic protein-filled cytoplasmic vacuoles (Fig. 1.14A), which may displace the nucleus toward the surface, persist longest in the distal small bowel.

Although bulk transport does not occur, experimental data suggest that nutritionally inconsequential amounts of macromolecules continue to be transferred by enterocytes in mature animals, via mechanisms analagous to those occurring in the neonate. For significant uptake to occur, molecules must escape intraluminal hydrolysis, and pinocytosis must exceed the rate of lysosomal degradation to permit molecules to be exported from the cell. This is presumably one mechanism by which antigens encounter immune-active cells in the mucosa. Macromolecules gaining entry to the portal circulation are largely phagocytosed by Kupffer cells in the liver. Certainly, these cells form a second line of defense against absorbed macromolecules from the gut and are particularly important in clearing endotoxin from the portal blood.

In addition to the pinocytotic activity of absorptive enterocytes, specific epithelial cells called **M cells**, associated with Peyer's patches and intestinal lymphoid follicles, actively "sample" particulate matter and macromolecules impinging on the mucosal surface. The M cells are called so because of the presence of microfolds, rather than microvilli, on their apical surface in humans, though this characteristic seems to be restricted to that species. The M cells are present, interspersed among cells resembling absorptive enterocytes, on the surface of the "dome" in the mucosa overlying lymphoid aggregates in the submucosa. In the neonatal calf, M cells cover the dome completely. These cells often adopt an inverted "cup" shape, with one or more lymphocytes and occasional macrophages in the basal concavity, in intimate contact with the membrane of the M cell. Macromolecular and particulate material taken up by M cells is transmitted to the associated lymphocytes or macrophages. The M cell is a likely portal of entry to the mucosa for bacteria, perhaps including *Salmonella, Yersinia,* and *Listeria* in some species, and some viruses. Neutrophils are seen transmigrating the epithelium of the dome and in the lumen over the dome, in enteric bacterial infections of calves in particular. Neutrophils may also play a role in phagocytosis in the enteric lumen in pigs under some conditions.

The **aggregated lymphoid follicles**, or **Peyer's patches**, and solitary lymphoid follicles are scattered in the mucosa of the small intestine of all species, and solitary lymphoid follicles stud the colonic mucosa. Peyer's patches are present throughout the length of the small intestine in all species, though they tend to be larger distally. They are grossly visible, usually as oval or elongate structures up to several centimeters wide, thickening the antimesenteric wall of the intestine. They may project slightly above the mucosal surface or appear as depressions, which must not be mistaken for ulcers, especially in dogs. In neonates of some species, including swine, they may be poorly developed and not visible grossly. Continuous, elongate Peyer's patches have been described in the distal 1 to 1.5 m of ileum in calves and piglets. Peyer's patches in sheep are reported to involute as the animal matures.

Peyer's patches are comprised of follicular aggregates of B lymphocytes in the submucosa, underlying a discontinuous muscularis mucosae. Between the upper borders of adjacent lymphoid follicles are aggregates of T lymphocytes. Overlying the lymphoid follicles is a mixed population of T and B lymphocytes, extending into the lamina propria in rounded mucosal projections, the domes, which lie between villi. Short crypts provide epithelium to domes and adjacent villi. Cell populations of Peyer's patches in newborns and gnotobiotes of most species tend to be sparser than those in older or bacterially colonized animals, though those in neonatal calves appear relatively well developed. The microscopic organization of solitary lymphoid follicles and associated mucosa essentially resembles that of the Peyer's patch.

The **B** and **T immunoblasts** gain access to Peyer's patches

via permeable postcapillary venules. The major cell populations in Peyer's patches appear to be B lymphocytes committed mainly to IgA production, while among the T cells is a large proportion of T-helper-cell precursors. How or whether antigen is processed in Peyer's patches is unclear; macrophages apparently are present in lower concentration in Peyer's patches than in lamina propria, and their place in the interaction among M cells and T and B lymphocytes is uncertain. They probably play an effector role in cell-mediated reactions to bacteria entering via Peyer's patches, and certainly in response to agents such as *Mycobacterium paratuberculosis* and *Histoplasma capsulatum* found in the lamina propria.

**Macrophages** scattered in the lamina propria may play a role in presenting antigen to sensitize lymphocytes present in the propria. In addition to functioning in defense against microorganisms, macrophages phagocytose inert particulate matter reaching the lamina propria from the lumen. They also may accumulate iron pigment under some circumstances and, by loss at the villus tip, may have some function in its excretion. Bile pigment, perhaps derived from meconium, is seen sometimes in macrophages in the tips of villi in neonates. The involvement of macrophages in the phagocytosis of cells (enterocytes, theliolymphocytes, fibroblast sheath) in the subepithelial lamina propria at the tips of villi or between the openings of colonic glands has been alluded to previously. This process is most obvious in equine large and small intestine, where it should be distinguished from necrotic foci in the lamina propria. Its pathologic significance is uncertain.

The **IgA lymphoblasts** leave the Peyer's patch for the mesenteric lymph node and, via the thoracic duct, the general circulation, whence they home in on the intestinal mucosa and other mucosal surfaces, including the respiratory tract, mammary gland, and salivary glands. In the lamina propria of the intestine they differentiate into IgA-secretory plasma cells, found mainly in close apposition to columnar epithelium of the upper crypt. Dimeric IgA may bind to glycoprotein "secretory component" present on the basolateral border of columnar crypt epithelial cells, though this is not certain. With secretory component, it is transported in vesicles through the cytoplasm to be released from the apical border of the cell into the lumen of the crypt. It then spreads over the intestinal surface, at least partly bound to mucus. Dimeric IgA entering the circulation is selectively taken up by hepatocytes and is secreted into bile, at least in some nonruminant species.

IgA-secreting cells are the predominant class of plasma cell in the lamina propria in most species. However, IgM-secreting plasma cells are prevalent in young calves, swine, and dogs. IgM is also taken up by secretory component in some species and transported to the intestinal lumen. This may be significant in the young piglet and calf. Although IgA and IgM are secreted, $IgG_1$ is the major antibody class in intestinal secretion in cattle; it appears to be selectively secreted by the gut and in the bile in that species. The situation in sheep is less clear.

The function of IgA in the gut lumen probably lies mainly in blocking attachment by bacteria and viruses to epithelial cells, neutralizing intraluminal toxins, and limiting absorption of antigens originating in food and produced by microorganisms in the gut. It thereby reduces the likelihood of reaginic and other forms of immune response in the propria. Secretion into the bile, by hepatocytes, of IgA complexed with antigen may, in the species in which it occurs, be a significant means of clearing the circulation of antigen absorbed from the gut.

**Plasma cells containing IgG** are relatively uncommon in the intestinal lamina propria in species other than ruminants. However, locally produced and systemically circulating IgG may assume significance when vascular permeability and inflammation occur, due to its ability to fix complement, facilitate antibody-dependent cell-mediated cytotoxicity, and opsonize.

**Plasmacytes producing IgE** are present in the lamina propria, and this class of immunoglobulin has been implicated particularly in immune responses to some intestinal parasites. Its significance may be in IgE-dependent cytotoxicity by eosinophils and perhaps by mast cells, as well as in mediating reaginic reactions in the mucosa.

**Intestinal mast cells** differ histochemically and physiologically from mast cells in most other tissues. They are not readily demonstrable after formalin fixation; Carnoy's fixative is best. The proliferation of intestinal mast cells (probably of bone marrow origin) appears to be dependent on factors derived from T cells and is a prominent feature of some parasitisms.

**Globule leukocytes** are visible in hematoxylin- and eosin-stained tissue sections as mononuclear cells with large, eosinophilic cytoplasmic granules, in the epithelium of the crypt and lower villus, and sometimes in the lamina propria. Possibly they are derived from intestinal mast cells. The effects of histamine, serotonin, and other mediators released by mast cells on vascular tone and permeability, motility, chemotaxis, and effector function of leukocytes, on immune-active cells, and possibly in mucus release are many and complex. Intestinal eosinophils probably do not differ functionally from eosinophils in other sites, being cytotoxic effector cells and modulators of local inflammation.

The T cells are present in Peyer's patches and are distributed throughout the mucosa, in the lamina propria, and are the great majority of the **intraepithelial lymphocyte population**. Lymphocytes may comprise in excess of 10 to 20% of cells present in the epithelial layer of the small intestine. A significant proportion of the intraepithelial lymphocytes contain granules resembling those in mast cells; these "large granular lymphocytes" may be natural killer cells. Many of the other intraepithelial lymphocytes may be suppressor T cells. In contrast, a lower proportion of proprial T lymphocytes have markers characteristic of suppressor cells, and some may also be T-helper cells or pluripotential stem T cells. As might be expected, B lymphocytes are numerous in the lamina propria and are most highly concentrated in Peyer's patches, where the greatest numbers of T-helper cells are also found.

The T immunoblasts from the gut seem to follow a pathway similar to that of B lymphocytes, through mesenteric lymph nodes and the systemic circulation before homing in on the lamina propria or intraepithelial intercellular space. Increased numbers of intraepithelial lymphocytes are associated with cell-mediated immune reactions in the intestinal mucosa. Understanding of the mechanisms of cell-mediated immunity in the intestine is still poor. They may be mediated by T-helper-cell-promoted antibody production, by local direct cytotoxic effects,

and by release of lymphokines. In some circumstances (intestinal parasitism, probably some food allergies, celiac disease in humans), soluble factors associated with cell-mediated immune events cause alterations in epithelial proliferation and differentiation that may culminate in villus atrophy.

Immunoinflammatory events in the large bowel are less well understood than those in the small intestine. Presumably, similar principles prevail. Lymphoglandular complexes, consisting of homogeneous submucosal lymphoid aggregates penetrated by glands extending from the mucosa, occur in the cecum and proximal colon of the dog and at the cecocolic junction in ruminants. Epithelium lining glands is in close contact with lymphocytes. Solitary submucosal lymphoid nodules, normally without penetrating glands, are also scattered throughout the cecum and colon in all species. Plasma cells in the lamina propria are principally IgA producing. Depending on the species, their location varies. In dogs, most tend to be in the deeper portion of the lamina propria between glands. Intraepithelial lymphocytes are present.

### *Gastrointestinal Microflora*

After birth, no part of the gastrointestinal tract is sterile. The species of bacteria inhabiting the stomach and intestine are several hundred in number, forming an ecosystem of enormous complexity. Generally speaking, bacterial populations are least in the stomach and upper small intestine of ruminants and carnivores, being limited by the acid gastric environment and by peristalsis. The anaerobes and facultative anaerobes, mainly *E. coli*, increase to $\sim 10^7$ per gram of content in the lower small intestine, and total bacterial populations in excess of $10^{10}$ or $10^{11}$ per gram of content are present in the cecum and colon. Prominent among colonic bacteria are coliforms, *Lactobacillus*, and strict anaerobes, including *Bacteroides*, *Fusobacterium*, *Clostridium*, *Eubacterium*, *Bifidobacterium*, and *Peptostreptococcus*. Spirochetes are found in swine and dogs. Anaerobic bacteria outnumber facultative anaerobes by a thousandfold in the large bowel.

The complex ecology of the gut flora imparts on it a considerable stability, and if disturbed it tends to return toward the original state. It is relatively resistant to the intrusion of new inhabitants, and this is one of the major factors protecting against the establishment of pathogenic bacteria. It is no coincidence that bacterial diarrhea occurs most commonly in the neonate with a poorly established flora, or after changes in husbandry or antibiotic therapy that may disturb the enteric bacterial population.

Normal flora acts as a barrier to colonization by pathogens through several means. The secretion of proteins such as colicins has little significance in modulating enteric bacterial populations; more important is the production of acetic and butyric acids by the anaerobes. Under the pH and anaerobic conditions in the large bowel, fatty acids are highly detrimental to members of the Enterobacteriaceae. The high population of lactobacilli in the gut of milk-fed animals probably reduces establishment of Enterobacteriaceae by this means. Facultative anaerobes are important in maintaining the redox environment for strict anaerobes, by scavenging oxygen. Competition for energy, and the effect of metabolites other than short-chain fatty acids produced by the native flora, militate against establishment by exogenous bacteria. Host factors influencing gut flora include composition of the diet; peristalsis, which continually flushes the small intestine of a large proportion of its bacterial population; lysozyme; lactoferrin; gastric acidity if unbuffered or undiluted; and in the abomasum of suckling calves, perhaps a lactoperoxidase–thiocyanide–hydrogen peroxide system.

The enteric microbial flora promotes the development of a population of immune and inflammatory cells in the lamina propria, by antigenic stimulation. Mucosal epithelial kinetics are also speeded up in conventional animals, in comparison with those that are germ free. In germ-free gut, the proliferative compartment in the crypts is smaller and less active, and epithelial transit times to the tips of villi are slower than in conventional animals. The effects of altered intestinal epithelial turnover and immune activity on normal flora are poorly defined and probably minor as far as luminal bacteria are concerned. IgA secretion into the lumen probably influences populations close to the mucosa, and immune activity as a whole must limit establishment on and ingress by microorganisms and their products into the mucosa. Colostrum has an inhibitory effect on enteric organisms if it contains specific antibodies against those organisms.

#### *Mechanisms of Bacterial Disease Arising in the Intestine*

Disequilibrium of the normal microflora, or a competitive advantage, may permit the establishment in the intestine of pathogenic strains of bacteria, or the abnormal proliferation by opportunistic pathogens of the resident flora.

An abnormal microflora, colonic in character, may develop in the small intestine. This bacterial overgrowth is due to achlorhydria and physical or physiologic derangements resulting in gut stasis or loss of normal peristaltic flushing. Deconjugation of bile salts and fat malabsorption result in steatorrhea and other complications considered more fully later, with malabsorption and diarrhea.

Availability of abnormally large amounts of nutrient substrate may permit the proliferation of strains of toxigenic *Clostridium perfringens*. The toxins produced can have a local necrotizing effect in the gut, as occurs in lambs, piglets, and calves, and may be implicated in canine intestinal hemorrhage syndrome and perhaps colitis X in horses. *Clostridium perfringens* type D produces $\epsilon$ toxin. It has no physical effect in the gut but exemplifies the principle of enterotoxemic diseases by being absorbed and acting at a site or sites distant from the intestine. The soluble factor released by strains of *E. coli* causing edema disease (gut edema), also falls into this category.

Certain strains of *E. coli* have the capacity to attach to the epithelium of the small intestine by pili, permitting colonization. Production of secretory diarrhea by the local effect of a toxin that has a physiologic, but little or no physical, effect on the gut is characteristic of these strains; some strains of *Salmonella* may also be **enterotoxic**. *Salmonella*, however, is generally considered to be **enteroinvasive**, traversing the epithelium at a number of sites, perhaps including solitary or aggregated lymphoid follicles. Enteroinvasive bacteria often stimulate acute inflammation

and cause extensive mucosal damage, including erosion and effusion of tissue fluid. Some strains of *E. coli* may also have this capability.

Changes interpreted as increased epithelial proliferation, associated with superficial erosion, are characteristic of *Treponema* infection in swine dysentery and some *Campylobacter* infections, particularly intestinal adenomatosis complex in pigs. The organisms penetrate the epithelial cells in the latter condition; spirochetes are essentially noninvasive in swine dysentery. The effect in both these diseases is to cause loss of absorptive function and to permit effusion of tissue fluid. In intestinal adenomatosis complex, severe mucosal damage, by unknown mechanisms, may culminate in hemorrhage.

Mucosal invasion by mycobacteria will produce granulomatous enteritis, lymphangitis, and lymphadenitis, associated with villus atrophy and intestinal protein loss in **Johne's disease**. Localization of *Corynebacterium equi* largely in local lymphoid tissue in the gut, with ulceration, may progress to suppurative lymphadenitis. Rarely in domestic animals, *Yersinia* may follow a similar route, which may culminate in caseous lymphadenitis and/or bacteremia.

The intestinal mucosa can be a site for embolic establishment by circulating bacteria, and subsequent ulceration, as occurs in *Haemophilus somnus* septicemia of cattle and *Pasteurella* septicemia in lambs. More often, bacteria originating in the gut enter the lymphatics or portal drainage, gaining access to the circulation and causing bacteremia or septicemia. Bacteria causing Tyzzer's disease in foals, septicemic salmonellosis in some species, and probably some cases of *E. coli* septicemia in calves and lambs arise in the gut. For details of the pathogenesis and pathology of disease caused by these agents, see Infectious and Parasitic Diseases of the Gastrointestinal Tract.

### *Congenital Anomalies of the Intestine*

Congenital **enzyme deficiencies** of the intestinal absorptive epithelium, such as the specific disaccharidase deficiencies of humans, have not been reported in domestic animals. Membranous cytoplasmic bodies have been reported in duodenal epithelial cells and in various cell types in the lamina propria in cats with generalized congenital gangliosidosis (see the Nervous System, Volume 1).

**Segmental anomalies** of the tubular intestine are commonly encountered. In early embryonal life the intestine consists of a simple tube, the lumen of which is lined by epithelial cells of endodermal origin. An outer layer of connective tissue from the splanchnic ectoderm surrounds and supports the tube. As the intestines grow with the developing fetus, they form coiled loops that herniate into the umbilicus. In the later stages of fetal development, the intestines withdraw, in an anterior to posterior direction, from the umbilicus into the abdomen. Although several theories have been proposed on the cause of segmental developmental anomalies, the most plausible is that there is impairment of blood supply to a segment of gut during early fetal life, resulting in ischemic necrosis of the affected area.

The segmental anomalies of the intestine may be divided into two types: **stenosis** implies incomplete occlusion of the lumen; complete occlusion is referred to as **atresia**. Atresia is further subdivided into membrane atresia, when the obstruction is formed by a simple membrane or diaphragm; cord atresia, in which the blind ends of the gut are joined by a cord of connective tissue; and blind-end atresia, in which a segment of gut and the corresponding mesentery are missing, leaving two blind ends.

**Atresia ilei** is the most common segmental anomaly in the small intestine. It is most prevalent in calves, and rare in lambs, piglets, and pups. **Atresia jejuni** in Jersey cattle and atresia ilei in Swedish highland cattle are inherited as autosomal recessive traits. **Atresia coli** is also commonly encountered, particularly in Holstein calves and in foals, in which it may be hereditary. These obstructions prevent the normal movement of gut content and meconium in the fetus. Therefore, they lead to dilation of the anterior segment, with abdominal distention that may be so marked as to produce fetal dystocia.

Congenital **colonic aganglionosis** has been reported in white foals that are the offspring of overo spotted parents. Clinically, the foals, which are predominantly white with a few pigmented dots on the muzzle, abdomen, and hindquarters, develop colic and die generally within 48 hr after birth. There is stenosis mainly of the small colon, but the entire colon and rectum may be involved. The intestine anterior to the stenotic segment is distended with gas and meconium. The descending colon is contracted but patent. Microscopically, ganglia of the myenteric plexus are absent in the walls of the ileum, cecum, and colon. Except for the few pigmented spots in the skin mentioned earlier, melanocytes are absent in the skin. The condition is similar in many respects to aganglionic colon in *piebald* and *spotted* mutant mouse strains. Cutaneous melanoblasts and the myenteric plexus are both derived from the neural crest, which may explain the association between unpigmented skin and lack of the myenteric ganglia.

**Atresia ani**, overall, is the most common congenital defect of the lower gastrointestinal tract. It may affect all species and is most frequently encountered in calves and pigs, in which it is hereditary. The defect may consist only of failure of perforation of the membrane separating the endodermal hindgut from the ectodermal anal tissue, or both anus and rectum may be atretic. Atresia ani may be an isolated abnormality, or it may be associated with other malformations, especially of the distal spinal column and the genitourinary tract; in this case the terminal portion of the intestine may empty into the vagina or urinary bladder.

**Persistent Meckel's diverticulum** is an uncommon anomaly of the lower small bowel, mainly in swine and horses. It is derived from the omphalomesenteric duct, which is the stalk of the yolk sac. This duct is normally obliterated before the end of the first third of pregnancy. Rarely, it may be retained in postnatal life as a patent tube extending from the antimesenteric side of the intestine to the umbilicus. More commonly, only that portion immediately adjacent to the intestine remains patent. This pouch or tubelike remnant is Meckel's diverticulum. Its mucosal lining is similar to that of the ileum. In swine it usually occurs as a tube the width of the ileum, 5–30 cm in length (Fig. 1.12A). In horses it is present as a short, cone-shaped sac ~10 cm in diameter, which may be attached by mesodiverticular

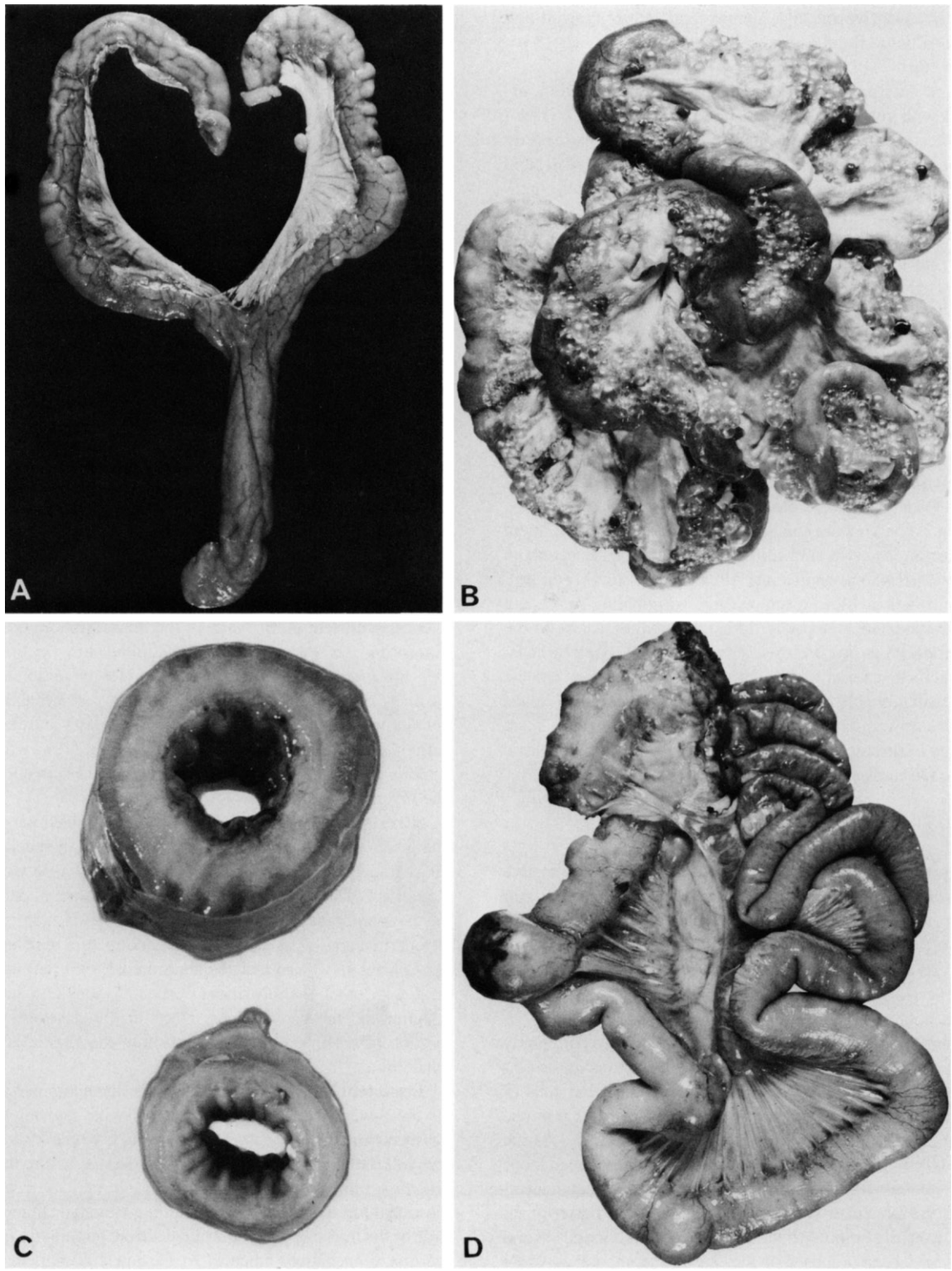


**Fig. 1.12.** (**A**) Persistent Meckel's diverticulum. Midjejunum. Pig. (**B**) Intestinal emphysema. Pig. (**C**) Ileal muscular hypertrophy. Horse. Normal equine ileum below. (**D**) Multiple saccular dilatations with impending perforation in muscular hypertrophy of ileum. Pig. (Courtesy of S. W. Nielsen and the *Journal of the American Veterinary Medical Association.*)

bands to the mesentery. It is usually an incidental finding, although in horses it has been associated with strangulation of the intestine herniating through the mesodiverticular bands.

### *Miscellaneous Conditions of the Intestinal Tract*

INTESTINAL LIPOFUSCINOSIS. Intestinal lipofuscinosis is characterized grossly by brown discoloration of the intestinal serosa. It may involve all areas from the stomach to the rectum but is most commonly present in the lower small intestine. The bladder and mesenteric and peripheral lymph nodes may also be affected grossly. Although the lesion is usually an incidental finding, it has more commonly been associated with chronic enteric and pancreatic disease. Lipofuscinosis has been reported in boxer dogs with histiocytic ulcerative colitis, but a definite correlation between the two conditions has not been established. A high prevalence of lipofuscinosis has also been reported in dogs that were fed rations high in polyunsaturated fats with a relative deficiency of vitamin E. Feeding of high levels of vitamin E has prevented the condition. It appears that any condition causing a reduction in the absorption of fats and consequently of the fat-soluble vitamins, especially in the presence of polyunsaturated fatty acids in the diet, may predispose to lipofuscinosis.

The microscopic lesions of brown gut are characterized by gray to brown granules in the perinuclear regions of smooth muscle cells in both inner and outer layers of the gut wall. The granules stain as lipofuscin.

MUSCULAR HYPERTROPHY OF THE ILEUM. Formerly a common finding in swine, muscular hypertrophy of the ileum appears to have diminished in prevalence in most areas. It may be found in apparently healthy animals at slaughter as a uniform thickening of the muscular coats of the terminal ileum. The segment involved always includes the most caudal portion, but it may extend a variable distance forward, usually between 25 and 50 cm. The affected area is thickened and has the turgid feel of a rubber hose. The lumen is small, and the mucosa is thrown into thick, convoluted folds suggestive of Johne's disease, but it is apparent that the major component of the increase in thickness of the wall is in the muscular layers. This condition must be differentiated from adenomatosis and necrotic ileitis, manifestations of enteropathy associated with *Campylobacter* spp. in swine.

The outcome of the condition is not always benign, and impaction and rupture are important and disastrous sequelae. It is probable that diet and intercurrent disease contribute to the tendency to rupture, as it may be associated with the impaction of dehydrated feed in the hypertrophic segment. The actual rupture may be a result of violent peristaltic contractions, or diverticula may develop (Fig. 1.12D), the mucosa undergoing necrosis with secondary bacterial inflammation. Perforation occurs at these weakened areas.

While the underlying basis of this condition is obscure, it is likely that the muscular hypertrophy is secondary to a functional obstruction of the ileocecal valve.

Muscular hypertrophy of the small intestine, of unknown cause, also occurs in horses (Fig. 1.12C). The lesions are similar to those described in swine, except that the affected segment may occur at any point along the small intestine, although the ileum is the most common site. Horses with this condition may have chronic mild colic or intermittent diarrhea with progressive loss of weight. Unlike pigs, perforation is an unusual complication in the horse.

DIVERTICULOSIS OF THE SMALL INTESTINE. Diverticulosis of the small intestine is sometimes, but not necessarily, associated with muscular hypertrophy in pigs and horses. It is characterized by the presence of cystic structures, which are lined by intestinal mucosa, in the muscularis and subserosa of the small intestine. The diverticula tend to follow the pathway of blood vessels and are mainly located adjacent to the mesenteric attachment. Rupture of the diverticula causes peritonitis.

In sheep, diverticulosis occurs independently from muscular hypertrophy, and the most common sites are the duodenum and ileum.

INTESTINAL EMPHYSEMA IN PIGS. Intestinal emphysema is a rare condition found mainly in postweaning pigs. The lesion is usually an incidental finding in slaughtered animals and has no economic significance. It is characterized by numerous thin-walled, gas-filled cystic structures, a few millimeters to several centimeters in diameter, in the gut wall and on the serosal surface (Fig. 1.12B). These are located mainly in the small intestine, although the large intestine, mesentery, and mesenteric lymph nodes may be involved. Microscopically, the cystic structures appear to be dilated lymphatics located in the lamina propria, submucosa, muscularis, subserosa, mesentery, and mesenteric lymph nodes. A pleocellular inflammatory reaction may be evident in the walls of the cysts. Although production of gas by bacteria has been implicated, the cause remains obscure.

RECTAL PROLAPSE. Rectal prolapse most commonly occurs in swine, sheep, and cattle. It may occur in any animal that has prolonged episodes of tenesmus or straining, usually associated with colitis or urinary infection or obstruction. In pigs, rectal prolapse occurs as a herd problem when the ration contains zearalenone, an estrogenic mycotoxin produced by fungi of the genus *Fusarium*. The toxin causes marked swelling and congestion of the vulva and vaginal mucosa, which may be followed by vaginal prolapse. Affected pigs strain continuously, and rectal prolapse is a common complication. Rectal prolapse in sheep may be the consequence of ingestion of estrogenic pastures and is accompanied by other signs of hyperestrogenism (see the Female Genital System, Volume 3).

The prolapsed rectum is edematous, congested, and there may be necrosis and ulceration of the everted mucosa. These lesions are ischemic in origin due to interference with venous blood flow from the prolapsed section. Only the mucosa, or all layers, may be involved in the prolapse. In swine surviving slough or amputation of the prolapsed tissue, rectal stricture may ensue. Rectal strictures are discussed further with salmonellosis.

### *Intestinal Obstruction*

Clinically acute obstruction typically involves the upper or middle small intestine; chronic blockage usually involves the ileum and large bowel. Intestinal obstruction may be the sequel to a physical blockage of the lumen resulting from **stenosis** due to an intrinsic lesion involving the intestinal wall, **obturation** by an intraluminal mass, or extrinsic **compression**. Failure of the intestinal circular smooth muscle to contract (paralytic ileus) blocks the peristaltic wave, causing **functional obstruction**. Ileus is a common sequel to peritoneal irritation and occurs proximal to any form of mechanical obstruction. Circulatory embarrassment of a segment of bowel, through embolism or venous infarction, will also cause functional obstruction without a physical blockage. Many of the displacements of gut that produce obstruction, such as volvulus, strangulation of a hernia, or intussusception, may cause ischemia. Mucosal hypoxia may also be a sequel to venous occlusion, resulting from distention of gut proximal to a site of obstruction, or it may result from local pressure caused by an adjacent mass. Ischemia in any circumstance is a serious complication, the pathogenesis of which is dealt with later.

We shall consider first the evolution of the sequelae to intestinal obstruction, then return for a closer look at the various types of blockage. Proximal to the point of obstruction there is accumulation of fluid, derived from ingesta and gastric, biliary, pancreatic, and intrinsic intestinal secretion, and gas, swallowed or originating with bacterial activity in the gut. Intestinal distention results in sequestration of water and electrolyte in the intestinal lumen, further secretion into the gut, edema of the mucosa, and in extreme cases, transudation from the peritoneal surface. Upper small bowel obstruction progresses rapidly to cause vomiting in those species that can vomit, with dehydration, hypochloremia, hypokalemia, and metabolic alkalosis due to loss of acid in vomitus, or sequestration of fluid in the forestomachs.

Obstruction of the lower small intestine may result in distention with dehydration. But there is usually less acute electrolyte and acid–base imbalance, since vomition is less severe and absorption of fluid proximal to the obstruction may prevent serious distention and its associated secretion for some time. Secretion into obstructed gut is mainly stimulated by distention but may partially be related to bacterial overgrowth of the stagnant intestinal content. Metabolic acidosis eventually ensues following dehydration and catabolism of fat and muscle due to cessation of food consumption and assimilation. Incomplete or slowly developing obstruction may be associated with compensatory muscular hypertrophy proximal to the offending lesion. Incomplete obstruction often becomes total due to progress of the primary lesion or the accumulation of solid digesta. Colonic obstruction may result in accumulation of large quantities of content in the bowel, with considerable abdominal distention.

If ischemia and its complications do not ensue, the animal with acute obstruction succumbs to the systemic effects of hypovolemia and electrolyte and acid–base disturbance. Lower intestinal or colonic obstruction may result in eventual metabolic acidosis and starvation following a chronic course.

In obstruction, the outstanding gross alteration in the bowel is distention proximal to the point of blockage due to paralytic ileus and the accumulation of fluid contents and gas. The location, degree, and duration of the obstruction determines the segment and length of bowel involved and the degree of distention. As distention increases, interference with venous return may develop and the mucosa and submucosa become congested. Devitalization of severely dilated gut, or pressure necrosis of the mucosa at the site of lodgment of intraluminal foreign bodies, may occur, leading to gangrene or perforation and peritonitis. Distal to the point of obstruction the bowel is collapsed and empty.

#### *Stenosis and Obturation*

Intrinsic obstruction due to congenital segmental atresia and imperforations is considered under Congenital Anomalies of the Intestine, above. Acquired stenosis due to pathologic processes arising within the wall of the intestine may be partial or complete. The primary lesions include intramural abscesses, primary neoplasms (Fig. 1.19A), and scarring following ulceration. Many of these develop slowly, with a course as described above for simple chronic obstruction.

All kinds of **foreign bodies** are commonly found. Small, rounded foreign bodies and even some sharp-edged objects may pass through the intestines uneventfully, but for these and many large foreign bodies the course is unpredictable. Some may reside in the intestine for long periods and produce no disturbance until they act as a nucleus for the development of an enterolith. Sand may remain sedimented in the colon of horses that have grazed on poorly covered sandy soils. It may cause a chronic colitis and, in some cases, obstruction. Sharp-pointed foreign bodies may become impacted in the intestine and cause pressure necrosis with ulceration and possibly perforation. Blunt foreign bodies that become impacted cause acute or chronic obstruction depending on their size and often too are the cause of local pressure necrosis, perforation occurring in some cases. Strips of cloth or string, which are not infrequently ingested by dogs and cats, may pass through the intestine. When they become impacted, however, they produce a typical lesion; one portion of a string becomes fixed and then is stretched taut distally by peristaltic movements. It progressively cuts into the lesser curvature of intestinal loops, causing first a puckering of the mesentery and finally perforation and peritonitis.

**Enteroliths** (mineral concrements) were common in the colon of horses in the past, are less so now, and are rare in other species. They vary greatly in size, some weighing as much as 10 kg, and in number, there being one or more large ones or many small ones. They are smooth and usually spherical, but contact and abrasion may smoothly flatten some surfaces. The stones are composed largely of phosphate. The concrement is deposited in concentric lamellae, and at the center there is a nucleus, comprising a foreign body or particle of feed. The development of an enterolith depends on the presence of soluble ingredients and a nidus for precipitation. The source of the magnesium phosphate is probably grain. Normally it is ionized in the acid gastric juice, and the phosphate is absorbed in the small intestine. Unsplit salt escaping to the colon combines with ammonia, produced as a

result of bacterial digestion of protein, to form magnesium ammonium phosphate (triple phosphate).

Fiber balls (**phytotrichobezoars**) consist largely of plant fibers impregnated with some phosphate salt. They are not as heavy as enteroliths, are moist, and have a velvety surface. They are usually round and smooth, but some are convoluted like the surface of the cerebrum. Hair balls (**trichobezoars**) sometimes occur in dogs and cats and in ruminants; in the latter they occur in the forestomachs and abomasum. Enteroliths and bezoars in horses are often without significance. Apparently they are moved about enough by peristalsis to avoid pressure necrosis. They become important when they are impacted, usually in the pelvic flexure. Small enteroliths may pass in the feces without consequence.

Parasites are capable of causing intestinal obstruction when they form ropelike, tangled masses in the lumen. This is not uncommon in pigs and foals infected with large numbers of ascarids. It also occurs rarely in sheep heavily infested with tapeworms.

Impaction of the colon, by feces in dogs and cats and by digesta in horses, is not uncommon and causes a simple intestinal obstruction, complicated in the horse by intestinal tympany from fermentative gases. In dogs, it may be the result of voluntarily suppressed painful defecation, as in prostatic enlargement and inflammation of the anal sacs. Occasionally it is due to an impaction with foreign bodies, especially fine bones in the colon or rectum. It may also complicate paralyzing lesions of the spinal cord.

Impaction of the cecum or colon in horses is largely a disease of older animals in which probably there is some degree of motor and secretory insufficiency. It is often precipitated by a change of diet from something soft and lush to hay or chaff, which because of the dental attrition of old age is poorly masticated and salivated. In these animals, impaction of the cecum may be recurrent. Ingestion of rope or pieces of conveyor belt has been associated with colonic impaction caused by indigestible synthetic fibers. Ingestion of large numbers of acorns and leaves may also cause impaction of the intestinal tract in ruminants.

### *Extrinsic Obstruction*

Compression of intestine causing obstruction is rather common and is caused by tumors, abscesses, peritonitis, and fibrous adhesions. Neoplasms involve the intestine by extension from adjacent viscera, particularly pancreas. Therefore, most of them involve the anterior–dorsal part of the abdominal cavity and impinge on the duodenum. Inflammatory peritoneal adhesions are common, and fibrous bands may stretch from the wall of the bowel to some fixed point or between two or more points along the bowel or mesentery; the obstruction develops gradually as cicatrization ties the bowel down or puts kinks in the mesentery. Large, firm masses of abdominal fat necrosis cause compression stenosis of small intestine, coiled colon, and particularly, descending colon and rectum of cattle. Peduncles of some tumors, especially mesenteric lipomas in older horses, occasionally become wound about loops of intestine and cause obstruction and strangulation. Incarceration in hernias, discussed elsewhere, is also a common cause of compression obstruction of the gut.

### *Functional Obstruction*

**Paralytic ileus** is in itself not of specific interest to the pathologist but is a rather common condition. It frequently follows abdominal surgery in transient episodes, especially when the intestines are handled roughly or traumatized. It also occurs in peritoneal irritation of any cause, especially in peritonitis. It probably is the result of a variety of neurogenic and reflex factors that interfere with the networks controlling the inhibitory neurons of the myenteric plexus. Continual tonic discharge by these neurons inhibits contraction of circular smooth muscle and prevents peristalsis.

The intestines are distended with a mixture of gas and fluid, and the wall is flaccid. The defect may be segmental, involving less than a meter of the intestinal length, but there may be many such segments involved, especially in diffuse peritonitis. Gastric rupture may occur in the horse as a complication of obstructive or postoperative ileus of the small intestine.

**Grass sickness** in **horses**, for which there is as yet no good pathologic definition, occurs chiefly in parts of the United Kingdom and western Europe, with few exceptions in animals at pasture. Although horses of any age may be afflicted, the disease is more common in those 3–6 years of age. Affected animals are dull but show occasional bouts of colicky restlessness. In the acute disease, there is progressively severe tympany, swallowing is avoided, and saliva drools freely. Any attempt to swallow is apparently painful and stimulates reverse peristalsis in the esophagus. Fine muscular tremors develop over the shoulders, and there is sweating. The course in acute cases is from 12 to 72 hr. Some survive the acute phase to live much longer, but most usually die in due course.

Lesions are confined to the alimentary tract. The esophageal wall is sometimes edematous, and the mucosa may show longitudinal bands of congestion and ulceration. The stomach is distended with fluid (up to 22 liters have been measured), often of khaki color and pea-soup consistency, although sometimes more watery with fibrous material. This fluid is alkaline and mucinous. Some stomachs are ruptured. There is also a great excess of fluid in the small intestine, but except for some hemorrhage and edema at the mesenteric junction, there is no other change. The large intestine is impacted with dry contents, and the fecal pellets in the colon are small and dry. These masses may have a surface blackened by a small amount of exuded blood. In chronic cases, the volume of alimentary content is reduced to scant amounts in the stomach and small intestine, and the content of the large intestine is soupy.

The cause of grass sickness is speculative. In Europe and Britain, degenerative lesions have been described in the autonomic ganglia, especially the celiacomesenteric, but these are difficult structures to work with histologically and claims for ganglion-cell degeneration must be very critically evaluated. Specific neutralizing antibodies to *Clostridium perfringens* type A have been demonstrated in horses that survived a disease claimed to resemble grass sickness in Colombia. Sera from recovered horses in Scotland did not contain such antibodies, suggesting that the diseases in these areas are not the same or that they have a different cause. Transfusion of whole blood from

donor horses that show clinical signs of grass sickness, into ponies, results in lesions in the autonomic ganglia that are similar to those present in spontaneous cases. However, the ponies remain clinically normal. The putative neurotoxic factor is in the plasma protein fraction of the blood and has a molecular weight of 30,000 or greater. Intraperitoneal injection of the neurotoxic factor into ponies produces characteristic lesions but not clinical disease. These observations suggest that the neurotoxic factor may be the result, rather than the cause, of grass sickness, or that relatively high plasma concentrations are required to cause clinical signs.

It is, however, difficult to avoid the conclusion that this disease is, in the final analysis, neurogenic ileus. Its differentiation from primary colonic impaction may be difficult.

### *Displacements of the Intestines*

#### *Eventration*

Eventration is displacement of a portion of the intestine, usually the small intestine, outside the abdominal cavity. These are commonly congenital as in schistosomus reflexus, patent umbilicus, and congenital diaphragmatic hernia. Acquired eventrations result from trauma and therefore are varied. In some cases, the displaced intestine herniates into the abdominal muscle or subcutis, or it may be completely exteriorized.

#### *Cecal Dilatation and Torsion in Cattle*

Cecal dilatation and torsion is a rare condition that occurs mainly in animals fed high-concentrate rations. About 30% of the carbohydrates in the ration are digested in the cecum of ruminants. Normally, the volatile fatty acids produced by fermentation are absorbed through the cecal mucosa by passive diffusion. Sudden change from a diet consisting mainly of roughage to a grain-based ration results in an increase in the concentration of volatile fatty acids, with only a slight decrease in pH in the cecal contents. When the increase in the concentration of dissociated volatile fatty acids, especially butyric acid, is severe, the cecum becomes atonic and dilation follows. Once the cecum is dilated and distended with watery ingesta, various degrees of clockwise or counterclockwise torsion can occur, which may incorporate adjacent viscera, particularly a loop of distal jejunum.

#### *Left Dorsal Displacement of the Colon*

Left dorsal displacement of the colon is encountered as a cause of obstruction and colic in horses. The cecum, small intestine, and stomach are distended as a result of compression of the displaced colon, and the stomach and spleen are displaced caudally and ventromedially. The altered gastric location is the result of displacement of the sternal and diaphragmatic flexures into the space cranial to the stomach, in apposition with the left lobe of the liver. The left dorsal and ventral colon move dorsally and are trapped between the suspensory ligament of the spleen and the dorsal abdominal wall. Pelvic flexure may double back on itself and become wedged between stomach and liver as well. Compression of the colon may cause partial ischemia of the displaced organ. The cause is unknown. Surgical intervention is necessary for resolution.

Abnormal flexion of the cecum and/or colon may occur in the horse. The pelvic flexure may be displaced medially, laterally, or dorsally. The tip of the cecum may similarly bend upon itself. In displacement of both organs there is the risk of vascular embarrassment and infarction due to kinking of the bowel.

#### *Internal Hernia*

Internal hernia is a displacement of intestine through normal or pathologic foraminae within the abdominal cavity without the formation of a hernial sac. It is uncommon.

**Herniation** through a **natural foramen** occurs in horses in two locations. A portion of small intestine may pass down into the omental bursa and become incarcerated if the normally short and slitlike epiploic foramen of Winslow is dilated for any reason. Occasionally the small intestine, small colon, or left large colon is incarcerated in the nephrosplenic space formed by the dorsal end of the spleen, its renal ligament, the left kidney, and the ventral spinal muscles.

**Omental hernia** occurs when a loop of intestine passes through a tear in the greater or lesser omentum. **Mesenteric hernia** is due to passage of intestine through a tear in the mesentery. These are probably traumatic defects and usually involve the mesentery of the small intestine and, in horses, that of the colon.

**Herniation** through a **natural foramen** occurs in horses in young ruminants and, more rarely, in other species following castration. During the operation, excessive traction on the spermatic cord may tear the peritoneal fold of the ductus deferens, which fixes the duct to the pelvic wall. A hiatus is formed between the ductus deferens and the lateral abdominal or pelvic walls, and through it, loops of intestine may become incarcerated.

#### *External Hernia*

External hernia typically consists of a hernial sac formed as a pouch of parietal peritoneum; a covering of skin and soft tissues; depending on the location of the hernia, a hernial ring; and the hernial contents. The hernial ring is an opening in the abdominal wall, and this may be acquired, or it may be natural as, for example, the inguinal ring. The hernia usually contains a portion of omentum, the more freely mobile portions of the intestine, and occasionally, one or more of the other viscera. Unless the sac is obliterated by adhesions, it contains a small amount of peritoneal fluid.

**Ventral hernia** occurs in horses, less commonly in cattle, and exceptionally in other species. These hernias may be apparently spontaneous in pregnant females or be a consequence of blunt trauma, horn injuries, surgical scars, or inflammations that cause weakening or perforation of the supporting musculature. They may attain very large size in herbivores because of the weight of the alimentary viscera and pregnant uterus.

**Umbilical hernia** is common and is often present as a congenital and inherited defect. It is most frequent in pigs, foals, calves, and pups and depends on persistent patency of the umbilical ring. The hernial sac is formed by peritoneum and skin, and the contents depend on the size of the ring and of the sac.

**Scrotal hernia** is an exaggerated degree of inguinal herniation in which the viscera pass down the inguinal canal and come

to lie in the cavity of the tunica vaginalis. The internal inguinal ring remains patent in male animals, but its diameter and the tendency to herniation is inherited. If the hernia is scrotal, there may be degeneration of the testicles. Routine castration of such animals may lead to eventration through the scrotal incision, and closed castration may cause infarction of the herniated loop of gut. The bitch differs from females of other species in having a patent inguinal ring and canal through which the round ligament, the omentum, and the uterus may pass. The herniated uterus may become incarcerated when pregnant or if pyometra develops. False inguinal hernias may also develop in males, the displaced viscus passing not within the cavity of the tunica vaginalis but outside it in a subcutaneous position in a true peritoneal hernial sac.

**Femoral hernias** develop as an outpouching of peritoneum through the femoral triangle along the course of the femoral artery. They contain omentum and small intestine.

**Perineal hernias** occur principally in old male dogs in association with prostatic enlargements and obstipation. They are precipitated by undue abdominal straining and are probably predisposed to by weakening of perineal fascia and muscles from some unknown cause, possibly hormonal. They are very unusual in females. The weakening of the pelvic diaphragm takes place between the coccygeus medialis muscle and the anterior border of the anal sphincter. Through this defect bulges the retroperitoneal pelvic fat. Usually this is the only tissue to prolapse, and the lesion consists essentially of a loss of support on one side of the anal ring. Concomitantly with the loss of pelvic support, the rectum deviates and diverticula may form, and the prostate and the bladder may move into the pelvis. Further displacement may occur occasionally, and then the latter organs are forced through the ruptured perineal fascia. Retroflexion of the bladder kinks the urethra and leads to an acute obstruction. Perineal hernias are most commonly unilateral, but the perineal fascia may fail bilaterally, and the anus, having lost its support on both sides, is forced directly back at each attempt at defecation. The bulging is then symmetric.

**Diaphragmatic hernias** are common. The defect in the diaphragm may be congenital, but most often it is acquired. In dogs and cats, acquired rupture of the diaphragm is a result of acute abdominal compression, usually from automobile accidents. Omentum and small intestine pass through the smaller clefts; liver, stomach, and other viscera may pass through the larger defects. The herniation is usually into one or other pleural sac, and only exceptionally into the pericardial sac. In cattle, diaphragmatic hernia is usually a consequence of traumatic reticuloperitonitis. Horses with diaphragmatic hernias often have a chronic history of intermittent colic that terminates with an acute fatal episode. The congenital form is often located in the left dorsal quadrant, and it may be associated with arthrogryposis and scoliosis. Acquired hernias mainly involve the tendinous portion of the diaphragm.

The **sequelae** of **hernias** depend largely on their location and content, but there are some generalities that are applicable to all. As long as the hernial contents remain freely movable and the hernia is reducible there may be no untoward sequelae. Fixation of the hernial contents (incarceration) is a serious development. It is most important when the small intestine is incarcerated because of the liability to intestinal obstruction and perforation, with death occurring from paralytic ileus or peritonitis. Incarceration may result from progressive stenosis of the hernial ring, adhesion between the contents and the sac, or distention of the herniated viscus. This distention may be due to accumulated gas or ingesta in the intestine, urine in a herniated bladder, and fetuses or pus in a herniated uterus. With some herniations, incarceration is the result of only slight pressure by the neck of the pouch, by which venous drainage is impaired and a vicious cycle is initiated; the edema caused by the venous stasis increases the bulk of the contents so that they become incarcerated.

### *Intestinal Ischemia and Infarction*

Inadequate or interrupted circulation of blood to the gut is a common problem, particularly in the horse. Obstruction of the efferent veins, blockage of afferent arteries, and reduced flow through an open circulation cause hypoxic damage to the intestine. Whatever the initiating agency, the effect of hypoxia at the level of the mucosa is the same.

In the small intestine, within 5 to 10 min of the onset of ischemia, changes are observed at the tips of villi in tissue sections examined under the light microscope, and lesions are well advanced by 30 min. Separation of the epithelium from the basement membrane, beginning at the tip of the villus and progressing with time toward the base, causes the formation of the so-called Gruenhagen's space. Epithelial cells appear relatively normal but may separate from the villus in sheets. Within 1 to 2 hr, the villus is completely denuded of epithelium and the mesenchymal core is disintegrating or collapsed and stumpy, with hemorrhage from capillaries. That the lesion is largely a function of hypoxia is indicated by the mitigating effects of intraluminal oxygen perfusion. The putative countercurrent exchange of oxygen between the afferent arteriole and efferent venules in the villus, and an associated progressive decline in oxygen tension distally in the villus, may render the tip prone to early damage in hypoxia. Intraluminal enzymes, especially elastase, may contribute to epithelial damage by altering glycoproteins in the vicinity of the brush border, perhaps opening the way for further damage by other pancreatic enzymes.

Dissociation and necrosis of cells in the crypts of Lieberkühn begins ~2 hr after the initiation of ischemia, and within 4 to 5 hr the mucosal epithelium appears completely necrotic or has sloughed, leaving a mesenchymal ghost of the mucosa. The muscularis mucosae may undergo necrosis, but the muscularis externa remains viable for 6 to 7 hr.

The colon, of the dog at least, seems less sensitive to ischemia than the small intestine. Mild morphologic damage is found after 1 hr, but severe mucosal lesions are evident by 3 hr.

If hypoxia is only partial, or ischemia is transient, with reflow occurring, the outcome may be variable. Short-term ischemia with preservation of at least the base of the crypts of Lieberkühn will permit resolution, as proliferation of cells in the crypts reepithelializes the mucosal surface within 1 to 3 days. Normal architecture is reestablished after up to 1 to 2 weeks, though necrotic muscularis mucosae is not replaced. Effusion of tissue fluid and acute inflammatory cells prevail until epithelium ex-

tends to fully cover the eroded surface. Partial damage to the proliferative compartment results in dilation of crypts, lined by flattened epithelium resembling that seen after radiation injury.

Ischemic necrosis of the full thickness of the mucosa will be bounded by an acute inflammatory reaction in the submucosa, which under favorable conditions evolves into a granulating ulcerated surface. Neutrophilic infiltration and effusion may be considerable if bacterial contamination of the lumen is heavy. Focal ulcerative lesions may ultimately heal by epithelial migration, over the bed of granulation tissue, from surviving crypts within the lesion and around the periphery.

Extensive mucosal ulcers that form following ischemia with vascular reflow have little chance of resolution, due to their large surface area. Chronic ischemic ulcers in the small bowel tend to develop a depressed, fairly clean, granulating surface, occasionally with some fibrinous exudate. Many ulcers in the large bowel, especially of horses, develop a dirty yellow-gray fibrinonecrotic surface, perhaps due to the effects of anaerobic bacteria. If the animal does not succumb to the effects of malabsorption and protein loss from the defect, or to transmural bacterial invasion, scarring and stricture may occur.

The sequelae of ischemia with reflow are seen mainly in strangulated segments of gut that have been reduced without, or with inadequately extensive, resection, and in some cases of presumed thromboembolic infarction of the equine colon.

Persistent ischemia results in necrosis involving all mural elements. The full thickness of the gut wall ultimately becomes gangrenous, green-brown or black, flaccid, and friable.

The consequences of ischemic lesions are partly a function of the species and of the level of bowel affected. Strangulation, volvulus, and similar lesions cause physical obstruction at the site, and ileus proximal to it. Reduced arterial perfusion or thromboembolism causes functional obstruction and ileus. Loss of mucosal integrity results in cessation of electrolyte and water absorption, and ultimately in effusion of tissue fluid and blood into the lumen. Proliferation of anaerobes occurs in the lumen of the stagnant ischemic area, with accumulation of gas and extreme distention of the closed loop in strangulation obstruction. Toxin production by anaerobes, particularly clostridia, plays a large part in gangrene and ultimate rupture of ischemic gut, as well as having systemic effects. Absorption of endotoxin or endotoxin-like molecules from the lumen may occur through devitalized mucosa via the portal flow, lymphatic return, or peritoneum. These compounds have a severe detrimental effect on cardiovascular function, contributing to the circulatory failure. If death from some other cause does not supervene, transmural invasion by enteric bacteria or perforation of the devitalized wall results in septic peritonitis, which is ultimately fatal.

### *Venous Infarction*

Obstruction of efferent veins is by far the most common cause of intestinal ischemia. This is a sequel to incarceration of herniated loops of bowel, strangulation by pedunculated masses, torsion (twist about long axis of the viscus), volvulus (twist across the long axis of the gut), and intussusception. In these circumstances, compression of thin-walled veins tends to occur before the influx of arterial blood is obstructed. Primary thrombosis of the mesenteric veins is a rare cause of infarction in domestic animals. Local invasion of the mucosa by mycotic agents may result in focal or segmental lesions, however, due to hyphal invasion of submucosal veins. The affected tissue field, sometimes including involved mesentery, becomes intensely edematous, congested, and hemorrhagic, so that the hypoxic bowel wall is thickened and eventually assumes a deep red-black appearance. Bloody fluid content and gas distend the lumen of the infarcted segment. As gangrene of the intestinal wall proceeds, the tissue becomes green-black and septic peritonitis eventually ensues, with or without perforation of the bowel.

Advanced venous infarction involves the full thickness of the intestinal wall, and the initiating intestinal accident is commonly evident, except in cases subjected to surgery. Even if a displacement, volvulus, or strangulation has been reduced, the limits of the infarcted segment are generally sharply demarcated. Microscopically, severe edema, congestion, distention of veins, sometimes venous thrombosis, and hemorrhage are present, initially most severe in the mucosa and submucosa. With time, the full thickness of the mucosa becomes necrotic, and the deeper layers of the muscular wall are also devitalized, with invading enteric flora present throughout.

Displacements of intestine that may progress to incarceration or strangulation and infarction have been discussed in the previous section. **Torsion** of the **long axis** of the **mesentery** occurs commonly in suckling ruminants, in swine, uncommonly in horses, and rarely in dogs and cats. In all species, the result is rapid death. The abdomen is distended, and on opening the cavity, the tensely dilated deep red to black loops of bowel are immediately apparent. In swine, the mesentery of the small intestine and sometimes the large bowel is often involved in a torsion that usually is counterclockwise, when viewed from the ventrocaudal aspect. In torsion involving the small and large intestines, the apex of the cecum may be pointing cranial in the anterior right quadrant of the abdomen, reflecting the rotation of ~180°. In swine, mesenteric torsion may be due to gas production from a highly fermentable substrate in the colon, and its subsequent displacement, with progression to mesenteric torsion. Mesenteric torsion is a common cause of sporadic sudden death in swine but may occur as a herd problem. Many cases of so called intestinal hemorrhage syndrome in that species are probably misdiagnosed mesenteric torsion (Fig. 1.13B). The presence of red-black or bloody content in the intestine of feeder swine, without torsion, may also signal bleeding gastric ulcer or proliferative hemorrhagic enteropathy associated with *Campylobacter*.

Death due to mesenteric torsion is common in suckling or artifically reared calves and lambs. In these species, vigorous ingestion of large amounts of feed over a short period may predispose to gas formation in the gut, or perhaps hypermotility, which induces torsion. Usually only the mucosa of the proximal duodenum and terminal ileum, cecum, and colon is spared the effects of infarction. Similar lesions are occasionally encountered in other species.

**Volvulus** of varying lengths of the small intestine may occur in any species but is perhaps most prevalent in the horse, where it is a common cause of strangulation obstruction of the bowel. Volvulus of the left large colon of the horse is predisposed to by its lack of mesenteric anchorage, and potential mobility. It usually occurs as the left dorsal colon moves mesially on the left

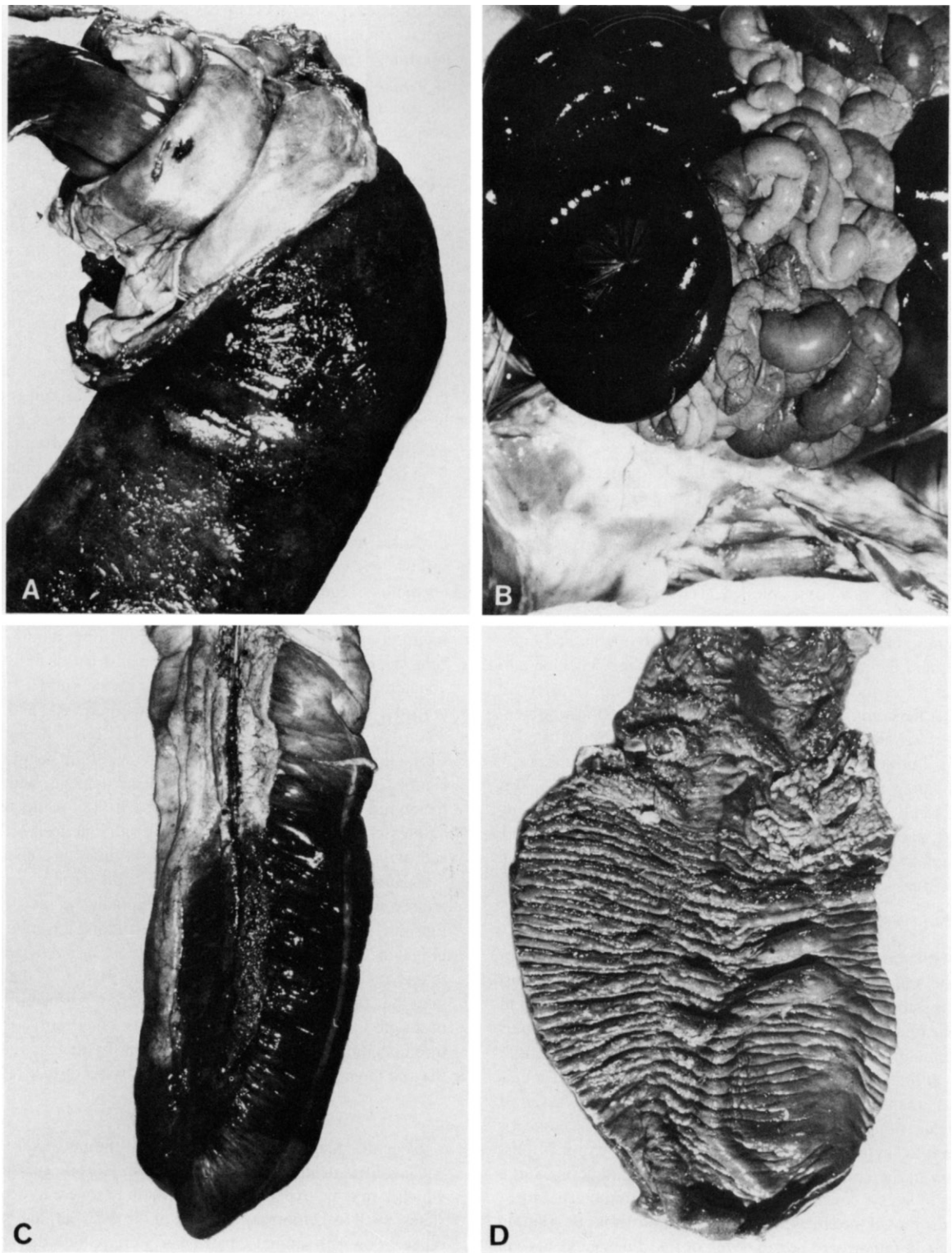


**Fig. 1.13.** (**A**) Intussusception. Intestine. Dog. Outer intestinal layer has been cut away to expose the edematous and congested infarcted mucosa of strangulated portion of the intussusception. (**B**) Deeply congested segment of small intestine, infarcted as a result of volvulus or mesenteric torsion. Pig. (**C**) Equine cecum. Infarction of distal half. Cecal artery contains a thrombus. Congestion and edema of serosa and musculature suggest that reflow and hemorrhage have occurred. (**D**) Mucosa of cecum in (**C**). Surface of infarcted mucosa is covered by a fibrinonecrotic membrane. Ulcerated areas along proximal margin of lesion are covered by fibrinous exudate.

ventral colon, progressing to volvulus at the sternal and diaphragmatic flexures. At autopsy, the usual signs of strangulation obstruction are evident, including dilatation and devitalization of the infarcted segment, distention of the cecum, and perhaps, postmortem rupture of the diaphragm or abdominal wall due to tympany.

**Intussusception** involves the telescoping of one segment of bowel into an outer sheath formed by another, usually distal segment of gut. Any level of the gut with sufficient mesenteric mobility may be involved. The cause is usually not apparent, though linear foreign bodies, heavy parasitism, previous intestinal surgery, enteritis, and intramural lesions such as abscesses and tumors may be associated. It also may be a terminal, agonal, or postmortem event. The history is that of partial or complete intestinal obstruction, perhaps with bloody feces. Intussusception is common in dogs (Fig. 1.13A), where most frequently it is ileocolic. It is much less common in cats. Intussusception is also moderately common in lambs, calves, and young horses, where it may involve small intestine, cecum, and colon.

The progressive invagination of the leading edge of the intussusceptum into the posterior segment is limited by the increasing tension on the mesentery drawn into the lesion, to about 10 to 12 cm in small animals, and about 20 to 30 cm in large animals. This tension along one edge of the gut causes the mass to become bowed or spiraled. Tension and compression of mesenteric veins cause the intussusceptum, or a portion of it, to undergo venous infarction. It swells, with edema and congestion, and the adjacent apposed serous surfaces become adherent as fibrin and inflammatory cells effuse from the affected bowel. Adhesion quickly renders the intussusception irreducible. Necrosis and gangrene of the invaginated intestine usually develop, but sometimes the intussusceptum will slough, and the remaining viable segments will maintain continuity of the gut, or rarely, will form two adjacent blind ends. Incidental terminal, agonal, or postmortem intussusception is recognized by the relative absence of congestion, edema, and adhesion of the involuted segment of gut.

### *Arterial Thromboembolism*

Ischemia due to arterial thrombosis and embolism is rare in domestic animals other than the horse. Mucosal and occasionally transmural focal or segmental infarctive lesions are seen in *Pasteurella* septicemia in lambs and in *Haemophilus somnus* bacteremia in cattle. In horses it is associated with endarteritis, mainly at the root of the cranial mesenteric circulation, in animals less than ~3 years of age, caused by migrating larvae of *Strongylus vulgaris* (see the Cardiovascular System, Volume 3). Suffice it to say here that endarteritis due to this worm is most common in the cranial mesenteric circulation, sometimes at a number of sites a considerable distance distal to the usual location at the root of the artery. Although endarteritis is common, in only a small minority of horses dying of intestinal accidents can the infarction be confidently attributed to *S. vulgaris*.

Candidates for a diagnosis of arterial thromboembolism are animals in which the anatomic distribution of an infarctive lesion is incomptabile with volvulus or strangulation, or where physical evidence for incarceration or strangulation obstruction is not present in the surgical history or at autopsy. In the horse, animals in this category may have relatively localized mucosal or transmural damage, or extensive transmural lesions of the distal small intestine, cecum, and large colon, that is, in the circulatory field of the cranial mesenteric artery. Lesions limited essentially to the mucosa appear usually to be subacute and are ulcerative or fibrinonecrotic. They may vary in area from tens to many hundreds of square centimeters. Transmural lesions are of two types. The least common is a large, irregular area of devitalized gut, sometimes involving most of the cecum or colon, with a dirty khaki-colored, flaccid, friable wall, which is not markedly thickened. Along the poorly defined margin of the necrotic tissue there may be transmural congestion, hemorrhage, and edema. The fluid content in the affected gut is foul-smelling, but not particularly blood tinged. More commonly, irregularly demarcated areas of infarcted intestine have a thickened, edematous, congested wall, which appears deep red-black or green-black on both mucosal and serosal aspects. Gut content is blood tinged. The peritoneal cavity may contain an excessive quantity of turbid yellow or blood-tinged fluid, and animals with both types of transmural lesions may progress to rupture of the bowel, with distribution of content throughout the abdomen.

We interpret devitalized gray-brown intestine of normal thickness to represent arterial obstruction without subsequent reflow, except along the boundary with viable tissue. Large edematous, congested, or hemorrhagic full-thickness lesions, physically or anatomically inconsistent with strangulation, we interpret as severe arterial obstruction of some duration, with subsequent reflow either by relief of the obstruction or by way of collaterals. Ischemic damage to the mucosa, submucosa, and perhaps, deeper structures results in hemorrhage and edema when blood flow returns (Fig. 1.13C,D). Ulcerative or fibrinonecrotic mucosal lesions are probably the result of transient ischemia and superficial or mucosal damage, with subsequent reflow. Similar lesions may occur following relief of strangulation of short duration, and in salmonellosis, which itself may be in part the result of mucosal microthrombosis.

Evidence of reflow, and failure to find thrombi lodged in arteries in the infarcted area, may be explained in several ways. Fibrinolysis may have removed the obstructing thrombi; thrombi may be multiple and microscopic (sometimes they are found in arteries in tissue sections of infarcted tissue); or the lesions may be the result of diminished tissue perfusion due to obstructed flow caused by verminous endarteritis (but not thromboembolism) or by vascular spasm. In the latter case they may be the result of "slow flow," discussed further below.

### *Reduced Perfusion*

Ischemia due to reduced perfusion of the intestinal vascular bed is a difficult and uncommon diagnosis. Circumstances under which it may be expected to occur include severe hypovolemic states, such as hemorrhagic shock in the dog, cat, and possibly other species; in animals, particularly dogs, with disseminated intravascular coagulation; in dogs with hepatic fibrosis and portal hypertension; as a result of hypotensive shock due to heart failure; and in animals with reduced mesenteric arterial perfusion, mainly horses with severe verminous endarteritis obstructing flow. In "shock gut" in dogs and, rarely, other species, associated terminally with heart failure, hemorrhage, hypo-

volemia, and disseminated intravascular coagulation, part or all of the mucosa of the small intestine is deeply congested and the content hemorrhagic. The pathogenesis of the lesion is related to reflex vasoconstriction in the mucosa and submucosa, shunting of blood away from the mucosa, dilation of mucosal capillaries, and reduction in rate of flow of blood through the villus. Countercurrent transfer of oxygen from the afferent to efferent vessels in the villus aggravates hypoxemia in the villus by increased shunting of oxygen to the efferent venule. Splanchnic pooling of blood, systemic arterial hypotension, and intestinal vasoconstriction occur in endotoxic shock in dogs, causing similar mucosal lesions. Microthrombosis associated with sluggish flow, disseminated intravascular coagulation, and endotoxemia may contribute to mucosal ischemia by obstructing capillaries in the villi, and mucosal and submucosal venules; microthrombi in these vessels in association with hemorrhagic mucosal necrosis suggest the possibility of ischemia due to slow flow.

Acute acorn poisoning in the horse may cause severe gastrointestinal edema and focal hemorrhage, with infarction and ulceration in the cecum and colon. Microscopic lesions in the small and large intestine are consistent with an ischemic pathogenesis, and microthrombi have been associated with mucosal infarcts in the large bowel as well as in other organs.

Transient or incomplete reduction in perfusion due to obstruction of the arterial blood supply has a similar effect on the mucosa. Mucosa devitalized by hypoxia will become hemorrhagic with continued blood flow. Since the primary problem may not involve a systemic state as complicated as severe shock, the animal may survive long enough to develop an effusive ulcerated or pseudomembranous mucosa, with some prospect of stabilization or repair if the lesion is not widespread. Slow flow due to reduced arterial perfusion with inadequate collateral flow may be expected to affect the "watershed" of a circulatory field preferentially. In the horse, this may be the explanation for mucosal lesions at the pelvic flexure and apex of the cecum in which thromboembolism cannot be implicated, but in which mural thrombi in the cranial mesenteric root could have caused significantly reduced perfusion. Ischemia at the periphery of the circulatory field of the caudal mesenteric artery may possibly predispose to rectal perforation in horses. The precarious perfusion of the mucosa at this site may contribute to ischemic ulceration and the development of rectal stricture in swine. This condition in many cases appears to be associated with *Salmonella* infection, and it is discussed further under Salmonellosis, in Swine.

Transient or noninfarctive slow flow has been proposed as a cause of intermittent colic due to verminous arteritis. It may also play a role in the development of functional obstruction and volvulus in horses with cranial mesenteric arterial lesions.

### *Epithelial Renewal in Health and Disease*

#### *Small Intestine*

The intestinal mucosa is lined by an extremely labile population of cells, ultimately derived from stem cells at the base of crypts or glands but with its proximate source in amplifier populations of undifferentiated columnar or oligomucous cells in the lower half of the crypts. These cells differentiate into goblet cells and the functional population of enterocytes as they move from the crypt to the villus, losing their ability to undergo mitosis. In most species, they are shed from the tips of villi in about 2 to 8 days. Relatively little definitive information is available on the transit time of epithelium moving from crypt to tip of villus in domestic animals. Generally, cells move off the villus more quickly in the ileum than in the duodenum; presumably this is related to the decline in height of villi with distance down the gut in most species. As well, in some species the number of crypts contributing cells to a single villus is lower in the ileum than in the duodenum.

Under normal circumstances, the mass and topography of the mucosa are quite stable. This steady state is the product of a dynamic equilibrium between the rate of movement of cells out of crypts and onto villi, and the rate at which they are lost from the tips of villi. The stability of this equilibrium suggests that local feedback exists between the functional compartment on villi and the proliferative compartment in the crypts. Soluble chalones released from the functional compartment have been proposed as the effectors of a negative-feedback mechanism acting on crypt cells, but they are poorly characterized. Experimental destruction of the functional epithelium on villi by transient local ischemia stimulates hyperplasia in the proliferative compartment serving affected villi, however, confirming that local feedback control is real.

In the young animal the intestine grows by generation of new crypts, and with them, new villi. As the bowel attains mature size, the number of villi stabilizes and apparently remains relatively constant. The number of crypts also stabilizes, but some adaptive variation in the ratio of crypts to villi may occur. Adaptive responses to a variety of factors alter the size and rate of turnover of the proliferative and functional epithelial-cell populations and with them the microtopography of the gut. The "normal" appearance of the small intestinal mucosa is a compromise, achieved by the equilibrium between the rate of cell production and rate of loss. At one extreme lies the intestine of the germ-free animal, with a short crypt containing a small proliferative compartment, and tall villi supporting a large functional compartment with a low rate of cell loss. At the other end of the spectrum is the animal suffering from severe intestinal helminthosis, with long crypts reflecting an increased proliferative compartment, yet a flat mucosal surface with relatively few functional enterocytes and an apparently high rate of cell loss.

In the diagnostic situation, it is necessary to make subjective or semiquantitative assessment of the status of the proliferative and functional compartments in tissue sections. The size of the proliferative compartment is reflected in the length and diameter of the crypts; no inferences can be drawn about the proportion of the crypt-cell population that is replicating, or the duration of the cell cycle. There is obviously also some correlation between the length and profile of villi and the functional surface area, though the three-dimensional structure of an abnormal mucosa is often poorly reflected in section. Hence, it is highly desirable to correlate the histologic appearance with the microtopography of the mucosa as seen under the dissecting or scanning electron microscope. The degree of differentiation, and therefore, the functional status of enterocytes on villi, can be inferred from their

appearance. Cytoplasmic basophilia, loss of regular basal nuclear polarity, low columnar, cuboidal, or squamous shape, and an ill-defined brush border all point to a poorly differentiated population of surface enterocytes, which is possibly turning over more rapidly than normal.

Fasting reduces the mucosal epithelial mass, the atrophy being related to prolongation of the postmitotic phase of the cell cycle in the proliferative compartment. Villi do not regress severely, however, since cells on the surface persist for twice as long, moving off the villus more slowly. The effect is reversed immediately by refeeding. Total parenteral nutrition does not abolish the effect of starvation. Surgical removal of a loop of bowel from the flow of digesta also causes atrophy of the epithelial population, which is reversed by restoration of continuity with the rest of the gut. Resection of a segment of gut causes hypertrophy of the mucosa remaining distal to the surgical site, which is reflected in dilation of the bowel and thickening of the mucosa due to longer crypts and villi. Postresectional hypertrophy also occurs in the mucosa of separated loops of gut and in cross-circulated animals, suggesting a hormonal influence. Diversion of the opening of the pancreatic and bile ducts to the distal small bowel causes hypertrophy of the ileal mucosa but does not result in atrophy of more proximal mucosa.

Many of these adaptive changes in experimental or surgical situations are interpreted as supporting the concept that stimulation of enterocytes by nutrients is trophic and an important factor in maintaining mucosal mass. The direct role of pancreatic secretion and bile is uncertain. Hormonal and, possibly, paracrine factors are also active. Gastrin appears to be trophic for duodenal mucosa; glucocorticoids also have trophic effects on intestine under some circumstances. Enteroglucagon is the prime candidate as a hormone trophic for the intestinal mucosa and is apparently elevated in calves with neonatal diarrhea, suggesting that it has a role in the adaptive response to mucosal damage. Such also appears to be the case in celiac sprue in humans, where crypt-cell proliferation is high and enteroglucagon levels are concurrently elevated. There is speculation that paracrine effects of other peptides released from enteroendocrine cells in the gut, in response to a variety of luminal stimuli, may also influence epithelial proliferation.

VILLUS ATROPHY. Atrophy of villi is a common pathologic change in the intestine of domestic animals. It results in malabsorption of nutrients and sometimes is associated with increased plasma protein loss in the gut. Mucosa with atrophic villi can be categorized morphologically into two broad types, recognition of which has implications with respect to pathogenesis and prognosis. The first category includes intestine with atrophy of villi to varying degrees, associated with apparently normal or hypertrophic crypts. The second category is comprised of gut with variable villus atrophy and some evidence of damage to the proliferative compartment. The recognition, evolution, and interpretation of each will be considered in turn.

Villus atrophy with an **intact** or **hypertrophic proliferative compartment** is seen in a wide variety of circumstances in domestic animals. A primary increase in rate of loss of epithelium from the surface of villi is one mechanism initiating such a lesion. This is the major pathogenetic action of transient ischemia, in which the effect is limited to the functional compartment; of a number of important virus diseases, including coronavirus (Fig. 1.30) and rotavirus (Fig. 1.31A–C) infection; of some coccidial infections that may damage surface enterocytes predominantly (Fig. 1.49A); of some enteroinvasive bacteria; and in some circumstances, of necrotizing toxins released by clostridia in the lumen of the bowel. The effect of these agents is to cause significantly increased loss of surface epithelium over a relatively short period of time. Villi contract as the size of the functional compartment is diminished, and they may become very stubby. If the animal survives the metabolic sequelae to the reduced absorptive function, which results from the usually transient damage to surface cells, compensatory expansion of the proliferative compartment in crypts permits complete recovery. New epithelium emerging from crypts causes regeneration of villi, resulting in a normal mucosal topography within a few days, and full function returns.

The microscopic appearance of the mucosa in section depends partly on the number of functional cells lost, which determines the initial degree of villus atrophy, and partly on the amount of regeneration that has occurred by the time the animal dies or the gut is sampled. During the early phase of cell loss, damaged epithelium may be seen exfoliating into the lumen of the gut, and villi are shorter or blunter than normal. Subsequently, the atrophic villi are covered by poorly differentiated, low columnar, cuboidal, or squamous cells (Fig. 1.30B). There may be fusion of the lateral surfaces or tips of villi in some areas (Fig. 1.30D). In severe atrophy there may be mild erosion if inadequate epithelium is available to cover even the much reduced mucosal surface area. In the acute phase, crypts appear of normal size, but within 12 to 24 hr, proliferative activity is noticeably increased. Crypts enlarge in diameter and length to accommodate more mitotic epithelial cells, which are basophilic, crowded, and obviously dividing, sometimes very close to the surface of the mucosa. The lamina propria appears moderately hypercellular, perhaps due to condensation, possibly due to a mild mononuclear-cell infiltrate. As regeneration occurs, progressively longer villi with increasingly well differentiated epithelium are evident, and hypertrophy of the proliferative compartment gradually subsides.

Atrophy of villi and hypertrophy of crypts in the small intestine are also associated with nematode parasitism (Fig. 1.45B,C); chronic coccidial infection of surface epithelium: giardiasis in some species; response to dietary antigens in some species, including that to soybean protein in calves; chronic inflammatory reactions in the lamina propria, such as Johne's disease (Fig. 1.42D) and histoplasmosis; and idiopathic granulomatous enteritis or chronic enteritis characterized by heavy lymphocytic and plasmacytic infiltrates in the mucosa. The epithelial kinetics have not been investigated in most of these situations in domestic animals. They all have in common a chronic antigenic exposure, parasitism, or an infectious process in the lumen, epithelium, or lamina propria, however, usually associated with a significant lymphocytic and plasmacytic infiltrate in the mucosa.

Experimental evidence is accumulating that cell-mediated immune events in the mucosa initiate villus atrophy and cryptal hypertrophy in graft-versus-host reaction, intestinal trichinellosis, and giardiasis in mice. These observations are being extrapolated in humans to intestinal allergy to some dietary anti-

gens, and to celiac disease; similar phenomena are likely to be active in domestic animals. In these conditions, villus atrophy and loss of cells from the mucosal surface persist despite obvious hyperplasia in the proliferative compartment.

Studies of the kinetics of experimental mucosal lesions induced by cell-mediated immunity show that hypertrophy of the proliferative compartment precedes the development of villus atrophy and is not a response to it. This also occurs in *Nippostrongylus*-infected rats and *Eimeria acervulina*–infected chickens. In experimental intestinal trichostrongylosis, hypertrophy of crypts appears to be an early event, preceding villus atrophy; the epithelium emerging from hypertrophic crypts exfoliates soon after reaching the surface, rather than moving up the villus.

Evidence now points to a local effect on the proliferative compartment, and perhaps, the associated fibroblast sheath by soluble mediators (lymphokines) released by lymphocytes engaging in cell-mediated immune reactions in the mucosa. Cytotoxicity or damage to the functional compartment is apparently not a necessary precursor to hyperplasia by crypt cells, though it is not ruled out. Epithelial cells leaving the crypts usually do not differentiate fully; they slough prematurely, and as preexisting enterocytes are shed, villi undergo atrophy. Surface epithelium is subsequently rapidly lost into the lumen, matching the rate of cell production. In experimental intestinal trichinellosis, fewer surface receptors for lectins are present on enterocytes, suggesting an altered cell membrane.

In villus atrophy of this type, the microtopography of the gut may vary from moderately short, cylindric villi, through short leaf or tongue shapes, to ridges on the mucosa. These would be interpreted in section as villi of varying height. More severely attenuated mucosal projections form convoluted intercrypt ridges, which in section may be misinterpreted as stumpy villi, with crypts opening directly onto the surface (subtotal villus atrophy; Fig. 1.45B). In extreme cases the mucosa becomes virtually flat, and crypt mouths project above the surface (total villus atrophy; Fig. 1.45C). In cases with moderate villus atrophy, the surface epithelium may appear relatively normal by light microscopy; enterocytes that appear poorly differentiated are usually present on more severely atrophic mucosa. In severe atrophy, the epithelium may become squamous, and the surface may be eroded.

Hypertrophy of crypts is the early and outstanding change in this lesion and is consistently present. In its milder forms, the lesion may be better characterized by elongate crypts than by obvious atrophy of villi. The proliferative compartment is expanded and active, and mitotic figures are numerous. Elongation of crypts may be so great that even with severe atrophy of villi the total mucosal thickness will not be much reduced from normal. The lamina propria often has a prominent population of lymphocytes, plasmacytes, and associated inflammatory cells, and intraepithelial lymphocytes are common. The etiologic agent, in the form of parasites, intracellular bacteria, or yeast, may be evident. Removal of the causal stimulus usually results in a return to "normal" within several weeks.

However induced, atrophy of villi with hypertrophy of crypts is associated with local malabsorption of nutrients and water; elongate crypts and, perhaps, poorly differentiated surface epithelium may secrete electrolyte and water; and if there is proprial inflammation and microerosion of the mucosa, effusion of tissue fluid may ensue. Increased turnover of epithelium may contribute to enteric loss of endogenous protein.

Villus atrophy associated with **damage** to the **proliferative compartment** is also seen commonly in domestic animals. It is the sequel to insults that cause necrosis of cells in crypts or impair their mitotic capacity. The agents that produce these lesions usually have a propensity for damaging dividing cells in any tissue; since ionizing radiation was recognized early as a cause of such lesions, they are often termed "radiomimetic." Other causative agencies include cytotoxic chemicals (Fig. 1.32E), mitotic poisons and viruses that infect proliferating cells, particularly the parvoviruses, bovine virus diarrhea, and rinderpest. Ischemia of duration sufficient to cause necrosis of some or all cells lining the crypts causes a lesion that may be included in this category also (Fig. 1.32F).

The microscopic appearance of affected mucosa depends on the severity and extent of the insult, and the interval since it occurred. The primary event is damage to the proliferative compartment, and except in ischemia, lesions will be evident in crypts well before significant atrophy of villi occurs. Necrotic or exfoliated epithelial cells and polymorphs may be present in the lumen of damaged crypts, which tend to dilate. If crypt-cell necrosis is severe, remaining cells become extremely flattened in the course of attempting to maintain the integrity of the crypt lining. Following radiation, cytotoxic damage, and parvovirus infection, bizarre irregular epithelial cells with large nuclei and nucleoli may be present in crypts and will migrate onto the surface. Preexisting surface epithelium continues to move off the tips of villi at an apparently normal rate even though few or no new cells emerge from crypts. Villi eventually become atrophic or collapse as the surface cell population shrinks. If most proliferative and stem cells have been damaged, crypts stripped of epithelium will also collapse or "drop out," perhaps leaving a few scattered cystic remnants, lined by attenuated epithelium, in the deeper lamina propria. The overlying surface will be covered by squamous epithelial cells derived from surviving crypts or will be eroded and may eventually ulcerate. Crypts that have not been so severely damaged will hypertrophy as compensatory hyperplasia of lining cells occurs within a week or so of the original insult (Fig. 1.32D).

In viral diseases the severity and appearance of the lesion often vary considerably at different sites in the gut and even within an individual tissue section. Lesions due to ischemia tend to be uniform in severity but may be localized; acute or subacute lesions are often hemorrhagic. Cytotoxic and radiation damage tend to be relatively uniform and more widespread, though some variation occurs due to differences in the proliferative activity, and therefore susceptibility, of the epithelium at the time of insult. The inflammatory reaction depends on the availability of leukocytes, which may also have been diminished by the same insult that caused the epithelial necrosis. In the early stages, neutrophils and eosinophils may be in and around damaged crypts. Extensive lesions of the gut lead to severe malabsorption and to effusion of tissue fluid and hemorrhage. The mucosa is often invaded by the enteric flora because the animal frequently is immunosuppressed. Local ulceration may lead to persistent plasma loss, and if circumferential, to stricture and stenosis. Small ulcers in areas where a few crypts have dropped out will

heal as epithelium from adjacent crypts moves over the surface, but crypts may not regenerate, and local villus atrophy will persist.

Villus atrophy occurs commonly in association with **alimentary lymphosarcoma**. Diffuse or focal infiltration of the lamina propria by neoplastic lymphocytes appears to separate and crowd out crypts. It also distorts the shape of villi, which become stubby and covered by low columnar or cuboidal epithelium. Presumably the atrophy of villi is related at least partially to a reduced density of crypts in the mucosa, and therefore fewer cells moving onto the surface per unit area. In severe cases, erosion of the epithelium will occur over lymphosarcomatous infiltrates.

### *Large Intestine*

Epithelial turnover in the cecum and colon is fundamentally similar to that in the small intestine, though villi are not present on the surface. Cells lose the ability to divide after leaving the proliferative compartment in the lower part of the gland. In the upper portion of the gland they differentiate into goblet cells or columnar absorptive cells that emerge and move out over the surface. They are lost into the lumen, probably within about 4 to 8 days of being produced, though no studies of colonic epithelial turnover have been made in domestic animals. Fasting reduces, and refeeding restores, proliferative activity in colonic glands in experimental animals, and physical distention and dietary bulk in the colon also appear to be trophic for the mucosa. The colon of gnotobiotic animals has a small number of proliferaive cells, limited to the lower portion of the glands.

Lesions presumed to be associated with increased epithelial turnover in large bowel include alteration in both surface and glandular epithelium. The number of goblet cells on the surface and in the upper portion of glands is diminished, and epithelium in these areas appears poorly differentiated, is more basophilic than normal, and may be low columnar, cuboidal, or squamous. In severe diseases, microerosion of the surface is present. The proliferative compartment in the gland may hypertrophy, causing glands to elongate and dilate. Crowded mitotic cells are present over a greater proportion of the length of the gland, sometimes virtually to the surface of the mucosa. Such changes may be associated with acute, chronic, or chronic active inflammation of the lamina propria. It is uncertain whether such changes are caused both by primary damage to surface epithelium and by primary immune-mediated stimulation to the proliferative compartment. Experimentally, cell-mediated immune reactions increase crypt-cell production, but not length of glands. Colonic lesions consistent with increased epithelial cell turnover occur mainly in swine dysentery, intestinal adenomatosis complex in swine, trichuriasis, canine histiocytic ulcerative colitis, granulomatous colitis due to a variety of agents, and idiopathic colitis of dogs.

The proliferative compartment in the cecal and colonic glands is damaged by the same insults that attack cells in the crypts of the small bowel. Cytotoxins and parvoviruses tend not to produce severe lesions so commonly in large bowel as they do in small intestine, however, perhaps because a lower proportion of the proliferative compartment is in mitosis at the time of maximum availability of drug or virus. Additions to the list of agents damaging the proliferative compartment in the large intestine include coronavirus in calves and several species of coccidia in ruminants, which develop in the cells lining glands in the large bowel.

The evolution and sequelae of lesions resulting from damage to proliferative epithelium in the large intestine are similar to those in small bowel. Dilatation of crypts containing necrotic debris, and lined by attenuated epithelium, indicates such damage. Severe lesions will lead to loss of glands and erosion and ulceration of the mucosa, perhaps with hemorrhage. Stricture and stenosis may ensue. Following milder damage, which spares some stem cells in each gland, the mucosa has the potential to recover fully after a period of reparative hyperplasia.

## *Pathophysiology of Enteric Disease*

The detrimental effects of gastrointestional diseases are mediated by a number of often interacting mechanisms. Common consequences of enteric disease include inability to eat or loss of appetite; reduced growth rate, weight loss, or cachexia; hypoproteinemia; and anemia, perhaps with obvious hemorrhage into the gut. Dehydration and acid–base imbalance are associated with reduced water consumption, obstruction, vomition, or diarrhea. Dysfunction of systemic homeostasis, and of other organs, may be caused by toxins, parasites, bacteria, or viruses originating in the gut.

The consequences of diseases of the upper alimentary system, of enteric obstruction, and of ischemia have already been considered. Malabsorption of nutrients occurs commonly in animals with gastrointestinal disease. Failure to assimilate nutrients may result in a reduced growth rate and in emaciation and cachexia if nutrient requirements for maintenance are not met. Malabsorption often occurs concurrently with enteric protein loss, and the contribution of these two factors, along with loss of appetite, to reduced growth rate or to cachexia must be recognized and differentiated. Diarrhea is a common sign of malabsorption, but its pathogenesis is only partly explained by this mechanism.

### *Malabsorption*

Digestion and assimilation of nutrients have an intraluminal phase, mediated by the biliary and pancreatic secretions, and an epithelial phase, carried out by enzyme systems on the surface and in the cytoplasm of absorptive enterocytes. The final step is delivery of the nutrient by the enterocyte to the interstitial fluid, and its uptake into the blood or lymph.

Pancreatic exocrine insufficiency is the major cause of intraluminal maldigestion, and it is usually due to pancreatic hypoplasia in dogs or to pancreatic fibrosis following repeated episodes of pancreatic necrosis (see the Pancreas, this volume). Bile salt deficiency as a cause of intraluminal maldigestion is rarely seen in domestic animals. The epithelial phase of digestion is impaired by loss of functional epithelial surface area. This occurs in short bowel syndrome following intestinal resection and, more commonly, in villus atrophy. Congenital deficiencies of enzymes normally present on the microvilli are not recognized in domestic animals. However, neonates and ruminants have low levels of maltase; ruminants lack sucrase. In most species, lactase levels decline with age, and malabsorption in

dogs fed milk has been attributed to low levels of lactase. The poorly differentiated surface epithelium present on atrophic villi may lack the full complement of enzymes on the brush border and in the cytoplasm necessary for nutrient digestion and assimilation. Delivery of nutrients, especially lipid, to the circulation may be impaired in lymphangiectasia. The pathogenesis of malabsorption of the major classes of nutrients will be considered briefly.

**Assimilation** of **fat** is susceptible to interference at all three phases of digestion and absorption. Lipolysis is impaired if insufficient lipase is available. Most commonly this is a result of pancreatic atrophy or fibrosis. It may be due to failure by atrophic intestinal mucosa to release the cholecystokinin/pancreozymin necessary for pancreatic secretion. The availability of bile salts for micelle formation is reduced in intrahepatic cholestasis or biliary obstruction and by depletion of the bile salt pool due to reduced ileal absorption following resection or atrophy. As a result, fatty acid and monoglyceride are not incorporated onto micelles and emulsified; they are therefore not as accessible to absorptive enterocytes. Reduced surface area for lipid uptake will contribute to malabsorption of fat. Poorly differentiated enterocytes on atrophic gut may be less able than normal epithelium to reesterify long-chain fatty acids to triglyceride and produce chylomicrons for export from the cell. In lymphangiectasia, granulomatous enteritis, and intestinal lymphosarcoma, lymphatic drainage may be obstructed, and with it the flow of chylomicrons to the systemic circulation.

Steatorrhea (excess fat in the feces) is the sequel to malabsorption of lipids. It is seen in monogastric animals, especially dogs, in which fat often forms a large proportion of the daily caloric intake. Severe fat malabsorption may result in deficiencies of fat-soluble vitamins. Malabsorption of calcium, magnesium, and zinc occurs due to their sequestration in soaps formed by combination with malabsorbed luminal fatty acids. Increased absorption of oxalate may be a sequel to reduced concentrations of calcium in the lumen due to soap formation. Malabsorbed lipid may cause colonic diarrhea, by mechanisms that will be discussed subsequently.

**Maldigestion** of **polysaccharides** occurs if levels of pancreatic amylase are reduced; this is encountered most commonly in dogs with pancreatic disease in which very little functional exocrine tissue remains. Calves and older ruminants normally lack significant amounts of pancreatic amylase and digest starch poorly in the small intestine. Mucosal oligosaccharidase deficiency occurs in villus atrophy, with reduced mucosal surface area. Poor differentiation of enterocytes results in irregular, short, and sparse microvilli and a reduced complement of oligosaccharidases. The result is impaired membrane digestion of disaccharide and malabsorption of carbohydrate, much of which is subsequently fermented by colonic flora. The osmotic effect of malabsorbed disaccharide augments intraluminal fluid accumulation in the small intestine, and this may be compounded by hydrolysis in the colon. Carbohydrate malabsorption is an important component of disease in neonatal diarrhea due to rotavirus and coronavirus, and in other conditions in which there is extensive villus atrophy in the small intestine.

**Protein digestion** in the lumen is reduced if pancreatic protease activity is decreased to ~10% of normal, as may occur with exocrine pancreatic insufficiency. Loss of gastric proteolytic activity is of little nutritional significance. In conditions with villus atrophy, reduced mucosal surface area and poor differentiation of enterocytes result in malabsorption of small peptides and particularly of amino acids by mechanisms similar to those involved in carbohydrate malabsorption. It is conceivable that atrophy of duodenal villi may result in reduced availability of the brush-border enzyme enterokinase, which is necessary for the activation of pancreatic trypsinogen to trypsin, initiating the subsequent activation of other pancreatic proteases by trypsin. Some dogs with mucosal malabsorption do appear to have partial pancreatic insufficiency, perhaps for this reason. The influence of reduced protein digestion and assimilation on energy metabolism and anabolic activity must be differentiated from the effects of the loss of plasma and other endogenous protein into the lumen of the gut.

A reduction in absorption of **minerals** and **vitamins** may be intuitively expected in animals with reduced absorptive surface in villus atrophy, above and beyond specific mechanisms alluded to previously. If villus atrophy is relatively localized, the reserve capacity of more distal small bowel may offset the effects of local nutrient malabsorption, and there may not be net malabsorption over the full length of the small intestine.

### *Diarrhea*

Diarrhea is the presence in feces of water in relative excess in proportion to fecal dry matter. Diarrhea usually reflects increased absolute fecal loss of water, but may not if absolute fecal dry matter excretion is markedly reduced. Loss of solute and water in diarrhea may lead to severe electrolyte depletion, acid–base imbalance, and dehydration, which are life threatening if not corrected.

Large volumes of fluid derived from ingesta and secretion from the stomach, bile, pancreas, and the gut itself enter the small bowel; in addition, considerable passive movement of water occurs into the upper small bowel from the circulation in response to osmotic effects. Absorption by enterocytes of osmotically active nutrient molecules and electrolyte draws water from lumen into the interstitial space. Overall, the bulk of the fluid entering the small intestine is absorbed, so that the volume leaving the ileum and entering the colon is but a small fraction of the total fluid flux through the small bowel. The large size of this flux implies that relatively small perturbations in unidirectional movement of electrolyte and water may have large effects on the net movement of fluid.

The colon, in addition to its fermentative function, has the ultimate responsibility for conserving electrolyte and water by absorption from the digesta, thereby minimizing fecal losses. It has a finite capacity for absorption of electrolyte and fluid, and if this is exceeded by the rate at which content enters from the small bowel, diarrhea occurs. This is thought to be important in "small bowel diarrheas," where the lesion is in the small intestine. Since the colon has a large reserve capacity for absorption, the excess volume entering from the ileum must be considerable for diarrhea to occur. The large absorptive capacity and fermentative function of the equine colon may mitigate to some extent the expression of small bowel diarrhea in mature animals of that species, even when malabsorption occurs in the small intestine.

SMALL INTESTINE. Small bowel diarrhea is classed as secretory, malabsorptive, and effusive, but the mechanisms are not mutually exclusive.

**Secretory diarrhea** is due to an excess of secretion over absorption of fluid in the small intestine and is probably the result of derangement of normal secretory and absorptive mechanisms in the mucosa. It is best exemplified by the effects of diarrheagenic bacterial enterotoxins. *Vibrio cholerae* and *E. coli* are the most important sources of such toxins, though only the latter occurs in domestic animals; some *Salmonella* serotypes, *Yersinia enterocolitica,* and perhaps *Shigella* also produce enterotoxin. Cholera and heat-labile *E. coli* enterotoxin act through the mediation of cyclic AMP. In surface enterocytes, toxin-stimulated cAMP shuts down sodium chloride cotransport at the luminal cell membrane, reducing passive water absorption. Meanwhile, in crypt epithelium, cAMP-stimulated chloride secretion is promoted, and water follows. The resultant increase in secretion by crypts and decrease in absorption by villi increases the solute and water load passing from the small bowel for the colon. Heat-stable *E. coli* and *Y. enterocolitica* enterotoxins apparently stimulate cGMP-mediated secretion by the mucosa.

**Malabsorptive diarrhea** is exemplified by the osmotic retention of water in the gut lumen by poorly absorbed magnesium sulfate, used therapeutically as a cathartic. Malabsorption commonly results from villus atrophy, no matter what the cause. Electrolyte and nutrient solute, malabsorbed as the result of reduced villous and microvillous surface area, are retained in the lumen of the bowel in abnormal amounts, along with osmotically associated water. If compensatory absorption does not occur in more distal small intestine, the additional solute and water is passed on to the colon. A secretory component probably contributes to diarrhea due to villus atrophy, at least in transmissible gastroenteritis in pigs. Here, since the "villous" limb of the postulated crypt–villus fluid circuit is diminished or missing, fluid secreted by the crypts may not be absorbed. However, it is not clear if crypts are abnormally secretory. Poorly differentiated cells emerging onto the intestinal surface from crypts also may retain some secretory capacity.

**Increased permeability** of the mucosa may contribute to diarrhea by permitting increased retrograde movement of solute and fluid from the lateral intercellular space to the lumen, or by facilitating transudation of tissue fluid. "Filtration secretion" is characterized by increased fluid movement through the epithelial membrane via the paracellular route; the force for secretion is provided by the transepithelial hydrostatic pressure gradient. Portal hypertension or right-sided heart failure, hypoalbuminemia, and expansion of plasma volume establish such conditions. Effusion may occur similarly in lymphatic obstruction or lymphangiectasia, and in inflamed lamina propria, with increased vascular permeability, proprial edema, and enteric plasma protein loss. Increased exfoliation of epithelium and transient microerosions provide further potential sites for effusion of interstitial fluid.

LARGE INTESTINE. Large bowel diarrhea is the product of a reduced innate capability of the colon to handle the solute and fluid presented by the more proximal bowel. A change in net absorption by the colon that is relatively small in absolute terms may be sufficient to cause fluid feces. Colonic diarrhea is characterized by frequent passage of small amounts of fluid feces. Colonic dysfunction has not received the same attention as small bowel disease, but secretory, malabsorptive, and effusive mechanisms are implicated here as well, and they frequently appear to act concurrently.

The colonic mucosa is not as innately "leaky" as the small intestinal mucosa due to the nature of the tight junctions between epithelial cells. As a result, it resists alterations in permeability due to increased hydrostatic pressure in the propria, when compared with the small intestine. Ulceration or erosion may be expected to result in reduced colonic function due to loss of absorptive surface epithelium. Although effusion is anticipated in these states, abnormal macromolecular permeability was not demonstrated in *Salmonella* colitis or swine dysentery. In swine dysentery, however, net electrolyte and water absorption ceases.

Bile acids mediate diarrhea associated with ileal disease, and fatty acids are the cause of diarrhea in steatorrhea. The mechanism of action of these agents appears to be similar; though both may affect the small bowel, the major effect is in the colon. Moderate ileal damage or resection results in the escape of excess bile acids to the colon. This loss is compensated by increased hepatic synthesis to maintain the size of the bile salt pool. But the increased load of bile salts entering the colon is converted to secondary bile acids by the colonic flora. Fatty acids enter the colon in increased quantities in steatorrhea resulting from bile salt depletion, or from other mechanisms in which lipolysis by pancreatic lipase is not severely inhibited. Both dihydroxy bile acids and long-chain fatty acids, especially hydroxy fatty acids produced by bacterial action, alter mucosal permeability and cause mild damage to the surface epithelium. They both also stimulate cAMP-mediated secretion by the colonic mucosa, perhaps by causing local prostaglandin release. The result is net fluid secretion by the colon, and diarrhea. This also is the mode of action of a number of laxatives, including senna and castor oil, which contains the hydroxy fatty acid ricinoleic acid.

Although colonic secretion stimulated by bacterial enterotoxin is not clearly implicated in diarrhea, alterations in the flora in the large bowel may be detrimental to normal function. Absorption of volatile fatty acids produced by bacterial fermentation is responsible for considerable concurrent absorption of water in the large intestine. Reduced production and absorption of volatile fatty acids, secondary to imbalance of the bacterial flora in the cecum and colon, may explain some problems of wasting and diarrhea in horses in which no morphologic abnormality of the mucosa can be found.

Osmotic overload of the large bowel results from the delivery by the small bowel of a large volume of fermentable substrate. This may be due to an excess of dietary carbohydrate or, more commonly, malabsorption in the small intestine. Of the malabsorbed nutrients, carbohydrate is the only one of significance in initiating colonic osmotic overload. Bacterial fermentation of carbohydrate results in the production of an increased number of molecules of volatile fatty acid. They are readily handled by the colon under normal circumstances, by rapid absorption, and by

bicarbonate buffering. A heavy carbohydrate load may overwhelm the colonic buffering capacity, however, and cause a reduced pH. This results in an altered gut flora dominated by organisms producing lactic acid, which is absorbed at a slower rate than the volatile fatty acids. Further acidification causes mucosal permeability, permitting an influx of water and solute into the lumen from the tissue, as a result of the increased osmotic pressure generated by lactic acid in the lumen. Diarrhea follows.

MOTILITY AND DIARRHEA. Increased intestinal motility probably does not have a primary role in the pathogenesis of diarrhea. Often the small intestine of animals with diarrhea is flaccid and fluid filled rather than hypermotile. Increased colonic motor activity is often segmental and antiperistaltic, and probably unrelated to increased transit. Hypermotility, if it does occur, may be in response to, rather than a cause of, increased volumes of fluid in the gut.

Ileus or hypomotility, partial small bowel obstruction, and radiation injury may set up conditions conducive to bacterial overgrowth in the small bowel. Achlorhydria or hypochlorhydria in the dog may also predispose to this problem. "Stagnant loop" or "blind loop" syndrome ensues, as anaerobes in particular proliferate in the lumen of the small intestine to levels approaching those in the large bowel. Mild or moderate villus atrophy may develop in the affected area, and bacteria will be seen on the mucosal surface in tissue sections, an unusual finding in the small bowel. Ultrastructural lesions and cytoplasmic lipid accumulation can be present in surface enterocytes, though the brush border may be intact. Deconjugation of bile acids by anaerobes results in free bile acids, many of which precipitate at the pH of the gut content and are lost to the recirculating pool. Some are absorbed passively, but dihydroxy secondary bile salts may be the cause of damage to enterocytes. Fat malabsorption occurs when conjugated bile acids fall below critical micellar concentrations, reducing emulsion and absorption. Malabsorption is further exacerbated by the toxic damage to cells. Steatorrhea results.

Protein digestion and absorption may not be affected by bacterial overgrowth; however, some amino acids may be deaminated by anaerobes and metabolized to ammonia which is absorbed, converted to urea in the liver, and largely lost through the kidneys. Plasma protein loss into the gut can also occur, as may impaired uptake of disaccharides. Binding of vitamin $B_{12}$ by enteric flora prevents absorption in the ileum and may lead to deficiency. Dihydroxy bile acids and malabsorbed fatty acids promote secretion by the small bowel and colon, resulting in diarrhea.

### *Protein Metabolism in Enteric Disease*

Disorders of protein metabolism attributable to enteric disease are responsible for significant economic loss in the form of reduced weight gain, wool growth, and milk production. Severe derangement in any species may lead to cachexia, hypoproteinemia, and death. Nitrogen economy may be affected at three main points: nitrogen intake may be reduced; there may be decreased protein digestion and assimilation; or increased catabolism and loss of endogenous nitrogen may occur. The metabolism and distribution of nitrogen in the body may vary, depending on the way in which its economy is disrupted.

Decreased protein intake is the most obvious threat to the nitrogen economy, and it is probably the most important in many chronic gastrointestinal diseases. Subclinical inefficiency in production, reduced growth, and emaciation may be the products of varying degrees of inappetence. If the quality of the feed available is poor, the effect of reduced intake on production will be compounded. Painful prehension or mastication, dental attrition, chronic dysphagia, or recurrent vomition are all obvious causes of reduced feed intake. A sharp decline in appetite, or anorexia, is a common sign of indigestion, obstruction, or systemic disease. In ruminants, loss of appetite to varying degrees is an important component of the pathogenicity of gastrointestinal parasites, including those infecting the abomasum (*Ostertagia*), small intestine (*Trichostrongylus*), and large bowel (*Oesophagostomum*). About 40–90% of the inefficiency in production in these parasitisms is attributable to reduced feed intake. The factors influencing satiety in animals are uncertain and deserve greater attention. Among them may be the hormones gastrin and cholecystokinin, which are elevated in association with inappetence in parasitized sheep. The bulk and particle size of the feed consumed influences distention of the reticulorumen and rate of throughput of digesta. Altered gastrointestinal motility or stasis may also detrimentally influence feed intake, as may reduced absorption of amino acids from the small intestine.

Malabsorption of peptides and amino acids may occur locally in the small intestine as a result of significant villus atrophy. Unless the lesion is widespread, or low in the small bowel, however, net absorption of nitrogen over the length of the small intestine may not be reduced, due to the compensatory capacity of more distal normal mucosa. Overall, the contribution of malabsorption to disordered nitrogen metabolism appears to be minor in most situations.

Protein-losing gastroenteropathy, increased catabolism, and loss of endogenous nitrogen via the gastrointestinal tract are important in many diseases. Excess endogenous protein entering the intestine is derived from two main sources, namely, increased turnover of cells lining the gut and effusion of plasma protein into the lumen of the bowel. The contribution to endogenous nitrogen loss by increased turnover of enterocytes and secretion of mucoprotein has not been well defined. In conditions causing chronic villus atrophy, such as intestinal parasitism by *Trichostrongylus* and *Strongyloides*, however, it may be substantial.

Plasma protein loss into the gut presupposes abnormal permeability of the mucosa to large molecules. This may be the product of the bloodsucking activity of nematodes such as *Haemonchus, Ancylostoma,* and *Bunostomum* or hemorrhage from sites of trauma in the mucosa caused by the feeding activity of worms such as *Oesophagostomum columbianum, Chabertia,* and *Strongylus*. Erosive lesions result in considerable loss of red blood cells and plasma protein. Such lesions may be due to infarction, severe cryptal necrosis, or acute inflammatory damage to the mucosa associated with bacteria, viruses, and coccidia, causing fibrinohemorrhagic enteritis. Microscopic

"leaks" in the mucosa also permit plasma loss into the gut. These may result from increased exfoliation of enterocytes into the lumen in villus atrophy, as transient gaps in the mucosa at the site where the cells sloughs. In villus atrophy with a high rate of enterocyte turnover, temporary microerosions may develop when flattened cells fail to maintain the integrity of the surface epithelium. The permeability of tight junctions between epithelial cells may be sufficiently altered to permit transit of plasma protein molecules when the hydrostatic pressure in the proprial interstitium is elevated in congestive heart failure, by increased vascular permeability in acute or chronic inflammation, and in lymphatic obstruction or lymphangiectasia.

Plasma protein loss into the gut is nonselective. Albumin, immunoglobulins, clotting factors, and a variety of transport or carrier proteins, including transferrin, ceruloplasmin, and transcortin, are lost. The physiologic consequences of protein-losing enteropathy may reflect increased catabolism of any of these molecules but are most obviously related to increased turnover of the albumin pool. Plasma albumin lost into the gut, when expressed as a proportion of the total body pool, will vary in absolute terms, depending on the size of the pool. This concept of *fractional catabolic rate* is essential to understanding the kinetics of plasma protein turnover.

In protein-losing enteropathy, albumin turnover may pass through three phases. During the first phase, the fractional catabolic rate increases, and with it, the absolute amount of protein lost into the bowel; as the size of the circulating pool of albumin shrinks, so does the absolute rate of loss of protein, even though the fractional rate remains the same. During the second phase, the size of the circulating pool stabilizes as the rate of albumin synthesis by the liver increases to match in absolute terms the rate of loss. The plasma albumin pool is then in a state of hyperkinetic equilibrium; the pool is smaller, with a higher than normal fractional catabolic rate compensated by an increased rate of hepatic synthesis. Provided that the size of the loss does not exceed the synthetic capacity of the liver, this equilibrium may persist for a considerable period. In the third phase, hypoalbuminemia develops as the fractional catabolic rate continues to increase so that it exceeds in absolute terms the synthetic capacity of the liver, or if the rate of synthesis declines, it develops as a result of deficiency in amino acids derived from the diet and by catabolism of other body protein. The hypoalbuminemia in enteric plasma loss is often associated with hyperglobulinemia, since compensatory synthesis of immunoglobulin is remarkable. Several times more immunoglobulin than albumin may be lost into the gut as a result.

The progress and clinical manifestations of protein-losing enteropathy vary with the rate of onset of plasma loss and the fractional catabolic rate. A sudden onset of severe plasma protein loss may cause death during the first phase, before there is time for compensatory synthesis. If the fractional catabolic rate is gradually and only slightly increased, so that compensation occurs with the albumin pool in equilibrium in only a marginally reduced state (perhaps near or within the "normal" range), subclinical protein loss occurs. Though the fractional catabolic rate is only slightly elevated, the relatively large size of the albumin pool may mean that the absolute loss of protein exceeds that in a hypoalbuminemic animal with a higher fractional catabolic rate but a smaller albumin pool.

Plasma protein leaking from the stomach or upper small intestine, and protein derived from exfoliated cells in villus atrophy with increased epithelial turnover, may be digested and absorbed in the small intestine. This is dependent on luminal proteolysis by pancreatic enzymes, and compensatory membrane digestion and absorption, making up for any malabsorption by proximal atrophic mucosa. But the efficiency of protein digestion, even if it is not reduced, is not total. Therefore, a proportion of the increased endogenous protein entering the lumen will be added to the protein escaping digestion in the small bowel and will enter the large intestine. There, most of this protein may be converted to ammonia by the colonic flora and absorbed, so that in animals losing protein high in the gut, there may be little or no increase in fecal nitrogen excretion. On the other hand, much of the protein lost into the colon from lesions at that level is passed in the feces, often as protein, and is lost. Ammonia nitrogen absorbed from the colon is converted in the liver mainly to urea. Animals with increased endogenous protein loss into the stomach or small intestine tend to have slightly raised levels of blood urea nitrogen and an elevated rate of urinary urea excretion.

Elevated hepatic synthesis of albumin due to increased turnover of the plasma albumin pool, and increased enteric protein synthesis in support of elevated epithelial turnover in conditions with chronic villus atrophy, is at the expense of anabolic processes elsewhere. Dietary amino acid is "diverted" to synthesis of enteric and plasma protein preferentially. If protein intake is poor due to inappetence or a low-quality ration, or if the rate of protein loss is high, the animal moves into negative nitrogen balance. Catabolism of peripheral protein then assumes an increasingly important role in maintaining the pool of amino acids available for plasma and intestinal protein synthesis. This explains in part the reduced growth rate, decreased muscle mass, and depressed deposition of bone matrix in sheep with subclinical or mild parasitism and the cachexia of severe parasitism. The additional metabolic cost of increased protein synthesis also causes inefficiency in energy utilization. These principles probably hold for all syndromes causing enteric loss of endogenous protein in any species.

Loss of enteric protein and, especially, plasma, should be suspected in cachectic or hypoproteinemic animals. Diarrhea is often, but not invariably, present. The two major routes of occult abnormal plasma protein loss are the kidney in glomerular disease and the gastrointestinal tract. Weeping skin lesions are another source. Anemia and hypoproteinemia may be due to hemorrhage externally or into the gastrointestinal tract. Advanced liver disease may cause hypoalbuminemia; other signs of hepatic failure will likely be concurrent (see the Liver and Biliary System, this volume). Inability to eat, inadequate nutrition, or starvation also cause emaciation, usually without profound hypoalbuminemia. The cachexia of malignancy must also be differentiated. Provided it is adequately hydrated, the hypoalbuminemic animal shows evidence of subcutaneous, mesenteric, or gastric submucosal edema, perhaps with hydrothorax or ascites. Wasting of muscle mass may be marked if the protein loss has been severe and of some standing. Unlike starvation,

protein-losing gastroenteropathy may be associated with the presence of internal fat depots, since assimilation of energy is not necessarily severely impaired.

### *Anemia*

The principles discussed in the kinetics of plasma albumin during enteric plasma loss may be applied also to the kinetics of the erythron following loss of blood into the gastrointestinal tract. Blood loss of any origin, including that due to hematophagous parasites, may cause anemia. Erythroid hyperplasia in the marrow or in extramedullary sites may not compensate for the continued bleeding. Resolution of the hemorrhage results in eventual restoration of normal red cell numbers and an ultimate decline in erythrocyte production. Chronic blood loss may culminate in depletion of iron stores and development of a nonresponsive hypochromic microcytic anemia.

## *Syndromes Associated with Malabsorption and/or Protein Loss in the Small Intestine*

Malabsorption of nutrients, electrolyte, and water is at the root of disease in animals caused by rotavirus, coronavirus, *Cryptosporidium,* and rarely, *E. coli;* significant loss of protein probably does not occur in these conditions. Intestinal nematode parasitism due to *Trichostrongylus* in ruminants, and *Strongyloides* in all species, causes malabsorption and plasma loss. Hookworms suck blood, causing anemia, hypoproteinemia, and perhaps, wasting. Johne's disease in ruminants, and probably intestinal adenomatosis in swine, are associated with plasma loss into the gut and malabsorption. Erosion, ulceration, and villus atrophy due to coccidiosis, enteroinvasive bacteria, parvoviruses, bovine virus diarrhea, and some other viruses cause malabsorption and increased mucosal permeability.

In dogs and horses, and to a lesser extent in other species, there may be idiopathic, sporadic or breed-related disease variably signaled clinically by chronic diarrhea, weight loss, hypoproteinemia, and often malabsorption, as defined by tests of carbohydrate and lipid assimilation. Intestinal biopsy is usually necessary to make a diagnosis, permitting the establishment of a prognosis and course of therapy. These syndromes are usually characterized by abnormal infiltrates in the lamina propria, perhaps associated with some degree of villus atrophy. Eosinophils, lymphocytes, and plasma cells, granulomatous inflammation, or amyloid are the infiltrates most commonly implicated. Lymphangiectasia may also produce a similar syndrome.

### *Lymphangiectasia*

Lymphangiectasia has been described in the dog, where it appears to be among the more common causes of malabsorption/protein-losing enteropathy. It is associated with a syndrome variably characterized by chronic diarrhea, wasting, hypoproteinemia, lymphopenia, hypocalcemia, and hypocholesterolemia. Peripheral edema, ascites, and hydrothorax result from hypoalbuminemia. The intestinal lesion is dilation of the lacteals, and often lymphatics of the submucosa, intestinal wall, serosa, and mesentery (Fig. 1.14D). Villi containing dilated chyle-filled lacteals may stand out grossly as white papillate foci in a thickened, transversely folded edematous mucosa (Fig. 1.14C). Serosal and mesenteric lymphatics may be prominent, white, and dilated. Small nodular white masses may be present on the serosa at the mesenteric border and along lymphatics.

In section, villi may be of normal length or somewhat blunt or stubby. The surface epithelium may appear normal or perhaps slightly attenuated, and lateral interepithelial spaces are often dilated. The lacteals in many villi are distended, and lymphatics in deeper portions of the mucosa may be also. Occasional lipid-laden macrophages are present in and around lacteals and lymphatics; large focal accumulations of lipophages form the grossly visible white masses sometimes present. The lamina propria is edematous, and the submucosa and deeper portions of the gut wall may be. The proprial inflammatory cell population may be normal, or the numbers of lymphocytes and plasma cells may be increased.

The cause of lymphangiectasia is presumably usually lymphatic obstruction. Many cases appear to be acquired, and some may be due to lymphosarcomatous or granulomatous infiltrates obstructing flow in mesenteric lymph nodes. Usually, no congenital or acquired obstruction of the lymphatic drainage is obvious. Experimental obstruction of mesenteric lymphatics produces hypoproteinemia and lymphangiectasia but not diarrhea and weight loss, suggesting that the etiology of the clinical syndrome may be more complex than simple lymphatic obstruction.

Moderate malabsorption of lipid, and plasma protein loss into the gut, cause the signs associated with lymphangiectasia. Malabsorbed lipid may contribute to diarrhea via the effects of fatty acids on colonic secretion. Mucosal permeability associated with increased proprial hydrostatic pressure may cause net intestinal secretion and contribute to plasma protein loss. It has been proposed that dilated lacteals may rupture, releasing lymph into the lumen of the intestine. Hypocalcemia may be related to loss of the mineral bound to plasma albumin, and perhaps to formation of soaps with malabsorbed lipid in the gut lumen. Hypocholesterolemia is due to lipid malabsorption and effusion of plasma. Lymphopenia is thought to be the result of the loss of lymphocyte-rich lymph into the gut.

In cattle, dilated lacteals and lymphatics in the small intestine have been associated with Johne's disease and hypoalbuminemia due to abomasal parasitism. In Johne's disease, the lesion may be the result of local edema due to inflammation in the propria and mesenteric lymphatics combined with hypoproteinemia. In the second situation, dilated lacteals may be secondary to edema resulting from reduced plasma oncotic pressure, rather than the cause of such a problem.

### *Chronic Inflammatory Disease*

EOSINOPHILIC GASTROENTERITIS. Eosinophilic gastroenteritis has been well described but is rarely encountered. Conditions typified by abnormally heavy eosinophilic infiltrates of the gastrointestinal mucosa occur in dogs, cats, and horses.

In **dogs**, eosinophilic gastroenteritis is a segmental or region-

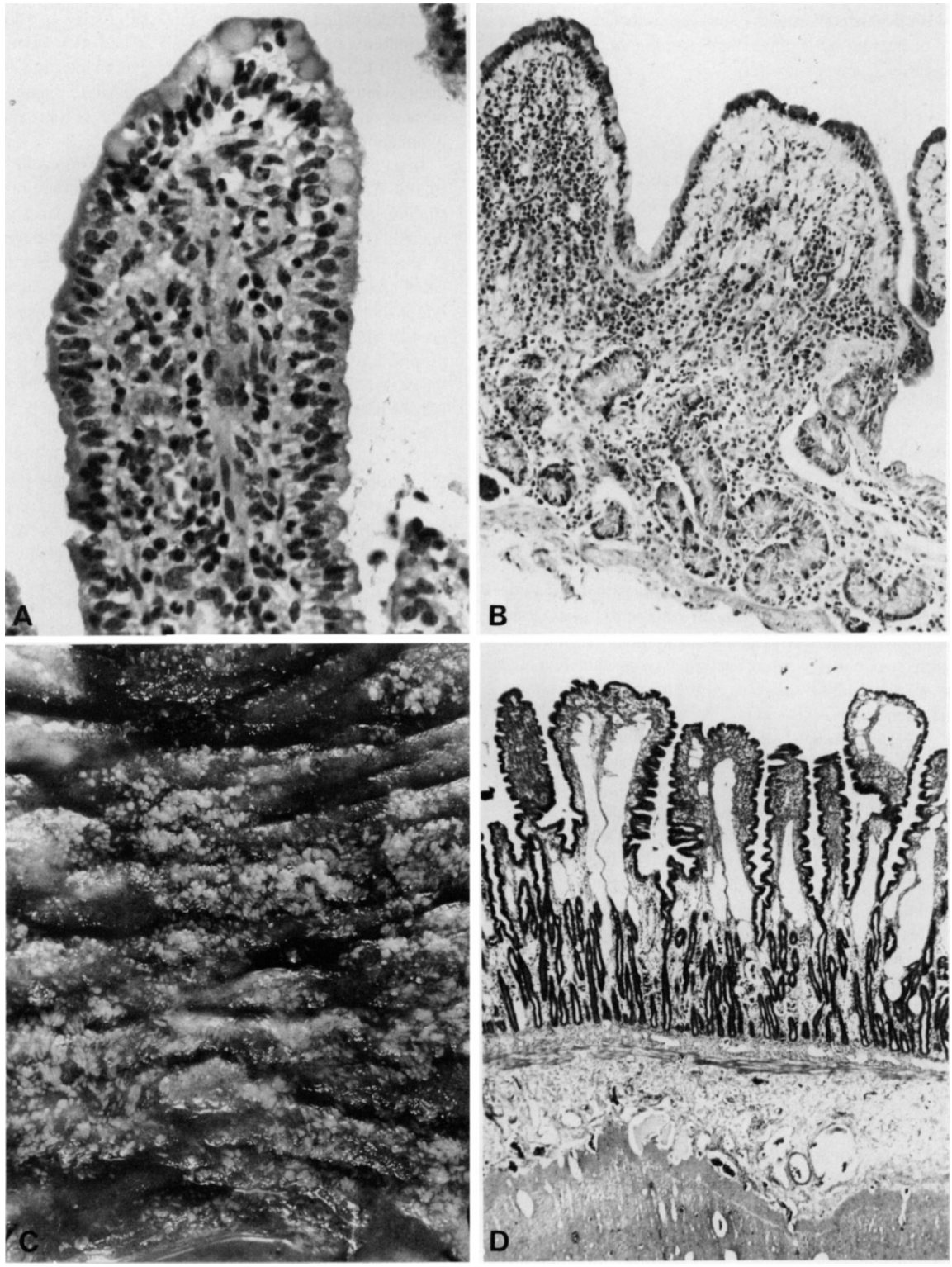


**Fig. 1.14.** (**A**) Distended vacuoles containing eosinophilic colostral protein in apical cytoplasm of enterocytes at the tip of the villus of a 2-day-old calf. (**B**) Intestine. Goat. Deposits of pale amorphous amyloid beneath the epithelium on villi, and scattered in the lamina propria. (Courtesy of J. R. Duncan.) (**C**) Lymphangiectasia. Small intestine. Dog. Mucosa, thickened by edema, is thrown in folds. Many villi contain white, chyle-filled lacteals. (**D**) Lymphangiectasia. Dog. Lacteals are dilated, lamina propria and submucosa are edematous, and lymphatics in submucosa and muscularis are open.

al affliction, affecting one or more areas of the alimentary tract from stomach to rectum. Signs may vary from vomition associated with gastritis, to chronic small bowel diarrhea, or chronic large bowel diarrhea with hematochezia resulting from ulcerative eosinophilic colitis. Diarrhea and weight loss suggest malabsorption and protein-losing enteropathy, and circulating eosinophilia is often present. The disease is best known in German shepherds, but it may occur in any breed.

At autopsy or laparotomy, aside from lesions attributable to cachexia and hypoproteinemia, there may be enlarged mesenteric lymph nodes. The affected segment of the alimentary tract is thickened, or the mucosa may be irregularly folded or nodular and perhaps hemorrhagic, eroded, or ulcerated. Gross lesions are associated with heavy infiltrates of normal eosinophils in the mucosa, submucosa, and often transmurally, involving muscularis and serosa. Villi may be mildly to severely atrophic; the epithelium can appear relatively normal, or enterocytes may be low columnar or cuboidal. In the colon the epithelium may be eroded or the mucosa ulcerated in areas with heavy infiltrates of eosinophils. Eosinophils may be present in sinusoids throughout affected lymph nodes.

In one series of German shepherds, eosinophilic granulomas were present in gastrointestinal tissues and other organs, and larvae of *Toxocara canis* were implicated. Granulomas are not reported in other cases, which probably represent a separate condition. Scirrhous eosinophilic gastritis and arteritis is also pathologically unique. The etiology of eosinophilic gastroenteritis in dogs may be related to a reaginic response to antigens in the lumen or wall of the gastrointestinal tract, with infiltration by immunomodulating eosinophils.

Eosinophilic enteritis in **cats** is rare and appears to be one manifestation of a hypereosinophilic syndrome that may involve many organs. Diarrhea, sometimes bloody, vomition, loss of appetite, and loss of condition may be represented in the history. Clinically, intestinal thickening, hepato- and splenomegaly, and enlarged mesenteric lymph nodes may be present, in association with circulating eosinophilia and hyperplasia of the eosinophil series in the marrow.

The postmortem picture reflects the clinical findings. Enlargment of the various organs, including liver, spleen, lymph nodes in many locations, and tan nodularities on the kidneys, are associated with heavy infiltrates of usually well differentiated eosinophils. In the small intestine the eosinophilic infiltrate may be transmural and is accompanied by hypertrophy of the muscle layers, causing a thickened appearance grossly. Lymph nodes may have hyperplastic follicles and many mature eosinophils in sinusoids, or they may vary through eosinophilic lymphadenitis with fibrosis to complete obliteration of normal architecture and replacement by eosinophils in a fibrillar stroma extending through the capsule into surrounding tissue.

Chronic eosinophilic enteritis in **horses** has been described in Australia as a distinct syndrome, and it occurs elsewhere. Affected animals have weight loss and diarrhea or unformed feces, associated with hypoalbuminemia, suggesting enteric loss of plasma protein. Reduced absorption of glucose occurs, but peripheral eosinophilia is absent. At autopsy, mucosal and sometimes transmural thickening may occur at any level of the alimentary tract from esophagus to rectum. Thickened mucosa is thrown into turgid, transverse folds, or occasionally is fissured and roughened. Focal caseous ulcers 1–15 mm in diameter may be present on the surface or in the mucosa and submucosa of the small and large intestine and common bile duct.

Microscopically, there is diffuse infiltration of the mucosa, submucosa, and often, deeper layers of the enteric wall by eosinophils, mast cells, macrophages, lymphocytes, and some plasma cells. Moderate to severe villus atrophy, fibroplasia in the lamina propria, and hypertrophy of the muscularis mucosae occur. Caseous foci in the mucosa and submucosa consist of central masses of eosinophils, sometimes surrounded by macrophages, giant cells, and occasionally, fibrous tissue. Eosinophilic granulomas have been described in the biliary and pancreatic ducts, pancreas, capsule and outer cortex of enlarged firm mesenteric lymph nodes, and near portal tracts in the liver. The skin may be thickened and hyperkeratotic, and the limbus of the hoof thickened and ulcerated. Acanthotic epithelium in affected areas is infiltrated by eosinophils, as is the underlying dermis.

Villus atrophy is common, but where large bowel lesions are absent, there is no diarrhea. Chronic inflammation in the mucosa may explain protein loss and hypoalbuminemia. The cause of this syndrome is unknown, though the involvement of a reaction to ingested allergens is suggested.

LYMPHOCYTIC–PLASMACYTIC ENTERITIS. Some animals, mainly dogs, showing signs consistent with malabsorption and/or plasma loss into the gut, have microscopic lesions in the small intestine described as lymphocytic–plasmacytic enteritis.

The cardinal finding is abnormally intense infiltrates of well-differentiated lymphocytes and plasma cells in the lamina propria of villi, between crypts, and sometimes in the submucosa. Normally, plasma cells are uncommon in the lamina propria of villi. A layer of lymphocytes, plasma cells, eosinophils, and histiocytes may be present along the proprial–submucosal junction above the muscularis mucosae. Villi may be normal, clubbed, or moderately atrophic, and occasionally fusion of villi may be prevalent (Fig. 1.15A,B). The surface epithelium may appear relatively normal, or low columnar to cuboidal with an indistinct brush border; theliolymphocytes may be common. Crypts may be hypertrophic. In this and other conditions with increased inflammatory infiltrates or edema in the lamina propria, some crypts may be obstructed and dilated and contain mucus and a few exfoliated epithelial cells. Occasionally, evidence of rupture of such crypts will been seen; lakes of mucus, reactive histiocytes, and occasional giant cells are present in the lamina propria (Fig. 1.15C,D). Other crypts may contain casts of eosinophilic glycoprotein. There may be edema of the lamina propria and dilatation of lacteals, suggesting concurrent lymphangiectasia.

Lymphocytic–plasmacytic enteritis must be differentiated from giardiasis, bacterial overgrowth, granulomatous enteritis, and intestinal lymphosarcoma.

In the Lundehund and in the basenji, syndromes of hypoalbuminemia, chronic diarrhea, and wasting occur with high prevalence. They seem primarily attributable to the development of lymphocytic–plasmacytic enteritis, perhaps with lymphangiectasia in some dogs. In the basenji, chronic gastritis

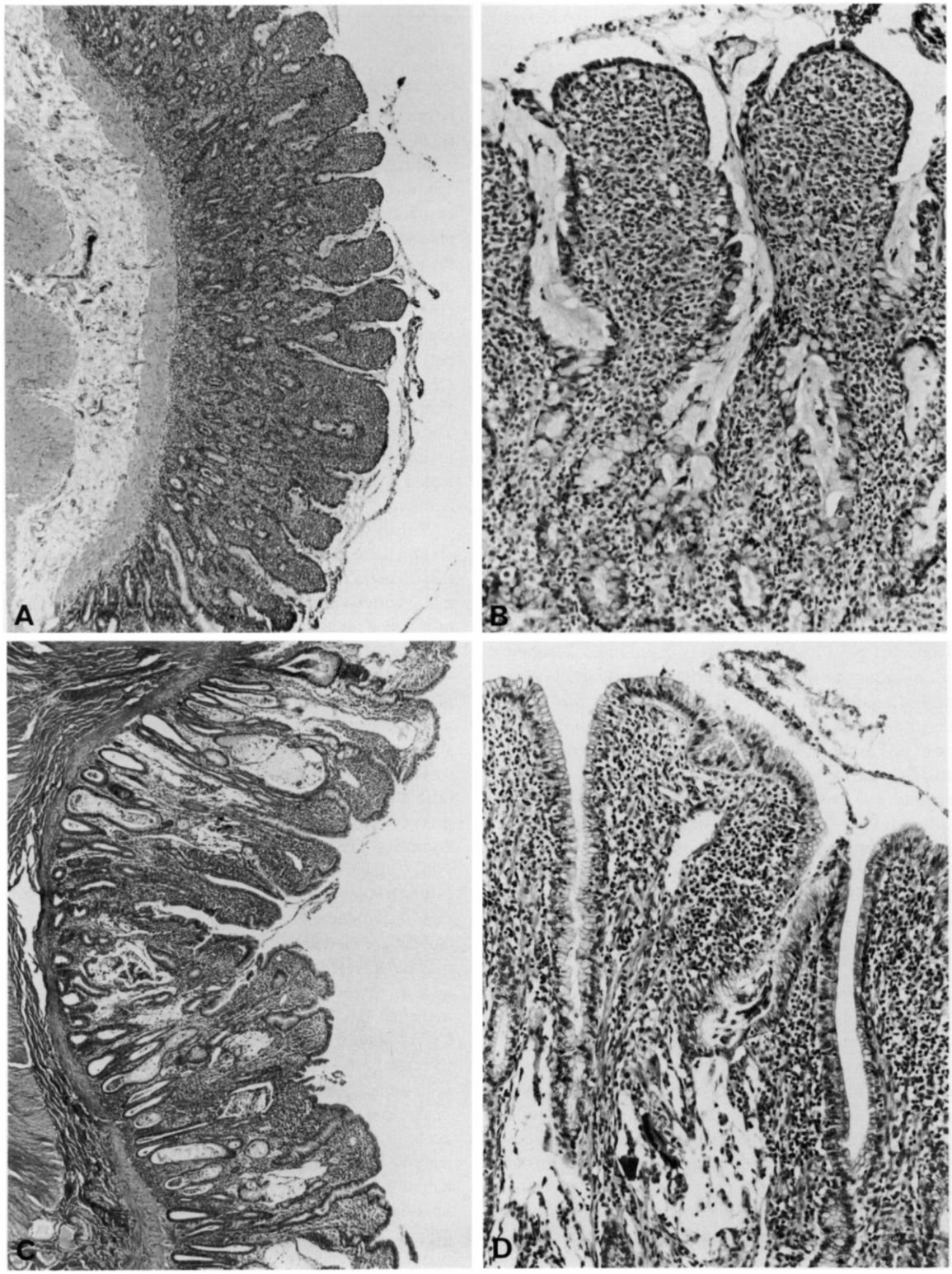


**Fig. 1.15.** (**A** and **B**) Lymphocytic–plasmacytic enteritis. Dog. (**A**) Villi are stumpy, club-shaped, or fused. Excessive mononuclear infiltrate at all levels of the mucosa, including between the base of crypts and the muscularis mucosae. (**B**) Blunt and club-shaped villi, cuboidal and attenuated surface epithelium, excess mucus secreted from crypts, and abnormal infiltrate of lymphocytes, plasma cells, and histiocytic cells in lamina propria. (**C**) Small intestine. Dog with malabsorption and intestinal protein loss. Blunt and occasionally fused villi, mononuclear cells in lamina propria, and elongate, dilated, and mucus-filled crypts. Some distended crypts have ruptured, releasing mucus into lamina propria. (**D**) Detail of (**C**), showing mucus in lamina propria due to rupture of a dilated crypt. Leak of cells and mucus from lamina propria and abnormal numbers of bacteria in lumen.

or hypertrophic gastritis may be associated. Hypergammaglobulinemia occurs commonly in the late stages of the syndrome in basenjis, and lymphosarcoma develops in some affected animals. Animals with the gray collie syndrome (cyclic hematopoiesis) also may have lymphocytic–plasmacytic enteritis (see the Hematopoietic System, Volume 3).

The cause of lymphocytic–plasmacytic enteritis is not known in any species. Though it may represent an abnormal response to antigen entering from the lumen, no dietary or other antigen has been conclusively implicated.

GRANULOMATOUS ENTERITIS. The presence of chronic inflammatory infiltrates including aggregates of histiocytes, and perhaps giant cells, in the lamina propria is the criterion for a diagnosis of granulomatous enteritis. Johne's disease, intestinal tuberculosis, and *Histoplasma* enteritis are specific examples, but usually the cause is not identified. Granulomatous enteritis occurs in all species. Transmural granulomatous enteritis is seen rarely in **dogs**. It is usually segmental and perhaps discontinuous in distribution, affecting the lower ileum, colon, and draining lymph nodes; the term "regional enteritis" is often applied. Idiopathic granulomatous enteritis as a cause of wasting and protein-losing enteropathy is most commonly seen as a sporadic problem in **horses**.

Depending on the duration of the disease, animals may be markedly cachectic, have subcutaneous edema especially of dependent areas, and there may be hydrothorax, hydropericardium, and ascites. Lesions in the horse usually affect the small intestine; stomach and large bowel are occasionally involved also. There may be thickened pale plaques or prominent lymphatics on the serosa of the bowel. The mucosa of the small intestine may be irregularly granular or thickened; there may be transverse corrugations of the mucosa, or raised firm gray areas with hyperemic foci may be evident. Linear ulcers of small and large bowel have been described. Mesenteric lymph nodes are usually enlarged, edematous, with mottled firm gray areas, fibrotic nodules, or rarely, caseous or mineralized foci on the cut surface. Granulomatous pale, caseous, or calcified foci may be scattered in the liver.

The microscopic lesion may be patchy, regional, or diffuse, and it may be mucosal, or transmural, ultimately gaining the draining lymph nodes. Villi are mildly to markedly atrophic with hypertrophy of crypts. The epithelium may vary from apparently normal to low columnar or cuboidal with an indistinct brush border. There may be leaks between cells on the surface, or microerosions may be present, through which neutrophils and proteinaceous exudate pass into the lumen. The lamina propria is edematous and contains scattered aggregates of histiocytes and perhaps giant cells, or less commonly, more organized granulomatous foci. Neutrophils and eosinophils are distributed diffusely throughout the lamina propria and may be concentrated in or near granulomatous foci. A heavy population of lymphocytes and plasma cells inhabits the lamina propria, and the infiltrate and edema may separate crypts abnormally from each other. The inflammatory reaction may follow lymphatics into the submucosa and through the muscularis to the serosa. The submucosa is usually edematous, and lymphatics are prominent. Granulomas may be present in the submucosa or at intervals along lymphatics. The affected lymph nodes are hyperplastic, usually with prominent sinus histiocytosis. Giant cells may be present in sinusoids, or granulomatous foci of varying sizes may be evident. Sinusoids contain numerous neutrophils and perhaps eosinophils, and neutrophils may accumulate in the center of granulomas.

Rarely are agents isolated or identified in such lesions in horses and dogs. *Mycobacterium avium* or environmental mycobacteria are incriminated occasionally. *Mycobacterium paratuberculosis* will also cause granulomatous enteritis rarely in horses. In **cats**, focal pyogranulomatous aggregates associated with blood vessels are found in the submucosa and especially subserosa of the intestine of animals with feline infectious peritonitis.

AMYLOIDOSIS. Amyloid deposition in the small intestine may be encountered occasionally, in animals with systemic amyloidosis. Sometimes the gastrointestinal lesions predominate and contribute to the clinical syndrome. Significant intestinal amyloidosis leads to signs consistent with malabsorption and enteric protein loss. Usually there is no gross indication of the deposition of amyloid in the intestine. Occasionally, however, focal ulceration or hemorrhage may be noted. Microscopically, amyloid is seen as the typical acellular, amorphous, eosinophilic, fibrillar deposit, beneath the epithelium or throughout the propria in villi, and perhaps around vessels in the submucosa (Fig. 1.14B). It must not be mistaken for collagen deposition, which is most unusual in these locations, though a band of collagenous material is sometimes present at the base of the mucosa in cats. The pathogenic effects of amyloid in the intestine seem to involve either impaired movement of interstitial fluid into lacteals or perhaps increased permeability of capillaries, possibly explaining protein loss into the lumen.

### *Inflammation of the Large Intestine*

The general reaction to insult of the cecal and colonic epithelium was considered above under Epithelial Renewal in Health and Disease.

Ischemia, obliteration of the proliferative epithelium by viruses or coccidia, severe inflammation in the mucosa, and perhaps, necrotizing toxic insults from the lumen are responsible for the development of focal or diffuse ulceration of the large intestine. Inflammatory infiltrates in the lamina propria may be classified broadly as acute, chronic or chronic active, and granulomatous. They may be limited in distribution to the mucosa or be transmural, involving submucosa, muscularis, serosa, and frequently, the draining lymph nodes. **Typhlitis** and **colitis** may be manifestations of a generalized or systemic disease; they may be part of an enterocolitis involving both small and large intestine; or they may be regional and limited to a segment of the intestine, often terminal ileum, cecum, and colon or some shorter part of the large bowel.

The colonic mucosa may provide the portal of entry for systemic bacterial invasion and for uptake of toxins. Increased mucosal permeability in the colon may permit enteric loss of plasma protein or of blood. Disordered large bowel flora in hindgut fermenters may compromise uptake of volatile fatty

acids and water. In any species, damage to the colonic mucosa may result in malabsorption of electrolytes and water, and perhaps net secretion. Colitis in each of the species will be considered in turn.

**Colitis cystica profunda**, the presence of dilated colonic glands protruding through the muscularis mucosae into the submucosa has been reported in several species. It is perhaps most often seen in swine, where it is an occasional finding (Fig. 1.39E). The dilated glands may be grossly visible through the serosa and muscularis as nodular masses a few millimeters in diameter. Microscopically, a single large, flask-shaped gland, lined by columnar epithelium and containing mucus and exfoliated cells or necrotic debris, may be present. Alternatively, a cluster of glands appears to herniate into the submucosa, where one or more may become dilated by mucus and debris. The cause is unknown; the lesion may be a sequel to colitis and local damage to the muscularis mucosae, or it may represent herniation into the space left by an involuted submucosal lymphoid follicle. Though the lesion has been seen with colitis in a variety of circumstances, it is usually found incidentally, and there is no specific etiologic association.

### *Typhlocolitis in Dogs*

Inflammation of the large bowel in dogs is usually associated with signs of diarrhea, typically frequent, small in volume, mucoid or bloody, and often accompanied by tenesmus. More severe acute necrotizing colitis, perhaps leading to ulceration and perforation of the proximal descending colon, with subsequent peritonitis, has been associated rarely with glucocorticoid administration and with trauma or surgery involving the spinal cord. Gastric ulceration may occur concurrently. The pathogenesis of the colonic lesions developing in these circumstances is unclear. Ulcerative enterocolitis, with lesions apparently centered mainly on lymphoid tissue, as well as gastric ulcer, has been produced experimentally by administration of the analgesic drug indomethacin to dogs. Necrotizing colitis, ulceration, and perforation may occur rarely in dogs in uremia. The mechanism is uncertain, but colonic damage may be the effect of high concentrations of ammonia evolved by urease-producing colonic flora from urea diffusing into the gut from the blood. In canine intestinal hemorrhage syndrome, possibly associated with clostridial overgrowth in the gut, the colon may be involved or at least contain hemorrhagic content.

*Trichuris vulpis,* the whipworm of dogs, may cause mucosal colitis, which rarely evolves into a granulomatous transmural condition. Clinical trichuriasis is generally associated with a population of worms that extends from the usual site of infection in the cecum and proximal ascending colon into more distal parts of the large intestine. Rarely, trichuriasis may be complicated by infection with *Balantidium coli,* which possibly contributes to the development of mucosal erosion or ulceration. Ulcerative colitis in dogs is also caused rarely by *Entamoeba histolytica.* An ulcerative granulomatous transmural colitis is more common as one of the enteric manifestations of histoplasmosis. *Prototheca* also is a cause of distinctive but rare enterocolitis in dogs. Canine parvovirus causes colonic damage, but virtually never without lesions elsewhere. Canine coronavirus has also been implicated as a cause of colonic as well as small intestinal lesions. The pathology of these conditions is discussed under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Spirochetes may be present in the canine colon, and although they are generally considered nonpathogenic, they are embedded in the microvillous border of surface epithelium and may be associated with mild mucosal colitis. *Campylobacter jejuni* is isolated from dogs with diarrhea, but its possible relationship to colitis in clinical cases is currently unclear. The association of giardiasis and colitis in dogs is considered to be fortuitous. The role of antigens gaining the mucosa is unknown. If they are significant, their identity, origin, and the factors predisposing to their entry are obscure. Colitis must be differentiated from ulcerating adenocarcinomas and infiltrative or ulcerative lymphosarcomas of the large intestine.

Most colitis in dogs is idiopathic and pathologically nonspecific; eosinophilic enterocolitis and histiocytic ulcerative colitis are the two distinctive patterns recognized microscopically.

Mild acute mucosal colitis, reflecting a grossly reddened, friable surface is characterized by congestion of superficial capillaries and venules, and proprial edema. Neutrophils are the most prominent inflammatory cells, and they are found mainly in the superficial lamina propria around vessels, and transmigrating or passing between surface epithelial cells into the lumen. The population of lymphocytes and plasma cells in the lamina propria may not differ subjectively from normal, but there is generally a moderate increase in mononuclear cells between glands. There is usually a reduced number of goblet cells on the surface and in glands, and surface epithelium may be basophilic, low columnar, or cuboidal (Fig. 1.16A,B). Hyperplasia of epithelium in glands is usually evident. Inflammatory cells, mainly neutrophils, may accumulate in a layer several cells deep along the mucosal side of the muscularis mucosae. The lesions in mild acute colitis in dogs often seem out of proportion to the severity of the clinical syndrome, which may be the result of irritation and tenesmus.

The spectrum of inflammation in colitis grades from acute toward an increasingly chronic infiltrate, which along with edema separates colonic glands and may accumulate deep in the mucosa between glands and muscularis mucosae (Fig. 1.16D). Neutrophils and eosinophils may be scattered in the propria and in glandular epithelium. Accumulation of granulocytes and necrotic debris in the lumen of glands forms so-called crypt abscesses. Greater severity of the lesion is reflected in attenuation and exfoliation of surface epithelium and the development of microerosions on the mucosal surface (Fig. 1.16C). Inflammatory cells, mainly neutrophils, and tissue fluid effuse into the lumen through defects in the epithelium. Persistent erosion or previous erosion in a healed mucosa is marked by the development of a thin, horizontally arrayed layer of connective tissue in the superficial lamina propria. With increasing chronicity in colitis of mild or moderate degree, there may be deposition of a collagenous stroma, throughout which inflammatory cells are interspersed, which separates glands abnormally throughout the mucosa. Downgrowth of glands into submucosal lymphoid follicles may occur in chronic colitis.

Severe erosion and ulceration is usually associated with local acute inflammation and with a heavy, mainly mononuclear-cell

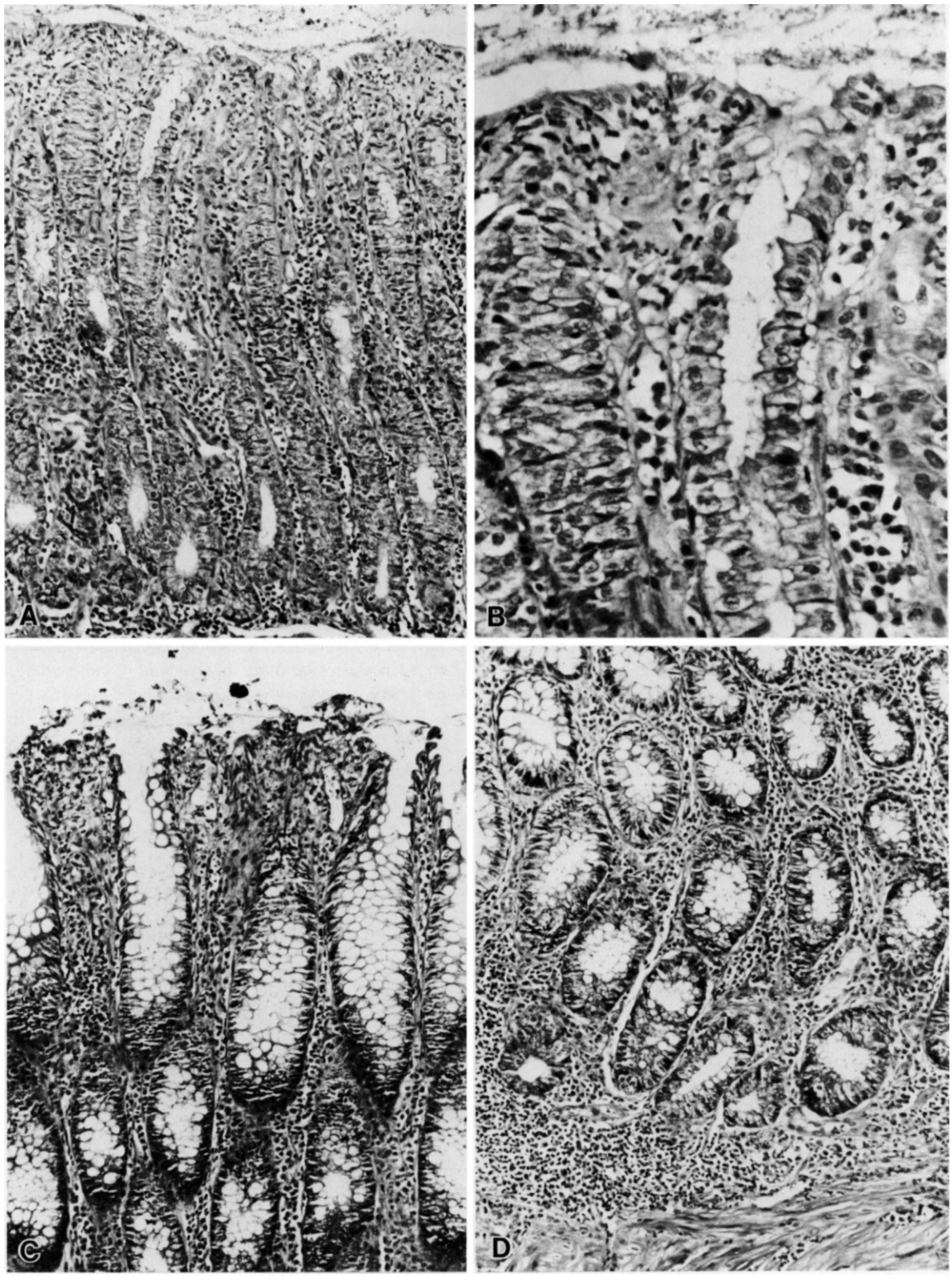


**Fig. 1.16.** (**A** and **B**) Mild acute colitis. Goblet cells are sparse or absent in glands and on the surface. Superficial epithelium is cuboidal and exfoliating in focal areas. Epithelium in glands is hyperplastic and crowded. The superficial lamina propria is edematous. (**C** and **D**) Chronic erosive colitis. Hypertrophic glands are lined by goblet cells. The mucosal surface has widespread erosion and effusion of tissue fluid and neutrophils. Edema of superficial lamina propria. Deeper in mucosa there is moderately increased population of mononuclear cells and increased fibrous stroma. Cells extend between base of glands and muscularis mucosae.

infiltrate in the lamina propria and, often, submucosa. The ulcerated areas extend usually no further than the muscularis mucosae and have a base of granulation tissue infiltrated heavily by neutrophils that effuse into the lumen of the bowel. The margin of surviving mucosa may overhang the ulcer. Crypt abscesses may be present in remaining mucosa, and all degrees of erosion and partial ulceration may be present. Idiopathic ulcerative colitis does not seem as severe as histiocytic ulcerative colitis of boxers and rarely comes to autopsy. Severely affected dogs may be cachectic, probably due in part to enteric loss of plasma protein. The mucosa in ulcerative colitis is usually deep red, swollen, folded, and granular due to edema and cellular infiltrates; the depressions may be punctate or up to several centimeters across, roughly round or oval, irregular or elongate. Their margins may be tattered or puckered. Colonic lymph nodes may be enlarged and edematous.

In canine colitis there is a broad, three-dimensional spectrum: in chronicity and density of the inflammatory infiltrate, in the distribution of the infiltrate within the wall of the bowel, and in the severity of the epithelial and mucosal change. Generally, milder lesions of superficial epithelium are associated with mild or moderate mucosal inflammation, which may be acute or chronic. In many cases of mild chronic mucosal colitis, the glands do not appear particularly hyperplastic; the mucosa may appear thin or atrophic. Severe erosion and ulceration are usually related to a more intense or heavy chronic inflammatory process, which may be limited to the mucosa, but which can extend into the submucosa. Truly granulomatous colitis is uncommon; when fully developed, perhaps as a component of a regional enteritis involving the ileocecocolic area, it is ulcerative and transmural.

**Eosinophilic colitis** forms part of the syndrome of eosinophilic gastroenteritis discussed previously. It conforms to the general description of the spectrum of lesions in idiopathic colitis, with the exception that eosinophils form a predominant part of the cellular infiltrate in the mucosa and superficial submucosa.

**Histiocytic ulcerative colitis** is a distinctive syndrome histologically, which has been recognized only in boxers and the related French bulldog. It is a chronic ulcerative colitis characterized by the presence of large numbers of macrophages, containing PAS-positive granules, in the deep mucosa and submucosa and in lymph nodes receiving drainage from the colon. Clinically, affected animals are usually under 2 years of age. This condition causes typical large bowel diarrhea, with mucus and blood; weight loss occurs, and chronic cases may become cachectic, probably due to protein loss into the gut.

Grossly, the colon of dogs with advanced disease is variably thickened, folded, and perhaps dilated and shortened, with some segmental or focal areas of scarring and stricture. Lesions on the mucosa may vary from patchy, punctate red ulcers to more extensive irregular, circular, or linear lesions that may coalesce, leaving only a few islands of persistent mucosa on a granulating colonic surface (Fig. 1.17A).

Early microscopic lesions are those of mild nonspecific inflammation. Microerosion of epithelium in the upper glands and on the surface is associated with local acute inflammation, migration of neutrophils into the epithelium, and effusion of neutrophils and tissue fluid into the lumen. Macrophages in these areas may contain phagocytized necrotic debris and bacteria. In some areas the mucosa is thinned, and glands are relatively shortened, though lining epithelium appears hyperplastic. Macrophages with cytoplasmic vacuoles, which contain PAS-positive material, are mainly deep in the lamina propria and in the submucosa (Fig. 1.17B,C). Sometimes they may be relatively sparse in the mucosa, and may be missed in small biopsy specimens if the submucosa is not sampled. These same cells may be found about lymphatics in the muscularis and the serosa, and they may be numerous in subcapsular, cortical, and medullary sinuses in the draining lymph nodes. The cecum is often involved, to a lesser degree, with similar lesions. True granulomatous foci and giant cells are rarely encountered.

Ulceration seems to progress from the superficial epithelial erosion and destruction of the basement membrane seen in early lesions. Ulcers usually do not progress beyond the submucosa, and they are lined by granulation tissue. The bed of the ulcer is necrotic, and numerous neutrophils and erythrocytes may be passing into the lumen.

The cause of the condition is unknown, as is the origin of the material in the characteristic vacuoles in macrophages. Ultrastructural study suggests that these are digestion vacuoles, containing mainly remnants of phospholipid membranes. The material being digested may be phagocytosed cell debris and microorganisms picked up in the superficial lamina propria and carried in "constipated" macrophages to deeper structures. Certainly, bodies resembling microorganisms have been found in macrophages, and the involvement of chlamydiae, ricketts-ias, and mycoplasmas has been postulated. It seems that a defect in lysosomal function may exist in some boxer dogs that can lead to the accumulation of partially digested phospholipid membrane in macrophages, since similar histiocytes do not accumulate in ulcerative colitis in other breeds of dogs.

### *Colitis in Cats*

Colitis in cats is rare. The most common cause is feline panleukopenia, in which over half the cases have colonic lesions. They are similar to, but rarely as severe or widespread as, the lesions found in the small intestine of all animals dying of the disease. The relative paucity and mildness of lesions in the colon is related to the lower rate of epithelial proliferation in comparison with the small intestine. The pathology of panleukopenia is considered under Infectious and Parasitic Diseases of the Gastrointestinal Tract.

Occasional cases of **mycotic colitis** are found in cats. These are associated with a hemorrhagic ulcerative colitis, in which focal or diffuse mucosal invasion by *Candida*, zygomycetes, or *Aspergillus* has occurred, sometimes causing microvascular thrombosis. These are mainly secondary to primary colonic damage and leukopenia caused by panleukopenia.

**Necrotic colitis** has also been described in cats, but very rarely. The condition is reported mainly in older animals, as a cause of chronic foul, and sometimes bloody, diarrhea. The colon and rectum are thickened, rough, and congested or hemorrhagic. The microscopic change is mucosal erosion or ulceration associated with severe damage to colonic glands (Fig. 1.17D). Crypt-lining cells are cuboidal or flattened, and necrotic debris may be in the lumen of glands. Some glands may be collapsed due to complete epithelial necrosis. The lesion resembles that of

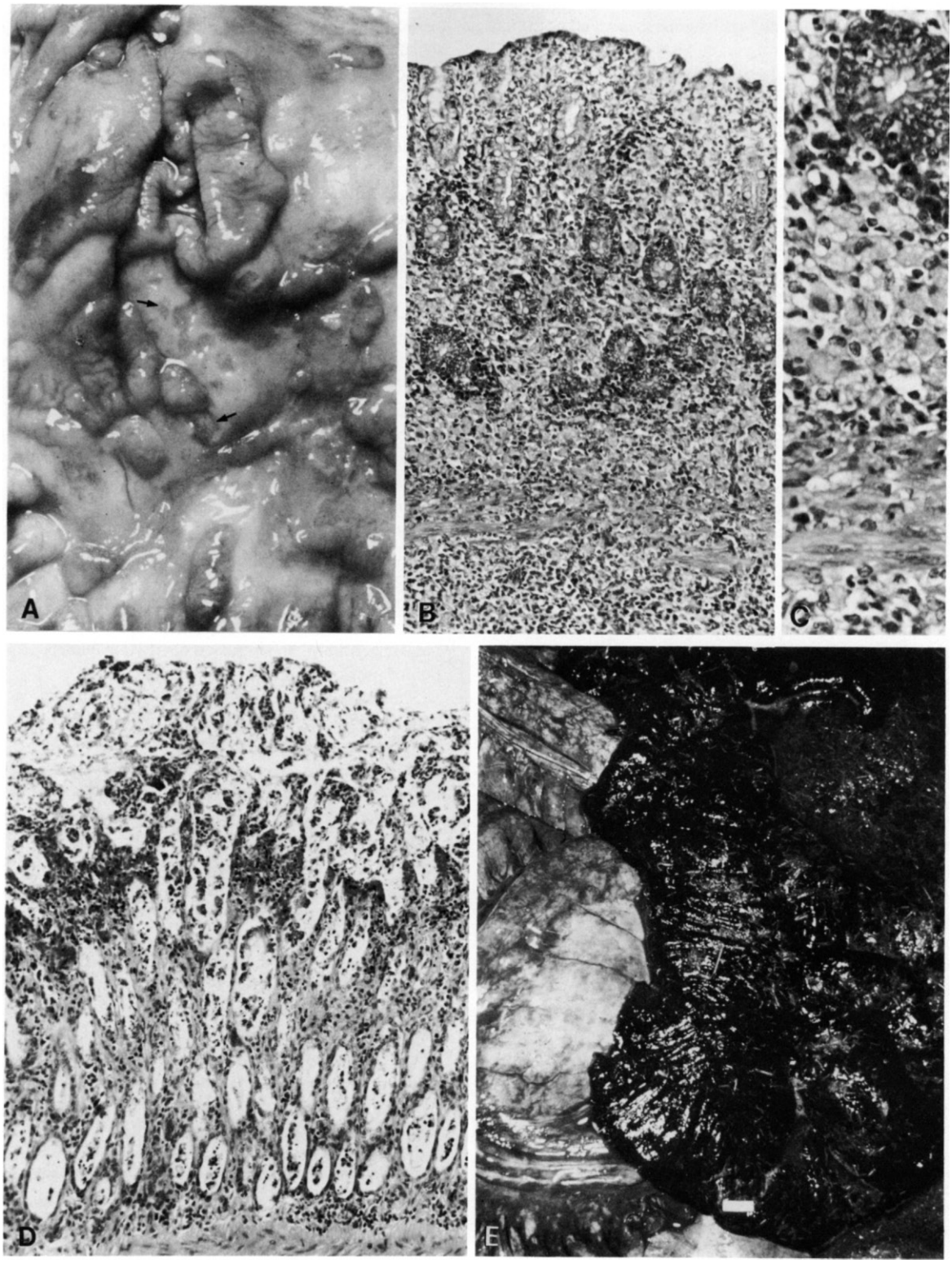


**Fig. 1.17.** (**A–C**) Histiocytic ulcerative colitis. Boxer dog. (**A**) Mucosa is thickened and edematous. There are numerous ulcers (arrows). (**B**) Accumulation of macrophages with extensive cytoplasm throughout mucosa, between base of glands and muscularis mucosae, and in submucosa. (**C**) Detail of macrophages in mucosa deep to crypts. (**D**) Necrotic colitis. Cat. Active necrosis on surface of mucosa. Glands are dilated, contain necrotic cellular debris, or are lined by extremely flattened epithelium. (Courtesy of J. S. Nimmo Wilkie.) (**E**) Acute colitis ("colitis X"). Horse. The mucosa is very congested and edematous.

panleukopenia but is generally more hemorrhagic and necrotic. The cause is unknown.

Ulcerative colitis, grossly and microscopically similar to idiopathic ulcerative colitis of the dog, occurs very rarely in cats. Granulomatous or pyogranulomatous foci in the subserosa or submucosa may cause regional enterocolitis, characterized by fibrosis and serosal nodularity of affected segments, usually without severe mucosal defects. Fibrinoid arteritis causing hemorrhage and edema in the colonic submucosa, and perhaps ischemic necrosis of the mucosa, is also reported. The granulomatous syndrome is attributed to feline infectious peritonitis, and there may be characteristic lesions in other organs.

### *Typhlocolitis in Horses*

The diagnosis of acute colitis in horses resolves into the differentiation of peracute and acute salmonellosis from a similar condition, colitis X. Both of these must be differentiated from the sequelae of intestinal accidents and thromboembolism involving the large bowel.

**Colitis X** is a sporadic acute disease, usually but not always associated with profuse, foul-smelling, but rarely bloody, diarrhea. Some horses may die without having diarrhea. The remainder of the clinical syndrome is a reflection of the profound shock that occurs. At autopsy the animal is dehydrated, and there may be subcutaneous and serosal petechial hemorrhage. The blood is dark and clots poorly. Enteric lesions are virtually limited to the large bowel, which is distended with abnormally fluid content. The serosa of the cecum and large colon may appear cyanotic from congestion and hemorrhage in the mucosa (Fig. 1.17E) and perhaps submucosa. The deeper tissues of the intestinal wall are not themselves compromised, as is the case usually in volvulus and often in thromboembolic infarction. The mucosa and submucosa are commonly markedly edematous, and edema is often present at the mesenteric attachment of the gut and in the cecal and colic lymph nodes. The mucosa may appear brown and necrotic with focal fibrinohemorrhagic exudate on the surface. More commonly it is deeply congested with focal hemorrhage, but blood is rarely present to significant degree in the contents. Gross lesions in other organs are those consistent with circulatory or endotoxic shock.

The microscopic lesions in the large bowel include superficial or full-thickness necrosis of the mucosa, associated with dilatation and perhaps thrombosis of small mucosal and submucosal venules. There is hemorrhage and edema in the mucosa, and the submucosa is markedly edematous, with dilated lymphatics. Some neutrophils may be evident in the mucosa or submucosa, and fibrin may be effusing from the damaged mucosal surface in less advanced cases. Submucosal lymphoid follicles show evidence of recent severe lymphocytolysis. Congestion, microvascular thrombosis, and hemorrhage may be found in a variety of other organs, especially the adrenal cortex.

The pathogenesis of colitis X is uncertain and may be multifactorial. It seems likely that it, probably salmonellosis, and some even less well defined chronic diarrheas in horses are the result of dysbacteriosis of the large bowel. Animals developing these conditions frequently have a recent history of change in feed, hard training, shipment, surgery, antibiotic (especially tetracycline) therapy, or other intervention.

Proliferation of *Clostridium perfringens* type A has been associated with the development of signs consistent in some cases with colitis X. Increased protein in the ration may predispose to establishment of *C. perfringens*, which is apparently an uncommon inhabitant of the equine bowel. Toxin that is locally necrotizing may be the factor initiating mucosal damage, and perhaps observed changes in function of the liver and other organs are partly the result of absorbed toxin. Experimental infusion of extracts of *C. perfringens* type A exotoxin in ponies has marked systemic effects and causes severe edema and hemorrhage of the colonic mucosa and submucosa as well as sloughing of epithelium on the tips of villi in the small intestine. The proliferation of *C. perfringens* precedes the clinical episode, and the organism may not be numerous in the large bowel at death.

Endotoxin may also play a role, either by absorption through a mucosa already damaged by previous insult or by release of abnormal amounts following a change in the flora in the large intestine. Systemic effects of endotoxin may contribute to shock and to the microthrombosis and disseminated intravascular coagulation that sometimes occur.

The precedent for clostridial toxin- or endotoxin-mediated typhlocolitis following disruption of the gut flora lies in similar antibiotic-induced lesions in rabbits, guinea pigs, hamsters, and humans. Lincomycin-associated colitis resembling colitis X has been reported in horses. Tetracycline is excreted in the bile, and high concentrations in the gut may alter the flora in treated horses, permitting the intrusion of new inhabitants or proliferation of previously minor components.

Subacute and chronic diarrheas in horses may be associated with small intestinal malabsorption, but most involve the large intestine, with or without the small bowel. *Salmonella* typhlocolitis must be suspected in such cases. Salmonellosis in horses may have an extremely variable course and pathologic manifestations (see Infectious and Parasitic Diseases of the Gastrointestinal Tract). Suppurative ulcers involving lymphoid tissue in the typhlocolic mucosa, and cecal and colic lymphadenitis, characterize enteric infection with *Corynebacterium equi* in foals. Extensive mucosal involvement by larval cyathostomes and strongyles and, rarely, ulcerative typhlitis due to anoplocephalid tapeworms also may cause diarrhea and wasting; they are discussed with specific parasitisms. Chronic diarrhea and, possibly, cachexia may also result from persistent ulceration of the cecum or colon due to ischemic mucosal lesions. These may be the product of arterial thromboembolism and slow flow or, less likely, corrected strangulation with reflow. Phenylbutazone administration also has been associated with cecal and colonic ulceration and plasma protein loss.

The specific cause of extensive ulceration may be difficult to determine. Smaller chronic ulcers and widespread subacute erosion and ulceration are most likely the result of salmonellosis, rather than ischemia, and the agent should be sought by culture of the affected area, preferably by trituration of tissue and use of selective media.

Granulomatous and eosinophilic typhlocolitis in horses are extensions of the lesions considered previously with syndromes in the small bowel causing diarrhea and protein-losing enteropathy.

Chronic diarrhea occurs that does not appear to be related to

morphologic lesions in the mucosa of the gut. Affected horses have a history of unformed cowpat-like feces, or overt diarrhea, which may persist for weeks, months, and occasionally, years with only periodic temporary remission. Examination of the feces may reveal none of the normal ciliate protozoan fauna, but often many flagellates, especially *Tritrichomonas,* are present. It seems likely that the large number of these flagellate protozoa, and the paucity of ciliates, reflect gross alterations in the microenvironment and flora in the large bowel. If these changes also cause altered fermentation of carbohydrate and, perhaps, reduced production and absorption of volatile fatty acids, the diarrhea, and gradual reduction in body condition that often occurs, might be explained. These horses will show transient response to therapeutic agents that affect anaerobic bacteria and protozoa, but they usually regress when medication is withdrawn. The response to implants of cecal or colonic content is variable and usually discouraging.

*Typhlocolitis in Swine*

The differential diagnosis of typholocolitis in swine revolves mainly around identifying swine dysentery, *Salmonella* enterocolitis, and the large bowel manifestations of the intestinal adenomatosis complex in weaned pigs. The latter condition is readily recognized by the consistent concurrent involvement of the terminal ileum by adenomatosis, with or without hemorrhage, or by necrotic ileitis. Mucosal thickening is reflected in the presence of the characteristic cerebriform folds of the serosal aspect of the bowel that is commonly seen. Lesions in the large bowel are present in a minority of cases and involve the cecum and proximal colon; they resemble the ileal lesions in being either adenomatous or necrotic.

**Swine dysentery** involves only the cecum and spiral colon. It is a catarrhal to mildly fibrinohemorrhagic erosive mucosal typhlocolitis. The colonic content is fluid and usually blood tinged. *Salmonella* enterocolitis, mainly due to *S. typhimurium,* is a fibrinous, erosive to focally ulcerative condition, mainly of the cecum and colon but perhaps involving the small intestine, especially terminal ileum. The content is fluid but usually not bloody. Mesenteric lymph nodes are prominent. Button ulcers or necrotic enteritis in the lower intestine may occur in chronic salmonellosis, in subacute to chronic forms of hog cholera, and perhaps in African swine fever.

*Campylobacter* associated with intestinal adenomatosis is readily identified in smears of affected mucosa stained with carbolfuchsin, and the large spirochetes causing swine dysentery may also be identified in mucosal scrapings at necropsy. Culture of affected tissues confirms these diagnoses and that of salmonellosis.

*Escherichia coli* may cause fibrinohemorrhagic enterocolitis in piglets about weaning, and intestinal adenomatosis may also occur in older suckling and in weanling piglets.

Fibrinohemorrhagic typhlitis is caused by heavy infestations with *Trichuris suis,* especially in weaned pigs with access to pastures and yards. Under similar circumstances, *Eimeria* infection rarely may cause ileotyphlocolitis.

Rectal stricture appears to be a product of ischemic proctitis, probably related in many cases to infection with *Salmonella typhimurium.*

*Typhlocolitis in Ruminants*

In cattle more than 2 or 3 months of age, diagnostic considerations in acute to subacute fibrinohemorrhagic typhlocolitis include salmonellosis, bovine virus diarrhea, rinderpest (in enzootic areas or populations at risk), coccidiosis, malignant catarrhal fever, and adenovirus infection. Lesions of the oral cavity and upper alimentary tract may be expected but are not necessarily present in bovine virus diarrhea, rinderpest, and malignant head catarrh; in the latter, lymphadenopathy and lesions of the trachea, bladder, parenchymatous organs, eye, and brain may also be present. Lesions affecting Peyer's patches in the small intestine strongly suggest bovine virus diarrhea or rinderpest. Coronavirus causes microscopic lesions in colonic crypts, as well as in small intestine, in young calves. Rarely, a mild fibrinous typhlocolitis is seen grossly. Salmonellosis affects all age groups from neonate to adult and may frequently involve both small and large intestine in catarrhal to fibrinohemorrhagic enteritis; mesenteric lymph nodes are usually enlarged. Coccidiosis may involve ileum and large intestine; it often can be diagnosed by mucosal scraping at autopsy. Adenovirus infection may cause severe hemorrhagic colitis, with few lesions elsewhere, as may malignant head catarrh on occasion. Arsenic, other heavy metals, and oak or acorn poisoning may also cause hemorrhagic typhlocolitis and dysentery. Rarely, trichuriasis causes a hemorrhagic mucosal typhlitis in calves.

Chronic fibrinous or ulcerative typhlocolitis may occur in salmonellosis, bovine virus diarrhea, and coccidiosis.

Granulomatous typhlocolitis associated with chronic diarrhea and wasting may occur in Johne's disease, concurrently with granulomatous ileitis and mesenteric lymphadenitis. The mucosa of the large bowel in these cases is thickened and rugose. Impressions of affected mucosa or ileocecal lymph node will contain acid-fast bacilli. Johne's disease in sheep and goats is associated usually with wasting but not diarrhea. The large bowel may be involved in a minority of cases; the ileum is consistently affected.

In sheep, hemorrhagic typhlocolitis may be present in animals with bluetongue; it is rarely the only lesion. Heavy-metal intoxication is the only other significant cause of hemorrhagic typhlocolitis and dysentery in older animals. Salmonellosis may cause fibrinohemorrhagic enteritis in lambs and pregnant ewes, and trichuriasis will occur rarely. Coccidiosis (*Eimeria* spp.) may be implicated in hemorrhagic ileotyphlocolitis in lambs and kids, though the small intestine is usually more commonly and severely involved; lesions of the large intestine are exceptional.

### *Hyperplastic and Neoplastic Diseases of the Intestine*

Tumors of the intestine, either benign or malignant, are uncommon in domestic animals. Polyps are generally hyperplastic or regenerative rather than neoplastic. The exceptions are rectal polyps in dogs, which are usually adenomas or, less commonly, carcinomas. Highly malignant scirrhous adenocarcinomas occur in all species. The prevalence of this tumor in sheep is high in certain areas of the world.

Lymphosarcoma is the most common malignant tumor of

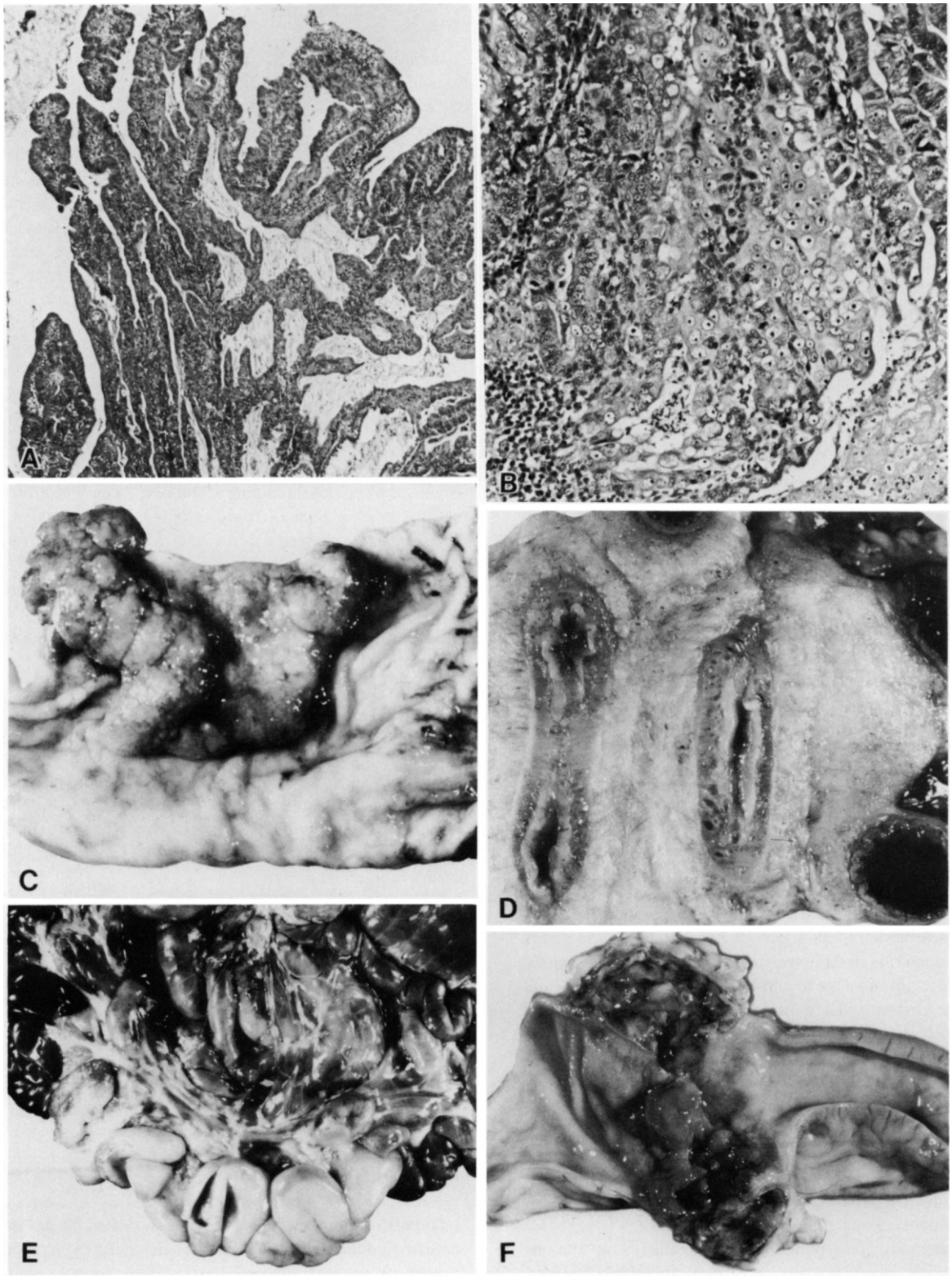


**Fig. 1.18.** (**A**) Tubulopapillary colorectal polyp. Dog. (**B**) Invasive carcinoma arising from the base of a tubulopapillary colorectal polyp in a dog. (**C**) Rectal polyp. Dog. (**D** and **E**) White areas of scirrhous intestinal adenocarcinoma invading colon (**D**) and ileum (**E**). Sheep. (**F**) Annular ulcerating leiomyosarcoma. Cat.

mesenchymal origin in most animals; it is most prevalent in the cat. Lymphosarcoma may arise in the gut, although involvement of this area is more often part of multicentric disease (see the Hematopoietic System, Volume 3).

A hyperplastic condition of intestinal crypts in the ileum and colon in swine and some other species, called intestinal adenomatosis or proliferative ileitis, is described under *Campylobacter* Enteritis.

### *Colorectal Polyps in Dogs*

These tumors are most common at the anal–rectal junction in middle-aged dogs. There is no apparent breed or sex predisposition. Prolapse of the polyp, rectal bleeding following defecation, chronic dyschezia, and diarrhea are the most common clinical signs associated with this tumor.

Macroscopically, the tumor is usually sessile or slightly pedunculated (Fig. 1.18C); it may be firm or friable and hemorrhagic. The mucosal surface is often ulcerated. It varies in size from one to several centimeters in diameter.

Microscopically, the polyp may have a predominantly tubular or papillary growth pattern (Fig. 1.18A). In well-oriented specimens the tubular pattern is characterized by branching crypts lined by usually well differentiated columnar to cuboidal epithelial cells. These are supported by the lamina propria. The papillary type consists of villus-like projections of proprial connective tissue covered by a single pseudostratified layer of columnar epithelial cells. There may be loss of nuclear polarity, and nucleoli are prominent in epithelium in both types of polyp. The number of mitotic figures varies from one tumor to another. The stalk of the tumor is highly vascular and is continuous with the lamina propria or submucosa of the rectum.

Some polyps are malignant (Fig. 1.18B). These are characterized by the presence of anaplastic epithelial cells *in situ* in the mucosa and, rarely, in the stalk of propria. There is little information on the biologic behavior of these tumors. Adequate surgical removal usually results in complete recovery. As in humans, the size of the tumor may be related to the prognosis. Polyps more than 1.0 cm in diameter tend to have a more anaplastic appearance and appear to recur more commonly. Some become invasive adenocarcinoma. Rectal polyps must be differentiated from rectal carcinoids, which they resemble grossly in dogs.

### *Polypoid Tumors in Other Species*

Polypoid masses varying in diameter from one to several centimeters may be found at any level of the intestine in other species, especially cattle, They are usually an incidental finding except in those cases where they are large enough to cause partial obstruction. The tumors are raised, often pedunculated, gray to brown masses on the mucosal surface. They may occur in grape-like clusters. Miscroscopically, they resemble benign rectal polyps in the dog.

A high prevalence of intestinal adenomas and to a lesser extent adenocarcinomas in cattle has been reported in upland areas in Scotland and northern England. These tumors often coexist with papillomas and squamous-cell carcinomas of the upper alimentary tract (see Neoplasia of the Esophagus and Forestomachs). Three types of adenoma are recognized in the intestine of affected cattle in these endemic areas: a sessile plaque, an adenomatous polyp, and a more proliferative adenoma of the ampullae, where the bile and pancreatic ducts open into the duodenum.

### *Intestinal Adenocarcinoma*

DOGS. Intestinal adenocarcinoma is uncommon in dogs. About 40% of all gastrointestinal carcinomas in dogs occur in the colon and rectum. The rest are equally divided between the stomach and small intestine, mainly duodenum. The average age of dogs with intestinal carcinomas is 8–9 years. Some investigators have reported a higher prevalence of intestinal carcinomas in male dogs, with a breed predisposition in boxers, collies, and German shepherds.

Macroscopically, the tumors appear as gray-white, firm, sometimes annular, stenotic areas that commonly affect the entire thickness of the intestinal wall (Fig. 1.19A). These tumors often do not ulcerate, and they usually do not project into the lumen of the gut. The papillary type of intestinal adenocarcinomas do form intraluminal masses, which tend to involve larger segments of the intestine, suggesting horizontal spread. There is dilation of the gut anterior to stenotic and obstructive tumors, and there may be hypertrophy of the intestinal muscularis proximal to such neoplasms.

On the basis of the microscopic appearance, intestinal carcinomas in dogs have been divided into four types, which may overlap. The **acinar type** is characterized by irregular glandular structures that obliterate the normal mucosa and infiltrate into submucosa and muscularis. The epithelial cells lining the acini are basophilic, cuboidal to columnar, and have small hyperchromatic nuclei in the basilar area of the cell. Amorphous eosinophilic material often fills the lumen of the glandular structures. Mucin is rarely found in this type of tumor. There is usually extensive necrosis, with marked inflammation and fibrosis in the gut wall of the affected areas. At the periphery of these tumors there may be hyperplasia of cryptal and villous epithelial cells.

In the **solid type** of intestinal carcinoma, the mucosa and gut wall are extensively infiltrated by nests and sheets of anaplastic epithelial cells. These have only a slight tendency to differentiate to acinar structures. The tumor cells have abundant amphophilic to basophilic cytoplasm and large vesicular nuclei with prominent nucleoli. There are some "signet-ring cells" and a few islets of mucin.

In the **mucinous type** of carcinoma, the anaplastic epithelial cells have pale eosinophilic cytoplasm. There are many "signet-ring cells." Large pools of extracellular mucin are evident in the stroma.

The **papillary type** consists of papilliferous projections into the lumen, covered by columnar, often highly anaplastic epithelial cells. The mitotic index tends to be high. There is goblet-cell hyperplasia of both crypts and villi. This type usually is only locally invasive.

With the exception of papillary adenocarcinomas, desmoplasia is is a prominent feature of these neoplasms, explaining their common tendency to cause stricture and obstruction of the intestine.

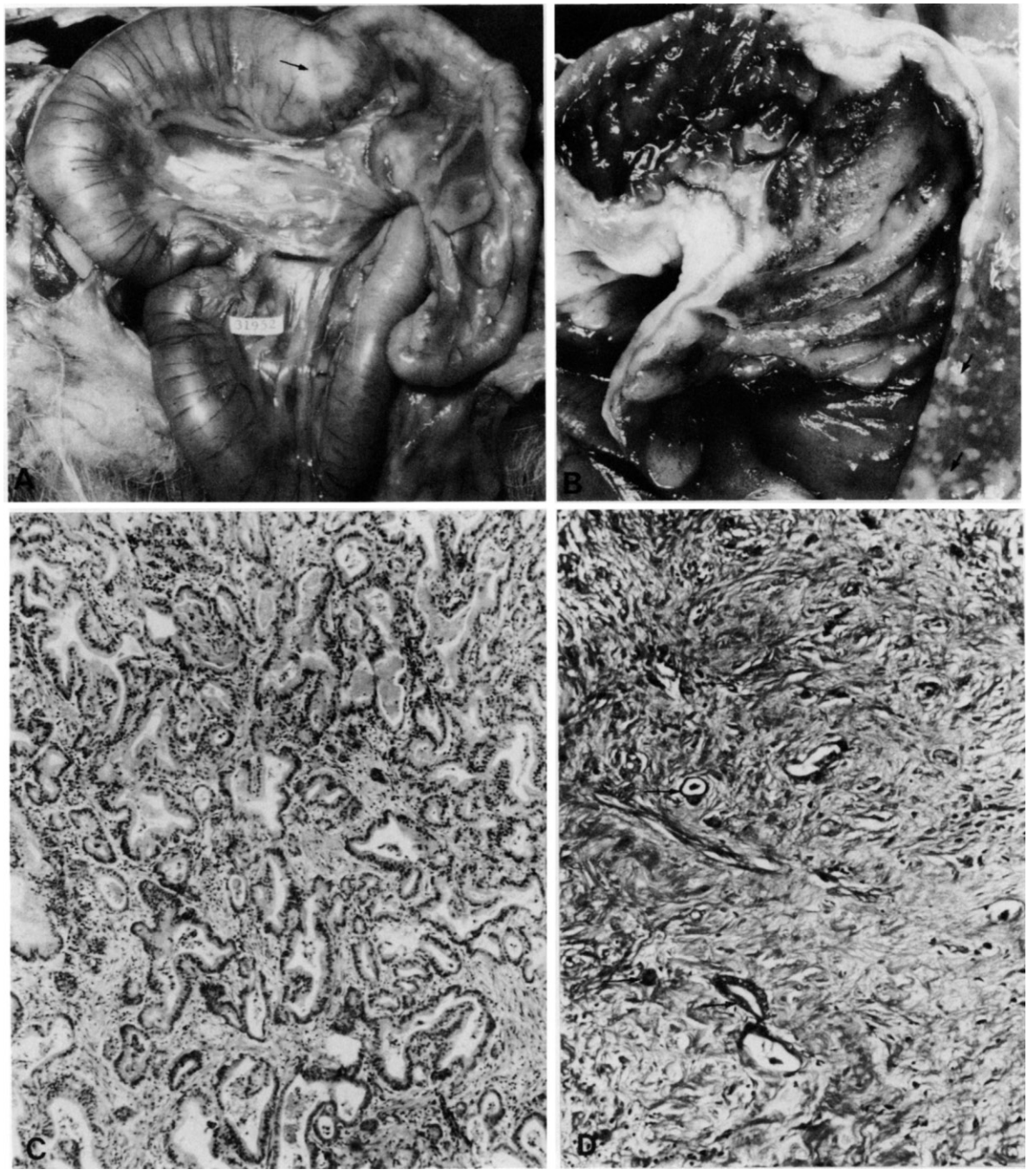


**Fig. 1.19.** (**A**) Scirrhous adenocarcinoma (arrow) infiltrating wall of small intestine, causing obstruction. Dog. Dilatation proximal to obstruction and contraction of empty distal intestine. (**B**) Intestinal carcinoma. Cow. There is annular thickening of intestine with carcinomatous serosal plaques (arrows). (**C**) Well-differentiated intestinal adenocarcinoma. Cat. (**D**) Intestinal adenocarcinoma. Sheep. Islands of neoplastic epithelium (arrows) scattered in extensive desmoplastic reaction.

All types, except possibly the papillary type, metastasize widely, mainly via the lymphatics to the regional nodes. Involvement of the small intestine leads to metastases mainly in the mesenteric lymph nodes, less commonly to other abdominal nodes, liver, spleen, and lungs. Colonic adenocarcinomas metastasize to colic, iliac, and other pelvic and abdominal nodes. Metastases may also occur in most abdominal organs and in the lungs. Implantation on serosal surfaces may result in obstruction of lymphatics, followed by ascites. In a few cases, malignant cells may migrate retrograde in the lymphatics of the abdomen and pelvic limbs, causing edema of the abdominal wall and legs.

CATS. Next to lymphosarcoma, intestinal adenocarcinoma is the most common intestinal tumor in cats. The prevalence of intestinal carcinomas is lower in cats than in dogs. They may be more common in Siamese cats compared to other breeds. As in dogs, male cats have been reported to have a higher prevalence of this tumor than females. The mean age of cats with intestinal carcinomas is 10 to 11 years with a range of 4 to 14 years.

The ileum is the most common site affected, followed by the jejunum. When the tumor is located at the ileocecal junction, both the large and small intestine are usually involved. Intestinal carcinomas in cats rarely arise in the large intestine. The clinical signs and gross appearance are similar to those in dogs.

With some minor variations, the morphologic types of intestinal carcinomas described for dogs also occur in cats (Fig. 1.19C). Osteochondroid metaplasia is a frequent feature of all types of adenocarcinoma in the cat. The rare carcinomas involving the large intestine have been mainly of the papillary type. They tend to be better differentiated and less scirrhous than carcinomas involving the small intestine.

The biologic behavior of intestinal carcinomas in cats is similar to that found in dogs.

SHEEP. Intestinal adenocarcinoma is relatively common in sheep in New Zealand, Iceland, Scotland, and southeastern Australia. The cause of the high prevalence of intestinal carcinomas in these areas is unknown but may be related to exposure to bracken fern. It occurs mainly in animals five years of age or older. Clinically, affected sheep lose weight and have distended abdomens.

The tumors are usually located in the middle or lower areas of the small intestine (Fig. 1.18E). They are dense, firm, white masses, $\frac{1}{2}$ to several centimeters long and up to 1.0 cm thick, which may form annular constrictive bands at the affected site. Cauliflower-like growths may be evident on the serosal surface. Polyps may protrude into the lumen, but ulceration of the mucosa is uncommon. The distal edge of the tumor is generally well demarcated. There is dilation of the intestine proximal to the lesion.

Metastasis occurs along the serosal lymphatics to the mesenteric lymph nodes. Implantations on serosal surfaces are common, and these appear as opaque to white plaques or diffusely thickened areas, which must be differentiated from mesothelioma. Obstruction of serosal lymphatics by tumor emboli may lead to ascites. Lung and liver metastases are rare.

Microscopically, the tumor is characterized by solid sheets or nests of highly anaplastic polyhedral, cuboidal, or columnar epithelial cells that may form irregular acinar structures. Mitotic figures and acinar differentiation are infrequent. The neoplastic cells infiltrate the submucosa and the muscularis through to the serosal surface, whence they spread via the lymphatics to the mesenteric lymph nodes. This is apparently followed by retrograde lymphogenous metastasis to the gut wall proximal to the primary tumor. These secondary tumors are particularly responsible for constriction of the gut lumen. The infiltrating tumor is always accompanied by a very scirrhous reaction (Figs. 1.18D and 1.19D). Sclerotic masses with anaplastic epithelial cells, which are located on the serosal surfaces of the abdominal organs, rarely infiltrate the parenchyma. Argentaffin cells may form part of some intestinal carcinomas, especially in lymph node metastases. Mineralization and osseous metaplasia may be evident in the stroma of some tumors.

OTHER SPECIES. Intestinal carcinomas generally are rare in cattle and swine (Fig. 1.19B), with the exception of those associated with bracken fern, papillomavirus, and upper alimentary cancer in cattle in certain parts of the United Kingdom, mentioned previously. They are usually an incidental finding at meat inspection. The location, morphology, and routes of metastasis are similar to those described for sheep, except that serosal lesions are less obvious. Liver and lung metastases may occur in cattle.

### *Carcinoid Tumors of the Intestine*

Carcinoid tumors arise from endocrine or paracrine cells, which are located in the mucosal lining of a wide variety of organs, including the stomach and the intestine. These cells secrete vasoactive amines, which are responsible for the argentaffinic and argyrophilic tinctorial properties of the tumors. Functional derangements from excessive production of amines have not been reported in animals.

Carcinoid tumors of the gastrointestinal tract are rare in domestic animals. They have been reported mainly in aged dogs and occur rarely in the cat and cow. In dogs, carcinoids are mainly located in the duodenum, colon, and rectum. Clinically, they may cause intestinal obstruction and anemia due to hemorrhage from ulcers. Rectal carcinoids may protrude from the anus and resemble adenomatous polyps.

Macroscopically, carcinoids are usually lobulated, firm, dark red to cream-colored masses in the wall of the intestine. The tumor may result in submucosal or subserosal nodule formation. Microscopically, carcinoids have a distinct endocrine appearance. Round or oval to polyhedral cells have abundant finely granular eosinophilic or vacuolated cytoplasm and vesiculate nuclei with prominent nucleoli. They form nests, ribbons, rosettes, or diffuse sheets in the mucosa, submucosa, and muscularis. A fine, vascularized stroma divides the tumor masses. Amyloid may be present in intercellular and perivascular spaces. Multinucleate giant cells are occasionally seen.

Confirmation of the diagnosis requires special stains to reveal argentaffinic and argyrophilic properties. These histochemical reactions may be negative, especially in rectal carcinoids. They may also be lost during fixation in formalin. Electron microscopic examination helps to differentiate carcinoids from intestinal mast-cell tumors. Carcinoid tumor cells have dense, round

to oval, membrane-bound secretory granules in the cytoplasm that vary in diameter from 75 to 300 nm. They have abundant rough endoplasmic reticulum, and the plasma membrane forms interdigitating processes. The ultrastructural characteristics of intestinal mast-cell tumors are described later. Carcinoid tumors are PAS-negative and do not show metachromasia with Giemsa stains.

Data on biologic behavior of intestinal carcinoids in dogs are limited. The few cases that have been reported were malignant. There may be extensive invasion of the gut wall and veins, with metastasis especially to the liver. In this respect their behavior is similar to intestinal carcinoids in humans.

### *Intestinal Mast-Cell Tumors*

Intestinal mast-cell tumors are uncommon. They occur mainly in aged cats and, rarely, in dogs. They resemble carcinoid morphologically under the light microscope, and a definitive diagnosis requires histochemical and ultrastructural examination of tumor cells. They appear to be more common than intestinal carcinoid tumors in cats. Abnormal mast cells do not appear in circulation.

These tumors are mainly located in the small intestine, rarely in the colon. Affected areas in the gut are tan-colored, firm, thickened, and may be one to several centimeters in length. The overlying mucosa bulges into the gut lumen but rarely ulcerates. Nests, cords, and whorls of pleomorphic mast cells infiltrate the mucosa and adjacent areas of the gut wall. Cells in intestinal mast-cell tumors are unlike mast cells in mastocytomas involving the skin and other organs. The latter are round and have an intensely eosinophilic granular cytoplasm with distinct cytoplasmic borders and central oval nuclei. In contrast, cells in intestinal mastocytomas are polygonal to spindle-shaped. They have a finely granular or vacuolated cytoplasm with indistinct cytoplasmic borders and oval, hyperchromatic, eccentrically located nuclei. The degree of metachromatic staining varies considerably, and there is a marked variation in the number of eosinophils.

Ultrastructurally, the cells in most respects resemble typical degranulated mast cells. The cytoplasm contains many membrane-bound granules, which appear as singular or fused vesicles. Fine fibrillar material forms a loose network within these vesicles. A few tumor cells contains electron-dense fibrillar granules or intermediate forms. None of the tumor cells contains the crystalline, electron-dense granules present in normal mast cells and in mastocytomas in other sites.

Metastases occur most often in the mesenteric lymph nodes, followed by the liver, spleen, and rarely, the lungs. Ulceration of the gastrointestinal mucosa occurs commonly with visceral mast-cell tumors in cats and large cutaneous mastocytomas in dogs. Mucosal ulceration is not a feature of intestinal mast-cell tumors in the cat. This may be due to low levels of histamine in the cells in intestinal tumors.

### *Other Mesenchymal Intestinal Tumors*

Leiomyomas and leiomyosarcomas (Fig. 1.18F) are probably more common than other types of mesenchymal tumors besides lymphosarcoma. These tumors occur most commonly in the small intestine, where they cause obstruction. They tend to be nodular rather than diffuse, and ulcerate and cavitate on the luminal surface. The histologic appearance is similar to smooth muscle tumors in other sites.

## Infectious and Parasitic Diseases of the Gastrointestinal Tract

### *Viral Diseases*

FOOT AND MOUTH DISEASE . Foot and mouth disease (aphthous fever) is a viral infection of ruminants and swine and of at least 30 species of wild animals. It is a problem of worldwide concern, being enzootic in large areas of Africa, Asia, Europe, and South America. In addition to these areas are others that are periodically visited by the virus and in whose susceptible populations the disease spreads rapidly. Some other areas, notably Japan, Australia, New Zealand, and North America, are currently free because of geographic isolation and quarantine restrictions. Foot and mouth disease is not notable for a high mortality rate, except in sucklings, but the morbidity rate is very high and in an affected population productivity is reduced substantially.

The virus of foot and mouth disease belongs to the Picornaviridae, in the genus *Aphthovirus* (*aphtha* = vesicles in the mouth). The virus is highly resistant under many circumstances but is inactivated by direct sunlight and moderate acidity. The acid production that accompanies rigor mortis in carcasses and meat inactivates the virus. The alteration in pH is not dependable, however, and the virus survives in offal, viscera, lymph nodes, and bone marrow for an indefinite period under refrigeration. It may survive on hay and other fomites for several weeks.

This resistance of the virus is of epidemiologic significance, especially where control policies involve slaughter rather than vaccination. But probably of much greater importance is the confirmation that many infected animals remain carriers. The carrier state has been observed in cattle, sheep, and African buffalo. Swine apparently become carriers, but less commonly than other species. Experimental transmission of virus from carrier swine to a susceptible animal, through contact, has never been accomplished. Virus recovered from carriers will infect susceptible animals by means of inoculation. Persistence of infection in convalescence has been extensively examined only in cattle, and the carrier state persists for up to 9 months. The virus is carried mainly in the pharynx and on the dorsal surface of the soft palate, but the host cells are unidentified and the carrier state exists even in animals with a significant level of serum neutralizing antibody.

Of equal importance to the persistence of the virus is its antigenic heterogeneity and instability. There are seven principal antigenic types, namely, the classical A, O, and C types, SAT-1, SAT-2, SAT-3, and Asia-1. These can be distinguished by serologic tests, although there are various degrees of overlap. In addition to being serologically different, these seven types are sufficiently different immunologically that infection with one type does not confer resistance to the other six. Within these seven major types there are antigenic subtypes, each different, to variable degrees, from the parent type. Generally, the subtypes cross-immunize to a useful degree, but exceptions do arise and

become recognizable, especially when vaccination fails. Antigenic drift can also be demonstrated experimentally; new subtypes can be produced by passing the virus in immune or partially immune animals, or by growing the virus *in vitro* in the presence of immune serum. There are presently at least 60 distinct antigenic strains of the virus of natural origin and no reason to think that the possibility of recombination of subtypes is exhausted.

As well as differences and variability in antigenic characters, strains of the virus differ in virulence, and a given strain is probably able to vary in virulence although this is difficult to measure satisfactorily. Certainly, comparing different outbreaks, there is considerable variation in the severity of the disease produced in a given host species. Virulence also varies between species. Although the virus is pathogenic for all cloven-footed, domestic, and wild species, a given strain at any time is of different virulence for the different species. Some strains, for example, will infect pigs but not cattle, and others are pathogenic for cattle and not for pigs. A similar relationship pertains for sheep and goats, but in general, virus strains are intermediate between these extremes. There can be little doubt, however, that the adaptation to a host species does occur and that this adaptive relationship may establish a reservoir of infection.

In addition to the domestic hosts, humans can become infected, but not importantly, either clinically or epidemiologically. The hedgehog, coypu, and some marsupials are highly susceptible to infection and could be important in the transmission of the disease. Some laboratory animals are also susceptible, the white mouse in particular. Suckling mice inoculated intraperitoneally are susceptible enough to be used for detection of small amounts of virus. They consistently develop degeneration of skeletal musculature, and in ~50% there is myocardial degeneration and, in a variable percentage, pancreatic necrosis. Young adult guinea pigs can be infected by infection into the footpad. They regularly develop pancreatic necrosis, with some necrosis of skeletal and cardiac muscle. In terms of evolution and epithelial lesions, the disease in guinea pigs is similar to that in cattle.

The main portal of entry and primary site of viral multiplication is the mucosa of the upper respiratory tract, especially the pharynx. The ability of the virus to establish in this area is not affected by the presence of circulating antibodies. Primary multiplication is followed by a viremic stage of 4 or 5 days duration, after which the virus localizes, replicates, and produces characteristic vesicles in several different sites referred to later. The highest virus titers occur during the early stages of the disease. Virus persists in the sites of lesions for 3 to 8 days after the appearance of significant neutralizing titers in serum but seldom persists in lesions beyond the eleventh day of clinical illness. High titers of virus develop in all areas of skin, not necessarily related to lesions, and in several visceral tissues, including pancreas and hypophysis. Here they have been related to persistent aftereffects of natural and experimental infections.

The decline in virus titer follows within a week or so the development of neutralizing antibody. Ordinarily, antibody titers decline progressively and fairly rapidly. The duration of persistence of antibody is correlated with the initial titer. In general, animals are resistant to reinfection with homologous strains by natural exposure for about 2 to 4 years; susceptibility increases as the antibody titer declines.

The characteristic lesions of foot and mouth disease are seen only in those animals examined at the height of disease. Later, the lesions heal or are obscured by secondary bacterial infection. In cattle, there is appreciable loss of weight, and the buccal cavity contains much saliva. In the living animal, there is diffuse buccal hyperemia and mild catarrhal stomatitis, but the hyperemia disappears at death. Vesicles form on the inner aspects of the lips and cheeks, the gums, hard palate, dental pad, and especially on the sides and anterior portion of the dorsum of the tongue. Sometimes they form on the muzzle and exterior nares. The primary vesicles are small, but by coalescence they produce bullae that may be 5 to 6 cm across; these bullae rupture in 12 to 14 hr, leaving an intensely red, raw, and moist base to which shreds of epithelium may still adhere. A seropurulent exudate develops on the base of the erosion, and this coagulates to a scab, which in turn is replaced by regenerated epithelium in less than 2 weeks. Secondary infection may complicate this course.

Foot lesions occur in the majority of cases. There is inflammatory swelling of skin of the interdigital space, coronet, and heels a day or so before vesicles form. The swellings persist until the vesicles rupture and the resultant erosions heal; healing may be considerably delayed on the feet. Vesicles may also occur in the other sites but much less frequently. When the teats and udder are involved, there is severe swelling.

Fluorescent-antibody studies indicate that there is infection of individual cells in the stratum spinosum, adjacent to the papilla on mucosal surfaces, or in the follicular sheath in skin. The papilla serves as a bridge for transport of the virus from the vascular lamina propria to the avascular squamous epithelium. Immunofluorescence occurs in mononuclear cells of the lamina propria before there is evidence of virus in the epithelial cells. The infected epithelial cells progressively swell, develop eosinophilia of the cytoplasm, and undergo acantholysis. There is extensive spongiosis of the stratum spinosum, and this along with the necrosis of keratinocytes results in the formation of vesicles. Superficial lesions may be formed in the stratum corneum. These vesicles tend to rupture as soon as they develop, with leakage of vesicular fluid followed by desiccation. The cells in this type of lesion remain spherical and adhere to each other by proteinaceous material. The early microvesicles coalesce and become macroscopically visible, and these in turn may form bullae. The base of the vesicle is formed by the basal germinative layer of epithelium, which is not usually breached, and the underlying dermis or lamina propria, which is infiltrated by inflammatory cells and intensely hyperemic.

Additional to the vesiculate and erosive lesions, there may be catarrhal inflammation of the respiratory passages. In animals dying of the disease, there are petechial hemorrhages of the abomasum and intestine, with congestion and diapedesis into the lumen. The abomasal hemorrhages quickly develop to ulcers. Pulmonary edema, modest splenomegaly, and hydropericardium with petechiae on the cardiac serosa are nonspecific changes in this disease.

As indicated earlier, a malignant form of the disease without vesiculation does occur in young animals. In these, death is common and no doubt coupled with the myocarditis that devel-

ops. The myocardial lesion involves the ventricular musculature and the papillary muscle as poorly defined pale foci of varying size. It is characteristic enough to be referred to as the typical "tiger heart" on account of the striping and mottling. The myocarditis is acute, and hyaline degeneration and necrosis of muscle fibers is accompanied by an intense, principally lymphocytic, infiltrate. Similar lesions occur in skeletal muscle.

Prolonged convalescence or residual illness is frequently referred to in cattle but is difficult to evaluate. Residual bacterial infections are common complications, especially in the oral cavity and mammary glands, and on the feet. Additionally, syndromes of panting and hypertrichosis and disturbances of the regulation of body temperature, lactation, and fertility (including abortion) and of emaciation or obesity have been described. Such disturbances could be referable to disturbances of endocrine glands and of the hypothalamic–hypophyseal system, and nonspecific changes can be found in these locations. Clinical myocardial disease is frequent in convalescent cattle and is ascribed to myocardial degeneration with concurrent degeneration of the conduction system. Diabetes mellitus has been reported as a complication of the experimental and natural disease. The pancreatic islets may disappear almost completely, and the pancreas also shows acinar necrosis and regeneration, the latter evident as proliferation of tubular structures.

Foot and mouth disease is not well documented in sheep; they are, in general, less susceptible than cattle, and the infection runs a milder course, though there may be exceptions. The incubation period in sheep is commonly 3–8 days, with fever lasting ~4 days. Lesions may not develop. When they do, the dental pad is the preferred site in the oral cavity. Lingual lesions tend to occur on the posterior dorsal portion as underrunning necrotic erosions rather than vesicles. These are small and easily missed, and they heal within a few days. Lameness is prominent in acute outbreaks. Typical vesicles develop in the interdigital cleft and on the coronet and bulb of heel. They may occasionally involve all of the coronet and lead to eventual shedding of the hoof. Vesicles also occasionally occur on the teats, vulva, prepuce, and on the pillars of the rumen. The peracute form will occur in lambs.

In pigs there is also considerable variability in virulence of strains and acuteness of the disease. The incubation period is somewhat longer than in cattle and may extend for a week or more. Lesions occur in the usual sites, although more commonly on the feet than in the mouth. They may be present on the snout and behind its rim, and on the teats of lactating sows. Abortion and stillbirth of infected piglets has been recorded. The peracute form with high mortality occurs in young sucklings.

The lesions of foot and mouth disease must be differentiated from other viral vesicular diseases such as vesicular stomatitis, vesicular exanthema, and swine vesicular disease and in the latter stages from diseases producing erosive–ulcerative lesions of the oral cavity. Laboratory tests are essential to confirm or rule out a diagnosis of foot and mouth disease. Complement-fixation tests using vesicular fluid or epithelial cells from early lesions as antigen are the most commonly used procedures, because results may be available within 3 hr. False negative results are possible, and these should be followed up with fluorescent-antibody techniques, isolation attempts on tissue culture, and inoculation of susceptible animals.

VESICULAR STOMATITIS. Vesicular stomatitis is a specific viral disease occurring naturally among horses, cattle, and pigs, and it is transmissible experimentally to a number of laboratory animals, including guinea pigs and mice. The disease is important because it causes a loss in production, especially in dairy herds, and it must be differentiated from foot and mouth disease in cattle and pigs. Vesicular stomatitis is the only vesicular disease naturally occurring in horses. Sheep and goats do not appear to be susceptible to the disease. Several wildlife species, such as white-tailed deer, raccoons, and feral swine, are susceptible to vesicular stomatitis. In humans, the virus may cause an inapparent infection or a mild influenza-like condition.

Vesicular stomatitis is enzootic in Central and South America and occurs sporadically elsewhere in the Americas. It has a seasonal occurrence, outbreaks occurring in the warmer seasons and ceasing abruptly with the onset of cold weather. The seasonal nature of the disease suggests that it is transmitted by insects; however, insect transmission is not essential. It is not known how the virus spreads from one geographic area to another. The intact mucosa is resistant to infection, but abrasions in the susceptible site readily result in infection when contaminated with saliva or exudate from a lesion. Swine may become infected through ingestion.

The virus of vesicular stomatitis belongs to the Rhabdoviridae, genus *Vesiculovirus*. It contains single-stranded RNA, and the virion is large, rod-shaped, 80 × 120 nm, and it has an envelope. Apart from having a greater susceptibility to heat, being inactivated by pasteurization temperatures, it shares qualities of resistance with the aphthovirus. There are two serologically and immunologically distinct types of the virus. The more common and more virulent New Jersey strain has only one serotype, is restricted to vertebrate hosts, and extends farthest north into more temperate zones. The Indiana strain has three serotypes and occurs in vertebrate hosts but also in arthropods such as *Phlebotomus* flies, sand flies (*Culicoides*), and mosquitoes. The epidemiologic significance of this observation is unknown.

The lesions of vesicular stomatitis occur mainly on the oral mucosa; occasionally they do occur elsewhere, including the feet, and in swine, foot lesions are common. This is by no means a dependable feature, and outbreaks of the disease in cattle have been described in which the lesions were predominantly on the teats. The incubation period following exposure by abrasion is 24–48 hr, and there is a viremic phase that persists longer than the vesicular, but secondary lesions are rare. In cattle, intramuscular injections will not initiate the disease, a useful distinguishing feature from foot and mouth disease.

The lesions of vesicular stomatitis are indistinguishable from those of foot and mouth disease (Fig. 1.20A). Initially, in cattle, there is a raised, flattened, pale pink to blanched papule a few millimeters in diameter in or near the mouth. These papules rapidly become inflamed and hyperemic. In the course of a day or so, they develop into vesicles 2–3 cm in diameter and by coalescence may involve large areas. The shallow erosions that follow rupture of vesicles heal within 1 to 2 weeks unless secondary infections occur; in the mouth, the latter are expected.

The first microscopic changes are seen in the deeper layers of the stratum spinosum, where increasing prominence of the intercellular spaces and stretching of the desmosomes are ac-

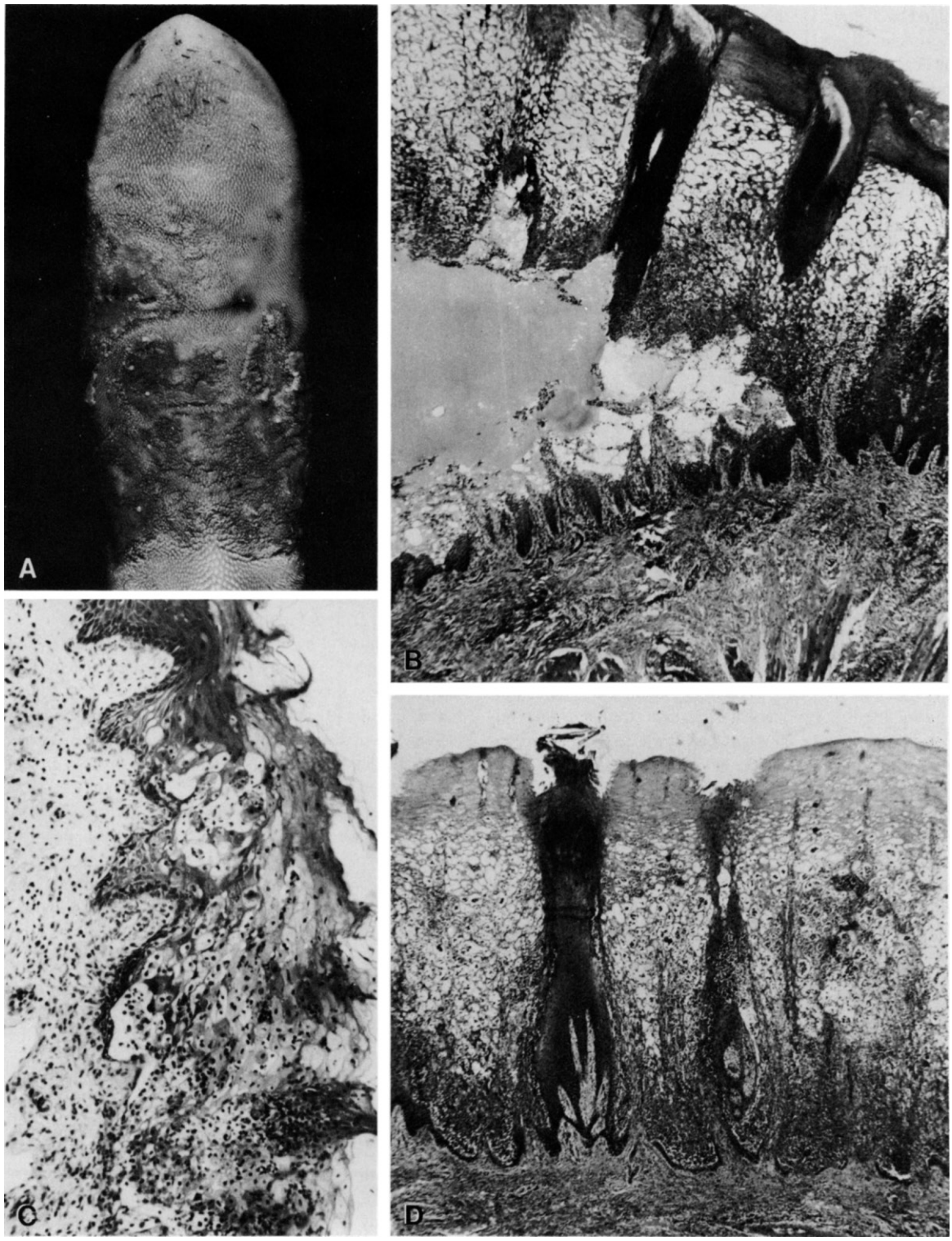


**Fig. 1.20.** (**A**, **B**, and **D**) Vesicular stomatitis. (Courtesy of H. R. Seibold and the *American Journal of Veterinary Research.*) (**A**) Erosion of vesicular lesions in tongue at 4 days postinoculation. (**B**) Edge of gross vesicle. (**C**) Margin of vesicle. Porcine vesicular exanthema. (**D**) Intraepithelial vesicle formation in vesicular stomatitis.

companied by a reduction in volume of the cell cytoplasm (Fig. 1.20B,D). This dissociation of cells proceeds to distinct intercellular edema (spongiosis), followed by further cytoplasmic retraction until the affected epithelial cells float freely in enlarging vacuoles, which in turn are loculated by strands of cytoplasmic debris. There is no hydropic degeneration of the epithelial cells, and the nuclei until now remain normal. With the onset of epithelial-cell necrosis there is a pleocellular inflammatory reaction in the mucosa and underlying lamina propria. Electron microscopic examination of epithelial cells adjacent to the vesicles confirms the intercellular edema and keratinocyte necrosis seen under the light microscope. Virions bud from the cytoplasmic membrane and are located in the dilated intercellular spaces. There is marked reduplication of desmosomes, and normal desmosomes are evident in the cytoplasm. These appear to be due to endocytosis of plasma membranes of adjacent damaged epithelial cells, and formation of desmosomes on invaginations of plasma membranes with subsequent migration into the cytoplasm of keratinocytes. The microvesicles coalesce to produce macroscopically visible ones. There are no inclusion bodies. The microscopic appearance of the lesions is not diagnostic.

The severity of vesicular stomatitis in swine approximates that of foot and mouth disease, but in other species it is much milder. Only ~30% of infected cattle develop vesicles. In light of its similarity to other vesicular diseases in cattle and swine, laboratory confirmation of vesicular stomatitis is essential.

VESICULAR EXANTHEMA. Vesicular exanthema is an acute, febrile, viral disease of swine that is characterized by formation of vesicles on the mouth, skin, and feet. It was first diagnosed in southern California in the 1930s and eventually spread to most swine-producing states in the United States. The last reported outbreak of vesicular exanthema was in New Jersey in 1959.

The virus that causes vesicular exanthema belongs to the Caliciviridae, genus *Calicivirus*. It has a single-stranded RNA genome and has only one major polypeptide. It is about 35–40 nm in diameter, and characteristic cup-shaped structures (calyces) are evident in electron microscopic preparations. There are 13 immunologically distinct serotypes, which vary in virulence.

In 1973, a virus biophysically similar to vesicular exanthema virus was recovered from sea lions with vesicles on their flippers, off the coast of California near San Miguel Island. This virus, called San Miguel sea lion virus, produces lesions identical to those of vesicular exanthema when inoculated into swine. It has many distinct serotypes, which are considered to be another range of variants of swine vesicular exanthema virus. It is found in marine fish as well as sea lions and Pribilof fur seals.

Most outbreaks of vesicular exanthema have been associated with feeding of raw garbage containing pork waste. Therefore, the disease may be transmitted by direct contact and fomites. Spontaneous outbreaks of vesicular exanthema in swine due to San Miguel sea lion virus have not been documented, though undiagnosed vesicular disease of swine, associated with the feeding of marine products, has occurred in Tasmania and New Zealand.

After inoculation, there is an incubation period of about 18 to 72 hr, followed by fever and development of vesicles on the mouth, lips, tongue, on the mucosa of the oral cavity, and on the sole of the hoof, coronary band, and interdigital skin. Occasionally, they are present on the teats of nursing sows and on the skin of the metacarpus and metatarsus. Secondary infections of the feet are common, and the hooves may slough. Pregnant sows may abort. Without complications, affected pigs recover completely within about a week.

The vesicular lesions are indistinguishable from those of vesicular stomatitis, swine vesicular disease, and foot and mouth disease (Fig. 1.20C). Laboratory confirmation of clinical diagnosis should always be attempted. This is possible through inoculation of susceptible pigs and laboratory animals (e.g., hamsters). The virus does not grow in chick embryos but can be isolated in tissue cultures of swine origin.

SWINE VESICULAR DISEASE. Swine vesicular disease is a highly contagious viral disease of pigs that is characterized by formation of vesicles around the coronary bands of the feet and to a lesser extent on the mouth, lips, and tongue.

The disease was first recognized in Italy in 1966, and it has since been reported from Hong Kong, the United Kingdom, Europe, and Asia. The economic importance of swine vesicular disease is related to losses in production and the fact that it is difficult to differentiate from other vesicular diseases in swine, including foot and mouth disease.

The cause of swine vesicular disease is a small RNA virus belonging to the Picornaviridae, genus *Enterovirus*. It is considered to be a porcine strain of human Coxsackie B5 enterovirus and occasionally infects humans, but not other domestic species. Swine vesicular disease virus is relatively resistant to environmental factors. Unlike foot and mouth disease virus, it is not inactivated at the low pH in muscle commonly associated with rigor mortis.

Most outbreaks of swine vesicular disease appear to originate by feeding raw garbage contaminated with pork products. Transmission within affected herds is by direct contact, especially during the early stages of the disease. The portal of entry is through damaged epithelium, and this is most likely to occur on the feet and to a lesser extent in the oral cavity. The tonsils and lower gastrointestinal tract may be routes of entry, but only when infective doses are high. Fluorescent studies and virus titer determinations have shown that swine vesicular disease virus has a strong affinity for the epithelial cells of the coronary band of the feet, tongue, snout, lips, lymphoid follicles of the tonsils, myocardial cells, and brain. Secretions and excretions have high viral titers for a period of 12 to 14 days. Feces may contain virus for up to 3 months, but titers are apparently not sufficiently high to transmit disease.

Clinically, vesicles are most common on the feet. Oral lesions occur only in ~10% of affected pigs. The foot lesions appear first at the junction between the heel and the coronary band. Initially, there is a 5.0-mm-wide, pale, swollen area that encircles the digit. A dark red to brown zone 2–3 mm wide surrounds the pale zone on both sides. In later stages a 1.0-cm-wide band of necrotic skin is located along the coronet. Well-demarcated areas of necrosis, resembling superficial abrasions, extend to the metacarpus, metatarsus, and interdigital cleft. Vesicles on the

mouth, lips, and tongue occur in clusters, and they are small, ~2.0 mm in diameter, white, and opaque. They coalesce and rupture within 36 hr and may be covered by a pseudodiphtheritic membrane due to secondary bacterial infections.

The development of vesicles tends to follow a course similar to that reported for foot and mouth disease. The virus infects individual epithelial cells in the stratum spinosum, which leads to focal areas of keratinocyte degeneration and vesicle formation. Frequently, the necrosis involves the entire thickness of the epithelium, including the basal layer. There is an intense leukocytic reaction in the necrotic areas, which is mainly neutrophilic. Spongiosis is less prominent in swine vesicular disease, compared to vesicular stomatitis, although this depends to some extent on the location of the vesicle. Intra- and intercellular edema may be extensive in the snout lesions.

After 1 week there are indications of epithelial regeneration. These consist of an increase in mitotic figures, and long, flat epithelial cells at the periphery of the erosion. In contrast to lesions of foot and mouth disease, which tend to heal in an orderly fashion, in swine vesicular disease long cords of epithelial cells proliferate parallel and perpendicular to the skin surface. A moderate mononuclear-cell reaction and fibroplasia may be evident in the underlying dermis. Necrosis and inflammation involve the external root sheath of hair follicles and the subepithelial glands, especially of the mouth.

The early lesions in the tonsils are characterized by degeneration of the squamous epithelial cells, which are replaced by large droplets of foamy, basophilic, PAS-positive material. The tonsillar crypts are plugged with exudate. Similar changes are found in the inter- and intralobular collecting ducts of the salivary glands and pancreas. There is degeneration and hypertrophy of the renal pelvic epithelium. Foci of necrosis with a mild interstitial mononuclear-cell reaction may be found in the myocardium. There is necrosis and depletion of lymphocytes in most lymphoid tissues.

Nervous signs and lesions have been reported in field outbreaks and reproduced experimentally in swine vesicular disease. The characteristic lesions are those of a nonsuppurative meningoencephalitis involving most areas in the brain. Some reports indicate that the lesions are more severe in the brain stem. Nonviral, intranuclear, amphophilic inclusion bodies may be found in the amphicytes of the Gasserian and dorsal root ganglia.

The minor differences in the distribution and morphology of the lesions in swine vesicular disease, compared with the other vesicular diseases affecting swine, may be of some assistance in the differential diagnosis. However, further laboratory confirmation is necessary. If virus titers in infected tissues used as antigen are sufficiently high, the complement fixation test using vesicular fluid or scrapings from lesions may give results in 4 to 24 hr. Counterimmunoelectrophoresis appears to be the test of choice as a follow-up to a negative complement fixation test, since it is highly specific and produces rapid results. The virus may be isolated in cell cultures of swine origin.

BOVINE VIRUS DIARRHEA. Virus diarrhea, as originally described in New York state in 1946, was an acute, highly contagious disease. The disease still occurs from time to time with these manifestations, but it also occurs sporadically. The fatal cases usually represent one or two severe infections in a group of animals otherwise subclinically affected.

Mucosal disease was described in 1953 in the United States as a disease with a morbidity rate of 2 to 50% and a mortality rate of ~100%. It was characterized by an initial febrile reaction, mucoid nasal discharge, anorexia, constant or intermittent watery diarrhea with feces often containing blood, rapid dehydration, and death. Erosions, ulcerations, and hemorrhages were always found in the alimentary canal.

Infection with bovine virus diarrhea virus results in a spectrum of signs that are compatible with both clinical syndromes: virus diarrhea and mucosal disease. The causative agent of bovine virus diarrhea is an RNA virus belonging to the Togaviridae, genus *Pestivirus*. It is antigenically related to hog cholera virus and the border disease virus. There is only one serotype of bovine virus diarrhea virus. Considerable variation in virulence is apparent among strains of the virus. Both cytopathic and noncytopathic strains may be isolated in tissue culture. Either may be virulent for cattle.

Transmission of the virus is still poorly understood; however, direct contact with clinically affected cattle or carriers and possibly with fomites is probably the main route. Aerosol transmission has been documented experimentally. A high prevalence is associated with the wide use of modified live virus vaccines.

After inoculation there is a viremia with a marked leukopenia. Fluorescent-antibody studies show that the virus infects a wide variety of tissues, including squamous epithelial cells of the upper alimentary tract and the interdigital area of the feet, glandular and cryptal epithelial cells of the lower alimentary tract, epithelial cells of the respiratory tract, and endothelial cells of submucosal vessels in the gut and several other organs. The virus has an affinity for lymphoid tissue, especially in the tonsils and Peyer's patches. Neurons, glomerular cells, and epithelial cells of renal convoluted tubules may be infected under certain conditions.

The virus may cross the placental barrier in pregnant animals. Depending on the stage of gestation, it may cause abortion, fetal mummification, or a wide spectrum of teratogenic lesions, including microencephaly, cerebellar hypoplasia and dysgenesis, hydranencephaly, hydrocephalus, and defective myelination of the spinal cord. Ocular lesions, such as microphthalmia, cataracts, retinal degeneration, atrophy and dysplasia, and optic neuritis, have all been associated with fetal infections by the virus (see the Nervous System, Volume 1). In addition, lesions of the alimentary tract similar to those seen in older animals may occur in fetuses and neonatal calves.

A condition in lambs, termed border disease, which is characterized by a hairy fleece, clonic rhythmic tremors, and unthriftiness, has been associated with prenatal infection by a togavirus that has a strong antigenic relationship to bovine virus diarrhea and hog cholera viruses. Affected animals are termed "hairy shakers" (see the Skin and Appendages, and the Nervous System, Volume 1).

All virulent strains of virus produce the same sort of experimental disease in susceptible calves. A slight fever with leukopenia at the third day is followed by a second phase of higher fever and more severe leukopenia at about the seventh day. At

the end of this second, febrile phase oral hyperemia with some erosions may develop, and perhaps slight diarrhea. The severe fatal disease has seldom, if ever, been produced by experimental transmission.

These observations emphasize that the natural disease is usually very mild, or infection is commonly inapparent. It is also very widespread, as indicated by serologic surveys. Severe clinical or fatal cases are exceptional in spite of their apparent prevalence. When acute cases occur in a herd, it is usual that many other animals show the mild disease. The mildly affected may develop substantial levels of neutralizing antibody, while those severely affected tend not to. While deaths may occur within 1 or 2 days of illness and almost always within 2 weeks, some cases remain clinically affected for months. The failure of immunogenic response may be associated with immunotolerance or destruction of immunocompetent cells, which is reflected in lymphopenia. In addition to a lack of humoral antibody response, there is also depression of cell-mediated immunity, as indicated by a poor response of cultured peripheral lymphocytes to various mitogens. Animals with deficient humoral and cell-mediated immunity ultimately die. There may also be impairment of polymorphonuclear-cell function in cattle infected with bovine virus diarrhea virus, which may explain in part the observation that such cattle are susceptible to secondary bacterial infections.

Acute fulminant bovine virus diarrhea closely resembles rinderpest. The onset is febrile, with serous to mucoid nasal discharge. Discrete oral lesions are preceded by an acute catarrhal stomatitis and pharyngitis, the mucosae being hyperemic and pink and covered by a thin, gray film of catarrhal exudate. White necrotic foci 1–2 mm in size, surrounded by a margin of hyperemia, then appear on the muzzle and the buccal mucosa. These erode or ulcerate and expand irregularly; the margins remain fairly discrete, except for those on the soft palate and pharyngeal mucosa. There is severe diarrhea and tenesmus, with feces containing little or no blood or mucus. Animals may die quickly.

The more chronic cases also begin with fever and serous nasal discharge. The nasal discharge becomes more mucinous in a couple of days and dries on the muzzle, causing excoriation. The temperature returns to normal in 2 to 5 days, and then oral lesions and a watery diarrhea develop. These animals remain alert. The development of the oral lesions is like that found in acute cases; by the time chronic cases die, however, there is usually some evidence of healing. The watery diarrhea of the early phase gradually gives way to feces that are passed frequently, are scant in volume, and contain a large proportion of mucus flecked with blood. Late in the clinical course, there is lethargy, emaciation, ruminal stasis, and frequent attempts at defecation accompanied by severe tenesmus. Interdigital dermatitis affecting all four feet may be present in chronically affected animals. In these, the skin is dry and scurfy, especially over the neck, withers, and back, and that on the medial aspect of the thighs and forelegs and in the perineal region becomes moist and discolored a dirty yellow with encrustations.

The gross lesions vary considerably, especially in the acute disease, in which either upper alimentary or intestinal lesions may be absent, and less so in the chronic disease, in which a broader pathologic picture is often present, perhaps partially obscured by healing or evolution of lesions.

Erosions and shallow ulcers are present on the muzzle and nares of many affected cattle. The anterior edges of the lower lip and its cutaneous junction are similarly affected. A similar loss of epithelium from much of the oral cavity is common. Diffuse hyperemia of the mucosa may persist after death. The most conspicuous oral erosions are on the palate, on the tips of the buccal papillae and on the gingiva. Many, especially on the papillae and in the pharynx, are ulcers and expose a denuded, intensely hyperemic lamina propria. The tongue is not always affected. When present, lesions may be evident on all surfaces (Fig. 1.21A,B). Those on the smooth lateral surfaces are typically erosive and irregular, although in some early cases the degenerate epithelium may remain attached, to form flat, white plaques that may be scraped off. On the anterior half of the dorsum, the degenerate epithelium may accumulate and develop deep, irregular crevices and pits, or ulcerate to denude the greater portion of the surface.

In some cases the oral lesions are sharp, punched-out ulcers. These occur on the dental pad, palate, ventral and lateral surfaces of the tongue, the gums about the incisors, and the inside of the cheeks and pharynx. In some lesions of longer duration, the defect is filled in from the margin by thickened white proliferative epithelium.

Esophageal lesions are usually present. They are common in the upper third of the esophagus. In some acute cases, the lesions are shallow erosions rather than ulcers. The erosions are more or less linear but otherwise irregular, have a dirty brown base, and little or no reactive hyperemia (Fig. 1.21C). Shreds of adherent necrotic epithelium give the surface a rough, worn, tattered appearance in animals that have not been swallowing. In more advanced cases, discrete ulcerations occur. In many chronically affected animals, the ulcers begin to heal and appear as yellowish white, slightly elevated plaques of proliferative epithelium at the periphery of the mucosal defect.

Lesions are found in the rumenoreticulum and omasum, but not in the esophageal groove. The ruminal content in chronically affected animals with prolonged anorexia is usually scant and dry. The surface of the ingesta is frequently blackened, and the villi of the ruminal wall are thick, black, and dry. In most acute cases the ruminal content is usually liquid and putrid. The lesions on the wall of the rumen resemble those present elsewhere in the upper alimentary tract, and although they occur anywhere, they are best seen on the pillars and other smooth or nonvillous portions of the mucosa (Fig. 1.21E). The omasal lesions are most numerous along the edges of the leaves, sometimes causing a scalloped margin or perforation.

The morphogenesis of the lesions in the squamous mucosa of the upper alimentary tract begins with necrosis of the epithelium (Fig. 1.21D). Individual cells and groups of cells deep in the epithelium are eosinophilic and swollen, with pyknotic nuclei. These foci enlarge progressively and form areas of necrosis that extend to, and may involve, the basal layer. In the early stages there is little or no inflammation of the lamina propria, but leukocytes infiltrate the necrotic epithelium. These small necrotic foci are elevated above the surface and form the friable

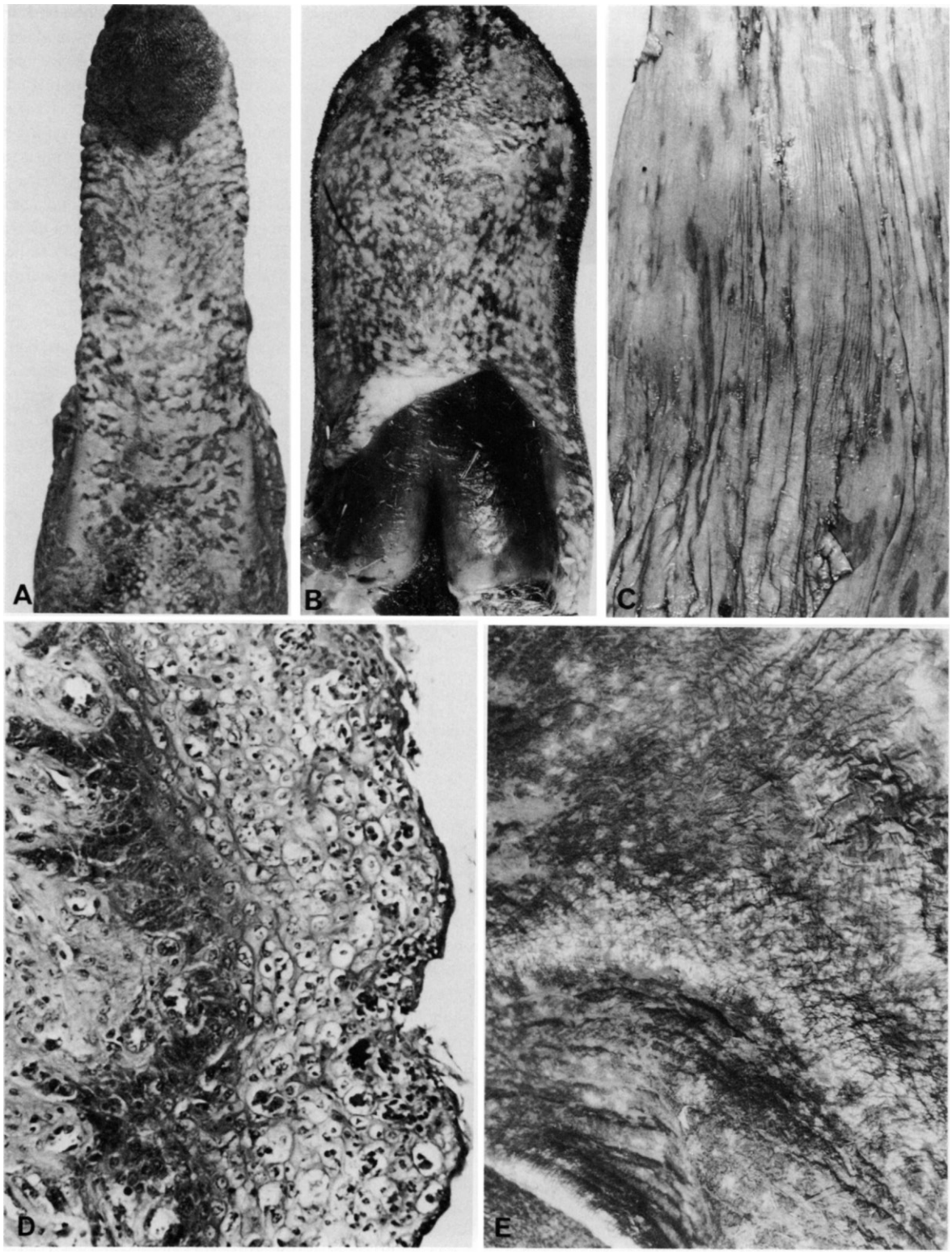


**Fig. 1.21.** Bovine virus diarrhea. (**A**) Dorsal and (**B**) ventral surface of tongue, showing multiple confluent ulcers. (**C**) Longitudinal erosions and ulcers on the esophagus. (**D**) Histologic appearance of esophageal lesion. (**E**) Focal and confluent lesions of dorsal sac of rumen.

plaques described earlier on the squamous mucosae. They enlarge progressively and by coalescence, and may form small cleavage vesicles along the proprial–epithelial junction (Fig. 1.23A). If the necrotic epithelium is abraded, erosions and ulcers develop.

The ulcerations of the squamous epithelium of the upper alimentary tract are accompanied by inflammation in the lamina propria, especially where this forms papillae (Fig. 1.23B). Capillaries are congested, the lymphatics are dilated, there is edema of the stroma, and a pleocellular inflammatory infiltrate is present. Focal hemorrhages may occur.

Changes are regularly present in the abomasum. The sides of the rugae bear what appear grossly to be ulcers, which may be punctate to 1.0 cm or more in diameter (Fig. 1.22A). They are lesions with raised margins and a distinct pale halo; there may also be some peripheral hemorrhage. The histologic changes in the glandular epithelium of the abomasum are characterized by epithelial necrosis, mainly in the depths of the glands. The necrotic cells fragment and slough and may cause dilation of affected glands. The mucosa is locally infiltrated by a variety of leukocytes and is edematous. In some affected foci, the glandular epithelium loses its differentiated appearance, becoming cuboidal, basophilic, and apparently mucus secretory. These glands too may be dilated with a small quantity of contained epithelial and leukocytic debris. In some abomasa, mucous metaplasia may be patchy but widespread and may reflect inflammation in the mucosa. There is some edema, hemorrhage, and modest leukocytic infiltration of the submucosa. Some necrotic foci in the abomasal glands appear to be associated with necrosis of adjacent mucosal lymphoid follicles.

The mucosa of the small intestine often appears normal over much of its length. There may be inspissated mucoid material in the lumen. In some cases the mucosa of the small intestine may have patchy or diffuse congestion. In rare cases, fibrin casts may be in the lumen of the small bowel. The wall is atonic but not dilated and may be greatly thickened by submucosal and subserosal edema, which may give a ground-glass appearance to the serosal surface.

In acute cases, it is usual to find coagulated blood and fibrin overlying and outlining Peyer's patches, the covering of which is eroded. This, when present, is a very distinctive lesion that is paralleled only in rinderpest. Severely affected Peyer's patches are often obvious through the serosa as red-black oval areas up to 10 to 12 cm long on the antimesenteric border of the gut (Fig. 1.22B). Less acutely affected Peyer's patches may be overlain by a diphtheritic membrane, while in milder or more chronic cases the patches may be depressed and covered by tenacious mucus. In chronic cases, exudate may not be evident over Peyer's patches, which become less obvious or sunken, resembling an ulcer. Mesenteric lymph nodes are usually not enlarged.

Lesions in the large bowel are highly variable. The mucosa may be congested, often in a "tiger stripe" pattern following the colonic folds. In acute cases there may be fibrinohemorrhagic typhlocolitis (Fig. 1.22D). In more chronic cases, fibrinous or fibronectrotic lesions and focal or extensive ulceration may be present at any level of the large bowel, but particularly in the cecum and rectum.

The characteristic lesion in the intestinal mucosa is destruction of the epithelial lining of the crypts of Lieberkühn. In the duodenum, a few glands only are affected, but more glands are affected more severely in the lower reaches of the small intestine and in the cecum and colon. Affected glands are dilated and filled with mucus, epithelial debris, and leukocytes. Remaining crypt-lining cells are attenuated in an attempt to cover the basement membrane. Reparative hyperplasia of crypt lining is rarely encountered. Crypt dropout may be evident microscopically. In the cecum and colon, extensive damage to crypts and attendant collapse of the lamina propria is the probable cause of ulceration seen grossly (Fig. 1.22E). Congestion of mucosal capillaries, and in acute or ulcerated cases, effusion of fibrin and neutrophils from the mucosal surface, may be evident.

The microscopic lesions of Peyer's patches are distinctive in bovine virus diarrhea, comparable lesions being caused only by rinderpest (Fig. 1.22C). In the acute phase of the disease, severe acute inflammation in the mucosa over Peyer's patches accompanies almost complete destruction of the underlying glands, collapse of the lamina propria, and lysis of the follicular lymphoid tissues. Later in the course of the disease, dilated crypts lined, at least in part, by cuboidal epithelium and filled with necrotic epithelial cells, mucus, and inflammatory cells appear to herniate into the submucosal space previously occupied by involuted lymphoid follicles. Peyer's patches should be sought assiduously at autopsy since their gross and microscopic appearance may provide useful evidence for diagnosis.

An important microscopic lesion, which may have been previously overlooked, is hyaline degeneration and fibrinoid necrosis of submucosal and mesenteric arterioles (Fig. 1.23C). A mild to moderate mononuclear inflammatory cell reaction is frequently present in the walls of the vessels and in perivascular areas. The vascular lesions are not limited to the intestine but may be present in a variety of other organs such as the heart, brain, and adrenal cortices, which may make it difficult to differentiate the disease from malignant catarrhal fever. The vascular lesions in bovine virus diarrhea are less consistently present and usually are milder.

In the acute disease, the lymph nodes of the head and neck are often enlarged and discolored reddish black by congestion and hemorrhage. Microscopically, the mesenteric lymph nodes show a diminished population of lymphocytes and necrosis of germinal centers. Similar lesions may be seen in the splenic lymphoid follicles, but they are not consistent and are difficult to interpret.

Coronitis may extend completely around the coronary band, with some separation of the skin–horn junction causing disturbance and overgrowth of the horn (Fig. 1.23D). Dermatitis may extend from the coronet up the back of the pastern. Milder dermatitis is generalized, with scurfiness especially from the ears to the withers. In sections of the skin of animals with virus diarrhea there are focal accumulations of necrotic epithelium, with intense hyperemia of the adjacent superficial dermis. The epithelial lesions are basically similar to those in the squamous mucosa of the upper alimentary tract (Fig. 1.23E). Necrosis often extends deeply to or through the basal layers; it results in minute erosions or ulcerations. These deeper lesions occur in the inner aspects of the legs and the perineum, and there is an exudation of serum in these areas. In chronically affected animals,

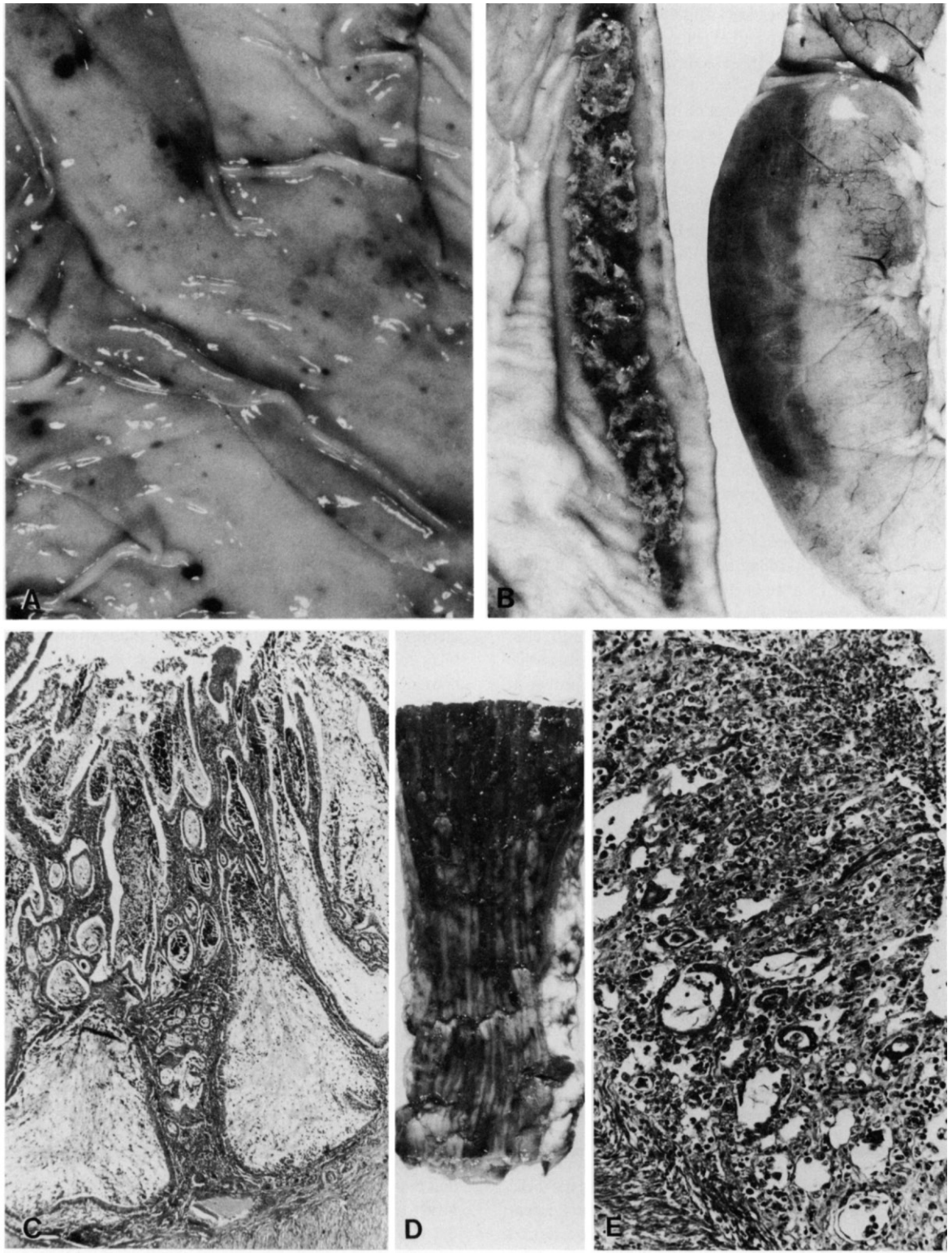


**Fig. 1.22.** Bovine virus diarrhea. (**A**) Hemorrhage and ulceration. Abomasum. (**B**) Fibrinohemorrhagic exudate over Peyer's patch in the ileum (left). Deep red Peyer's patch visible through serosa of small intestine (right). (**C**) Herniation of crypts of Lieberkühn into the submucosa, replacing necrotic lymphoid follicles in Peyer's patch. Mucus and inflammatory exudate is in the cystic glands and on the surface of the mucosa. (**D**) Fibrinohemorrhagic colitis. (**E**) Colon. Dilated and denuded glands, collapse of lamina propria, and pseudomembrane formation.

basal hyperplasia occurs in the skin. The overlying degenerate epithelium becomes disorderly and eventually is lifted off.

Some animals with chronic disease develop mycotic infections secondary to lesions in the forestomachs, abomasum, and Peyer's patches. The lesions are areas of hemorrhagic necrosis involving the mucosa, submucosa, and sometimes deeper layers of the wall. Fungal hyphae are found invading the stroma and causing thrombosis in venules.

Abortion in the acute febrile stage or in convalescence occurs in virus diarrhea. Enteric lesions of the disease may be observed in the fetus. Punctate hemorrhages with ulcers 1–3 mm in diameter may be profuse in the oral cavity, excepting the dorsum of the tongue, and in the esophagus, larynx, trachea, conjunctiva, and abomasum. The fetal lesions of squamous epithelium evolve in somewhat the same manner as those described above, with focal hemorrhages in the lamina propria and epithelial necrosis beginning in the basal layer.

More recently, a syndrome of inapparent persistent infection by the virus has been recognized. Virus is present in a variety of tissues and body fluids, but serum neutralizing antibodies are absent. These animals may be chronic shedders of virus and are an important source of infection for other animals. Although they do not show any evidence of infection clinically, they have microscopic lesions in the kidney and brain. The renal lesions consist of diffuse and focal thickening of the basement membranes of the glomerular tufts. There is an increase in mesangial cells. Fluorescent-antibody tests show antigen in glomeruli, epithelial cells of convoluted tubules, and endothelial cells in the interstitial blood vessels. The glomerular lesions are probably due to deposition of antigen–antibody complexes on the basement membrane.

Antigen is also present in the neurons, especially of the cerebral cortex. The neurons are pyknotic, and there is astrocytic and lymphocytic neuronal satellitosis. A few vessels are mildly cuffed by lymphocytes and have hypertrophic endothelial cells. The neuronal changes are probably due to direct action of the virus. Antigen is present in many other tissues that do not have microscopic lesions, such as vascular endothelial cells in many organs, mononuclear cells of the spleen, mesenteric and mediastinal lymph nodes, and cryptal epithelial cells. It has been suggested that the lack of serum neutralizing antibodies in these cattle is due to formation of antigen–antibody complexes in the kidney and other tissues.

Confirming a diagnosis of bovine virus diarrhea is often difficult. The wide variety in signs and lesions, coupled with inconsistent and often negative virologic and serologic results, can be a challenge to most diagnosticians. It is therefore important that clinical and pathologic findings should be supported by laboratory tests, including fluorescent-antibody techniques, and virus isolation. Spleen and Peyer's patch should be collected for these purposes. Serologic tests, preferably on acute and convalescent serum samples from several animals in a herd, should be carried out. Bovine virus diarrhea resembles rinderpest, thus it is important to confirm the diagnosis. Other diseases that must be differentiated include the vesicular diseases, malignant catarrhal fever, systemic infectious bovine rhinotracheitis, salmonellosis, and coccidiosis. The triad of erosive–ulcerative upper alimentary lesions, cryptal necrosis in large or small intestine, and lesions of Peyer's patches provides a presumptive diagnosis of bovine virus diarrhea on morphologic grounds, in areas where rinderpest does not occur.

RINDERPEST. Otherwise known as "cattle plague," rinderpest is an acute, highly contagious disease of cattle characterized by erosive or hemorrhagic lesions of all mucous membranes. It is now enzootic in tropical Africa, the Middle East, and the Orient, to which places it is restricted by sanitary precautions. Unfortunately, the long and interesting history of its pandemic plunges across continents cannot be followed here.

The virus that causes rinderpest belongs to the Paramyxoviridae, genus *Morbillivirus*. It has a single-stranded RNA genome and is antigenically and morphologically closely related to the viruses causing canine distemper and human measles (rubeola). The three viruses have immunologically identical nucleocapsids and shared envelope antigens. The virus is highly fragile under ordinary environmental conditions; it is incapable of surviving more than a few hours outside the animal body under normal circumstances. The agent is readily adapted to the chorioallantoic membrane of the developing chick embryo and can be adapted to rabbits, although strains differ in the ease with which this is accomplished. Once adapted, the virus causes fever and characteristic grayish white, granular necrotic patches in the intestinal lymphoid tissue. Goats and sheep do respond, but inconsistently, to artificial inoculation, although their susceptibility to rinderpest in the field is unclear. Probably all cloven-hoofed animals are naturally susceptible to infection, but the expression of infection varies considerably.

The virus of rinderpest is antigenically uniform and, when suitably modified, is an effective vaccine. Control of the disease in endemic areas is impeded by difficulties inherent in systems of husbandry and in the coexistence of cattle with large populations of susceptible ungulate wildlife. The lability of the virus is such that the spread of infection from endemic areas is most likely to be by live animals with mild or subclinical disease.

The disease in cattle may be mild, especially in endemic areas, but probably will be acute or peracute in new foci. The different degrees of severity are in part due to real differences in virulence of strains, and largely due to differences in susceptibility of breeds or races of cattle. Such variations are well documented and apply also to modified vaccine strains, which although quite safe in some breeds of cattle cause high mortality in others.

The upper respiratory tract appears to be the main portal of entry in spontaneous cases of rinderpest. The virus localizes in the palatine tonsils and regional lymph nodes. This is followed after a 10- to 15-day incubation by a 2- to 3-day period of viremia that coincides with the fever seen clinically. In circulation, the virus is located mainly in lymphocytes. After the viremic stage, the virus replicates in all lymphoid tissues, the bone marrow, and the mucosa of the upper respiratory tract and the gastrointestinal tract. Nasal and oral secretions and the feces contain high titers of the virus. In general, excretion of virus ceases by about the ninth day of the clinical disease. Recovered animals do not appear to be carriers.

Fever and its attendant signs usher in the clinical syndrome

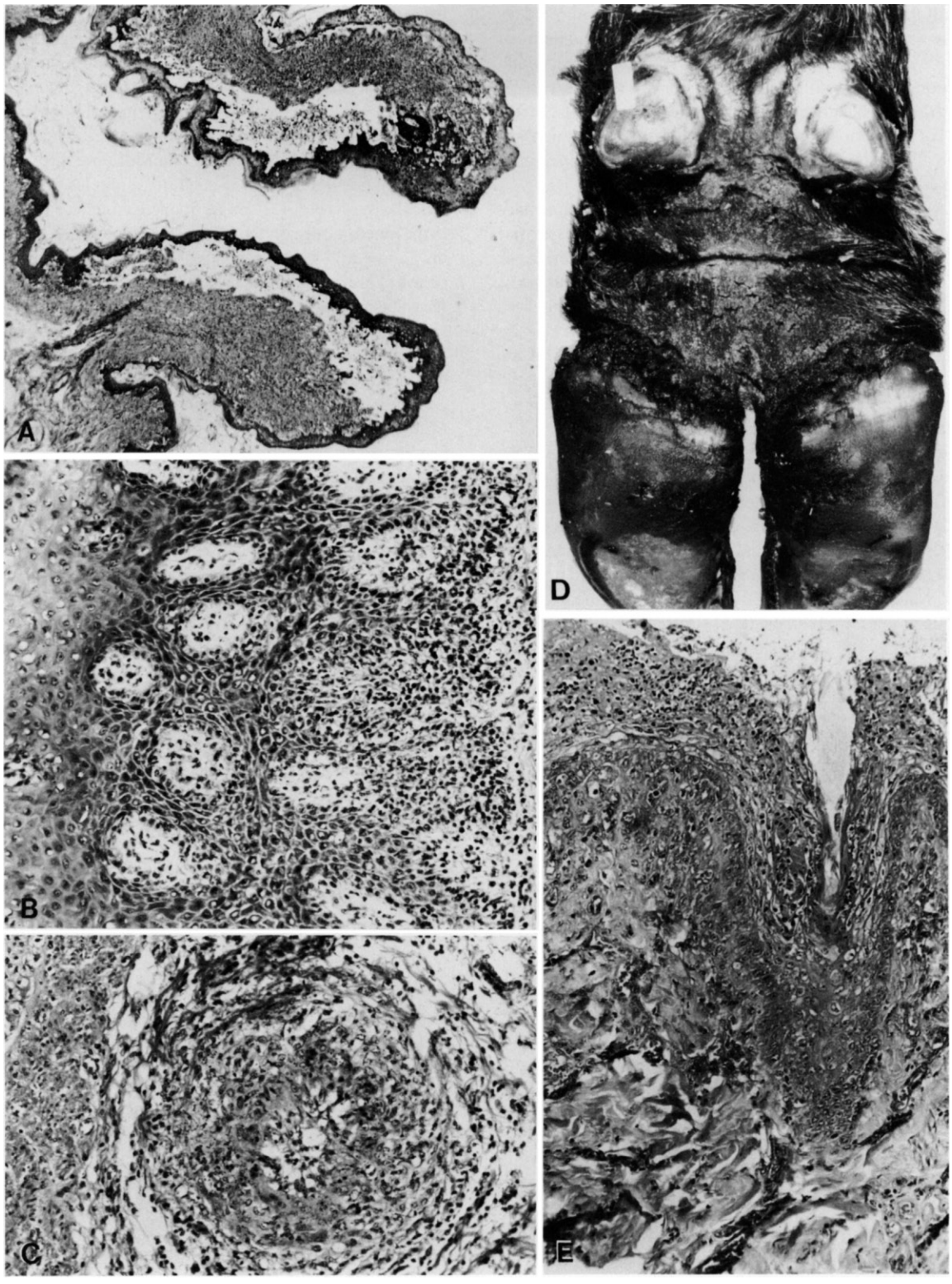


**Fig. 1.23.** Bovine virus diarrhea. (**A**) Cleavage vesicles in rumen papillae. (**B**) Early lesion. Edema of proprial papillae and acute focal inflammation of papilla and propria. There is necrosis of scattered cells deep in the epithelium. (**C**) Fibrinoid necrosis and mild periarteritis of a mesenteric arteriole. Colon. (**D**) Coronitis and erosive–ulcerative dermatitis of pastern. (**E**) Skin. Superficial epidermal necrosis extending into hair follicle. Hyperplasia of the stratum germinativum.

with early leukopenia. Fever reaches its maximum in ~3 days and falls with the onset of diarrhea. There is severe abdominal pain, tachypnea, occasional cough, severe dehydration and emaciation, and prostration. Death occurs in 6 to 12 days.

The gross morbid anatomic changes in rinderpest are characteristic but not pathognomic and are identical with bovine virus diarrhea. The lesions in the upper alimentary tract are necrotizing and erosive–ulcerative.

The virus of rinderpest has an affinity for the alimentary epithelium, which it gains hematogenously. Oral lesions are not invariably present. The oral lesions typically involve the inner side of the lower lips, the buccal papillae at the commissures, and the ventral surface of the free portion of the tongue. In severe cases, however, all mucous surfaces of the mouth may be involved, with the regular exception of the dorsal surface of the tongue. Esophageal erosions are usually mild and affect the anterior portion. The forestomachs rarely exhibit any lesions. When they do occur, the omasal leaves are involved.

The lesions of stratified squamous epithelium originate in the basal layer. A few and then many epithelial cells undergo necrosis, the nuclei become pyknotic and fragmented, and the cytoplasm coagulated and eosinophilic, but true vesicles do not develop. Multinucleate syncytia form in the epithelium (Fig. 1.24A–C). The necrotic foci produce, initially, white pinpoint papules. Natural movements cause the necrotic tissue to lift off and produce shallow erosions. This occurs so readily that erosions are usually the first lesions observed. Their margins are sharp, and the bases are reddened by the underlying congested capillaries. The initial minute erosions enlarge and coalesce to form extensive defects. Ulceration may supervene.

The abomasum is usually involved in this disease, its pyloric mucosa most consistently and severely. The lesions of the fundus are linear on the margins of the mucosal folds, and in the pylorus they are more rounded. The mucosa becomes necrotic and grayish in affected foci and then sloughs, leaving sharply marginated irregular erosions, the bases of which are intensely hyperemic and ooze blood. Ulcerations sometimes occur. There is usually a profuse submucosal edema that thickens the fundic plicae.

Lesions in the small intestine are less severe than those elsewhere but are of the same general character, streaks of congestion and erosion developing on the margins of mucosal folds. They are best developed in the upper duodenum and in the ileum. The ileocecal valve and surrounding cecal mucosa are congested and eroded. The linear lesions of the mucosal folds are well developed in the cecum and colon. Occasionally, the red foci are so numerous as to appear as diffuse hemorrhage, although they are, in reality, severely congested vessels of the lamina propria. The colon and rectum are more severely affected as a rule than the rest of the enteric mucosa.

The Peyer's patches and other gastrointestinal lymphoid follicles, especially at the cecocolic junction, become necrotic (Fig. 1.24D), and this may be extensive enough to cause necrosis of the overlying mucosa, leaving lesions resembling deep ulcers.

Microscopically, the cryptal epithelium in the small intestine may become necrotic, and syncytia may form in crypts. Associated villi may be somewhat atrophic. Small hemorrhages occur from the intensely congested blood vessels. There is diffuse edema of the submucosa, but little leukocytic infiltration.

The rinderpest virus is tropic for lymphoid tissues. Necrosis of lymphocytes is extreme, but gross inspection, which reveals little abnormality except of nodes, is misleading. There is no hemorrhage or inflammation of lymph nodes. The necrosis begins in the germinal centers and proceeds until virtually all mature lymphocytes are lost in individual follicles, leaving only a reticular mesh (Fig. 1.24E). Multinucleate cells, similar to those in the mucosa, form in the lymph and hemolymph nodes. All or only some follicles may be involved, and there is often an increase of other leukocytes in the sinuses. Similar lesions occur in the spleen, tonsils, and as already noted, in the Peyer's patches.

Petechiae are common in the upper respiratory mucosae, and small erosions may develop on the larynx. Hemorrhages beneath the epicardium and endocardium are common but nonspecific, and there may be mild nonspecific myocardial degeneration. Mild erosive lesions develop in the mucosa of the bladder and vagina. Acute congestion and edema of the conjunctiva may be followed by purulent conjunctivitis and corneal ulceration. Skin lesions have been described, especially in buffalo, but are considered rare. A moist eczematous lesion of the udder, scrotum, inner aspect of thighs, neck, and flank may develop. Animals with such lesions usually die, but if recovery occurs, the dried scabs of exudate peel off, removing the superficial epithelium and hair.

The lesions of rinderpest can only provide a presumptive diagnosis. Confirmation of the diagnosis requires detection of antigen by immunodiffusion, using infected tissue such as lymph node; virus isolation and identification in bovine cell culture systems; and serologic tests such as virus neutralization and complement fixation. The virus may be isolated from unclotted blood, especially from the buffy coat, lymph nodes, and spleen, collected during the febrile and early erosive stages of the disease. Cellular syncytia and intranuclear and intracytoplasmic inclusion bodies occur in epithelial and lymphoid tissues and perhaps are found more easily in the tonsils than elsewhere. The presence of these may assist in differentiating rinderpest from bovine virus diarrhea on morphologic grounds.

PESTE DES PETITS RUMINANTS. *Peste des petits ruminants* (*kata*, stomatitis pneumoenteritis complex) is a disease of sheep and goats in west Africa that closely resembles rinderpest. The causative agent is closely related to rinderpest virus, with which it shares common antigenic determinants. The virus cross-reacts with rinderpest virus in the immunodiffusion and complement fixation tests. It does not infect cattle through contact; however, experimental infection stimulates antibody formation in cattle that is protective against challenge with rinderpest virus. Infection of sheep and goats with rinderpest virus will protect them against the *peste* virus. The clinical signs and lesions of the disease in sheep and goats are similar to those of rinderpest, except that the disease is more acute in onset, especially in goats, and follows a more rapid course.

MALIGNANT CATARRHAL FEVER. Malignant catarrhal fever (malignant head catarrh, *snotsiekte*) is of worldwide distribu-

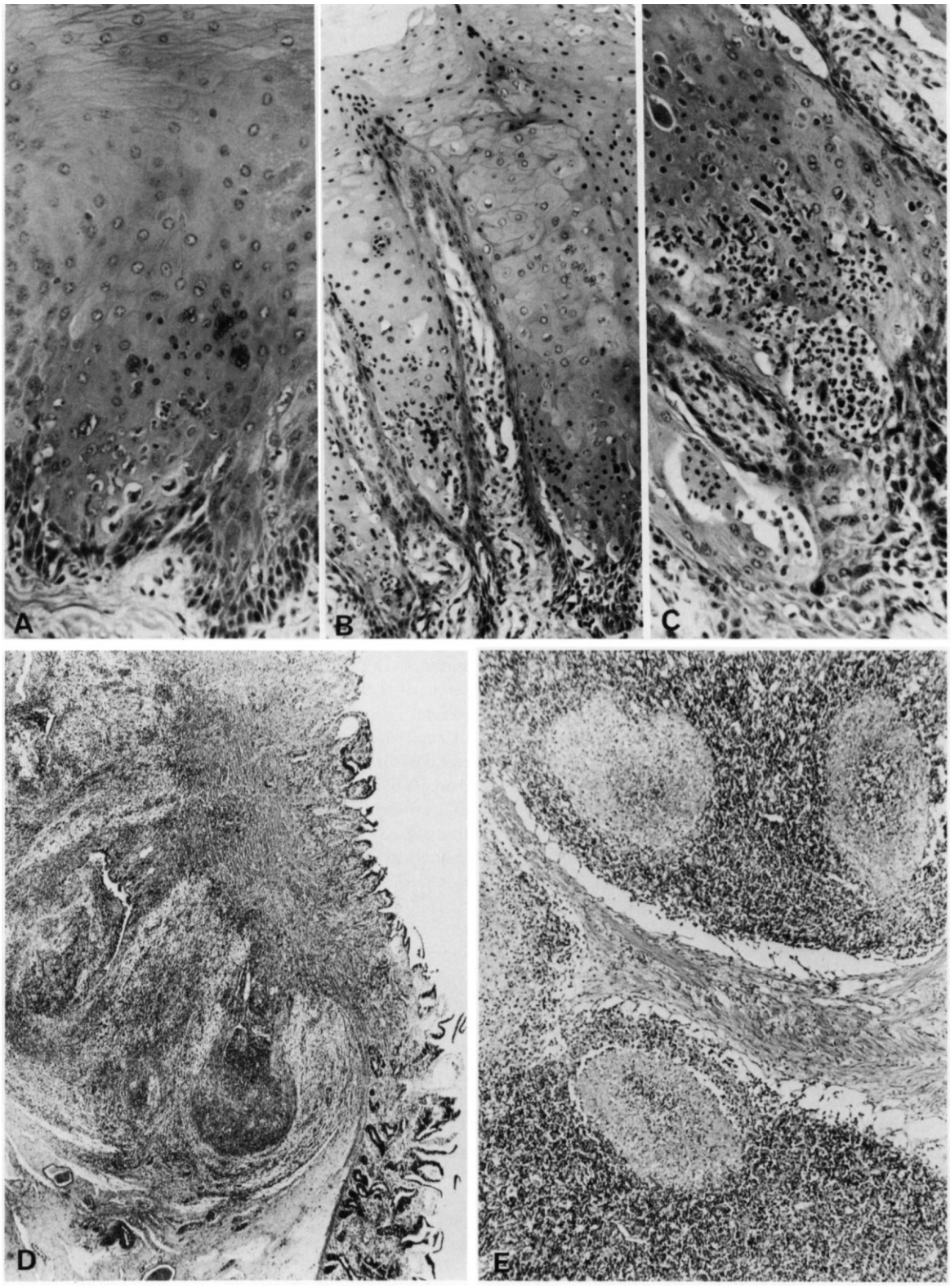


**Fig. 1.24.** Rinderpest. Ox. (AFIP 625840.) (**A**) Early stage of oral lesion, showing disorganization of epithelium above the basal layer and formation of syncytial cells. Tongue. (**B** and **C**) Slightly later stage, with beginning separation sparing basal cells. (**D**) Necrosis of Peyer's patch. Ileum. (**E**) Necrosis of germinal centers. Lymph node. (AFIP 623162.)

tion. It is generally sporadic in occurrence, although severe herd outbreaks have been reported in feedlot, dairy, and range cattle and zoo animals, mainly several species of deer, and bison. Other susceptible species of ungulates include banteng and greater kudu. Mortality usually reaches 100%, and although transmissible, it is apparently not contagious among cattle by direct contact. There are two forms of the disease: the African form, which occurs in cattle associated with wildebeest, and the sheep-associated form, which occurs in many other countries. The cause has only been determined for the African form of the disease. The cause of the sheep-associated form of malignant catarrhal fever has never been determined, in spite of numerous attempts. The diseases are clinically and morphologically very similar. Rabbits are susceptible to experimental inoculation with infective material from cattle affected with the African form of the disease. In these animals, lesions similar to those seen in cattle are produced.

The cause of the African, wildebeest-derived form of malignant catarrhal fever is an apparently cell-associated herpesvirus belonging to the alcelaphine herpes group. The cytopathic effect in calf thyroid monolayers is characterized by formation of intranuclear basophilic (Cowdry type A) inclusions and syncytia. Serial culture requires the transfer of cells because free virus is not present in the culture fluids. Freezing of infected tissues destroys most of the virus; however, infected tissue cell cultures can be stored at −70°C.

The cause of the sheep-associated form of malignant catarrhal fever is not known. A herpesvirus, morphologically and immunologically similar to that causing the African form, has been identified in cell cultures infected with material from an outbreak of malignant catarrhal fever in dairy cattle in Minnesota. Experimental inoculation of cattle with this virus failed to induce clinical disease. Cattle immunized with this agent survived a challenge with lethal doses of the virulent African strain. Several cell-associated polykaryon-forming viral agents, including a morbillivirus, have been recovered from cattle affected with malignant catarrhal fever in the United States. The significance of these isolates is not known. None of these isolates was related to the herpesvirus of the African form of malignant catarrhal fever.

The mode of natural transmission of malignant catarrhal fever is not known. Experimentally, the disease can be transmitted with large quantities of whole blood and lymphoid tissue, but not by cell-free filtrates. This indicates that the agent is cell associated, probably with lymphocytes. This virus is present in nasal secretions in wildebeest, and this may be important with regard to transmission to cattle, since steers have been infected experimentally via the respiratory route.

The incubation period of malignant catarrhal fever is 2–8 weeks but may on occasion be much longer than this. Initially, there is high fluctuating fever and depression. There is usually enlargement of the superficial lymph nodes, which may be readily visible. There is edema of the eyelids and conjunctivae and congestion of the nasal and buccal mucosae. There is copious lacrimation; nasal discharge dries on and excoriates the nasolabium and partially obstructs the nares. The conjunctivitis is accompanied by an increasing rim of opacity at the filtration angle, and later, the aqueous humor may become opaque. Corneal edema and ulceration occur in some cases, but in those that die quickly the infiltration of the filtration angle may be all that is seen, and this is easily overlooked.

The clinical picture may be divided into four forms, namely, the peracute, the intestinal, the head and eye, and the mild. There is considerable overlap in the syndromes observed. The naturally acquired disease is usually fatal. In the peracute form, there is hyperthermia and hemorrhagic gastroenteritis. The clinical course is 1–3 days. The intestinal form is characterized by fever, diarrhea, diffuse exanthema, lacrimation, and enlargement of lymph nodes. The course is 4–9 days. The head and eye form is of slightly longer duration, and in addition to the above, there are nervous signs. This is the typical clinical syndrome. The mild form is an occasional experimental phenomenon and may be followed by recovery.

Gross morbid changes may not be present in animals that die of peracute malignant catarrhal fever, and in these the diagnosis must rest on the detection of the characteristic histologic changes and positive results of transmission experiments. With the sheep-associated disease, diagnosis is based usually on the microscopic findings. Bearing in mind the wide variation in the development and severity of lesions, the changes described below are what one hopes to see in any case.

The carcass is dehydrated and may be emaciated if the course has been prolonged. There is a mucopurulent conjunctivitis, which may glue the edematous eyelids together. The muzzle and nares are heavily encrusted and, if wiped, reveal irregular raw surfaces, although in some cases there may only be a slight serous discharge. Cutaneous lesions are common but often overlooked. There may be, acutely, a more or less generalized vesicular and papular exanthema, with sufficient exudation to wet and mat the hair and to form detachable crusts; in unpigmented skin there is obvious hyperemia. In due course, the crusts become 1.0 mm or more in thickness, and there is patchy loss of hair. Sometimes these cutaneous changes begin locally about the bases of the hooves and horns and on the loin and perineum and remain localized or become generalized.

The respiratory system may show minor or severe lesions (Fig. 1.26A). When the course is short, the nasal mucosa may show congestion and slight serous exudation only. Later, there is a copious discharge. The mucosa is then intensely hyperemic and edematous, and erosions of a few millimeters diameter are common. These are irregular in shape, with a hemorrhagic base. Occasionally, dirty brown pseudomembranes form, and if these are removed, raw surfaces remain. Lesions of severity similar to those on the septum and turbinates may develop in the sinuses. The pharyngeal and laryngeal mucosae are hyperemic and swollen and later develop multiple erosions or ulcerations and are often covered in part by grayish yellow pseudomembranes. The tracheobronchial mucosa is hyperemic and usually petechiated, but ulceration may occur, and in a small percentage of cases a pseudomembranous tracheobronchitis is present (Fig. 1.26B). The lungs are usually edematous and emphysematous, but in peracute cases they may appear perfectly healthy. A nonspecific bronchopneumonia may complicate chronic cases.

The alimentary mucosae may show no significant lesions in the peracute disease. Minor erosions are first observed on the lips adjacent to the mucocutaneous junction. Sometimes appar-

ently normal epithelium on the surface of the tongue peels off in sheets (Fig. 1.25C). Later, erosive and ulcerative lesions may involve a large area of oral mucosa (Fig. 1.25A), occurring especially on all surfaces of the tongue, the tips of the buccal papillae, gingivae, both divisions of the palate, and the cheeks. In some areas, the cheesy or tattered necrotic epithelium may not be sloughed at the time of inspection. Esophageal erosions, similar to those that occur in the other diseases causing ulcerative stomatitis, occur in malignant catarrhal fever and, as in rinderpest, are most consistent in the anterior portion. Lesions of the same sort are revealed in the forestomachs by careful examination. The abomasal mucosa is hyperemic and edematous, diffusely or in patches, and sprinkled with petechiae. Hemorrhagic ulcerations may be present, especially on the margins of the plicae and along the greater curvature. The wall of the small intestine is firm and thickened by edema. Its serosa is dull, very finely granular, and often peppered with fine petechiae. Its content is mucoid or hemorrhagic. The mucosa is thickened and has few or many petechial hemorrhages and minor erosions. Similar lesions occur in the large intestine and rectum but are more obvious; there are lines of congestion along the longitudinal mucosal rugae, and severe ulceration and hemorrhage may be present. The contents of the large intestine are scant and may be dry and pasty or bloody.

Rather characteristic lesions may occur in the urinary system. Renal changes are not always present. They are infarcts or 2- to 4-mm foci of nonsuppurative interstitial nephritis (Figs. 1.25D and 1.27A). They may be numerous enough to produce a mottled appearance. These foci may form slight, rounded projections from the capsular surfaces. The pelvic and ureteral mucosa frequently have petechial and ecchymotic hemorrhages. Similar lesions are present on the mucosa of the urinary bladder, or there may be more severe hemorrhage associated with erosion and ulceration of the epithelium, and hematuria (Fig. 1.26F). Superficial lesions of the vagina, similar to those of the oral cavity and skin, occur.

The liver is slightly enlarged; close inspection will reveal, in some cases, a diffuse mottling with white foci that are periportal accumulations of mononuclear cells. There may be numerous small hemorrhages and a few erosions of the mucous membrane of the gallbladder.

Among the characteristic lesions of malignant catarrhal fever is enlargement of lymph nodes. All nodes may be involved, but some may appear grossly normal. Affected nodes may be many times the normal size, and some, including hemolymph nodes, which are usually too small to recognize, may become quite obvious. There is edema of the affected nodes, but on cross section it is apparent that much of the increase in size is due to lymphocytic hyperplasia. Some of the nodes are congested. The spleen is slightly enlarged, and the lymphoid follicles are prominent.

There is an excess of cerebrospinal fluid, which contains much protein and moderate numbers of mononuclear cells (Fig. 1.26C). The meninges are wet, and there is some cloudiness in the subarachnoid space of the sulci. There also may be scattered petechial hemorrhages in the meninges. These lesions are usually most concentrated in the cerebellar leptomeninges.

Gross changes usually are not visible in the heart and larger blood vessels. Polyarthritis, characterized by increased amounts of cloudy synovial fluid and red, swollen synovial membranes, has been reported in experimentally infected cattle.

Reliance must be placed on the histologic changes for the diagnosis of malignant catarrhal fever and its differentiation from similar diseases. The characteristic histologic changes are found in lymphoid tissues and in the adventitia and walls of arterioles and arteries in any organ, and these will be described before other lesions. The protean manifestations of this disease are due largely to the vascular lesions. They comprise fibrinoid necrotizing vasculitis and accumulation of mainly mononuclear cells in the adventitia (Figs. 1.25B,D, 1.26E, and 1.27B). These changes may be focal or segmental and may involve the full width of the wall or be confined more or less to one of the layers. When the intima is involved, there is often endothelial swelling and hyperplasia. Thrombi are difficult to demonstrate in damaged vessels. The media may be selectively affected, or perhaps the adventitia alone. The affected segments of vessel are replaced by a coagulum of homogeneous, eosinophilic material, in which nuclear remnants are seen. The altered nuclei are small, distorted, and fragmented. The perivascular accumulation of cells is particularly characteristic. They are mainly lymphoid cells with large, open nuclei and prominent nucleoli; occasionally, small lymphocytes and plasma cells may be present.

In some forms of the experimental disease, fibrinoid necrosis, endothelial-cell hyperplasia, and thrombosis are not prominent. Electron microscopic studies in these cases have shown that the endothelial reaction consists primarily of lymphocytes and macrophages rather than endothelial cells. The degree of the mononuclear-cell reaction in the vessel walls and the medial necrosis increase with progression of the disease.

These changes in the blood vessels strongly suggest malignant catarrhal fever; arteritis may be seen in bovine virus diarrhea, however, mainly in the submucosa in the lower alimentary tract. Fortunately for diagnostic purposes, arteritis is present in all cases of malignant catarrhal fever, whether peracute, acute, or mild with recovery, but it may be necessary to examine many sections to find it. The best organs to examine for vascular lesions are the brain and leptomeninges, carotid rete, kidney, liver, and adrenal capsule and medulla, and any area of skin or alimentary tract showing gross lesions.

Several hypotheses have been proposed to explain the pathogenesis of the vascular lesions, but none of these is well substantiated. Malignant catarrhal fever may be an immune-mediated disease, like other diseases that are characterized by vascular necrosis and vasculitis, such as equine viral arteritis of horses, Aleutian disease of mink, and periarteritis nodosa of humans. The vascular lesions of malignant catarrhal fever are similar to those seen in graft rejections. The long incubation period and prepatent viremic stage are also suggestive of an immune-mediated disease. The pathogenesis of the vascular lesions is discussed with the Cardiovascular System (Volume 3).

All lymphoid tissues show an active proliferation of lymphoblasts, which form extensive homogeneous populations of cells in the cortical and paracortical zone of the lymph node. There may be focal necrosis associated with arteritis in both cortex and medulla. The pathogenic mechanisms involved in the proliferation of lymphoid cells are poorly understood. Areas containing

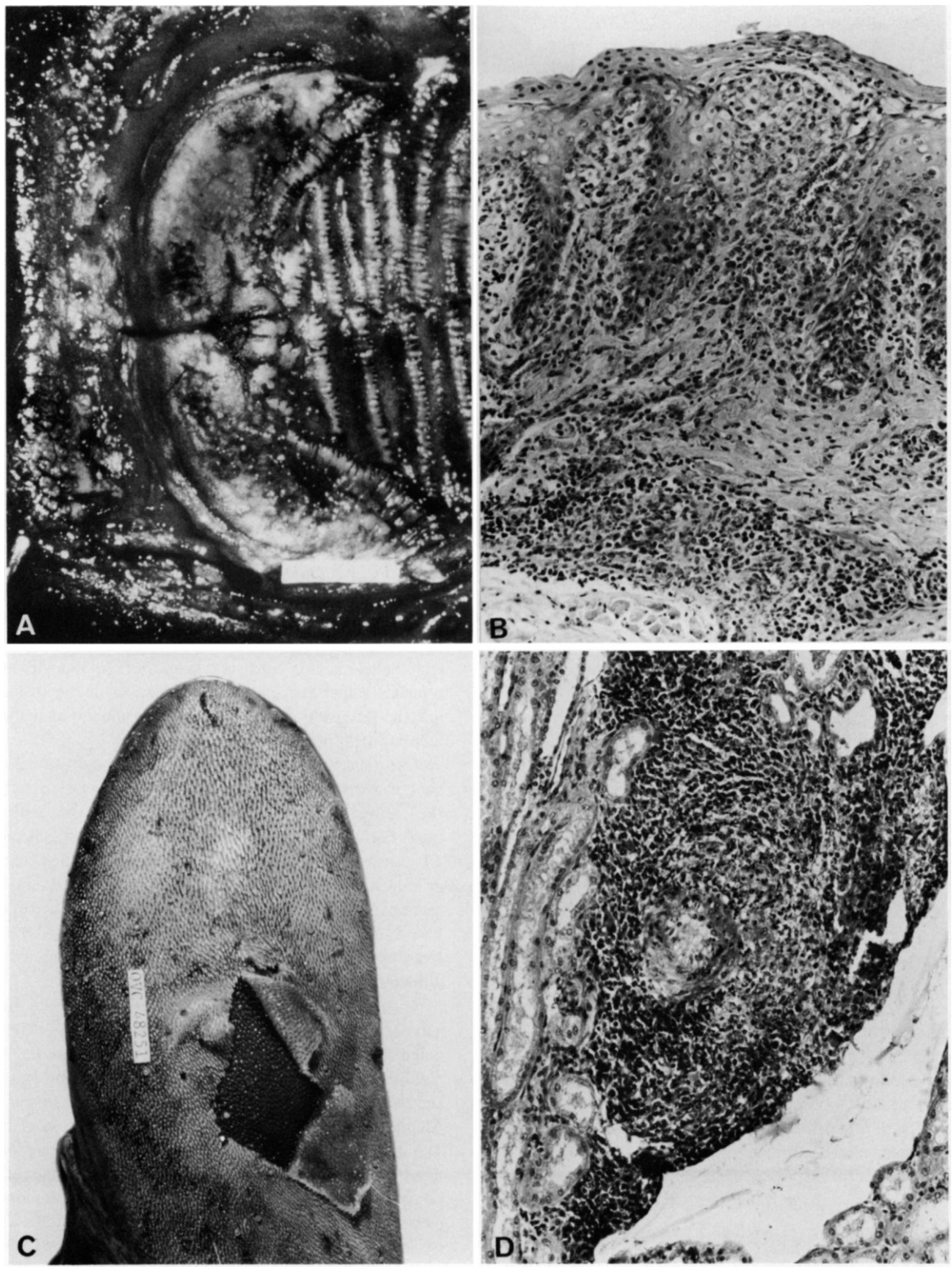


**Fig. 1.25.** Malignant catarrhal fever. Ox. (**A**) Erosion and ulceration of lips, palate, and dental pad. (**B**) Tongue. Vasculitis and infiltration of lamina propria by lymphocytic cells, with developing ulcer over papilla. (**C**) Separation of necrotic lingual epithelium from underlying propria. (**D**) Extensive cuff of mononuclear cells, and fibrinoid necrosis in the wall of a small arteriole. Kidney.

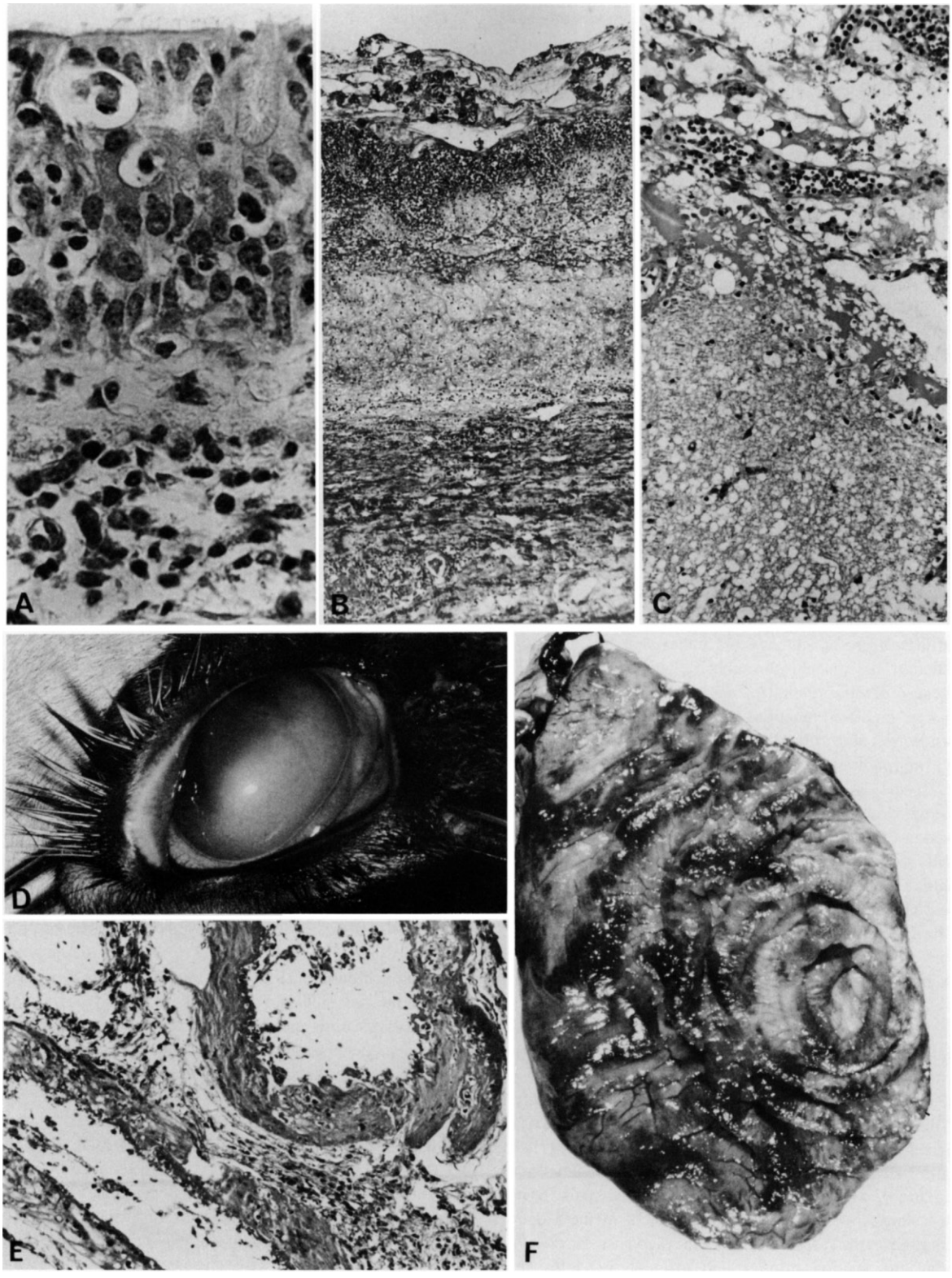


**Fig. 1.26.** Malignant catarrhal fever. (**A**) Nasal mucosa. Degeneration of epithelium and infiltration of lymphocytic cells in uncomplicated rhinitis. (**B**) Pseudomembranous tracheitis. (**C**) Meningeal exudate and vasculitis. (**D**) Edema of cornea. (**E**) Necrosis of arteries and periarterial reaction. Carotid rete. (**F**) Hemorrhages in mucosa of urinary bladder.

both B and T cells are obviously affected. Comparisons have been made to the lesions in lymphoid tissue in humans caused by the Epstein–Barr virus, another cell-associated herpesvirus.

Microscopic arteritis similar to that present in other organs occurs in the nervous system of many cases. Necrotizing arteritis, plasma exudation into the menginges or Virchow–Robin space, and the predominantly adventitial lymphocytic response are, in cattle, unique to malignant catarrhal fever and allow it to be differentiated from other nonsuppurative encephalitides (Fig. 1.26C). Degenerative changes in nervous parenchyma can be explained on the basis of the vascular changes.

The lesions in skin and squamous mucosae of the alimentary tract are histologically similar. The dermis or propria (and often the epithelium) is diffusely infiltrated with a mainly lymphocytic cell population. The dermis, especially its superficial portion, is edematous, and typical arteritis, involving small- and medium-sized vessels, is present. Epithelial changes are related to the presence of a diffuse mononuclear infiltrate and arteritis in the underlying dermis (Fig. 1.25B). Groups of cells become necrotic with swollen, strongly acidophilic cytoplasm; ultimately, the full thickness of epithelium in affected areas undergoes necrosis and erodes. Large areas of epithelium may thus be detached or lost, and there is not much acute leukocytic reaction in the exposed propria or dermis.

The severity of the lesions in the oral squamous mucosa is, in experimental cases at least, related to the degree of lymphoid-cell infiltration in the mucosa and underlying lamina propria rather than to the vascular thrombosis, which is minimal. The pathogenesis of the epithelial lesions has been compared to other lymphocyte-mediated reactions such as tuberculin, contact hypersensitivities, and graft rejection. The graft-rejection reaction, which is morphologically similar to malignant catarrhal fever in many respects, is purported to represent a model of B- and T-cell-mediated autoimmunity, and similar mechanisms may be involved in this disease. These lesions are all characterized by vasculitis, and perivascular mononuclear-cell reactions that extend into the epithelium.

These changes in the epithelium and its lamina propria account for the macroscopic lesions in the vagina, prepuce, bladder, and although there is often much less hemorrhage, oral cavity, nasal mucosa, esophagus, and forestomach. Although gross lesions are not present in the salivary glands, there are microscopic degenerative changes in the epithelium of the interlobular and excretory ducts, with multiple foci of parenchymal necrosis associated with arteritis.

The mottling of liver and the focal nephritis seen grossly is due to the accumulation of mononuclear cells in the portal triads of the liver (Fig. 1.27D) and in the cortices of the kidney. In the liver, these cuffs may be very large and invest the branches of the hepatic artery, which may undergo fibrinoid necrosis. Microscopic lesions are rather consistently present in the kidneys, even though gross lesions are not; they consist of vasculitis involving the smaller arteries and afferent arterioles (Fig. 1.25D). Extensive diffuse lymphocytic infiltrates disrupt the normal renal cortical architecture, and in some cases infarcts appear to be associated with vasculitis involving arcuate arteries.

The mucosa of the stomach and small and large intestine is also densely infiltrated focally and/or diffusely with large lymphocytes. Mucosal infiltrates and necrosis are associated with inflammation of arterioles in the underlying submucosa. In the abomasum, the glandular epithelium in affected areas becomes basophilic, cuboidal, or flattened mucous in type; eventually necrosis and focal ulceration occur. In the small intestine and large bowel, the lesion resembles ischemic damage. The superficial mucosa undergoes necrosis, and there is erosion and hemorrhage. Surviving crypts and glands are lined by flattened basophilic epithelium. In mucosa in which the epithelium is completely destroyed, the collapsed proprial stroma and mononuclear infiltrate are left resting on the muscularis mucosa (Fig. 1.27C). The full thickness of the intestinal wall is edematous, and there is often mesenteric arteritis.

The microscopic lesions in the joints are characterized by a marked, mainly lymphocytic reaction in the synovial membrane and underlying connective tissue, especially in the perivascular areas. Focal areas of necrosis and desquamation may be evident over regions that are heavily infiltrated by lymphocytes. Fibrinous exudate may cover the necrotic areas. Joint lesions have only been reported in experimental cases of malignant catarrhal fever, and a bovine syncytial virus was recovered from most of the affected joints. The significance of this agent in relation to the development of the arthritis is not known.

This completes a description of the histologic changes that are the basis of the gross lesions. These same changes may be found in any tissue, however, even in the absence of gross lesions. Rather constantly, there are vascular lesions of this sort in the neurohypophysis, but not the adenohypophysis, and in the adrenal glands. The adrenal changes are in the capsule and its vessels and trabeculae, and in the medullary vessels. There may be minor focal necrosis of the cortex in consequence, and more often there is disorganization of the medulla and a diffuse lymphocytic infiltrate.

Ophthalmitis occurs with some consistency, and its presence is a useful differential criterion from other ulcerative diseases of the alimentary tract. All portions of the globe may be affected. Rather consistently there is fibrinocellular exudation from hyperemic ciliary processes, and the accumulation of this exudate in the filtration angle is responsible for the rim of opacity observed clinically. Later and as a result of conjunctivitis and inflammation of the limbic vessels, the cornea is edematous and may be ulcerated and vascularized (Fig. 1.26D). There is a retinal vasculitis and, in some cases, hemorrhagic or inflammatory detachment of the retina in focal areas (Fig. 1.27B).

The differential diagnosis of malignant catarrhal fever in cattle should include other erosive–ulcerative diseases of the alimentary tract, including bovine virus diarrhea, rinderpest, bluetongue, and epizootic hemorrhagic disease in wildlife species. The African form of the disease may be confirmed by the isolation of the causative virus on bovine tissue cell cultures, especially thyroid. The diagnosis of the sheep-associated form is based on clinicopathologic findings and may be confirmed by reproduction of the disease following inoculation of whole blood into susceptible species.

BLUETONGUE AND RELATED DISEASES. **Bluetongue** is caused by a member of the genus *Orbivirus* (Reoviridae). There are more than 20 recognized serotypes of bluetongue virus dis-

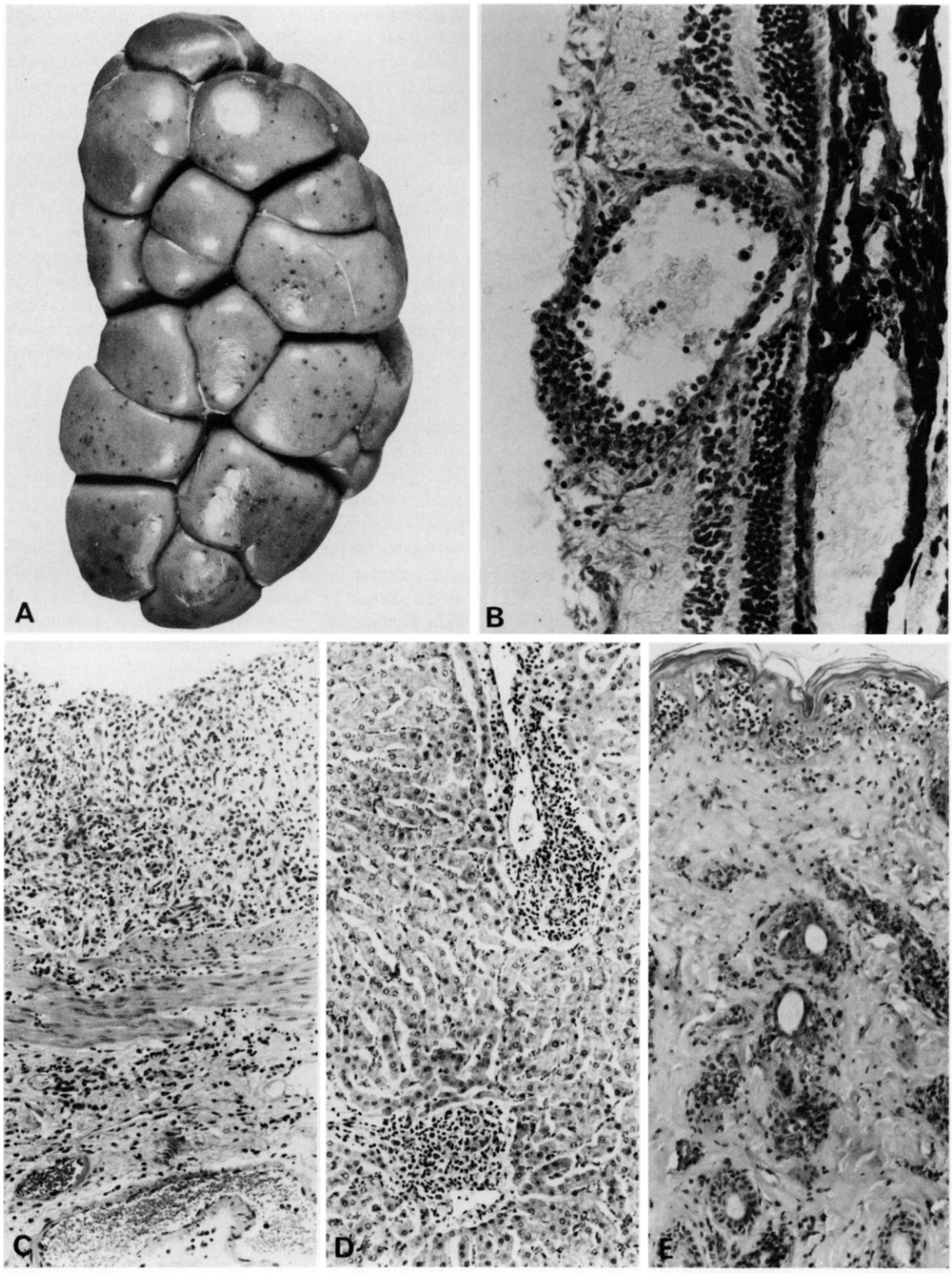


**Fig. 1.27.** Malignant catarrhal fever. (**A**) Focal nonsuppurative interstitial nephritis. (**B**) Vasculitis in retina. (**C**) Colitis with collapse of glands and edema of submucosa. (**D**) Accumulations of lymphocytic cells in portal triads. (**E**) Necrosis of epithelium. Skin.

tinguished by neutralization tests, though they may represent not so much distinct types as points in a spectrum of antigenicity brought about by recombination of the segmented orbivirus genome. Immunity to one serotype does not confer resistance against another and may cause "sensitization," with a more severe syndrome following infection by second type.

**Epizootic hemorrhagic disease** of deer is caused by a virus that represents another subgroup of *Orbivirus*. The virus causing **Ibaraki disease**, recognized in cattle in Japan, is closely related to, if not a variant of, epizootic hemorrhage disease virus; seropositive animals also have been found in Taiwan and Indonesia. Several other known orbiviruses are not associated with disease. Bluetongue, epizootic hemorrhagic disease, and related viruses are spread by *Culicoides*, known variously as midges, gnats, or sand flies. The virus multiplies by a factor of $10^3$ to $10^4$ in the *Culicoides* within 2 or 3 days of ingestion of the infected blood meal. Transovarian transmission of virus in *Culicoides* does not occur.

**Bluetongue** virus circulates in a broad belt across the tropics and warm temperate areas, with incursions or recrudescence during the *Culicoides* season, annually, or at irregular longer intervals, in cooler temperate areas. The condition is enzootic or seasonally epizootic in most of Africa, the Middle East, the eastern Mediterranean basin, the Indian subcontinent, the Caribbean, and the United States. A strain of bluetongue has been isolated from *Culicoides* in northern Australia, but spontaneous disease has not been recognized. It has made sporadic appearances in the Iberian peninsula, and seropositive cattle have been detected in Canada. Cattle, sheep, and goats are the susceptible domestic species wherever bluetongue occurs. Infection in cattle usually produces only inapparent infection or mild clinical disease. Goats, though susceptible to infection, rarely show signs; however, significant disease has occurred in goats in the Middle East and India. Sheep are the domestic species most highly susceptible to bluetongue, but there is considerable variation in expression of the disease, depending on the breed, age, and immune status of the sheep, the environmental circumstances under which they are held, and the strain of virus. In Africa, a wide variety of nondomestic ungulates and some small mammals may be inapparently infected; mortality has occurred in naturally or experimentally infected topi, cape buffalo, and kudu. In North America, wildlife species, particularly white-tailed deer, black-tailed or mule deer, elk (wapiti), bighorn sheep, and pronghorn antelope, are also infected. Bluetongue is responsible for significant mortality in all these species except elk, which usually develop mild or inapparent infection.

**Epizootic hemorrhagic disease** virus, or a closely related virus, has been isolated in Nigeria, but the natural vertebrate hosts there are not known. In North America, white-tailed deer, black-tailed or mule deer, pronghorn antelope, and elk are susceptible to infection. The white-tailed deer is extremely susceptible, and widespread epizootics have occurred among this species in the United States. A single outbreak has been recognized in Alberta, Canada. The rate of survival is much higher among black-tailed deer and pronghorn antelope, and elk are only very mildly affected. Clinical disease similar to that produced by bluetongue may occur in cattle, but sheep do not develop disease when infected with this virus. In Japan, the closely related virus of Ibaraki disease also produces a clinical syndrome resembling bluetongue in cattle, but not in sheep.

The viruses of bluetongue and epizootic hemorrhagic disease circulate together in North America. Both viruses may be involved simultaneously in outbreaks of hemorrhagic disease in wild ruminants, and both have been isolated from *Culicoides* in a single locality at the same time. Cattle, among domestic animals, may play a major role as reservoir or overwintering host for bluetongue, since inapparent or latent infection may persist for a number of years, and recrudescence of viremia may be stimulated by the bites of *Culicoides*. Venereal transmission of bluetongue from an infected bull to the bred cow has been demonstrated, and infected progeny may result. Vertical transmission of bluetongue from dam to offspring also occurs in cattle, sheep, and elk. Immune tolerance may occur in prenatally infected calves.

The pathogenesis of bluetongue, epizootic hemorrhagic disease, and Ibaraki disease is fundamentally similar in all species in which disease is seen. Primary viral replication following insect bite probably occurs in regional lymph nodes and spleen. Viremia about 4–6 days after inoculation results in secondary infection of endothelium in arterioles, capillaries, and venules throughout the body, with microscopic lesions and fever beginning a day or so later, about a week after inoculation. Bluetongue virus in the blood appears to be closely associated with, or in, erythrocytes, and it may cocirculate with antibody. Endothelial damage caused by virus infection initiates local microvascular thrombosis and permeability. This is reflected microscopically by the presence of swollen endothelium, and fibrin and platelet thrombi in small vessels, with edema and hemorrhage in surrounding tissue. These lesions in turn mediate the full spectrum of gross findings. These are fundamentally ischemic necrosis of many tissues, edema due to vascular permeability, and hemorrhage resulting from vascular damage compounded, in severe cases, by consumption coagulopathy due to thrombocytopenia and depletion of soluble clotting factors.

Bluetongue in sheep is a highly variable disease; it may cause inapparent infection or an acute fulminant disease. Typically, leukopenia and pyrexia occur, even in mild infections, coincident with viremia. The degree and duration of fever do not correlate with the severity of the syndrome otherwise. In the early phase there is hyperemia of the oral and nasal mucosa, salivation, and nasal discharge within a day or two of the onset of fever. Hyperemia and edema of the eyelids and conjunctiva may occur, and edema of lips, ears, and the intermandibular area becomes apparent. Hyperemia may extend over the muzzle and the skin of much of the body, including the axillary and inguinal areas. Focal hemorrhage may be present on the lips and gums, and the tongue may become edematous and congested or cyanotic, giving the disease its name. Infarcted epithelium thickens and becomes excoriated, erosions and ulcerations develop along the margins of the tongue opposite the molars, and the mucosa of much of the tongue may slough. Excoriation and ulceration also occur on the buccal mucosa, the hard palate, and dental pad. Affected areas of skin may also become encrusted and excoriated with time, and a break in the wool can result in parts or much of the fleece being tender or cast. The coronet,

bulbs, and interdigital areas of the foot may become hyperemic. Coronary swelling and streaky hemorrhages in the periople may be evident as a result of lesions in the underlying sensitive laminae. These hemorrhages may persist in the hoof as brown lines that move down the hoof as it grows. A defect parallel to the coronet may also be evident in the growing hoof in recovered cases.

Internally, in acute cases, there is subcutaneous and intermuscular edema, which may be serous or suffused with blood. Superficial lymph nodes are enlarged and juicy. Bruiselike gelatinous hemorrhages and contusions, which may be small and easily overlooked if not numerous, are often present in the subcutis and intermuscular fascial planes. Focal or multifocal pallid areas of streaky myodegeneration may be present throughout the carcass, perhaps partly obscured by petechial or ecchymotic hemorrhage. Resolving muscle lesions may be mineralized or fibrous.

Necrosis may be present deep in the papillary muscle of the left ventricle and perhaps elsewhere in the myocardium. The lesion that is perhaps most consistent and closest to pathognomonic for bluetongue is focal hemorrhage, petechial or up to 1.0 cm wide by 2 to 3 cm long, in the tunica media at the base of the pulmonary artery. These hemorrhages are visible from both the internal and adventitial surfaces and may be present in clinically mild cases with few other lesions. Petechial hemorrhage may also be present at the base of the aorta and in subendocardial and subepicardial locations over the heart.

There may also be edema and petechial or ecchymotic hemorrhage in the pharyngeal and laryngeal area. In severe cases the lungs may assume a purplish hue, with marked edematous separation of lobules. Animals with pharyngeal or esophageal myodegeneration may succumb to aspiration pneumonia.

Hyperemia, occasionally marked hemorrhage, or in advanced cases, ulceration of the mucosa may occur on rumen papillae, the pillars of the rumen, and the reticular plicae. In convalescent animals, stellate healing ulcers or scars on the wall of the forestomachs may be apparent. Petechial hemorrhage may be present in the abomasal mucosa, with congestion of the subserosa at the pylorus. The remainder of the intestinal mucosa may be congested, and occasionally there may be hemorrhage, particularly in the large bowel. Petechial hemorrhage of the mucosa of the gallbladder may also be seen.

The kidneys are commonly congested, and there may be petechial hemorrhage of the mucosa of the urinary bladder, urethra, and vulva or prepuce.

Acute lesions are characterized microscopically by microvascular thrombosis, and edema and hemorrhage, in affected sites recognized at autopsy. In squamous mucosa and skin, capillaries of the proprial and dermal papillae are involved, resulting in vacuolation and necrosis of overlying epithelium. There is a mild, local neutrophilic infiltrate acutely and a similarly mild mononuclear reaction in the dermis or propria in uncomplicated chronic lesions, which may granulate if widely or deeply ulcerated. Similar microvascular lesions are associated with necrosis and fragmentation of infarcted muscle. Muscle during the reparative phase follows the usual course of regeneration of fibers or fibrous replacement, depending on whether or not the sarcolemma retains its integrity.

In cattle, clinical bluetongue usually is apparent in only 5 to 10% of infected animals; mortality is low and often is attributed to secondary infection. Fever, loss of appetite, and leukopenia are usually seen after an incubation period of 6 to 8 days, and there may be a drop in milk production in dairy cattle. There is reddening of the epithelium of the mucous membranes, and of thin exposed skin, especially notable on the udder and teats. Edema of the lips and conjunctiva may be present. Salivation may become profuse, and as the disease progresses over the next several days, hyperemia and congestion of the mucosae become more intense. Ulcerations of the gingival, lingual, or buccal mucosa occur, most consistently on the dental pad. There may be necrosis of epithelium on the muzzle. Muscle stiffness is a feature of the disease in some animals. Laminitis, characterized by hyperemia and edema of the sensitive laminae at the coronet, may be apparent, and in some cases, hooves on affected feet may eventually slough. Sloughing or cracking of crusts of necrotic epithelium also may occur on affected parts of the skin, but the ulcerative or erosive defects heal readily. Viral antigen and thrombosis are present in small vessels in affected tissues during the acute phase.

The signs and lesions of Ibaraki disease are essentially similar to those of bluetongue in cattle, though perhaps a little more severe in some cases. As well as the signs and lesions described in cattle with bluetongue, there may be difficulty in swallowing in 20 to 30% of clinically affected animals, and the swollen tongue may protrude from the mouth. At autopsy, in addition to the lesions observable externally, there may be congestion, erosion, or ulceration of the mucosa of the abomasum, and less commonly, the esophagus and forestomachs. Ischemic necrosis and hemorrhage of the striated muscle in the tongue, pharynx, larynx, and esophagus causes the difficulty in swallowing seen clinically, and similar changes are seen in other skeletal muscles. Necrotizing aspiration pneumonia is a sequel to dysphagia in some animals.

The hemorrhagic diseases in bighorn sheep, pronghorn antelope, and white-tailed and black-tailed or mule deer in North America tend to resemble bluetongue in sheep. White-tailed deer may develop a particularly severe and fulminant acute hemorrhagic disease, with high mortality. Bluetongue in goats, though usually inapparent, can resemble bluetongue in sheep.

Bluetongue in sheep must be differentiated from foot and mouth disease, *peste des petits ruminants*, contagious ecthyma, and photosensitization in particular. In cattle, the condition must be differentiated from foot and mouth disease, vesicular stomatitis, bovine virus diarrhea, rinderpest, malignant head catarrh, and photosensitivity. In Japan, Ibaraki disease must in addition be differentiated, at least clinically, from ephemeral fever, and this would be the case in parts of Australia were the disease introduced into that continent.

In addition to the systemic disease described, abortion, perhaps unobserved, and birth of progeny with various congenital defects may follow bluetongue infection of pregnant sheep and cattle. In sheep, bluetongue infection of ewes early in gestation may result in hydranencephaly. Anomalous calves produced by bluetongue-infected cattle have excessive gingiva, an enlarged tongue, anomalous maxillae, dwarflike build, and rotations and contractures of the distal extremities. Hydranencephaly and ar-

throgryposis are also reported in calves infected *in utero* with bluetongue. Antibody may be sought in neonates that have not sucked, and attempts should be made to isolate virus, since some prenatally infected animals will have immune tolerance and persistent infection. The anomalies of the brain are considered further with the Nervous System (Volume 1).

BOVINE PAPULAR STOMATITIS. Papular stomatitis of cattle (infectious ulcerative stomatitis and esophagitis, proliferative stomatitis) has been known in Europe since at least the 1930s, and it occurs worldwide. It is generally an insignificant disease but needs to be differentiated from other, more serious diseases affecting the oral cavity and skin. It is caused by a DNA virus belonging to the Poxviridae, genus *Parapoxvirus*. The virus is closely related but not identical to the paravaccinia virus that causes pseudocowpox in cattle, and milker's nodules in humans. It is morphologically similar to, and shares at least one antigen with, the virus of contagious ecthyma (orf, contagious pustular dermatitis) of sheep and goats (see viral diseases of skin, in the Skin and Appendages, Volume 1).

Bovine papular stomatitis virus is host specific; it grows on tissue cultures and produces specific intracytoplasmic, acidophilic inclusions in infected epithelial cells. Neutralizing antibody is not readily demonstrated. Infection does not confer significant immunity, and successive crops of lesions and relapses can occur. The disease is more common in calves than in older animals, although the susceptibility of the latter may be increased by intercurrent debility or disease.

The papular lesions of this disease occur on the muzzle and in the anterior nares, on the gums, the buccal papillae, the dental pad, the inner aspect of the lips, the hard palate (Fig. 1.28A), the floor of the oral cavity behind the incisors, the ventral and lateral (not dorsal) surfaces of the tongue, and occasionally, in the esophagus (Fig. 1.28B) and forestomachs. The lesions may be few or many; they may be transient, or repeated crops of them may take a course of several months.

The initial lesions, which are likely to be detected on the muzzle or lips, are erythematous macules, about 2–15 mm in diameter. Shortly, the central portion becomes elevated as a low papule, although the elevation is not easy to see, and by the second day a grayish central zone of epithelial hyperplasia has developed on which there is superficial scaliness and necrosis. The lesions expand slowly to assume a "coin" shape, maintaining a hyperemic periphery and grayish center; the central necrotic area may slough to form a shallow craterous defect surrounded by a slightly raised red margin. The course of individual lesions is about a week.

Histologically, there is focal but intense hyperemia and edema in the papillae of the lamina propria, with the accumulation of a few mononuclear leukocytes. The epithelium is thickened, sometimes to twice its normal depth, by hyperplasia and ballooning degeneration in the deep layers (Fig. 1.28C). The cytoplasm of affected cells is clear, and the nucleus may be shrunken. A single round, dense, eosinophilic inclusion body lies in the vacuolate cytoplasm, especially in cells at the active margin of the lesion. In the central, more advanced part of the lesion, a mainly neutrophilic infiltrate into the superficial propria and epithelium is associated with erosion of the upper layers of necrotic cells. The basal layer survives and may be very flattened in eroded areas. Vesicles do not form.

Papular stomatitis is probably more common and widespread than reports indicate. Variation in the extent and gross appearance of the lesions is to be expected, depending on the usual host–parasite factors and the nature of superimposed infections. They may predispose to the development of necrotic stomatitis. The infection can be transmitted to humans to produce small papules, which may persist for several weeks on the skin, usually of the fingers or forearms.

Parapoxvirus particles may be demonstrated in negatively stained material from lesions examined under the electron microscope.

CONTAGIOUS ECTHYMA. Contagious ecthyma (orf, contagious pustular dermatitis) is a poxviral disease of sheep and goats that is characterized mainly by proliferative scabby lesions on the lips, face, and feet (see viral diseases of skin, in the Skin and Appendages, Volume 1). Lesions may extend into the oral cavity, involving the tongue, gingiva, dental pad, and palate. Involvement of the esophagus and forestomachs occurs but is very unusual. In general, the evolution of the lesions is similar to papular stomatitis of cattle, though they are more exudative and usually much more proliferative. In the upper alimentary tract they may consist of focal red, raised areas, which coalesce to form papules followed by pustules. The latter rupture, and on the muzzle and in the mouth they may become covered by a gray to brown scab, although scab formation may not occur in the mucosa of the upper alimentary tract.

INFECTIOUS BOVINE RHINOTRACHEITIS. Bovine herpesvirus type 1 has been associated with a wide range of clinicopathologic conditions in cattle. These include necrotizing rhinotracheitis, infectious pustular vaginitis and balanoposthitis, encephalitis, abortions, and latent infection (see appropriate chapters).

A systemic form of the disease may occur spontaneously in neonatal calves (in which it may be congenital, or acquired shortly after birth) and in feedlot cattle; it has been reproduced experimentally in young calves. Clinically affected animals have fever, leukocytosis, excessive salivation, nasal discharge, inspiratory dyspnea, depression, and often, diarrhea. The oral and nasal mucosae are hyperemic, and focal areas of necrosis, erosion, and ulceration, a few millimeters up to 3.0 cm in diameter, are located on the nares, dental pad, gums, buccal mucosa, palate, and caudal, ventral, and dorsal surfaces of the tongue. Characteristically, the lesions tend to be punctate with a slightly raised margin; the necrotic areas are covered by grayish white layer of fibrinonecrotic exudate, which leaves a raw, red base when removed.

The lesions may extend into the esophagus, usually only the upper third, and the forestomachs. In the esophagus, the erosions and ulcers may be irregular, circular, or linear and often have a punched-out appearance and a hyperemic border (Fig. 1.29A). The ruminal lesions, which are most commonly located in the dorsal and anterior ventral sacs, vary considerably. The earliest lesions consist of foci of necrosis and hemorrhage, a few millimeters in diameter. In some cases, the necrosis may involve

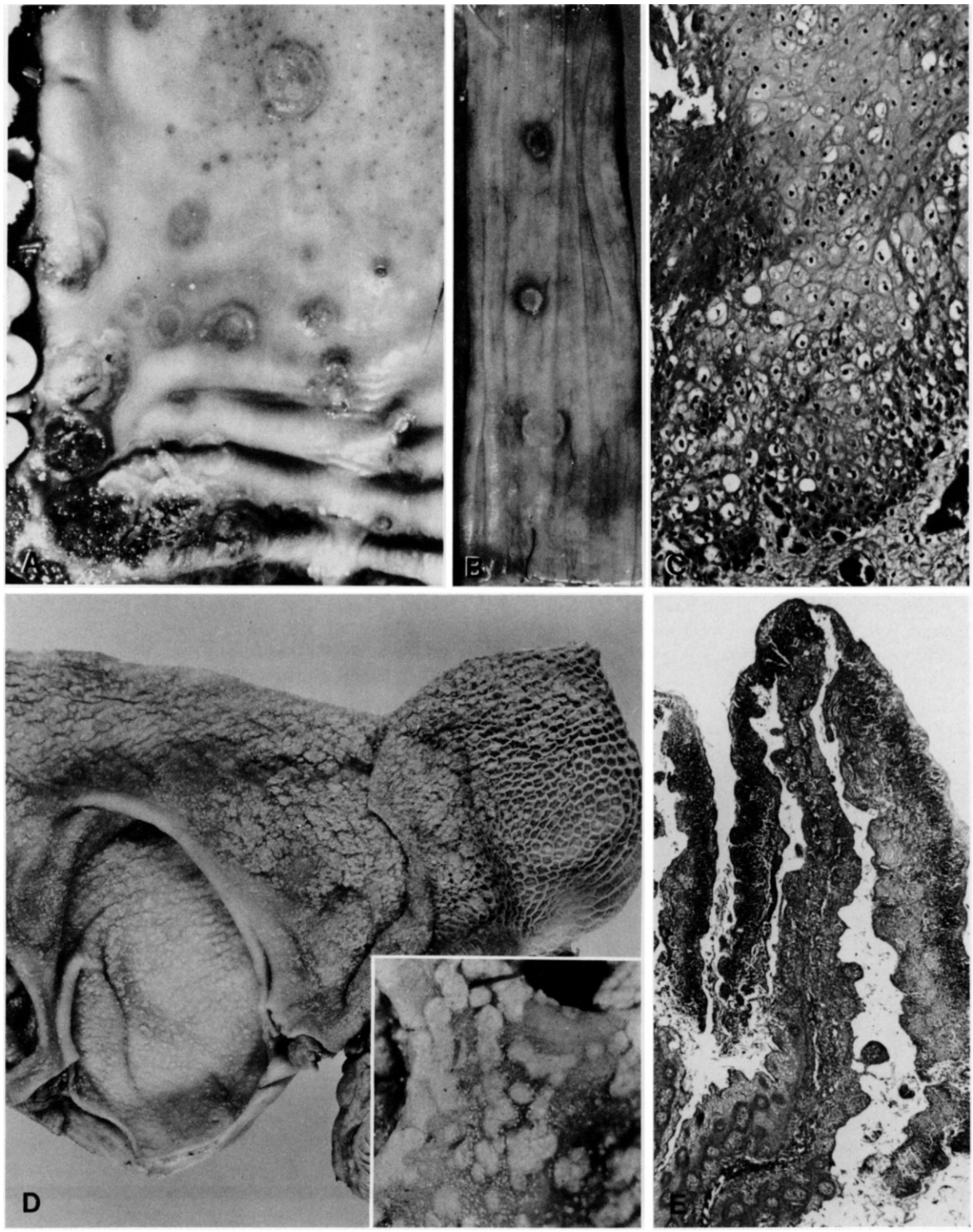


**Fig. 1.28.** (**A–C**) Bovine papular stomatitis. (**A**) Lesions at various stages of evolution in palate. (**B**) Lesions in esophagus. (**C**) Thickened epithelium at the margin of a lesion, with ballooning degeneration of cells in the deeper layers. (**D** and **E**) Infectious bovine rhinotracheitis. (**D**) Cheesy necrotic debris in rumen and reticulum. Calf. (Inset) Detail of rumen lesion. (**E**) Necrosis of omasal fold. Neonatal calf.

almost the entire surface of the ruminal mucosa, which becomes covered by a thick, dirty gray layer of exudate, resembling curdled milk, that adheres tightly to the wall (Fig. 1.28D). Similar lesions may be evident in the reticulum. Focal areas of necrosis result in the formation of holes, up to 1.5 cm in diameter, in the leaves of the omasum. In addition, these calves may have focal areas of necrosis in the abomasal mucosal folds, which may coalesce to form areas of necrosis 2–3 cm in diameter. The intestines are red and dilated, and the serosal surface may be covered by a thin layer of fibrinous exudate.

The enteric lesions may be accompanied by changes in the upper respiratory tract. When present, the respiratory lesions are similar to those described for older cattle, although they are milder and generally limited to the nasal mucosa, larynx, and upper third of the trachea (see the Respiratory System, this volume).

Gray to yellow necrotic foci 2–5 mm diameter may be evident macroscopically on the capsular and cut surfaces of the liver and the adrenal cortices, and in Peyer's patches.

Microscopically, the lesions in the squamous mucosa are characterized by focal areas of necrosis (Fig. 1.28E), erosion, and ulceration. A marked leukocytic reaction, predominantly neutrophilic, is evident in the basilar areas of the lesions, often extending from the underlying lamina propria. The epithelial cells at the periphery of the lesions are markedly swollen, and the cytoplasm is vacuolated. Severe necrosis may involve the entire papilla or mucosa more diffusely. Cowdry type A and B inclusions may be present in epithelial cells in the periphery of the lesion, although these are an inconsistent finding. They are more likely to be found if tissues are collected in the early stages of the disease and fixed in Bouin's fluid. The abomasal lesions consist of necrosis of glandular epithelial cells. Affected glands are dilated and filled with necrotic debris. Focal necrotic lesions involving crypts and lamina propria may be present in both the small intestine (Fig. 1.29B) and large bowel. Abomasal and intestinal lesions may predispose to the development of secondary mycosis, which is a common complication.

Foci of coagulation necrosis may occur in the liver, lymph nodes, Peyer's patches, spleen, and adrenal cortices. Typically, there is little inflammation associated with the necrosis. Herpes inclusions are inconsistently seen in cells at the periphery of the necrotic foci.

The lesions in the upper alimentary tract of cattle associated with bovine herpesvirus infection must be differentiated from those of calf diphtheria, bovine papular stomatitis, and bovine virus diarrhea. Bovine herpesvirus type 1 may be demonstrated in the lesions by means of electron microscopic examination-fluorescent-antibody technique, and tissue culture in a wide variety of systems. The ruminal lesions must be differentiated from those of bovine adenovirus infection and nonspecific rumenitis, described elsewhere in this chapter. The liver lesions may be confused with focal necrosis associated with septicemias, for example, listeriosis or salmonellosis (see Liver and Biliary System, this volume).

CAPRINE HERPESVIRUS. A herpesvirus that shares some antigens with, but is immunologically distinct from, bovine herpesvirus-1 has been isolated from neonatal goat kids in California and Switzerland. The name caprine herpesvirus-1 has been suggested for this virus, which grows on embryonic bovine lung tissue cultures and causes severe systemic disease with erosions and ulcerations of the alimentary tract in neonatal goats. Adult goats may be latent carriers of the virus. Experimental infection of pregnant does causes abortion. The virus is nonpathogenic for calves and lambs.

The disease in neonatal kids is characterized by fever, conjunctivitis, ocular and nasal discharges, dyspnea, anorexia, abdominal pain, weakness, and death, usually within 1 to 4 days after onset of clinical signs. Affected kids have leukopenia and hypoproteinemia.

Macroscopic lesions are most obvious throughout the entire alimentary tract. Round or longitudinal erosions, which have a hyperemic border, are evident in the oral mucosa. These are particularly prominent on the gums around the incisor teeth and to a lesser extent in the pharynx and esophagus. Focal red areas of necrosis, which may be slightly elevated above the surrounding mucosa, occur in the rumen. In the abomasum, numerous longitudinal red erosions are located in the mucosa. The most severe lesions occur in the cecum and ascending colon, which are dilated, with a thickened wall, and contain focal to large areas of mucosal necrosis and ulceration, frequently covered by a pseudodiphtheritic membrane. The contents are yellow and mucoid. Hemorrhagic foci may be visible in the bladder mucosa.

Microscopically, the lesions in the upper alimentary tract are typical areas of necrosis and erosion of the squamous epithelial cells. The epithelial cells at the periphery of the necrotic areas are swollen and vacuolated, and these may contain herpes inclusions. There is marked inflammatory reaction in the underlying lamina propria. The abomasal lesions consist of acute foci of mucosal necrosis. Inclusions are particularly evident in this area. Lesions in the cecum and colon are more extensive and consist of large areas of mucosal ulceration and necrosis, which may involve the entire thickness of the wall. The submucosa is edematous and markedly infiltrated by inflammatory cells. The mesenteric nodes are edematous, and the germinal centers are depleted of lymphoid cells. Focal areas of necrosis with mild inflammatory cell reaction are evident in the bladder mucosa.

The alimentary lesions in goat kids in many respects resemble the lesions in calves infected with bovine herpesvirus type 1. Focal areas of necrosis in other organs, such as liver, spleen, and adrenal glands, which are often present in calves, are not reported in the goats.

OTHER HERPESVIRUSES. **Canine herpesvirus** causes a systemic disease of neonatal puppies that is characterized by foci of necrosis and hemorrhage in a wide variety of organs, especially the lungs and renal cortices (see herpesvirus infections of the fetus and newborn, in the Female Genital System, Volume 3). Focal areas of necrosis may occur in the intestine as part of the systemic syndrome.

**Feline viral rhinotracheitis** virus (feline herpesvirus-1) causes alimentary tract lesions (see Erosive and Ulcerative Stomatitides). Viruses antigenically related to feline herpesvirus-1 have been isolated from dogs with diarrhea, but descriptions of lesions are not available.

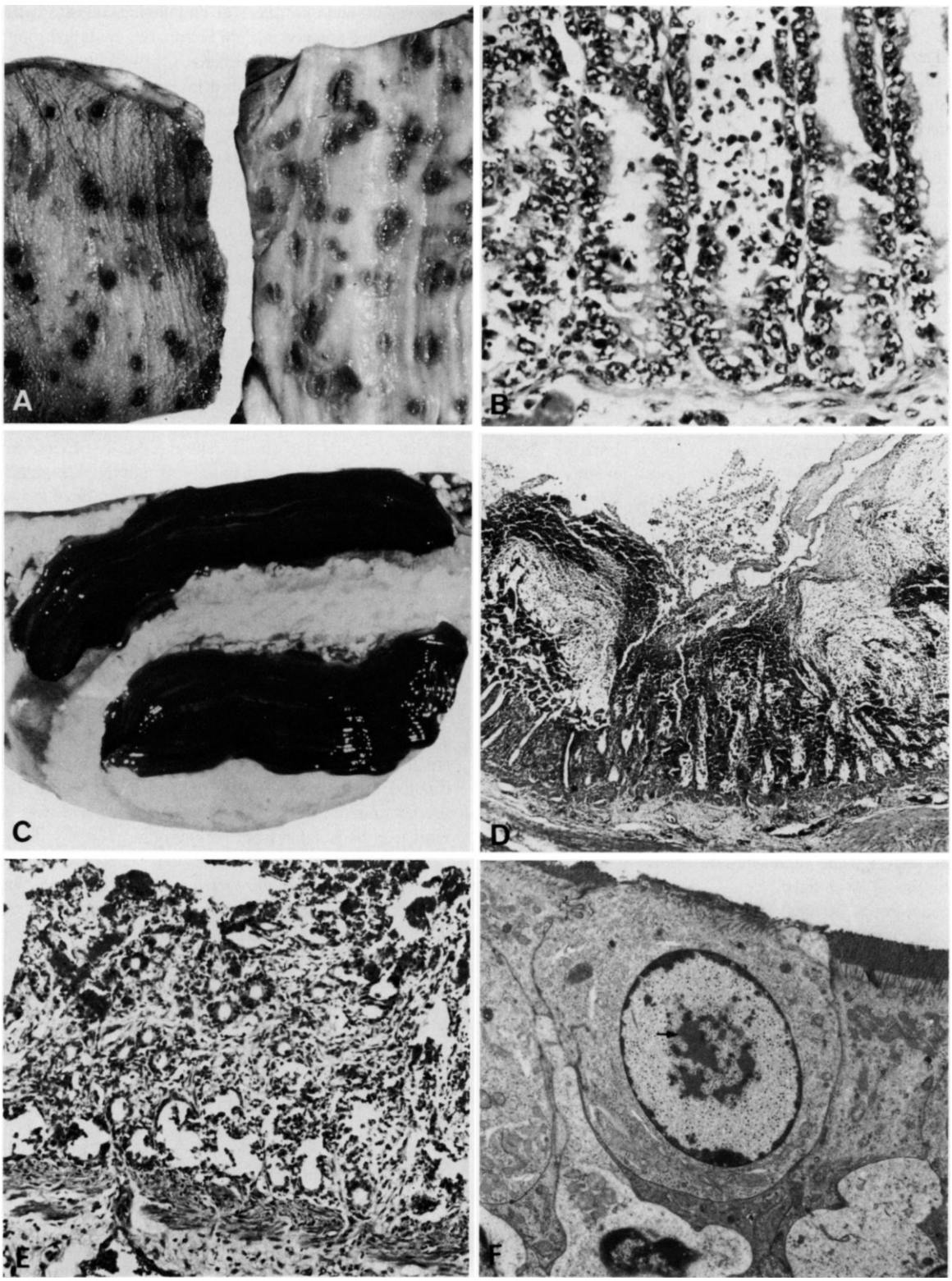


**Fig. 1.29.** (**A** and **B**) Infectious bovine rhinotracheitis. (**A**) Foci of necrosis on mucosa of esophagus and rumen. Neonatal calf. (**B**) Necrosis of epithelium in the crypts of Lieberkühn. Small intestine. Neonatal calf. (**C–E**) Bovine adenovirus infection. (**C**) Congested and hemorrhagic colon. (**D** and **E**) Infarctive necrosis and hemorrhage. Colon. (**F**) Porcine adenovirus infection. Adenovirus-infected cell in epithelium of dome over Peyer's patch. Note inclusion (arrow). (Courtesy of D. M. Hoover and S. E. Sanford.)

### *Adenovirus Enteritis*

The adenoviruses that have been associated with enteric infections in humans, cattle, swine, horses, sheep, and dogs belong to the Adenoviridae, genus *Mastadenovirus*. *In vivo* and *in vitro* infection of cells results in the formation of both Cowdry type A and B inclusions. Adenoviruses are relatively heat resistant and can survive for several days at room temperature. Infected animals may remain carriers for weeks. Adenovirus infections in both humans and animals appear, in general, to be systemic, and disease seems to occur more commonly in immunologically compromised individuals. Certain strains have a tropism for the respiratory tract, others for the alimentary tract. Their enteric manifestations will be considered here.

BOVINE ADENOVIRUSES. Serologic surveys indicate that adenovirus infections in cattle are worldwide in distribution. In many areas there is a high prevalence of antibodies, indicating that infection is common, but overt disease is sporadic. There are 10 different serotypes of bovine adenovirus, and this number is likely to increase. Infection has been mainly associated with keratoconjunctivitis and respiratory disease. Many strains have been isolated from normal cattle. Serotypes 3, 4, 5, 7, and 8 have all been associated with a pneumoenteritis complex. Experimental infection with most strains usually produces only a mild respiratory infection, and Koch's postulates have not been fulfilled for the enteric form of the disease. It appears that after an initial viremic stage, the virus localizes in the endothelial cells of vessels in a variety of organs, resulting in thrombosis with subsequent focal areas of ischemic necrosis.

Clinically, enteric infections with bovine adenovirus occur sporadically in 1- to 8-week-old calves and in feedlot animals. Affected animals have fever and diarrhea, which may contain blood. They are dehydrated, and the mucous membranes of the muzzle and mouth are congested. Dry encrusted exudate may cover the muzzle, and there may be serous to mucopurulent ocular and nasal discharges.

The macroscopic lesions may be present in the forestomachs, abomasum, and intestine. Those in the forestomachs are characterized by irregular, raised, red to gray necrotic areas 2–4 mm in diameter on the mucosa of both the dorsal and ventral sacs of the rumen. In some cases the areas of necrosis coalesce to give rise to a diffuse necrotizing rumenitis. Ulcers up to 1.5 cm in diameter may be located on the ruminal pillars, and these may be visible through the serosa. Similar lesions may be evident in the omasum. The abomasal mucosal folds are edematous and congested, with focal necrosis and ulceration in the mucosa, which, like those in the forestomachs, may be visible on the serosal surface.

The intestinal lesions vary from slight dilation and distention with excessive fluid to severe multifocal or diffuse fibrinohemorrhagic enteritis. The Peyer's patches are often necrotic and may be covered by a pseudodiphtheritic membrane. In feedlot cattle, the lesions may be most prominent in the colon. The mucosa is dark red, and there is marked edema of the mesocolon. The mesenteric lymph nodes are enlarged and edematous.

Microscopically, large, basophilic to amphophilic inclusions completely or partially fill the nuclei of endothelium in the vessels of the lamina propria and submucosa of the rumen, abomasum, and intestine. The endothelial cells are swollen and necrotic, and some veins and lymphatics contain thrombi. Foci of ischemic necrosis are evident in the overlying mucosa, and in more advanced lesions, the necrosis extends across the muscularis mucosae. Fibrinocellular exudate often covers the mucosal surface. There is usually marked submucosal edema, congestion, and fibrinous exudation. Foci of necrosis are evident in the lymphoid follicles of the Peyer's patches, which are also depleted of lymphocytes. Intestinal crypts are dilated, lined by flat epithelial cells, and usually contain necrotic debris.

Typical inclusions may also be found in endothelial cells of vessels and sinusoids of the adrenal glands, mesenteric lymph nodes, liver, spleen, glomeruli, and interstitial capillaries in the kidney and in the mucosa of the urinary bladder. Ultrastructurally, adenovirus particles are located in large numbers in the nuclei of endothelial cells.

Confirmation of enteric bovine adenovirus infection depends on the demonstration of the typical intranuclear inclusions in endothelial cells, the ultrastructural presence of virus particles, and isolation of the virus in tissue cell cultures. The latter is often difficult because different serotypes and strains of the virus require specific tissue cell cultures, and several blind passages may be required before cytopathic changes are evident.

Enteritis due to bovine adenovirus must be differentiated from bovine virus diarrhea, malignant catarrhal fever, the enteric form of infectious bovine rhinotracheitis, salmonellosis, coccidiosis, and enteric mycotic infections.

PORCINE ADENOVIRUS. There are five different serotypes of adenoviruses in swine, which, according to serologic surveys, are all common. Serotype 4 appears to be the most widely distributed strain of the virus in Europe and North America. Asymptomatic infections are most common in swine, and the virus may be isolated from normal pigs.

The importance of adenoviruses as a cause of enteric disease in the field remains controversial. In Belgium, serotype 3 has been associated with diarrhea, occasional vomiting, dehydration, and reduced growth rate in 2- to 3-week-old pigs. Experimental oronasal infection of hysterotomy-derived, colostrum-deprived pigs with this same serotype produces diarrhea, after an incubation period of about 3 to 4 days. Diarrhea has also been produced experimentally with serotype 4 and other strains of the virus. Other lesions produced with serotype 4 are interstitial pneumonia, nonsuppurative meningoencephalitis, and focal interstitial nephritis. In general, however, these lesions do not appear to cause clinical disease.

The macroscopic lesions in the intestine consist of excessive yellow, watery contents and moderate enlargement of the mesenteric lymph nodes.

In contrast to the situation in calves, where the inclusions are located in the nuclei of endothelial cells, in pigs the inclusions are in enterocytes in the distal jejunum and ileum. Initially the inclusions are amphophilic to basophilic and fill the entire nucleus, and the nuclear membrane is thickened. In later stages of the infection, the inclusions are smaller and are surrounded by a halo. The infected nuclei are enlarged, round, and displaced to the apical portion of the cell. The inclusions are mainly located in cells on the sides of the villi, which may be short and blunt.

They are often seen in epithelium, and occasionally, in associated lymphocytes, on the dome over Peyer's patches. They may persist for up to 15 days postinfection. There may be a moderate mononuclear-cell reaction in the lamina propria. Inclusions are also found in the squamous epithelial cells of the tonsils.

Ultrastructurally, infected nuclei of enterocytes are round and swollen and contain numerous typical adenovirus particles (Fig. 1.29F). Affected enterocytes are cuboidal, and the apical portion protrudes slightly into the lumen. The cell membrane and microvilli are irregular, and the terminal web is absent. The rough endoplasmic reticulum shows local distension, with formation of large multivesicular bodies. Eventually, there is complete loss of microvilli, and the cell membrane ruptures with release of cell contents and virus particles into the gut lumen.

The presence of inclusions in enterocytes must be interpreted with caution. A survey in Canada revealed that 4.4% of 5-day- to 24-week-old pigs had adenovirus inclusions in enterocytes, mainly in the ileum. More than 50% of the pigs had diarrhea; however, other enteropathogenic organisms were found in most of these animals. Enteric adenovirus infection may be an incidental infection, and more research is needed to determine the prevalence and significance of adenovirus infection in swine.

The infection must be differentiated from other diseases that may cause villus atrophy, including rotavirus, coronavirus, and coccidiosis.

EQUINE ADENOVIRUS. Equine adenovirus serotype 1 has a worldwide distribution. Subclinical infections are common. Clinical disease occurs mainly as an upper respiratory infection in foals less than 3 months of age. The infection is particularly important in Arabian foals with combined immunodeficiency, in which intestinal involvement is common. The virus is capable of replication in the intestinal epithelium and produces duodenal villus atrophy after experimental infection.

There is a single case report of an unidentified alimentary tract adenovirus infection in an Arabian foal that did not have lesions of combined immunodeficiency. The foal had diarrhea and progressive weight loss over a 2-month period. The macroscopic lesions consisted of ulcers in the distal esophagus and nonglandular mucosa of the stomach. The intestine contained soft to semifluid ingesta.

Histologically, there was necrosis and ulceration of the esophageal and gastric squamous mucosa. Typical adenoviral inclusions were found at all levels of the small intestine. These were most commonly located in the villous epithelial cells, less often in the crypts, and only occasionally in the submucosal glands. There was focal to diffuse villus atrophy through the small intestine.

ADENOVIRUSES IN OTHER SPECIES. **Ovine adenovirus** type 1 has been recovered, in France, from feces of diarrheic lambs that also had coccidiosis. Serotype 4 replicates and persists in the alimentary tract of sheep, but there is no information on the pathogenesis and lesions associated with the virus in this site.

Diarrhea has been reported in dogs with **infectious canine hepatitis**. The virus has a particular tropism for hepatocytes and endothelial cells. The serosal hemorrhages in the gastrointestinal tract and possibly the diarrhea may be related to the vascular damage in the serosa and mucosa, respectively (see the Liver and Biliary System, this volume).

### *Enteric Coronavirus Infection*

Coronaviruses cause disease affecting a number of organ systems in a variety of species, many of which are outside our scope. Among domestic mammals, they cause mainly enteric infections; the major exceptions are feline infectious peritonitis and hemagglutinating encephalomyelitis virus of swine.

*Coronavirus* is the only genus in the Coronaviridae. These viruses have a single-stranded RNA genome. They are pleomorphic or roughly spherical and vary in size from about 70 to 200 nm in diameter, averaging approximately 100 to 130 nm. There is a phospholipid-bearing envelope probably derived in part from host cell membrane. They gain their name from the characteristic "corona" of petal- or droplet-shaped radial surface projections (peplomeres) visible under the electron microscope in negatively stained preparations. Some coronaviruses hemagglutinate. The coronaviruses infecting each species of host appear to be distinctive; some species are infected by more than one type of coronavirus. There are antigenic relationships among some viruses from various hosts, and experimental cross-infection will occur between some host species, generally without pathologic consequences.

Virus replication in the intestinal epithelium by coronaviruses is similar in all the species studied. Coronavirus infects and replicates in the apical cytoplasm of absorptive enterocytes on the tips and sides of intestinal villi. Virions are probably taken up by the apical border of the cell, perhaps by endocytosis or fusion with the plasmalemma. Replication and maturation appear to involve budding of virions from the cytosol through the membrane and into the lumen of vacuoles or cisternae in the smooth endoplasmic reticulum, where they accumulate. Virions are found in tubules of the Golgi apparatus. They may exit via that route from infected cells, by exocytosis at the apical cell membrane, or on the lateral cell surface, since virus particles are often seen lined up between microvilli or in the lateral intercellular space between infected cells. Coronaviruses will also infect some mesenchymal cells in villi and, probably, mesenteric lymph node.

By about 12 to 20 hr after infection, mitochondria in virus-infected cells swell, cisternae of smooth and rough endoplasmic reticulum dilate, the cytoplasm of infected cells loses its electron density, and cells lose their columnar profile. The terminal web is fragmented; microvilli swell and become irregular, perhaps in association with blebbing of the apical membrane. Damaged epithelium may lyse *in situ,* releasing virus retained in cytoplasmic vacuoles, or it may exfoliate into the lumen. Profuse diarrhea usually begins about the time that early cytologic changes become apparent, but before there is extensive epithelial exfoliation.

Exfoliation of damaged epithelium may be massive over a relatively short period of time, leading to the development of villus atrophy, the severity of which largely reflects the degree of initial viral damage. Villi may appear fused along their sides or tips, and during the exfoliative phase some villi with denuded tips may be present. The enterocytes present on villi shortly after the initial exfoliative episode are mainly poorly differentiated, low columnar, cuboidal, or squamous cells, with stubby irreg-

ular microvilli. Within 2 or 3 days, villi begin to regenerate and the epithelium becomes progressively more columnar, though still lacking a well-developed brush border and its complement of enzymes. Defective fat absorption is reflected in the accumulation of lipid droplets in the cytoplasm of enterocytes on villi. This is particularly marked over the period of about 2 to 5 days after experimental inoculation. With progressive epithelial regeneration from the crypts, the villus fusion, which may be the result of adhesion of temporarily denuded lamina propria of adjacent villi, regresses. Separation begins along the basal margins of the adhesions and progresses toward the tips of the villi. There may be focal acute inflammation in the lamina propria of temporarily denuded villi, and a mild mononuclear infiltrate in the stroma of collapsed villi. Though several cycles of virus replication may occur, poorly differentiated enterocytes appear relatively refractory to infection, and the virus titer falls, presumably as local immune mechanisms also come into play. Hyperplasia of epithelium in crypts usually results in eventual resolution of the villus atrophy, restoring normal function.

The diarrhea that occurs is a result of electrolyte and nutrient malabsorption, with some contribution by secretion from cells in crypts, and probably by poorly differentiated surface epithelium in the reparative phase. Mechanisms of diarrhea in villus atrophy have been discussed under Pathophysiology of Enteric Disease. Remission of signs occurs within about 4 to 6 days as regeneration of villi occurs, providing the animal survives the dehydration, electrolyte depletion, and acidosis brought about by diarrhea.

SWINE. Three coronaviruses cause gastrointestinal signs in swine. Hemagglutinating encephalomyelitis virus causes vomiting and wasting disease in suckling piglets; this is a condition mediated mainly by infection of the central and peripheral nervous system (see the Nervous System, Volume 1). **Transmissible gastroenteritis** virus and **coronavirus 777** (porcine epizootic diarrhea virus) both cause syndromes of acute diarrheal disease in all age groups, and chronic diarrhea and runting in weaned pigs. In some areas, coronaviruses, especially transmissible gasteroenteritis, are the major cause of diarrhea in neonatal swine.

Transmissible gastroenteritis may affect swine of any age, causing vomition, severe diarrhea, and in piglets, high mortality. The disease is recognized throughout most of the world, including the United Kingdom, Europe, all of North America, Central and South America, and the Far East. Australia and New Zealand seem to be free.

The epizootiology of transmissible gastroenteritis depends on the overall immune status of the herd and of the various age groups within the herd. Introduction of virus into a naive herd results in a rapid spread of disease with high morbidity affecting all age groups. Sows and older pigs will show transient inappetence, possibly diarrhea, and perhaps vomition. Signs may be more severe in sows exposed to high virus challenge from infected baby pigs. Agalactia may occur in recently farrowed sows. Suckling piglets develop severe diarrhea, and mortality may approach 100% in piglets less than 10 to 14 days old. Older pigs usually develop less severe signs and have lower mortality. In herds with enzootic infection, high piglet mortality may occur in the offspring of recently introduced naive sows, and diarrhea with lower mortality may occur in piglets more than about 2 to 3 weeks of age as milk intake and concomitant lactogenic immunity wane. Infected pigs in the late suckling or weanling age group may runt. Transmissible gastroenteritis is more prevalent in the winter months, perhaps because the virus is not resistant to summer environmental conditions of warmth and sunlight. Baby pigs that are chilled also seem less able to survive the effects of infection.

The severity of disease in baby pigs is related partly to their inability to withstand dehydration, due to their small size. Probably as significant is the differentiation, and low rate of turnover, of epithelium in the neonate. Villi in piglets under ~5 days of age are very tall, about 700–1200 μm long, with a villus:crypt ratio of about 7:1 to 9:1. The surface epithelium is mature and has an extensive vesicular network in the apical cytoplasm associated with uptake of macromolecules and colostrum during the first day or two after birth. Crypts are short and relatively inactive. The population of epithelium susceptible to infection on each villus is therefore large, and the capacity to regenerate new enterocytes is small. By ~3 weeks of age, villi are about 400–700 μm long, and crypts are longer and their epithelium is actively proliferative, so that the villus:crypt ratio is of the order of 3:1 or 4:1. Virus production by infected enterocytes in older pigs seems less efficient, and replacement of cells lost to infection is more rapid, contributing to the relative resistance seen in swine more than 2 to 3 weeks of age.

Pigs infected with transmissible gastroenteritis often continue to suck, and at necropsy the stomach may contain a milk curd. The small bowel is flaccid and contains yellow frothy fluid with flecks of undigested milk. Chyle is not usually evident in mesenteric lymphatics since there is fat malabsorption. The content of the large intestine is usually yellow, and watery to creamy in consistency. The carcass is dehydrated, and there is usually evidence of diarrhea at the perineum. Yellow granular deposits may be evident in the renal medulla and pelvis. These are urates precipitated as the result of dehydration (see the Urinary System, this volume).

The microscopic lesions are those of villus atrophy (Fig. 1.30A–C), the severity of which is a function of the age of the pig and the stage of the disease. The lesions are most severe about the time of the onset of diarrhea in young piglets. In later phases or in older pigs there may be subtotal to moderate atrophy, and the mucosa may be lined by cuboidal to low columnar epithelium, with irregular nuclear polarity and an indistinct brush border. Severe atrophy is readily recognized at necropsy of neonatal piglets, by examination of the mucosa under a dissecting microscope. Lesions are most common in the middle and lower small intestine, and villi in the duodenum are usually tall and cylindric. Lesions may be patchy, and several areas of lower small intestine must be examined before atrophy is considered not to be present. In animals beyond the neonatal age group, atrophy may not be so severe and readily recognized under the dissecting microscope, and the contrast with the normally shorter villi in the duodenum of older pigs is not as marked. Histologic assessment of the gut is essential.

Confirmation of a diagnosis of transmissible gastroenteritis is dependent on the demonstration of specific antigen in epithelium in frozen sections of lower small intestine by immunofluores-

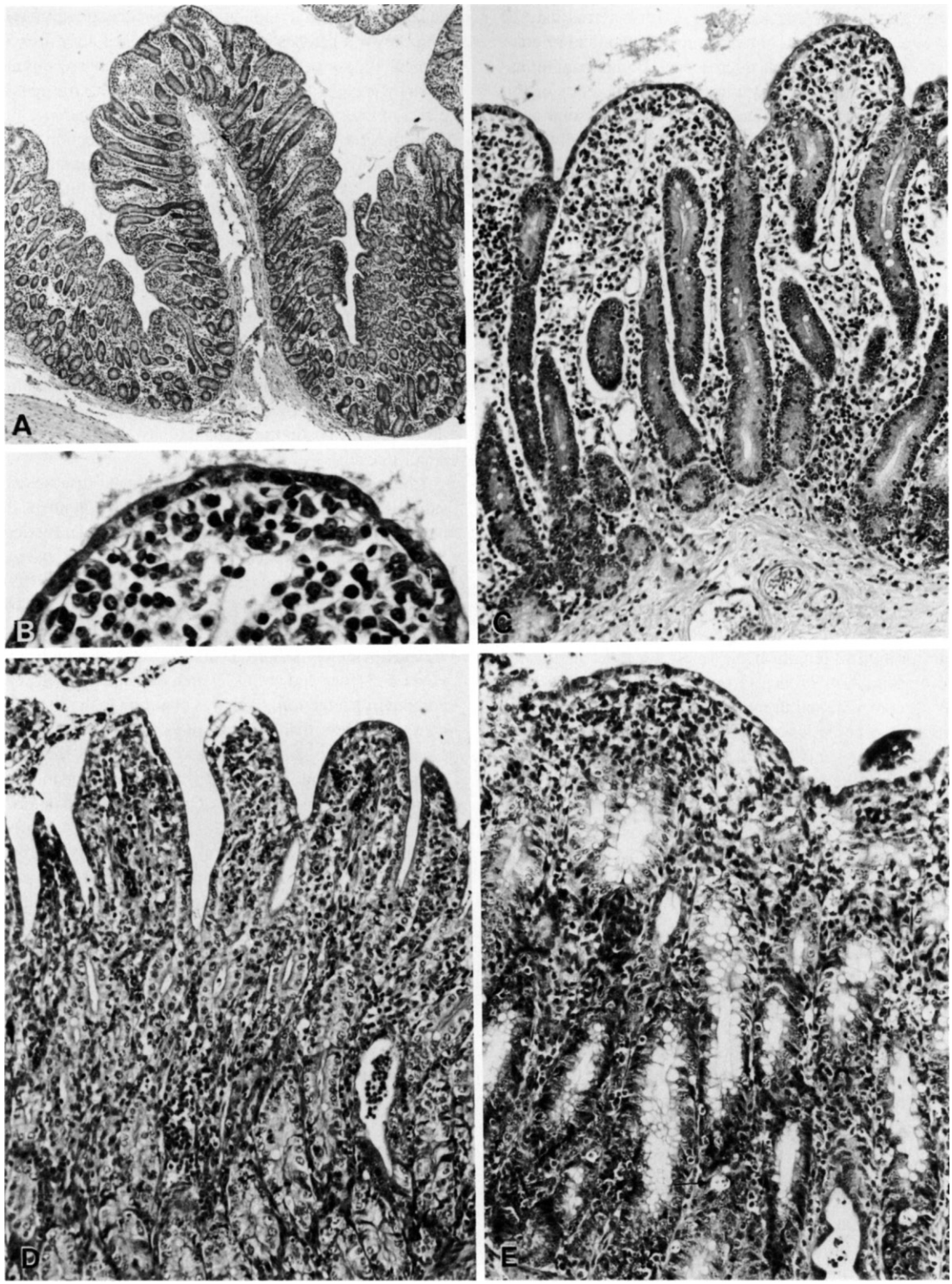


**Fig. 1.30.** (**A–C**) Transmissible gastroenteritis. Pig. (**A**) Atrophy of villi in small intestine. (**B**) Detail of (**C**). Enterocytes on surface of atrophic villus. (**C**) Atrophy of villi, with hypertrophy of crypts of Lieberkühn. Surface epithelium is cuboidal or flattened. (**D** and **E**) Bovine coronavirus infection. (Courtesy of M. Morin). (**D**) Blunt, fused villi with cuboidal surface epithelium. Small intestine. (**E**) Attenuation of surface epithelium and necrosis of gland epithelium (arrow). Colon.

cence or immunoperoxidase techniques. Coronavirus may be found by direct examination of negatively stained ileal or colonic content under the electron microscope. Immunoagglutination of virus in the content may improve the efficiency of this technique and allows differentiation from CV777. Isolation of virus in tissue culture on appropriate cell lines, especially swine testis, may be accomplished, but other methods of diagnosis are faster. To make a diagnosis it is essential to examine material taken from freshly killed piglets in the very early stages of clinical disease, before viral antigen is dissipated.

The differential diagnosis of diarrhea in suckling and weanling pigs includes, in piglets less than 5 days of age, transmissible gastroenteritis and enterotoxic *E. coli* diarrhea as the main candidates, with CV777 and clostridial enterotoxemia a possibility. Piglets 5 days of age to weaning may have transmissible gastrocnteritis, CV777, rotavirus, adenovirus, *Isospora*, *Strongyloides*, or enteropathic *E. coli* infection.

Coronavirus 777 is reported mainly from England and Europe. It appears to cause disease that is essentially similar to transmissible gastroenteritis in epidemiology, pathogenesis, and pathology but may be milder.

CATTLE. Coronavirus infection is a common cause of diarrhea in neonatal beef and dairy calves, either alone or in combination with other agents, particularly rotavirus and *Cryptosporidium*. The virus is capable of infecting absorptive epithelium in the full length of the small intestine, and in the large bowel. Viral antigen is also found in macrophages in the lamina propria of villi and in mesenteric lymph nodes. In field infections, microscopic lesions are most consistently found in the lower small intestine and colon. Calves with coronavirus infection usually develop mild depression but continue to drink milk despite developing profuse diarrhea. With progressive dehydration, acidosis, and hyperkalemia, the animals become weak and lethargic, death ensuing as a result of hypovolemia, hypoglycemia, and potassium cardiotoxicosis. Diarrhea in survivors resolves in 5 or 6 days.

At autopsy, affected animals have the nonspecific lesions of undifferentiated neonatal calf diarrhea. Rarely, mild fibrinonecrotic typhlocolitis is recognized at necropsy in calves with coronavirus infection. Mesenteric lymph nodes may be somewhat enlarged and wet.

The microscopic lesions of coronavirus infection in calves vary with the severity and duration of the infection; villus atrophy in combination with colitis is typical (Fig. 1.30D,E). In the small intestine, villus atrophy is rarely as severe as that seen in neonatal swine. Rather, villi are moderately shortened or have subtotal atrophy, with a villus:crypt ratio of about 1:1 or 2:1. Villi are stumpy, club-shaped or pointed at the tips, and villus fusion may be common. In the early phase of the clinical disease, villi are often pointed and covered by cuboidal to squamous epithelium. Exfoliation of epithelium and microerosion may be evident. Later, the epithelium is cuboidal to low columnar and basophilic, with irregular nuclear polarity and an indistinct brush border. Cryptal epithelium is hyperplastic. The lamina propria may contain a moderate infiltrate of mainly mononuclear inflammatory cells, some of which may have pyknotic or karyorrhectic nuclei. In the early stages of infection, necrosis of cells in mesenteric lymph nodes is associated with viral replication. Peyer's patches in animals examined after 4 or 5 days of clinical illness often appear involuted and are dominated by histiocytic cells. Whether this is the result of viral activity or the effect of endogenous glucocorticoids is unclear.

In the colon during the early phase of infection, surface epithelium may be exfoliating, flattened and squamous, or eroded in patchy areas, and some colonic glands lined by flattened epithelium will contain exfoliated cells and necrotic debris. A moderate mixed inflammatory reaction is present in the lamina propria, and neutrophils may be in damaged glands or effusing into the lumen through superficial microerosions. Later in infection, some dilated, debris-filled colonic glands will remain, but other glands will be lined by hyperplastic epithelium, and the surface epithelium will be restored to a cuboidal or low columnar cell type. Goblet cells are usually relatively uncommon. Colonic lesions may be recognizable in tissues from animals submitted dead, though postmortem change has obscured changes in the small intestine.

Live calves in the early stages of clinical disease are the best subjects for confirmation of an etiologic diagnosis. In calves becoming ill at less than 4 or 5 days of age, enterotoxic *E. coli* is the main alternative diagnosis. Rotavirus, *Cryptosporidium*, and combined infections must be considered in calves 5–15 days of age. Infectious bovine rhinotracheitis, salmonellosis, and bovine virus diarrhea must also be considered. Both salmonellosis and bovine virus diarrhea may be associated with depletion of Peyer's patches and colitis, which can be confused with that of coronavirus infection; neither is common in the strictly neonatal age group (less than 7 to 14 days of age). Demonstration of coronavirus antigen in frozen sections from the lower small intestine, in combination with direct electron microscopy or immunoelectron microscopy of content from the ileum or colon, will confirm the diagnosis. Hemadsorption–elution hemagglutination assay and enzyme-linked immunosorbent assay (ELISA) techniques have also been developed for demonstration of bovine coronavirus in intestinal contents or feces. Preferably, more than one animal should be examined to establish the cause of a herd problem. Isolation of the virus in cell culture can be accomplished in several systems but is not a practical means of rapid diagnosis.

In addition to its implication in neonatal diarrhea in calves, coronavirus has been associated with a diarrheal syndrome in older cattle in New Zealand, Japan, and France compatible with "winter dysentery." Mortality is low or nonexistent. Since it has been demonstrated in feces in the absence of other known pathogens, it has been considered causally associated with outbreaks of diarrhea. That coronavirus does cause colitis in calves makes it a plausible cause of transient colitis and diarrhea in older animals. Whether it is the agent (or one among others) responsible for winter dysentery is not known.

DOGS. A coronavirus was first associated with diarrhea in military dogs in Germany, and subsequent reports have emerged of coronavirus in normal canine feces, or associated with diarrhea, in Australia, North America, and Belgium. Although dogs of all age groups appear to be susceptible to infection by coronavirus, the condition is probably most important as a transient,

generally nonfatal diarrhea in puppies. Coronaviruses were at first associated with the pandemic of diarrhea in dogs in 1978, which was subsequent demonstrated to be due to canine parvovirus-2. Coronavirus is probably widely prevalent in the dog population, but a cause of diarrhea in only a minority of animals. Very few animals with lesions consistent with coronavirus infection are submitted to biopsy or come to autopsy.

Viral replication is reported to occur in the enterocytes of the small intestine, and in experimental infections in neonatal puppies, the lesions resemble the villus atrophy associated with coronavirus infection in other species. Diarrhea began as early as 1 day after inoculation, and in most animals by 4 days. Onset of signs coincided with the development of moderate villus atrophy and fusion. Enterocytes on villi became cuboidal, contained lipid vacuoles, and had an indistinct brush border. Lesions were most consistent and severe in the ileum. Resolution of villus atrophy within 7 to 10 days was associated with remission of signs.

Colonic infection by canine coronavirus was not demonstrated by immunofluorescence in experimental animals, though mild colonic lesions were described, including loss of sulfomucins from goblet cells and some epithelial shedding. In the only available report of lesions due to spontaneous canine coronavirus infection, however, colonic infection and lesions were demonstrated. There was watery content in the lumen of the small and large intestine, and in the cecum and colon fibrin mixed with some blood was evident. Mesenteric lymph nodes were enlarged and edematous. Villus atrophy in the jejunum was inconsistent, but there was necrotic debris in many glands in the cecum and colon. Virus-infected cells were exfoliating into the lumen.

It seems, therefore, that canine coronavirus must be differentiated from common causes of small bowel diarrhea in the young dog, especially parvovirus infection, rotavirus infection, and coccidiosis, and from other forms of acute mucosal colitis. Demonstration of coronavirus particles in intestinal content or feces in association with villus atrophy and/or acute mucosal colitis, and preferably, demonstration of virus-infected cells under the electron microscope, would confirm an etiologic diagnosis in dogs.

OTHER SPECIES. Our understanding of the enteric implications of the coronavirus infections of **cats** is still confused. Feline infectious peritonitis is caused by a coronavirus that cross-reacts serologically with the virus of transmissible gastroenteritis in swine. Equivocal lesions, including mild villus atrophy, have been described in cats with feline infectious peritonitis, but intestinal lesions are not a feature of the disease. A morphologically similar, but probably different coronavirus, that also cross-reacts serologically with feline infectious peritonitis virus has been associated with diarrhea in cats. A third coronavirus, with distinctive peplomere morphology, has been described in the feces of clinically normal cats.

Coronaviruses have been recovered from the feces of **sheep** with transient diarrhea, and they have been associated with severe villus atrophy in several spontaneous outbreaks of diarrhea. No experimental confirmation of the pathogenicity of coronavirus in sheep is available.

Coronavirus infection may also be associated with diarrhea in **foals**, but again, experimental confirmation of pathogenicity is lacking.

### *Rotavirus Infection*

Members of the genus *Rotavirus*, in the Reoviridae, infect the gastrointestinal tract of a very wide range of mammals and birds. In the earlier literature they are frequently referred to as reovirus-like. The ability to infect cells, and serologic specificity of individual types of rotaviruses, are conferred by elements of the outer capsid layer. Some strains of rotaviruses isolated from one species can be transmitted successfully to other species, sometimes producing significant lesions and disease in experimental infections. The factors influencing viral host specificity and virulence and their epizootiologic connotations are unclear. The viruses are probably generally host specific, however, with little significant zoonotic potential.

Rotaviruses infect the absorptive enterocytes and occasionally goblet cells on the tips and sides of the distal half or two-thirds of villi in the small intestine. Virus production and the pathogenesis of infection are similar in all species studied. The mode of entry of rotaviruses into the cell is unclear; presumably it is across the apical cell membrane or by endocytosis at the base of microvilli. Granular "viroplasm" containing incomplete virions is seen in the apical cytoplasm of infected cells, and virions acquire their complete capsid after budding into dilated cisternae of rough endoplasmic reticulum, where they accumulate. Elongate tubular structures are found in the nuclei and rough endoplasmic reticulum of some infected cells. Virus-infected cells are most prevalent 18–24 hr after experimental infection, and they tend to diminish in number rapidly, so that by 3 or 4 days after infection few cells containing viral antigen are present. Infected enterocytes lose cytoplasmic electron density, and mitochondria swell, as does the cell generally. Microvilli become irregular and somewhat stunted, and there may be some blebbing of membranes. Infected cells exfoliate into the intestinal lumen, and virus is probably released by lysis of damaged epithelium prior to or after exfoliation.

The pathogenesis of rotavirus infection resembles that of coronavirus. Exfoliation of infected epithelium over a relatively short period of time results in villus atrophy. The mucosal surface is covered by cuboidal, poorly differentiated epithelium that has an ill-defined microvillous border and may contain lipid droplets in the cytoplasm. Diarrhea is mediated probably by electrolyte and nutrient malabsorption, perhaps exacerbated by the effect of cryptal secretion. It begins about the time of early viral cytopathology, 20–24 hr after infection, and may persist for a variable period, from a few hours to a week or more. Regeneration of the mucosa by epithelium emerging from crypts, and differentiating on reformed villi, is associated with remission of signs in animals surviving the effects of diarrhea.

Rotaviruses are widespread, if not ubiquitous, among populations of most species, and they are relatively resistant to the external environment. Protection against infection in neonates is apparently conferred largely by the presence of lactogenic immunity. Probably, many individuals in a population undergo inapparent infection. Disease is seen in the various species when viral contamination of the environment is heavy, perhaps as a

result of intensive husbandry practices, and lactogenic immunity is waning or absent. Though rotavirus infection is usually associated with younger age groups, naive older animals may become infected, sometimes with the development of diarrhea.

CATTLE. Rotavirus infection is implicated mainly in diarrhea of neonatal beef and dairy calves, both suckled and artifically reared, though there are reports of its association with diarrhea in adult cattle. Diarrhea may be produced in calves by rotavirus infection alone, but the condition is usually considered to be relatively mild or transient in comparison with that induced by enterotoxic *E. coli* or coronavirus. Combinations of agents including rotavirus are frequently involved in outbreaks of diarrhea in neonatal calves. Rotavirus may be implicated in animals developing signs at any time over the period up to about 2 to 3 weeks of age, and it is more commonly encountered in animals more than 4 or 5 days of age.

The gross lesions of rotaviral infection are the nonspecific findings of undifferentiated neonatal diarrhea in calves. Microscopic lesions in the small intestine cannot be differentiated from those of coronavirus infection. They may vary somewhat, depending on the severity of the initial viral damage and the stage of evolution of the sequelae. Blunt, club-shaped villi, mild or moderate villus atrophy, and perhaps villus fusion may be present (Fig. 1.31B,C). Villi are covered by low columnar, cuboidal, or flattened surface epithelium with a poorly defined brush border. There is usually a moderate proprial infiltrate of mononuclear cells and eosinophils or neutrophils, and hypertrophic crypts may be evident. The distribution of lesions may vary between animals and perhaps with time after infection within an individual animal, since the onset of maximal viral damage may not occur synchronously throughout the full length of the intestine. Lesions and viral antigen always should be sought in the distal small intestine, and preferably at several sites along its length. Rotavirus does not cause gross or microscopic lesions in the colon, in contrast to coronavirus.

SWINE. Rotavirus infection is widespread and enzootic in most swine herds, and subclinical infection of piglets is common. It assumes particular importance as a cause of diarrhea in pigs with reduced lactogenic immunity, either as a result of removal of piglets from the sow at an early age or following normal weaning practice. High environmental levels of virus may result in disease in piglets suckling the sow, but in these circumstances the signs are usually relatively mild. Rotavirus may be an important cause of "3-week," "white," or post-weaning scours in piglets 2 to 7 or 8 weeks of age. The signs may resemble those of transmissible gastroenteritis, although rotavirus infection is considered to be less severe. Vomition is less commonly encountered than with transmissible gastroenteritis, but depression, diarrhea, and dehydration are usual. The character of the feces varies with the diet. Steatorrhea occurs in white scours of suckling piglets. Rotavirus infection in swine may be associated with other causes of diarrhea, including *E. coli*, coccidiosis, adenovirus infection, and *Strongyloides*.

The gross and microscopic lesions and pathogenesis of rotavirus infection in pigs resemble those of transmissible gastroenteritis (Fig. 1.31A).

OTHER SPECIES. Rotavirus may cause diarrhea in neonatal **lambs** and has proved a useful model for the demonstration of the importance of lactogenic immunity in preventing the disease. Rotavirus may cause diarrhea in neonatal lambs alone or in combination with enterotoxic *E. coli* and *Cryptosporidium*. The pathogenesis and lesions of rotavirus infection in lambs are like those caused in other species, with the exception that viral infection of the colon may occur.

In **foals** less than 3 or 4 months of age, diarrhea may be associated with rotavirus infections. Limited experimental work indicates that rotavirus alone or in combination with enterotoxic *E. coli* is capable of inducing diarrhea in foals. The natural and experimental disease resembles that seen in other species, with significant viral infection limited to enterocytes in the small intestine, where villus atrophy occurs.

Diarrhea, occasionally fatal, may be caused by rotavirus infection in young **puppies**, especially those less than 1 or 2 weeks of age. Little information is available on the pathology of the disease in naturally or experimentally infected animals, but it is presumably like that in other species.

Rotavirus infection should be sought in cases of diarrhea in young animals of any species, and it should be particularly suspected in animals with villus atrophy in the small intestine.

### *Parvoviral Enteritis*

Members of the genus *Parvovirus* infect a variety of species of laboratory and domestic animals. Syndromes associated with parvovirus infection include disease in cats, dogs, and mink, dominated clinically by enteritis; diarrhea in neonatal calves; and reproductive wastage in swine.

The bovine parvovirus is immunologically distinct. The parvoviruses infecting cats, mink, and dogs are antigenically related, though subtle antigenic differences do exist among them. On the basis of DNA restriction enzyme analysis, feline panleukopenia virus and mink enteritis virus are very closely related to each other and somewhat less related to canine parvovirus-2, the agent causing parvovirus enteritis in dogs. The latter virus is antigenically distinct from canine parvovirus-1, or minute virus of canids, which causes little or no disease. Feline panleukopenia virus, mink enteritis virus, and canine parvovirus-2 are each biologically distinct, varying somewhat in their hemagglutination characteristics, *in vitro* host-cell ranges, infectivity, and virulence in experimentally inoculated hosts. Feline panleukopenia virus and canine parvovirus-2 will infect the heterologous host when inoculated parenterally, apparently without producing significant disease.

Though parvoviruses may infect cells at any phase of the cell cycle, replication is dependent on cellular mechanisms functional only during nucleoprotein synthesis prior to mitosis. Hence the effects of parvovirus infection are greatest in tissues with a high mitotic rate; these include a variety of tissues during organogenesis in the fetus and neonate. In older animals, the proliferative elements of the enteric epithelium, hematopoietic, and lymphoid tissue are particularly susceptible. At the time of virus assembly, large basophilic or amphophilic Feulgen-positive intranuclear inclusions may be found in infected cells, especially in Bouin's-fixed tissues. Parvovirus may be demonstrated in these inclusions by electron microscopy. The chromatin in inclusion-bearing nuclei is usually clumped at the nu-

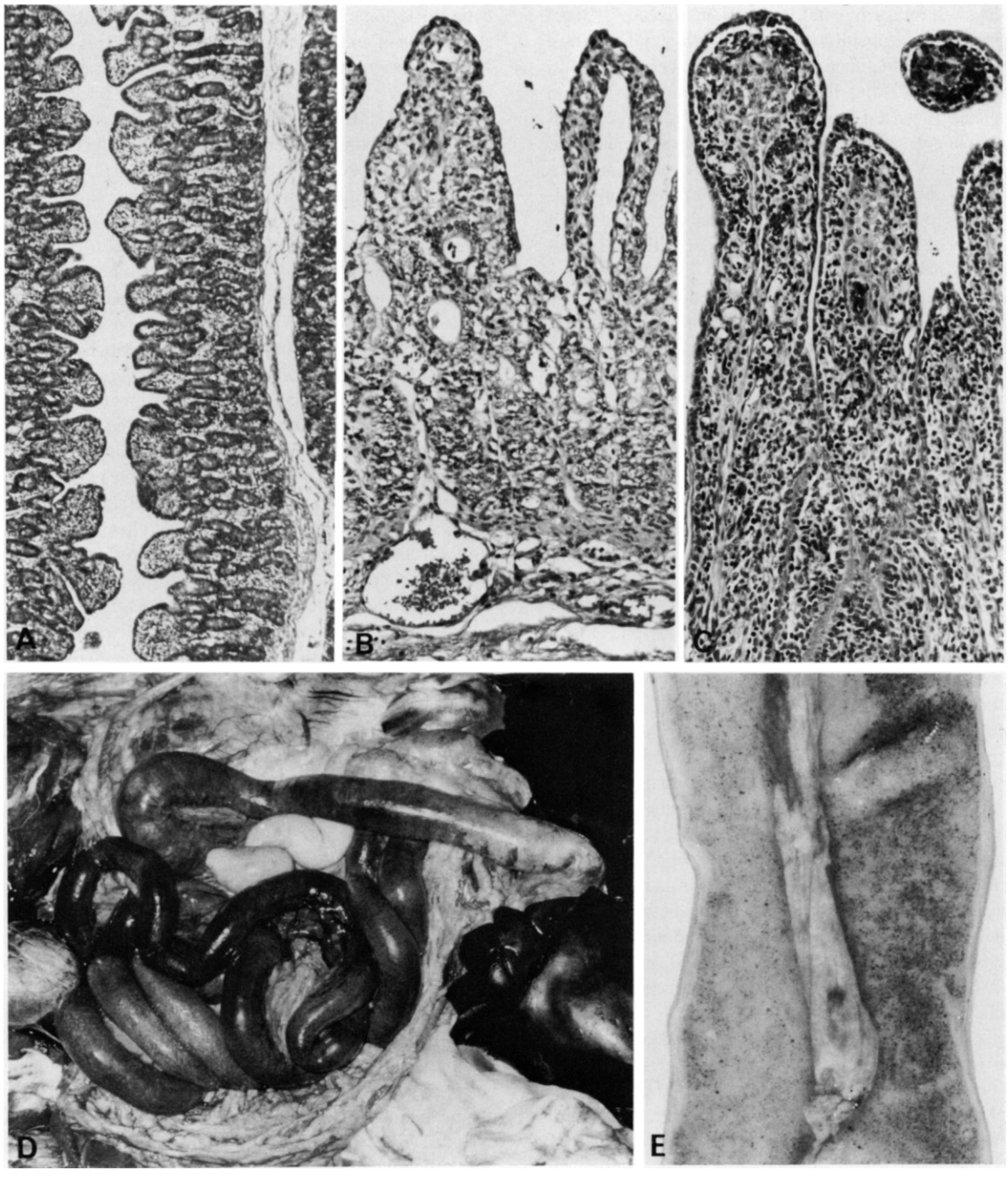


**Fig. 1.31.** (**A**) Porcine rotavirus infection. Atrophy of villi. Small intestine of 3-week-old piglet. (**B** and **C**) Bovine rotavirus infection. (**B**) Stumpy villi with severely attenuated surface epithelium. (**C**) Club-shaped villi with cuboidal or flattened epithelium. (Courtesy of M. Morin.) (**D**) Canine parvovirus infection. Segmental subserosal hemorrhage and mild fibrinous exudation on intestinal serosa. (**E**) Feline panleukopenia. Petechiae and fibrin cast on mucosal surface of small intestine.

clear membrane. Inclusions are most prevalent late in the incubation period, prior to extensive exfoliation or lysis of infected cells. Hence they are not commonly encountered in animals submitted for autopsy after a period of clinical illness culminating in death. Large nucleoli, seen in proliferative cells encountered in the intestine of parvovirus-infected animals, should not be confused with intranuclear inclusions.

The pathogenesis of feline panleukopenia and of canine parvovirus-2 infection is not firmly established but is probably sufficiently similar for them to be considered together here, followed by separate discussions of the specific diseases. Oronasal exposure results in uptake of virus by epithelium over Peyer's patches and, possibly, tonsils. Infection of draining lymphoid tissue is indicated by isolation of virus from mesenteric lymph

nodes 2 days after experimental inoculation. Release of virus into lymph and dissemination of infected lymphoblasts from these sites may result in infection of other central and peripheral lymphoid tissues, including thymus, spleen, lymph nodes, and Peyer's patches, detected 3 or 4 days after infection. Lysis of infected lymphocytes in these tissues releases virus, reinforcing cell-free viremia. Viremia is terminated when neutralizing antibody appears in circulation about 5–7 days after infection. Moderate pyrexia occurs at about this time, perhaps associated with pyrogens released from lysing lymphocytes or with the formation of antigen–antibody complexes.

Infection of the gastrointestinal epithelium is a secondary event. It follows primary viral replication in lymphoid tissue and the resulting dissemination of virus by circulating lymphocytes and cell-free viremia. Peyer's patches are consistently infected at all levels of the intestine, and epithelium in crypts of Lieberkühn over or adjacent to Peyer's patches usually becomes infected a day or so later. Infection of gastrointestinal epithelium at other sites in the gut is less consistent. It may be the result of virus free in circulation or carried by infected lymphocytes homing to the mucosa. Maximal infection of cryptal epithelium occurs during the period about 5–9 days after infection. In experimental studies it tends to be heaviest in the duodenum and cranial jejunum early, but in the ileum later during the course of infection.

The occurrence and severity of enteric signs is determined by the extent of damage to epithelium in intestinal crypts. This seems to be a function of two main factors. The first is the availability of virus, which is influenced by the rate of proliferation of lymphocytes and, therefore, their susceptibility to virus replication and lysis. The second factor influencing the degree of epithelial damage is the rate of proliferation in the progenitor compartment in crypts of Lieberkühn. If many cells are entering mitosis, large numbers will support virus replication and subsequently lyse. Destruction of cells in the crypts of Leiberkühn, if severe enough, ultimately results in focal or widespread villus atrophy and, perhaps, mucosal erosion or ulceration. The recognition, evolution, and sequelae of radiomimetic insult to the intestine, such as that caused by parvovirus, have been described under Epithelial Renewal in Health and Disease.

Regeneration of cryptal epithelium and partial or complete restoration of mucosal architecture will occur if undamaged stem cells persist in most affected crypts and the animal survives the acute phase of clinical illness. In some survivors, focal villus atrophy is associated with local "drop out" of crypts completely destroyed by infection. Rarely, in animals recovering from acute disease, chronic malabsorption and protein-losing enteropathy are associated with persistent areas of ulceration caused by more extensive loss of crypts and collapse of the mucosa.

The relatively low rate of replication of intestinal epithelium in germ-free cats explains failure to produce significant intestinal lesions and clinical panleukopenia in experimentally infected animals. In spontaneous cases, the lower prevalence of parvoviral lesions in the colon and stomach, in comparison with the small intestine, reflects the relatively lower rate of epithelial proliferation in those tissues. The consistency of epithelial lesions in the mucosa over Peyer's patches probably results from high local concentrations of virus derived from infected lymphocytes in the dome and follicle. Possibly this is coupled with local stimulation of epithelial turnover by lymphokines released by T lymphocytes in the vicinity. Variations in the rate of epithelial proliferation related to age, starvation, and refeeding or concomitant parasitic, bacterial, or viral infections may also influence the susceptibility of crypt epithelium to infection and therefore affect the extent and severity of intestinal lesions and signs. It is difficult to duplicate fatal parvovirus infection experimentally, and work is required to define further the host factors influencing the severity of disease.

Diarrhea in parvovirus infections is mainly the result of reduced functional absorptive surface in the small intestine. Effusion of tissue fluids and blood from a mucosa at least focally denuded of epithelium probably also contributes to diarrhea. Dehydration and electrolyte depletion are the result of reduced fluid intake, enteric malabsorption, effusion of tissue fluid, and in some animals, vomition. Hypoproteinemia is common, and anemia may occur in severely affected animals; both are exacerbated by rehydration. Anemia reflects hemorrhage into the gut.

Proliferating cells in the bone marrow are also infected during viremia. Lysis of many infected cells is reflected in hypocellularity of the marrow caused by depletion of myeloid and erythroid elements, particularly the former. Megakaryocytes also may be lost, but they seem the least sensitive cell population in the marrow. Reduction in the number of neutrophils in circulation ensues quickly in severely affected animals. This is due to failure of recruitment from the marrow, and peripheral consumption, especially in the intestine. Transient neutropenia, of about 2 or 3 days duration, occurs consistently in cats, and less commonly in dogs. In surviving animals, regeneration of depleted myeloid elements from remaining stem cells results in restoration of the circulating population of granulocytes within a few days. Neutrophilic leukocytosis with left shift may occur during recovery.

Lymphopenia, relative or absolute, results consistently from viral lymphocytolysis in all infected lymphoid tissue. Relative lymphopenia is more consistently observed in dogs than neutropenia. When lymphopenia and neutropenia occur together, the combined leukopenia may be profound in both dogs and cats. In dogs surviving the lymphopenic phase, numbers of circulating lymphocytes return to normal within 2 to 5 days as regenerative hyperplasia occurs in lymphoid tissue throughout the body. Lymphocyte number increases rapidly, sometimes producing lymphocytosis in recovering dogs. However, there is evidence of at least transient immunosuppression in gnotobiotic pups subclinically infected with canine parvovirus-2. Transient depression of T-cell response to mitogens occurs in cats a week after experimental infection with feline panleukopenia virus, but immunosuppression by this agent appears to be of little practical significance.

Most infected cats and dogs do not develop clinical disease. When it occurs, signs usually begin during the late viremic phase, about 5–7 days after infection. Severe involvement of the gut is the major cause of mortality. Shedding of infective virus in feces begins about 3–5 days after infection, when Peyer's patches and cryptal epithelium first become infected. Virus shedding persists until coproantibody appears to neutralize virus entering the gut, about 6–9 days after infection. Virus-infected

cells still may be detected in crypts and Peyer's patches at this time, and virus complexed with antibody may be found in feces or intestinal content by direct electron microscopy. Attempts to isolate virus from tissues or feces after several days of clinical disease or at death, however, are often thwarted by the fact that virus is neutralized by antibody present in tissue fluids. Persistent or sporadic shedding of virus by recovered animals may be the result of virus replication in cells entering mitosis days or weeks after they were infected during the viremic phase.

Infection of the fetus during late prenatal life by feline panleukopenia virus causes anomalies of the central nervous system, mainly hypoplasia of the cerebellum. Although reproductive success may be depressed in kennels infected with canine parvovirus-2, parvovirus infection has not been conclusively associated with fetal or congenital disease in dogs. Rarely, however, a syndrome of generalized infection may occur in neonatal dogs. Infection of proliferating cardiac myocytes in young puppies with canine parvovirus-2 results in a nonsuppurative myocarditis and sequelae of acute or chronic heart failure. Similar syndromes have not been associated with spontaneous feline panleukopenia infection.

PANLEUKOPENIA. The virus of panleukopenia (infectious feline enteritis) infects all members of the Felidae, as well as mink, raccoons, and some other members of the Procyonidae. Panleukopenia virus is ubiquitous in environments frequented by cats, and infection is common, though generally subclinical. The disease usually occurs in young animals exposed after decay of passively acquired maternal antibody, but it may occur in naive cats of any age. Clinical signs of several days duration, including pyrexia, depression, inappetence, vomition, diarrhea, dehydration, and perhaps anemia, may be evident in the history. Many cases, however, particularly poorly observed animals or those prone to wander, may present as "sudden death." The pathogenesis of panleukopenia has been considered above, with that of canine parvovirus-2 infection in dogs. Lesions of central nervous system in kittens are considered in the Nervous System (Volume 1).

At autopsy, external evidence of diarrhea may be present, the eyes may be sunken, and the skin is usually inelastic, with a tacky subcutis reflecting dehydration. Rehydrated animals may have edema, hydrothorax, and ascites due to hypoproteinemia. There is pallor of mucous membranes, fat, and internal tissues in anemic animals. Gross lesions of internal organs most consistently involve the thymus and the intestine. The thymus is markedly involuted and reduced in mass in young animals. Enteric lesions may be subtle and easily overlooked in some cases. Hence it is mandatory that intestine be examined microscopically despite the apparent absence of gross change.

The intestinal serosa may appear dry and nonreflective, with an opaque, ground-glass appearance. Uncommonly in cats there may be petechiae or more extensive hemorrhage in the subserosa or muscularis of the intestinal wall. The small bowel may be segmentally dilated and can acquire a hoselike turgidity in places, perhaps due to submucosal edema. However, turgidity is difficult to assess in the intestine of the cat. The content is usually foul smelling, scant, watery, and yellowish gray at all levels of the intestine. The mucosa may be glistening gray or pink, with petechiae, perhaps covered by fine strands of fibrin (Fig. 1.31E). Patchy diphtheritic lesions may be present, especially over Peyer's patches in the ileum. Flecks of fibrin, and sometimes casts, may be in the content in the lumen. Formed feces are not evident in the colon. Lymph nodes may be prominent at the root of the mesentery. Gross lesions elsewhere in the carcass are usually restricted to pulmonary congestion and edema in some animals, and pale gelatinous marrow in normally active hematopoietic sites.

Microscopic changes are consistently found in fatal cases in the intestinal tract and are usual in lymphoid organs and bone marrow. The intestinal lesions vary with the severity and duration of disease. Their interpretation may be obscured by autolysis. Lesions may be patchy, and several levels of gut should be examined, preferably including ileum and, if possible, Peyer's patch. During the late incubation period and early phase of clinical disease, there is infection of crypt-lining epithelium. Intranuclear inclusions may be found, and there is exfoliation of damaged epithelium into the lumen of crypts. Crypts appear dilated and are lined by cuboidal or more severely attenuated epithelium. The lamina propria between crypts contains numerous neutrophils and eosinophils at this time, and some emigrate into the lumen of crypts, where they join the epithelial debris.

Subsequently, severely damaged crypts may be lined by extremely flattened cells and by scattered large, bizarre cells with swollen nuclei and prominent nucleoi (Fig. 1.32C). Enterocytes covering villi are not affected, but as they progress off the villus, they are replaced by a few cuboidal, squamous or bizarre epithelial cells, so that villi in affected areas undergo progressive collapse. If cryptal damage is severe and widespread, the mucosa becomes thin and eroded or ulcerated, with effusion of tissue fluids, fibrin, and erythrocytes. Inflammatory cells are usually sparse in the gut of such animals, and superficial masses of bacteria may be present, occasionally accompanied by locally invasive fungal hyphae or pseudohyphae. In less severely affected animals with disease of longer duration, corresponding to about 8 to 10 days after infection, scattered focal drop out of crypts, or focal mucosal collapse and erosion or ulceration, may be evident. Remaining crypts recovering from milder viral damage show regenerative epithelial hyperplasia (Fig. 1.32D) in these animals. Mucosal lesions are often most marked in the vicinity of Peyer's patches.

Lesions in the colon generally resemble those found in the small bowel, though they are frequently less severe or more patchy in distribution. When sought, colonic lesions are found in about half of fatal cases of panleukopenia. Gastric lesions resulting from damage to mitotic epithelium are relatively uncommon in cats. They are recognized by flattening of basophilic cells lining the narrowed isthmus of gastric fundic glands, with some reduction in number of parietal cells in the upper portion of the neck of glands.

Lesions of lymphoid organs during the early phase of the disease consist of lymphocytolysis in follicles and paracortical tissue in lymph nodes, in the thymic cortex and splenic white pulp, and in gut-associated lymphoid tissue. Infected cells rarely may contain inclusion bodies. Lymphocytes are markedly depleted in affected tissue, and large histiocytes are prominent, often containing the fragmented remnants of nuclear debris.

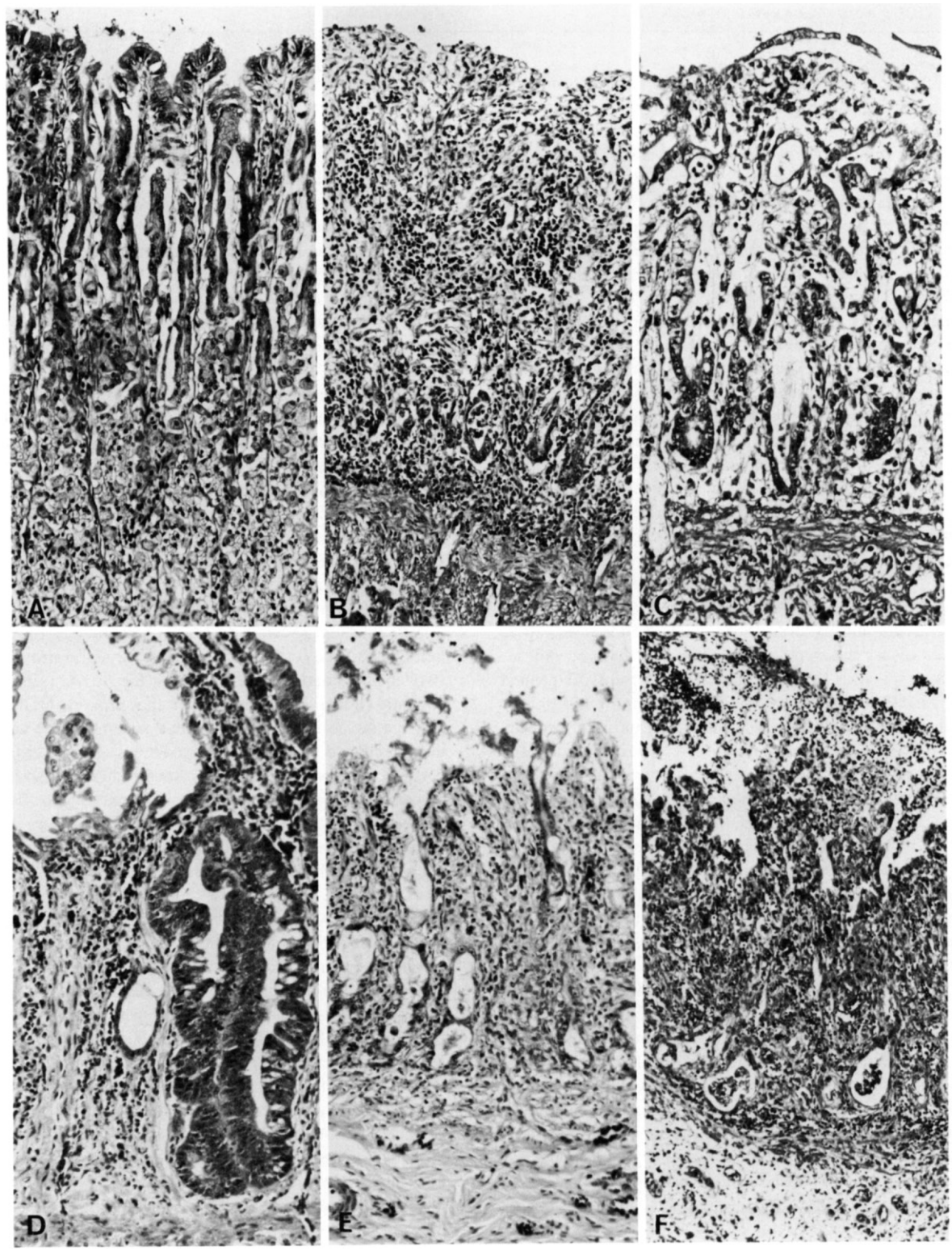


**Fig. 1.32.** (**A–D**) Parvovirus infections. (**A**) Attenuation of epithelium lining isthmus and upper neck of fundic gastric glands. Dog. (**B**) Loss of crypts of Lieberkühn and collapse of proprial stroma in small intestine. Remnants of crypt-lining epithelium persist deep in lamina propria. Dog. (**C**) Severe atrophy of villi associated with damage to crypts of Lieberkühn. Cat. Attenuation of surface epithelium and depletion of proprial inflammatory infiltrate. (**D**) Loss of crypts and collapse of proprial stroma. Gland is lined by hyperplastic epithelium. Mink virus enteritis. (**E**) Small intestinal mucosa following cyclophosphamide. Radiomimetic lesion, with attenuation of crypt-lining cells, and atrophy of villi. (**F**) Small intestine, sequel to transient ischemia 2 days previously. Ulcerated mucosa and dilated crypts lined by attenuated epithelium and containing necrotic debris. Inflammatory cells and fibrin exude from the mucosa, which is devoid of villi.

Follicular hyalinosis, the presence of amorphous eosinophilic material in the center of depleted follicles, may be seen. Erythrophagocytosis by sinus histiocytes may be seen in lymph nodes, especially those draining the gut. Severely depleted Peyer's patches may be difficult to recognize microscopically. Later in the course of clinical disease, corresponding to the period beyond about 7 or 8 days after infection, prominent regenerative lymphoid hyperplasia may be found.

In severely affected animals at the nadir of the leukopenia, virtually all proliferating elements in the bone marrow may be depleted. The extremely hypocellular, moderately congested marrow is populated only by scattered stem cells. Milder lesions affect mainly the neutrophil series, generally sparing megakaryocytes and the committed erythroid elements. During the later phases of the disease, marked hyperplasia of stem cells and, eventually, of amplifier populations in the various cell lines is evident.

In the liver, dissociation and rounding up of hepatocytes, and perhaps some periacinar atrophy and congestion, may be evident. This is probably associated with dehydration and anemia. Pancreatic acinar atrophy is also usual, reflecting inappetence. The lung may be congested and edematous. In leukopenic animals, few white cells are seen in circulation in any organ.

A diagnosis of feline panleukopenia may be made on the basis of the characteristic microscopic intestinal lesions, in association with evidence of involution or regenerative hyperplasia of lymphoid and hematopoietic tissues. Inclusions may be sought in these tissues but are usually present in significant numbers only during the late incubation and early clinical period. Application of fluorescent-antibody or immunoperoxidase techniques may identify viral antigen in tissue as late as 8 to 10 days after infection.

CANINE PARVOVIRUS-2 INFECTION. Canine parvovirus-2 infection presumably resulted by mutation of the virus of feline panleukopenia. It appeared spontaneously and virtually simultaneously in populations of dogs on several continents in 1978 and rapidly spread worldwide. Retrospective observation of antibody to this virus in the canine population suggests that it was circulating unnoticed in western Europe in late 1976 and 1977. In addition to domestic dogs, several species of wild canids, including coyotes, bush dogs, crab-eating foxes, raccoon dogs, and maned wolves, are susceptible to infection.

Enteric disease due to this virus was epizootic for several years in naive populations of dogs, affecting animals of all ages. As the prevalence of antibody due to natural infection and vaccination increased in the dog population, the problem subsided to one of an enzootic disease. It now affects those animals with reduced levels of passively acquired maternal immunity, or scattered naive individuals. During the epizootic period, nonsuppurative viral myocarditis due to canine parvovirus-2 was prevalent in the juvenile offspring of naive bitches unable to protect pups with maternal antibody. This syndrome has declined in frequency as the prevalence of antibody has increased in the reproductive population. Enteric and myocardial disease rarely occur together in the same individual or cohort of animals. Occasional cases of generalized parvovirus infection are reported in susceptible neonates. Necrosis and inclusion bodies are found in organs such as kidney, liver, lung, heart, gut, and vascular endothelium. They are presumably related to mitotic activity during organogenesis.

Dogs with typical disease due to canine parvovirus-2 become anorectic and lethargic and may vomit and develop diarrhea, perhaps in association with transient moderate pyrexia. Relative or absolute lymphopenia or leukopenia of 1 or 2 days duration may occur. Diarrhea may be mucoid or liquid, sometimes bloody, and is malodorous. After a period of 2 or 3 days, dogs either succumb to the effects of dehydration, hypoproteinemia, and anemia or begin to recover.

Gross findings at autopsy of fatal cases are those of dehydration, accompanied by enteric lesions characteristic of the disease. There is often segmental or widespread subserosal hemorrhage, often extending into the muscularis and submucosa of the intestine. The serosa frequently appears granular due to superficial fibrinous effusion (Fig. 1.31D). Peyer's patches may be evident from the serosal and mucosal aspects as deep red oval areas several centimeters long. The intestinal contents may be mucoid or fluid; sometimes they look like tomato soup due to hemorrhage. The mucosa is usually deeply congested and glistening or covered by a patchy fibrinous exudate. Severe enteric lesions may be widespread or segmental, and their distribution is irregular; thus tissues from several levels of the small intestine should be selected for microscopic examination. Gross changes are less common in the colon. The stomach may have a congested mucosa and contain scant bloody or bile-stained fluid. Mesenteric lymph nodes may be enlarged, congested, and wet, or reduced in size. Thymic atrophy is consistently present in young animals, and the organ may be so reduced in size as to be difficult to find. The lungs often appear congested and have a rubbery texture.

The microscopic lesions in stomach, small intestine (Fig. 1.32A,B), colon, lymphoid tissue, and bone marrow due to canine parvovirus-2 infection do not differ significantly from those described above in cats with panleukopenia. Gastric lesions are perhaps more frequently encountered in dogs with parvovirus infection. Small intestinal lesions are invariably severe in fatal cases. The colon is involved in a minority of animals. Pulmonary lesions such as alveolar septal thickening by mononuclear cells, congestion, and effusion of edema fluid and fibrin into the lumina of alveoli may be related in part to terminal Gram-negative sepsis. However, interstitial pneumonitis is commonly found and may be a function of uncomplicated viral infection. Periacinar atrophy and congestion in the liver are attributable to anemia, hypovolemia, and shock, and prominent Kupffer cells probably reflect endotoxemia.

The diagnosis of parvoviral enteritis in dogs follows the principles described for that of panleukopenia in cats. The disease must be differentiated from canine coronavirus infection, which appears to be very rarely fatal, and from canine intestinal hemorrhage syndrome, shock gut, intoxication with heavy metals or warfarin, infectious canine hepatitis, and other causes of hemorrhagic diathesis. Involution of gut-associated lymphoid tissue caused by parvovirus must be differentiated from that due to canine distemper.

BOVINE PARVOVIRUS INFECTION. The antigenically distinct bovine parvoviruses have been recognized since at least the 1960s and apparently occur widely in cattle populations. Bovine

parvovirus is nondefective and replicates independently. Isolations have been made from the feces of normal and recently diarrheic calves as well as from conjunctiva, and from an aborted fetus. The role of bovine parvovirus infection as a significant pathogen is unclear. It is rarely diagnosed as a cause of death and unless sought specifically by culture or direct electron microscopy, would be missed as a cause of clinical diarrhea. Its significance may be greatest in neonatal calves and animals exposed while passive maternal antibody levels are waning.

The pathogenesis of infection with bovine parvovirus is not well defined. Viral antigen has been identified by immunofluorescence in the nuclei of epithelium in intestinal crypts and in cells in thymus, lymph nodes, adrenal glands, and heart muscle, suggesting similarities to the pathogenesis of feline panleukopenia and canine parvovirus-2. The pathology of natural or experimental infections has not been described. Intravenous inoculation of bovine parvovirus into young calves causes severe watery diarrhea and prostration. Milder diarrhea occurs in calves infected orally. The severity of the disease may be potentiated by concurrent infection with other enteric pathogens.

### *Bacterial Diseases*

#### *Escherichia coli*

*Escherichia coli* infections in animals and humans cause disease by at least five different general mechanisms. The first is **enterotoxic colibacillosis**: secretory small bowel diarrhea stimulated by enterotoxins produced by *E. coli* colonizing the muscoa of the small intestine. This condition is an important cause of diarrhea in neonatal animals. The second mechanism involves **enterocyte-adherent** *E. coli* strains, which colonize the surface of epithelial cells, do not produce recognized enterotoxin, but are associated with villus atrophy. They currently are not known to occur in domestic animals. **Enterotoxemic colibacillosis** is represented by **edema disease** of swine. In this condition a toxin produced by specific strains of *E. coli* colonizing the small intestine is absorbed and has its pathogenic effect on tissues other than the gut. Postweaning *E. coli* enteritis is also caused by the same strains, presumably by different means. **Enteroinvasive** *E. coli* strains induce disease by a fourth mechanism. They have the capacity to invade the epithelium of the intestine and cause acute exudative enteritis, often endotoxemia, and perhaps terminal septicemia. Enteroinvasive colibacillosis is apparently rare in domestic animals. **Septicemic colibacillosis** is the final, and common, manifestation of disease caused by this organism. The intestine is not necessarily the portal of entry, and there may not be alimentary disease. The signs of *E. coli* septicemia are referable mainly to bacteremia, endotoxemia, and the effect of bacterial localization in a variety of tissue spaces throughout the body.

ENTEROTOXIC COLIBACILLOSIS. Enterotoxic colibacillosis is one of the major causes of diarrhea in neonatal pigs, calves, and lambs. It is also a significant cause of diarrhea in humans. Consequently, considerable information is available on the pathogenesis and prophylaxis of this condition.

Two major attributes confer virulence on certain diarrheagenic strains of *E. coli*. These are the ability to colonize the intestine and the capacity to produce toxins that stimulate secretion of electrolyte and water by the intestinal mucosa. Colonization and enterotoxin production must occur together for disease to occur. The diarrhea produced by enterotoxic *E. coli* is accompanied by minor microscopic evidence of inflammation and by little or no architectural change in the mucosa. As a result, overt enteritis usually is not evident at autopsy, and the disease is part of the syndrome of undifferentiated diarrhea of neonatal animals.

**Intestinal colonization** results from the capacity of certain strains of *E. coli* to adhere to the surface of enterocytes on villi in the small intestine (Fig. 1.33A) and to proliferate there. By adhering to the mucosal surface, they are able to resist the normal peristaltic clearance mechanisms. Large numbers of organisms, of the order of $10^7$ or more per gram of mucosa, or 20 to 30 per enterocyte, line the surface of villi. The ability to attach to enterocytes is conferred on most adhesive strains of *E. coli* by pili- (= fimbriae) fibrillar proteinaceous appendages that protrude from the surface of the bacterial cell; they bind with receptors on the surface of the cell (Fig. 1.33B). The cell receptors have not been clearly defined; carbohydrate moieties in mucosal glycolipids are probably involved. The pilar adhesins are distinct from type 1 fimbriae present on many strains of *E. coli*. Type 1 fimbriae do not confer recognized virulence characteristics on the organism.

A number of different pilar adhesins, which promote colonization, have been recognized on *E. coli* infecting domestic animals. **Adhesin K88** occurs in at least three combinations of four antigenic subunit variants, K88ab, ac, and ad, on *E. coli* infecting piglets. Five phenotypes of swine are recognized with resistance or susceptibility to enterocyte adhesion by the different K88 antigenic variants. **Adhesin 987P** is found on some strains of *E. coli* infecting piglets, as is F-41. **Adhesin K99** is also found on some strains infecting swine and is the only adhesin known to promote *E. coli* colonization in calves and lambs. Enterotoxic strains of *E. coli* lacking K88, K99, and 987P, but adherent to porcine enterocytes, are also recognized. Bacteria possessing K88 colonize the entire small bowel, while those with K99 or 987P adhere mainly in the jejunum and ileum.

Genetic control of pilus production is invested in plasmid DNA, with the exception of 987P, information for which appears to be encoded in chromosomal DNA. Combinations of more than one type of pilus adhesin occur on a single strain, exceptionally. Susceptibility to bacterial pilus adhesins appears to be somewhat age related; the ability of adhesin-bearing *E. coli* to colonize the small intestine is greatest in animals only a few days old. Stimulation of maternal immunity to appropriate pilus antigens causes antibody secretion in the milk, which agglutinates adhesins and prevents colonization of the gut of suckling animals.

**Enterotoxin production** is of two types, heat labile (LT) or heat stable (ST), both coded by plasmic DNA. In strains of *E. coli* causing diarrhea in animals, adhesin and enterotoxin production are generally controlled by separate plasmids. However, certain combinations of adhesin and toxin tend to occur together.

Heat-labile enterotoxin resembles cholera toxin in its structure and mechanism of action. It is a large molecular weight, antigenic protein, comprised of A and B subunits. The B sub-

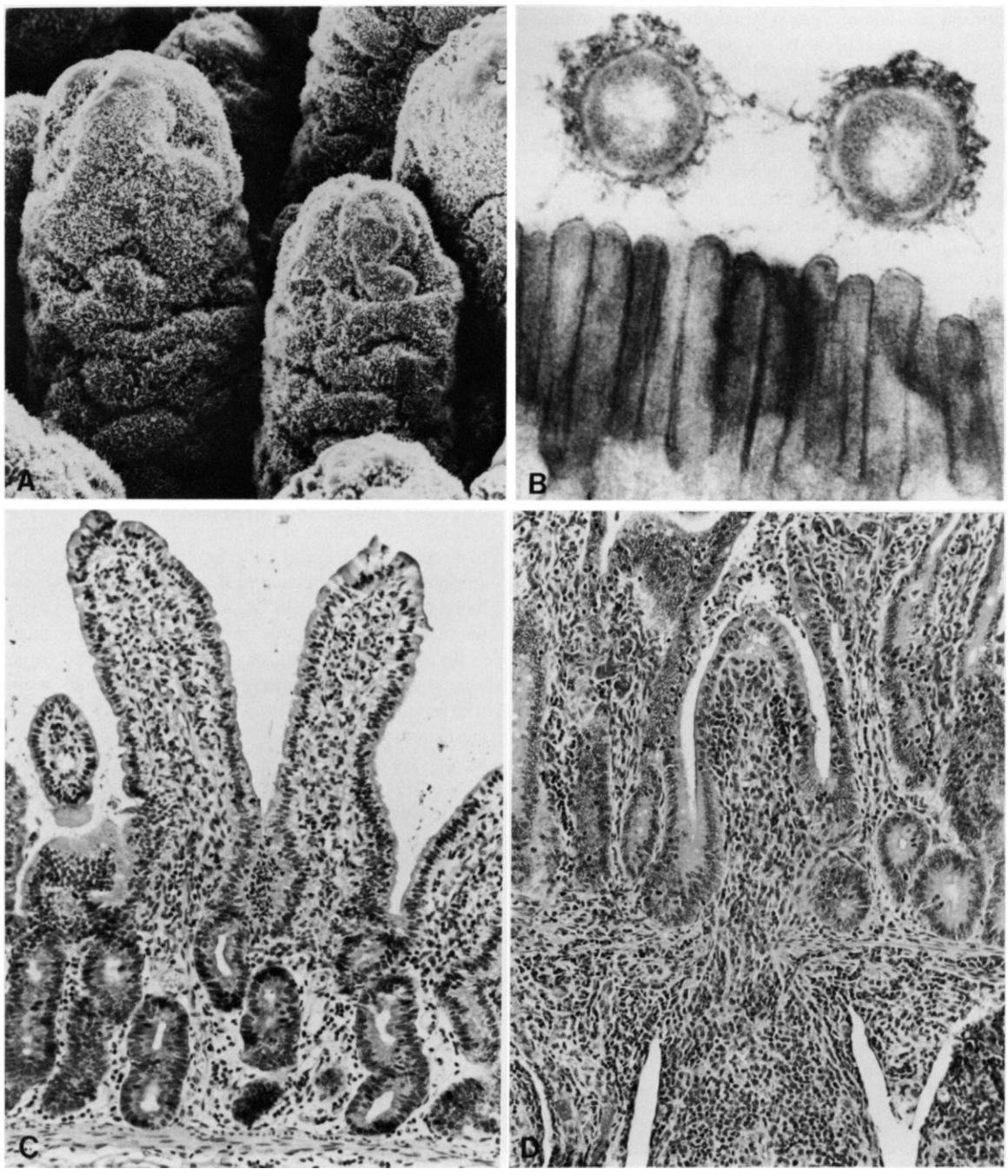


**Fig. 1.33.** (**A**) Scanning electron micrograph. *Escherichia coli* adherent to the surface of villi. Small intestine. Calf. (**B**) Transmission electron micrograph. Fimbriate *E. coli* adherent to microvilli. Small intestine. Calf. (**C**) Enterotoxic colibacillosis. Calf. Mild neutrophil infiltrate in lamina propria and between bases of villi. Atrophy of villi not evident, surface epithelium normal. (**A**–**C** courtesy of J. J. Hadad and C. L. Gyles.) (**D**) Enterotoxic colibacillosis. Calf. Neutrophil effusion into lumen over dome of Peyer's patch. (Courtesy of J. E. C. Bellamy.)

units bind to oligosaccharide moieties of ganglioside $GM_1$ in the apical cell membrane. The toxin complex then undergoes dissociation and the A subunit enters the cell, where it stimulates the adenyl cyclase system. Via mediation of cAMP it causes secretion of chloride, with sodium and water following, from the crypts. Cotransport of sodium chloride and associated water absorption by enterocytes on villi is probably shut down at the same time, though other mechanisms of sodium and water absorption are not impaired.

Heat-stable enterotoxin is a poorly antigenic, low molecular weight polypeptide, which occurs in several forms with differing physical and functional characteristics. These are reflected

by variations in host and age-group susceptibility to the toxin. The mechanism of action of the heat-stable toxin is not clearly understood. It may act by reducing chloride absorption and perhaps by causing cellular secretion of electrolyte and water, associated with accumulation of intracellular cGMP. This is probably mediated by stimulation of a transmembrane flux of calcium ions by toxin, with intracellular generation of prostaglandins that active guanylate cyclase. The rate of intestinal transit may also be reduced by ST-enhancing proliferation of *E. coli* and perhaps promoting absorption of toxin. The effect is rapid in onset and requires persistence of toxin, in contrast to that of the heat-labile toxin, which has a latent period after exposure and is relatively irreversible.

Enterotoxic colibacillosis in **pigs** is among the commonest causes of diarrhea in animals from a few hours old to about a week of age. At autopsy it cannot be separated readily from the other common causes of undifferentiated neonatal diarrhea without laboratory assistance. Generally there is dehydration, usually with evidence of diarrhea, or a history of its occurrence in the herd. Other than the presence of characteristic fluid content in the flaccid small and large bowel, perhaps with clotted milk still in the stomach, the internal findings are unremarkable. In order to establish the cause, one or more piglets early in clinical disease should be killed and examined. Tissue sections from several levels of the small bowel should be fixed rapidly. Bacterial cultures of intestinal content should be made. Intestinal content for electron microscopy, and mucosal smears or frozen tissue for fluorescent-antibody tests, should be reserved to incriminate or eliminate the intestinal viruses.

In contrast to the viruses and *Isospora,* enterotoxic *E. coli* does not consistently cause significant villus atrophy (Fig. 1.34A). Small clumps or a continuous layer of bacteria may be found on the surface of enterocytes on villi in mucosal sections (Fig. 1.34B). Neutrophils may be present in the proprial core of villi and transmigrating the epithelium into the lumen. Inflammation is not marked, however, and epithelial lesions and erosion generally are not seen in well-fixed tissue in enterotoxic colibacillosis. Rare cases of villus atrophy associated with *E. coli* infection do occur in neonatal swine. These are considered under Enteroinvasive Colibacillosis.

In **calves**, enterotoxic colibacillosis accounts for a significant proportion of cases of undifferentiated neonatal diarrhea; depending on the locality and circumstances, up to 20 to 30% of cases may be due to *E. coli*. The infections typically occur within the first 2 or 3 days of life, probably due to the resistance of enterocytes in older calves to K99 adhesion. In that age group they cause profuse yellow diarrhea and severe dehydration, with a high mortality in untreated animals. Enteric colibacillosis must be differentiated from the other major causes of undifferentiated diarrhea in neonatal animals; coronavirus, rotavirus, and *Cryptosporidium*. Enterotoxic *E. coli* is often found in combination with coronavirus or rotavirus infection. Experimental evidence suggests that prior or concomitant infection with rotavirus may permit or promote establishment by enterotoxic *E. coli* in calves older than 2 days. Combined infection may enhance the severity of disease in calves less than, and in some cases more than 2 days of age.

The gross findings in calves with enterotoxic colibacillosis are the nonspecific appearances of diarrhea and dehydration. The infection is differentiated in tissue sections from the other infectious causes of this syndrome in calves by the absence of severe villus atrophy and by the presence of bacteria on the surfaces of villi in the distal small intestine. As in piglets, application of a variety of presumptive or specific tests for the presence of enterotoxic *E. coli* in the intestine confirms the diagnosis.

Enterotoxic *E. coli* is not considered to induce diarrhea by villus atrophy and malabsorption, in contrast to the significant viruses and *Cryptosporidium,*. In the jejunum and ileum of calves, however, where bacterial colonization of the surface of enterocytes is heavy, stumpiness, lateral corrugation and contraction, or moderate atrophy of villi may be present. It is sometimes associated with villus fusion later in the course of the disease and as a result may resemble viral lesions. Cells on the surface of villi may be cuboidal, and subepithelial capillaries may be dilated. Transmigration of neutrophils from the lamina propria to the lumen is present in colonized areas of gut, especially in the vicinity of the domes over Peyer's patches (Fig. 1.33D). Colonization of the mucosa precedes the development of atrophy, which seems to occur prior to the onset of diarrhea. Atrophy of villi is related to degeneration and exfoliation of individual epithelial cells or small groups of enterocytes from the surface of villi, but the cause of the cell loss is unclear.

Enterotoxic colibacillosis should be suspected in neonatal calves having large numbers of Gram-negative rods in smears of ileal scrapings. Though enterotoxic *E. coli* may be isolated from mesenteric lymph nodes or other parenchymatous tissues at autopsy, systemic invasion is not a significant component of the disease. Enterotoxic colibacillosis must be differentiated from enteric colibacillosis in calves that appears to be due to enteroinvasive strains, and from septicemic colibacillosis.

Enterotoxic colibacillosis in **lambs** is a significant problem in some areas. The serotypes involved and pathogenesis and diagnosis of the condition are similar to those in calves. Strains of *E. coli* have been associated with diarrhea in neonates of other species, but their enterotoxigenicity and other attributes of virulence have not been adequately described.

EDEMA DISEASE OF SWINE AND POSTWEANING *ESCHERICHIA COLI* ENTERITIS. Edema disease (gut edema) is a distinct syndrome in pigs characterized by sudden death, or the development of nervous signs, associated with enteric colonization by certain serotypes of usually hemolytic *Escherichia coli*. The disease occurs most commonly in pigs within a few weeks after weaning, or after other change in feeding or management. It often occurs in association with outbreaks of postweaning *E. coli* enteritis. Rare reports exist of edema disease in suckling and mature animals. The disease may be sporadic or occur as an outbreak, usually affecting the best animals in a group, and mortality often approaches 100% of affected animals. Edema disease and postweaning *E. coli* enteritis have apparently declined in prevalence in many parts of North America, perhaps with the use of concentrate rations based largely on soybeans and corn, rather than other grains.

Although the etiopathogenesis of edema disease is still incompletely understood, a soluble factor (''edema disease princi-

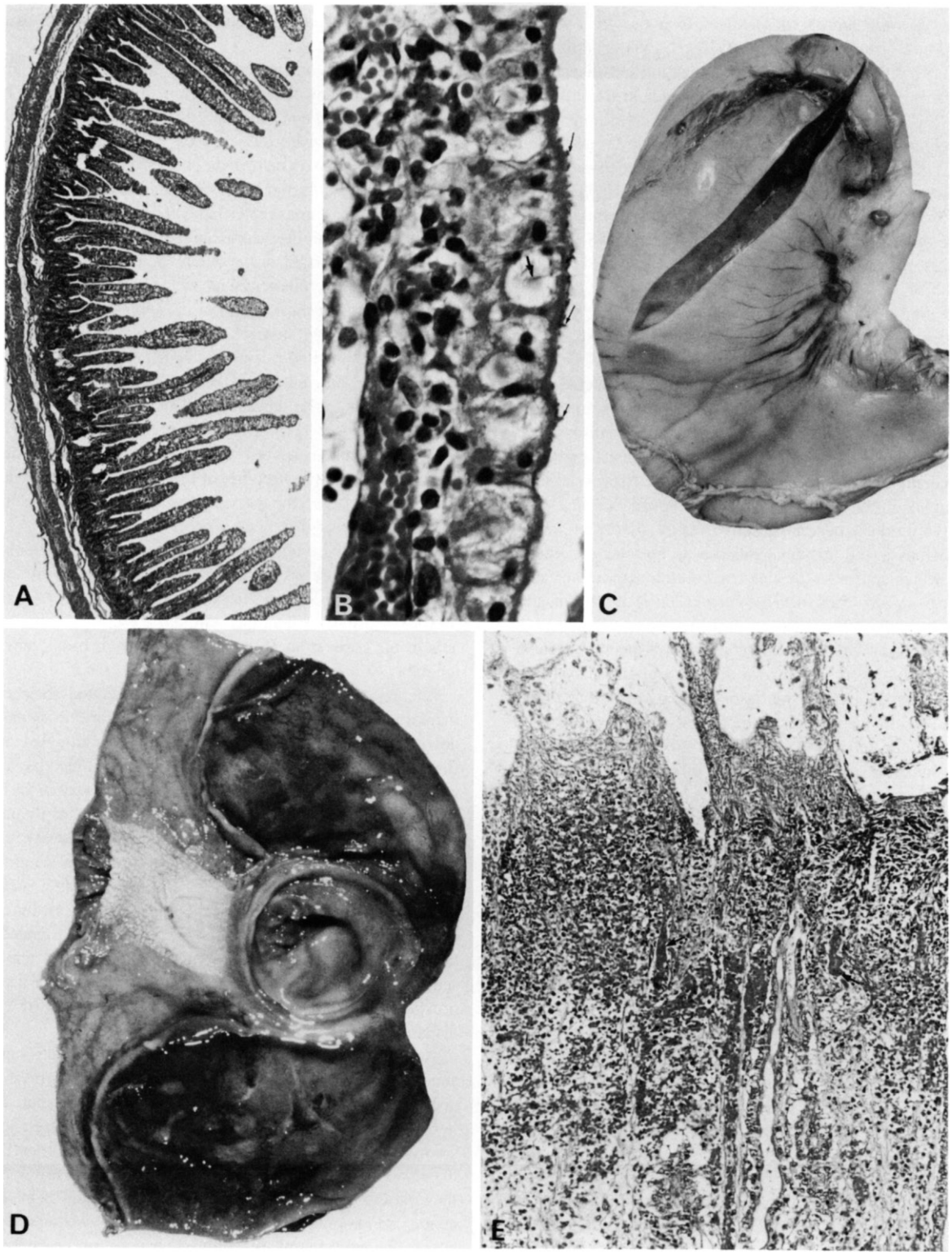


**Fig. 1.34.** (**A** and **B**) Enterotoxic colibacillosis. Piglet. (**A**) Villi are tall, and crypts short, as expected in a 2- to 3-day-old animal. (**B**) Bacteria are present on surface of enterocytes (arrows). Cytoplasmic vacuoles containing eosinophilic spicules (arrow) are normal in the ileal mucosa of young piglets. (**C**) Edema of stomach wall. Edema disease. Pig. (**D**) Postweaning colibacillosis in a pig. Deep red areas of venous infarction in the gastric mucosa. (**E**) Postweaning colibacillosis in a pig. Thrombosis of venules (arrows) and necrosis of the superficial gastric mucosa in venous infarction.

ple'' or ''*E. coli* neurotoxin'') released in the gut by some serotypes of *E. coli* (mainly O138, O139, O141) is implicated. The factors predisposing to enteric colonization and adhesion by these strains are unknown. Weaning, changes in ration, or accompanying alterations in the enteric microenvironment may favor proliferation of some strains of *E. coli*. The *E. coli* stick to the microvillus border of enterocytes on villi in the small intestine, presumably by the medium of some sort of ''adhesin'' or perhaps by mechanisms analogous to the enterocyte-adhesive strains in other species. They do not possess the K88, K99, or 987P pilus antigens, and pili are not obviously involved in adhesion.

The edema disease principle is not related to ''O'' or ''K'' antigens, nor to the hemolytic trait displayed by most, but not all, strains of *E. coli* causing the disease. It is heat labile but is distinguishable from both heat-labile and heat-stable enterotoxins responsible for the secretory diarrhea caused by some strains of *E. coli*. Some strains of *E. coli* that cause edema disease also produce secretory enterotoxin. Diarrhea is not a usual concomitant of edema disease in individual animals. However, some other animals in the group may develop typical *E. coli* ''post-weaning'' diarrhea, described subsequently. Gross or microscopic lesions in the intestinal mucosa do not occur in edema disease, which appears to be classical enterotoxemia, the active principle being absorbed from the gut and acting at a distant site.

The edema disease principle can be neutralized by antitoxin prepared against crude toxin extracts. It shows specific titratable cytotoxicity for Vero cells grown *in vitro* and also may be assayed by intravenous injection in mice. It appears to be analogous to *Shigella* neurotoxin, which has been recognized for many years, and perhaps to certain ''verotoxins'' or ''neurotoxins'' produced by serotypes of *E. coli* of human origin.

The mechanism of action of the edema disease principle is uncertain. Its effect seems to be on the walls of small arteries and arterioles throughout the body. Lesions at this level of the vascular tree are sometimes seen in animals dying acutely and showing typical postmortem lesions of edema. They are more consistently encountered in survivors or in pigs with a subacute clinical course in which nervous signs are prominent but in which gross edema at autopsy is not. The angiopathy, in its early stages, is recognized by swelling of endothelial cells and pyknosis and karyorrhexis of smooth muscle nuclei, often accompanied by fibrinoid degeneration or hyaline change, in the tunica media. Proliferative mesenchymal elements are found in the tunica media and tunica adventitia in more advanced cases. Inflammation is not at any stage a prominent component of the angiopathy, nor of the associated edema in most sites, however, and thrombosis of vessels is rarely encountered. Edema is probably due to vessel damage during the early stages of the angiopathy, and perhaps to associated hypertension. The lesions are distinct from those that might be expected with the alternative hypotheses advanced to explain the pathogenesis of edema disease, either endotoxemia or a hypersensitivity to soluble factors released by *E. coli*.

Swine with edema disease may die without premonitory signs. Others may have anorexia or, more characteristically, show nervous signs, usually of less than a day's duration. An unsteady, staggering gait, knuckling, ataxia, prostration and tremors, convulsions, and paddling occur. A hoarse squeal attributed to laryngeal edema, and dyspnea, may also be noted clinically.

At autopsy, lesions in acute deaths may be subtle or absent. Typically, edema is variably present in one or more sites. It may be mild, however, and must be carefully sought, especially by ''slipping'' the suspected area over subjacent tissue. Subcutaneous edema may be present in the frontal area and over the snout, in the eyelids, and in the submandibular, ventral abdominal, and inguinal areas. Internally, there may be some hydropericardium and serous pleural and peritoneal effusion, perhaps accompanied by mild or moderate pulmonary edema. More commonly, the serous surfaces merely appear glistening and wet. Edema of the mesocolon, of the submucosa of the cardiac glandular area of the stomach over the greater curvature, and of mesenteric lymph nodes is most consistently found. The gastric submucosal edema should be sought by gently cutting through the muscularis to the submucosa. The edema fluid is clear and slightly gelatinous (Fig. 1.34C). It is rarely blood tinged, and overt hemorrhage is never present in uncomplicated edema disease. The stomach is often full of feed, but the small intestine is relatively empty and the mucosa grossly normal. The colon may contain somewhat inspissated feces.

In swine dying after a more prolonged clinical course, gross edema often is not present, though enlargement of mesenteric lymph nodes is present in a large proportion of cases. A few pigs may show usually bilaterally symmetric foci of yellowish malacia in the brain stem at various levels, from basal ganglia to medulla.

Edema in the sites of predilection mentioned above is the main microscopic lesion in swine dying acutely. It is generally devoid of much protein and contains few erythrocytes and inflammatory cells. A proportion of animals will also have meningeal edema and distended Virchow–Robin spaces in the brain. Vascular lesions may not be well developed in pigs dying suddenly. When present, they usually consist of mycocyte necrosis, edema, and hyalin degeneration in the tunica media. Angiopathy is more consistently found in cases of longer standing. Affected vessels may be found in any tissue in the carcass. Brain edema and focal encephalomalacia in the brain stem are associated with the presence of lesions in cerebral vessels; necrosis may be a sequel to edema and ischemia. The entity known as swine cerebrospinal angiopathy is probably a manifestation of edema disease.

A diagnosis of edema disease is based on nervous signs or sudden death in growing pigs, in association with typical gross and microscopic lesions, when they are present. In acute cases, heavy growth of hemolytic *E. coli* of one of the three common serotypes associated with edema disease is usual on culture of the small and large bowel. In animals with more chronic signs, these strains may have been superseded by others as the dominant *E. coli* populating the intestine. Tests for production of the edema disease principle by cultured bacteria, or for its presence in gut content, may become routine as techniques for *in vitro* assay are developed.

The disease must be differentiated from enteritis and endotoxemia due to *E. coli* in postweaning pigs, from mulberry-heart disease in animals dying suddenly, and from salt poisoning, *Salmonella* meningoencephalitis, and other infectious encephalitides in animals with nervous signs.

**Postweaning *E. coli* enteritis** (coliform "gastroenteritis" of weaned pigs) typically occurs during the first week or two following weaning or after some other change in feed or management. It is usually associated with hemolytic *E. coli* of the same three serotypes primarily implicated in edema disease, as well as serotype O149. The two diseases often occur in the same population of pigs, though usually affecting different animals. Typically, postweaning colibacillosis is a disease of high morbidity and variable mortality, with loss of condition in pigs suffering prolonged illness. Diarrhea is usually yellow and fluid and stains the perineum. Deaths that occur may or may not follow a prior episode of diarrhea and often appear to be related to endotoxemia.

In fatal cases, there may be bluish red discoloration of the skin and evidence of dehydration. Deep red gastric venous infarcts are present in almost all cases (Fig. 1.34D,E). The small intestine is flaccid. The mucosa may be normal in color and the content creamy. In other animals, the mucosa of the distal small intestine will be congested and the contents watery and perhaps blood stained or brown with flecks of yellow mucus (Fig. 1.35A). Cecal and colonic lesions are usually mild, but there may be some congestion and fibrinous exudate in the proximal large bowel. Mesenteric lymph nodes may be somewhat enlarged, congested, and juicy. Other organs are usually unremarkable grossly.

The pathogenesis of postweaning *E. coli* enteritis is poorly understood, and the microscopic pathology is not well described. In swine with diarrhea, *E. coli* is attached to the surface of villi by means not necessarily related to known adhesins. Atrophy of villi does not seem to be evident, and diarrhea is presumed to be enterotoxin mediated. Mortality in animals with prolonged diarrhea and few gross intestinal lesions may be ascribed to dehydration. In animals dying of more acute disease, there is local microvascular thrombosis in sections of congested mucosa, and the gross and microscopic lesions are suggestive of endotoxemia (Figs. 1.34E and 1.35B). Hemolytic *E. coli* of the implicated strains are consistently isolated in virtually pure culture from the lower small intestine and colon. They are present in the spleen and liver in only a minority of cases, however, suggesting terminal bacteremia but not usually septicemia.

The factors predisposing to the massive colonization of hemolytic *E. coli* are unclear. Loss of lactogenic immunity, a favorable environment for proliferation of bacterial strains with specific nutrient requirements, and promotion of epithelial colonization by the effects of antecedent rotavirus infection have been variously implicated.

A diagnosis of postweaning colibacillosis is suggested by the gross lesions in animals dying acutely or subacutely, and it is confirmed by culture and serotyping of associated strains of *E. coli*. The fatal disease must be differentiated from edema disease, intestinal adenomatosis complex, salmonellosis, and swine dysentery. Postweaning diarrhea due to uncomplicated rotavirus infection or transmissible gastroenteritis is usually nonfatal.

ENTEROINVASIVE COLIBACILLOSIS. Strains of *E. coli* are recognized, infecting humans and certain other species, that have the capacity to invade surface enterocytes of the small and large intestine. In this sense they resemble *Shigella* in primates, and *Salmonella*. The enteroinvasiveness of *Shigella* and some strains of *E. coli* appears to be correlated with the presence of a high molecular weight plasmid. Multiplication of the organism within cells results in local erosion and ulceration, associated with acute inflammation in the mucosa. Although in shigellosis septicemia does not usually occur, bacteria may be present in inflamed mesenteric lymph nodes or liver in some enteroinvasive *E. coli* infections in laboratory animals.

Among domestic animals, enteroinvasive colibacillosis has been confirmed experimentally only in neonatal swine, using a strain of O101 *E. coli*. Spontaneous enteritis, which appears to be due to enteroinvasive *E. coli*, is occasionally encountered in piglets up to weaning and in calves less than 2 weeks of age. Diarrhea in experimentally infected piglets is described as gray-yellow, watery, and containing small clots. The gross findings may not be remarkable, or the intestine may appear congested in comparison with that in most diarrheic piglets. In spontaneous cases suspected of being due to enteroinvasive *E. coli*, the gastric fundus may be congested also, and this correlates with the presence of venous infarction visible microscopically. Experimental enteroinvasive colibacillosis in piglets causes villus atrophy comparable in severity to that induced by the common viruses of neonates. Enterocytes appear cuboidal or flattened, and some are seen lysing. The lamina propria is edematous and capillaries are congested and infiltrated by neutrophils and other inflammatory cells. In spontaneous cases, thrombi may be evident in proprial capillaries and submucosal lymphatics. Neutrophils and tissue fluid effuse into the lumen between villi through epithelial discontinuities. Similar microthrombosis, proprial inflammation, enterocyte destruction, and effusion may be found in the cecum and colon. Intracellular organisms of strain O101 were demonstrated by immunoperoxidase staining in the experimental study but are not generally recognized in spontaneous cases suspected to be due to enteroinvasive *E. coli*. Edema and neutrophil accumulation in sinusoids of mesenteric lymph nodes are present. Experimental enteroinvasive colibacillosis in piglets has been associated with malabsorption and protein loss into the gut, presumably due to villus atrophy and effusive enteritis, respectively.

In calves, lesions suspected to be due to enteroinvasive *E. coli* grossly resemble mild salmonellosis. The mucosa of the lower small intestine, cecum, and spiral colon is congested and may be covered by a fine fibrinous exudate. The content is fluid and may appear blood tinged. Mesenteric lymph nodes are enlarged and wet. The microscopic lesions resemble those described above in pigs.

SEPTICEMIC COLIBACILLOSIS. Generalized systemic infection with *E. coli* occurs commonly in **calves** and less commonly or sporadically in young animals of the other domestic species. Predisposition to infection is a prerequisite for *E. coli* septicemia caused by a variety of strains. This usually results from reduced transfer or absorption of maternal immunoglobulin from colostrum, or intercurrent disease or debilitation. But certain strains of *E. coli*, especially O78:K80 and O2:K1, are particularly associated with septicemia in calves and lambs and may possess characteristics that enhance their ability to invade and proliferate systemically.

Among factors conferring virulence on these strains are plas-

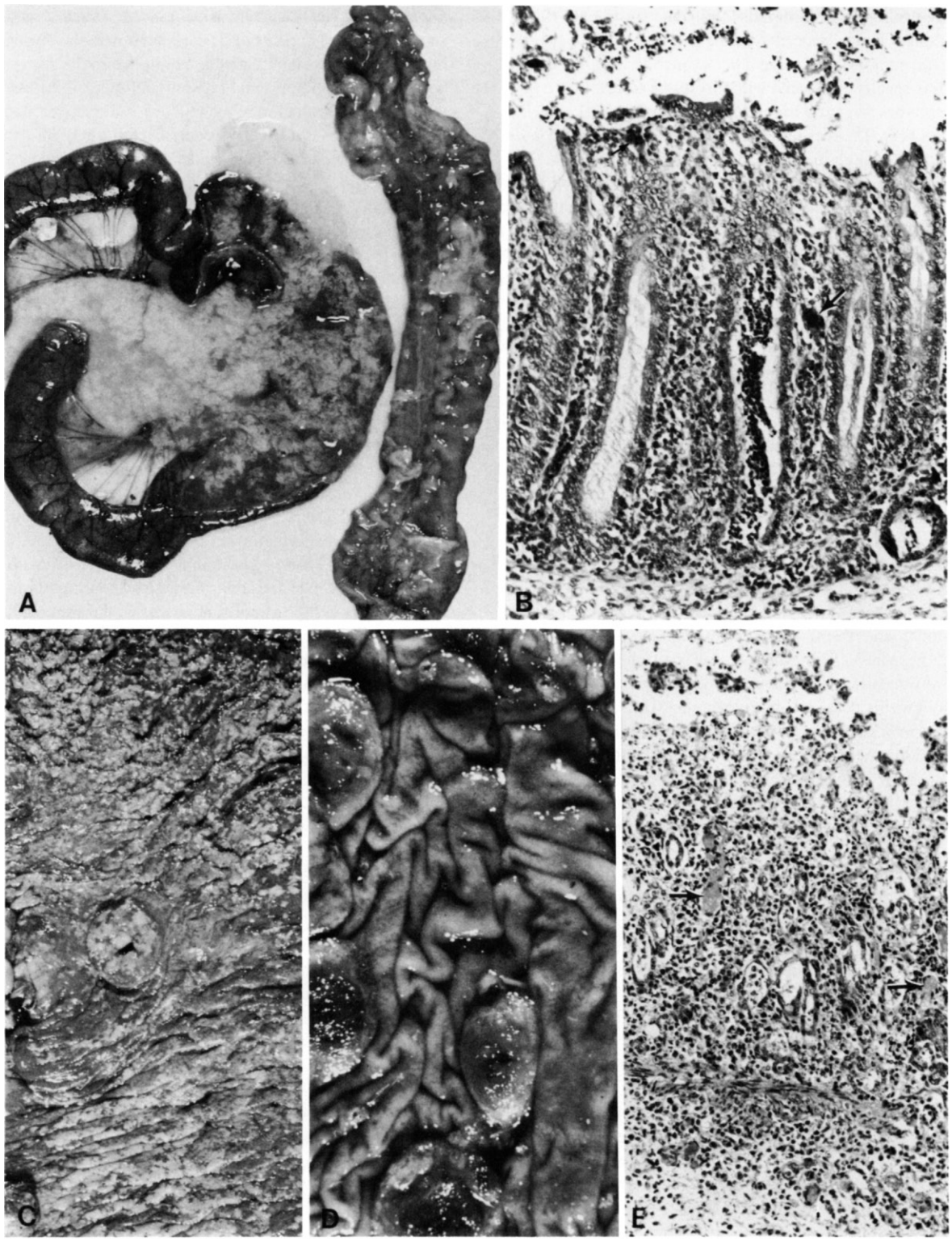


**Fig. 1.35.** (**A** and **B**) Postweaning colibacillosis. Pig. (**A**) Acute catarrhal enteritis. Congested, flaccid small intestine. (**B**) Erosion and effusion from colonic surface, and accumulation of neutrophils in glands, associated with thrombosis of some venules in the lamina propria (arrows). (**C–E**) Equine salmonellosis. (**C**) Focal and coalescent ulceration and diphtheresis involving ileocecal valve and cecal mucosa. (**D**) Nodular ulcerative lesions in colon. Chronic salmonellosis. (**E**) Superficial necrosis and effusion from colonic mucosa. Foal. *Salmonella typhimurium*. Several thrombosed vessels are in the propria (arrows).

mids coding for colicin V (Col V) and for the production of a specific toxin and surface antigen (Vir). Colicin V enhances the ability of the organism to resist host defense mechanisms, possibly by interfering with phagocytosis or complement activation. The Vir plasmid causes production of a toxin lethal in chicks and presumably active in other hosts. Hemolysin seems to promote virulence of some invasive strains of *E. coli* in experimental situations.

The portal of entry of *E. coli* causing septicemia is unclear and probably varies somewhat. The navel in the neonate, the upper respiratory tract, possibly the tonsil, and the intestine are likely sites. The nasopharyngeal route appears to be particularly important. Enteritis is not a necessary, or even common, concomitant of colisepticemia in animals. Invasive strains given to animals with adequate levels of immunoglobulin are usually limited to colonization of the intestine and local carriage to the mesenteric lymph nodes.

The lesions associated with colisepticemia in young animals of any species, especially calves, lambs, and foals, may vary from subtle to obvious. Mortality in hypogammaglobulinemic neonates may occur acutely with little in the way of abnormal gross findings. These may be limited to mildly congested or blue-red, slightly rubbery lungs and a firm spleen, perhaps with evidence of omphalitis. Microscopic changes in the lungs include thickening of alveolar septa by mononuclear cells and neutrophils, and effusion of lightly fibrinous exudate and a few neutrophils into alveoli. There may be a corona of neutrophils around white pulp in the spleen, and neutrophils may be present in abnormal numbers in circulation in many organs, including lung and hepatic sinusoids. Kupffer cells also may be prominent in sinusoids in the liver. Fibrin thrombi may be evident in pulmonary capillaries, glomeruli, and hepatic sinusoids. Some calves will develop acute interstitial nephritis with foci of neutrophil accumulation, which with time evolves into "white-spotted kidney" in surviving animals.

More severe acute cases will show evidence of serosal hemorrhage, including petechiae or ecchymoses on the epicardium and endocardium and perhaps parietal and visceral pleura. There may be slight serosanguinous pericardial fluid. The lungs may be deep red-blue and rubbery and fail to collapse. Interlobular septa may be slightly separated by edema, and froth or fluid may be present in the major airways. Meningeal vessels may be congested, and the meninges wet. The abomasum or stomach may have focal superficial ulcers or more extensive deep red areas of venous infarction. There may be evidence of diarrhea and dehydration, with congestion of the small intestine. Microscopic lesions resemble those previously described, with more severe congestion, thrombosis, and edema in lungs and, perhaps, other tissues. In cases not examined by some time after death, clumps of small bacilli may be seen in vessels throughout the body. The vascular permeability, thrombosis, and hemorrhage reflect endotoxemia.

Subacute cases may develop localized infection, often multiple, on serous surfaces, in the joints, meninges, and rarely, anterior chamber of the eye. Fibrinous peritonitis, pleuritis and pericarditis, and fibrinopurulent arthritis and meningitis are commonly found, alone or in variable combinations. Affected animals may have a history of lameness ascribable to arthritis, nervous signs due to meningitis, or general debilitation. Microscopic examination reveals the lesions already described in animals with active systemic disease, with the addition of extensive congestion and edema of inflamed serous surfaces, associated with an acute inflammatory exudate.

In **lambs**, congestion and edema of the mucosa of turbinates and sinuses, perhaps with mucopurulent to hemorrhagic sinusitis, have been described. Fibrinous polyserositis and arthritis are sporadic manifestations of *E. coli* septicemia in **swine** and must be differentiated from the more significant *Haemophilus, Mycoplasma,* and *Streptococcus* infections causing these lesions. Colisepticemia is a sporadic cause of mortality in litters of young **puppies**.

Diagnosis of *E. coli* septicemia is based on the isolation of *E. coli* in large numbers from more than one parenchymatous organ or other internal site other than mesenteric lymph node (preferably liver, spleen, lung, or kidney) or from a site of serosal localization, in conjunction with compatible gross and/or microscopic lesions.

### *Salmonellosis*

The genus *Salmonella* is named for D. E. Salmon, who was the first to describe one species, *S. choleraesuis,* in detail, although diseases in humans caused by members of this genus had been described earlier. Each antigenically distinct type is accorded species status and assigned a specific name. This usually designates the locality in which the specific type was first isolated and identified. Some 2000 or more serotypes have been defined, including members of the *arizona* group. All known types are pathogenic, or potentially so, for humans or animals or both. For the most part, however, salmonellosis is caused by a few types that are somewhat host specific, like *S. abortusovis,* and a few which are not host specific, like *S. typhimurium.* Salmonellosis is one of the most serious zoonotic diseases. Phage typing is indicated when there is evidence of transmission from animals to humans. This technique should also be used when the offending serotype is found in feed, or other epidemiologic tracing is necessary.

Knowledge of the pathogenesis of salmonellosis has not advanced in parallel with our more purely bacteriologic knowledge, so that much that is important about the disease remains vague. Probably, salmonellosis in animals (here excepting birds and humans) should be regarded as many diseases by reason of the variety of animal species that are susceptible, the variety of bacterial species that are pathogenic, and the poorly defined variety of circumstances in which host and pathogen interact to produce the disease. However, there are some general features of salmonellosis that may be noted here.

The more common "stress" factors that have been associated with salmonellosis in most species of domestic animals include transportation, starvation, changes in ration, overcrowding, age, pregnancy, parturition, exertion, anesthesia, surgery, intercurrent disease, and oral treatment with antibiotics and anthelmintics. A few of these factors will be considered in more detail.

There is clearly an age susceptibility to clinical disease and somewhat also to infection. Adult animals are less likely to suffer generalized or septicemic infections than are the young. When adults become infected, they are more likely to cast it off

or become symptomless carriers for indefinite periods. The greater susceptibility of young animals is only partially explained by their failure to obtain specific antibody in colostrum; there is no sound explanation of why young animals are more susceptible than adults. The containment of many young animals in limited areas is conducive to high degrees of contamination of the local environment and to rapid spread of the infection. The concentration of animals is also of importance in adults, particularly horses and sheep. In these species, outbreaks are more common when the animals are closely confined. Often coupled with close confinement are the rigors attending it, especially during long travel with irregular and inadequate feeding and watering. Less tangible environmental effects are suggested by the seasonal occurrence of salmonellosis in pigs and horses.

There are many examples of enhancement of susceptibility to salmonellosis by intercurrent disease. The best known association is that between the virus of hog cholera and *Salmonella choleraesuis*, an association so close as to have caused early pathologists to disregard the bacterium as a primary pathogen. Salmonellosis sometimes complicates viral disease of carnivores and has also been observed in cattle infected with the viruses of foot and mouth disease and bovine virus diarrhea.

The disease in adult cattle is usually sporadic, and there are often noninfectious predisposing diseases such as parturient paresis, ketosis, mastitis, and parasitic infestations. The stress of anesthesia and surgery may account for the serious outbreaks of salmonellosis that occur in hospitalized animals at veterinary schools. The significance of antibiotic treatment in relation to salmonellosis is discussed under Typhlocolitis in Horses.

The pathogenesis of salmonellosis in domestic animals is poorly understood. The main route of transmission is undoubtedly by ingestion. Most of the more basic information on the pathogenesis has been obtained through experimental infection in laboratory animals. Although the data obtained from these experiments are valuable, they may not be completely applicable to domestic animals. There are obvious differences in susceptibility of animal species to particular serotypes of *Salmonella*. Some strains of *S. typhimurium* may cause a subclinical infection in mice but prove to be highly fatal for calves.

There are three basic requirements which must be met before infection with *Salmonella* induces disease. The bacteria have to be present in sufficient numbers; generally a minimal infective dose of $10^7$ to $10^9$ organisms is needed to infect large domestic animals. The strain must also colonize and invade enterocytes to produce enteritis; noninvasive strains of *Salmonella* are nonpathogenic. The ability to cause intestinal secretion is a property of some invasive strains.

Some *Salmonella* species have the ability to adhere to the brush border, but the mechanism by which this occurs is not understood. Adherence of *S. typhimurium* to the ileal mucosa of germ-free or specific-pathogen-free mice is not associated with O or H antigens or pili. In chicks, colonization and adherence of *Salmonella* occur more readily throughout the gastrointestinal tract in the absence of the normal microflora.

In experimental infections of guinea pigs, *Salmonella* invades the enterocytes, especially those in the ileum, and within 12 hr large numbers of organisms are present in the lumen, on the surface of the brush border, and in enterocytes. There is an increase in the number of neutrophils in the gut lumen and within intercellular spaces, and some of these contain bacteria. Bacteria are also located in the lamina propria, mainly in macrophages. Degeneration of microvilli characterized by loss of filamentous cores is associated with close adherence of bacteria. Other degenerative changes consist of elongation, budding, and fusion of microvilli and loss of the terminal web. The organisms usually appear to invade the cells through the brush border; however, they may also enter the mucosa through the intercellular junctional complex. The bacteria are located in the cytoplasm within membrane-bound vacuoles, which may also contain remnants of microvilli and cytoplasmic debris. The *Salmonella* bacteria remain largely intact during their transcellular migration. Many bacteria are often present in a single enterocyte during the early stages of infection, but cellular damage is mild and transient. After 24 hr, most of the bacteria are located in macrophages in the lamina propria. Many organisms are evident in the lumina of crypts, but invasion of cryptal epithelial cells evidently does not take place.

In addition to causing obvious morphologic changes in the gut mucosa, some strains of invasive *Salmonella* are associated with fluid exsorption into the gut lumen. The secretion of fluid is probably toxin mediated. The significance of heat-labile or heat-stable enterotoxins, the effects of which are described under Enterotoxic Colibacillosis, is not defined for enteric salmonellosis. The cAMP system may play a role in secretion of fluids into the gut lumen, but the mechanism involved is poorly understood. *Salmonella* infection stimulates adenyl cyclase activity in the rabbit ileum, but the level of stimulation is considerably less than that produced by cholera toxins. Enterocolitis associated with salmonellosis may result in increased synthesis and secretion of prostaglandins, which in turn stimulate mucosal adenyl cyclase activity, causing abnormalities in fluid, sodium, and chloride transport.

As a result of the fluid exsorption that occurs, mainly in the lower small intestine, a large volume of fluid reaches the colon. Diarrhea is at least in part due to the inability of the damaged colon to absorb this fluid.

A cytotoxin similar to the cytotoxin or "neurotoxin" produced by *Shigella dysenteriae* has been associated with several serotypes of *Salmonella*. This toxin causes extensive detachment of intact Vero cells in tissue culture. The cytolytic activity is probably due to inhibition of protein synthesis rather than being a direct effect of the toxic factor on membrane integrity. The degeneration and necrosis of enterocytes in salmonellosis may be associated in part with such cytotoxin.

Vascular degeneration and thrombosis of mucosal vessels are common features of *Salmonella* enteritis. The vascular lesions may be due to action of large amounts of endotoxins absorbed through the damaged mucosa or released locally. The effects of cytotoxin on the endothelial cells also may be involved in the pathogenesis of these lesions.

Once the *Salmonella* organisms have crossed the mucosa, they may enter the blood stream via the lymphatics, perhaps carried in macrophages, and cause septicemia or transient bacteremia. Or they may remain indefinitely in the gut-associated lymphoid tissues and mesenteric lymph nodes. Increased susceptibility to salmonellosis in animals with intercurrent disease

or subjected to stress may be related to relaxation of cell-mediated immunity to the organism. Septicemia may be of variable duration and severity, but as a rule, it is rapidly fatal in young animals. If, however, there is transient bacteremia, the organisms are removed by the fixed macrophages, especially of the spleen, liver, and bone marrow. They may continue to proliferate in such extravascular locations and cause another bacteremic phase that may be fatal as a septicemia or result in secondary localization.

The carrier state is of particular importance to the epidemiology of the disease. Swine especially may carry the organism in the intestine and excrete it in the feces. Whether *Salmonella* can maintain itself in the intestine is not clear; to some extent, at least, the fecal flora is likely to depend on intermittent seeding from the gallbladder or from macrophages in the lamina propria and gut-associated lymphoid tissue. The duration of the carrier state may be prolonged, or animals may rid themselves of the infection. The carrier state is an unstable one, for it appears that if the carrier is subjected to some stress or debilitating disease, it may succumb to disease; this often seems to be the case in adult cattle. The carrier animal is a potential threat to any other animal it contacts, either directly or through the medium of its excreta, or through by-products such as bone meal.

HORSES. The most common serotype in horses in most areas is *Salmonella typhimurium,* and its prevalence is increasing. Other serotypes are usually associated with sporadic outbreaks of disease. The high prevalence of salmonellosis in veterinary teaching hospitals has been mentioned. Many are carriers when they are admitted, and when they are stressed, diarrhea follows. Salmonellosis in horses may be manifested clinically as peracute, acute, chronic forms and as an asymptomatic carrier state.

The septicemic form occurs most commonly in foals 1–6 months of age. These animals are usually with their dams at pasture, and predisposing factors are unclear. The infection in foals tends to be fatal. Affected animals are lethargic and develop severe diarrhea, often with characteristic green color, which may contain casts and blood. They are febrile and waste rapidly, to die in 2 or 3 days. Some survive for a week or more, and these may develop signs of pneumonia, osteitis, polyarthritis, and meningoencephalitis.

The primarily enteric forms of the disease are more likely to occur in older horses. Most of the predisposing factors mentioned earlier apply to horses. Salmonellosis is an occupational hazard of horses since many are exposed to long periods of transport and exertion due to overwork or excessive training.

Clinically, the acute disease is characterized by diarrhea and fever for a period of 1 to 3 weeks, followed by recovery. The chronic form persists for weeks or months. Affected horses pass soft, unformed manure that resembles cow feces. They lose their appetite, with subsequent progressive loss of weight and condition. In later stages, they become dehydrated and emaciated. The carrier state is somewhat controversial. Some investigators were unable to confirm long-term carriers in horses; others were able to recover *Salmonella* from feces of recovered animals for months. Reinfection may complicate attempts to determine whether an animal is a carrier.

The gross lesions are those of enteritis and/or septicemia; the former are most consistently found at autopsy. As a rule, the longer the course, the lower in the intestine one finds the most severe lesions. Acute septicemic cases show small hemorrhages on the serous membranes, especially the pericardium and peritoneum, and enlargement of the spleen. In others, petechiae are present on the valvular endocardium, vesical mucosa, renal and adrenal cortices, and meninges, but none of these is consistent. The splenic enlargement is most marked in peracute cases, and the organ is dark and pulpy. Hepatic lipidosis seems to be common, but this may be related more to inanition than to the infection. The visceral lymph nodes are always enlarged, juicy, and often hemorrhagic.

The main lesions are in the stomach and intestines. In peracute cases, there is intense hyperemia of the gastric mucosa, probably venous infarction, with some edema and scattered hemorrhage. The small intestine may be congested with a mucous or hemorrhagic exudate. In acute cases, there is diffuse and intense hemorrhagic inflammation of the cecum and colon, overshadowing any lesions in the upper intestine and leading rapidly to superficial necrosis of the mucosa and a grayish red pseudomembrane (Fig. 1.35C). In chronic salmonellosis, enteric lesions may be few or subtle. Some animals have extensive or patchy fibrinous or ulcerative lesions of the cecum and colon. In others, raised circumscribed lesions about 2–3 cm in diameter may be evident, with a gelatinous submucosa and ulcerated mucosa. Some such lesions are more fibrinous and resemble button ulcers (Fig. 1.35D).

Histologic alterations of significance are usually limited to the intestine. In septicemic animals, however, there is sometimes focal Kupffer-cell hyperplasia in the liver, acute ileocecocolic lymphadenitis, and inflammation in sites of localization. Depending on the duration of the enteritis there may be hemorrhage, necrosis, or diphtheresis, but the infiltrating leukocytes are largely mononuclear. The superficial coagulation necrosis of the mucosa may extend over large areas. A layer of fibrinocellular exudate may cover the necrotic mucosa. Fibrin thrombi are frequently present in the capillaries of the lamina propria (Fig. 1.35E). There is usually marked congestion of submucosal vessels, which is accompanied by considerable edema.

Salmonellosis must be differentiated from septicemia due to *Actinobacillus equuli* in foals and colitis X and ischemic lesions of the large bowel in older horses. The differential diagnosis of typhlocolitis has been discussed previously. For some unknown reason, *Salmonella* is often difficult to isolate from horses that have typical signs and lesions of the disease. The tissues of choice for isolation are the mesenteric and ileocolic lymph nodes and gut, which should be ground up and inoculated into enrichment media. Repeated fecal cultures are necessary to identify carrier animals. It has been suggested that five consecutive negative cultures are required to rule out the carrier state.

CATTLE. There are differences between salmonellosis in young and adult cattle. The serotypes usually incriminated are *Salmonella typhimurium, S. enteritidis,* and *S. dublin,* the latter having often in the past been classified as *S. enteritidis.* These serotypes are of worldwide distribution. *Salmonella dublin* is not common in North America east of the Rockies, and wherever it is found it tends to show some specific adaptation to cattle and

to occur in epizootics, whereas the other infections are more often sporadic. *Salmonella muenster* has become enzootic in cattle in Ontario and appears to be spreading to other eastern Canadian provinces and the northeastern United States. The behavior of this serotype is similar to that of *S. dublin*. Whatever the infecting serotype, the manifestations of infection in individual animals are the same.

It is unusual to find salmonellosis in calves less than 1 week of age, in contrast to colibacillosis, which usually affects very young animals. In calves, salmonellosis is a febrile disease typified by dejection, dehydration, and usually diarrhea. Diarrhea is not always present, but when it is, the feces are pulpy, yellow or grayish, and have a very unpleasant odor. In older calves there is often blood and mucus in the feces. In less acute cases there may be delayed evidence of localization in the lung and synovial structures. Morbidity and mortality may be considerable, especially in calves that are confined, such as in vealer operations. Experimental infections in calves indicate that survival is inversely related to the numbers of *Salmonella* in the inoculum and directly to the age of the calves.

The general appearance at autopsy of a calf with salmonellosis may be the same as one with colibacillosis. However, enlargement of mesenteric lymph nodes and gross enteric lesions are generally observed in salmonellosis. There are moderately severe gastrointestinal inflammation, acute swelling, and hemorrhage of the visceral lymph nodes, and some petechiation of serous membranes. The gastroenteritis may be catarrhal, but sometimes it is hemorrhagic or more commonly causes exudation of yellowish fibrin (Fig. 1.37A,B). The mucosa overlying the lymphoid tissues may become necrotic and slough. In animals with fibrinous enteritis, the bowel wall is somewhat turgid and the serosa may have a ground-glass appearance. There is often a diffuse, but perhaps mild, fibrinous peritonitis.

The intestinal lesions are usually most severe in the ileum, especially during the early stages of the disease. With time the jejunum and colon become involved, but the duodenum remains relatively normal. The regional distribution of the lesions may, at least in part, be related to differences in the level of bacterial colonization of the mucosa. Twelve hours after oral infection of calves with *Salmonella typhimurium*, the numbers of bacteria are generally lower in the abomasum and duodenum than in the lower intestinal tract, where they are relatively constant from the jejunum through to the rectum.

The early microscopic lesions in the small intestine consist of a thin layer of fibrinocellular exudate on the surface of short and blunt villi (Fig. 1.36B). This is followed by extensive necrosis and ulceration of the mucosa, with fibrin and neutrophils exuding from the ulcerated areas into the lumen (Fig. 1.36C,D). The lamina propria may be moderately infiltrated by mononuclear inflammatory cells. Fibrin thrombi are often evident in proprial capillaries. There is also marked submucosal edema, and the centers of lymphoid follicles in the Peyer's patches are necrotic. The mucosal damage is usually too extensive to be explained solely on the basis of ischemia due to microvascular thrombosis. Similar erosion, ulceration, and fibrinous effusion occur in the proximal large bowel.

Scanning electron microscopy of small intestine shows large numbers of bacteria on a tattered mucosal surface. Clusters of enterocytes slough off short and blunt villi (Fig. 1.36A). Strands of fibrin emerge from the mucosal defects and cover the mucosa. Ultrastructurally, the lesions are similar to those described above for guinea pigs, except that there is more damage to epithelium in calves experimentally infected with *Salmonella typhimurium*.

Characteristic changes usually occur in the liver and spleen but may be absent in peracute septicemic cases. There is often fibrinous inflammation in the gallbladder. In acute cases, the spleen is enlarged and pulpy as a result of congestion, but this is soon replaced by acute splenitis, present as miliary, tiny foci of necrosis or as reactive nodules. The liver is often pale and beset with many minute foci of necrosis, which may require microscopy for detection. They are referred to as "paratyphoid nodules," although all transitional stages from foci of simple nonspecific necrosis to reactive granulomas occur. Typically there are few neutrophils, and whether the nodules are necrotic or reactive depends on their duration. The initial change is focal coagulation necrosis. About the margins, the macrophages accumulate and form small histiocytic granulomas, which expand and displace the surrounding parenchymal cords. In the spleen, macrophage reaction is sometimes diffuse. "Paratyphoid" granulomas may also be found microscopically in the kidney, lymph nodes, and bone marrow. In calves with acute septicemia, interstitial thickening of pulmonary alveolar septa by mononuclear cells and edema is usually found. There may be thrombosis of septal capillaries, and some effusion of edema fluid and macrophages into alveolar spaces.

In chronic salmonellosis, there is almost always an anterior bronchopneumonia, usually with adhesions and small abscesses, and purulent exudation in synovial cavities. The organism is recoverable in pure culture from such affected joints and tendon sheaths but may be mixed with *Corynebacterium* and *Pasteurella* in the lungs.

Salmonellosis in adult cattle may occur in outbreaks as it does in calves, but more often it is sporadic. The source of infection is usually the carrier animal. Other sources, such as feed containing protein of animal origin or bone meal, should be considered when the disease is caused by an uncommon serotype. Abortions are common with *Salmonella dublin* and *S. muenster* but may occur with any serotype. In some herds this may be the only clinical evidence of infection, although other animals often excrete the offending serotype in the feces. The morbid changes in adults correspond to those in calves, except that there is more pleural hemorrhage and the enteritis may be more hemorrhagic and fibrinous. The histologic changes seen in the liver and other organs are the same as those seen in calves with salmonellosis.

SHEEP. As well as abortion caused by *Salmonella abortus-ovis*, abortion and neonatal death may attend infection of pregnant ewes by any species of *Salmonella*. Otherwise it is not a common disease in sheep, but outbreaks are always severe and may cause very heavy losses. Predisposing influences are necessary, and these are usually provided by circumstances that enforce congregation. Deprivation of food and water for 2 or 3 days may be sufficient and, coupled with fatigue, is the usual predisposing factor when sheep are transported or confined in holding yards. Deaths usually continue for a week to 10 days after debilitating circumstances have been remedied.

The serotypes usually found in sheep are *Salmonella ty-*

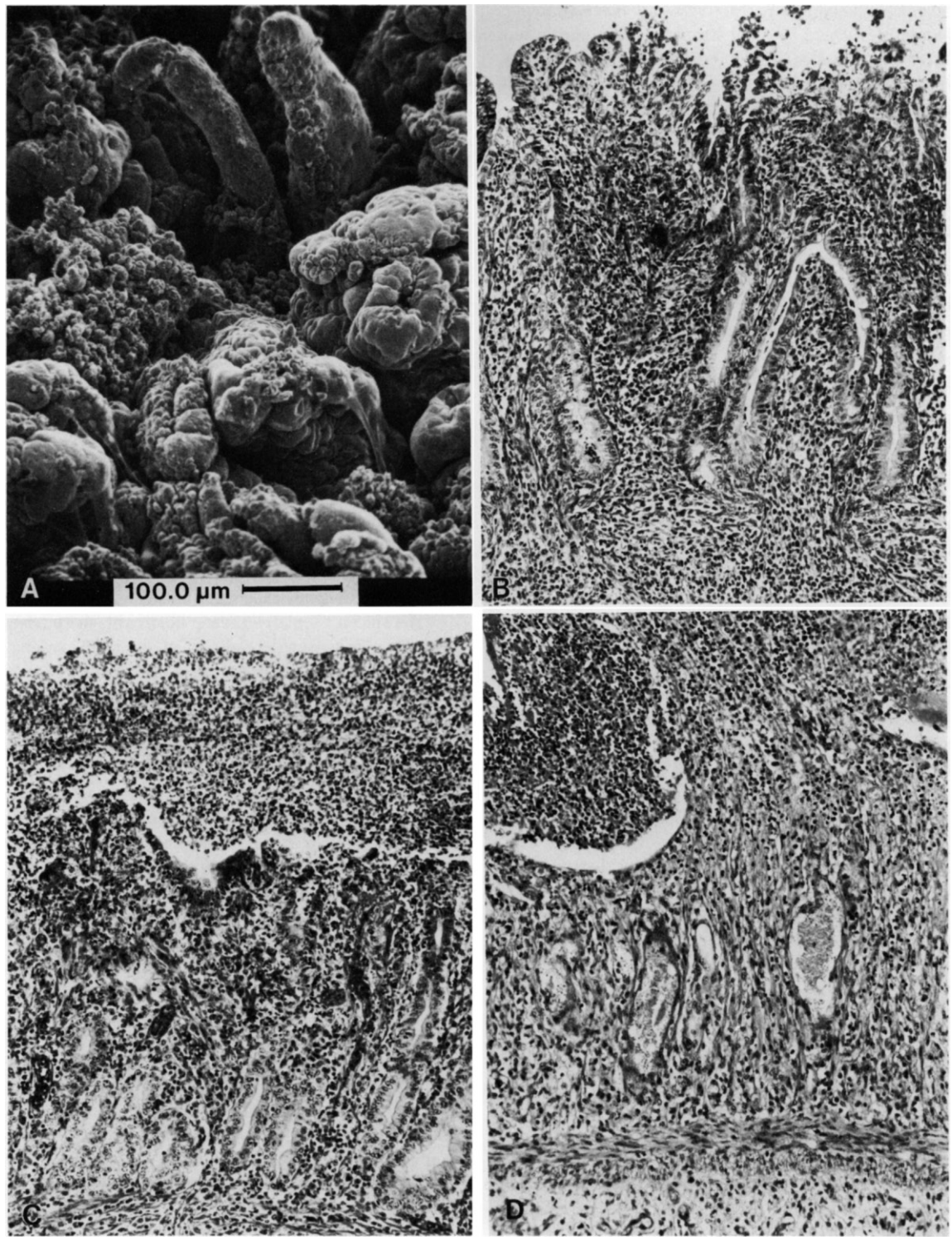


**Fig. 1.36.** Bovine salmonellosis. (**A**) Scanning electron micrograph. Ileum. Calf 12 hr postinoculation with *Salmonella typhimurium*. Villi are atrophic, and rounded cells are exfoliated from surface. (**B**) Atrophy of villi, exfoliation of surface epithelium, and effusion of neutrophils in ileum 12 hr after inoculation with *S. typhimurium*. (**C**) Atrophy of villi, erosion, and effusion of neutrophils and fibrin into lumen. Some thrombosis of proprial vessels. Thirty-six hours after inoculation with *S. typhimurium*. (**A**–**C** courtesy of R. C. Clarke and C. L. Gyles.) (**D**) Eroded ileal mucosa, largely devoid of crypts of Lieberkühn. Fibrin and neutrophils in lumen.

*phimurium, S. arizona,* and *S. enteritidis. Salmonella dublin* is increasing in prevalence in Great Britain and the midwestern states of the United States. They produce the same sort of disease, which closely resembles that seen in cattle both clinically and at autopsy. The major findings are fibrinohemorrhagic enteritis and septicemia.

SWINE. Many serotypes of *Salmonella* have been isolated from swine, and with poultry they form the most important reservoir of the organism. The bacteria are carried in the intestine but also in the regional lymph nodes of the alimentary tract so that carrier animals may not excrete the organism in the feces.

Salmonellosis occurs in feeder pigs, usually those 2–4 months of age. It is very uncommon in sucklings and adult swine.

Three syndromes are associated with *Salmonella* infections in swine. **Septicemic salmonellosis** is usually associated with *S. choleraesuis* var. *kunzendorf,* although enteric lesions may be present with this serotype. Sporadic infections with *S. dublin* have also been associated with septicemia in nursing pigs. *Salmonella typhimurium* most commonly causes **acute** or **chronic enterocolitis**, including a necrotizing proctitis that may lead to rectal structure. *Salmonella typhisuis* infection is characterized by **caseous tonsillitis** and **lymphadenitis** as well as ulcerative enterocolitis. Detailed consideration of the three syndromes just outlined is warranted because salmonellosis is one of the most important diseases of swine.

*Salmonella choleraesuis* was once thought to be the cause of hog cholera because gross lesions of the two diseases are similar. Hog cholera may be complicated by *S. choleraesuis.* It has been estimated that the bacterium may be recovered from 10 to 50% of hog cholera infections. Other predisposing factors mentioned earlier generally also apply to salmonellosis in swine.

The major clinical manifestations of *Salmonella choleraesuis* infection are septicemia and enteritis; they usually occur separately. Septicemia is more common. It is probable that the pathogenesis of the infection follows the system given for *Salmonella* in general. The bacteremic phase may develop into a fatal septicemia, or the organism may localize in the intestine, causing enteritis that is not necessarily chronic or even clinically manifest.

Salmonellosis that is clinically septicemic is usually fatal. Death may occur quickly without observed illness, or after a course of a week or more. There is a high fever; characteristic but not pathognomonic blue discoloration of the skin, especially of the tail, snout, and ears; posterior weakness; dyspnea, which often leads to misdiagnosis of primary pneumonia; and sometimes terminal convusions. Pigs recover from this phase may have dry gangrene of the ears and tail, posterior paralysis, blindness, and diphtheritic enteritis. The chronic or enteric form may develop from the acute but is usually insidious from the onset. It is characterized by loose yellow feces containing flakes of fibrin, progressive emaciation and debility, and eventual death. Some recover but fail to thrive, often partly owing to chronic bronchopneumonia.

At autopsy there is a bluish or purplish discoloration of the skin, which may be very intense about the head and ears. There may be superficial necrosis of the ears. The internal lesions are typically hemorrhagic; the hemorrhages are petechial. The lymph nodes are almost invariably hemorrhagic but not much enlarged unless the course is prolonged. The visceral nodes are more frequently and obviously involved than the peripheral ones, with the exception of those of the throat, which are consistently hemorrhagic. The mesenteric lymph nodes are greatly enlarged; they may be speckled with parenchymal hemorrhages, or the extravasations may be in the peripheral sinus.

There may be hemorrhages, petechial or as small discrete blebs, on the laryngeal mucosa (Fig. 1.37D). The lungs do not collapse because there is frothy fluid in the respiratory passages. They may be pale blue or purple. Beneath the visceral pleura there are small dark foci of hemorrhage. The lungs are wet, and there is fluid in the interlobular tissue. The changes are best appreciated in the posterior lobes, because the anterior lobes are often the seat of acute lobular pneumonia. These pulmonary changes account for the respiratory signs observed clinically. The pneumonia is interstitial because of the influence of the organism on the alveolar vessels. The lobar anteroventral pneumonia may be due to ascending *Salmonella* alveolitis and bronchiolitis. Occasionally, the injury to the alveolar septa by *Salmonella* results in copious outpouring of fibrin and extensive fibrinous pneumonia of the posterior lobes. The cardiac serosae often bear petechiae, and in some more virulent infections there is fibrinohemorrhagic pericarditis with scant fluid exudation.

The spleen is enlarged, deep blue, with sharp edges. There may be petechiae on the capsule, but the small marginal infarcts of hog cholera or the larger ones of porcine erysipelas are not present. The enlargement of the spleen and absence of infarcts distinguish salmonellosis from hog cholera. In acute erysipelas, the spleen is enlarged but the sectioned surface is the same blue color as the capsular surface and is firm and rubbery. These points are made as generalizations and are not totally reliable. Other causes of splenomegaly must be differentiated.

The liver is usually congested, and focal hemorrhages may be visible in the capsule. In some cases the hemorrhages are very large, involving up to half of the central area in a lobule. They may be scattered at random throughout the liver or grouped, often at the edge of a lobe. Occasionally, almost every lobule is affected, and the lesions may resemble those of hepatosis dietetica. In some, there are tiny yellow foci of necrosis, the "paratyphoid nodules" described above for calves (Fig. 1.37C).

Pinpoint hemorrhages are consistently present in the renal cortex. There may be only a few in each kidney, or they may be so numerous as to cause the "turkey egg" appearance. The kidneys may be of normal color, or the cortices may be pale and the medulla intensely congested as in other septicemias. In some, there are petechiae in the pelvic and ureteral epithelium. In almost all cases, hemorrhages are present beneath the epithelium of the bladder.

The stomach shows the intense red-black color of the severe congestion and infarction common to endotoxemia in postweaned pigs. If the animal survives a week or more, the superficial layers of the affected gastric epithelium slough. There may be no lesions in the intestine. There may be a catarrhal enteritis, or more frequently, the enteritis is hemorrhagic, increasing in severity lower in the tract and terminating in a hemorrhagic ileitis. The mucosae of the colon and cecum may be normal, but

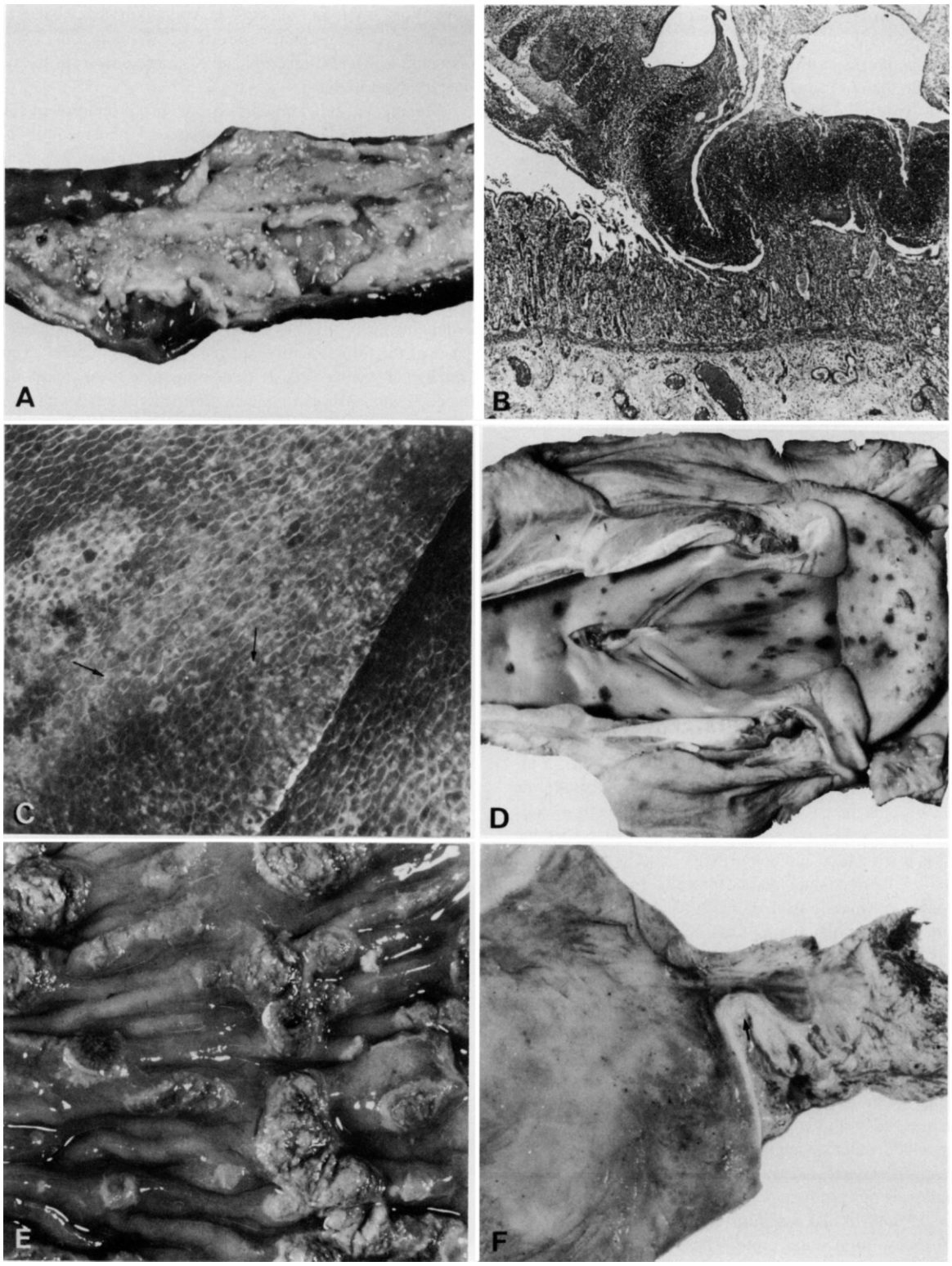


**Fig. 1.37.** (**A**) Diphtheritic enteritis. *Salmonella enteritidis*. Calf. (**B**) Bovine salmonellosis. Diphtheritic membrane on the surface of the ileum. Exudate arises from eroded mucosa, in which crypts of Lieberkühn are sparse or absent. (**C–F**) Porcine salmonellosis. (**C**) Paratyphoid nodules (arrows) in liver. *Salmonella* septicemia. (**D**) Laryngeal hemorrhages. (**E**) Ulcers in colon. (**F**) Rectal stricture. Opened colon is massively dilated anterior to stricture in rectum (arrow).

if the course if prolonged, there is hyperemia or fibrinohemorrhagic inflammation.

Petechial hemorrhages may occur in the meninges and brain, but there is no sign of gross inflammation. Localization sometimes occurs in synovial membranes, producing polysynovitis and sometimes polyarthritis. It is more usual to have an increase in the volume of fluid with red, velvety hypertrophy of the synovial villi.

The gross features that have been described are a composite, and they are usually not all present in any one case. The splenic, gastric, renal, and lymphatic lesions are most consistent.

The development of the experimental intestinal lesions in salmonellosis has been well described. The morphogenesis and microscopic appearance of the enteritis resemble those described in calves. The result may be diffuse diphtheritic enteritis in the cecum and colon and, occasionally, ileum, or focal "button ulcers." Focal ulcers in salmonellosis may occur at points where the bacteria have breached the epithelium, or they may be centered on Peyer's patches and solitary lymphoid follicles. Button ulcers that occur along the cecum and colon are to be distinguished from nonspecific ulcers that occasionally occur on and about the ileocecal valve. Necrotic enteritis due to secondary invasion of the eroded ileum and large bowel by pathogenic anaerobes and *Balantidium coli* may also supervene. Porcine adenomatosis is probably a more important forerunner of necrotic enteritis.

The histologic changes that occur in internal organs in acute disease are mainly associated with endothelial damage due to endotoxin and focal localization of bacteria. The discoloration of the skin is initially due to intense dilation, congestion, and thrombosis of capillaries and venules in the dermal papilla. There is activation and necrosis of the endothelial cells in affected vessels. The renal lesions vary but affect principally the glomeruli. In some there is diffuse glomerulitis, and this is associated with mild nephrosis and hyaline casts. In others the glomerulitis is exudative and hemorrhagic, and in these a great many capillary loops contain hyaline thrombi. The hemorrhages seen grossly come mainly from glomeruli and the wide venules of the outer cortex, although some are from intertubular capillaries; this is always the case in the medulla. Embolic bacterial colonies are occasionally seen in the glomerular and intertubular capillaries. Fibrin thrombi may also be found in the afferent arterioles and interlobular arteries.

It has been suggested that the pathogenesis of the renal vascular lesions can be explained on the basis of a generalized Shwartzman reaction. However, disseminated intravascular coagulation initiated by endotoxemia may be all that is necessary to cause these and other vascular lesions in septicemia due to Gram-negative bacteria.

The microscopic pulmonary lesions similarly are characterized by thrombosis and vasculitis and a largely mononuclear cellular response in alveolar septa. There is a flooding of the alveoli by edema fluid and moderate numbers of alveolar macrophages. This is the usual histologic picture; the extremes are an acute fibrinous inflammation or only a few scattered parenchymal hemorrhages.

In the spleen there are some scattered hemorrhages, but the overall histologic impression is of increased histiocytes with a scattering of neutrophils. The follicles are small and rather inactive. Very small foci of necrosis, containing many bacteria, are scattered in the sections or are relatively numerous, and these develop a reactive macrophage response and form the typical paratyphoid nodules.

Meningoencephalomyelitis occurs in a proportion of cases of septicemic salmonellosis. The lesion is fundamentally a vasculitis. There may be petechiae in the meninges, but microscopically, there is an infiltration of large mononuclear cells in the pia–arachnoid and concentrated about the veins. There is also sludging of these cells and polymorphs, including eosinophils, in the veins. Similar lesions may occur at any level in the brain. In some cases the walls of many veins are necrotic, and there may be a mononuclear-cell reaction in the walls and surrounding neuropil. Only a few neutrophils and eosinophils form part of the inflammatory cell reaction in these areas. The parenchymal lesions consist of a disseminated focal granulomatous encephalitis. Areas of malacia may be associated with the granulomas. Microabscesses form in those few cases in which bacterial emboli are detectable. Glial nodules are typical of the healed phase. These lesions occur in the spinal cord as well.

*Salmonella typhimurium* infection in swine produces a syndrome that differs from *S. choleraesuis* in a number of ways. Clinically, the disease occurs in feeder pigs and is characterized by fever, inanition, and yellow, watery diarrhea, which may contain blood and mucus, especially in the later stages. The diarrhea may be chronic and intermittent. There is a high morbidity but low mortality. Most pigs recover but may remain carriers for variable periods of time.

The pathogenesis and morphology of the enteric lesions are similar to those described for *Salmonella choleraesuis* enteritis. The lesions with *S. typhimurium* infection are mainly confined to the colon (Fig. 1.37E), cecum, and rectum, however, with rare involvement of the distal small intestine.

**Rectal stricture** is thought to be a sequel in most cases to ulcerative proctitis of ischemic origin caused by *Salmonella typhimurium*. It is characterized clinically by marked progressive distension of the abdomen, loss of appetite, emaciation, and soft feces. At autopsy, there is marked dilatation of the colon, which is caused by narrowing of the rectum, 1–10 cm anterior to the anus (Fig. 1.37F). The stricture is usually less than 1.0 cm in diameter and varies in length from 0.5 to 20 cm. There is marked fibrous thickening of the rectal wall, which may contain microabscesses. The dilatation of the colon, anterior to the stricture, may consist of a well-demarcated, widened area several centimeters long and wide. The colonic mucosa in this area is usually ulcerated and may be covered by fibrinous exudate. In some cases, there is more gradual dilatation of the entire colon, with ulceration of the mucosa just anterior to the stricture. The mucosa is always excessively corrugated; this is mainly the result of marked thickening of the internal muscularis. Localized chronic peritonitis is often associated with the dilated segments of the colon.

Microscopically, the strictures are the result of marked fibrosis of the gut wall, with almost complete obliteration of the normal structures. The mucosa is generally completely absent. The luminal surface is covered by debris, fibrin, and neutrophils. A few veins in the wall contain well-organized thrombi. The colonic lesions are those of a mild to severe necrotizing ulcerative colitis, described earlier.

The stricture is located in an area of rectum that has a relatively poor blood supply, namely, the junction of the circulatory fields of the caudal mesenteric and pudendal arteries. Ulcerative proctitis is consistently found in swine with typhlocolitis due to *Salmonella typhimurium* infection. Granulation of such lesions probably leads to cicatrization and stricture. The location, the persistent nature of this lesion in some pigs, and its limited capacity to heal are probably related to the restricted blood supply of the affected area. The lesions in the colon and cecum, with greater collateral blood supply, heal more rapidly, usually without further complications. At the time of autopsy, *S. typhimurium* may not be isolated due to loss of the carrier state. Alternatively, rectal stricture in some cases may result from ischemia due to noninfectious causes, such as rectal prolapse.

*Salmonella typhisuis* infection is an uncommon condition in pigs, with a limited geographic distribution. The disease is called paratyphoid in Europe. It is a progressive disease of 2- to 4-month-old pigs that is clinically characterized by intermittent diarrhea, emaciation, and frequently, massive enlargement of the neck region. The lesions are those of circular or button-like to confluent ulceration of the mucosa of the ileum, cecum, and colon. Other typical findings are caseous palatine tonsillitis and cervical lymphadenitis, parotid sialoadenitis, and caseous lymphadenitis of the mesenteric lymph nodes.

The differential diagnosis of septicemic salmonellosis includes other septicemias that occur in feeder swine, such as peracute erysipelas, *Haemophilus,* and *Steptococcus* infections. It is important to differentiate *Salmonella choleraesuis* infection from hog cholera and African swine fever.

The enteric forms of salmonellosis must be differentiated from other enteritides in postweaning swine, particularly postweaning *E. coli* enteritis, swine dysentery, and *Campylobacter* enteritis.

CARNIVORES. *Salmonella* may often be recovered from dogs. However, primary disease rarely, if ever, occurs. Salmonellosis is most commonly secondary to canine distemper and may cause bronchopneumonia, acute gastroenteritis, splenic swelling, serosal hemorrhages, and foci of necrosis in the liver and other organs. There is also enlargement of the mesenteric lymph nodes. Salmonellosis has also been reported in dogs with lymphosarcoma, shortly after the initiation of chemotherapy. The immunosuppressive effect of the treatment probably predisposes to the development of disease.

Various serotypes have been isolated from cats, and most of these appear to cause subclinical infections. Salmonellosis may be a problem in catteries and hospitals, however, affecting animals subjected to the usual stressful conditions mentioned earlier. *Salmonella typhimurium* is most commonly associated with such outbreaks. The disease is characterized by gastroenteritis and septicemia.

Because of their close association with humans, especially children and the aged, dogs and cats, which are carriers, may be a source of zoonotic infection.

### *Yersiniosis*

*Yersinia enterocolitica* causes sporadic cases of mucoid enterocolitis in young dogs and produces ulcerative ileocolitis in humans. The significance of the organism in human disease has finally been recognized. Strains of *Y. enterocolitica* from dogs, and from pigs, which are regarded as reservoirs of infection, cause disease in humans. Outbreaks of disease in pigs and goats due to *Y. enterocolitica* have been recorded. In goats, sudden deaths sometimes preceded by diarrhea occur; the diarrhea is associated with acute catarrhal enteritis. Kids are particularly susceptible. Certain strains of *Y. enterocolitica* are enterotoxigenic and/or invasive. Invasion occurs via the lymphoid tissue of the ileum and cecum.

*Yersinia (Pasteurella) pseudotuberculosis* infection may cause enteritis and diarrhea in animals. The organism is carried in the alimentary tract of rats, mice, and birds. Following oral infection, a local lesion in the intestine may be produced. In some animals, systemic spread, with multifocal hepatic necrosis and splenitis, occurs. Captive wild ruminants commonly show enteric lesions as well as visceral lesions, and this combination is seen occasionally in sheep. In dogs and cats, signs of enteritis occur, but lesions have not been described. *Yersinia pseudotuberculosis* occasionally can be isolated from small green abscesses in the mesenteric lymph nodes of asymptomatic dogs and cats. The organism also causes pneumonia and septicemia in foals and sporadic abortions in ruminants.

### *Campylobacter Enteritis*

Enteritis in animals and humans associated with *Campylobacter,* or *Campylobacter*-like organisms, appears in two forms. The first is characterized by adenomatous proliferation of epithelium in the crypts of Lieberkühn in the small intestine (especially ileum) and in mucosal glands in large bowel. Bacteria that have been confirmed as *Campylobacter* or that resemble *Campylobacter* morphologically are found within proliferating epithelial cells. Conditions that fall into this category include ileal hyperplasia or proliferative ileitis in hamsters, typhlitis in rabbits, duodenal hyperplasia in guinea pigs, intestinal adenomatosis affecting the cecum and colon in blue foxes, proliferative colitis in ferrets, intestinal adenomatosis in horses, and a cluster of syndromes in swine grouped under the name intestinal adenomatosis complex. Terminal ileitis or regional enteritis in lambs has not been firmly associated with intracellular *Campylobacter*-like organisms. The second group of conditions comprises enteritis and mucosal colitis associated with apparently noninvasive *C. jejuni* and perhaps *C. coli.* Diarrhea in humans, dogs, and cattle is associated with *C. jejuni.* The causal role of *C. jejuni* and *C. coli* in spontaneous enteritis in sheep, cats, and swine is less clearly established.

The intestinal adenomatosis complex of swine, the most significant expression of *Campylobacter*-associated proliferative enteritis, and the syndromes associated with *C. jejuni* and *C. coli,* will be considered more fully.

INTESTINAL ADENOMATOSIS COMPLEX OF SWINE. This group of conditions is associated with intracellular proliferation of *Campylobacter* spp. in the mucosal glands of the ileum and proximal large bowel of swine. Its components have been variously recognized in the past as intestinal adenoma of swine, adenomatous intestinal hyperplasia, terminal regional ileitis, regional ileitis, terminal ileitis, proliferative ileitis, and as part of hemorrhagic bowel syndrome, necrotic enteritis, and ileal muscular hypertrophy.

The agent associated most commonly with the intestinal adenomatosis complex is *Campylobacter sputorum* var. *mucosalis*, which has been isolated from the mucosal lesion and from the oral cavity of swine in affected herds. It has proved difficult consistently to reproduce the disease, or its essential lesions, even using crude inocula comprised of infected intestinal mucosa. Cultures of the organism may inconsistenly produce disease in Caesarian-derived, colostrum-deprived, but not germ-free pigs. A second species, *C. hyointestinalis*, has been recovered commonly, alone or in association with *C. sputorum* var. *mucosalis*, from lesions in naturally infected swine. Immunofluorescence suggests that *C. hyointestinalis* is more numerous and widespread in cells in hypertrophic crypts, while *C. sputorum* var. *mucosalis* is limited to more superficial foci in affected tissue. The etiologic significance of each of these agents and their possible interactions with each other and the rest of the enteric flora remain to be clarified.

A number of clinicopathologic syndromes comprise the intestinal adenomatosis complex in swine. They may be found concurrently in a single herd and are manifestations of different phases of the interaction between the host and the invasive *Campylobacter*. The fundamental lesion is porcine intestinal adenomatosis—proliferation of *Campylobacter*-infected epithelial cells in crypts and glands and associated mucosal alterations (Fig. 1.38A). Necrotic enteritis, regional ileitis, and proliferative hemorrhagic enteropathy are the other defined components of the complex. Each syndrome will be discussed in turn.

**Porcine intestinal adenomatosis** and its sequelae, necrotic enteritis or regional ileitis, occur most commonly in postweaning feeder pigs. Piglets as young as 3 weeks of age, however, as well as adults, may have lesions of adenomatosis. Intestinal adenomatosis is associated with a syndrome that may vary from subtle subclinical disease with a mild decrease in growth rate to diarrhea and unthriftiness. Animals with extensive lesions, developing necrotic enteritis, or regional ileitis may show anorexia, intermittent or persistent diarrhea, and severe weight loss. Death may follow a period of diarrhea and progressive cachexia, or it may occur occasionally as a result of perforation of an ulcerated intestine in regional ileitis.

In adenomatosis, infection of cells lining mucosal glands may occur initially in the vicinity of Peyer's patches and mucosal lymphoid aggregates in the ileocecal colic region. In some experimental studies, lesions were first seen there, and in mildly affected spontaneous cases, lesions sometimes seem associated with these structures preferentially. *Campylobacter* invades epithelium in crypts and glands, where the bacteria lie free in the apical cytoplasm and replicate. Goblet cells disappear from affected glands, and infected epithelium is transformed to a population of highly mitotic cells. These form a crowded, pseudostratified columnar epithelium, with basophilic cytoplasm. Nuclei may be open and vesiculate with prominent nucleoli, or laterally compressed. Glands become elongate, dilated, and branching, causing thickening of the mucosa. Isolated plaques of affected mucosa may project above adjacent unaffected tissue. The derivation of the term adenomatosis to describe such a change is obvious. Hypertrophic glands sometimes protrude into lymphoid tissue in the submucosa.

Enterocyte migration from crypt to lumen appears to decline, and villi undergo progressive atrophy so that they may be entirely absent in well-established lesions. Adenomatous areas merge sharply with adjacent normal mucosa. Masses of *Campylobacter* are readily recognized in silver-stained tissue sections as curved rods, sometimes seagull- or W-shaped, infecting especially the apical cytoplasm of cells in adenomatous glands (Fig. 1.38B). *Campylobacter* also has been identified ultrastructurally in degenerate cells and macrophages in the lamina propria. However, proprial and submucosal inflammation in areas of uncomplicated adenomatosis is not marked.

How *Campylobacter* induces such lesions is unknown. The lesion may be the result of cell-mediated immune reactions stimulating, by lymphokine, crypt-cell hyperplasia. Proliferation of the bacteria appears to be largely intracellular, and the effect of continual mitosis of cells in crypts may be to increase the population of cells able to support bacterial growth and replication.

In animals with the relatively mild syndrome of uncomplicated intestinal adenomatosis, lesions are always found in the terminal portion of the ileum, extending proximally from the ileocecal–colic orifice for usually less than a meter. In a proportion of cases they involve the cecum and proximal third of the spiral colon. Lesions of the cecum and colon do not occur without ileal involvement. In mild cases, which are likely to be subclinical, only a few ridge- or plaquelike thickened areas project above the remainder of the mucosa. However, more typical widespread lesions cause the thickened mucosa to form irregular longitudinal or transverse folds or ridges. The surface may be intact, but commonly, small foci of fibrin exudation or necrosis may be evident (Fig. 1.38F).

Thickening of the adenomatous mucosa, and perhaps some edema of the submucosa, is reflected in accentuation of the normal reticular pattern on the serosa of the ileum (Fig. 1.38D). This results in a "cerebral" or gyrate pattern of projections and depressions on the serosal aspect of the intestine, which is readily recognized and virtually pathognomonic for this condition. Mucosal lesions in the large intestine often form thickened plaquelike or almost polypoid masses, which may be confluent in some areas. Serosal folds may be evident on extensively affected large intestine. The ileocolic lymph nodes are enlarged and hyperplastic. Occasionally, microscopic foci of adenomatous epithelium may be found in submucosal lymphatics or the regional lymph node.

Coagulation necrosis of adenomatous mucosa occurs commonly. **Necrotic enteritis** may be partly the result of pathogenic anaerobic large bowel flora, colonizing the affected terminal ileum. There may be effusion of fibrin from superficial lesions, and a pseudodiphtheritic membrane or luminal fibrin cast may be present. Caseous yellow-brown or blood-tinged necrotic mucosa may be found focally or widely in the distal ileum and proximal large intestine. The cerebral pattern of serosal folding is evident in such cases (Fig. 1.39B). Necrotic enteritis may be a sequel to other enterocolitides in swine, but adenomatosis is probably the most common primary lesion.

Microscopically, coagulation necrosis of the mucosa may be focal and superficial, with local effusion of neutrophils and fibrin into the lumen and an acute inflammatory infiltrate at the margin of the necrotic tissue. Frequently, necrosis extends to

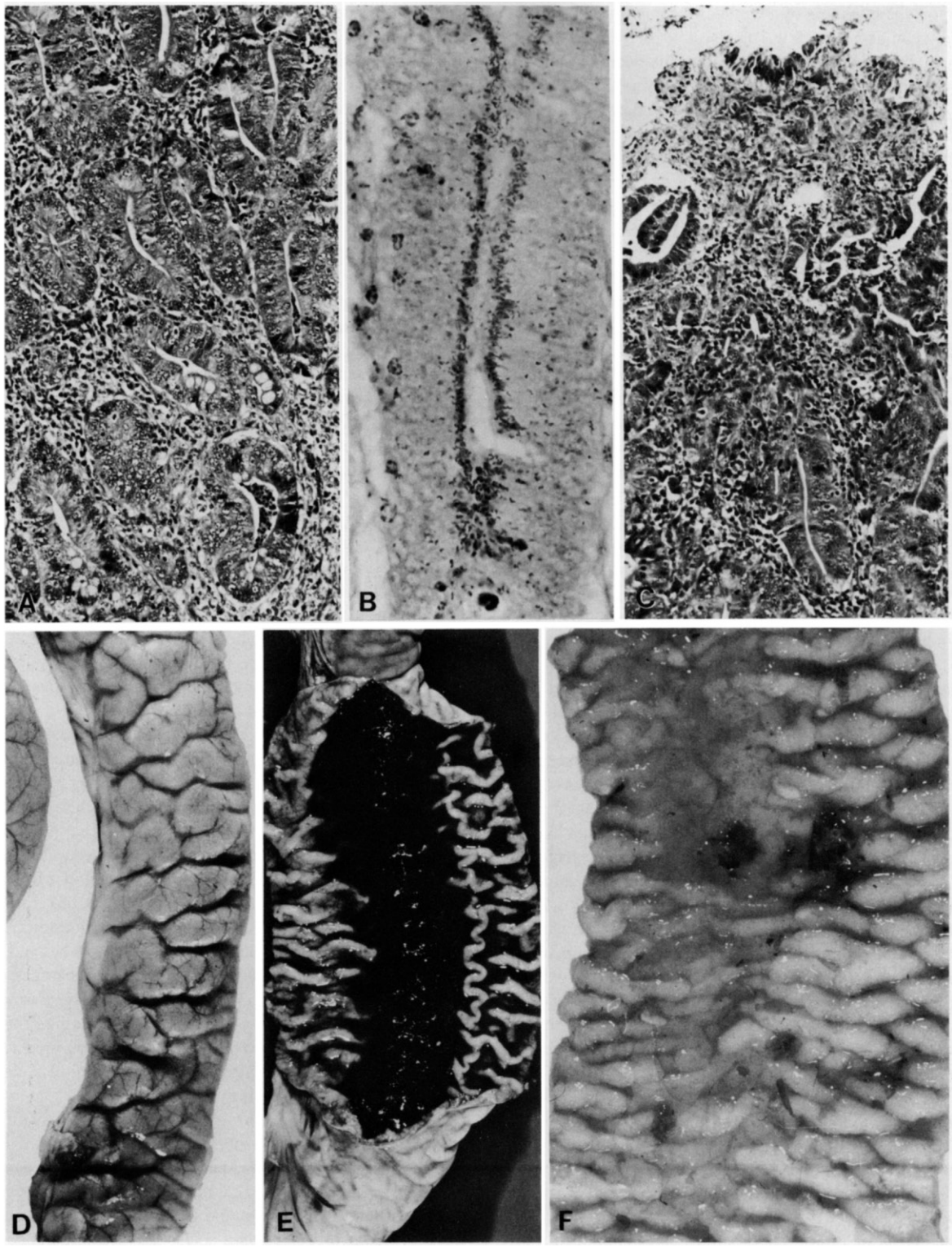


**Fig. 1.38.** Porcine intestinal adenomatosis complex. (**A**) Adenomatous change in glands in lamina propria. (**B**) Masses of silver-stained *Campylobacter* in cytoplasm of hyperplastic epithelium lining intestinal glands. (**C**) Proliferative hemorrhagic enteropathy. Superficial necrosis of mucosa associated with thrombosis of small vessels, hemorrhage, and effusion of fibrin and neutrophils. (**D**) Exaggerated reticular pattern of folds on serosal aspect of the ileum. (**E**) Proliferative hemorrhagic enteropathy. Hemorrhage and blood clot in terminal ileum. Nodular folded mucosa. (**F**) Raised nodular or ridgelike areas of thickened mucosa in the ileum, resulting from hypertrophy of glands.

involve most the thickness of the mucosa, sometimes penetrating to the submucosa. A few islands of viable adenomatous crypts or glands may be left deep among the necrotic debris. Tissue in the upper ileum at the proximal margin of the zone of mucosal necrosis should be examined for adenomatosis, since in severe cases of necrotic enteritis, no remnants of abnormal mucosa may persist elsewhere. Masses of bacteria, presumably fecal anaerobes, are found superficially in the necrotic tissue. With time, granulation tissue develops in ulcerated areas.

**Regional ileitis** is the term applied to contracted tubular distal ileum, which may have an ulcerated mucosa, perhaps with a few raised foci of surviving proliferative mucosa. Granulation of ulcerated gut may result in progressive stricture of the lumen. More characteristically, there is hypertrophy of the external muscle layer. Idiopathic ileal muscular hypertrophy also occurs in swine, apparently independent of antecedent adenomatosis. Granulomatous regional ileitis and mesenteric lymphadenitis in swine, nontuberculous and distinct from adenomatosis, has been described from Finland.

**Proliferative hemorrhagic enteropathy** is the fourth syndrome in the intestinal adenomatosis complex. It is a distinctive clinical entity, characterized by acute or subacute intestinal hemorrhage and anemia. Animals may exsanguinate so quickly as to die without passing blood. Others pass dark, tarry feces for several days. This syndrome is more common in young adults rather than growing pigs. It is usually sporadic or of relatively low morbidity, but up to half the clinically recognized cases may die.

Animals dead of proliferative hemorrhagic enteropathy are pale. The typical cerebral pattern is evident on the external surface of the distal ileum, which is thickened and turgid (Fig. 1.39A). Fluid blood, or a loose or firm fibrin and blood clot, may be present in the ileum (Fig. 1.38E), and the contents of the cecum and colon may contain dark, bloody digesta and feces. The mucosa of the affected ileum usually resembles that in uncomplicated adenomatosis, and overt points of hemorrhage or ulceration are rarely appreciated grossly. Rather, the animals appear to suffer widespread diapedesis from the mucosa. In tissue section there is extensive degeneration and necrosis of adenomatous epithelium (Fig. 1.38C). An acute inflammatory infiltrate is present in the upper lamina propria, small vessels are thrombosed, and heavy effusion of neutrophils onto the mucosal surface and into lumina of glands is evident. Fibrin and hemorrhage emanating from superficial mucosal vessels are in the intestinal lumen. More extensive coagulation necrosis of the mucosa is associated occasionally with the hemorrhagic syndrome. It has been suggested that proliferative hemorrhagic enteropathy is the result of a hypersensitivity reaction to release of normally occult intracellular bacterial antigen from its intracellular location, by degeneration or phagocytosis of infected epithelium.

The diagnosis of proliferative hemorrhagic enteropathy at autopsy is based on the presence in the distal ileum of gross lesions characteristic of adenomatosis, in association with massive hemorrhage from the lower small intestine. The condition must be differentiated from hemorrhagic ulceration of the pars esophagea, mesenteric torsion, and acute swine dysentery as well as from less common causes of gastrointestinal bleeding in swine. Less hemorrhagic manifestations of the adenomatosis complex must be differentiated from acute or chronic salmonellosis.

The diagnosis of components of the intestinal adenomatosis complex is confirmed by finding *Campylobacter*. They may be seen in smears of mucosal scrapings stained by the modified Koster's acid-fast method or with specific immunofluorescent techniques. Their intracellular location and association with typical adenomatous lesions is demonstrated in silver-stained tissue sections.

ENTERITIS ASSOCIATED WITH OTHER *CAMPYLOBACTER* SPECIES. *Campylobacter jejuni* and *C. coli* have been recognized recently as common causes of diarrhea in humans. *Campylobacter* enteritis rivals salmonellosis in significance in this regard in many areas. Like salmonellosis, *Campylobacter* infection may be zoonotic. Many human infections appear to be acquired by drinking raw milk or come from other animal foodstuffs, especially poultry products. Chickens are common asymptomatic shedders of *C. jejuni*. Some human cases have been associated with diarrhea in family pets, particularly puppies.

Despite the fact that it can be isolated from nondiarrheic animals, *Campylobacter jejuni* has been associated with diarrhea characterized by the presence of blood and mucus in some dogs. It has also been isolated from dogs with parvoviral enteritis and other viral infections; it is not known if concurrent infection with these agents is synergistic. The role of *Campylobacter* as a significant primary pathogen in dogs is not proven. Mild enteritis and colitis have been described in naturally infected dogs, while in experimentally infected gnotobiotic dogs, lesions are limited to mild mucosal colitis.

*Campylobacter jejuni, C. fetus* subsp. *fetus,* and *C. fecalis* have been isolated from the feces of normal cattle and from diarrheic calves and cattle, many of them suffering from disease due to other agents. Experimental inoculation of these agents has resulted in passage of dark, fluid feces with mucus and flecks of blood. The intestine was described as thickened and patchily reddened, especially in the ileum, cecum, and colon. Mild enteritis with stunting of villi and some accumulation of neutrophils in crypts was described in sections of the small intestine. There was hyperplasia of lymphoid tissue in Peyer's patches and mesenteric lymph nodes. *Campylobacter jejuni* and perhaps other species are thought to be primary agents causing diarrhea in cattle, but further work is needed to define their significance. For many years *Campylobacter (Vibrio) coli* was proposed as the cause of "winter dysentery," a clinical entity in cattle, the etiology of which has not been determined.

*Campylobacter jejuni,* in addition to causing a significant proportion of "vibrionic" abortions, is isolated from the intestine of sheep with diarrhea, but its causal association is unproven. The same agent also has been isolated from the feces of a number of scouring foals, but the significance of the infection is unclear. *Campylobacter jejuni* is also isolated commonly from cats, but not usually in association with diarrhea.

*Campylobacter coli* is the species commonly isolated from the intestine of swine. As "*Vibrio coli*" it was long associated with swine dysentery but did not induce enteritis in experimentally inoculated gnotobiotic pigs. More recent reports of diarrhea in conventional swine inoculated orally with *C. coli* need confirmation.

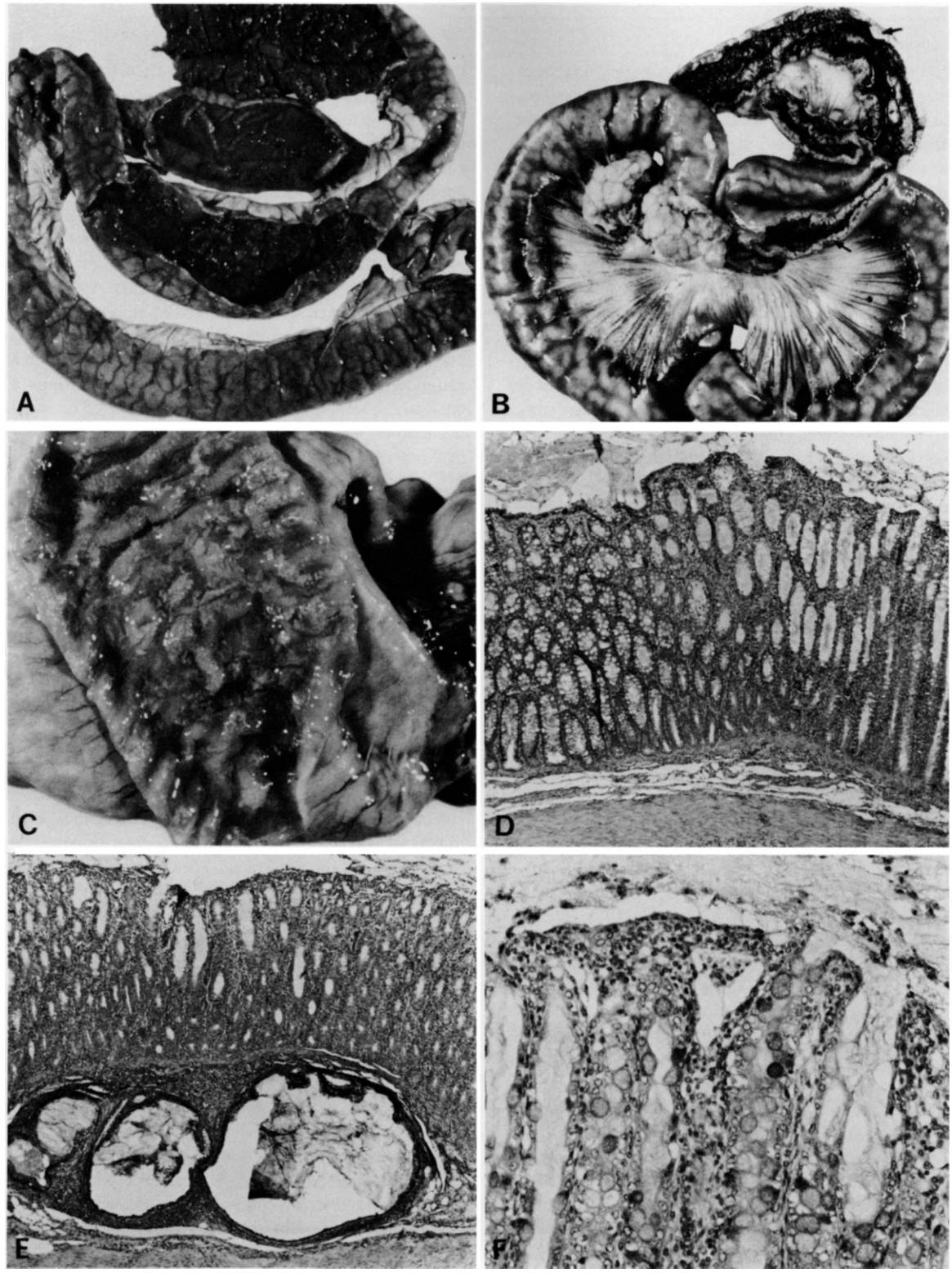


**Fig. 1.39.** (**A** and **B**) Porcine intestinal adenomatosis complex. (**A**) Folded necrotic mucosa, and fibrinohemorrhagic exudate in terminal ileum. (**B**) Necrotic enteritis. Thick ileal wall (arrows), enlarged lymph nodes, and opaque mesentery. (**C**–**F**) Swine dysentery. (**C**) Patchy fibrinocatarrhal exudate on the colonic mucosa. (**D**) Hyperplastic glands with few goblet cells adjacent to mucosa with normal density of goblet cells. Mucus in large amounts on mucosal surface. (**E**) Hyperplastic glandular lining virtually devoid of goblet cells; "colitis cystica profunda," or herniation of mucous glands into submucosal lymphoid tissue. (**F**) Flattened and exfoliating epithelium on mucosal surface, and edema of superficial lamina propria. Mucus in glands and on surface, mixed with neutrophils and exfoliated epithelium.

SWINE DYSENTERY. Swine dysentery is a highly infectious disease mainly of weaned pigs that is characterized by diarrhea, with mucus, blood, or fibrin in the feces. The disease has been reported from a number of countries and probably occurs wherever swine are raised. It has been recognized for nearly half a century, and as long ago as 1924 was known to be experimentally transmissible by dosing young pigs with colonic contents from affected swine. *Campylobacter coli* (formerly *Vibrio coli*) was thought to be the etiologic agent of swine dysentery for many years, but *Treponema hyodysenteriae* is now considered to be the causative agent. It is a Gram-negative, anaerobic but oxygen-tolerant spirochete, 6–8.5 μm long and 0.5 μm in diameter. It produces strong β-hemolysis on blood agar plates. The organism is motile, moving in serpentine fashion; it is loosely coiled and has 7–13 axial filaments. Swine dysentery can be reproduced by feeding pure cultures of *T. hyodysenteriae* to specific pathogen-free and conventionally reared swine. Experimental reproduction of the disease in gnotobiotic pigs requires the presence of anaerobic bacteria indigenous to the normal colon, along with *T. hyodysenteriae*. There is apparently a synergistic action between the spirochete and the other anaerobes, mainly *Bacteroides* and fusiforms. These probably provide a suitable microenvironment for the *Treponema* to proliferate. *Treponema hyodysenteriae* is also pathogenic for guinea pigs and mice. Oral inoculation causes colitis in both species.

Other *Treponema* organisms occur in the colon of normal pigs. These spirochetes are approximately half the size of *T. hyodysenteriae*, are nonhemolytic or only weakly so, and differ in other biochemical reactions. It has been suggested that these spirochetes be called *T. innocens*. Their role in spontaneous disease is controversial, since they have been associated with diarrhea that resembled a mild form of swine dysentery. It appears that at least some strains of *T. innocens* are mildly pathogenic for swine.

The pathogenesis of swine dysentery is still incompletely understood. *Treponema hyodysenteriae* invades the epithelial cells of the superficial mucosa of the colon. Although there is no evidence to suggest that invasion is essential for epithelial necrosis to occur, lesions in the mucosa are associated with the presence of large numbers of spirochetes and other anaerobic bacteria. Only the spirochetes invade the epithelial cells. It has been suggested that liberation of large amounts of toxins by *T. hyodysenteriae* and possibly other anaerobes results in the superficial necrosis of the mucosa. *Treponema* usually does not invade beyond the mucosal epithelial cells. The morphologic lesion is mucosal colitis characterized by hypersecretion of mucus, and superficial erosion with hyperplasia of cells in colonic glands. Thrombosis of capillaries and venules in the superficial areas of the mucosa in the colon and the gastric fundic mucosa (venous infarction) is probably due to absorption of endotoxins released by Gram-negative bacteria.

The diarrhea in swine dysentery is due to failure of absorption of fluids and electrolytes in the colon. This presumably results from damage to the superficial colonic epithelium. The normal colon of the pig has a tremendous absorptive capacity. Interference with this absorption results in severe diarrhea and dehydration. There is no evidence of active fluid secretion associated with bacterial enterotoxins. Fluid and electrolyte transport are normal in the small intestine. Thus the pathogenesis of diarrhea associated with swine dysentery differs from that seen with enterotoxigenic *E. coli* and *Salmonella* spp. Prostaglandins released during the inflammation do not appear to be implicated in the development of diarrhea, as they are in salmonellosis.

Histories usually recount the introduction of pigs, presumably carriers, into a herd some days, weeks, or even months before the disease breaks out. Once established in a herd, the infection tends to remain enzootic, and although treatment can effect a rapid clinical amelioration, it is not curative, and relapses at greater or lesser intervals are the rule. Apparently infection is not followed by a substantial immunity, although individual pigs are resistant to challenge with *Treponema hyodysenteriae* after recovery. The morbidity may reach 90% and mortality 30%. Many of the factors predisposing to salmonellosis also apply to swine dysentery. Pigs fed diets deficient in vitamin E and selenium develop more severe signs and lesions of swine dysentery.

The disease occurs in pigs of all ages more than about 2 to 3 weeks old, but particularly in pigs 8 to 14 weeks of age. Once initiated, it spreads rapidly by pen contact. The disease is initially febrile, but with the onset of diarrhea, fever tends to subside. The initial diarrheic feces are thin, semisolid, and without blood or mucus; it is usually only after 1 or 2 days of diarrhea that blood and mucus appear in the feces. Some pigs die peracutely without showing diarrhea and many that show diarrhea do not have dysentery but pass feces composed almost wholly of mucus.

Pigs that die of swine dysentery are usually gaunt with a contracted abdomen, the eyes are sunken, and there may be bluish discoloration of the abdominal skin. Incidental lesions may include pericardial serous effusion and intense congestion and infarction of the stomach. The intestinal lesions, especially in young pigs dying acutely, can be easily overlooked because the mucosal colitis may be mild, patchy, and often more catarrhal than fibrinous.

In typical cases, dehydration gives to the serosa a semiopaque, ground-glass appearance, and the wall of the cecum and colon is thickened. The colonic content in these cases is usually scant and of a porridge-like, dirty gray to reddish brown and greasy appearance. The mucosa, with patchy foci of light fibrin exudation, has the velvety thickening of catarrhal secretion (Fig. 1.39C). The most severe lesions approach those of salmonellosis in extent and severity of fibrinous effusion. The production of mucus in swine dysentery becomes copious in many chronic cases, and there is a remarkable goblet-cell metaplasia. It is common to find foul-smelling straw and bedding in the stomach and colon of such cases, evidence of pica.

The earliest microscopic lesions are characterized by expulsion of mucus from the basilar portions of the crypts (Fig. 1.39D). There are discrete areas of necrosis and erosion in the superficial mucosa. Thin layers of fibrinocellular exudate cover the eroded areas. In more advanced cases, the areas of necrosis become more diffuse but remain superficial, and exudation is more copious (Fig. 1.39F). There may be minor bleeding from small vessels in eroded mucosa. Fibrin thrombi are evident in the capillaries and venules of the superficial lamina propria. There is usually some edema of the lamina propria, submucosa, and serosa. Many crypts are dilated and contain necrotic debris; others show marked goblet-cell hyperplasia. In response to the

increased turnover of epithelial cells associated with the superficial necrosis, there is hyperplasia of cells deeper in the glands. The crypts are elongated, lined by proliferative basophilic epithelial cells that have large nuclei, and have few differentiated goblet cells (Fig. 1.39E).

Large numbers of spirochetes are easily demonstrated using Warthin–Starry silver stain or similar stains. They are mainly located in the areas of superficial erosion and in the lumen of crypts.

Ultrastructurally, large numbers of spirochetes are located on the surface and within the cytoplasm of epithelial cells. Fewer organisms are present in the intercellular spaces between superficial epithelial cells, in the lumen of crypts, and occasionally in the lamina propria. Degenerative changes in the epithelial cells are characterized by loss of microvilli, clumping of nuclear chromatin, and swelling of the mitochondria and the rough endoplasmic reticulum.

The diagnosis of swine dysentery is usually based on the characteristic clinical signs and gross and microscopic lesions, since it is difficult to isolate the causative agent under practical conditions. Selective media are required to isolate *Treponema hyodysenteriae*. Colonic contents may be examined by phase contrast or dark field microscopy. Large numbers of the characteristic motile spirochetes are present in affected cases. Fluorescent-antibody and special stains such as crystal violet, Victoria 4-R, and modified acid fast are all used to demonstrate the spirochetes in mucosal smears. However, culture is required conclusively to differentiate *T. hyodysenteriae* from other spirochetes such as *T. innocens*.

The differential diagnosis of swine dysentery from salmonellosis, especially that due to *Salmonella typhimurium*, intestinal adenomatosis complex, and trichurosis, is discussed under Typhlocolitis in Swine.

### *Diseases Associated with Enteric Clostridial Infections*

Most of the important enteric clostridial diseases occur in herbivores and are caused by one or other of the five toxigenic types of *Clostridium perfringens*. Occasionally, other members of the genus are associated with enteric disease, examples being *C. sordellii* and *C. botulinum* in cattle and *C. strasburgense* in dogs.

There are five types of *Clostridium perfringens*, designated A–E, which are differentiated on the basis of their production of the four major antigenic lethal exotoxins. A strain formerly classified as type F is now regarded as a subtype of type C. The major exotoxins are alpha (α), beta (β), epsilon (ϵ), and iota (ι); the relationships between the five types and the four toxins are tabulated here:

| Toxin | α | β | ϵ | ι |
|---|---|---|---|---|
| Type A | ++ | − | − | − |
| B | + | ++ | + | − |
| C | + | ++ | − | − |
| D | + | − | ++ | − |
| E | + | − | − | ++ |

++, Significant toxin; +, small amount, −, none produced.

Eight minor toxins (antigens) are produced by *Clostridium perfringens*, and it is suggested that some of these may be useful in identification of types and in division of types A, B, and C into varieties.

The α toxin is a lecithinase that acts on cell membranes, producing hemolysis or necrosis of cells. The chemical nature of the β toxin is not clear. It is common to those strains (B and C) that cause enteritis and is necrotizing, trypsin labile, and appears to have a paralyzing effect on the intestine. The ϵ toxin is produced as an inactive prototoxin that is activated by enzymatic digestion. In culture, the appropriate enzymes [the minor toxins kappa (κ) and lambda (λ)] may be produced by the organism. In the intestine, trypsin is an effective activator. The prototoxin is produced only during periods of growth. The ι toxin also is elaborated as a prototoxin and activated by proteolytic enzymes either in culture (λ toxin) or in the intestine. The κ toxin is a collagenase, and λ a nonspecific proteinase. Other minor toxins include mu (μ), a hyaluronidase, and delta (δ), a hemolysin. The enterotoxin produced by certain strains is discussed below.

There is not always a clear distinction between the different types of *Clostridium perfringens*. Some strains lose their ability to produce one or more of their toxins when stored or cultured, and this complicates the identifications of isolates and the assessment of their significance in disease outbreaks.

Clostridial diseases of the intestine often are called enterotoxemias. Disease produced by *Clostridium perfringens* type D, whose ϵ exotoxin is elaborated in the intestine but exerts its important effects on distant organs such as brain and kidney, is an enterotoxemia. The hemolytic disease attributed to type A is also an enterotoxemia, but in general the other types produce local intestinal lesions. The production of an enterotoxin, distinct from the classical exotoxins, by some types of *C. perfringens* is potentially confusing. This enterotoxin is elaborated only by sporulating cells and is released on lysis of the cells. It is almost exclusively a product of type A strains but is identified occasionally from type C and very rarely from type D strains. The enterotoxin is not involved in the pathogenesis of enterotoxemia ("pulpy-kidney disease") caused by the latter strains. It is significant in food poisoning by type A strains in humans.

*CLOSTRIDIUM PERFRINGENS* TYPE A. *Clostridium perfringens* type A is the most common of the five types and is the only one associated with the microflora of both soil and intestinal tract. Its major toxin is the α toxin and it also produces the enterotoxin. Some type A strains may produce either very small amounts or no α toxin. Strains yielding large quantities of this toxin are rare.

*Clostridium perfringens* type A is one of several clostridia that produce gas gangrene in humans and animals. The production of gas gangrene in wound and puerperal infections probably is a composite effect of the major and minor toxins elaborated by the organism. The necrotizing and hemolytic activity of the α toxin is assisted by the collagenase and hyaluronidase, which disrupt connective tissues and permit the infection to spread. Other wound contaminants, not necessarily clostridial, also can be important in lesion development.

The significance of type A strains in enteric diseases other than food poisoning in humans and necrotic enteritis of chickens is not clear. Their postulated causative association with equine colitis X is discussed elsewhere. A very rare disease of calves

and lambs characterized by acute intravascular hemolysis is also associated with type A infections. Affected animals may be found dead or moribund, and jaundice and hemoglobinuria may be evident clinically. At autopsy, icterus, anemia, and other changes of severe acute intravascular hemolysis are prominent. Severe diarrhea may occur in calves, but enteric lesions are likely to be obscured by rapid autolysis. This hemolytic disease must be distinguished from other causes of acute intravascular hemolysis such as leptospirosis, bacillary hemoglobinuria caused by *Clostridium novyi* type D (*haemolyticum*), and chronic copper poisoning. Presumably the hemolytic effect of this toxin is responsible for the intravascular hemolysis. Given that type A strains are commonly found in the intestines of ruminants, and that α toxin given intravenously is destroyed rapidly, it is apparent that there must be complex pathogenetic requirements for the development of this disease. The pathogenesis may be somewhat analagous to that of enterotoxemia caused by type D, which is discussed below.

*CLOSTRIDIUM PERFRINGENS* TYPE B. *Clostridium perfringens* type B is reported from Europe, South Africa, and the Middle East, but not from North America and Australasia. It causes "lamb dysentery," usually in lambs up to about 10 to 14 days of age, dysentery in calves of approximately the same age, and dysentery in foals within the first few days of life.

In **lambs**, death may occur without premonitory signs, but there is usually abdominal pain, especially when forced to rise, and passage of semifluid dark feces mixed or coated with blood. The abdomen is often tympanitic. A more chronic form in older lambs, which among other diseases is known as "pine" in England, is characterized by unthriftiness and depression, reluctance to suckle, and a peculiar stretching when the animal rises; such cases are reputed to respond well to specific antiserum. Proof of the nature of their illness is lacking, although epidemiologically it does appear to be a chronic form of this disease.

Typical lesions are usually present, although in exceptional peracute cases they may be indistinct. The first impression on opening the abdominal cavity is that there is intestinal strangulation, an occasional accident in young lambs. The characteristic lesion is an extensive hemorrhagic enteritis. Discrete and then confluent ulcerations develop if the course is long enough. In peracute cases, there may be only a few small patches of necrosis. The peritoneal cavity often contains a small amount of serous or bloodstained fluid.

In cases with more severe and deeply penetrating mucosal ulcerations, there may be an overlying peritonitis with red fibrin strands on the local mesentery and intestinal adhesions. The ulcers are usually visible through the serosa as purplish areas, and they may be limited to the small intestine or also involve the large intestine. On the mucosal surface, they are irregular but well defined by a sharp margin and rim of intense hyperemia, and they contain a yellow necrotic deposit; they may coalesce to form extensive areas of necrosis. Usually the intestinal contents are bloodstained and may appear to be composed of pure blood, but in lambs that live for 3 or 4 days, there may be little or no staining with blood. In acute cases, the abomasal mucosa may be intensely congested. The mesenteric lymph nodes are edematous or intensely congested. Histologically, the wall of the intestine is suffused with blood, and the areas of necrosis extend deeply into the mucous membrane and may penetrate the muscularis mucosa to the muscle layers and peritoneum. In the necrotic tissue, there are large numbers of typical bacilli, but the cellular inflammatory response is slight.

The lesions in other organs are those of severe toxemia. The liver is usually pale and friable but may be congested. The spleen is normal or slightly enlarged and pulpy, owing to congestion and dissolution of its delicate reticulum. The kidneys may be enlarged, edematous, pale, and soft from toxic degeneration. The pericardial sac contains abundant clear gelatinous fluid, the myocardium is pale and soft, and hemorrhages beneath the serous membranes of the heart are almost constant. The lungs are often slightly congested and very edematous.

In areas in which this disease occurs, the diagnosis can be made with reasonable certainty on the basis of the history and the presence of the typical macroscopic lesions. Confirmation depends on finding large numbers of clostridia in the necrotic tissue of the ulcers and on the detection of toxins in the intestinal contents of fresh cadavers. The organism may be isolated only from the intestine of fresh cadavers.

The disease in **calves** caused by type B *Clostridium perfringens* closely resembles that in lambs, usually affecting sucklings less than 10 days of age, with a course of 2 to 4 days characterized by prostration and dysentery. Older calves up to 10 weeks of age sometimes are affected. It appears that calves are more likely to recover, albeit slowly, than lambs. The intestinal lesion is an acute hemorrhagic enteritis with extensive mucosal necrosis and patchy diphtheritic membrane formation, especially in the ileum.

In **foals** also there is hemorrhagic enteritis with severe diarrhea. Suckling foals of 2 days to, rarely, some weeks of age are affected. The course of the illness is 1 or 2 days. The intestine is intensely hyperemic, with a number of dark foci up to 1.0 cm in diameter that may develop into ulcerations. The contents of the intestine are bloodstained. The disease is apparently rare in foals but should be differentiated bacteriologically from infection with *Actinobacillus equuli,* and from salmonellosis, which more typically involves the large bowel.

*CLOSTRIDIUM PERFRINGENS* TYPE C. *Clostridium perfringens* type C has a worldwide distribution and causes disease in adult sheep and goats, feeder cattle, and lambs, calves, foals, and baby pigs. The prevalence of disease varies widely between countries, and between regions and species within countries. There appear to be several varieties within type C that possibly are associated with different diseases.

In **adult sheep**, *Clostridium perfringens* type C causes "struck," a disease of pastured animals that has a mortality rate of 5 to 15% in some areas. The disease in adult goats probably is similar in most respects to that in sheep. Death usually occurs suddenly with terminal convulsive episodes, but some animals, with infections not so peracute, stand in a straining position that probably indicates acute abdominal pain. In adult sheep there is no diarrhea or convulsions.

At autopsy, the peritoneal cavity contains up to 3 liters of clear, pale yellow fluid that clots on exposure to air and that becomes stained with hemoglobin if autopsy is delayed. The

peritoneal vessels, especially of the omentum, small intestine, and urinary bladder, are intensely congested, and multiple subperitoneal hemorrhages may be present. The small intestine is intensely hyperemic, either in patches or along most of its length, and in the zones of hyperemia there may be ulcers that vary in size, in diameter from 2 to 3 mm and in length from 6 to 12 cm. Ulcers usually are present, mostly in the jejunum, and are surrounded by a zone of hyperemia with deep red base, although in some the necrotic material is dark green and adherent. The large intestine is normal. The primary intestinal lesion is superficial mucosal necrosis, which advances more deeply into a developing leukocytic reaction, congestion, and hemorrhage. The organisms do not invade the healthy mucosa but appear in tissue already necrotic, apparently invading from the lumen of the bowel.

Lesions in other organs are those of severe toxemia and include copious pleural and pericardial transudate of gelatinous fluid and hemorrhages beneath the serous membranes of the heart. There is congestion and sometimes gross hemorrhage of the zona reticularis of the adrenal.

The causative organism is usually distributed in all organs, and this accounts for the very different appearance when autopsy is delayed for some hours. In such instances, there is extensive bloodstained gelatinous fluid in the intermuscular septa and subcutis, and fluid in the serous cavities is stained. The muscles are soft, stained pink to black with blood, and emphysematous. Because of this change, "struck" may be confused with blackleg if postmortem examination is delayed.

The disease in **feedlot cattle** is similar to "struck." Animals are found either dead or moribund, and congestion and hemorrhage of the gastrointestinal tract are prominent. The jejunal and ileal content is bloody with fibrin clots and necrotic debris. Excessive straw-colored pleural and pericardial fluid and petechiation of epicardium and endocardium are present. Autolysis and postmortem bloat occur rapidly, and differentiation from ruminal tympany and other clostridial diseases is necessary.

The diseases caused by type C in **calves**, **lambs**, and **foals** are very similar and will be discussed together. Affected animals are young sucklings, which contract the disease within the first few days of life, often within the first 12 hr if they have been confined. Foals and most clinically affected lambs die, but in calves, subacute cases may occur in which there is diarrhea and unthriftiness.

Often, affected animals are found dead. Sick lambs may shiver, show abdominal pain, abdominal distension, dysentery, and prostration and die in 12 hr or less. Sick calves show abdominal pain, some show diarrhea of sudden onset, and death is preceded by spasmodic convulsions.

Similar lesions occur at autopsy in all species but may be less severe in lambs. In lambs, the intestinal changes vary from catarrhal to acute hemorrhagic enteritis with mucosal necrosis, which, like lamb dysentery, suggests strangulation. The most prominent changes occur in the jejunum and ileum, the lumen of which may contain free blood, which forms a clotted cast in fresh cadavers; sometimes there is merely acute hyperemia of a segment of jejunum with edema of the wall, a scant creamy intestinal content, and a few small ulcerations of the mucosa. The peritoneal cavity contains a small quantity of serous, blood-stained fluid, and the local mesentery and peritoneum are often mildly inflamed, hyperemic, and bear red strands of fibrin. The mesenteric nodes are enlarged, wet, and congested. There is usually an excess of pericardial fluid, and pulmonary interstitial edema. Ecchymoses on the serous membranes are nearly constant, and in a few cadavers all tissues, but especially the meninges and brain, are liberally sprinkled with small hemorrhages; these are sites of bacterial embolism, a massive terminal bacteremia by *Clostridium perfringens* occurring in such cases.

Other lesions are those of toxemia, and the histologic changes are the same as those of lamb dysentery; indeed, there is no reliable distinction between the two diseases except for the geography of their occurrence and the results of toxin analyses, which must be performed both on the intestinal contents and the cultured organism since only the β toxin may be detectable in the intestinal contents.

*Clostridium prefringens* type C causes hemorrhagic enteritis of **suckling piglets** in many parts of the world. The disease occurs as epizootics in affected herds and regions and may then remain enzootic. Whole litters are affected, usually within the first week of life and often within the first 24 hr; the clinical course is ~1 day. Rarely, epizootics occur in 2- to 4-week-old pigs and in weaned pigs. Affected animals pass bloodstained feces in the terminal stages, and there is marked hyperemia of the anus just prior to death. The predominant lesions occur in the small intestine, especially the jejunum, but the cecum and spiral colon often are involved, and occasionally lesions are confined to the large intestine. Lesions are similar in all areas and in acute cases consist of intestinal and mesenteric hyperemia, extensive necrosis of the intestinal mucosa, and staining of the contents (Fig. 1.41A). There may be emphysema of the intestinal wall, which becomes fragile. Mesenteric lymph nodes are red, and sanguinous peritoneal and pleural fluid is present. Fibrinous intestinal adhesions may develop.

Microscopically, the necrotic process extends deeply and sometimes penetrates the muscularis mucosa. Numerous typical bacilli inhabit the necrotic tissue and line up along the margin of involved villi. Older pigs may not show intestinal hemorrhage but do show mucosal necrosis and peritoneal and pericardial effusion.

Infection is acquired from the sow's feces, and lesions begin in the jejunum with adhesion to and necrosis of epithelium on the villus tips. The cells are sloughed, and extension of the necrotizing process then is nonselective and involves all the structures of the villi as it extends toward the crypt. The disease is not reproducible with toxins of *Clostridium perfringens* type C but requires viable organisms with the ability to attach to the enterocytes.

*CLOSTRIDIUM PERFRINGENS* TYPE D. Enterotoxemia ("pulpy-kidney disease," "braxy-like disease," "overeating disease") through the toxins of *Clostridium perfringens* type D is an important disease of sheep and goats, with a worldwide distribution. It occurs occasionally in calves. Focal symmetric encephalomalacia of sheep is caused by the epsilon toxin of type D.

In most lambs and calves with type D enterotoxemia, the

course is peracute and the animal is found dead. Lambs and calves may die in a few minutes in convulsions, and calves often bawl as from severe pain. Animals that survive longer may show excessive salivation, rapid breathing, hyperesthesia, straining, opisthotonus, and terminal coma or convulsions. In adult sheep, in which the clinical course may be 2 days, diarrhea with the passage of dark, semifluid feces is common. In sheep, subacute cases may occur and be followed by recovery. In some such cases, neurologic signs may develop. These include blindness, ataxia, head pressing, and posterior paresis, and the lesions of focal symmetric encephalomalacia are present in the brains of such cases. On other occasions these lesions are not preceded by signs of enterotoxemia. In goats, signs of enterotoxemia similar to those in sheep and lambs may be seen, but chronic enterotoxemia characterized by abdominal distension and pain, depression, and dark green diarrhea may persist for several days to weeks. Focal symmetric encephalomalacia does not occur in goats.

In **lambs** dead of acute enterotoxemia, the carcass usually is well nourished. In those with a course of 1 or 2 days, often there is evidence of a dark scour about the buttocks. Putrefactive changes occur rapidly. In some rapidly fatal cases there are no lesions. Often there is excessive straw-colored pericardial fluid that clots on exposure to air, congestion and edema of the lungs that may be severe enough to produce froth in all the respiratory passages, and hemorrhage beneath the endocardium of the left ventricle. There may be hemorrhages beneath other serous membranes (Fig. 1.40A), such as the epicardium, and blotchy hemorrhages beneath the parietal peritoneum are characteristic. Sometimes the liver is congested and the spleen enlarged and pulpy. There is no gastrointestinal inflammation visible at autopsy, although there is a mild microscopic enteritis. Short lengths of the small intestine are distended with gas and are pink from hyperemia. The intestinal content is creamy in cases of rapid death, but in those that live for some hours, the contents, especially the lower intestine, are more fluid and dark green.

In experimental cases and natural cases examined immediately after death there are no specific renal lesions. The kidneys often are congested, and postmortem degeneration leads within a few hours to the intertubular "hemorrhages" characteristic of the disease (Fig. 1.40D). Similarly, autolysis that is unusually rapid is responsible for the "pulpy kidney" of enterotoxemia. Both of these "lesions" can be useful diagnostic aids.

In **adult sheep**, the lesions are the same as those in lambs but are more constant and more developed, with the exception of renal autolytic changes, which occur less rapidly and rarely progress to the stage of "pulpiness."

Brain lesions occur in lambs with enterotoxemia that is not immediately fatal, and these are sufficiently constant to be of diagnostic significance. They develop in two patterns; each is bilaterally symmetric. The commonest pattern involves the basal ganglia, internal capsule, dorsolateral thalamus, and substantia nigra; there are some minor variations of the pattern, but the lesions always are of the same type and are symmetric (Fig. 1.40B). The second pattern affects the white matter of the frontal gyri, sparing only the communicating U fibers. The lesion begins with edema and the leakage of plasma and then red cells from the venules and capillaries in the affected area. The altered permeability of the vessels is diffuse throughout the brain, sparing only heavily myelinated tracts such as the optic tracts and corpus callosum. This is well demonstrated by vital staining with trypan blue. The least change visible by light microscopy is the accumulation of protein droplets around small venules. Electron microscopically severe damage to vascular endothelium is apparent, and there is swelling of protoplasmic astrocytes. The foot processes around blood vessels and the processes around neurons are most severely swollen. Edema and hemorrhage lead to malacia in the affected areas.

In goats with chronic enterotoxemia, enterocolitis occurs and is characterized by atrophy of villi and mucosal ulceration. Specific systemic signs do not develop.

Lesions in **calves** dying of enterotoxemia caused by *Clostridium perfringens* type D closely resemble those in lambs. Affected calves are usually 1–3 months of age. Splenic swelling is more common in calves than in lambs, and rapid autolysis of the kidney is not a prominent finding. Subcapsular congestion and hemorrhage occur (Fig. 1.40C), however, and sometimes a blackish clot of blood up to 1.0 cm thick forms a rather even cast for the kidney.

The histologic changes in enterotoxemia include, in addition to the brain lesions described above, mild degeneration and necrosis of the epithelium of the proximal convoluted tubules with edema, congestion and interstitial hemorrhage in the renal cortex, and congestion of the medulla (these are autolytic changes but are useful diagnostically); superficial desquamation in the intestine with congestion, and numerous typical bacilli in the contents; congestion and hemorrhage of the spleen with disruption of reticulum; subepicardial hemorrhage and degeneration in the Purkinje network; and proteinaceous edema fluid in the lungs. All of these changes are secondary to endothelial damage produced by the $\epsilon$ toxin. The nature of the clinical syndrome, including the severity and extent of the nervous disorder, probably depends on the amount and rate of absorption of this toxin.

Significant biochemical abnormalities that occur in enterotoxemia include hemoconcentration and hyperglycemia. Hemoconcentration is secondary to loss of fluid into tissues and cavities through injured vascular endothelium. The increase in blood glucose is due to rapid mobilization of hepatic glycogen, possibly stimulated by hepatocyte-bound $\epsilon$ toxin. The blood glucose may reach 400 mg % and spills into the urine, providing the basis of very good circumstantial evidence for diagnosis of the disease. The absence of glucosuria after some hours postmortem is of no significance, as early postmortem growth of bacteria in the urine destroys the glucose. Glucosuria may occur in calves and presumably in kids but does not occur in starved animals with depleted glycogen stores.

*CLOSTRIDIUM PERFRINGENS* TYPE E. *Clostridium perfringens* type E causes a rare disease that occurs in calves and rabbits. Calves die acutely and have a congested ulcerated abomasum and hemorrhagic enteritis, which occurs segmentally along the small intestine. Mesenteric nodes are enlarged and red, and pericardial effusion and serosal hemorrhages may be present.

**Hemorrhagic canine gastroenteritis** (canine gastrointestinal hemorrhage syndrome) occurs sporadically in associa-

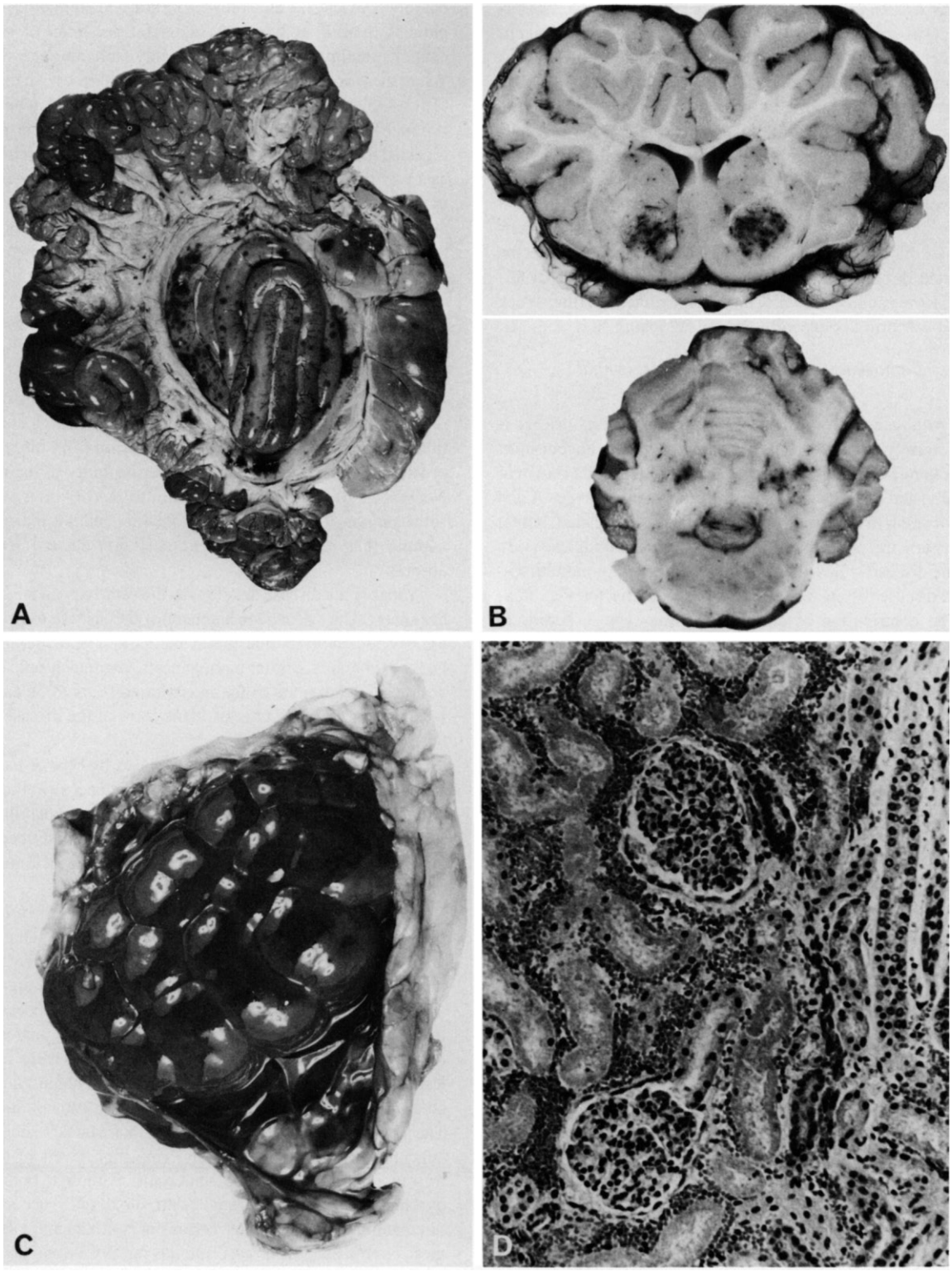


**Fig. 1.40.** *Clostridium perfringens* type D enterotoxemia. (**A**) Peritoneal hemorrhages. Sheep. (**B**) Focal symmetric encephalomalacia. Sheep. Hemorrhages and softening in internal capsules and cerebellar white matter. (**C**) Renal cortical hemorrhage. Calf. (**D**) Nephrosis and intertubular hemorrhage. Sheep.

tion with *Clostridium perfringens*. Usually a peracute hemorrhagic gastroenteritis develops, and the specific *C. perfringens* type is not identified; recurrent diarrhea associated with a type A strain has also been recorded. Dogs with the peracute disease often are found dead, lying in a pool of bloody excreta. Sometimes hemorrhage from the anus is noted prior to death. Autopsy reveals hemorrhagic enteritis and colitis, and sometimes superficial gastritis is present. Colonic lesions tend to be more severe. Microscopically, there is hemorrhagic necrosis of the intestinal mucosa, with accumulation of necrotic cells in crypts. Numerous clostridia may line the necrotic intestinal structures or be distributed through the detritus. The condition must be differentiated from canine parvoviral enteritis, canine hepatitis, shock gut, and warfarin toxicity or other coagulopathy.

### *Pathogenesis and Diagnosis of Clostridial Enteric Infections*

The pathogenesis of some of the enteric clostridial disease is extraordinarily circuitous. More is known of the pathogenesis of enterotoxemia caused by *Clostridium perfringens* type D than of the others, and this can be exemplary: disease due to types A and E may develop in the same way, but types B and C usually affect the newborn and probably have a more simple pathogenesis. In all of the diseases, the organism multiplies rapidly in the intestine and disease results from the activity of the bacterial exotoxins. (The contribution of enterotoxin from type A strains to enteric diseases of animals probably is minimal.) Many animals harbor the specific clostridial organisms in their alimentary canal for greater or lesser periods but in small and harmless numbers. Under certain circumstances they grow profusely and produce toxins in overwhelming concentration.

Enterotoxemia of pastured lambs occurs mainly in the spring, when pastures are abundant and lush, and usually the best lambs are affected. It is possible that intestinal hypomotility may be a primary factor that allows clostridia to proliferate in the small intestine instead of being carried by peristalsis to the colon. Whether it is the level of nutrients or other factors in ingested pasture that predispose to the development of enterotoxemia is unclear. "Pulpy kidney" is not solely a disease of green, lush pastures; it also occurs on pastures of little but coarse fibrous grass, and in sheep fed pelleted feeds. In these circumstances the relationship to diet is obscure.

Lambs fed large amounts of grain or concentrate are highly susceptible, thus the synonym "overeating disease." The manner in which overeating leads to clostridial enterotoxemia is complex. Cultures of *Clostridium perfringens* type D given orally are largely destroyed in the rumen and abomasum. The few organisms that reach the intestine proliferate rapidly and produce toxin, but when the numbers are no longer reinforced by escapees from the stomachs, they are rapidly cleared from the intestine by peristalsis. If the cultures are administered into the duodenum, the concentrations of organisms and toxin in the intestine become much larger than after oral dosing but not large enough to cause anything but diarrhea. The disease can be reproduced successfully if the diet of the sheep is suddenly changed to grain or concentrate before administering the culture.

The critical factor is almost certainly the presence of starch in the small intestine, providing a suitable substrate for these saccharolytic bacteria, and they proliferate to immense numbers perhaps more than $1 \times 10^9$ organisms per gram of intestinal contents, and produce correspondingly large amounts of toxin. When the rumen is provided suddenly with excessive quantities of food, or food of a different type, there is a delay before the ruminal flora can adapt; in this period, undigested or partially digested food may escape into the intestine, and if starch is there, as it is with overeating on grain, *Clostridium perfringens* type D is likely to take advantage of it.

It appears that the concentration of toxin must be maintained at high levels for several hours on end if it is to cause intoxication rather than just diarrhea. The outcome depends not only on the concentration of toxin in the intestine but also on the length of time it is maintained, the size of the sheep, and whether there is circulating antitoxin. Some sheep possess $\epsilon$ antitoxin, attesting to previous nonfatal intoxication, and they are highly resistant to the disease. Even with high intestinal concentrations of toxin, only small amounts reach the blood stream. A high concentration of $\epsilon$ toxin facilitates its own absorption from the intestine, probably in part by increasing the permeability of the mucosa. Necrosis of epithelium and moderate atrophy of villi is evident in some animals with type D enterotoxemia, and it is reasonable to assume that epithelial damage must precede the facilitated absorption.

Probably the disease develops in the same way in the calf as in the sheep. The virtual confinement of the disease to calves that are overfed suggests that this is the case. The acute disease in goats likely has a similar pathogenesis, but the chronic disease, with lesions confined to the intestine, appears to be caused by local effects of type D toxins. This form of the disease has not been investigated in detail.

The pathogenesis of disease produced by type A bacteria is obscure. In lambs it occurs under circumstances similar to type D enterotoxemia. Nothing is known of the permeability of the ruminant intestine to $\alpha$ toxin, but the syndrome described in both lambs and calves is consistent with the action of a hemolytic toxin in the circulation.

The diseases caused in young animals by *Clostridium perfringens* types B and C are principally diseases of the intestine, and this suggests that the pathogenesis is more direct. This is particularly true of type C hemorrhagic enteritis in pigs.

Cultures of type B or C given orally produce disease much more consistently than type D. Types B and C possess the $\beta$ toxin, which is probably responsible for the severe intestinal lesion, and it is possible that these types need not attain the high concentration in the intestine that type D must to initiate illness. The $\beta$ toxin is trypsin labile, and circumstances such as low enzyme levels in young animals, very high levels of toxin, or trypsin inhibitors could be important. Although both "lamb dysentery" and "hemorrhagic enterotoxemia" occur in pastured animals, they are most serious in confined animals. Under these circumstances, disease spreads rapidly among the susceptible age group, as would be expected of any virulent infection.

Often the most vigorous and presumably the best nourished lambs and calves succumb, and on occasion there may be a nutritional predisposition to these diseases. "Pig bel," a necrotizing jejunitis of humans in New Guinea that probably is caused by the $\beta$ toxin, has been causally related to consumption

of heat-stable trypsin inhibitors in sweet potatoes. Naturally occurring protease inhibitors in soybeans appear to have a similar effect in guinea pigs.

"Struck" in adult sheep, caused by type C, is prevalent when the grass is short in late winter or early spring. It is also a disease of the best conditioned sheep, but the place of nutritional factors in its pathogenesis, and in the pathogenesis of disease caused by type C in feedlot cattle, has not been examined.

The diagnosis of outbreaks of enteric diseases caused by clostridia usually is not difficult. A history of sudden deaths in appropriate environmental circumstances, age groups, etc. should provoke a suspicion. Gross lesions in one or more reasonably fresh carcasses are often characteristic enough to provide a working diagnosis. Glucosuria may be demonstrable in type D enterotoxemia, but its absence does not preclude the disease. Confirmation of type D enterotoxemia can be based on microscopic brain lesions, but in this and other suspected clostridial diseases, bacteriologic proof should be sought. Examinations should be made as soon after death as is possible. Very autolyzed carcasses generally are unsuitable as the toxin is rapidly destroyed postmortem and the intestinal flora very quickly becomes mixed.

The contents of the small intestine should be examined for toxin; in adult sheep that have shown diarrhea, it is well to examine the contents of cecum and colon if toxin is not found in the small intestine. One drop of chloroform per 10 ml of content should be added to preserve the toxin. There is no critical concentration of toxin diagnostic for pulpy-kidney disease or other enteric clostridial diseases. The presence of toxin in conjunction with typical lesions is considered significant. The absence of demonstrable toxin does not preclude a presumptive diagnosis if other characteristic findings are evident.

Negative results on a toxin analysis made more than 4 hr after death do not eliminate clostridial disease as the cause of death. Gram-stained smears should be made from various levels of the intestine or from discrete mucosal lesions. The smears should reveal large numbers of bacilli with the morphology of *Clostridium perfringens*. In pulpy-kidney disease, and the other clostridial enteritides, the bacteria are present in smears in pure, or virtually pure, population.

ENTEROCOLITIS OF FOALS CAUSED BY *CORYNEBACTERIUM EQUI*. *Corynebacterium equi*, thought formerly to be primarily a soil-associated organism, is now believed to be part of the normal intestinal flora of horses. The organism usually is associated with pyogranulomatous pneumonia of foals (see the Respiratory System, this volume). About half the pneumonic foals also have ulcerative colitis. In some foals intestinal lesions occur alone.

The development of intestinal lesions appears to be dose related in that reproduction of the disease requires repeated oral infection. In natural disease, continual exposure to bacteria in swallowed respiratory exudate probably is an important source of infection in those animals with pneumonia.

Gross lesions may occur throughout the small and large intestines but usually are most severe in the cecum, large colon, and related lymph nodes. Mucosal lesions consist of irregular ulcers up to 1 to 2 cm in diameter, often covered by purulent or necrotic debris (Fig. 1.41D). Edema of the wall of the gut may be severe. Lymph nodes often are massively enlarged by edema and by caseous or purulent foci that may destroy the structure of the node (Fig. 1.41C). Occasionally, massively enlarged abscessed lymph nodes are found without evidence of concurrent enteritis.

Microscopically, infection seems to occur by penetration of the specialized epithelium over intestinal lymphoid follicles. An initial neutrophilic response occurs, and erosions of the epithelium develop. Macrophages and a few neutrophils accumulate in the lamina propria. The macrophages contain *Corynebacterium equi* but do not destroy them. Later, multinuclear giant cells form, deep ulcers develop, and necrosis of lymphoid follicles occurs. Lymphangitis and pyogranulomatous mesenteric lymphadenitis characterize the chronic enteric disease.

### *Mycobacterial Enteritis*

Various *Mycobacterium* species may cause enteric disease in animals. *Mycobacterium avium* has been incriminated as a cause of colonic ulceration and of granulomatous enteritis in horses; *M. intracellulare* has been isolated from granulomas in mesenteric lymph nodes of pigs in various countries, but enteric lesions have not been described; the primary complex of *M. bovis* may include an enteric lesion (see tuberculosis, in the Respiratory System, this volume). All of these infections are of minor importance compared to that caused by *M. paratuberculosis* in ruminants.

JOHNE'S DISEASE. Johne's disease (paratuberculosis) is a specific infectious disease of ruminants caused by *Mycobacterium paratuberculosis*. Infections by *M. paratuberculosis* can be produced in pigs and horses, but gross lesions are modest or absent. Typical histologic lesions may develop, but are mild. The disease can be transmitted to mice, hamsters, rats, and rabbits.

There are several strains of *Myobacterium paratuberculosis*, differing in cultural characteristics and in pathogenicity for different species. A pigmented strain that produces an intensely orange pigment in tissues and in cultures sometimes is isolated from sheep and occasionally from cattle. Each strain can infect and produce disease in cattle, sheep, and goats.

The epidemiology and pathogenesis of Johne's disease are best understood in cattle. It is assumed that the disease develops in sheep and goats in a similar way. Young animals are more susceptible than the old to experimental infection. Adults may become infected but are less likely to develop the disease and often recover from the infection. The critical age determining susceptibility to an infection that will ultimately produce clinical disease is not known. For many calves it is probably ~6 months. This age-dependent resistance is reflected in the ability of the macrophages of resistant animals to restrict intracellular growth of bacteria, but not to lyse them.

Although the major lesions of Johne's disease usually are confined to the ileum, colon, and draining lymph nodes, the infection is generalized; organisms may be excreted in milk, semen, and urine, and intrauterine infections occur. Bovine fetuses may be infected as early as 2 months of gestation. The excretion of the organism in milk and the fact of intrauterine infection have important implications for the epidemiology of

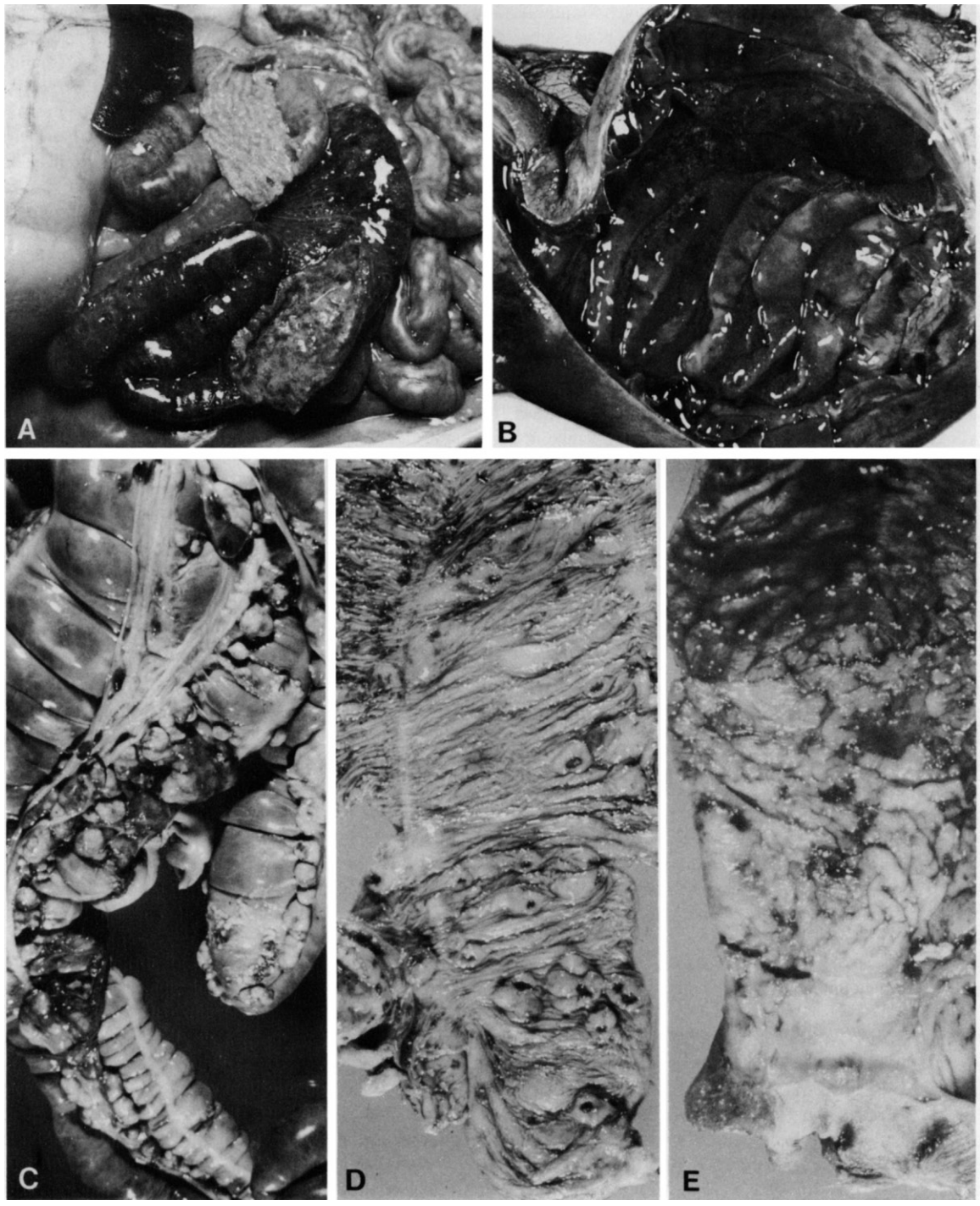


**Fig. 1.41.** (**A**) Necrotizing enteritis. *Clostridium perfringens* type C. Piglet. (**B**) Braxy-like clostridial abomasitis (*C. septicum*). Calf. (**A** and **B** courtesy of M. Bergeland.) (**C**) *Corynebacterium equi* infection. Foal. Enlarged suppurative cecal and colic lymph nodes. (**D**) *Corynebacterium equi* infection. Foal. Craterous ulcerated lesions on colonic mucosa. (**E**) Ulcerative colitis. Dog. Histoplasmosis.

the disease. A prevalence of 50% has been reported for intrauterine infection when the dam is clinically diseased.

Intrauterine infection can occur when the dam is clinically normal. In both clinical and nonclinical cases of the disease, the organism can be cultured from a variety of parenchymatous organs and widely distributed lymph nodes and has also been found in the gonads of both sexes. In fulminating infections, there is a bacteremia, and it is in these unusual cases that the organism is excreted in the milk. Excretion of the organism in the milk of ewes has not been demonstrated, but congenital and uterine infections have.

The incubation period of Johne's disease is protracted and irregular. Following oral infection, *Mycobacterium paratuberculosis* enters the lymphatic system through the tonsils (and probably the intestinal mucosa) and spreads through the body. It localizes mainly in the small intestine, and in the first 2 to 3 months after infection the organisms multiply there. Depending on their resistance, some animals clear themselves of infection while others become carriers. In the latter, bacteria persist in the mucosa and draining lymph nodes. Some carriers may be infected for life without showing signs of disease. This tolerance to infection may result from compromised immunologic reactivity at the time of infection. Fetal infection may fall into this category. When there is a breakdown of tolerance, hypersensitivity and cell-mediated immunity develop, the mucosal lesions progress, and clinical disease occurs. Shifts between levels of tolerance and hypersensitivity probably are responsible for the clinical exacerbations that are characteristic of the disease.

The diarrhea of Johne's disease has a complex pathogenesis. It is related to the moderate villus atrophy that develops, probably as a result of the immune response in the lamina propria. In addition, there is leakage of plasma proteins, amino acid malabsorption, and increased gut motility with decreased intestinal transit time.

Exacerbations of clinical disease often are associated with parturition, a low nutritional plane, heavy milk yield, and intercurrent disease. A change of environment often leads to clinical disease. Often this can be attributed to differences in the lime content and pH of the soil; soils high in lime tend to inhibit clinical breakdowns, and transfer from alkaline to acid soils often precipitates clinical disease within a few weeks.

The typical manifestation of Johne's disease is profuse diarrhea passed effortlessly. Emaciation is progressive and ultimately fatal, but the appetite is retained, and animals remain bright until the terminal stages. Clinically affected animals are usually 2 years of age or older, and Channel Island breeds and beef shorthorn cattle appear to be unusually susceptible.

Johne's disease in sheep and goats is comparable to that in cattle, occurring in adults and characterized by chronic wasting. The feces are soft, but there is usually no diarrhea, except intermittently in the terminal stages.

There is no correlation between the severity of the clinical syndrome and the severity of the lesions. Many animals allowed to die have gross and microscopic lesions so slight that they would be easily missed unless looked for specifically, and in some of these even detailed gross inspection is unrewarding; on the other hand, severe lesions can be found in animals that appear healthy. In goats and sheep, gross changes usually are minimal.

Advanced cases of Johne's disease are emaciated with gelatinous atrophy of fat depots, intermandibular edema, and serous effusion in the body cavities, more voluminous in sheep and goats than in cattle. Specific gross lesions occur in the intestine and regional nodes. The mesenteric nodes, particularly the ileocecal, are always enlarged, sometimes remarkably so, pale so that there is little corticomedullary distinction, and edematous, especially in the medulla. Lymphangitis of some degree is constant, and the lymphatic vessels can often be traced as thickened cords from the intestine through the mesentery to the mesenteric nodes. Often, lymphangitis is the only recognizable gross change and is specific enough to justify a diagnosis of Johne's disease. In sheep and goats, the lymphatics may be knotted as well as corded, the knots being focal granulomatous accumulations of epithelioid cells and lymphocytes. Sometimes lymphangitis is not recognizably grossly. The intestinal serosa has a slight granular and diffusely opaque appearance because of subserosal edema and cellularity (Fig. 1.42A).

The specific intestinal lesions may occur from the duodenum to the rectum, but in many animals both of these regions are unaffected. Lesions are usually best developed in the lower jejunum and ileum (Fig. 1.42B). Reference is frequently made to enlargement of the ileocecal valve, and to this vicinity as the earliest and most consistently affected, but specific changes of, and immediately adjacent to, the valve are so inconsistent as to deserve deemphasis. The classical intestinal change is diffuse hypertrophy, with the mucosa folded into thick, tranverse rugae, like the convolutions of the cerebral cortex.

When well developed, the mucosal folds cannot be smoothed out by stretching, and they fissure if the intestinal wall is bent sharply. These mucosal changes are partly due to thickenings of the mucosa itself, but largely they are due to abundant accumulations of epithelioid cells in the submucosa. The crests of the folds are often slightly reddened by congestion, and the mucosal surface is velvety, but there is no excess of mucus except in occasional sheep and goats. The minimal recognizable gross change is a very slight fleshy or velvety thickening of the mucosa.

In sheep and goats, enteric lesions are usually mild, resembling the minimal lesions of cattle. Occasionally the bowel is quite remarkably thickened and contains nodules of caseation and calcification. Necrosis occurs rarely in the lesions in cattle, but there is almost never any caseation or calcification. This is a distinguishing feature from intestinal tuberculosis of cattle. Other distinguishing features are the diffuseness of the lesion and the absence of ulceration in Johne's disease. The lesion in cattle is characterized by the virtual absence of necrosis, the absence of inflammatory hyperemia, and the absence of reactionary fibrosis. Orange pigmentation of the mucosa and lymph nodes may be seen in sheep infected with the pigmented strain of the organism.

When gross lesions are well developed, histologic changes are obvious and very characteristic, but in those bovine cases in which gross changes are minimal or absent, the microscopic changes in the mucosa are more indefinite; this is probably true

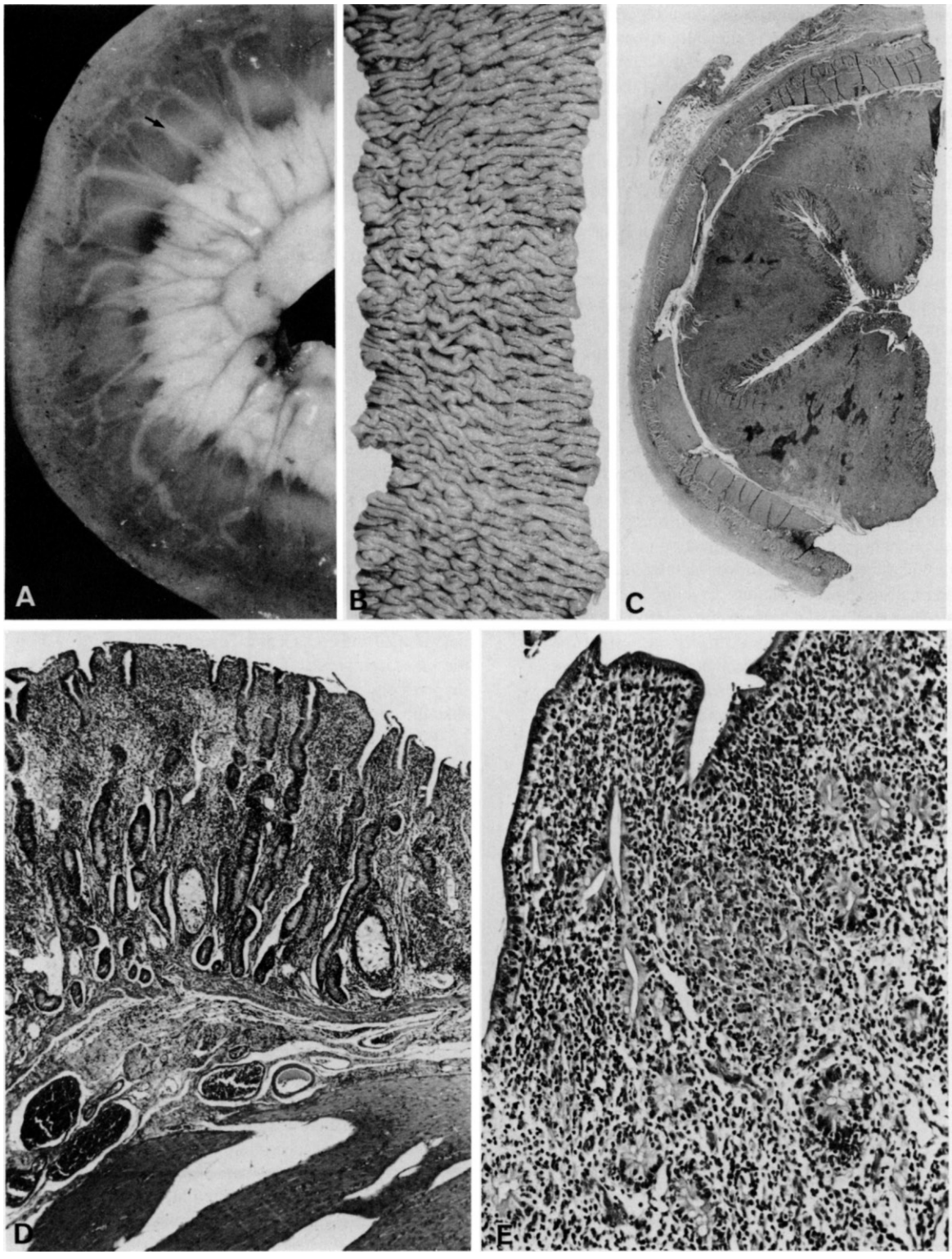


**Fig. 1.42.** Johne's disease. (**A**) Serosal edema and lymphangitis (arrow). Sheep. (**B**) Thickened mucosal folds. Jejunum. Cow. (**C**) Hemisection of ileum, showing diffuse infiltration of cells and small (dark) areas of necrosis. (**D**) Blunt atrophic ileal villi and hyperplastic, and occasionally cystic, crypts. Edema of the lamina propria, submucosa, and muscularis. A heavy inflammatory infiltrate is in the lamina propria. Cow. (**E**) Macrophages in hypercellular lamina propria.

too of very early lesions. In these, the lamina propria is diffusely but loosely infiltrated with lymphocytes and plasma cells and a large number of eosinophils. There may be very few epithelioid cells (Fig. 1.42E), and the most characteristic change is usually a loose infiltration of lymphocytes and plasma cells in the submucosa and in association with the submucosal and mesenteric lymphatics. As the epithelioid cells increase in number, the other cells are proportionately reduced. In single sections of bowel, the epithelioid cells may infiltrate diffusely from the onset, especially when the outer layers of the mucous membranes are involved, or the infiltrations may be predominantly nodular, either in the tips or the bases of the villi.

The cell accumulations tend to be progressive, and they gradually compress and obliterate the crypts, although some glands persist for a while as cystic remnants containing cellular detritus (Fig. 1.42D). The infiltrating cells congregate in the submucosa, and when gross thickening of the intestine occurs, it is largely due to this submucosal infiltration of typical epithelioid cells. Almost invariably there are lymphocytes in the cellular masses, both as a diffuse distribution of isolated cells and as microscopic foci. Giant cells may be present. Foci of necrosis occur within the cell masses, but in cattle, caseation and calcification are extremely rare (Fig. 1.42C).

A significant proportion of sheep and goats develop foci of tubercle-like caseation with some calcification in the mucosa, the submucosa, on the peritoneal surface of the bowel, in the lymphatics, and in the lymph nodes; some are recognizable grossly as whitish foci, 1–4 mm in diameter, and there is modest surrounding fibrosis. These lesions in sheep are the only suggestion that affected animals may develop resistance or hypersensitivity comparable to that seen in tuberculosis. It is usual for the organism to be demonstrable in vast numbers both intracellularly and extracellularly in the lesions when appropriately stained by acid-fast techniques. When there are few organisms, they are best demonstrated by fluorescent staining; this technique is applicable to tissue but not to feces, as these exhibit autofluorescence. The pigmented strains of the organism are invariably present in large numbers in sheep, but in those infected with nonpigmented strains and showing evidence of tubercle formation, the organisms may be too few to be demonstrated except by culture.

Lymphangitis is one of the most consistent changes. Initially the lymphatics are surrounded by lymphocytes and plasma cells, and many contain plugs of epithelioid cells in the lumen. These changes are progressive, and small mononuclear cells are replaced by large ones; epithelioid granulomas form in the wall and project into the lumen. These nodules frequently show some necrosis.

Specific lesions similar to those in the intestine occur also in the lymph nodes. In the early stages, the subcapsular sinus is infiltrated loosely with epithelioid cells. The infiltrations are progressive, forming follicular or diffuse areas of epithelioid and giant cells, which may ultimately replace much of the cortex. When tubercles form in the intestine of sheep and goats, they form in lymph nodes, too, and may be large enough to replace much of the node.

Of the other organs and tissues in which the bacilli may be found, lesions have been described only in the liver, tonsils, and lymph nodes. These lesions are of characteristic type. They are common in the liver and consist of foci of epithelioid cells and lymphocytes in the triads and indiscriminately in the lobules. These lesions contain bacilli, which can be readily demonstrated.

Antemortem diagnosis of Johne's disease and infection with *Mycobacterium paratuberculosis* is difficult. Various immunologic tests are more or less useful, depending on the immune status of the host and the stage of the disease. Textbooks of medicine and the Bibliography should be consulted for details.

Biopsy of the ileocecal lymph node appears to be a useful diagnostic test, much more so than rectal biopsy, since rectal infection often is absent. The examination of feces for organisms is a useful diagnostic aid in clinical cases; it is too cumbersome and too often negative for use as a screening procedure on preclinical cases. In fecal smear examinations, individual acid-fast organisms are ignored (they are probably incidental saprophytes) and significance is given only to clumps of two or more organisms of typical size. It may be validly objected that such organisms may be merely ingested ones being passed in the feces even when they are certainly *Mycobacterium paratuberculosis,* but nevertheless, reliance can be placed on positive smears when the animals are typically diseased and other causes of chronic diarrhea have been eliminated by appropriate means. A negative fecal smear should not be given any significance. The slow growth of the organism in culture and the variable requirements for growth of different strains limits this examination to the experimental rather than the diagnostic procedure.

### *Enteritis Due to Chlamydia psittaci*

Chlamydiae are obligate intracellular parasites. There are two species, *Chlyamydia trachomatis,* which infects humans, and *C. psittaci,* which infects animals and humans. *Chlamydia psittaci* is divisible into two types: type 1 is associated with abortion, pneumonia, or enteric disease; type 2 with polyarthritis, encephalitis, or conjunctivitis. The nonenteric diseases are discussed in the appropriate chapters.

The intestinal tract is the natural habitat for chlamydiae. Most infections probably are inapparent, but the intestine may be an important portal of entry in the development of systemic infections leading to arthritis, encephalitis, pneumonia, and abortion in ruminants. Enteritis may accompany or presage these diseases, and occasionally chlamydiae cause severe enteric disease in calves.

Following oral infection, chlamydiae infect mainly the enterocytes on the tips of ileal villi. These cells are in the $G_1$ phase of the cell cycle; cells in this phase are required by chlamydiae as a site for multiplication. Chlamydiae also infect other cells, including goblet cells, enterochromaffin cells, and macrophages. Macrophages may transport chlamydiae systemically prior to destruction by the organisms they carry.

Chlamydiae are adsorbed on the brush border of enterocytes and enter the cell by pinocytosis. Following multiplication of organisms in the supranuclear region, the cells degenerate. Chlamydiae are released into the gut lumen and into the lamina propria, where they infect endothelial cells of lacteals, are released, and become systemic.

Gastrointestinal disease caused by chlamydiae usually is a problem of calves less than 10 days old but may affect older calves and may produce recurrent diarrhea. Watery diarrhea, dehydration, and death are often accompanied by lesions, though not necessarily signs, of arthritis. Gross lesions may occur in the abomasum and throughout the intestinal tract but are most consistent and severe in the terminal ileum. Mucosal edema, congestion, and petechiae, sometimes with ulceration, are usually observed. Serosal hemorrhages and focal peritonitis may occur. Histologically, chlamydial inclusions may be demonstrable with Giemsa stain in the supranuclear region of the enterocytes. Central lacteals and capillaries are dilated, and neutrophils and monocytes infiltrate the lamina propria. Occasionally, granulomatous inflammation occurs in the intestinal submucosa and extends into the mesentery and to the serosa to produce the peritonitis observed grossly. Crypts in the small and large intestine may be dilated, lined by flattened epithelium, and contain inflammatory exudate.

### *Mycotic Diseases of the Gastrointestinal Tract*

Mycotic invasion of the wall of the gastrointestinal tract is a common sequel to many diseases and lesions affecting the mucosa. Although it is generally agreed that one or more of lowered host resistance, disruption of the normal flora, or a local lesion is required for establishment of mycotic disease in the gut, it is possible that spores are carried across the mucosa in macrophages.

Organisms usually associated with alimentary tract mycoses are zygomycetes of the genera *Absidia, Mucor,* and *Rhizopus,* and the phaeohyphomycete *Aspergillus. Candida* may also invade the wall of the alimentary canal (see below). Zygomycoses are characterized in their invasive mycelial form by infrequent septation and broad, coarse hyphae. *Aspergillus* has a filamentous tissue form with relatively numerous septa.

Lesions occur anywhere in the gastrointestinal tract, including the forestomachs of ruminants. Clinical signs may be related specifically to the location of lesions (vomition, bloody diarrhea) or be nonspecific (malaise, weight loss) or absent. Three types of lesion are produced: hemorrhagic and infarctive, caseating, and granulomatous. Hemorrhagic and infarctive lesions are illustrated by mycotic rumenitis following grain overload in ruminants (Fig. 1.8A,B). They often complicate Peyer's patch necrosis in cattle with bovine virus diarrhea and are seen along the tips of the abomasal folds in calves in the later stages of bacterial gastroenteritis. The fungi have a propensity to invade mucosal and submucosal veins, producing thrombosis and necrosis. Usually there is full-thickness necrosis of the gut wall, which is edematous and blue-black due to venous stasis (Fig. 1.11A–C). Often there is a relatively mild inflammatory response to the fungi. Spread to the liver and other organs via portal and systemic circulations is common (Fig. 1.8D). Mycotic ileitis and colitis in cats occasionally may be a sequel to panleukopenia. Intestinal lesions caused by the fungi (usually *Aspergillus*) may be hemorrhagic and necrotizing with a prominent cellular response but sometimes are small, localized, and difficult to find. In the latter cases, lesions of panleukopenia in the intestine and multifocal mycotic emboli in the lung suggest the pathogenesis. The lung appears to be the favored site of dissemination in cats. Mycotic enteritis with dissemination is a rare sequel to canine parvovirus enteritis.

The gastrointestinal tract is probably a common portal of entry for many sporadic, disseminated zygomycoses in animals. The presence of fungal hyphae in mesenteric lymph node granulomas of many clinically normal cattle indicates that contrary to general impressions, invasion by these agents across the intestinal mucosa does not lead invariably to systemic disease. It seems likely that the ability of the fungus to cause thrombosis and necrosis determines whether generalization occurs. In the absence of infarctive lesions, fungi may produce a localized granulomatous lesion in specialized lymphoid tissue of the Peyer's patch or may be carried to the regional lymph node while the mucosal lesion heals. In the lymph nodes, a granulomatous response with giant cells that contain hyphal fragments often develops; asteroid bodies may form around *Aspergillus*. Usually the granulomatous lesions produce no or moderate enlargement of lymph nodes, but sometimes a massive, caseating lymphadenitis with adhesions to adjacent structures results.

CANDIDIASIS. *Candida* species are normal inhabitants of the alimentary tract of animals, existing as budding yeasts in association with mucosal surfaces. When there are changes in the mucosae, particularly squamous mucosae, or in the mucosal flora, the yeasts may become invasive, and branching, filamentous pseudohyphae largely replace the yeast forms. In order of prevalence, the species producing candidiasis in animals are *C. albicans, C. slooffii,* and *C. parapsilosis.*

Changes in the mucosal flora usually result from antibiotic therapy, which reduces the numbers of bacteria and allows proliferation of *Candida*. Antibiotics may also inhibit antibody synthesis and phagocyte activity and may directly injure the mucosa, but these effects probably are of minor significance. Treatment with anticancer and antiinflammatory agents may also predispose to candidiasis.

Pseudohypha formation is favored by carbohydrates such as sucrose or polysaccharides, which are less readily fermentable than glucose. Glucose is necessary for keratolysis by the fungus. An endotoxin released during reproduction and death of *Candida* organisms probably causes local irritation and damage and permits deeper penetration into squamous epithelium.

*Candida* occasionally is an opportunistic invader of mucosal lesions anywhere in the alimentary tract, but other fungi are more likely to take advantage of this kind of lesion, particularly in older animals. Candidiasis is mainly a disease of keratinized epithelium in young animals, especially pigs, calves, and foals. Accumulation of keratin due to anorexia probably contributes to the extensiveness of lesions in all species by increasing the substrate available to the fungus.

In **pigs**, *Candida* often invades the parakeratotic material that accumulates in the gastric squamous mucosa. Apparently these infections are innocuous. "Thrush" is candidiasis of the oral cavity; it is seen occasionally in young pigs, especially those raised on artificial diets, or in pigs with intercurrent disease. Lesions may be confined to the tongue, hard palate, or pharynx but often involve the esophagus and gastric squamous mucosa as well. Rarely, the glandular stomach is involved. Grossly, the

lesions are yellow-white, smooth or wrinkled plaques, more or less covering the mucosa. Histologically, the epithelium is spongy and contains abundant pseudohyphae and, particularly with *C. albicans* infections, pockets of neutrophils and bacteria beneath the cornified layer. There is congestion of vessels, and a few inflammatory cells are present under the epithelium. Desquamation of the epithelium may produce small ulcers.

In **calves**, candidiasis occurs following prolonged antibiotic therapy and in association with rumen putrefaction. Lesions are seen most often in the ventral sac of the rumen but may involve the omasum and reticulum and occasionally the abomasum. Grossly, the lesions resemble those of thrush in pigs, but the keratinaceous layer tends to be thicker, less diffuse, and light gray. In the omasum, the leaves may be stuck together by the mass of fungus-riddled keratin. Disseminated candidiasis occurs more often in calves than in pigs, probably because of the relatively prolonged survival of calves with alimentary lesions. Candidiasis in calves must be differentiated from alimentary herpesvirus infections.

Gastroesophageal candidiasis in **foals** involves the squamous epithelium and is associated with ulceration adjacent to the margo plicatus. Colic and anorexia are seen and are probably related to the development of the ulcers, which may perforate, causing peritonitis.

In tissues, the presence of blastospores mixed with pseudohyphae or hyphae permits a provisional identification of *Candida*.

INTESTINAL HISTOPLASMOSIS. *Histoplasma capsulatum* is a soil organism of worldwide distribution. The disease histoplasmosis is endemic in certain areas for example, the Mississippi and Ohio River Valleys of the United States. In is important in humans and dogs and occurs sporadically in other species. Infection usually occurs via inhalation of spores, and if lesions occur, usually they are confined to the lungs. Dissemination with hepatic, splenic, and sometimes gastrointestinal lesions develops in some dogs and probably requires a degree of host immunoincompetence. Infection can be produced by ingestion, and possibly the rare examples of disease confined to the gastrointestinal tract develop in this manner. Intestinal infection by ingestion of infected sputum also is possible.

Disseminated histoplasmosis is a disease predominantly of young dogs, which usually present with weight loss, generalized lymphadenopathy, and often, diarrhea with blood, and tenesmus. Intestinal histoplasmosis has been reported as part of a disseminated disease of cats and as an isolated lesion in a horse.

At postmortem there may be hemorrhagic enteritis involving the small and large intestine, or granulomatous thickening of the mucosa and intestinal wall with ulceration (Fig. 1.41E), or no apparent lesions. Mesenteric lymph nodes often are markedly enlarged. Histologically, lesions may occur in the stomach and small or large intestine. The nonulcerated areas of the mucosa contain focal to diffuse infiltrations of macrophages laden with *Histoplasma capsulatum* organisms within cytoplasmic vacuoles. The mucosa may be grossly thickened by the infiltrate, causing necrosis and ulceration. The cellular reaction may extend through the muscularis to the serosa. Macrophages filled with organisms are particularly prominent in the lymphoid tissue of the gut and the mesenteric nodes. Microscopic diagnosis of gastrointestinal histoplasmosis is not difficult, but grossly the disease must be distinguished from intestinal lymphoma and, in the colon, from colitis of other types. Histoplasmosis is discussed in detail with the Hematopoietic System (Volume 3).

### *Protothecal Enterocolitis*

*Prototheca* species are colorless algae closely related to the blue-green alga *Chlorella*. They are ubiquitous in raw and treated sewage and in water and are found in feces, plant sap, and slime flux of trees.

Lesions caused by *Prototheca* include cutaneous infections of cats (see the Skin and Appendages, Volume 1) and humans, mastitis in cows, and disseminated infections in dogs. The intestine and the eye (see the Eye and Ear, Volume 1) are the most commonly involved sites in protothecosis of dogs.

Clinically, chronic, intractable, bloody diarrhea or passage of bloodstained feces are frequent presenting signs. Hemorrhagic and ulcerative colitis is a prominent enteric lesion, but changes may develop also in the small intestine. Mesenteric lymph nodes may be enlarged. Characteristic of protothecosis is the mild host response to infection; usually only a few lymphocytes and monocytes are present. In early lesions, the organisms are scattered in the lamina propria, but later they fill the lamina propria and often are packed in cords between the connective tissue of the submucosa. Lacteals are distended, while the lymphatics proximal to them and the sinuses of draining lymph nodes are filled with organisms.

Factors predisposing to the development of intestinal protothecosis are poorly understood. Skin infections are thought to result from traumatic inoculation, and it is possible that in the alimentary tract, *Prototheca* is an opportunistic invader of existing mucosal lesions. The chronicity of the disease and the mild host response are inconsistent with a virulent infection. Two species, *P. zopfii* and *P. wickerhamii*, cause disease in animals; infections with both may occur in the same animal.

*Prototheca* in sections somewhat resembles cryptococcal organisms. They range from 5-mm spheres to 9 × 12 μm ovoids and are positive with PAS and silver stains. The presence of endosporulation with formation of 2 to 20 sporangiospores within a single sporangium characterizes *Prototheca* and *Chlorella*. *Chlorella* contains PAS-positive cytoplasmic starch granules that are PAS-negative following diastase digestion; *Prototheca* does not contain these granules. Differentiation of the genera by a fluorescent-antibody test using formalin-fixed material is also possible.

Clinically, and grossly at postmortem, protothecal enterocolitis must be distinguished from histiocytic ulcerative colitis of boxer dogs, histoplasmosis, and intestinal lymphoma.

### *Gastrointestinal Helminthosis*

The diagnosis of disease due to gastrointestinal helminths must be made with knowledge of their pathogenic potential and the mechanisms by which it is expressed. Parasites are much more common than the diseases they cause, and *helminthiasis*, the state of infection, must be differentiated clearly from *helminthosis*, the state of disease.

Gastrointestinal helminths fall into five categories, according to pathogenesis of disease. The first group resides free in the lumen of the intestine, competing with the host for nutrients in the gut content. They are of generally low pathogenicity, except for rare overwhelming infections, and are not likely to cause lethal infection, except by obstruction. These worms, present in sufficient numbers, may cause subclinical disease, such as inefficient growth, or clinical disease in the form of ill thrift. The ascarids, small stronglyes (cyathostomes), and tapeworms such as *Moniezia* and *Taenia* fall into this group, as may *Physaloptera,* in the stomach of carnivores.

A second group of helminths, all nematodes, causes disease exclusively or primarily by causing blood loss. These worms feed on the mucosa, causing bleeding, or actively suck blood. Anemia, hypoproteinemia, and their sequelae cause production loss, clinical disease, and death. *Haemonchus* in the abomasum, and in the intestine the hookworms of carnivores and ruminants, the large strongyles of horses, and *Oesophagostomum radiatum* in cattle are the main examples.

The third group, composed of nematodes and some flukes, in heavy infestations causes mainly protein-losing gastroenteropathy, usually associated with inappetence and diarrhea. In the abomasum, *Ostertagia* and *Trichostrongylus axei* cause mucous metaplasia and hyperplasia of gastric glands, achlorhydria, and diarrhea. In the intestine, several species cause villus atrophy. This may cause malabsorption of nutrients, electrolytes, and water. But probably more important is the associated loss of endogenous protein into the gut. *Cooperia* and *Nematodirus* live in the lumen, coiled among villi, against which they brace. Longitudinal cuticular ridges (the synlophe) may aid them in holding position among villi, resisting peristalsis. The members of the genera *Strongyloides* and *Trichostrongylus* are buried, at least partly, in tunnels within, but not normally beneath, the epithelium about the base of villi (Fig. 1.45A,B). Flukes, especially larval paramphistomes in sheep and cattle, attach by their suckers to the mucosa.

The villus atrophy that occurs in these infections may be largely immune mediated. Crypts become hypertrophic, and cells on the mucosal surface in animals with subtotal or total villus atrophy are often attenuated. There may be transient "leaks" of tissue fluid and inflammatory cells through the epithelium, and microerosion of the mucosa occurs in severe cases. Physical damage to the mucosa due to feeding activity of the nematodes is unlikely; however, in fluke infestations this may be superimposed. Disease due to these agents is marked by diarrhea and weight loss, the latter probably mainly the result of the interaction of inappetence and enteric protein loss.

In infection of the cecum and colon by *Trichuris,* the worms reside partly in tunnels in the epithelium on the mucosal surface. Mucosal typhlocolitis results, which may be in part related to the immunoinflammatory response to the worms. In heavy infestations, erosion results in loss of absorptive function and effusion of tissue fluids, or in severe cases, hemorrhagic exudate. More subtle alteration in colonic function, perhaps again immune mediated, is caused by *Oesophagostomum columbianum* in sheep. Mucus hypersecretion and diarrhea occur.

The fourth group causes physical trauma to the intestinal wall by burrowing into or inciting inflammatory foci in the submucosa or deeper layers. In the stomach, various species of spirurids embed in the mucosa or establish in cystic spaces in the submucosa. In the intestine, Acanthocephala cause local ulceration by their thorny holdfast organ; larval stages of equine cyathostomes, and *Oesophagostomum,* become encapsulated in the submucosa. Protein loss may occur from ulcerated areas or when larvae emerge from the submucosa. The potential exists for perforation of the stomach or bowel, or for complications due to sepsis of submucosal nodules. Adhesion of inflamed serosal surfaces associated with nodules or perforations may impair motility.

Finally, some intestinal helminths, among them a few in the categories above, have effects at sites distant from the gut. This is usually the result of migrating larval stages of the worm, either in definitive or intermediate hosts. Larval *Habronema,* ascarids, hookworms, and equine strongyles may cause lesions in a variety of extraintestinal sites in the definitive host. Larval ascarids and taeniid cestodes may cause lesions or signs due to migration in nonenteric locations in accidental or intermediate hosts.

A diagnosis of helminthosis should be reserved for cases where, ideally, three criteria are met: the helminth is present, and in numbers consistent with disease; the lesions (if any) typically caused by the agent are identified; and there is a syndrome compatible with the pathogenic mechanisms known to be associated with the worm. A presumptive diagnosis only can be made if the syndrome, and preferably lesions, are present, but worms are not. This is appropriate only if treatment is very recent, and the condition of the animal is such that it would have been virtually moribund prior to therapy, since response to treatment is usually rapid.

In many cases, it may be necessary and reasonable to base the diagnosis only on the presence of an adequate number of worms, associated with an appropriate syndrome, since autolysis may preclude critical examination of intestinal tissues. This is also appropriate for the establishment of a rapid presumptive diagnosis at autopsy. However, quantitation of the worm burden is highly desirable. To this end, appropriate samples of gastric and intestinal content and mucosa should be collected, and estimates made of the number of worms they contain, using standard parasitologic techniques. Many species of nematodes are difficult to see and impossible to enumerate with the naked eye. Others, such as hookworms, though usually visible, may be so sparsely distributed that they are overlooked or dismissed. An accurate estimate of their number might indicate that they were present in numbers sufficient to represent a significant burden.

It is not acceptable to diagnose helminthosis only on the basis of the presence of worms, without evidence of an appropriate disease state. Nor it is an acceptable diagnosis when a syndrome such as wasting and diarrhea, or anemia, is recognized without identifying the presence of worms or their characteristic lesions.

### *Parasitic Diseases of the Abomasum and Stomach*

OSTERTAGOSIS. Ostertagosis is probably the most important parasitism in grazing sheep and cattle in temperate climatic zones throughout the world. It causes subclinical loss in production, and clinical disease characterized by diarrhea, wasting, and

in many cases, death. *Ostertagia ostertagi, O. lyrata,* and *O. leptospicularis* infect cattle; the first species is most important. Sheep and goats are infected by *O. circumcincta,* which is most significant, and by *O. trifurcata.* Some cross-infection by these species occurs between sheep and cattle but is of minor significance. Related genera, including *Marshallagia, Teladorsagia,* and *Camelostrongylus,* may infect sheep and goats; their development and behavior resemble those of *Ostertagia.*

The life cycle is direct. Third-stage larvae exsheath in the rumen and enter glands in the abomasum, where they undergo two molts. Normally, early fifth-stage larvae emerge to mature on the mucosal surface, beginning between the eighth and twelfth days after infection in *Ostertagia circumcincta* infections in sheep, and about 17–21 days after *O. ostertagi* infection in cattle. A proportion of larvae ingested may persist in glands in a hypobiotic state at the early fourth stage, however, only to resume development and emerge at a future time, perhaps many months hence. The prepatent period is ~3 weeks.

During the course of larval development, the normal architecture of the gastric mucosa is altered by interstitial inflammation, and mucous metaplasia and hyperplasia of the epithelium lining glands. In sheep infected with *Ostertagia circumcincta,* mucous metaplasia and hyperplasia occur in infected and surrounding glands early in infection, reaching a peak about the time of emergence of larvae onto the mucosal surface. In cattle with *O. ostertagi* (Fig. 1.43D), only glands infected with larvae undergo significant mucous change until about the time larvae leave the glands for the surface of the mucosa (Fig. 1.43E). Mucous change then becomes more widespread, involving uninfected glands in the vicinity of those that contained larvae.

In both species, affected glands are lined by mucous neck cells, which proliferate, displacing parietal cells. Glands elongate, and the affected areas of mucosa thicken. In developing lesions the gland lining is cuboidal or low columnar, and mitotic figures are frequent. In infected glands the lining in many cases is flattened adjacent to worms (Fig. 1.43F) but is composed of tall columnar mucous cells elsewhere in the gland. The undifferentiated mucous cells lining uninfected glands also eventually differentiate into tall columnar mucous cells. If infection is not heavy, lesions are limited to a radius of a few millimeters around infected or previously infected glands. These form raised, nodular pale areas in the mucosa, often with a slightly depressed center. Confluence of these lesions in heavily infected animals leads to the development of widespread areas of irregularly thickened mucosa with a convoluted surface pattern, likened to Morocco leather. With time, severely affected mucosa may be comprised almost totally of somewhat dilated, elongate glands lined by columnar mucous cells. With loss of the worm burden, through treatment or natural attrition, the mucosa gradually returns to normal.

Mucous metaplasia and hyperplasia are accompanied by a mixed population of inflammatory cells in the lamina propria. As has been speculated earlier, under Gastritis, the epithelial lesion itself may be immune mediated. Infiltrates of lymphocytes are present between glands deep in infected mucosa within a few days after infection of sheep with *Ostertagia,* and lymphoid follicles with germinal centers evolve in these sites. Lymphocytes, plasma cells, eosinophils, and a few neutrophils are present between glands in the infected abomasum. There may be edema of the lamina propria associated with permeability of proprial vessels, which in experimental *Camelostrongylus* infection occurs as early as 4 days after infection. Globule leukocytes are common in the lining of infected glands. A few eosinophils, neutrophils, and effete epithelial cells may be seen in the lumen of glands.

Mucosal lesions lead to achlorhydria, elevation of plasma pepsinogen levels, and loss of plasma protein. Widespread replacement of parietal cells by mucous neck cells results in progressive and massive decline in hydrogen-ion secretion. In severe cases, the abomasal content has a pH of up to 7 or more, and a high sodium-ion concentration. The pathogenic significance of associated failure to hydrolyze protein in the abomasum, and of increased numbers of bacteria in content, is unclear. Mucous metaplasia and achlorhydria in ovine ostertagosis occur in the face of substantially increased gastrin secretion, which is not stimulated simply by failure of antral acidification. The permeability of the mucosa is also increased, which is reflected in back diffusion of pepsinogen from the lumen of glands to the propria, and ultimately to the circulation. Intercellular junctions between poorly differentiated mucous neck cells are permeable also to plasma protein in tissue fluids, emanating from the leaky small vessels in the inflamed lamina propria. Significant loss of protein occurs into the lumen of the abomasum.

The cardinal signs of ostertagosis in sheep and cattle are loss of appetite, diarrhea, and wasting. The cause of reduced appetite is unclear. Diarrhea is associated with marked elevation in abomasal pH, but the mechanism by which it occurs is also obscure. Plasma protein loss into the gastrointestinal tract, in combination with reduced feed intake, seems largely responsible for the weight loss and hypoproteinemia that occur in clinical ostertagiosis, and for loss in productive efficiency that occurs in subclinical disease. The interaction of protein-losing gastroenteropathy and nutrition has been discussed previously.

Clinical ostertagosis occurs under two sets of circumstances. The first, type I disease, is seen in lambs or calves at pasture during or shortly following a period of high availability of infective larvae. It is due to the direct development, from ingested larvae, of large numbers of adult worms over a relatively short period of time. In contrast, type II disease is due to the synchronous maturation and emergence of large numbers of hypobiotic larvae from the mucosa, and it occurs when intake of larvae is likely low or nonexistent. It may occur in yearlings during the winter in the northern hemisphere, or during the dry summer period in Mediterranean climates. Heifers about the time of parturition may succumb, and this syndrome is also occasionally seen in animals experiencing environmental stress of any type.

Type I and II ostertagosis do not differ fundamentally in the signs or lesions they present. Animals will have a history of depression, inappetence, and diarrhea, and weight loss consistent with the severity and duration of the other signs. There may be edema of subcutaneous tissues and mesenteries, and accumulation of fluid in the body cavities. The carcass may be wasted, and the liver is often atrophic and the gallbladder dilated as a result of inanition. The content of the abomasum is fluid. It may be slightly foul smelling, in contrast to the normal sharply

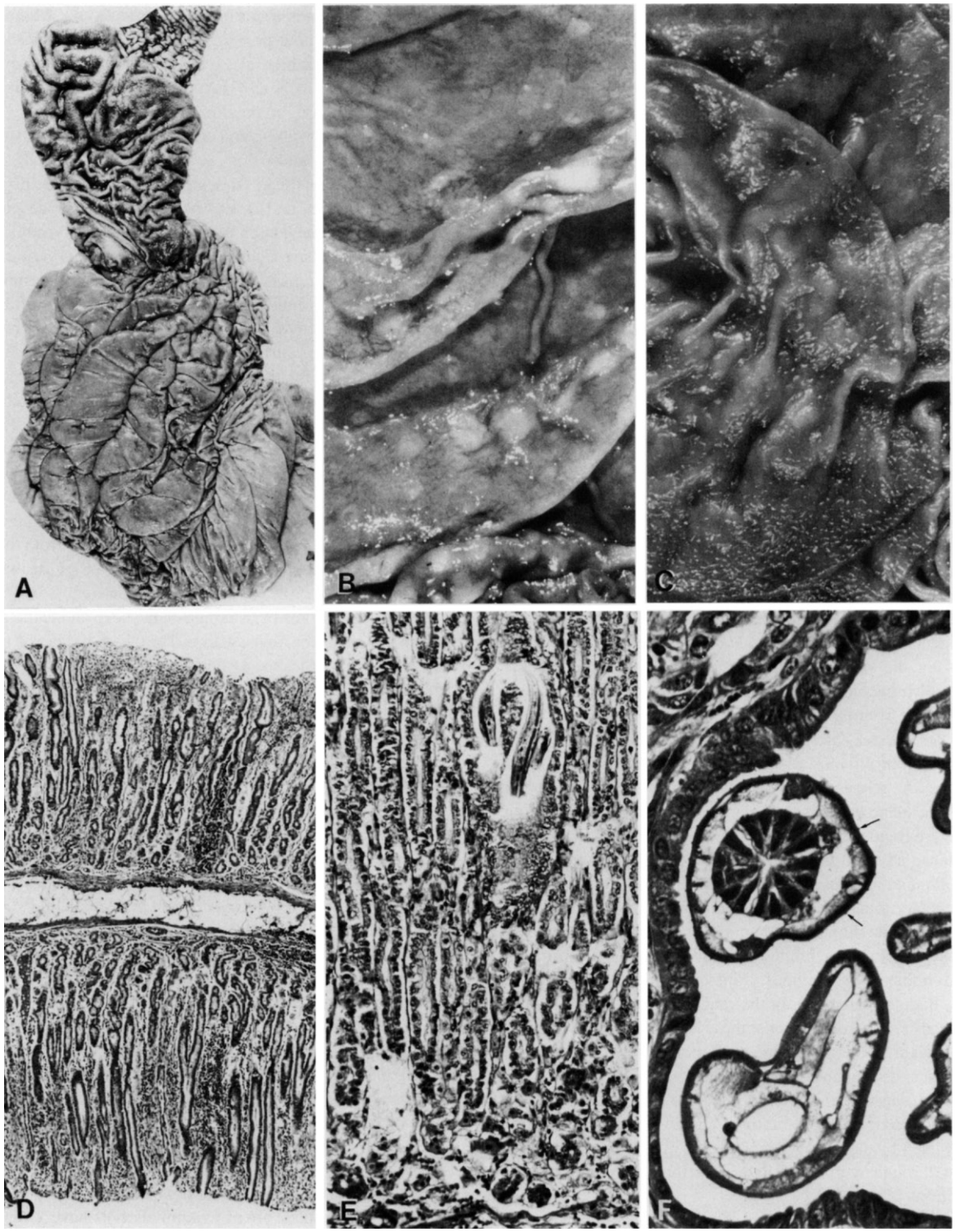


**Fig. 1.43.** Ostertagosis. Abomasum. (**A**) Acute edematous gastritis. Ox. (**B**) Individual nodules and some confluent lesions are present. Sheep. (**C**) Confluent thickening of hyperplastic glandular mucosa. Sheep. (**D**) Mucous metaplasia and hyperplasia thickening fundic mucosa on an abomasal fold. Moderate inflammatory infiltrate in propria between glands. Ox. (**E**) Mucous metaplasia and hyperplasia deep in fundic mucosa. Larva in section in gland. Ox. (**F**) *Ostertagia* in a dilated gland lined by cuboidal, mucous neck cells. The longitudinal cuticular ridges are visible as fine projections on the nematode in cross section (arrows).

acidic odor of abomasal content. The rugae often have substantial submucosal edema (Fig. 1.43A). The mucosa will have widespread individual or confluent thickened pale mucosal nodules (Fig. 1.43B,C) or will show diffuse thickening and corrugation over much of the gastric lining. Both fundic and pyloric areas are involved. The mucosa may be reddened and perhaps focally eroded, with a superficial light fibrinous exudate in occasional cases.

The diagnosis is indicated at autopsy by an abnormally elevated abomasal pH (>4.5), in association with typical gross lesions on the mucosa. The adult worms are brown and threadlike, up to 1.5 cm long but very difficult to see on the mucosa with the unaided eye. Abomasal contents and washings should be quantitatively examined for the presence of emergent or adult *Ostertagia* and other nematodes. The mucosa, or a known portion of it, should be digested to permit recovery and quantitation of preemergent stages. Significant worm burdens in sheep are in the range 10,000 to 50,000 or more. In cattle, more than 40,000 to 50,000 adult worms may be present, and in outbreaks of type II disease, hundreds of thousands of hypobiotic larvae are often detected in the abomasal mucosa. Typically, there is widespread mucous metaplasia and hyperplasia in dilated glands in sections of abomasum. *Ostertagia* is recognized, in glands, or on the mucosal surface, in sections by the presence of prominent longitudinal cuticular ridges that project from the surface of worms cut transversely (Fig. 1.43F). In some cases, the worm burden may have been lost through attrition or treatment, and the diagnosis must be presumptive, based on the characteristic mucosal lesions.

Ostertagosis must be differentiated in sheep from other gastrointestinal helminthoses (except haemonchosis) and from chronic coccidiosis. In cattle, gastrointestinal helminthosis, chronic bovine virus diarrhea, chronic salmonellosis, and in older animals, Johne's disease, must be considered.

HAEMONCHOSIS. Haemonchosis may be a common and severe disease in parts of the world where it occurs. *Haemonchus contortus* infects mainly sheep and goats, while *H. placei* occurs mainly in cattle. Though *H. contortus* and *H. placei* will infect the heterologous host, the host–parasite relationship appears to be less well adapted, and the species do appear to be genetically distinct. *Mecistocirrus digitatus* causes disease very similar to haemonchosis in cattle and sheep in Southeast Asia and Central America. *Haemonchus* species require a period of minimum warmth and moisture for larval development on pasture. As a result, they tend to be most important in tropical or warm temperate climates with hot, wet summers. By exploitation of hypobiosis or retardation of larvae, populations of *H. contortus* are able to persist in the abomasum of the host through periods of climatic adversity, such as excessive cold or dryness. Disease can be expected in animals, especially females, experiencing the synchronous "spring rise" or periparturient development and maturation of previously hypobiotic larvae, and in young animals heavily stocked at pasture during periods of optimal larval development and availability. Resistance to reinfection occurs much more reliably in calves infected with *H. placei* than in sheep infected with *H. contortus*.

*Haemonchus*, commonly called the large stomach worm or barberpole worm, is ~2.0 cm long. Females give the species its common name by their red color, against with the white ovaries and uterus stand out. The male is a little shorter and a uniform deep red. These worms are equipped with a buccal tooth or lancet, and fourth-stage and adult worms suck blood. Ingested third-stage larvae enter glands in the abomasum, where they molt to the fourth stage and persist as hypobiotic larvae, or from which they emerge as late fourth-stage larvae to continue development in the lumen. The prepatent period of *H. contortus* in sheep is about 15 days, and for *H. placei* in cattle about 26–28 days.

Haemonchosis may present as peracute or acute disease, resulting from the maturation or intake of large numbers of larvae. It may cause more insidious chronic disease if worm burdens are low or moderate. The pathogenicity of *Haemonchus* infection, whatever its manifestation, is the result of anemia and hypoproteinemia caused by bloodsucking activity. Large numbers of *Haemonchus* administered to sheep cause changes resembling those occurring in ostertagosis, including achlorhydria, increased plasma pepsinogen, and some architectural alterations in the abomasal glands. These appear to be experimental phenomena, however, and do not contribute to the spontaneous disease.

Individual *Haemonchus* worms in sheep cause the loss of ~0.05 ml of blood per day. Of the order of a tenth to a quarter of the erythrocyte volume may be lost per day by heavily infected lambs; the plasma loss is concomitant, several hundreds of milliliters. The potential for the rapid development of profound anemia and hypoproteinemia in heavily infected animals is obvious. Such animals succumb quickly, some even before the maturation of the worm burden. Less severely affected animals may be able to withstand the anemia and hypoproteinemia for a period of time. They compensate by expanding erythropoiesis two- or threefold and increasing hepatic synthesis of plasma protein. They are unable adequately to compensate for the enteric iron loss, however, despite intestinal reabsorption of a proportion of the excess and they ultimately succumb some weeks later to iron-loss anemia, when iron reserves are depleted. Low-level infections may contribute to subclinical loss of production or ill thrift through chronic enteric protein and iron loss.

The clinical syndrome may vary somewhat. Some animals are found dead, without the owner's observing illness. Others lack exercise tolerance, fall when driven, or are reluctant to stand or move, so weak are they from anemia. Sometimes edema of dependent portions, especially the submandibular area or head in grazing animals, is observed. In primary haemonchosis, there is no diarrhea; this sign may be present if intercurrent infection with large numbers of other gastrointestinal helminths occurs.

The postmortem appearance of animals with haemonchosis is dominated by the extreme pallor of anemia, apparent on the conjunctiva and throughout the internal tissues. The liver is pale, friable, and perhaps somewhat fatty. There is usually edema of subcutaneous tissues and mesenteries, with hydrothorax, hydropericardium, and ascites, reflecting the severe hypoproteinemia. In animals with more chronic disease, perhaps complicated by a low plane of nutrition, there may be depletion of fat depots and atrophy of muscle mass. The abomasal content is usually fluid

and dark red-brown, due to the presence of blood (Fig. 1.44D). The abomasal rugae may be edematous due to hypoproteinemia, and focal areas of hemorrhage are evident over the surface. In animals not decomposing, the worms will be evident to the naked eye: if alive, writhing on the mucosal surface; if dead, less obvious and free in the content. The mucosa should be washed and the washings combined with content for determination of the worm burden.

In clinically affected sheep and goats, usually about 1000–12,000 worms are found. The severity of the disease is partly a function of the number of worms, and to some extent, the size of the animal. In lambs, 2000–3000 worms is a heavy burden, while in adult sheep and goats, 8000–10,000 are associated with fatal infection. Burdens of less than 500 to 1000 *Haemonchus* worms are unlikely to cause death in animals on a good plane of nutrition but may contribute to inefficiency in production or cause ill thrift and perhaps mortality if the quality of feed declines.

A high egg count is usually found on fecal flotation since *Haemonchus* is a prolific egg layer. In peracute prepatent infections, however, no eggs will be present. In recently treated animals, no worms may be present, and the diagnosis may have to be presumptive. On the other hand, animals returned to contaminated pasture may succumb to reinfection within 2 to 3 weeks of treatment. A diagnosis of haemonchosis in one or two animals from a group indicates the necessity of treatment and a move to clean pasture for the remainder of the flock or herd.

Other causes of acute anemic syndromes in sheep and goats, from which haemonchosis should be differentiated, include *Bunostomum* infection, acute fascioliasis, coccidiosis, and eperythrozoonosis. Chronic copper poisoning is more marked by icterus than anemia, though hemolytic anemia occurs. In cattle, sucking lice, infections with *Bunostomum, Oesophagostomum radiatum,* coccidiosis, and hemolytic anemias due to babesiosis, anaplasmosis, leptospirosis, and bacillary hemoglobinuria must be considered. At some stage, all of the hemolytic anemias cause hemoglobinuria, and icterus is often present. Neither occurs in haemonchosis.

*TRICHOSTRONGYLUS AXEI* INFECTION. *Trichostrongylus axei* infects the abomasum of cattle, sheep, and goats, and the stomach of horses. It has a direct life cycle, third-stage infective larvae entering tunnels in the epithelium of the foveolae and isthmus of gastric glands in fundic and pyloric areas. The worms live throughout their life at least partly embedded in intraepithelial tunnels at about this level of the mucosa. They molt to the fourth stage about a week after being ingested and to the fifth stage by ~2 weeks after infection. The prepatent period is ~3 weeks in calves and sheep and ~25 days in horses.

Infections with *Trichostrongylus axei* are usually part of a mixed gastrointestinal helminthosis. In all hosts, however, this species alone is capable of inducing disease if present in sufficient numbers. After a period of several weeks, mucous metaplasia and hyperplasia are seen in glands in infected areas of the mucosa. Mucous neck cells replace parietal and peptic cells, and the glands increase markedly in depth and appear slightly dilated. This change is associated with an infiltrate of eosinophils and lymphocytes, especially in the superficial lamina propria. In severely affected animals, flattening of surface epithelium with desquamation, or erosion of the mucosa, develops, accompanied by effusion of neutrophils, eosinophils, and tissue fluid, The inflammatory reaction in the propria is most intense in the vicinity of erosions, and no specific reaction is associated with worms in epithelial tunnels. Fibroplasia may occur in the superficial propria in eroded areas.

In light infestations there may be no changes visible in the abomasum, other than congestion of the mucosa. The gross lesions present in heavy *Trichostrongylus axei* infections reflect the hypertrophy of glands and superficial erosion. Circular or irregular, raised white plaques of thickened infected mucosa stand out against the background of more normal tissue. The surface of the mucosa generally is covered by a heavy layer of mucus. Erosions or shallow ulcers may be present, especially on the tips of abomasal folds. In severe infections the entire mucosa appears edematous and congested.

Infection in horses is uncommon and is related usually to sharing pasture with sheep or cattle. In chronically infected horses, white raised plaques (Fig. 1.44B) or nodular areas of mucosa are present, covered by tenacious mucus and surrounded by a zone of congestion. Mucosal lesions may be confluent in heavily infected animals, and erosions and superficial ulceration may be encountered. Infection may extend into the proximal duodenum, where polypoid masses of hypertrophic glandular mucosa are occasionally observed.

Achlorhydria develops in heavily infected sheep and cattle, associated with diarrhea particularly in the latter species. Dehydration may prove severe in scouring calves. Plasma pepsinogen levels increase, and hypoproteinemia and wasting occur. This suggests that the mucous metaplasia in the glands is associated with increased permeability and that plasma protein loss occurs into the gastrointestinal tract.

Though *Trichostrongylus axei* is not common as a primary cause of disease in any species, it should be sought at autopsy of animals with signs of wasting and perhaps diarrhea. The typical gross lesions in the stomach are distinctive in horses. They must be differentiated from those due to *Ostertagia,* with which animals may be intercurrently infected, in ruminants. The worms are very fine, and gastric washes or digestion are required to recover them quantitatively. The distinctive intraepithelial location of *T. axei* in section differentiates it from other nematodes inhabiting the abomasum of ruminants and the stomach of horses.

GASTRIC PARASITISM IN HORSES. The commonest parasites of the equine stomach are larvae of the botflies of the genus *Gasterophilus*. Though they are not helminths, it is convenient to consider them here. There are six species of the genus, the common ones being *G. intestinalis, G. nasalis,* and *G. haemorrhoidalis,* and the uncommon ones *G. pecorum, G. nigricornis,* and *G. inermis*. The ova are deposited on the ends of the coat hairs. The larvae of *G. inermis* and *G. haemorrhoidalis* are able to penetrate the cheeks of horses, but those of *G. intestinalis* and *G. pecorum* must be licked to stimulate hatching and to convey the larvae to the mouth. The first-stage larvae penetrate the oral mucosa and migrate down the alimentary canal.

*Gasterophilus intestinalis* usually wanders about in the super-

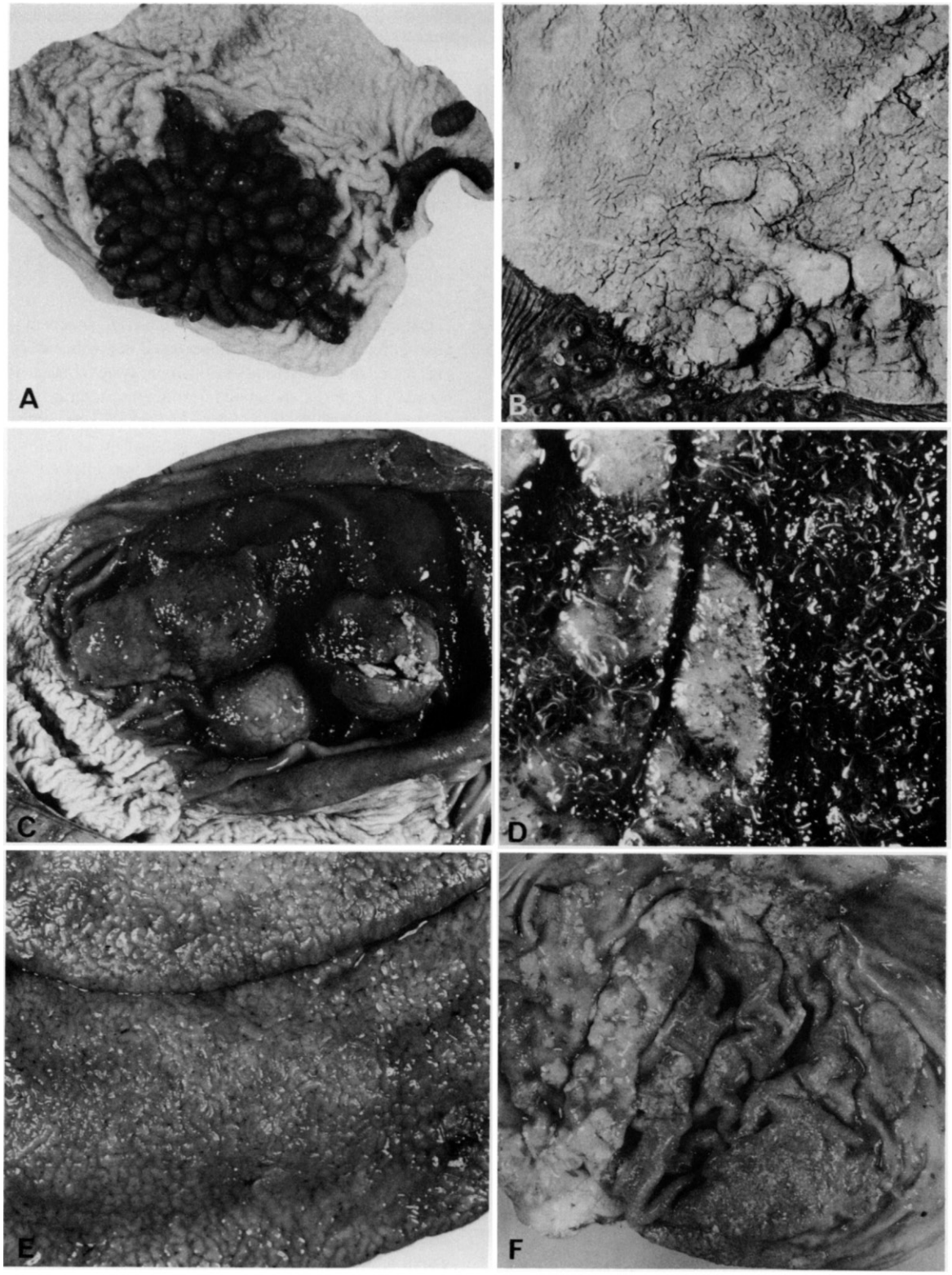


**Fig. 1.44.** (**A**) *Gasterophilus* larvae on gastric mucosa. Horse. (**B**) Hypertrophic gastritis. Fundic mucosa. Trichostrongylosis. Horse. (Courtesy of N. O. Christensen and the *Skandinavisk Veterinartidskrift*.) (**C**) Nodules containing *Draschia megastoma* in the submucosa of glandular mucosa, near margo plicatus. Purulent content in sectioned nodule. (**D**) *Haemonchus contortus* in acid/hematin-tinged abomasal content. Sheep. (**E**) Hyostrongylosis. Abnormally rugose mucosa. Pig. (**F**) Hyostrongylosis. Pig. Hypertrophic catarrhal gastritis.

ficial tissues of the tongue or gums for 3 to 4 weeks before molting and moving on. This is the most common species, and in the stomach it attaches itself to the squamous mucosa of the cardia to complete its subsequent molts. The larvae of *G. nasalis* first invade the gums, then pass to the stomach and settle on the pyloric mucosa and in the duodenum. Members of any of these species may occasionally be found attached to the pharynx and esophagus, but except for *G. pecorum,* which congregates in the pharynx and causes pharyngitis, these preliminary migrations are uneventful for the host. In the summer following the deposition of the ova, the larvae leave the stomach and pass out in the feces to pupate. Those of *G. pecorum* and *G. haemorrhoidalis* may attach themselves for a short while to the wall of the rectum.

It is generally assumed that the larvae of *Gasterophilus* have little effect on their host. They may, however, produce significant gastric lesions. Infestations by bots usually involve scores or occasionally hundreds, scattered or more commonly grouped together in rosette-like colonies (Fig. 1.44A). The larvae fasten themselves to the mucosa by the chitinous oral hooks, and they bore into the mucosa. They apparently subsist on blood, exudate, and detritus and produce focal erosions and ulcerations at the point of contact. These defects in the cardia are surrounded by a narrow rim of hyperplastic squamous epithelium. Usually the number of epithelial defects exceeds the number of larvae, suggesting that they move about on the mucosa. Undoubtedly many are removed mechanically, and often some are found free in the ingesta. Severe infestations produce a dense, pockmarked appearance with chronic inflammatory thickening. Ulcers may occur in the glandular mucosa, and a large proportion of the pyloric mucosa may be lost. Healing occurs when the larvae migrate, but may be complicated by secondary bacterial infection. Histologically, the ulcers penetrate the submucosa, which is chronically inflamed. The deep layers of eroded epithelium and the epithelial margins of ulcers in the squamous mucosa become hyperplastic and develop rete pegs. Other exceptional untoward sequelae include subserosal abscessation, or perforation with hemorrhage or peritonitis, and inflammatory stricture of the pylorus.

The spirurid nematodes *Draschia megastoma, Habronema majus* (formerly *microstoma*), and *H. muscae* are also parasitic in the stomachs of horses. The adult worms are 1–2 cm in length. The latter two species lie on the mucosal surface and are probably pathogenetically insignificant except possibly for a few erosions and mild gastritis. *Draschia megastoma* burrows into the submucosa to produce large, tumor-like nodules (Fig. 1.44C). *Habronema majus* mainly uses *Stomoxys calcitrans* as its intermediate host, and the other two species use various muscid flies. The *Habronema* larvae in the feces are swallowed by maggots of the appropriate intermediate host and persist through pupation and maturation of the fly. They leave the host fly via the proboscis when it eats. Horses may also be infected when they swallow parasitized flies. Larvae deposited on or in cutaneous wounds invade them and provoke an intense local reaction that becomes granulomatous and densely infiltrated with eosinophils (see the Skin and Appendages, Volume 1).

The only one of concern in the stomach is *Draschia megastoma,* which burrows into the submucosa of the fundus, usually within a few centimeters of the margo plicatus. Within the submucosa, the worms provoke a surrounding granulomatous reaction, which contains them in a central core of necrotic and cellular detritus. Eosinophils are present in large numbers. The granulomas cause the overlying mucosa to bulge into the gastric lumen. Except for a small fistulous communication through which the ova pass, the epithelium is not defective, even though the protrusions may be 5.0 cm or so in diameter. The nodules generally produce no clinical disturbance though they have been considered to lead rarely to abscessation or perforation when secondarily infected with pyogenic bacteria.

*Trichostrongylus axei* in horses has been considered in the previous section.

GASTRIC PARASITISM IN SWINE. Gastric parasitism is not of great clinical or pathologic importance in swine and is rare in pigs reared in modern total-confinement systems. *Ascaris suum,* normally inhabiting the small intestine, may migrate or reflux to the stomach after death. *Hyostrongylus rubidus* is probably the most significant parasite of the stomach of swine, while the various spirurids are more common in pigs allowed to forage. *Ollulanus tricuspis* has been reported to occur in pigs. It is more commonly encountered in cats and is discussed under Gastric Parasitism in Dogs and Cats.

*Hyostrongylus rubidus* is a trichostrongylid nematode with a typical life cycle. Third-stage larvae enter glands in the stomach, especially in the fundic region, where they develop and molt twice. Preadult and adult worms emerge onto the gastric mucosa about 18–20 days after ingestion. The lesions produced by *Hyostrongylus* resemble those caused by *Ostertagia* in ruminants. During the course of larval development, there is mucous metaplasia and hyperplasia of the lining of infected and neigboring glands, and dilation of infected glands. The lamina propria in infected mucosa is edematous and infiltrated by lymphocytes, plasma cells, and eosinophils, and lymphoid follicles develop deep in the mucosa. Neutrophils and eosinophils may transmigrate the epithelium into dilated glands, the lining of which may become quite attenuated. Effusion of neutrophils and fibrin may occur through transient gaps, or more extensive erosions, in the surface of the mucosa. Larval nematodes are found in the gastric glands in sections, while adults are mainly on the surface of the mucosa.

During the course of development of the worms, the mucous metaplasia and hyperplasia cause the formation of pale nodules in the vicinity of infected glands (Fig. 1.44F). In heavy infections these may become confluent, causing the development of an irregularly thickened convoluted mucosa (Fig. 1.44E), most notable in the fundic area and along the lesser curvature. Adult worms are fine, red, and threadlike in the gastric mucus; they are difficult to see with the naked eye. Mucosal nodularity is most apparent during larval development and perhaps persists around glands containing inhibited larvae. In established heavy infections, the mucosa is not so thickened. It is pinkish brown, corrugated, and covered with excess mucus. There may be focal or diffusely eroded areas with pale fibrin evident on the surface, and occasionally ulceration of the glandular mucosa has been associated with hyostrongylosis.

Experimental infections of moderate degree do not produce obvious clinical signs or loss of production. Plasma protein loss

has been documented in *Hyostrongylus* infections, however, following heavy doses of larvae. Inappetence, diarrhea, and reduced weight gains also occur in these circumstances. In the field, hyostrongylosis is associated mainly with the "thin-sow syndrome." It seems probable that hyostrongylosis may interact with nutritional and metabolic factors in contributing to this syndrome. Hyostrongylosis is confirmed by total worm count on the gastric mucosa and digests, in association with compatible gross and microscopic lesions in the stomach.

Spirurid nematodes parasitizing the porcine stomach include *Physocephalus sexalatus, Ascarops strongylina, A. dentata,* and *Simondsia paradoxa. Physocephalus* and *Ascarops* utilize dung beetles as intermediate hosts; the intermediate host of *Simondsia* is not known. *Ascarops* and *Physocephalus* are common in swine with access to grazing in many parts of the world. Large numbers of worms are required to cause disease. Worms in affected pigs may be free in the lumen or partly embedded in the mucosa, which may be congested and edematous, or eroded and ulcerated with a fibrinous exudate on the surface. *Simondsia* is found in swine in Europe and Asia. The posterior portion of the female worms is globular and embedded in palpable nodules up to 6 to 8 mm in diameter in the gastric mucosa. *Gnathostoma hispidum* may cause lesions in the liver, and submucosal nodules in the gastric wall of pigs, similar to those produced by *G. spinigerum* in carnivores.

GASTRIC PARASITISM IN DOGS AND CATS. Parasites are relatively uncommonly encountered in the stomach of dogs and cats at autopsy, and most are incidental findings or postmortem migrants from the intestine to the stomach.

*Gnathostoma spinigerum* occurs in the stomach of dogs and cats and a variety of nondomestic carnivores. It is more common in areas with warm climates. The life cycle of this spirurid nematode involves *Cyclops* as an aquatic invertebrate intermediate host, and a variety of fish, amphibians, or reptiles as second intermediate hosts. Third-stage larvae may also persist in the tissues of a variety of mammalian transport hosts. The life cycle dictates that infected animals have the opportunity to forage and scavenge. Ingested third-stage larvae may migrate in the liver, leaving tracks of necrotic debris, which eventually heal by fibrosis. In heavy infections, lesions associated with larval migration may be found elsewhere in the abdominal and pleural cavities.

Adults are found in groups of up to 10 in nodules in the gastric submucosa. Nodules are up to ~5.0 cm in diameter, and open into the gastric lumen. Portions of nematodes may protrude through this opening. The worms lie in a pool of blood-tinged purulent exudate in the lumen of the nodule, the wall of which is comprised of granulation tissue and reactive fibrous stroma. A mixed inflammatory infiltrate is in the wall of the nodules, and focal granulomas may center on nematode ova trapped in the connective tissue. Infection with *Gnathostoma* has been considered significant. Illness and death may be associated with disturbance of motility, chronic vomition, and occasional rupture of verminous nodules onto the gastric serosa, leading to peritonitis.

A number of species of *Physaloptera,* including *P. praeputialis* (cat), *P. rara* (dogs and wild Canidae and Felidae), and *P. canis* (dog), are found in the stomach of dogs and cats. These nematodes utilize arthropod intermediate hosts, and probably some vertebrate transport hosts. The adult worms, which may be mistaken for small ascarids, are found in the stomach, where they may be free in the lumen. More commonly they are attached as individuals or in small clusters to the gastric mucosa. Ulcers may be formed, and the anterior end of the worm may be embedded in the submucosa. A hyaline, PAS-positive material surrounds the anterior end of some worms, perhaps anchoring them in the tissue. These nematodes are not highly pathogenic, though heavy burdens may have the potential to cause significant gastric damage and protein loss into the lumen.

*Cylicospirura felineus* and members of the genus *Cyathospirura* may be found in the stomach of domestic and wild felids. *Cylicospirura* is usually found in the submucosal nodules, similar to those formed by *Gnathostoma,* while *Cyathospirura* is usually found free in the lumen, or sometimes associated with *Cylicospirura* in gastric nodules. The pathogenicity of these species is poorly defined, but is likely low.

*Ollulanus tricuspis* is a small trichostrongyle, ~1.0 mm long. which inhabits the stomach of cats and swine. It is viviparous, and third stage larvae developing in the uterus of the female are transmitted in vomitus. As a result, infection is usually not detected by usual coprologic examination, and infection with this species may go unnoticed. In some parts of the world it is common, particularly in cat colonies and cats that roam. Clinical signs and gross lesions due to *O. tricuspis* are uncommon.

The worms lie beneath the mucus on the surface of the stomach, or partly in gastric glands. Infection is associated with the presence of increased numbers of lymphoid follicles deep in the gastric mucosa, increased interstitial connective tissue in the mucosa, and elevated numbers of globule leukocytes in the gastric epithelium. Heavy infection results in mucous metaplasia and hyperplasia of gastric glands, causing the surface of the stomach to be thrown into thickened, convoluted folds. Gastric glands are separated by the heavy, reactive fibrous stroma in the mucosa. *Ollulanus* is characterized in section by the numerous longitudinal cuticular ridges recognized as projections on the surface of sectioned worms.

*Capillaria putorii* has also been reported from the stomach of cats. It is probably an uncommonly recognized inhabitant of the intestine, found in the stomach due to intestinal reflux at or after death. It is likely of little significance in either site.

Ascarids, hookworms, and tapeworms normally found in the small intestine may also be found as postmortem artifacts in the stomach.

### *Intestinal Nematode Infection*

*STRONGYLOIDES* INFECTION. *Strongyloides* species parasitize all species of domestic animals considered here. Ruminants are infected by *S. papillosus,* horses by *S. westeri,* swine mainly by *S. ransomi,* dogs by *S. stercoralis,* and cats by *S. cati,* perhaps *S. stercoralis,* and *S. tumefaciens* in the colon. The parasitic worms are parthenogenetic females, which produce larvae capable of direct infection of the host, or of development into a free-living generation of males and females. The offspring of this generation then adopt a parasitic existence.

Infection by third-stage larvae takes place by skin penetration, or to a lesser extent by ingestion and probably subsequent

penetration of the gastrointestinal mucosa. Larvae attain the bloodstream, and in young animals they break out into pulmonary alveoli. They migrate to the large airways, whence they are carried up the mucociliary escalator to be swallowed, and established in the small intestine. Alternatively, prenatal, or much more importantly, transmammary, infection occurs. Infective early fourth-stage larvae are mobilized from muscle or adipose tissue in the periparturient female. They may cross the placenta shortly before birth or are shed in the milk for several weeks after parturition. No somatic migration is required prior to establishment of these larvae in the gut of the new host.

The suckling young may develop patent infections within 1 or 2 weeks of birth. The prepatent period is short, and development of free-living larvae or the free-living generation is rapid. If sanitation is poor, and large numbers of larvae derived from parasitic or free-living generations of the worm are in the substrate, infection through the skin may be considerable. Dermatitis of contact surfaces may be associated with skin penetration (see the Skin and Appendages, Volume 1). Heavy intestinal infections may be a significant cause of morbidity and mortality in neonatal or suckling animals under appropriate epizootiologic circumstances.

Typically infecting the anterior small intestine of all species, *Strongyloides* larvae establish in tunnels in the epithelium about the base of villi, and they persist in that location (Fig. 1.45A). Adult worms are small, only 2–6 mm long, depending on species. In sufficient numbers, they cause the development of villus atrophy, associated with a mixed but mainly mononuclear inflammatory cell infiltrate into the lamina propria. Cryptal epithelium is hyperplastic. Villi are stumpy, or there is subtotal villus atrophy. Surface epithelium is usually low columnar to cuboidal, with an indistinct brush border. It may be squamous or, in some cases, eroded. In such circumstances, local effusion of neutrophils and tissue fluid into the lumen is seen. The nematodes are usually seen in tunnels in the surface epithelium, not beneath the basal lamina. In animals with severe atrophy, they may be in crypts of Lieberkühn. Embryonated or larvating ova may be retained in epithelial tunnels and help to distinguish this nematode in tissue section from *Trichostrongylus* in hosts in which both species occur.

*Strongyloides ransomi* is responsible for diarrhea in suckling piglets in some parts of the world. Minor local hemorrhage occurs as larvae migrate through the lungs and thickening of alveolar septa, associated with scattered aggregates of lymphocytes and plasma cells is reported. In the duodenum, villus atrophy is associated with local malabsorption of amino acids and with protein loss into the gut. In heavy infections, amino acid malabsorption is not compensated for by increased absorption in more distal intestine. Diarrhea occurs, presumably the result of malabsorption. Debilitation is the product of anorexia, protein loss into the gut, and nutrient malabsorption. Plasma gastrin levels are elevated in this infection, but the pathogenetic significance of this is obscure. This disease must be considered in enzootic areas and differentiated from the other causes of undifferentiated diarrhea in suckling piglets more than 6 to 10 days of age. Specific gross lesions other than those associated with diarrhea may be absent. Moderate to severe clinical disease in 3-month-old pigs is associated with 20,000 to 70,000 worms, most in the anterior 30 to 40% of the small intestine. Worms are evident in mucosal scrapings at autopsy.

*Strongyloides westeri* commonly infects foals. It is associated with diarrhea, occasionally fatal, in some animals less than 4 to 5 months of age. It is claimed that skin lesions by larval penetration may permit entry of *Corynebacterium equi*, which causes lymphadenitis. Millions of infective larvae are necessary to cause fatal infections experimentally. The gross findings at necropsy do not indicate the etiology, which may be suggested by finding worms in gut scrapings, and confirmed by their association with atrophic villi in tissue section.

In suckling ruminants, or young animals artifically reared, *Strongyloides papillosus* may cause diarrhea and, in occasional overwhelming infection, death. The pathology, and presumably the pathogenesis of *S. papillosus* infection, are typical of the genus.

*Strongyloides stercoralis* infections are most commonly fatal in puppies up to 2 to 3 months old, often from kennel environments. Affected dogs are wasted and dehydrated with evidence of diarrhea, perhaps blood tinged, but the intestine may only be congested or unremarkable at autopsy. Severe villus atrophy and heavy mononuclear interstitial infiltrates are evident in the duodenum of affected dogs. Occasionally, larvae may be present in granulomas in the lamina propria and submucosa. This suggests the possibility of autoinfection, or penetration and systemic migration by larvae originating in the gut. This may occur in *S. stercoralis* infections in humans and primates but is not confirmed in dogs.

*Strongyloides tumefaciens* in cats has been associated rarely with chronic diarrhea. It differs from the other species discussed above, however, being associated with the formation in the colon of submucosal nodules of proliferative glands infected by *Strongyloides*. It is uncertain whether this is a specific lesion induced by infection, or merely herniation of infected colonic glands into space left by involution of a submucosal lymphoid follicle.

TRICHOSTRONGYLOSIS. Members of the genus *Trichostrongylus* parasitize the anterior small intestine of ruminants the world over. They cause significant subclinical inefficiency in production, or clinical disease characterized by diarrhea, ill thrift, and in some cases, death. The most important species infecting sheep and goats are probably *T. colubriformis, T. vitrinus,* and *T. rugatus;* others include *T. longispicularis, T. falculatus, T. capricola,* and *T. probolurus. Trichostrongylus colubriformis* and *T. longispicularis* also parasitize cattle. Though some *T. axei* may be found in the duodenum of cattle and sheep, this species is primarily parasitic in the abomasum and has been considered earlier with parasites of that organ.

Trichostrongylosis is most important in zones with a cool wet climate at some time of the year, but without extreme winters. It is an extremely important problem in many sheep-grazing areas of New Zealand, Australia, South Africa, South America, and the United Kingdom in particular. Though gastrointestinal helminthosis is usually a mixed infection, *Trichostrongylus* often dominates and appears to be a significant pathogen in its own right.

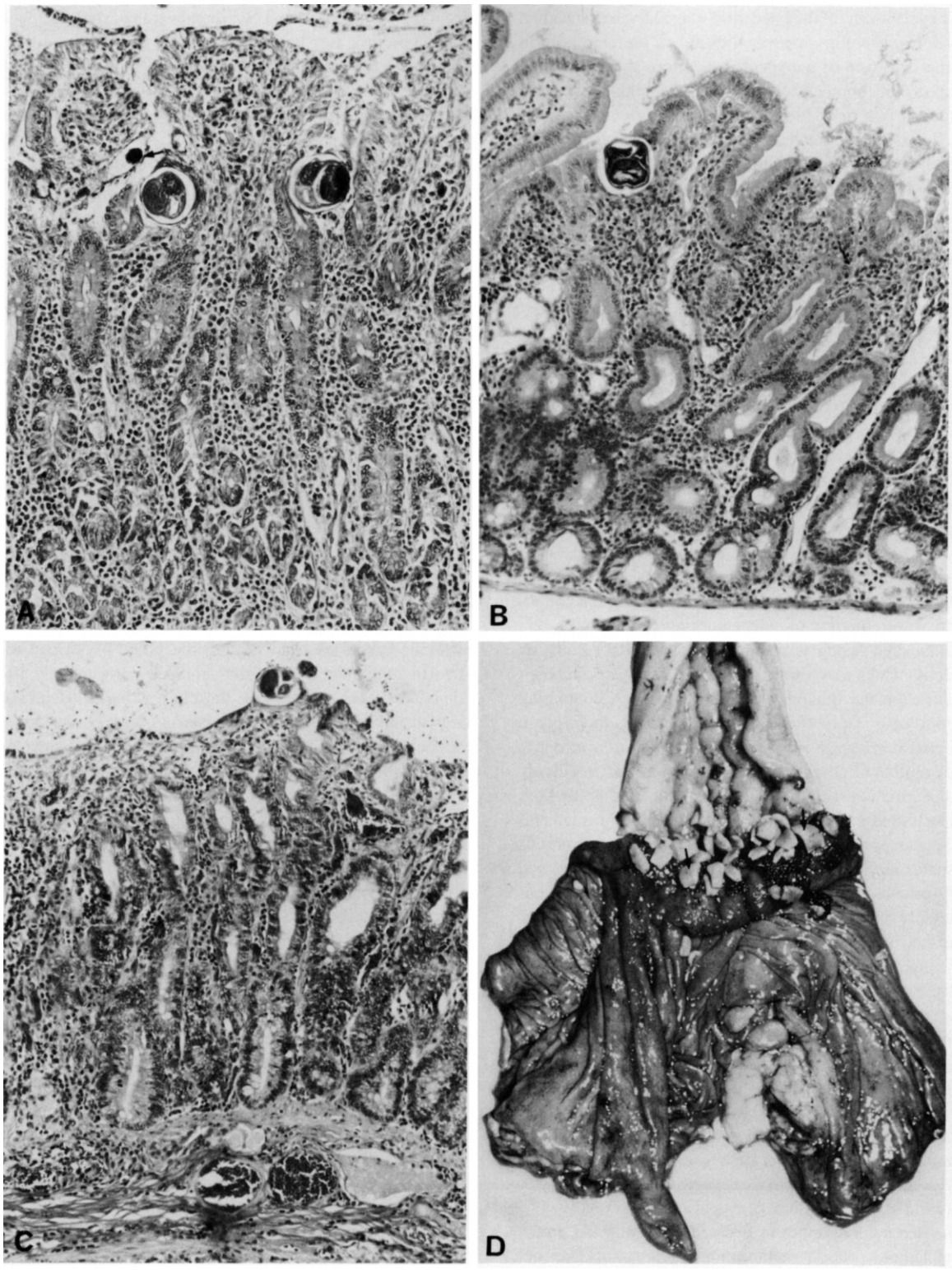


**Fig. 1.45.** (**A**) *Strongyloides westeri* in tunnels at base of a moderately atrophic villus. Intestine of foal with diarrhea. An ovum is in a tunnel on an adjacent villus (arrow). (**B**) Subtotal villus atrophy. *Trichostrongylus colubriformis*. Intestine. Sheep. Exfoliation of enterocytes, focal effusion of tissue fluid, dilated crypts, and mononuclear cells in lamina propria. (**C**) Severe villus atrophy in intestinal trichostrongylosis. Sheep. Surface epithelium is attenuated or eroded, and crypts are hyperplastic. Nematode in tunnel in surface epithelium. (**D**) *Anoplocephala perfoliata* (arrows) at ileocecal junction. Horse. Local ulceration and hemorrhage.

The life cycle is direct. Ingested third-stage larvae exsheath in the acid abomasal environment and establish preferentially in the proximal 5 to 6 m of the small intestine in sheep. A small proportion of the population settles in the abomasal antral mucosa near the pylorus. The larvae in the intestine enter tunnels above the basal lamina, between enterocytes, mainly at the base of villi, and they persist throughout their life at least partially embedded in the epithelium. Usually, infecting larvae all develop, over about 2 weeks, into adult worms, with a prepatent period of about 16 to 18 days. Hypobiosis appears to be relatively uncommon among members of the genus *Trichostrongylus*, and the circumstances by which it is stimulated are unclear. When it occurs, larvae are retarded in development at the parasitic third stage.

Experimental infections of all *Trichostrongylus* species studied indicate that the pathology and pathogenesis of disease caused by them is similar (Fig. 1.45B,C). Villus atrophy occurs in areas of intestine populated heavily by the worms, and the severity of the lesion within individual animals is correlated with the local density of the worms. The mechanism by which the atrophy occurs has not been investigated. In experimental infections, however, hyperplasia of cryptal epithelium seems to precede the onset of villus atrophy. It may be that the lesion is induced by cell-mediated immune mechanisms that stimulate proliferation by the epithelial proliferative compartment and interfere with differentiation of cells emerging from crypts.

The established lesion is characterized microscopically by villus atrophy, which may vary considerably in severity, in association with elongate, dilated, often straight crypts, containing many mitotic cells. Goblet cells may be numerous in crypts in some infected animals. In animals with subtotal villus atrophy, the surface epithelium may vary from tall columnar, relatively normal-appearing cells, to more domed or cuboidal epithelium lacking a well-defined brush border. Ultrastructurally, such epithelium appears poorly differentiated, containing numerous polyribosomes in the cytoplasm, and with stumpy, sparse, and irregularly oriented microvilli. The levels of brush-border enzymes, notably alkaline phosphatase, peptidases, and maltase, are diminished in affected areas of intestine. In animals with subtotal villus atrophy, exfoliating, rounded enterocytes are seen, as are focal and probably transient "leaks" of neutrophils and tissue fluids through the epithelial surface. In animals with more severe atrophy, the surface epithelium is flattened between the openings of crypts, and erosions of the mucosa may be evident, from which inflammatory cells and tissue fluid effuse.

The lamina propria in the affected area of intestine is populated by a moderately heavy mixed inflammatory cell population. Lymphocytes and plasma cells are prominent between crypts, with an admixture of eosinophils. Globule leukocytes may be present in the epithelium of crypts and occasionally villi, but this is often not marked in severely affected mucosa. In the superficial lamina propria, neutrophils often accumulate beneath the epithelium, and in areas of erosion or previous erosion, there may be a thin, transversely oriented layer of connective tissue. No specific attraction of inflammatory cells is evident to worms in tunnels in the surface epithelium. Abnormal permeability of the endothelium of capillaries and venules in heavily infected mucosa has been demonstrated, and edema of the lamina propria may be evident in these areas.

The disease is marked clinically by depression, inappetence that may be mild or profound, diarrhea, and wasting. The cause of the inappetence is unclear. It is suggested that it may be related to abormalities in levels of some gastrointestinal hormones, and it can be associated with concurrent gastric hyposecretion of acid and apparent atrophy of fundic parietal cell mass. The pathogenesis of the diarrhea is also uncertain. It too is associated with the period when inappetence and gastric dysfunction occur. Though local malabsorption of nutrients, and presumably electrolyte and water, occurs in the duodenum, it seems unlikely that the absorptive capacity of the remaining small intestine and large bowel would be overwhelmed.

Weight loss or reduced productive efficiency is not related to nutrient malabsorption, since net absorption of nutrients over the length of the small intestine does not seem to be severely affected. Rather, the interaction of reduced feed consumption with increased loss of endogenous nitrogen into the gut seems to be responsible. There is considerable effusion of plasma protein into the intestine of infected animals, and this, coupled with exfoliation of epithelium, which appears to be turning over at an increased rate, is the source of protein loss. The pathogenesis of protein-losing gastroenteropathy has been discussed earlier. In trichostrongylosis, compensation for increased catabolism of plasma protein and mucosal epithelial protein is at the expense of anabolic processes elsewhere in the body. Wool and muscle growth are hindered in subclinical disease. In severely affected animals, breaks in the wool, muscle wasting, reduced skeletal growth, and osteoporosis are related to reduced deposition, or catabolism, of somatic and cutaneous protein, associated probably with functional hyperadrenalcorticism. In addition, reduced mineralization of bone may be attributable to reduced intestinal absorption of calcium and phosphorus (see osteoporosis, in Bones and Joints, Volume 1). The pathogenesis of trichostrongylosis in calves and goats is similar to that in sheep.

Animals succumbing to trichostrongylosis are usually cachectic and dehydrated. Dark green, scoured feces will be on the skin or wool of the escutcheon or breech. There may be serous atrophy of internal fat depots, and marked atrophy of skeletal muscle. The subcutis is tacky. There may be edema of the mesentery and perhaps serous effusion into the body cavities, associated with hypoproteinemia, if dehydration is not severe. Mesenteric lymph nodes are enlarged and juicy. The content of the abomasum is abnormally fluid, and its pH may be greater than 4. The intestines are flaccid, and the small bowel contains thin, fluid, green content, which in the duodenum may appear somewhat mucoid. The large intestine may contain similar fluid or pasty green feces. These are usually foul smelling, probably due to products of bacterial action on protein.

The mucosa of the duodenum in the freshly killed animal may be glistening and pink, but in spontaneous mortalities with superimposed postmortem change, it will be unremarkable. Examination of the duodenal mucosa of freshly dead animals using a hand lens or dissecting microscope will reveal patchy or diffuse atrophy of villi, and fine white or translucent, threadlike worms, about 5–8 mm long, entwined on the mucosal surface. The

proximal third of the small intestine (about 5–7 m) contains the bulk of the population of *Trichostrongylus*. A worm count on the small bowel usually reveals 15,000–80,000 *Trichostrongylus* in severe clinical infections. Subclinical or mild disease may be associated with fewer worms. The diagnosis is based on recovery of substantial populations of *Trichostrongylus* in association with the clinicopathologic syndrome and villus atrophy described above. Mixed infections with other genera are common, and the additive effects of populations of several species of worms should be considered.

*NEMATODIRUS* AND *COOPERIA* INFECTION. *Nematodirus* species infect the anterior third of the small intestine of ruminants. The most important species are *N. helvetianus,* which infects cattle; *N. spathiger* and *N. filicollis,* which infect sheep, goats, and cattle; and *N. battus,* which is a parasite mainly of sheep.

The life cycle is direct. However, the hatch of infective larvae of *Nematodirus battus* and *N. filicollis* from the egg is delayed. Eggs of *N. battus* deposited on the ground in one year hatch the next spring, following a period of conditioning by cold over winter. The epizootiologic pattern is that of infection of a susceptible lamb crop during one year by larvae produced by the previous year's lambs. Under these conditions, with high availability of infective larvae, parasitic enteritis dominated by *Nematodirus* may occur. The larvae of *N. spathiger* and *N. helvetianus* are not delayed in hatching, and their epizootiologic pattern resembles that of *Trichostrongylus* in grazing animals. They often form part of a mixed population of worms in parasitic gastroenteritis in grazing lambs and calves. The disease may occur in yarded calves as well as animals at pasture.

Third-stage larvae enter the deeper layers of the mucosa, perhaps penetrating into crypts. Larvae emerge at the fourth or fifth stage to take up residence coiled among the villi, with their posterior ends protruding toward the lumen. They normally do not penetrate the epithelium.

The presence of large numbers of *Nematodirus* is associated with the development of villus atrophy, which is usually moderate in comparison with that induced by *Strongyloides* or *Trichostrongylus*. The villi are compressed by the pressure of entwined nematodes, and the impression of the longitudinal cuticular ridges is present on the surface of enterocytes adjacent to the worms. Local erosions may occur at such sites. Villi are stumpy, bifurcate, perhaps fused; or ridgelike surface alterations may replace the normal villous structures. Crypts may appear elongate and dilated. The surface epithelium may be domed, with loss of the prominent brush border, and irregular nuclear polarity. Ultrastructurally, such cells appear poorly differentiated and have irregular, defined microvilli. Biochemical studies reveal reduction in levels of mucosal alkaline phosphatase and disaccharidases, which correlate with the severity of diarrhea in affected sheep. If villus atrophy is severe, the ability of the worms to maintain their position may be compromised. They may enter crypts with their anterior end, move to more normal mucosa lower in the small bowel, or perhaps be lost from the gut.

The pathogenesis of the villus atrophy has not been determined, but it may be related to the development of immune responses to the presence of nematodes in the lumen. A moderate mixed inflammatory response with substantial numbers of lymphocytes, plasma cells, and eosinophils is evident in the lamina propria. The presence of such an infiltrate, and moderate shortening of villi associated with poorly differentiated surface enterocytes, is consistent with the postulated induction of villus atrophy by cell-mediated immune activity in the lamina propria.

Lambs and calves with nematodirosis develop severe dark green diarrhea, which stains the escutcheon or the breech of lambs. Affected animals may become inappetent, scour and waste for several weeks before recovering, or may die acutely. Disease is presumably mainly related to malabsorption and loss of appetite. Protein loss into the gut apparently has not been investigated. At necropsy, other than the changes associated with dehydration and perhaps cachexia, findings are limited to fluid mucoid content in the upper small intestine, and soft or fluid feces in the colon. The mucosa of the duodenum is usually unremarkable or perhaps hyperemic with excess mucus on the surface. Worm counts will reveal tangled, cottony masses of elongate, lightly coiled nematodes in heavy *Nematodirus* infections. Clinical disease is associated with populations of about 10,000 to 50,000 or more *Nematodirus* worms.

*Cooperia* infect the upper small intestine of ruminants. The important species include *C. curticei,* mainly in sheep and goats, and *C. pectinata, C. punctata,* and *C. oncophora,* mainly in cattle. Though both sheep and cattle may suffer from mixed burdens of helminths containing or dominated by populations of *Cooperia,* this genus seems to be most significant in cattle, especially in cool temperate regions. *Cooperia oncophora* appears to be less pathogenic for cattle than *C. pectinata* or *C. punctata.*

*Cooperia* has a typical trichostrongylid life cycle, but larvae do have the capacity to undergo hypobiosis to carry the population through periods of regular climatic adversity. The normal prepatent period is about 16–20 days. Like *Nematodirus, Cooperia* does not tunnel in the epithelium, but rather the worms brace or coil themselves among villi to maintain their place in the intestine. In sections, the compression of epithelium adjacent to the worms, and the impressions left on enterocytes by the longitudinal cuticular ridges, are apparent. In light infections, the worms are concentrated in the anterior third of the small intestine. Heavier infections, perhaps because they are associated with villus atrophy and therefore loss of the substrate against which to brace, are more evenly distributed down the intestine.

Heavy burdens of *Cooperia* in calves, in excess of 70,000 to 80,000 nematodes, may be associated with reduced weight gain, or weight loss and diarrhea. The associated atrophy of villi is concomitant with reductions in the brush-border enzymes. The syndrome is typical of intestinal helminthosis, and the diagnosis is confirmed by finding large numbers of the fine, coiled *Cooperia* in the small intestine.

HOOKWORM INFECTION. Members of the Ancylostomatidae infect dogs, cats, ruminants, and swine. Hookworms of the genus *Globocephalus* appear to be of little significance in swine. In dogs, *Ancylostoma caninum, A. braziliense,* and *A. ceylanicum* occur. The former is most common in tropical, subtropical, and warm temperate zones of Africa, Austrialia, Asia,

and North America, where adequate humidity for larval development occurs. *Ancylostoma braziliense* occurs in dogs and cats in the tropics and subtropics, while *A. ceylanicum* is found in both species in Sri Lanka and Southeast Asia. *Uncinaria stenocephala* occurs in dogs in cool temperate regions of Europe and North America. *Ancylostoma tubaeformae* occurs only in the cat.

Members of the genus *Ancylostoma* are capable of infecting the host by four routes: orally, with direct development to adult worms in the intestine; by skin penetration, resulting in movement through the bloodstream to the lungs, and thence via the trachea to the pharynx and gut; by the lactogenic transmission of third-stage larvae mobilized from dormancy in the skeletal muscle of parturient bitches; and in occasional instances, by prenatal transplacental transmission of mobilized larvae in pregnant bitches. The latter route of transmission does not apparently occur in *A. braziliense* infection. Some larvae of *A. caninum* may become arrested at the third stage in the intestine, to resume development at a later time.

*Ancylostoma* species all usually inhabit the small intestine, where they move about the surface, several times a day attaching to feed, then moving on. They penetrate deeply into the mucosa, sometimes to, or through, the muscularis mucosa, taking a plug of tissue into the large buccal capsule. Tissue is lacerated by the prominent teeth, and anticoagulant is released permitting persistent blood flow. Bloodsucking activity begins when larvae enter the adult stage, in *A. caninum* ~8 days after infection. Blood loss is maximal while worms are attaining maturity, between 12 and 16 days after infection, and then again during the peak period of egg production, after ~$3\frac{1}{2}$ weeks of infection. The prepatent period for *A. caninum* is ~15 days.

Ancylostomosis is the result of persistent blood loss, resulting in anemia and hypoproteinemia. There is considerable variation in the bloodsucking activity, and therefore the pathogenicity, of the members of the genus. *Ancylostoma caninum* consumes in the range of 0.01 to 0.2 ml of blood per worm per day. The amount of blood lost per worm is least in heavier infections. Pups several months old with populations of the order of 300 to 400 worms may lose 10 to 30% of their blood volume per day, depending on body weight. *Ancylostoma ceylanicum* also causes anemia, but *A. braziliense* seems to cause insignificant blood loss. *Ancylostoma tubaeformae* in cats is a significant bloodsucker. Experimentally, ~200 worms may cause anemia, weight loss, and mortality in 1.5-kg cats. The anemia in ancylostomosis is at first normochromic and normocytic. If adequate iron reserves and hematopoietic capacity are mustered, the animal may be able to equilibrate the rate of red cell production with the increased rate of loss, stabilizing the mass of the reduced circulating red cell population. Small size, poor iron reserves, and the low level of iron in bitch's milk make suckling pups with ancylostomosis susceptible to rapid development of the microcytic hypochromic anemia characteristic of iron deficiency.

Acute fatal ancylostomosis occurs most commonly in pups only 2–3 weeks of age, infected via the bitch's milk. Heavy infections acquired by this route may result in death from anemia and hypoproteinemia within a few days of the initiation of bloodsucking activity, and before eggs are present in the feces. Anemia may also lead to mortality of pups after a course of longer duration. Percutaneous infection results in disease in older dogs held in runs or kennels under conditions of moisture and temperature conducive to larval development on the ground. Dermatitis due to larval penetration may be observed between the toes or on ventral contact surfaces of the body. The condition is usually typified by anemia, lack of exercise tolerance, weakness, and emaciation. Feces may be diarrheic, dark red or black, and often mucoid. Though diarrhea may occur, and there is some evidence for mild malabsorption and subtle atrophy of the intestinal mucosa, the major effect of ancylostomosis is due to increased loss of erythrocytes, iron, and plasma protein.

Animals dying of ancylostomosis are characteristically extremely pale. There is often glistening edema of subcutaneous tissues and mesenteries, and serous effusion into body cavities, attributable to hypoproteinemia. In chronic infections, cachexia may be evident. If recent exposure to heavy percutaneous infection has occurred, there may be dermatitis and numerous focal hemorrhages scattered in the pulmonary parenchyma, reflecting disruption of vessels by larvae breaking out into alveoli. The liver has the blotchy pallor of anemia. The intestinal content throughout the entire length is mucoid and deep red, from the erythrocytes voided into it by the worms. The latter are visible, about 1.0–1.5 cm long, translucent, gray or red (depending on when they last consumed blood), and dispersed over the mucosa, sometimes into the large intestine. They are often attached to the mucosa, and pinpoint, red sites of recent feeding activity may be scattered over the intestinal surface. Relatively few *Ancylostoma caninum* worms are required to cause death. In a young pup, as few as 20 to 50 may be present in fatal infections, and they may be sufficiently sparsely scattered as to be overlooked if not sought. In older animals with chronic or more acute fatal disease, 300 to 400, or less commonly, several thousands of worms, may be present.

*Uncinaria stenocephala* infects mainly by the oral route; percutaneous infection is not efficient, though dermatitis may result; and prenatal and lactogenic transmission appear not to occur. This species sucks little blood and is much less pathogenic than *Ancylostoma caninum*. Heavy infections with this species, however, arising usually in contaminated communal kennel environments, may cause clinical disease and, occasionally, mortality in pups. Nonspecific lethargy, inappetence, and ill thrift are signs of infection, perhaps with diarrhea; anemia does not occur. Disease is associated with burdens of a thousand or more worms, each about 5–10 mm long, in the small intestine. Worms may be particularly distributed in the distal small bowel in heavy infections and are often embedded in the mucosa in freshly dead animals. The intestinal mucosa appears thickened, and focal hemorrhages at sites of attachment may be scattered over it.

The presence of large numbers of worms is associated with moderate atrophy and thickening of villi. The surface epithelium is irregular. Focal aggregates of mononuclear cells and some neutrophils are in the vicinity of the anterior ends of worms embedded deep in the mucosa, a plug of tissue within their buccal cavity. It seems that disease due to *Uncinaria stenocephala* may be related to villus atrophy, perhaps with malabsorption and protein loss into the gut, since hypoproteinemia,

but not anemia, may be evident. A similar syndrome may be associated with heavy infections of *Ancylostoma braziliense*, in which hypoproteinemia also occurs.

The **hookworms** of **ruminants** include, in cattle, *Bunostomum phlebotomum*, and in India and Indonesia, *Agriostomum vryburgi;* in sheep, *B. trigonocephalum*, and in India and Southeast Asia and Africa, *Gaigeria pachyscelis*. The life cycle of these nematodes is typical of hookworms. *Bunostomum* third-stage larvae infect by the oral or percutaneous routes, while *Gaigeria* infects only across the skin. Eggs and larval stages on the ground are extremely susceptible to desiccation, and hookworm disease in ruminants is most common in tropical or subtropical areas during wet seasons. However, stabled animals in cooler temperate areas may suffer disease resulting from larvae invading the skin from contaminated bedding. Following skin penetration, the usual pattern is seen, with migration of larvae to the lungs, where they molt to the fourth stage, subsequently passing up the trachea to the digestive tract. Larvae taken in by ingestion spend some time in the deep mucosa of the intestine before emerging to mature in the lumen of the small intestine. The prepatent period of *Bunostomum* is long, about 7–8 weeks. *Gaigeria* larvae migrate via the lungs, and worms begin to lay eggs ~10 weeks after infection.

Both *Bunostomum* and *Gaigeria* cause hemorrhagic anemia and hypoproteinemia, especially in animals under a year of age. These species often occur with mixed gastrointestinal helminth burdens, and their effects are at least additive to those of the other worms. They may be primary pathogens. Several hundred *Bunostomum* worms may cause signs in lambs, and a few hundred to a few thousand are found in clinical or fatal infections in calves. As few as 20 to 30 *Gaigeria* worms will cause anemia and hypoproteinemia in lambs, though several times that number may be more usual in fatal cases. The size of the animal, the status of its iron reserves, and the plane of nutrition, especially the level of protein, likely influence the pathogencity of these species.

At autopsy, the lesions expected in anemia and hypoproteinemia are evident. *Bunostomum* are found often in the lower half of the small intestine, while *Gaigeria* tends to be concentrated high in the duodenum. Blood spots and bite marks may be evident on the mucosa in the infected areas of intestine, but hemorrhage may be occult. The relatively low numbers of worms associated with disease, and their peculiar distribution, dictate that the entire gut be examined and flushed and a careful search be made for these species in suspect cases. Haemonchosis may occur concurrently or should be eliminated as a diagnosis, as should fascioliasis, and in cattle, *Oesophagostomum radiatum* infection.

*TRICHURIS* INFECTION. *Trichuris* species, the whipworms, are so called because of their long, thin anterior end and shorter, stouter posterior portion. They inhabit the cecum and, occasionally, the colon of all the domestic animals considered here, except the horse. The host–parasite relationships include, in dogs, *T. vulpis;* in cats, *T. campanula* and *T. serrata;* in swine, *T. suis;* in sheep and goats, *T. ovis, T. globulosa,* and *T. skrjabini;* in cattle, *T. discolor* and, less commonly, *T. ovis* and *T. globulosa*.

The life cycle is direct. Larvated ova are resistant to climatic insult and persist in contaminated environments for several years. Ingestion of larvated eggs leads to release of third-stage larvae, which enter the mucosa of the anterior small intestine for up to 7 to 10 days before returning to the lumen and passing on to the cecum, where they establish their adult existence. The prepatent period varies from about 6 to 7 weeks in the case of *T. suis* to 11 to 12 weeks for *T. vulpis*. In rare instances, disease may occur during the prepatent period, in which case ova will not be in the feces.

In all species the anterior ends of the worms are embedded at least partially in tunnels within the surface epithelium (Fig. 1.50E), but not normally breaching the basal lamina. Light infections apparently cause little morphologic alteration in the mucosa, and no disease. While *Trichuris* worms are reputed to ingest blood, disease associated with them is not related to this activity. Moderate infection of *T. vulpis* in dogs, at least, is associated with a mild mucosal colitis. There is a moderate mixed inflammatory infiltrate in the lamina propria between glands. Superficial vessels are congested, and scattered neutrophils may be present in the lamina propria beneath the surface epithelium. There is at least focal loss of goblet cells on the surface. These are replaced by low columnar or cuboidal cells, some of which may be exfoliating. Focal erosion may also be evident, and effusion of a few neutrophils and tissue fluid is evident through "leaks" or erosions on the surface. Goblet cells may be sparser than normal in glands in affected areas, which often appear longer than usual, and are lined by hyperplastic epithelium.

Heavy infection with *Trichuris* is associated with severe and often hemorrhagic typhilitis or typhlocolitis in all species. In the dog, large populations of worms overflow their normal habitat and infect the mucosa of the ascending, and often more distal, colon, sometimes extending to the rectum. The signs are chronic diarrhea or dysentery, perhaps with some weight loss. The blood and foul odor of the feces is related to hemorrhage and effusion of tissue fluid from the eroded mucosal surface. The mucosa is thickened, red, and edematous. The colonic content is fluid or porridge-like, and brown, tinged pink or red. Masses or tangled worms are visible on the mucosa (Fig. 1.50D). Microscopically, the mucosa is widely eroded or mildly ulcerated, and effusion of inflammatory exudate and blood is evident. Glandular epithelium is hyperplastic. Occasionally, *T. vulpis* infection may be associated with local or regional transmural lesions, with granulomatous foci and fibroplasia in deeper layers of the mucosa. Sometimes ova or worms are in these aberrant locations. Other transmural lesions may be the result of bacteria entering through mucosa damaged by *Trichuris*. *Balantidium* infection has been reported as a rare complication of *Trichuris* infection, in dogs with access to swine yards.

*Trichuris suis* infection in swine, if heavy enough, may cause mucohemorrhagic typhlocolitis associated with anorexia, diarrhea or dysentery, dehydration, ill thrift, and in some cases, death. The disease is most common in animals exposed to dirt yards contaminated with infective *Trichuris* ova. The lesion is one of mucosal colitis, resembling that described in the dog. There is thickening of the mucosa, with ultimate mucus hypersecretion from hypertrophic glands, coupled with erosion of,

and effusion from, the mucosal surface. Lesions are more severe in swine with conventional gut flora than in those reared germ free or free of known enteric pathogens. Some contribution of the normal anaerobe flora to the development of lesions more severe than mild catarrhal colitis is apparent.

The large bowel in swine with *Trichuris* is thickened and congested, possibly with focal hemorrhages. The surface is glistening with mucus, perhaps with some fibrin exudation. The appearance may resemble that found in swine dysentery. Since the microscopic lesions are similar, this is logical. However, closer examination at autopsy will reveal the presence of the nematodes over the mucosa. Usually the thicker posterior ends of the worms are noted. They may resemble at first glance *Oesophagostomum,* and only on more careful observation is the elongate, threadlike anterior end seen.

The signs of the disease appear to be referable to loss of colonic absorptive function, and probably partly to effusion of protein into the lumen. Though erythrocyte loss does occur, it is a minor component of the pathogenesis.

Trichurosis in sheep and cattle resembles that described in swine. The disease usually occurs in animals concentrated in areas contaminated by ova. Hence it may occur in stabled or yarded calves or cattle. Outbreaks in sheep may be associated with hand feeding or congregation of animals at watering points. Affected animals develop chronic diarrhea with brown feces or dysentery and loss of condition. At autopsy the lesions are those of cachexia and hypoproteinemia, associated with a mucohemorrhagic typhlitis or typhlocolitis.

A diagnosis of trichurosis in all species is usually readily made at autopsy. The worms have a characteristic morphology and are usually easily seen on the inflamed mucosal surface. In section, the thin anterior end of the nematodes, embedded in tunnels in the surface epithelium, contains the stichosome esophagus typical of members of the Trichuroidea. The ova may be seen in the body of worms, in the gut lumen, or occasionally in tissue. They are barrel-shaped, have a thick wall, and plugs at both poles of the egg. *Capillaria* worms and ova may be similar in tissue section but are not expected in the cecum and colon of domestic animals.

*OESOPHAGOSTOMUM* AND *CHABERTIA* INFECTION. Members of the genus *Oesophagostomum* infect sheep, cattle, and swine. Their pathogenic effects are related to the formation of inflammatory nodules in the wall of the intestine incited by histotropic stages, and to ill thrift and diarrhea induced by adult populations in the lumen of the colon.

In sheep, two species, *Oesophagostomum columbianum* and *O. venulosum,* are probably most significant; the former is considerably more pathogenic and is particularly important in warm temperate to tropical areas. Third-stage *O. columbianum* larvae penetrate deep into the lamina propria, or sometimes to the submucosa, mainly in the small intestine, where they normally spend a week or so. They molt, emerge, and mature in the colon. However, a proportion of fourth-stage larvae enter a second histotropic phase in nodules in the colonic submucosa. Adult worms in the colon may be pathogenic for lambs. Burdens of only a few hundred *O. columbianum* worms are associated with anorexia, mucoid feces or diarrhea, and ill thrift, associated perhaps with hypoproteinemia. The effects of infection may be exacerbated by intercurrent malnutrition.

At autopsy of animals with clinical oesophagostomosis, the carcass is emaciated, the mesenteric lymph nodes are enlarged, and the colonic mucosa is thickened, congested, and covered by a layer of mucus in which the worms are scattered. There is hyperplasia of goblet cells, and the lamina propria contains a heavy mixed inflammatory infiltrate with eosinophils and many immune-active cells. Globule leukocytes are in epithelium of glands. Nodules caused by histotropic fourth-stage larvae, mainly in the large intestine, are 0.5–3 cm in diameter and comprise a central caseous or mineralized core surrounded by a thin, fibrous, encapsulating stroma. Microscopically, the nematode or its remnants are present among a mass of necrotic debris in which eosinophils are prominent. Giant cells and macrophages may surround the necrotic material. Similar nodules may be found in liver, lungs, mesentery, and mesenteric lymph nodes. Those in the deeper layers of the gut project from the serosal surface, hence the name "pimply gut." They may cause adhesion to adjacent loops of gut or to other organs, and rarely may incite intussusception or peritonitis. In most cases, however, nodules are incidental findings at autopsy. They are probably the response to histotropic fourth-stage larvae in hosts sensitized by third-stage larvae, or the result of prior infection. The nodules caused by the histotropic third stage consist of small concentrations of suppurative exudate, which resolve as minor foci of granulomatous inflammation after the evacuation of the larvae. *Oesophagostomum venulosum* is a much less significant parasite. It seldom causes significant nodule formation; when it does, the nodules are small and mainly in the cecum and colon. Adult worm burdens are usually not considered particularly pathogenic.

In cattle, two species, *Oesophagostomum radiatum* and *O. venulosum* occur, the former being the significant parasite. The life cycle is similar to that of *O. columbianum.* The disease caused by *O. radiatum* is characterized by loss of appetite, reduced productive efficiency, anemia, hypoproteinemia, and diarrhea. Anemia results from hemorrhage at sites of larval emergence, and from mucosal erosions and discontinuities in the gland lining, associated with maturing and adult populations of worms. Blood loss is exacerbated by impaired coagulation, probably the result of consumption of clotting factors, the iniating mechanism for which is unclear. Considerable exudation of tissue fluids and plasma protein from colonic lesions, in addition to that due to hemorrhage, contributes to the hypoproteinemia and gastrointestinal protein loss. Reduced growth, or loss in condition, is mainly the product of the interaction between protein effusion into the gut and inappetence. Diarrhea presumably results in part from loss of colonic absorptive capacity.

Oesophagostomosis may be fatal in calves. Animals may be pale from anemia, and edematous from hypoproteinemia. Cases of some duration will be cachectic. Colonic lymph nodes are enlarged. The mucosa of the colon is grossly thickened and folded by edema and increased mixed inflammatory cell infiltrates, including many immune-active cells, in the lamina propria. Colonic submucosal lymphoid follicles are large and active. Effusion of tissue fluid and blood cells may be evident through small leaks between cells, or from erosions in glands or

on the surface. Pathogenic burdens in calves are in the range of about 1000 to 10,000 *Oesophagastomum radiatum* worms. Although repeated exposure to infective larvae may result in the accumulation of large numbers of fourth-stage worms in nodules, formation of nodules has little pathogenic significance in cattle.

In swine, *Oesophagostomum dentatum, O. quadrispinulatum,* and several other species occur in the large intestine; the two mentioned are most widespread. The life cycle is typical of the genus. Third-stage larvae enter the wall of the cecum and colon, where they encyst and molt to the fourth stage, emerging about a week later to mature in the lumen. The larvae initially lie about the level of the base of the mucosa. They incite a reaction causing local loss of the muscularis mucosae, so that the nodule formed involves both mucosa and submucosa, and the larvae ultimately reside in the submucosa. The nodules are grossly about 1–20 mm in diameter, umbilicate, and may contain yellow or black, cheesy exudate in the center. An eosinophilic "cyst" wall surrounds the third-stage larva. Nearby lymphatics may undergo thrombosis. Once the larvae molt and begin to move to the lumen, an intense influx of eosinophils and neutrophils occurs into the nodules, and a focus of necrotic debris and fibrin lies over the evacuated nodule. Mucosal and submucosal edema cause thickening of the wall of the large bowel and contraction of the cecum. Gross and microscopic lesions resolve over the ensuing weeks as most larvae leave the mucosa.

Oesophagostomosis in swine is a mild, usually subclinical disease. Occasional diarrhea, depression in weight gain, and inefficiency of feed conversion may occur, especially during the period of emergence of larvae and maturation of worms in the lumen of the large intestine. Burdens of about 3000 to 20,000 adult worms are associated with subclinical disease experimentally. The nematodes are about 1–2 cm long, white, and present in mucus on the surface of the gut or in luminal content. Occasionally, infection with *Oesophagostomum,* particularly mucosal damage precipitated by larval encystment, may predispose to necrotic enteritis in association with anaerobic flora and perhaps *Balantidium.* Massive repeated challenge will cause severe typhlocolitis, but this seems to be purely an experimental phenomenon. Mortality should rarely, if ever, be ascribed to esophagostomosis in pigs.

*Chabertia ovina,* a robust worm about 1–2 cm long, inhabits the colon of sheep, goats, and cattle. It is particularly a problem in cooler climatic zones, mainly in sheep. The life cycle resembles that of *Oesophagostomum,* third-stage larvae encysting in the wall of the small intestine, then emerging to mature in the cecum and colon. Disease in sheep is associated with the presence of mature worms in the colon. Feces are soft, mucoid, and perhaps blood flecked, and ill thrift may occur. The adults penetrate to the muscularis mucosae and take a plug of mucosa into the buccal capsule; minor hemorrhage may be related to physical trauma to the mucosa. More significant is loss of plasma protein from the mucosa, associated with numerous focal sites of trauma, and widespread areas of mononuclear infiltration in the mucosa and submucosa. There is also hyperplasia of goblet cells. Grossly, the lesions are characterized by edema of all layers of the wall of infected parts of the colon, and enlargement of colonic lymph nodes. Worms are generally concentrated in the proximal portion of the spiral colon, and the area they inhabit may have numerous hemorrhagic foci corresponding to sites of former attachment. Pathogenic burdens may be as few as 150 worms, and the species must be sought in its usual site of predilection or be missed.

EQUINE STRONGYLOSIS. Members of the Strongylidae are abundant and common nematode parasites of the cecum and colon in horses, usually present as mixed infections. The subfamily Strongylinae are the large strongyles, including the important genus *Strongylus* and the less significant genera *Triodontophorus, Oesophagodontus,* and *Craterostomum.* Members of this group are plug feeders or bloodsuckers, and *Strongylus* species undergo extensive extraintestinal migrations. The subfamily Cyathostominae, or small strongyles, includes eight genera of nematodes, among several of which the species of the superseded genus *Trichonema* have now been dispersed. Adults of this group feed mainly on intestinal contents and are of little pathogenic significance. However, emergence of histotropic larval stages from the gut wall may cause disease.

*Strongylus vulgaris* is common and the most significant nematode parasitic in horses. Larval forms cause endoarteritis in the mesenteric circulation, resulting in colic and thromboembolic infarction of the large bowel, while the adults cause anemia and ill thrift. Infective third-stage larvae, ingested from pasture, penetrate the mucosa of the small and large intestine and molt to the fourth stage. They enter the lumina of small arterioles, up which they migrate, on or under the intima, to reach the cranial mesenteric artery within 3 weeks. Three or four months later, after molting in that location to the fifth stage, the immature adults return down the mesenteric arteries to the wall of the cecum or colon, where they encapsulate in the subserosa, forming nodules about 5–8 mm in diameter. Returning larvae in nodules are surrounded by necrotic debris, neutrophils, some eosinophils, and perhaps some macrophages, and the adjacent arteriole may be thrombosed. They eventually break into the lumen of the large bowel, especially cecum and right ventral colon, where they mature in another month or two, about 6–7 months after infection. Some larvae may become trapped and encapsulated in arterioles in the mesentery on their way back to the gut and remain there to eventually die.

Endoarteritis associated with migration and establishment of larvae in the cranial mesenteric artery and its branches is discussed with the Cardiovascular System (Volume 3), as are the consequences of aberrant migration in the aorta, coronary artery, brachiocephalic trunk, and spermatic and renal arteries. Lesions of the cranial mesenteric artery and of the cecal and colic arteries may lead to colic as a result of reduced perfusion or thromboembolism, or perhaps due to impingement on autonomic ganglia in the vicinity of the arterial root at the aorta. The recognition and diagnosis of infarctive lesions of the equine bowel, and their sequelae, have been discussed with ischemia and infarction of the intestine. Though many older horses are infected with adult worms, or have arterial lesions, the complications of colic and infarction caused by this parasite are most common in young horses. An acute syndrome, characterized by pyrexia, anorexia, depression and weight loss, diarrhea or constipation, colic, and infarction of intestine, occurs in foals in-

fected with large numbers of larvae, but not often in animals previously exposed to infection.

*Strongylus edentatus* is also common and has a life cycle characterized by extensive larval migration. Third-stage larvae enter the intestinal wall and pass in the portal system to the liver, where they incite inflammatory foci. Here they molt to the fourth stage, and ~30 days after infection, begin migrating through the hepatic parenchyma. The foci of inflammatory reaction in the liver are probably related to antigens released by migrating and trapped larvae. They consist of a core of necrotic eosinophils, with a surrounding fibrous capsule, a mixture of neutrophils, eosinophils, and mononuclear cells, or recent necrotic foci or tracks infiltrated by neutrophils and a few eosinophils.

By 8 to 10 weeks after infection, larvae are migrating from the liver via the hepatic ligaments. Hemorrhagic tracks may be produced in the hepatic parenchyma. Parenchymal scars and tags of fibrous tissue on the hepatic capsule, especially the diaphragmatic surface, commonly found at autopsy, are the legacy of migrating *Strongylus edentatus*. Those migrating in the hepatorenal ligament enter the retroperitoneal tissue of the flank, where they are frequently encountered, often associated with local hemorrhage. Larvae in aberrant locations in the omentum, hepatic ligaments, and diaphragm may become encapsulated in eosinophilic granulomas and destroyed. Omental adhesions may also be a sequel to aberrant larval migration. In the flank, larvae persist for several months, molting to the fifth stage before returning from the right flank via the cecal ligament to the cecum and origin of the colon. There they form nodules and hemorrhagic foci in the wall of the gut, eventually perforating to the lumen, where they mature and begin to lay eggs about 10–12 months after infection. Lesions associated with the larval migration of *S. edentatus* are usually incidental findings at autopsy.

*Strongylus equinus* is relatively less prevalent and abundant than the other two members of the genus. Exsheathed third-stage larvae penetrate to the deeper layers of the wall of the cecum and colon, molt to the fourth stage, and produce hemorrhagic subserosal nodules before moving to the liver through the peritoneal cavity. They migrate in the hepatic parenchyma for 6 to 7 weeks, then leave the liver, probably via the hepatic ligaments, to the pancreas and peritoneal cavity, where they molt to the fifth stage ~4 months after infection. They regain the lumen of the cecum, and to a lesser extent, the colon, by an unknown route, probably by direct penetration from the peritoneal cavity or pancreas. Eggs appear in the feces of the horse about 8–9 months after infection. Larval migration by this species causes lesions in the bowel wall and hepatic parenchyma similar to those produced by *S. edentatus*.

**Hemomelasma ilei** is the term applied to slightly elevated subserosal hemorrhagic plaques, up to 1 to 2 by 3 to 4 cm in size, found usually along the antimesenteric border of the distal small intestine or, rarely, on the large bowel. They are associated with trauma by migrating larvae of *Strongylus edentatus* in particular but may be caused by larvae of any species of *Strongylus*. These lesions are composed of edema, hemorrhage, and a mixed population of leukocytes, with macrophages ingesting erythrocytes prominent in evolving lesions. Occasionally a fragment of nematode or cuticle, or a migration track, may be found in section. With time these lesions resolve to yellow, brown, or tan fibrotic plaques, as red cells engulfed by macrophages are destroyed and the products of hemoglobin breakdown reduced to iron and bile pigments and removed from the site, which scars. The presence of hemomelasma ilei is sometimes associated with clinical, but nonfatal, colic. The lesion is not uncommon as an incidental finding, however, and probably is a rare cause of clinical signs.

The other genera in the Strongylinae, *Triodontophorus, Oesophagodontus,* and *Craterostomum,* have life cycles that probably involve local migration of developing larvae into the deeper layers of the mucosa or the submucosa in the large intestine. Here they form small nodules before emerging to mature in the lumen of the cecum and colon. Larval members of these genera may contribute to the syndrome associated with emergence of larval cyathostomes, described below.

Adults of all species in the Strongylinae are plug feeders and bloodsuckers. In sufficient numbers they may cause ill thrift, and perhaps anemia, as the result of active hematophagia and blood loss from recent sites of feeding activity. Increased albumin catabolism causing accelerated turnover of the plasma pool, and reduced red cell survival, have been demonstrated in horses infested with relatively low numbers (<100) of *Strongylus vulgaris*. *Triodontophorus tenuicollis,* the most important species of that genus, tends to attach to the mucosa in clusters, usually in the right dorsal colon, causing local congestion and ulceration. *Triodontophorus* may be associated with significant blood loss.

The small strongyles, or cyathostomes, are essentially nonpathogenic as adults, despite the fact that tens or hundreds of thousands may be in the content of the large bowel and may browse on the mucosal surface to some extent. The larval stages migrate into the deep mucosa or submucosa of the large bowel to molt and develop before emerging to the lumen to molt again and mature. In the mucosa they are surrounded by a fibrous capsule, and there may be a moderate mixed inflammatory reaction containing eosinophils in the mucosa and adjacent submucosa. A similar but more intense reaction is seen around larvae in the submucosa. Emergence of larvae causes rupture of the muscularis mucosae and intense local eosinophilia and edema, followed by infiltration of neutrophils and macrophages. The larvae of some species may undergo hypobiosis or retarded development, persisting in the mucosa, only to mature sporadically, or perhaps more synchronously, as the adult population in the lumen turns over or is lost.

Mucosal nodules are up to only a few millimeters in diameter, slightly raised, red or blackish, and maybe umbilicate. Incision reveals a small, translucent, gray or red larval nematode. In heavy infections, the mucosa of the cecum and colon may be diffusely pocked by such nodules, which may attain a density of up to 60 per square centimeter.

Disease attributable to larval cyathostomes usually occurs in heavily infected horses at the time of turnover of the adult population and is due to emergence of large numbers of hypobiotic larvae over a short period. This occurs in the late winter, spring, and early summer in northern temperate climates. It is a disease of horses over a year of age. Little resistance is apparent to repeated infection. Animals develop a syndrome characterized by diarrhea, ill thrift or cachexia, and hypoalbuminemia, per-

haps with passage of immature cyathostomes in the feces. In animals dying or killed at this time, numerous nodules, containing immature cyathostomes or recently ruptured, are present in the mucosa of the cecum and colon. The mucosa and submucosa are edematous, and the mucosa congested. If mucosal damage is severe, there may be a fibrinous exudate on the eroded or ulcerated surface. Many recently emerged fourth-stage or early fifth-stage larvae may be in the luminal content. The cecal and colic lymph nodes may be enlarged and wet, and the mesentery of the large bowel edematous. Diarrhea and wasting are presumably due to reduced absorptive function, and loss of protein is associated with the damage to the colonic mucosa caused by emerging larvae.

ASCARID INFECTION. Members of the Ascaridae are common and important parasites of swine, horses, dogs, cats, and to a lesser extent, cattle. They do not occur normally in sheep and goats. Their importance is related to incidental and sometimes significant lesions caused by larvae during migration in the tissues of definitive and accidental hosts, and to the effects of adult worms in the small intestine of the definitive host.

*Ascaris suum* is a large parasite, females measuring up to 40 cm long, usually found in the upper half of the small intestine of swine. The life cycle is direct. Infective larvae, present in the resistant egg, are released in the intestine and penetrate the mucosa to be carried in the portal blood to the liver. They then pass to the lungs in the blood and break out of capillaries into alveoli. Third-stage larvae may be found in liver and lung 3–5 days after infection. Larvae move up the respiratory tree to the pharynx, where they are swallowed, arriving in the intestine about a week after infection. Worms mature in the intestine and begin to lay eggs ~2 months after infection. Small doses of eggs more commonly give rise to patent infections than large doses. This probably results from excessive loss of migrating larvae due to resistance incited by the antigenic mass of the heavier infections.

Larval migration induces lesions in the liver and lungs (Fig. 1.46). Infections heavy enough to cause clinical signs are rare in swine reared under conditions of good hygiene and husbandry. However, respiratory signs characterized by dyspnea (commonly termed "thumps") may occur in piglets if large numbers of larvae migrate through the lungs. Gross lesions in pigs, associated with pulmonary migration of ascarids, are limited largely to numerous focal hemorrhages scattered over and through the pulmonary parenchyma. There may be some edema, congestion, and failure of the lung to collapse at autopsy, due to bronchiolar constriction and alveolar emphysema.

Microscopically, there is an eosinophilic bronchiolitis. Bronchioles are surrounded by macrophages and eosinophils, and the bronchiolar mucosa is thrown into small folds, the epithelium frequently disorganized or perhaps eroded. The bronchiolar wall is infiltrated by eosinophils, which are also present, with necrotic debris, in the lumen. The architecture of small airways may be obscured or obliterated by the reaction, the outlines of some bronchioles recognizable only by the persistent smooth muscle of the wall. Interstitial infiltrates of eosinophils and macrophages are most dense about bronchioles, but diffuse out into surrounding parenchyma, thickening alveolar septa and diminishing the size of alveoli. Small branches of the pulmonary artery are also cuffed by eosinophils, lymphocytes, and macrophages, and eosinophils may be seen transmigrating the wall of vessels.

Larvae are usually readily found in section. They may be present in alveoli, alveolar ducts, bronchioles, or bronchi, perhaps surrounded by eosinophils. In more chronic cases, larvae in tissue are in eosinophilic granulomas. The worms may be dead in cases of some standing and are recognized only as an eosinophilic remnant or some bits of cuticle. Like all larval ascarids of mammals, *Ascaris suum* in the lungs have lateral alae visible in section.

Lesions in the liver due to migrating *Ascaris suum*, though not causing clinical disease, do result in considerable economic loss from condemnation at meat inspection. At first exposure to larvae, the lesions are related to mechanical damage caused by the worms, subsequent repair, and hypersensitivity reactions to excretory and secretory products of the larvae. Initially, hemorrhagic tracks are present near portal areas and throughout lobules. They are visible through the capsule as pinpoint red areas, perhaps slightly depressed and surrounded by a narrow pale zone. Erythrocytes, and within a few days, neutrophils and eosinophils, fill the space left in the parenchyma by the larva. These lesions collapse and heal by fibrosis, causing scarring, which involves most intensely the adjacent portal tracts. Fibrosis extends diffusely through more distant tracts, however, emphasizing lobular outlines. There is a heavy eosinophil infiltrate in fibrotic septa, which becomes most obvious beginning about 10–14 days after infection. In sensitized pigs, fewer larval tracks and hemorrhages occur, but a heavy infiltrate of eosinophils is found in portal tracts within a few days of infection, followed several weeks later by the formation of lymphocyte aggregates and follicles. Granulomatous foci containing giant cells, macrophages, and eosinophils may center on the remnants of larvae trapped and destroyed in the liver.

The inflammatory infiltrates in livers of animals exposed to larval ascarids may become severe and diffuse, and this is reflected in the gross appearance of the liver, which has extensive "milk spots" and prominent definition of lobules. The liver is firm, and heavy scars may become confluent, obliterating some lobules and extending out to exaggerate interlobular septa throughout the liver. Where pigs are raised intensively, it is now rare to encounter extreme fibrosis of the liver associated with ascarid migration.

The pathogenicity of adult ascarids in the intestine is poorly defined. Heavy infections may obstruct the gut, being visible as ropelike masses through the intestinal wall. Ascarids may occasionally pass to the stomach and be vomited or migrate up the pancreatic or bile ducts. Sometimes biliary obstruction and icterus, or purulent cholangitis, may ensue. Rarely, intestinal perforation occurs. Relatively subtle morphologic changes are induced in the intestine by *Ascaris* infection in swine. These include substantial hypertrophy of the muscularis externa and elongation of the crypts of Lieberkühn, though height of villi is not significantly reduced. Hypertrophy and exhaustion of the goblet-cell population and increased prorial infiltrates of eosinophils and mast cells are also observed in infected intestine. The presence of about 80 to 100 worms in 3-month-old

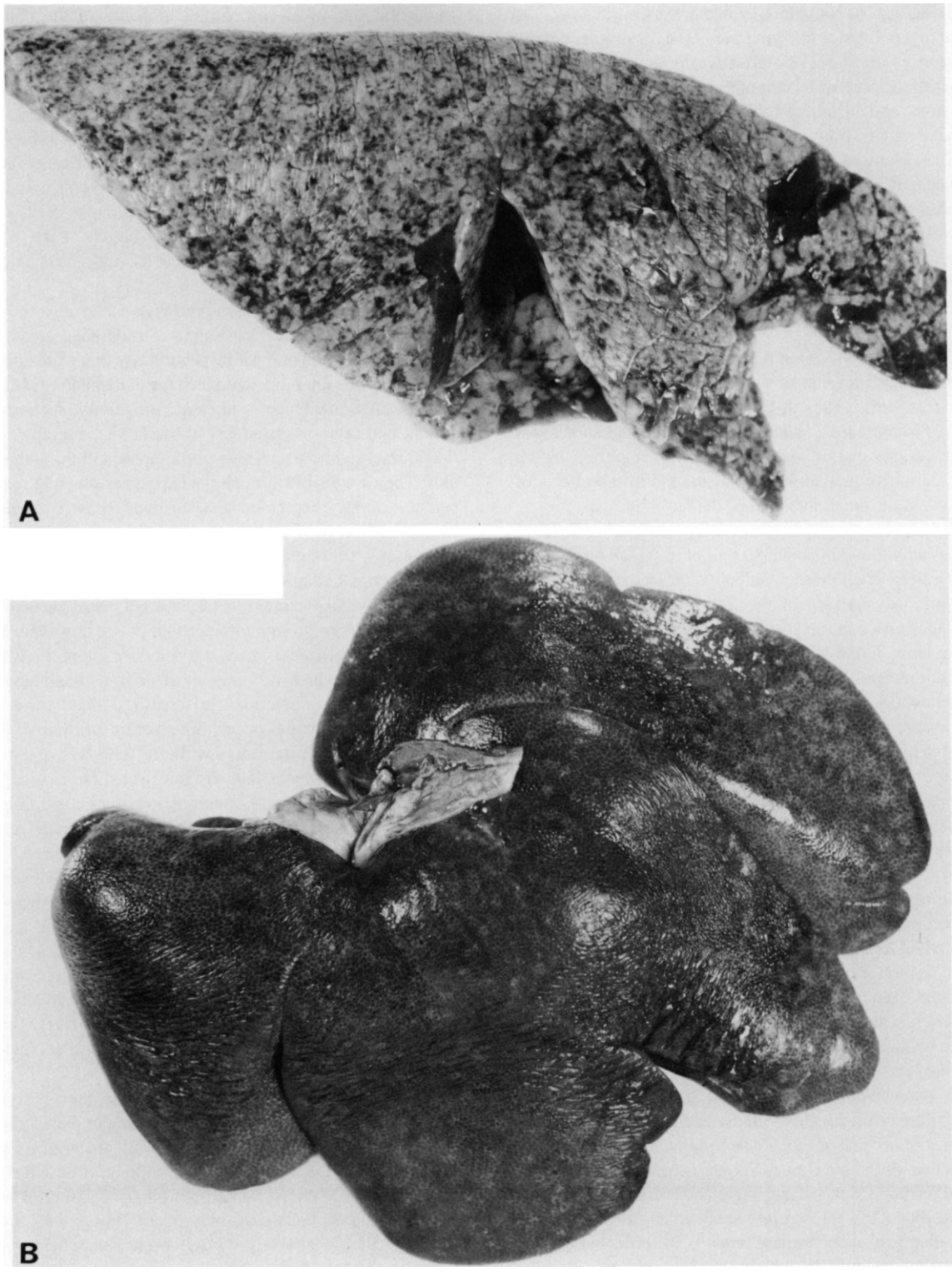


**Fig. 1.46.** (**A**) *Ascaris suum*. Lung. Pig. (**B**) Interstitial hepatitis caused by larvae of *Ascaris suum*. Pig.

swine fed low-protein rations may depress feed intake and the efficiency of feed conversion. *Ascaris lumbricoides* in humans interferes with carbohydrate, fat, and protein absorption, and *A. suum* probably has a similar influence. The effects of infection seem to be most apparent in animals on diets marginal in energy and in quantity and quality of protein.

*Ascaris suum* also infects animals other than swine. In sheep, and occasionally cattle, immature ascarids may be found in the intestine. Eosinophilic granulomas and interstitial hepatitis and fibrosis with heavy eosinophil infiltrates may occur in the livers of sheep-grazing areas contaminated by ascarid ova. Larval ascarids may be found in section. In calves exposed to yards contaminated by pig feces containing *Ascaris* eggs, severe acute interstitial pneumonia may occur. Respiratory signs typified by dyspnea, tachypnea, coughing, and increased expiratory effort are usually first seen about 7–10 days after exposure when large numbers of larvae are present in the lungs. Deaths may ensue over the following few days, and the lungs are moderately consolidated, light pink to deep red, with alveolar and interstitial emphysema and interlobular edema. Microscopically, there is thickening of alveolar septa, and effusion of fibrin, proteinaceous edema fluid, and macrophages into alveoli. Hemorrhage into alveoli may also occur. Larvae are present in alveoli and bronchioles and provoke acute bronchiolitis. Neutrophils are found around larvae in bronchioles; eosinophils may be present but are not prominent in animals dying acutely. In addition to being usually readily observed in tissue sections, larvae may be recovered from the airways by washing with saline, or from minced lung in saline or digestion fluid by use of a Baermann apparatus. Tens of thousands to millions of larvae may be present in the lungs of fatal cases.

*Parascaris equorum* is the ascarid of horses. It is widespread and common in young horses; it may contribute to ill thrift and occasionally causes death. *Parascaris equorum* is a large nematode, females being up to $\frac{1}{2}$ m long. The life cycle resembles that of *Ascaris suum*. Similarly, hepatic and pulmonary lesions are associated with larval migration, and coughing may occur at the time larvae are in the lungs if infections are heavy. The prepatent period is about 10–15 weeks. The lesions in the lungs of foals with migrating *Parascaris* larvae, ~2 weeks after infection, are like those described in swine with *Ascaris*. Animals with resolving pulmonary lesions develop subpleural nodular accumulations of lymphocytes up to 1.0 cm in diameter, and there may be lymphocytic cuffing of pulmonary vessels.

It is possible to establish heavy infections of *Parascaris equorum* in the intestines of foals a few months old, but not in yearlings, where larvae appear to be killed during hepatopulmonary migration. In heavily infected foals, however, many worms are lost from the intestine prior to patency, suggesting the possibility of an effect of crowding on the population of growing worms. A heavy burden of ascarids in the intestine may reduce weight gains in growing foals. Inappetence occurs, but increased plasma protein catabolism or loss into the gut does not. Reduced weight gain and hypoalbuminemia may be due to decreased protein intake. Ascarid infection may reduce rate of intestinal transit. Heavy burdens can be associated with obstruction, intussusception, or rarely, perforation of the intestine.

The ascarids of small animals are *Toxascaris leonina*, infecting both cats and dogs, and *Toxocara canis* and *T. cati*, infecting the dog and cat, respectively. All occur in the small intestine, mainly in young animals. *Toxascaris leonina* has a life cycle that may be direct but can involve an intermediate host. In the definitive host, larvae ingested in infective ova enter the wall of the gut, where they remain for several weeks, molting to the fourth stage and emerging to the intestinal lumen to molt again and mature. The prepatent period is about 10–11 weeks. In the intermediate host, such as the mouse, third-stage larvae are found encapsulated in granulomas in many tissues but mainly the wall of the intestine, there they may be visible as pale foci 1–2 mm in diameter. They are infective to the definitive host if the intermediate is eaten.

*Toxocara canis* has a complex life cycle. Puppies may be infected by ingestion of larvated ova, in which case they follow the pathway of hepatopulmonary movement in the bloodstream, and tracheal migration to the pharynx and gut, though some larvae reach other tissues in the circulation. In older dogs, most larvae ingested in eggs are disseminated in the circulation to various tissues, where they encyst still in the second stage rather than undergoing development and a tracheal migration. In the pregnant bitch, these larvae are mobilized, crossing the placenta to infect the fetus in the 7 to 10 days before parturition. In the fetus, they molt in the liver and pass to the lungs as third-stage larvae, where they are present at birth. Transmammary transmission of mobilized second-stage larvae also occurs, infecting the neonate via the colostrum. In addition, paratenic hosts may be infected by ingestion of larvated eggs. In a wide variety of species, second-stage larvae are disseminated hematogenously to many organs, where they settle mainly in muscle. In some abnormal hosts, including humans, a syndrome termed visceral larva migrans has been described, characterized by eosinophilia, general malaise, and perhaps signs related to granulomatous reactions to larvae in the eye, liver, lungs, and brain. Larvae in paratenic hosts eaten by dogs develop in the gut of the definitive host.

*Toxocara cati* may infect cats directly from the larvated egg, via paratenic hosts, or in kittens, by the transmammary route from the postparturient queen. Prenatal infection apparently does not occur. Second-stage larvae hatching from eggs migrate via the liver, lungs, and trachea, while those taken in from milk or prey do not. Following tracheal migration or ingestion in milk or prey, larvae molt to the third stage in the gastric wall, while fourth-stage larvae are found in the gastric contents and the wall and lumen of the small intestine. *Toxocara cati* may also be a cause of visceral larva migrans in humans.

Heavy infections of ascarids in puppies and kittens, usually those reared in unhygienic communal environments, may result in ill thrift or occasionally death. The most significant effects are those caused in the stomach and intestine by maturing *Toxocara canis* in young puppies infected prenatally or in the bitch's milk. The animals may develop weakness, lethargy, and vomition, which is occasionally fatal. At autopsy, the animal appears poorly grown for its age, potbellied, and cachectic, and masses of maturing worms are present in the intestine and perhaps stomach. Sometimes up to 20% of the body weight of young puppies may be accounted for by the worm burden. *Toxocara cati* may be associated with clinical disease but usually not death, in kittens up to several months of age. Pathogenic effects are rarely

attributed to *Toxascaris leonina*. Mature *Toxocara cati* are up to ~10 cm long, *T. canis* up to ~18 cm long. In freshly dead animals they are often coiled like a spiraled spring. They may maintain their place in the intestine by bracing against the gut wall in this way. The mechanism by which adults of these ascarids in the intestinal lumen impair growth has not been investigated. Ascarids occasionally enter the bile or pancreatic ducts, and many perforate those structures or the intestine.

Focal hemorrhages may be found in the lungs of puppies with migrating *Toxocana canis* larvae. Larval *T. canis* is occasionally found in or associated with granulomas in the tissues of pups and older dogs, though a clinical syndrome comparable to visceral larva migrans occurs only very rarely, if at all, in the dog. Inflammatory foci are most commonly seen grossly in the kidney, as white, elevated spots 1–2 mm in diameter in the cortex beneath the capsule. They may be encountered in section in any organ and are composed of a small focus of macrophages, lymphocytes, and plasma cells, perhaps with a few eosinophils, and possibly containing a larva. Larvae may be destroyed in such foci, which heal by scarring. Considering the large numbers of larvae that must move through the tissues of dogs, and in many cases be sequestered there, relatively few are encountered incidentally, free or encapsulated in granulomas. Occasionally, granulomas incited by *T. canis* larvae may be found in the eye on ophthalmoscopic examination. There are rare reports of encapsulated *T. canis* larvae associated with eosinophilic gastroenteritis in German shepherd dogs, and a somewhat similar syndrome has been produced experimentally by superinfection with large numbers of *T. canis*.

Larval *Toxocara cati* developing in the mucosa of the stomach and intestine may provoke a mild granulomatous response comprising lymphocytes and a few macrophages about the coiled larva. Larvae free of such a response are also found in the mucosa and submucosa.

*Toxocara (Neoascaris) vitulorum* infects the small intestine of young calves of domestic Bovidae, mainly in the tropics and subtropics, and it is significant especially in water buffalo. The life cycle involves transmammary transmission of third-stage larvae mobilized from the tissues of the dam. The larvae apparently do not migrate through the lungs of the calf. Patency occurs within about a month of birth, but worms are expelled within a short time, and after a few months, none are present. Signs of infection include foul diarrhea and ill thrift, and perhaps colic suggestive of impaction. Heavily infected calves may die in an emaciated state, with burdens of up to 400 to 500 worms as much as 30 cm long in the intestine. Occasionally, migration up the bile duct and perforation of the gut may occur.

PROBSTMAYRIA AND OXYURIS. *Probstmayria vivipara*, the small pinworm of horses, is viviparous, and as a result, massive proliferation of the population can occur endogenously. The worms are small, ~3.0 mm long, and may be present in the millions on the mucosa and in the content of the cecum and right ventral colon. Despite the large number that may be present, they do not appear to be pathogenic.

*Oxyuris equi*, the large pinworm of horses, also is relatively nonpathogenic. The fourth-stage larvae in the dorsal colon do have a large buccal capsule and feed on plugs of mucosa; in massive numbers they may be of significance. The adults probably live in the content. The male is ~1.0 cm long, but the female may be 4–15 cm, with a narrow tail comprising up to 75% the body length. They lay eggs on the perianal area, and their main significance is the irritation this activity causes.

### *Cestode Infection*

Adult tapeworms inhabit the gastrointestinal tract or the ducts of the liver and pancreas, where they are generally of minor pathologic significance. They are flattened, segmented colonies of sequentially maturing hermaphroditic reproductive units, or proglottids, forming an elongate strobila a few millimeters to many meters long. The Eucestoda are attached to the host by a specialized holdfast organ (scolex), which usually has four suckers, and perhaps a rostellum, sometimes armed with hooks. The Cotyloda may have elongate muscular grooves (bothridia) on the scolex. Cestodes lack an alimentary tract and absorb nutrients through the specialized absorptive surface or tegument of the proglottids. Any effects they have on the host are related to competition for nutrients in the lumen of the intestine or result from tissue damage caused by scolices of species that embed themselves deeply in the mucosa or submucosa.

Carnivores may be infected by tapeworms that use as intermediate hosts certain prey species. Metacestodes, or larvae, of members of the Taeniidae use as intermediate hosts some species of domestic animals and, accidentally, humans. They may cause disease, result in economic loss due to condemnation of tissues or organs at meat inspection, or have zoonotic significance.

Adult cestodes in tissue section are flattened, with internal organs in a loose, parenchymatous matrix, often containing calcareous corpuscles in the outer region and lacking tubular digestive structures. They are segmented, and the scolex may be encountered at the anterior end, attached to the intestine.

In ruminants, the more common and widely distributed intestinal tapeworms are *Moniezia expansa, M. benedini,* and *Thysaniezia (Helictometra) giardi. Stilesia globipuncta* is found in the small intestine of sheep and goats in Europe, Asia, and Africa, while *S. hepatica* occurs in the bile ducts of ruminants in Africa and Asia. *Thysanosoma actinioides* occurs in the small intestine and pancreatic and bile ducts of ruminants in North and South America. *Avitellina* species occur in the small intestines of sheep and other ruminants in parts of Europe and Asia. The intermediate hosts of these tapeworms are oribatid mites or psocids (book lice).

Heavy infestations of the small intestine by *Moniezia, Thysaniezia,* and *Avitellina* may be associated with diarrhea and ill thrift in young lambs and calves. Concomitant gastrointestinal nematode parasitism may well be present and of greater significance.

The solex of *Stilesia globipuncta* may be embedded in mucosal nodules 6–10 mm in diameter in the upper small intestine, with the threadlike strobila streaming into the lumen. There is a chronic inflammatory reaction around the scolex, which is deep in the mucosa, plugs of tissue being grasped by the suckers. Glands in the vicinity are hyperplastic, causing the nodules. The presence of up to a hundred of these nodules has been associated

with wasting, edema, and in some animals, diarrhea. Enteric protein loss perhaps occurs from the sites of attachment in the nodules.

*Stilesia hepatica* and *Thysanosoma actinioides* may cause mild fibrosis and ectasia of the bile ducts. Worms are often concentrated in the segmented, saclike dilations in the duct. These worms cause economic loss through condemnation of infected livers at meat inspection, and in areas where infection is common, this cost may be very significant.

In horses, the cestodes found are *Anoplocephala perfoliata,* which colonizes the proximal cecum, especially at the ileocecal junction, and *A. magna* and *Paranoplocephala mamillana* in the small intestine and occasionally the stomach. The latter worm is small, less than 5.0 cm in length, and is rarely associated with disease or lesions. *Anoplocephala magna* tends to live in the lower small intestine, where it can attain a length of up to 80 cm and a width of 2.5 cm. All use oribatid mites as intermediate hosts. Heavy infections have been associated with erosive or ulcerative enteritis, and rarely with intestinal perforation. *Anoplocephala perfoliata* is more commonly associated with lesions, and occasionally with mortality. In areas of concentrated mucosal attachment by clusters of this stumpy species, especially at the ileocecal orifice, erosion and ulceration of the mucosa occur (Fig. 1.45D). The depressed surface is often covered by a fibrinous exudate, perhaps with some hemorrhage, or there may be a local verrucous granulating mass projecting into the lumen. Chronic lesions of this sort may be associated with unthriftiness. Partial obstruction of the ileocecal orifice may occur rarely, but no relationship is established between infection with *A. perfoliata* and the development of ileal muscular hypertrophy. Ileocecal and cecal–cecal intussusception, and occasionally, perforation of the intestine, have also been associated with infection by this tapeworm.

Dogs may be parasitized by *Diphyllobothrium latum,* as may be humans, cats, occasionally swine, and many other fish-eating mammals. The adults can be large, attaining lengths of up to 12 to 15 m in humans, though those in animals tend to be shorter. The worm is ~2.0 cm across, and marked centrally by the dark uterus and eggs. Ova passed in feces are operculate, and the hatched coracidium is ingested by a copepod, where it develops into a procercoid stage. This in turn develops into a wormlike plerocercoid in the body cavity of various predatory fish. Plerocercoids develop into the adult worm in the intestine of piscivorous mammals. Macrocytic hypochromic anemia associated with vitamin $B_{12}$ deficiency, probably induced by competitive absorption from the gut by the worm, has been reported in some infected people. Infection by *D. latum* is rarely, if ever, associated with clinical disease in animals.

*Spirometra* species are, like *Diphyllobothrium,* members of the class Cotyloda, and their life cycle is similar. The taxonomy of the genus is difficult, but among recognized species are *S. mansonoides,* infecting dogs, cats, and raccoons in North and South America, *S. mansoni* in dogs and cats in eastern Asia and South America, and *S. erinacei,* found in cats and dogs in Australia and the Far East. Prospective hosts must have the opportunity for predation, since they are infected by the plerocercoid or "sparganum" found in the body cavity of the second intermediate host, usually an amphibian or reptile, or in another transport host. Spargana can also occur in carnivores, swine, or even humans if the procercoid in the first intermediate host, *Cyclops,* is ingested, usually while drinking. Spargana are white, ribbon-like, but otherwise structureless worms up to several centimeters long. They may be found free or encysted in a thin, noninflammatory fibrous capsule in the peritoneal cavity and intermuscular or subcutaneous tissue. A chronic inflammatory reaction may occur about dead spargana. The adult worms are nonpathogenic. Plerocercoids are of significance in humans, where they migrate mainly in the subcutaneous tissues.

*Mesocestoides* occasionally infects dogs, as well as other mammals and some birds, in North America, Europe, Asia, and Africa. These members of the Eucestoda have a life cycle involving an insect or mite, and a vertebrate as intermediate hosts. In the latter, infective tetrathyridia, about 1–2 cm long, flat, narrow, and bearing an invaginated scolex with four suckers, are found in body cavities, liver and lung. Tetrathyridia have the capacity for asexual multiplication, and massive infections of intermediate hosts such as amphibians and reptiles may result. In definitive hosts, *Mesocestoides* adults may also replicate asexually, and heavy intestinal infections may occur as a result of this or of the consumption of larger numbers of tetrathyridia in an intermediate host. Animals infected with intestinal *Mesocestoides* may develop diarrhea. Tetrathyridia in the abdominal cavity of dogs and cats may cause peritoneal effusion and adhesions.

*Dipyllidium caninum* occurs in the dog, cat, fox, and occasionally, children. It is ubiquitous. The narrow worms, up to $\frac{1}{2}$ m long, have distinctive cucumber-seed-like segments and are often encountered incidentally in the small intestine at autopsy. They are of no pathologic significance. Cysticercoids develop in fleas and perhaps in the dog louse *Trichodectes canis.* Infection in the normal definitive hosts, or in accidental ones such as humans, is by ingestion of fleas containing cysticercoids.

Tapeworms of the genus *Taenia* are the most important in domestic animals, not because of the effects of the adult worm in the carnivorous definitive host, but rather because of the metacestodes or larval forms. Taeniid metacestodes assume four basic forms. Single oncospheres hatch in the upper small intestine, penetrate the epithelium, and are carried in the portal blood to the liver. Some migrate in the liver, eventually to enter the peritoneal cavity. Others persist to develop in the liver, while still other metacestodes pass on to the heart, lungs, and systemic circulation, establishing in muscle or a variety of other sites and tissues. The **cysticercus** is a fluid-filled, thin-walled, but muscular cyst, into which the scolex and neck of a single larval tapeworm are invaginated. The **strobilicercus** is a modification on this theme; late in larval development the scolex evaginates and becomes connected to the terminal bladder by a segmented strobila, so that it resembles a tapeworm, several centimeters long. The **coenurus** is a single or loculated fluid-filled cyst, on the inner wall of which up to several hundred nodular invaginated scolices are present in clusters. Each scolex is capable of developing into a single adult cestode in the intestine of the definitive host. The **hydatid cyst** is a uni- or multilocular structure, on the inner germinal membrane of which develop brood

capsules. Within the brood capsules, invaginated protoscolices form. Brood capsules may float free in the cyst fluid, where they are termed "hydatid sand." Internal daughter cysts can develop. Release of brood capsules or protoscolices into tissues, as a result of rupture of the hydatid cyst, may lead to development of new cysts. The alveolar hydatid cyst proliferates by budding externally.

*Taenia taeniaeformis* infects the intestine of domestic cats and some wild felids, and the strobilicercus, *Cysticercus fasciolaris,* is found in the liver of small rodents. The adults are up to 60 cm long, have no neck, and posterior segments are somewhat bell-shaped, so this species is readily differentiated from the other cestodes found in the feline small intestine. Usually only a few worms are present in the cat, and they are of little consequence.

*Taenia pisiformis* is common in the small intestine in dogs and some wild canids that prey on rabbits and hares. *Cysticercus pisiformis* migrates in the liver of the intermediate host, causing hemorrhagic tracks that are infiltrated by a mixed inflammatory reaction and ultimately heal by scarring. The pea-size cysticerci encyst in a thin, noninflammatory fibrous capsule on the mesentery or omentum or on the ligaments of the bladder. Occasionally cysticerci persist beneath the hepatic capsule. Burdens of up to 20 to 30 worms, sometimes more, may be present in the intestine of the dog.

*Taenia hydatigena* infects the dog, and the metacestode, *Cysticercus tenuicollis,* the long-necked bladder worm, or false hydatid, is found in the peritoneal cavity of sheep, cattle, swine, and occasionally, other species. Immature cysticerci in the liver migrate through the parenchyma for several weeks as they develop, before emerging to encyst on the peritoneum anywhere in the abdominal cavity. The immature cysticerci are less than a centimeter long, ovoid, and translucent. They cause tortuous hemorrhagic tracks similar to those produced by immature liver flukes, and if large numbers are present, they may cause a syndrome of depression and icterus identical to acute fascioliasis. Heavily infected livers, with 4000 or 5000 actively migrating cysticerci, are mottled due to the subcapsular and parenchymal hemorrhagic foci and tracks. Cysticerci up to 6 to 8 mm long may be present beneath or breaching the capsule by ~3 weeks after infection. In severe cases, hemorrhage into the abdominal cavity may occur, but this is uncommon. Hepatic necrosis due to migrating cysticerci may predispose to germination of clostridial spores and the development of black disease or bacillary hemoglobinuria, though these are more often complications of fascioliasis. Cysterci trapped in the liver may persist in a fibrous capsule or be destroyed in a cystic eosinophilic granuloma, which may mineralize; this is common on the diaphragmatic surface, where the falciform ligment is attached. Usually the intensity of infection is low, and a few, but occasionally scores of cysticerci, delicate, translucent, fluctuant, fluid-filled cysts up to 5.0 cm or more in diameter, are contained in individual thin, noninflammatory fibrous capsules scattered on the peritoneal serosa. A single invaginated scolex on a long neck is present in each cysticercus. When a cyst degenerates, it is destroyed by a granulomatous reaction, and the fibrotic mass may mineralize.

*Taenia ovis* infects the intestine of the dog, while the metacestode, *Cysticercus ovis,* is in the muscle of sheep, where is causes cysticercosis, or "sheep measles." Cysticercosis of muscle caused by *C. ovis, C. bovis* in cattle, and *C. cellulosae* in swine is considered with disease of muscle (in Muscles and Tendons, Volume 1). The adult stages of the latter two cysticerci, *T. saginata* and *T. solium,* respectively, occur in the small intestine of humans.

*Taenia serialis* infects dogs and foxes throughout the world. The larval coenurus is found in the subcutaneous and intermuscular connective tissue of lagomorphs. Usually, large numbers of tapeworms are found in individual infected dogs, presumably due to the development of many individuals from the numerous scolices in one or more coenuri.

*Taenia multiceps* occurs in the intestine of dogs and wild canids, but the metacestode, *Coenurus cerebralis,* develops in the brain and spinal cord of sheep and other ungulates, and rarely, humans. In the goat, coenuri may also occur in other organs, beneath the skin and intramuscularly. The migration of small metacestodes in the central nervous system may cause tortuous red or yellowish gray tracks in the brain due to traumatic hemorrhage and malacia, and nervous signs or death may occur at this stage. More commonly, signs of central nervous disease, termed "sturdy" or "gid," do not develop until coenuri, up to 4 to 5 cm in diameter, have developed more fully, 4–8 months after infection. Cysts may be present at any level and depth in the brain and spinal cord and projecting into the cerebral ventricles, but they are most common near the surface of the parietal cortex in the cerebrum. They cause increased intracranial pressure, hydrocephalus, necrosis of adjacent brain, and sometimes lysis, perhaps extending to perforation, of the overlying cranial bone. Coenuri developing in the spinal cord may cause paresis.

Cysticerci and coenuri are recognized in tissue sections as generally cystic structures with an eosinophilic outer layer or tegument, which may appear fibrillar or almost ciliate on the outermost surface. Beneath the tegumental cells a less cellular area, which may contain calcareous corpuscles, gives way to a light, weblike, lightly cellular matrix, and the central, open, fluid-filled portion of the cyst. No internal organs are seen. Muscular inverted scolices, with suckers and (in all but *Cysticercus bovis*) hooks on the rostellum, may be encountered in favorable sections, extending into the center of the metacestode. Immature migrating metacestodes lack organized scolices. The reader is referred to other sources for details on the taxonomy and specific identification of adult and larval taeniid tapeworms.

*Echinococcus* tapeworms occur in the small intestine of a number of species of carnivores, predominantly canids. In enzootic areas the distinctive metacestodes, or hydatid cysts, are commonly found in normal or accidental intermediate hosts. Humans may become infected with the metacestode, and echinococcosis or hydatidosis is a significant public health problem where carnivores carrying *Echinococcus* come in close contact with people.

The taxonomy of the genus is complex and in dispute. There appear to be four species, of which at least some have strains or biotypes that may be recognized on the basis of biochemical characteristics, biologic behavior, and ecology. These strains

seem to be based on adaptations to prey–predator relationships among definitive and intermediate hosts, which are relatively isolated geographically and ecologically. Since *Echinococcus* species may be self-fertilizing, they have a high potential for forming double recessives. The large number of genetically identical worms that may result from asexual reproduction by the cystic metacestode developing from a single oncosphere gives the genus a high capacity for establishment of mutant populations. These adaptive advantages may predispose to the development of strains. The species recognized are *E. granulosus, E. multilocularis, E. oligarthus,* and *E. vogeli.* The latter two involve sylvatic cycles in South America, with felids and canids as definitive hosts, respectively, and rodents as intermediate hosts. The other two species may use domestic animals as definitive hosts and will be considered further here.

*Echinococcus granulosus* uses the dog and some other canids as the definitive host. The most widespread strain uses a sheep–dog cycle and has been disseminated wherever there is pastoral husbandry of sheep. It is significant as a potential zoonosis in many parts of Eurasia and the Mediterranean region, some parts of the United Kingdom, North and South America, continental Australia, and Africa. Eradication has been accomplished, or virtually so, in Iceland, New Zealand, and Tasmania. Other strains affecting domestic animals use horse–, cattle–, camel–, pig–, buffalo–, goat–, and human–dog cycles. Sylvatic cycles include, in North America, moose–wolf; in Argentina, hare–fox; in Sri Lanka, deer–jackal; and in Australia, macropod–dingo. Typically, cysts that develop in the intermediate host to which the strain is adapted are fertile, and a high proportion contains brood capsules and protoscolices. Oncospheres infecting other hosts either may not establish or, more commonly, develop into sterile cysts that do not produce protoscolices. Thus knowledge of the local cycles of *E. granulosus* permits interpretation and prediction of the patterns of fertility and sterility of cysts found in the various potential intermediate hosts.

In the small intestine of the definitive host, protoscolices evaginate and establish between villi and in the crypts of Lieberkühn. The scolex distends the crypt, and the epithelium is gripped by the suckers and occasionally eroded. The worms that develop are short, usually less than 6 to 7 mm long. They commonly have only three or four proglottids, the caudal gravid one making up almost half the length of the worm. Burdens of *Echinococcus granulosus* are often heavy, no doubt due to the large numbers of protoscolices ingested at a meal containing one or more hydatid cysts. The heavily infected intestine is carpeted by the tiny white, blunt projections, partially obscured between the villi; the lesion may resemble lymphangiectasia. Enteric signs are not normally encountered in dogs with intestinal hydatid tapeworms.

Penetration of oncospheres released from eggs in the intestine of the intermediate host takes them into the subepithelial capillaries, or perhaps the lacteal. The majority probably migrate via the liver, some carrying on to the lungs and general circulation. Those gaining the lacteal may bypass the liver, however, entering the vena cava with the lymph, and are either filtered out in the pulmonary circulation or disseminated. Hydatid cysts occur most commonly in the liver and lung, with some species variation in the relative prevalence in these organs. In sheep, they may be more common in lungs, while in cattle and horses, the liver is the usual site of establishment. Less commonly, the brain, heart, and bone may be sites of development of hydatid cysts.

Hydatid cysts are usually spherical, turgid, and fluid filled. They commonly measure 5–10 cm in diameter in domestic animals; rarely, cysts in animals may be larger, but in humans, hydatid cysts can become huge. On the other hand, some fertile cysts in horse livers may be as small as 2 to 3 mm across. The lining of fertile cysts is studded with small, granular brood capsules, and hydatid sand is in the fluid. The lining of sterile cysts is smooth. Though the potential exists for development of internal daughter cysts, and rare exogenous budding by herniated cysts, most hydatid cysts in domestic animals are unilocular. They may be irregular or distorted in shape, however, due to the variable resistance of parenchyma and portal tracts or bronchi and the differing profiles of bone or other resistant tissues. A single cyst or up to several hundred may be present, displacing tissue in infected organs. Disease is rarely attributed to hydatidosis in animals, even in those heavily infected.

Immature hydatid cysts are surrounded by an infiltrate of mixed inflammatory cells including giant cells and eosinophils. As they develop, a layer of granulation tissue, which may contain round cells and eosinophils, invests the cysts, and this evolves so that the inner portion of the fibrous capsule is composed of mature collagenous connective tissue, which is relatively acellular. Within this, and in close apposition, is the lamellar hyaline outer layer of the hydatid cyst wall, which with time may become hundreds of micrometers thick. The cyst is lined by the thin, cellular germinal layer, from which the brood capsules form on fine pedicles.

Hydatid cysts frequently degenerate. The inner structures collapse, and the mass becomes caseous and may mineralize. Degenerate hydatid cysts may resemble tuberculous lesions or squamous-cell carcinoma but for the fact that they can often be shelled out of the fibrous capsule. In section, among necrotic debris, macrophages and giant cells, remnants of the lamellar outer membrane, and perhaps the rostellar hooklets of degenerate protoscolices may be recognized, confirming the origin of the lesion.

*Echinococcus multilocularis* has a holarctic distribution, the adults occurring mainly in foxes, and the metacestodes in small rodents, especially voles and lemmings. Dogs and cats may also become infected with the worms in enzootic areas. Though the parasite is principally arctic, the cycle is found in the northern prairie area of North America as far south as Iowa, and in parts of central and western Europe. The mature cestodes in the intestine are similar to, but smaller than, *E. granulosus.* In the intermediate host, the metacestode infects mainly the liver, forming a cystic structure with internal brood capsules and protoscolices; but it is capable of external budding. As a result, racemose proliferative masses of metacestodes infiltrate infected livers. They may metastasize via the bloodstream to the lungs or bone, or implant in the peritoneal cavity. The inflammatory reaction to alveolar hydatids is composed of macrophages, perhaps giant cells, lymphocytes, and plasma cells in an encapsulating fibrous

stroma. The metacestodes are rarely found in domestic animals but they infect humans exposed to the eggs shed by infected carnivores.

*Intestinal Fluke Infection*

Trematode infections of the intestine of domestic animals are, on the whole, uncommon. Dogs and cats in many parts of the world may be infected with *Alaria*, the second intermediate hosts for which are frogs or other amphibians. *Heterophyes heterophyes, Metagonimus yokagawi,* and *Echinochasmus perfoliatus* may infect dogs and cats fed fish containing metacercariae. The former two occur in the Mediterranean area and the Far East; the latter in Eurasia. *Cryptocotyle,* most commonly parasitic in piscivorous birds, may also be found in dogs, cats, and mink fed infected marine fish. Enteritis is attributed to *Alaria, Echinochasmus,* and *Cryptocotyle*. The effects are related to attachment of flukes to the mucosa by suckers, and perhaps to local irritation, erosion, and ulceration, which large numbers of them may induce. The production of excessive intestinal mucus, and hemorrhagic enteritis, have been associated with intestinal fluke infection in small animals. The flukes involved are small, less than 4 to 5 mm long, and must be sought carefully at autopsy.

*Nanophyetus salmincola* occurs in the small intestine of dogs and cats, and a wide variety of fish-eating wild mammals, birds, and people in the northwestern United States and eastern Siberia. Its distribution is determined by that of the snails that are the first intermediate hosts. The second intermediate hosts are various fish, especially Salmonidae. The adult flukes inhibit the small intestine, where they penetrate and attach to the mucosa. Large numbers may cause mucoid or hemorrhagic enteritis. *Nanophyetus salmincola,* however, transmits the distinct rickettsia of Elokomin fluke fever and salmon-poisoning disease. The former is caused by a distinct rickettsia and affects a wide range of carnivores, while salmon-poisoning disease may be caused by *Neorickettsia helminthoeca* alone or possibly in combination with the agent of Elokomin fluke fever. *Neorickettsia helminthoeca* causes disease only in Canidae. Both diseases are reported only in North America.

**Salmon poisoning** disease has an incubation period of about 5 to 7 days and is characterized clinically by pyrexia, anorexia, depression, weakness, and weight loss. There may be serous nasal discharge and mucopurulent conjunctivitis. Diarrhea with tenesmus develops; feces are scant, yellowish, and mucoid or watery, perhaps with some blood. The condition usually is fatal, only 5–10% of infected dogs recovering. These dogs are immune to reinfection. At autopsy, lesions are most consistently found in the lymphoid tissues. There is generalized enlargement of lymph nodes, especially in the abdominal cavity. Involved nodes are edematous, and on cut surface they have a yellowish hue with prominent cortical follicles. Enlarged tonsils are everted from their fossae. The thymus is often increased in size in young dogs, and the spleen may be swollen and congested. Prominent splenic lymphoid tissue has been reported in foxes but is not obvious in dogs. Intestinal lymphoid tissue stands out prominently. Peyer's patches and other intestinal lymphoid aggregates are elevated above the mucosal surface, and there may be petechial hemorrhages on the mucosa. Lymphoid tissue near the ileocecalcolic valve may ulcerate and bleed. Ileocolic intussusception occurs in many cases. The liver of foxes becomes friable and may rupture, causing hemorrhage into the peritoneal cavity. Focal hemorrhages may be seen in the mucosa of the bladder, and subpleural hemorrhages up to 2.0 cm in diameter usually occur.

The microscopic changes in lymph nodes include depletion of lymphocytes, focal necrosis with neutrophilic infiltrates, and an increase in the number of histiocytes in the cortex and medulla. Similar changes may occur in the thymus, and splenic follicles may undergo necrosis. Elementary bodies of *Neorickettsia* may be demonstrated by use of Giemsa or Macchiavello stains in the cytoplasm of macrophages in lymphoid tissue and in other visceral organs. In the small intestine, the flukes may be present embedded deep in the mucosa, though usually little reaction to them is present.

Lesions of the central nervous system occur in the great majority of cases. Leptomeninges may be somewhat opaque, but the lesions are best recognized microscopically. They are composed of macrophage accumulations in the leptomeninges and Virchow–Robin spaces, and focal gliosis in the parenchyma. Meningeal reaction is perhaps most consistent over the cerebellum and is composed of mild or moderate perivascular or more diffuse accumulations of histiocytes. Similar cells may cuff small- and medium-sized vessels throughout the parenchyma. Focal gliosis is relatively sparsely distributed but seems most common in the brain stem. Elementary bodies are also demonstrable in macrophages in the central nervous system, and the diagnosis is usually made on the basis of this finding in macrophages in lymphoid tissue and/or brain. The organisms can be isolated and grown on primary canine monocyte cultures and in several other cell culture systems, but this is not a routine procedure.

**Paramphistome infections** in **ruminants** may cause significant intestinal disease. Adults of the genera *Paramphistomum, Cotylophoron, Calicophoron, Ceylonocotyle, Gastrothylax, Fischoederius,* and *Carmyerius* occur in the forestomachs of ruminants, including sheep or cattle, or both, in various areas around the world. Infection is most common in warm temperate to tropical areas. In the rumen, the reddish, pear-shaped adult flukes, with their characteristic anterior and posterior suckers, are considered innocuous, though some papillae may become atrophic and slough. Metacercariae encysted on herbage give rise to immature flukes, which inhabit the duodenum, where massive infections may cause severe enteritis. In cattle, water buffalo, and bison, the species incriminated in disease include *P. cervi, P. microbothrium, P. explanatum, Calicophoron calicophorum,* and various species of *Cotylophoron, Gastrothylax,* and *Fischoederius*. In sheep and goats, *P. microbothrium, P. ichikawai, P. cervi, P. explanatum, G. crumenifer, Cotylophoron cotylophorum,* and *F. cobboldi* have been associated with disease. The species involved vary with the host and geographic area. After about 3 to 5 weeks in the small intestine, the worms normally migrate forward, through the abomasum, to establish and mature in the reticulorumen. If massive infection occurs, however, growth in the small intestine is retarded, and flukes

may persist for months in the duodenum, prolonging the course of disease.

Calves and lambs with intestinal paramphistomosis are depressed and inappetent. Fetid diarrhea usually develops within several weeks of infection and may contain immature flukes. Soiling of the perineum and escutcheon, and tenesmus, may be severe. Hypoproteinemia is reflected in submandibular edema in some animals, and anemia has been reported to occur occasionally. Sheep may die within 5 to 10 days, and cattle and water buffalo after a course of 2 to 3 weeks of disease. Morbidity and mortality can be substantial, and survivors may suffer considerable loss in condition. The carcass may be in good or cachectic condition, depending on the duration of the disease, and there may be edema of subcutaneous tissues, abomasal folds, and mesentery and fluid in the body cavities, due to hypoproteinemia. The gallbladder is frequently distended with bile, associated with inappetence. The mesenteric lymph nodes are enlarged and edematous. The anterior small intestine appears congested externally, and immature paramphistomes, deeply penetrating the intestinal wall, may be visible through the serosa. Occasionally they will perforate the gut and be found free in the abdominal cavity. The mucosal surface of the duodenum is edematous, thickened, corrugated, and covered with mucus. Many immature pink or brown paramphistomes, a few millimeters long, are scattered over the surface and embedded in the mucosa. Some are free in clusters in the lumen, and the digesta, which is thin and mucoid, may appear somewhat blood tinged. Most larval paramphistomes are in the first 3 m of small intestine. In advanced infections, some may be present migrating forward on the abomasal mucosa, or already in the forestomachs.

In section, small larval paramphistomes are found deep in the lamina propria, occasionally in the submucosa, or perhaps in Brunner's glands. Larger immature forms are attached to the surface of the mucosa by a plug of tissue taken into the acetabulum. There is atrophy of villi, elongation of crypts, and possibly erosion or ulceration of the mucosa in heavily infected areas. A mixed inflammatory infiltrate is in the lamina propria, but often, little specific reaction is present to flukes in tissue, the lesions are somewhat reminiscent of those in severe trichostrongylosis but for the difference in appearance of the offending helminths. Protein loss into the gut, coupled with loss of appetite, seems to be the most important pathophysiologic consequence. The pathogenesis of the diarrhea is unclear.

The other fluke occurring in the intestine of ruminants is *Skjrabinotrema ovis,* associated with catarrhal enteritis in sheep in Eurasia.

In swine, the paramphistomes *Gastrodiscoides* and *Gastrodiscus* may be found in the colon, where they are of little significance. *Fasciolopsis buski* may also infect the small intestine of swine as well as humans. It is of little importance in pigs other than as a reservoir for human infection.

In horses in Africa and India, the paramphistomes *Gastrodiscus aegyptiacus* and *Pseudodiscus colinsi* occur in the large bowel. Larvae of the former species have been associated with severe colitis in horses, but they are generally nonpathogenic.

Intestinal schistosomiasis, due mainly to *Schistosoma* in ruminants, and *Heterobilharzia* in dogs, may cause protein-losing enteropathy, associated perhaps with granulomatous enteritis in response to deposition of ova in mucosal venules (see the Cardiovascular System, Volume 3).

Flukes in tissue section are generally somewhat flattened or globose, with a loose mesenchymal parenchyma in which the internal structures are suspended. The cuticle is eosinophilic and may be spiny. Muscular oral and acetabular suckers, and pharynx, may be encountered in sections. Ceca are usually present, and elements of the male and female reproductive systems in these typically hemaphroditic adult worms (excepting the schistosomes) may be seen. The uterus may contain ova with a tan-yellow or brown shell, perhaps with an operculum, and ova are often seen in the intestinal lumen or in tissue. The developing miracidium may be present in ova. Schistosomes are recognized by their intravascular location and sexual dimorphism, the leaf-like male perhaps enveloping the slender cylindrical female within the gynocophoric canal in section.

### *Acanthocephalan Infection*

The Acanthocephala are a phylum of parasitic animals, apparently related to the Nematoda, that have an elongate, saclike body, no internal alimentary canal, and use as the holdfast a spiny protrusible proboscis. The life cycle typically involves obligate development in an intermediate host, usually an arthropod, and perhaps the utilization of a paratenic host to facilitate transmission. The Acanthocephala of concern in domestic animals are in the genera *Macracanthorynchus* and *Oncicola.*

*Macracanthorynchus hirudinaceus* is the thorny-headed worm of swine, infecting the small intestine. The life cycle involves dung beetles or other Scarabaeidae, and foraging or rooting swine are prone to infection. Males are ~10 cm long, and the females up to 30 to 40 cm long, slightly pink, curved, and tapering posteriorly. The proboscis has about six rows of hooks and is used to penetrate deeply the intestinal wall. It incites a local granulomatous nodule called a "strawberry mark," with a purulent focus about the embedded proboscis. The proboscis may penetrate the muscularis, and the nodules, up to a centimeter or more in diameter, may be visible on the serosal surface of the gut as gray or yellow suppurative foci, surrounded by a halo of hyperemic tissue. They occasionally perforate, causing peritonitis. As the parasites move about in the gut, abandoned sites of attachment granulate, forming a firm, fibrous nodule, which may persist for some time in the wall of the gut. Severely infected pigs may suffer ill thrift and perhaps anemia, probably related partly to the potential for plasma protein loss and hemorrhage from numerous focal ulcerative lesions. *Macracanthorynchus catalinum* and *M. ingens* are smaller but similar thorny-headed worms that inhibit the intestine of a variety of wild carnivores, and occasionally the dog.

*Oncicola canis* occurs in the small intestine of wild carnivores, and occasionally the dog and cat. Intermediate hosts are presumably arthropods, with insectivorous vertebrates acting as paratenic hosts. Up to several hundred worms, 0.5–1.5 cm long and dark gray, may infest the small intestine; infections usually are light. The proboscis is embedded to the subserosal level, and

a focal nodular lesion develops about it. Associated disease, or complications such as perforation, are apparently rare.

### *Protozoal Enteritis*

#### *Coccidiosis*

The coccidia are members of the protozoan phylum Apicomplexa, intracellular parasites characterized at some stage of the life cycle by a typical "apical complex" of organelles at one end of the organism. Members of the suborder Eimeriina, which we shall consider together here, all have a similar basic life cycle. It begins with infection of a cell, usually in the intestinal mucosa, by a sporozoite released from a sporocyst in the lumen of the gut. One or more stages of asexual division, termed schizogony or merogony, follow, and the merozoites produced infect other cells. Separate sexual stages or gamonts subsequently develop into nonmotile macrogametes and motile male forms or microgametes. A nonmotile zygote produced by union of micro- and macrogametes forms an oocyst. Sporogony, or production of sporocysts containing infectious sporozoites within the oocyst, may occur in the host, or more commonly after the resistant oocysts are passed in feces. Members of the genus *Eimeria* are homoxenous, sexual and asexual development taking place in a single host. *Isospora* may be homo- or heteroxenous (*Cystoisospora*), with asexual stages occurring in an intermediate host. The members of the genera *Toxoplasma, Sarcocystis, Hammondia, Besnoitia,* and *Frenkelia* are all heteroxenous. The heteroxenous genera exploit natural prey–predator relationships. Sexual development takes place in the intestinal mucosa of a predator. At least one generation of asexual replication, often several, occurs in the tissues of one or more species of prey.

In the domestic animals we are considering, asexual and sexual development of *Eimeria* is limited normally to the intestinal mucosa and may involve stages within the lamina propria or epithelium. In the definitive host, asexual and sexual development of the *Isospora* species parasitic in domestic animals is also usually limited to the intestinal mucosa. In the heteroxenous *Isospora, Toxoplasma, Sarcocystis, Hammondia, Besnoitia,* and *Frenkelia,* asexual stages in the intermediate hosts may be found in a variety of tissues. Depending on the parasite and the stage of development, the range of tissues infected may be wide or narrow. As examples, *Toxoplasma* may infect phagocytic and parenchymal cells in many organs in the intermediate host, while *Sarcocystis* typically infects endothelium and, finally myocytes.

The endogenous stages of coccidia are all intracellular, except, temporarily, the merozoite and microgamete. Mature developmental stages are usually readily recognized; immature forms may not be easily identifiable. Trophozoites, small, undifferentiated, rounded, basophilic forms with a single nucleus, within a parasitophorous vacuole in the host cell, are found at three stages of the life cycle: following invasion by the infective sporozoite, prior to merogony; following invasion by a merozoite, prior to a subsequent generation of merogony; following invasion by a merozoite, prior to differentiation into a recognizable gamont. Developing meronts or schizonts are multinucleate. Merogony may occur by a variety of mechanisms that may or may not involve apparent "budding" of merozoites from the periphery of the meront or from infoldings of it. A single residual body, surrounded by slightly curved, fusiform, or banana-shaped, uninucleate merozoites, or many spherical clusters of merozoites with a central residuum, may be present. The location of a schizont, and the number of merozoites it contains, vary with the species and the generation of schizogony. A very few, or up to tens or hundreds of thousands of merozoites, may be released from a single schizont.

Microgamonts mature in two steps. The first involves enlargement of the gamont and proliferation of nuclei. During the second phase, the microgametes differentiate about the periphery of the gamont, which may become deeply folded or fissured by invaginations. Immature microgametocytes during these stages may resemble developing schizonts. However, fully differentiated microgametes differ from merozoites in being small, densely basophilic, comma-shaped, with two or three flagella. They may be present in swirling masses, perhaps with some residual bodies, in mature microgametocytes. Macrogametes, the female stage, have a large nucleus with a prominent nucleolus and with time usually enlarge to contain refractile eosinophilic "plastic granules" or wall-forming bodies, which give rise to the layers of the oocyst wall. Mature macrogametes typically have prominent wall-forming bodies and contain clear or PAS-positive amylopectin granules and a large nucleus and nucleolus.

Fertilization by the microgamete leads to development of the zygote and subsequent formation of the oocyst wall. The oocyst wall is composed of one or two clear or eosinophilic, refractile membranes in most species of coccidia, but the outer wall of some species can be very thick and densely amphophilic. The contained sporont is spherical, with nucleus and nucleolus, and amylopectin granules in the cytoplasm. Sporulation usually occurs outside the host, but in *Sarcocystis* and *Frenkelia,* it occurs in the tissue of the definitive host. Sporozoites are enclosed within sporocysts, which in turn are contained by the oocyst wall. Oocysts of most coccidia, or sporocysts of *Sarcocystis* and *Frenkelia,* are passed in the feces.

Coccidia are typically highly host, organ, and tissue specific. Species of coccidia rarely occur in more than one genus of host. Similar coccidia occurring in related genera of hosts, when tested, usually prove incapable of cross-infection. The coccidia of sheep and goats exemplify this, and our concepts of the species infecting these hosts have been modified considerably as a result. The epizootiologic connotations of high host specificity are obvious. Within a host, infections are commonly organ or site and tissue specific, so that a given life-cycle stage of a species of coccidium typically infects a certain type of cell at a particular level of the intestine or other target site. Asexual and sexual stages may have different site and tissue specificites. The location of the endogenous stages, and their morphology, may give a strong indication of the species of coccidium infecting the animal.

The economic cost of coccidiosis in cattle, sheep, and pigs is considerable, in terms of mortality, morbidity, subclinical disease, and the cost of prevention and treatment. It is even more so in chickens. In dogs and cats, coccidiosis is a minor problem,

and in horses, coccidia probably do not cause disease. The development of coccidiosis is a function of the innate virulence of the organism, the size and viability of the inoculum, and the susceptibility of the host. Some species of coccidia are much more commonly associated with disease than others. Species virulence reflects a number of factors. Among these are the location and type of cell infected by various stages of the organism, the function of infected cells, and the degree of host reaction stimulated by infection. The biotic potential of the organism within the host (i.e., the degree of asexual replication) coupled with the size of inoculum determines to some extent the number of cells infected by subsequent asexual and sexual generations of the coccidium. Provided the later generations are pathogenic, a high biotic potential increases the virulence of the organism.

The effects of infection on the host cell are several and vary somewhat with the infecting species. Infected cells may be functionally compromised. They may hypertrophy; nuclei may enlarge or a considerable amount of cytoplasm may be displaced; and the outer membrane of infected cells may be modified highly, perhaps to facilitate metabolic exchange. The intercellular relationships may be affected. The rate of movement of infected epithelial cells up villi appears to be altered in some cases, and epithelial cells infected by some species seem more resistant to autolysis. At least in chickens, and perhaps in mammals, epithelial cells infected by coccidia may migrate into the lamina propria. The release of merozoites and oocysts is cytolytic, and if this is synchronous and widespread, as may occur in heavy infections, considerable loss of function may be expected. This may result in villus atrophy if many surface epithelial cells are lost, as in piglets infected by *Isospora suis*. On the other hand, massive coccidial infection and cytolysis in the intestinal crypts and glands may have a radiomimetic effect; erosion and ulceration of the colon is a sequel to severe cryptal damage in bovine coccidiosis.

Immunoinflammatory reactions may be incited by coccidial infection. In experimental systems, resistance to coccidial infection is thymus dependent and is largely mediated by functions of T cells other than as helper cells for immunoglobulin production. It seems to be directed mainly against asexual stages in the life cycle. Villus atrophy may also be related to cell-mediated immune reactions. In chickens infected with *Eimeria acervulina*, atrophy of villi is preceded by a hyperproliferative state in the crypts of Lieberkühn, characteristic of atrophy associated with cell-mediated immunity. In *E. neischultzi*–infected rats, the development of villus atrophy is also associated with competent cell-mediated immune mechanisms. Villus atrophy associated with chronic coccidiosis in sheep and goats perhaps has a similar pathogenesis.

In mammals, acute inflammatory reactions in intestinal coccidiosis are most commonly associated with heavy infection and destruction of cells by the sexual stages and oocysts, rather than in response to asexual stages. This contrasts with *Eimeria necatrix* infection in chickens, where acute hemorrhage occurs around schizonts in the lamina propria. In toxoplasmosis, necrosis and focal acute or chronic inflammatory reactions may be incited by actively replicating asexual stages in many organs. A syndrome characterized by hemorrhage occurs in some species infected with asexual stages of *Sarcocystis*, about the time that merogony occurs in vascular endothelium. This may be mediated in part by endothelial damage and by activation and consumption of clotting factors.

The effects of intestinal coccidiosis in mammals vary with the host–parasite system. They mainly relate to malabsorption induced by villus atrophy, or to anemia, hypoproteinemia, and dehydration due to exudative enteritis and colitis caused by epithelial erosion and ulceration. Many species of coccidia appear to have little pathogenic effect under normal circumstances. This may reflect relative insulation from host defense mechanisms due to their largely intraepithelial location or it may be associated with a relatively low biotic potential. However, even some species of coccidia developing in cells in the lamina propria, in large numbers, seem innocuous.

Coccidiosis is typically a disease of intensively managed animals. It is especially important in susceptible young animals exposed to a high level of infection. This is predisposed by high contamination rates associated with crowding, yarding, or high stocking rates on pasture. A damp substrate promotes oocyst sporulation and survival, and practices such as feeding on the ground, or the natural propensity of young animals to nibble or perhaps indulge in coprophagy, may promote infection. Although infections may not proceed to patency, chronic ingestion of oocysts may cause an intestinal immune response, villus atrophy, and perhaps ill thrift in some situations, Immune reactions may only halt development of, but not kill, endogenous asexual stages. Epizootiologic evidence suggests that under some circumstances there may be relaxation of resistance and resumption of development of the organisms, ultimately expressed in disease. This seems the likely explanation for outbreaks of bovine coccidiosis occurring during midwinter in freezing climates, or in postparturient stabled dairy cattle.

The members of the genera *Eimeria* and *Isospora*, and coccidiosis caused by them in the various species, will be considered further here. Cryptosporidiosis and the heteroxenous cyst-forming organisms, including *Toxoplasma* and *Sarcocystis*, will be considered subsequently.

CATTLE. About 13 species of *Eimeria* parasitize cattle; of these, *E. zuernii* and *E. bovis* are potentially highly pathogenic, while several others, notably *E. ellipsoidalis* and *E. auburnensis*, may cause diarrhea, but probably not death. Coccidial infection is common and usually comprises a mixture of species. Disease occurs mainly in calves or weaned feeder cattle under about a year of age, if one or both of the potentially pathogenic species produce heavy infection. It may occur in animals at range, concentrated at waterholes, but is most common in animals in feedlots or yards, where the level of sanitation is not high. The stress of shipping, cold weather, or intercurrent disease may be associated with outbreaks, which can occur in midwinter, when oocyst transmission is expected to be poor. Morbidity may be high, but mortality is usually low. The disease is characterized by diarrhea, which may progress to dysentery with mucus, and tenesmus, perhaps causing rectal prolapse. Animals dehydrate and become hyponatremic and perhaps anemic. The duration of severe disease is about 3–10 days, after which most cases recover, since infection is essentially self-limiting. Some animals develop concurrent nervous signs, including tremors,

nystagmus, opisthotonus, and convulsions, and many of these die within a few days.

The signs in bovine coccidiosis due to *Eimeria zuernii* and *E. bovis* occur when the epithelium in the glands of the cecum and colon is infected by second-generation schizonts and gametocytes. In heavily infected animals, disease, and perhaps death, can occur before many oocysts are passed in the feces. The life cycles of both agents are similar, two schizogonous generations preceding gametogony. The first-generation schizont of *E. bovis* infects hypertrophic endothelial cells in lacteals on the upper part of villi in the lower small intestine, several meters proximal to the ileocecal valve. These schizonts may be large, up to ~300 μm in diameter, and are visible to the naked eye as pinpoint white nodular foci in the mucosa. They contain tens of thousands of merozoites but are invested by only a narrow rim of mononuclear inflammatory cells, unless they degenerate, when a marked local mixed reaction develops, including neutrophils and macrophages. Merozoites released from these schizonts about 14–18 days after infection enter cells deep in cecal and colonic glands. In heavy infections, crypts of Lieberkühn in the terminal ileum may also be infected. Here they produce small, second-generation schizonts, which in turn release merozoites, infecting other cells in the gland. Gametogony may begin as early as 15 days after infection, and oocyst production peaks about 19–21 days after infection.

The first generation schizonts of *Eimeria zuernii* may be about the same size as those of *E. bovis*. They are most common in the terminal meter of the ileum, however, and are located in the lamina propria below the crypt–villus junction, often deep near the muscularis mucosae rather than in the endothelium of the lacteal. Hence, they are not so readily visible grossly as those of *E. bovis*. The second-generation schizonts and gamonts of *E. zuernii* also occur in glands of the cecum and colon, but not the terminal ileum. The merozoites tend to be somewhat longer (up to 15 μm) and the schizonts more numerous and of greater diameter (~14 μm) than those of *E. bovis*. The timing of the development of *E. zuernii* infection is similar to that of *E. bovis*.

Animals dying of coccidiosis have fecal staining of the hindquarters, and may be somewhat cachectic and anemic. The gross lesions in severe cases are those of fibrinohemorrhagic typhlocolitis, which may extend to the rectum; if *Eimeria bovis* is involved, the terminal ileum may be affected (Fig. 1.47A), and perhaps a few schizonts will be visible in ileal villi. The contents of the large bowel are usually abnormally fluid and may vary from brown to black to overtly bloody, possibly with flecks of mucus or fibrin. The mucosa is edematous, with exaggerated longitudinal and perhaps transverse folds, which may be congested in a "tiger stripe" pattern, or more diffusely petechiated. Submucosal edema is also marked. Fibrin strands or a patchy diphtheritic membrane may be present on the mucosa (Fig. 1.47B), and fibrin casts can form. In milder cases, lesions are limited to congestion and edema of the mucosa.

In animals dying at the peak of infection, virually all cells lining cecal and colonic glands in many areas are infected by small schizonts, gamonts, or developing oocysts. Cells infected by *Eimeria bovis* tend to dissociate and project into the lumen of the gland. Where infected epithelium remains more or less intact, the surface does not erode, and effusion of exudate is not apparent. As cells are disrupted and oocysts are released into the lumen of glands, however, the remaining glandular epithelium becomes extremely attenuated, or the gland collapses (Fig. 1.47C,E). Concurrently, the surface epithelium becomes squamous, or the mucosa is eroded, and effusion of fibrin, neutrophils, and some hemorrhage occurs from dilated, congested superficial vessels. Oocysts released into the lumen of the colon may be seen in the exudate (Fig. 1.47D). At the same time, the mucosa begins to collapse, and the lamina propria is infiltrated by neutrophils, eosinophils, lymphocytes, macrophages, and plasma cells. Oocysts trapped in denuded glands in the collapsed mucosa may be surrounded by small giant cells.

If destruction is widespread, and the animal survives sufficiently long, the mucosa may ulcerate to the level of the muscularis mucosae and begin to granulate. In areas where the lesion is patchy, glands that have been relatively spared may become lined with hyperplastic epithelium, making an attempt to regenerate the mucosa. Flattened epithelial cells spread from these glands across the denuded surface, beneath the diphtheritic exudate. A few crenated oocysts in small giant cells in the stromal remnants of the mucosa may be all the evidence of coccidiosis found in lesions in animals surviving for 7 to 10 days.

Malabsorption due to mucosal damage in the cecum and colon, and inflammatory effusion and hemorrhage, explain the enteric signs of coccidiosis. The nervous signs in bovine coccidiosis are not associated with recognized lesions in the brain, and their cause remains unknown.

The gross lesions of coccidiosis in cattle must be differentiated from those in salmonellosis, bovine virus diarrhea, rinderpest, malignant catarrhal fever, and bovine adenovirus infection, all of which may cause typhlocolitis. Coccidiosis can often be simply confirmed at autopsy by finding developing stages in mucosal scrapings. Oocysts of *Eimeria bovis* are ovoid, smooth, and about 28 × 21 μm; those of *E. zuernii* are subspherical to ovoid, smooth, and about 18 × 15 μm.

While other coccidia are unlikely to be the primary cause of diarrhea or death in cattle, several have distinctive endogenous stages that may be recognized in tissue section. *Eimeria auburnensis* has a giant first-generation schizont that may be confused with those of *E. bovis* and *E. zuernii*. They are present, however, usually 6–12 m cranial to the ileocecal valve, and form in the epithelium deep in crypts of Lieberkühn, though this may not be apparent due to plane of section or migration into the lamina propria. Second-generation schizonts and gamonts of *E. auburnensis* develop in the lamina propria in the ileum, small schizonts in villi, and gamonts in the deeper lamina propria. Microgametocytes may be several hundred micrometers across. Oocysts are about 38 × 23 μm. The other bovine coccidium with gamonts apparently developing in the lamina propria is *E. bukidnonensis*. Oocysts of this species are large, about 48 × 35 μm and thick walled, with a micropyle, and have been found in the lamina propria. *Eimeria alabamensis* develops in vacuoles within the nucleus of epithelial cells in small intestine and, in heavy infections, the large bowel. Both schizonts and gamonts may be found together within the same nucleus. Gamonts of *E. kosti* have been described in the epithelium deep in the abomasal glands. None of these organisms is considered particularly pathogenic.

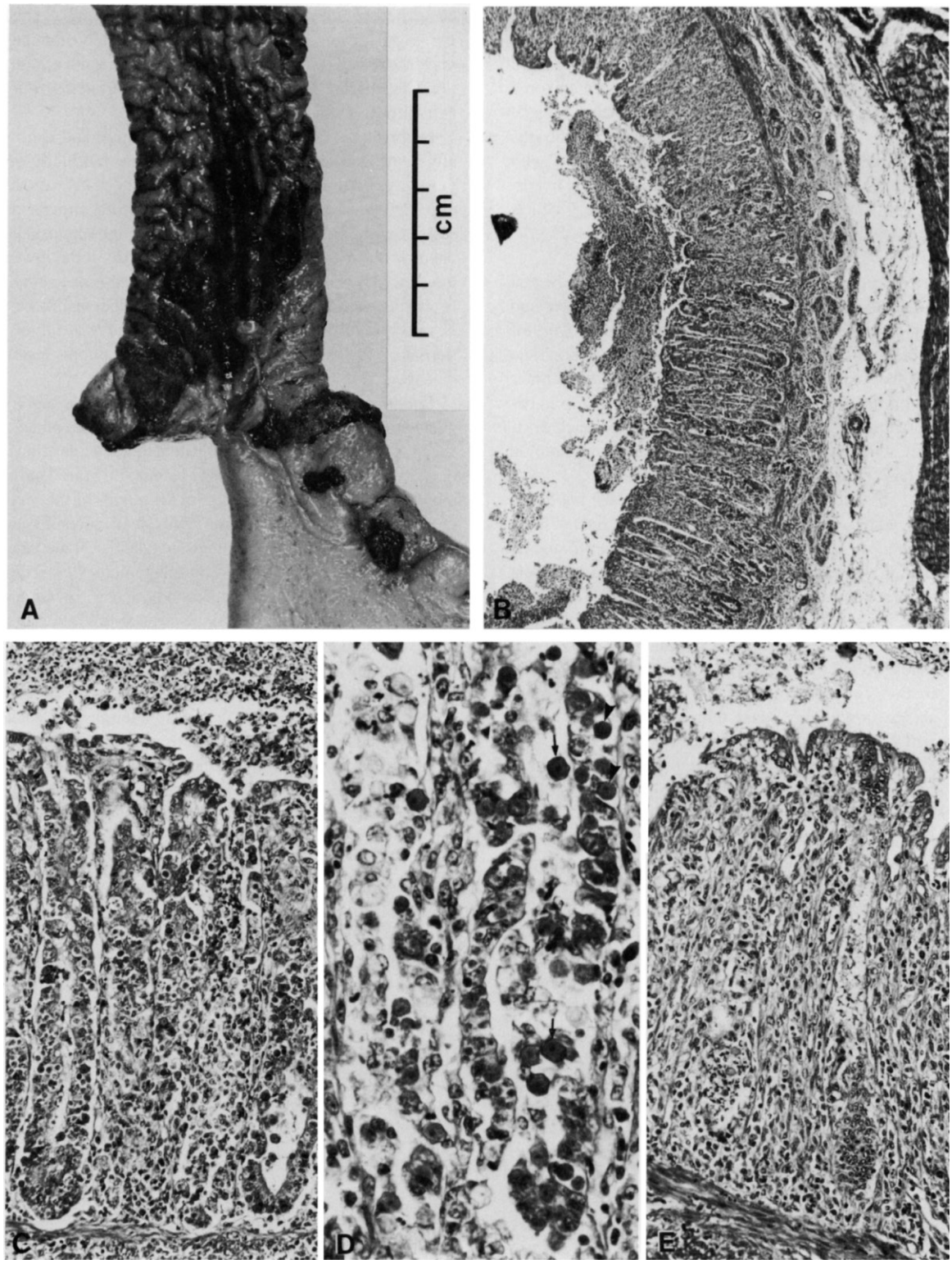


**Fig. 1.47.** Bovine coccidiosis. (**A**) Acute enteritis. Mucosal thickening, large and minute ulcerations, and hemorrhages. (**B**) Damaged colonic glands and inflammatory exudate. (**C**) Heavy infection and destruction of colonic glands by gamonts. Exudate covers mucosa. (**D**) Destruction of colonic glands by developing gamonts (arrowheads). Oocysts are in the lumen of some glands (arrows). (**E**) Destruction of colonic glands. Only a few glands remain in the mucosa.

*Eimeria bareillyi* is associated with clinical coccidiosis in water buffalo calves. The serosal vessels in the distal half of the small intestine are congested, and the lumen of the lower small bowel contains creamy or yellow fluid content in which some mucus, fibrin, or blood may be present. Focal to coalescent pale raised plaques or polypoid masses may be present on the mucosa, or the surface may appear granular and necrotic, with petechial hemorrhages. The gross changes are caused by hypertrophy of crypts and villi, upon which virtually every cell is infected with developing gamonts or oocysts.

SHEEP AND GOATS. Coccidial infection is virtually universal in sheep and goats, and coccidiosis can be a significant problem in the young of both species. Consideration of the etiology of coccidiosis in these species is complicated by the morphologic similarity of the coccidia infecting sheep and goats. Former assumptions on the potential for cross-infection of coccidia between sheep and goats, and of the species found in each host, have been revised considerably as new taxonomic and biologic information has come to light.

At present, about a dozen species of coccidia each are found in sheep and goats. Of these, seven (*Eimeria crandallis, E. faurei, E. granulosa, E. intricata, E. pallida, E. parva,* and *E. punctata*) are recognized in both sheep and goats, and among these further taxonomic revision is expected. *Eimeria ninakohlyakimovae, E. arloingi, E. christenseni, E. caprovina,* and *E. caprina* occur in goats; *E. ahsata, E. ovinoidalis* (formerly *E. ninakohlyakimovae*), *E. ovina* (formerly *E. arloingi* "A"), *E. weybridgensis* (formerly *E. arloingi* "B"), and *E. marsica* are found in sheep. In addition, giant schizonts of unknown coccidia, termed *Globidium gilruthi,* are seen incidentally as pinpoint white foci in the abomasum of sheep and goats. The taxonomic confusion has been carried over into descriptions of the natural or experimental disease, since many infections were of mixed species, resulted from inocula of poorly defined species of coccidia, or occurred under circumstances where the oocysts associated were not described. While the taxonomic picture has changed, the syndromes associated with coccidiosis in sheep and goats have not.

Coccidiosis in these species is a disease of young animals. Under conditions of intensive pastoral husbandry or confinement, lambs and kids are exposed to oocysts of many species of coccidia within the first few days of life. Oocyst production peaks fairly rapidly between 20 and 90 days of age, sometimes at levels of millions of oocysts per gram of feces. It then gradually drops off, but usually persists for the rest of the animal's life. A degree of protection against subsequent challenge with oocysts of a species of coccidium is conferred by previous infection with that species. Coccidiosis seems to occur mainly in susceptible animals, those with relatively limited experience of infection, exposed to conditions where infection pressure is relatively high. Hence the disease may occur in lambs and kids held in sheds or yards with the ewes or does. Under these circumstances, animals as young a 3 weeks of age may develop signs and perhaps die. Weaned lambs, presumably exposed to only light infections while at range, are also prone to coccidiosis when brought into feedlots. In young, suckled animals and those in feedlots, exposed to large numbers of oocysts, signs may occur before oocysts are passed. Suckling lambs, about 5–8 weeks old, reared at pasture at relatively heavy stocking rates, may also develop signs and occasionally die. Under these conditions, the disease needs to be differentiated from gastrointestinal helminthosis, which may be concurrent.

Outbreaks of coccidiosis in confined lambs and kids are usually acute and characterized by moderate morbidity and low mortality; there is green or yellow, watery diarrhea, occasionally with blood or mucus. Yarded and grazing animals may also suffer weight loss or subclinical ill thrift. Signs are usually associated with infection by species developing in the lower small intestine and perhaps large bowel, including *Eimeria ovinoidalis, E. ahsata,* and *E. ovina* in lambs, and their analogs in goats, *E. ninakohlyakimovae, E. christenseni,* and *E. arloingi.* Infections are usually mixed, and gross and microscopic lesions may be expected to reflect this.

*Eimeria ovinoidalis* in sheep and *E. ninakohlyakimovae* in goats presumably have similar endogenous development. In the sheep, giant schizonts up to 300 μm in diameter develop in cells deep in the lamina propria, in the terminal ileum. They release merozoites that enter epithelium in the glands of the cecum and colon, and perhaps distal ileum. There small, second-generation schizonts evolve, and other cells in glands in the same area subsequently become infected by the gametocytes. These species are considered highly pathogenic, and *E. ovinoidalis* is a species often encountered in association with disease in feedlot lambs. Lesions other than those related to diarrhea, dehydration, and hypoproteinemia are limited to the terminal ileum, and especially the cecum and proximal colon, and are associated with second-generation schizogony and gametogony. Affected areas of gut are edematous and thickened, and there may be focal or more diffuse congestion and hemorrhage in the mucosa. Heavily infected animals may have bloodstained feces. Occasionally, pinpoint white foci, the giant schizonts, may be seen in the mucosa of the ileum. In sections, schizonts and gamonts are in many or most cells lining glands in affected areas. Neutrophils and macrophages may accumulate in response to merozoites released from ruptured giant schizonts, but the most significant microscopic lesions are those in the cecum and colon, which resemble those in cattle due to *E. bovis* and *E. zuernii.*

*Eimeria christenseni* and *E. arloingi* in goats and *E. ahsata* and *E. ovina* in sheep are also associated with serious disease. They seem to have somewhat similar developmental cycles and lesions, though interpretation of the literature is clouded by confusion among these species. Many cases of coccidiosis in lambs attributed to *E. arloingi* (*E. ovina*) may have in fact been due to *E. ahsata,* since the unsporulated oocysts, though of differing sizes, can be confused.

*Eimeria christenseni* has a developmental cycle that involves giant schizonts up to nearly 300 μm across in the endothelium of the lacteal in villi in the middle small intestine. The more mature of these may detach and appear to lie free in the lacteal, dilating the villi. Second-generation schizogony, and gametogony, occur in epithelial cells lining the crypts and villi, mainly in the small intestine 4–6 m below the abomasum, but in heavy infections, also in terminal small bowel. Gamonts are usually below the host-cell nucleus, though this is variable, and multiple infections of host cells are common. In heavy infections, every cell in

a number of contiguous crypt–villus units may be infected. Though there may be an acute local reaction around ruptured primary schizonts, clinical disease is associated with the subsequent stages of development, diarrhea occurring during the late prepatent and patent periods. Affected intestine may be congested and edematous. Numerous pale white or yellow foci from a few millimeters up to a centimeter in diameter, often visible from the serosa, are present as slightly raised plaques on the mucosa of the small bowel. These foci are areas of intense infection of cryptal and villus epithelium by gamonts and developing oocysts. There may be some hemorrhage into the intestine, but the feces are rarely bloody.

*Eimeria arloingi* undergoes a development similar to that of *E. christenseni* (Fig. 1.48C,D) and causes similar gross and microscopic lesions in goats, with minor differences. First-generation schizonts are most numerous in the lacteals of villi in the lower jejunum, gamonts are mainly above the host-cell nucleus, and the associated, grossly visible plaques in the mucosa (Fig. 1.48A,B) may tend to be more distal in the small intestine, and occasionally involve the large bowel; *E. ahsata* and *E. ovina* in sheep are similar.

Nodular polypoid structures, sometimes pedunculate and about 0.3–1.5 cm in diameter, are encountered in the small intestinal mucosa of sheep and goats, usually as an incidental finding. These masses are composed of hypertrophic crypt–villus units, in which virtually every epithelial cell is infected by mainly gametocytic stages of coccidia. Adjacent mucosa appears normal and is uninfected. The term "pseudoadenomatous" has been used to describe these polypoid lesions and the plaques discussed above in coccidia-infected sheep and goats. The infected epithelial cells also appear somewhat hypertrophic, with eosinophilic cytoplasm, and often these coccidia-infected cells do not slough rapidly postmortem, in contrast to their uninfected fellows. This may aid a histologic diagnosis in otherwise autolytic gut in clinical cases. Why nodular masses of infected cells apparently persist in chronically infected animals without clinical disease is unclear.

Large schizonts are often encountered incidentally in submucosal lymphatics or in the subcortical or medullary sinusoids of mesenteric lymph nodes in sheep and goats. Sometimes they may be visible grossly in these locations as pinpoint white foci. Occasionally, coccidial gametocytes or oocysts may also develop in the mesenteric lymph nodes, where they may invoke a mild granulomatous reaction. These stages probably result from establishment of sporozoites or primary merozoites swept from the lacteal into the lymphatic drainage early in infection. Development in such locales is to be regarded as not uncommon, but aberrant, and likely dead-end. The species involved appear mainly to be those considered above, with a giant primary schizont developing in the lacteal.

Ill thrift and diarrhea in suckling or weanling lambs 5–6 weeks old, heavily stocked on pasture, may also be due to coccidiosis. In the United Kingdom, *Eimeria crandallis,* which develops largely in the ileum, and *E. ovinoidalis* are associated mainly with this syndrome. *Eimeria weybridgensis* (*E. arloingi* "B"), which infects most of the length of the small intestine, may contribute also. Under some circumstances, several of these species cause villus atrophy in infected areas of intestine. Villi may be stumpy or absent, and crypts are straight, hypertrophic, and contain proliferative epithelium. Asexual or, more commonly, sexual stages of coccidia are present in epithelium on the surface of the mucosa. Such lesions, if widespread, may cause malabsorption or perhaps be associated with protein-losing enteropathy. It is unclear whether atrophy of villi is the result of excess loss of epithelium directly due to the effects of coccidial infection or is mediated by an immune response. In addition to villus atrophy, which may cause subclinical disease, perhaps diarrhea but rarely death, mortality may be associated with the presence of a grossly congested or edematous thickened intestine or segment thereof.

Oocyst numbers are usually high in feces, but this is neither constant in, nor necessarily indicative of, coccidiosis. Mucosal scrapings or tissue sections of mucosa containing large numbers of asexual and gametogenous coccidial forms, in association with diarrhea, and perhaps some hemorrhage into the intestine, support the diagnosis in the absence of other syndromes such as gastrointestinal helminthosis. Bacterial enteritis, particularly clostridial enterotoxemia and septicemic pasteurellosis, and in young lambs and kids, viral diarrhea or cryptosporidiosis, must be differentiated. In light of the large number of relatively innocuous species of coccidia infecting sheep and goats, and the uncertainty of the lesions associated with some, sporulation and positive identification of oocysts in mucosal scrapings or feces is desirable.

HORSES. The only coccidium of horses reported with any frequency is *Eimeria leuckarti,* which is found in horses and donkeys the world over. In one survey of foals in the United States, it was found in nearly 60%. It may also occur in older animals. Its reputation for pathogenicity rests largely on the distinctive large gamonts found by pathologists in the lamina propria of the small intestine in animals dead of obscure enteric disease. Implication of *E. leuckarti* in the disease process is rarely, if ever, convincing, however, and it is encountered incidentally in the intestine of horses dead of other clearly defined conditions. Furthermore, heavy experimental inoculations, producing many gamonts in the gut and heavy oocyst passage, have failed to elicit clinical signs.

The stages present in the lamina propria of villi are giant microgametocytes and macrogametes, developing in markedly hypertrophic host cells, probably of mesenchymal origin (Fig. 1.48E). The microgametocytes are up to ~250 μm in diameter, and when mature they contain swirling masses of microgametes. Immature microgametocytes very much resemble some of the giant schizonts of other species of coccidia and have frequently been referred to as such; this stimulated the application of the term *Globidium* to the organism. Schizonts containing merozoites have never been recognized in this organism, however, nor in several similar species of coccidia developing in the lamina propria in other hosts. The macrogametes have distinctive large eosinophilic or PAS-positive granules, which may be individual or confluent. The host cells are markedly hypertrophic with a fibrillar periphery, and the enlarged nucleus forms a crescent along one side of the parasitophorous vacuole. There is no inflammatory response to the gamonts, and only a mild reaction to degenerate stages in the lamina propria.

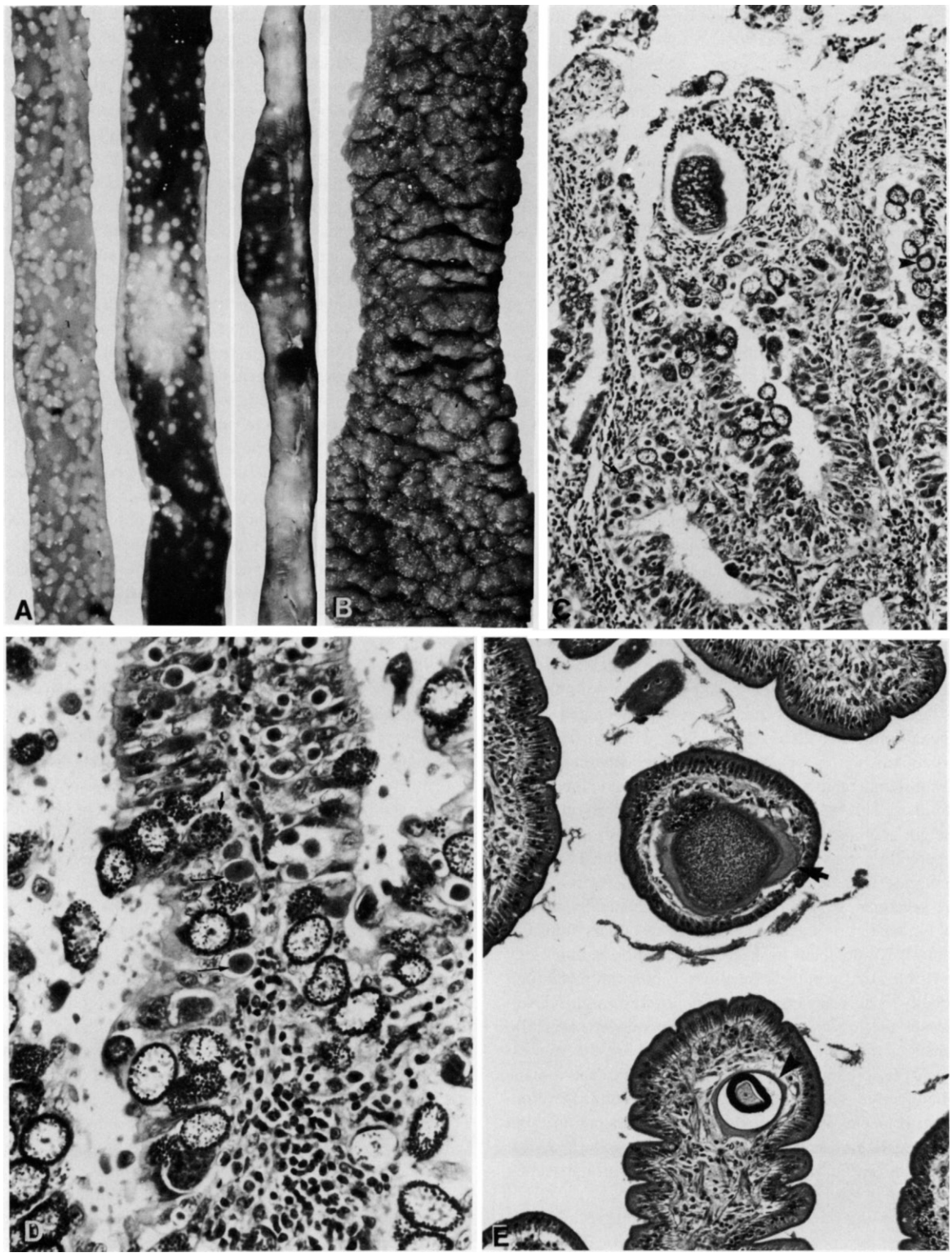


**Fig. 1.48** Coccidiosis. (**A–D**) Goat. (**A**) White nodules on mucosa are visible from serosa (right). Hemorrhage in lumen. *Eimeria arloingi*. (Courtesy of P. A. Taylor.) (**B**) Chronic coccidiosis, showing mucosal hypertrophy. (**C**) *Eimeria arloingi*. Ileum. Large schizont in lacteal and gamonts (arrow) and developing oocysts (arrowhead) in epithelium of crypts and villi. (**D**) *Eimeria arloingi*. Goat. Undifferentiated gamonts (long arrow), macrogametocytes (short arrow), and microgametocytes infect epithelial cells. (**E**) Microgametocyte (arrow) and developing oocyst (arrowhead) of *E. leuckarti* in lamina propria. Horse.

SWINE. At least 8 to 10 species of *Eimeria* are thought to occur in swine, as does a single species of *Isospora*. The latter, *I. suis*, is the most important, causing porcine neonatal coccidiosis, a disease of piglets from about 5 or 6 days to about 2 to 3 weeks of age. This disease is recognized in the United States, Canada, the United Kingdom, and western Europe; it also occurs in Australia, and probably wherever swine are reared intensively. The condition is most severe in herds where continuous farrowing and total confinement are practiced, and some laboratories report a prevalence of 10 to 50% among scouring baby pigs.

Porcine neonatal coccidiosis has a high morbidity, and usually a low but variable mortality. It causes yellow, watery diarrhea, dehydration, loss of condition, and death, or at least temporary check in growth. Some animals may runt severely. Illness usually begins at about 7 to 10 days of age. Piglets continue to nurse but may vomit clotted milk. At autopsy, many piglets have the typical appearance of undifferentiated neonatal diarrhea, with no specific gross findings in the gastrointestinal tract other than fluid yellow content. The intestine in animals with coccidiosis may look turgid rather than flaccid, however, and in a minority of animals, a fibrinous or fibrinonecrotic exudate is present in the lower portion of the small intestine. Occasionally, casts will form.

*Isospora suis* replicates in the epithelium on the distal third of villi, mainly in the jejunum and ileum, though infected cells may be found in the duodenum and colon in a few animals. Piglets usually become infected within the first day or two of life, perhaps by coprophagy of the sow's feces. Merogony occurs in two phases in vacuoles in the cytoplasm of the host cell. Infection of host cells is maximal 4 or 5 days after infection, and by 5 days, gametogony is evident. The onset of lesions and clinical signs corresponds with this period of heavy infection of cells. Villi may become markedly atrophic (Fig. 1.49A). The surface epithelium that remains is cuboidal to squamous, and infected epithelial cells may be seen undergoing lysis. Erosions may develop at the tips of villi (Fig. 1.49B). In the remnant of the villus, neutrophil infiltration, a moderate increase in round cells, and an eosinophilic proteinaceous material, perhaps collagen, may be present in the lamina propria. Effusion of neutrophils and fibrin from the eroded tips of villi contributes to the fibrinonecrotic membrane seen in some animals, and ulceration can occur. Gram-positive cocci are often present in the exudate. In animals surviving for a few days, the cryptal epithelium may be markedly hyperplastic.

The severity of the lesions is a function of the size of the inoculum and the age of the pigs. Heavier inocula, within limits, produce more cellular damage and villus atrophy; fibrinonecrotic enteritis indicates ingestion of a large dose of oocysts. Severe lesions may not be associated with heavy shedding of oocysts, however, since relatively few gamonts are able to develop in the reduced population of epithelial cells remaining on villi. The severity of lesions and signs is much greater in piglets a few days old in comparison with those 2 weeks of age. This relates partly to the lower rate of replication of epithelium in the crypts of young piglets, and therefore, the development of more severe villus atrophy. The smaller size of young piglets also makes them more susceptible to dehydration. Animals previously exposed to *Isospora suis* have relatively strong resistance to challenge.

A diagnosis of coccidiosis must be considered in scouring piglets of the appropriate age group and is suggested strongly by the presence of fibrinonecrotic enteritis in the distal small bowel. Atrophy of villi may be recognized at autopsy using a hand lens or stereomicroscope, or in tissue section. Asexual or sexual stages may be found in smears of mucosal scrapings. The distinctive binucleate type 1 meronts and pairs of large (12–18 μm in smears, 8–13 μm in sections) type 1 merozoites may be found in jejunal mucosa in the early phase of diarrheal disease. Multinucleate type 2 meronts and numerous small type 2 merozoites are the predominant stage during the clinical phase of disease. In section, these form clusters of 2 to 16 organisms like bunches of bananas, perhaps with a small residual body, in the parasitophorous vacuole.

Macro- and microgamonts are present in moderate numbers by the fifth day of infection, and a few oocysts may also be seen. Microgametocytes are about 9–16 μm in diameter and are multinucleate while developing. Oocysts in tissue sections are oval, about 15 × 12 μm, while those in smears are about 18 × 16 μm. Coccidial stages may be difficult to find in animals that have been ill for several days. Oocysts may not be found in feces, either because the infection is not yet patent, the patent period has passed, or the lesions are very severe, reducing the number of oocysts produced.

Coccidiosis may occur concurrently with the other infectious and parasitic diseases causing diarrhea in neonatal pigs, and it also must be differentiated from them. If coccidia are found in atrophic mucosa, even associated with other agents, they should be considered potentially significant. Enterotoxic colibacillosis usually affects a younger age group, though some piglets with coccidiosis may also have adherent *Escherichia coli*. Rotavirus and coronavirus also cause villus atrophy and are the main conditions to differentiate from coccidiosis in animals with atrophic villi. When they occur together with coccidiosis, they may have additive effects.

Coccidiosis in older swine is due to several *Eimeria* species and is uncommon. It typically occurs in animals with access to yards or pasture contaminated with oocysts. Weaners and growing pigs are affected. The species considered potentially pathogenic include *E. debliecki*, *E. scabra*, and *E. spinosa*. Rare massive infections of some other species may also cause disease. Coccidiosis in swine due to *Eimeria* is usually sporadic or affects a few pigs in a group. Typically it causes diarrhea of a few days durations, loss of appetite, and perhaps transient ill thrift, or in severe cases, emaciation. Occasionally animals die.

Lesions are usually limited to the lower small intestine, which may be congested or hemorrhagic, though overt blood is rarely found in the feces. Large numbers of schizonts, gamonts, and developing oocysts are in epithelial cells on villi and sometimes in crypts. Atrophy of villi or erosion and local hemorrhage may be evident, the lamina propria is edematous, and desquamated epithelium and oocysts are in the lumen of the gut. Rarely, heavily infected animals may have lesions in the large intestine. The species involved are diagnosed on the basis of the morphology of oocysts in feces or mucosal scrapings.

Coccidial gamonts and oocysts of a species resembling

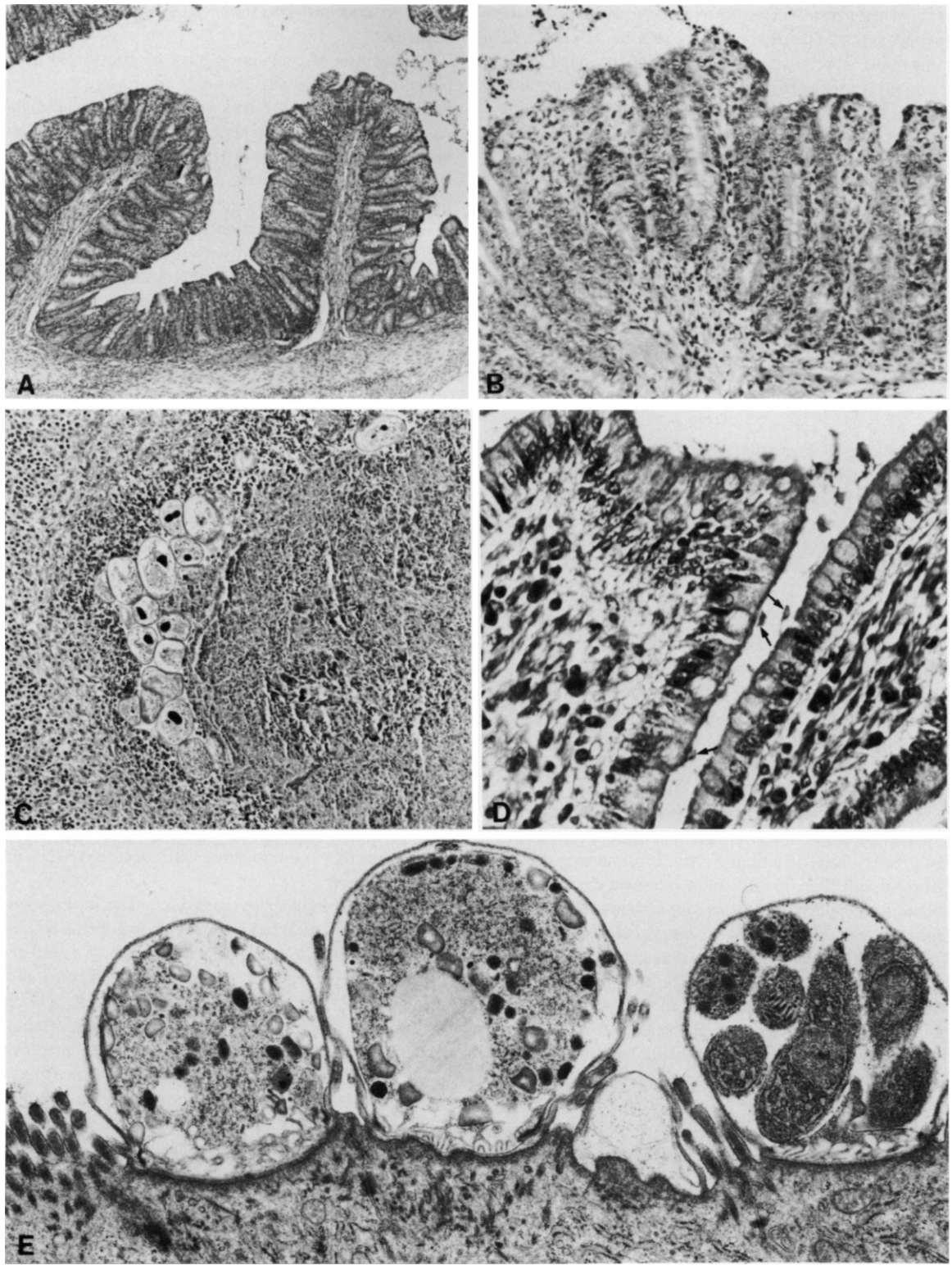


**Fig. 1.49.** (**A**) Villus atrophy. Small intestine. Piglet. *Isospora suis* infection. (**B**) Detail of (**A**). Surface epithelium is severely attenuated, and there is some erosion and effusion at tips of villi. (**C**) *Balantidium coli* in ulcerated colon of pig with intestinal adenomatosis and necrotic enteritis. (**D**) *Giardia lamblia* (arrows) applied to brush border of enterocytes on villi. Cat. (**E**) Cryptosporidia attached to apex of enterocytes in small intestine. Two macrogametes, and a schizont containing merozoites. (Courtesy of S. Tzipori.)

*Eimeria debliecki* have been found infecting epithelium on the papilliform mucosa of cystic bile ducts in porcine liver. This is probably an aberrant site of development.

DOGS AND CATS. Although several species of *Eimeria* have been reported from dogs and cats, their status as genuine parasites of these hosts is in doubt. The significant coccidia of dogs and cats are members of the genus *Isospora,* considered here, and *Toxoplasma, Sarcocystis, Hammondia,* and *Besnoitia,* dealt with subsequently.

*Isospora* is characterized by oocysts that are passed unsporulated in feces, and that when sporulated have two sporocysts, each with four sporozoites. Some species are apparently homoxenous, others heteroxenous. Following ingestion of sporulated oocysts, transport hosts, usually prey species such as mice and other small rodents, but sometimes other hosts, are infected by large sporozoite-like "hypnozoites" in phagocytic cells in lymph nodes and other tissues. These, when ingested by the predator, resume development in the intestine and lead to asexual and sexual development in the definitive host. Heteroxenous passage is not obligatory, and sporulated oocysts are also directly infective to the definitive host.

Coccidiosis in the dog and cat is largely a clinical entity, usually nonfatal. The lesions of coccidiosis in small animals are poorly defined, and care must be taken not to ascribe disease to these organisms simply on the basis of the presence of endogenous stages in the mucosa of animals dead of enteric disease. Rotavirus and coronavirus might be expected to produce similar signs. Some genuine cases of fatal coccidiosis do occur, however, though few are recorded in the literature. Affected animals are young and usually from environments such as pet shops, animal shelters, or kennels, where standards of sanitation may not be high. There is a history of diarrhea of several days duration, and the animal is dehydrated. Other than mild hyperemia of the mucosa and excessively fluid content of the small intestine and colon, gross lesions in the gut may not be evident. Microscopically, there may be moderate atrophy of villi, with attenuation of surface enterocytes, and perhaps effusion of acute inflammatory exudate from the tips of some eroded villi. Asexual and sexual stages of coccidia will be evident in moderate to large numbers in the epithelium or lamina propria of villi. In some cases the large bowel may be infected, with exfoliation of surface epithelium and the accumulation of necrotic debris in some dilated glands.

In dogs, four species of *Isospora* have been recognized, and the endogenous stages of these must be differentiated from those of *Hammondia* and *Sarcocystis*. Meronts of *I. canis* develop in the subepithelial lamina propria of the villi in the distal small intestine and, to a lesser extent, in large bowel. Gamonts occur beneath and within the epithelium of the ileum and large intestine, and the oocyst is the largest among *Isospora* of dogs, being about 38 × 30 μm. Endogenous stages of *I. burrowsi* occur in epithelial cells and in the lamina propria of the tips of villi in the distal two-thirds of the small intestine. *Isospora neorivolta* develops mainly in proprial cells beneath the epithelium in the tips of villi in the distal half of the small intestine, and rarely in the cecum and colon. Occasional stages may be in the epithelium. *Isospora ohioensis* develops exclusively in epithelial cells, mainly in the distal portions of villi along the length of the small bowel, especially in the ileum, and occasionally in the large bowel. The oocysts of *I. burrowsi, I. ohioensis,* and *I. neorivolta* are similar. Original literature should be consulted for details that permit differentiation of these species in tissue. *Isospora canis* and *I. ohioensis* are known to be heteroxenous.

In cats, two heteroxenous *Isospora* species occur. Meronts and gamonts of *I. felis* develop in epithelium of villi in the small intestine, and occasionally in epithelium in the large bowel. The oocyst is large, about 43 × 33 μm. *Isospora rivolta* also develops in epithelium on villi and in crypts and glands in the small and large intestine. Oocysts are ovoid, about 25 × 23 μm.

*TOXOPLASMA, SARCOCYSTIS, BESNOITIA, HAMMONDIA,* AND *FRENKELIA.* These heteroxenous members of the Apicomplexa utilize carnivores as definitive hosts and have one or more generations of merogony in the tissues of various species of prey. *Frenkelia,* as far as is known, utilizes only raptorial birds as definitive hosts, and small rodents as intermediate hosts. It will not be considered further.

***Toxoplasma gondii*** uses members of the Felidae as definitive hosts. The organism is optionally heteroxenous; cats may be infected directly by ingestion of oocysts, or probably most commonly by ingestion of asexual stages developing in the tissues of prey species. These intermediate hosts are infected by oocysts shed in the feces of cats, or perhaps by a variety of other routes considered below. Five stages of asexual development have been recognized in the intestinal epithelium of cats infected with tissue cysts from intermediate hosts. The gametocytes also develop in epithelium on villi, especially in the ileum. In heavy infections, exfoliation of infected epithelium from villi is associated with the development of villus atrophy, and occasional spontaneous cases of diarrhea in kittens seem to be caused by *Toxoplasma*-induced atrophy of villi and malabsorption.

In intermediate hosts, and in cats, extraintestinal asexual development occurs in a variety of organs and tissues. Rapidly dividing forms (tachyzoites) may proliferate in many sites for an indefinite number of generations and are the stage associated with acute toxoplasmosis in cats and other species. Eventually, tachyzoites enter host cells, induce the formation of a cyst wall, and divide slowly by endodyogeny, forming bradyzoites.

*Toxoplasma gondii* is unique among the protozoa in its ability to parasitize a wide range of hosts and tissues. It is one of the most ubiquitous of organisms; experimentally, essentially all homeothermic animals can be infected, and natural infections have been shown to occur in nonhuman primates, rodents, insectivores, herbivores, and carnivores, including domestic species and humans. Serologic surveys indicate that infection is widespread in most species of domestic animals; except for abortions in sheep and goats, however, overt disease is sporadic.

Transmission may occur by a number of different routes. The shedding of oocysts in the feces of cats and wild Felidae has been mentioned earlier. Transplacental infection occurs commonly in sheep and goats and sporadically in swine and humans. Carnivorous animals and humans may become infected by ingesting cysts containing bradyzoites in tissues of infected animals. Pro-

longed excretion of *Toxoplasma gondii* in the semen of goats and rams has been observed experimentally. The importance of venereal transmission, under field conditions, is unknown and warrants further investigation.

Tachyzoites have been demonstrated in milk from experimentally infected goats. However, the chance of the organisms being in the milk of spontaneously infected goats is very small. Apparently, large numbers of infecting oocysts are required for tachyzoites to be excreted in the milk. Consumption of raw goat milk has been associated with human cases of toxoplasmosis. Milk is, however, not considered to be an important source of toxoplasma for humans because tachyzoites are destroyed by gastric juices and pasteurization. *Toxoplasma* has also been isolated from the milk of lactating sows, and in this species it may be a source of infection to neonatal piglets.

Systemic toxoplasmosis occurs most commonly in young animals, especially neonates. In the latter age group the infection may be acquired pre- or postnatally. After ingestion, *Toxoplasma* organisms penetrate the intestinal mucosa. In cats, the enterointestinal cycle and systemic infection occur almost simultaneously. In other animals the tachyzoites are the first stage of infection, after the bradyzoite is released from the cysts in the intestine.

Dissemination of *Toxoplasma* occurs in lymphocytes, macrophages, granulocytes, and as free forms in plasma. From the intestine the organism may follow two routes. It may spread via the lymphocytes to the regional nodes and from there via the thoracic duct to the lungs; or it may pass in the portal circulation to the liver and from there to the lungs. Further dissemination from the lungs occurs to a wide variety of organs. Entry to the host cell may be the result of both phagocytosis and active penetration. The ability of *Toxoplasma* to survive in the intracellular environment is apparently due to failure of fusion of lysosomal membranes with membranes of the parasitophorous vacuole. The reasons for this failure of phagocytic degradation of *Toxoplasma* are still poorly understood. Cell-to-cell transmission may occur within infected organs.

Necrosis is a feature in organs heavily infected with tachyzoites, and this appears to be directly related to the rapid replication of the organism. There is no evidence that *Toxoplasma gondii* produces a toxin. The outcome of infection is determined by a number of factors, including the number and strain of *Toxoplasma* in the infecting dose, and the species, age, and immune status of the host. Lesions in visceral organs are usually evident within 1 to 2 weeks after oral infection. Variable numbers of tachyzoites are usually found in the vicinity of the necrotic areas. Specific immunity develops within a few days after infection. This reduces the severity of infection but usually does not terminate it. Immune animals develop a chronic or dormant form of *Toxoplasma* infection characterized by the formation of cysts, containing bradyzoites, which are mainly located in the brain, skeletal muscle, and myocardium. The formation of cysts is accompanied by the disappearance of tachyzoites from the circulation and visceral organs. Cyst formation may take place as early as 1 to 2 weeks after infection, and they may persist for months, possibly years. Intracellular encystment protects the bradyzoites from both cellular and humoral immune mechanisms. Inflammation is usually not associated with cysts. When the level of immunity drops below a critical level, for example, due to treatment with immunosuppressive drugs, intercurrent disease, or other factors that depress immunity, a chronic infection may become reactivated. The cysts rupture and cause a severe inflammation that is mainly hypersensitive in character. Apparently, released bradyzoites rarely infect other cells.

The clinical signs of toxoplasmosis vary considerably, depending on the organs affected. The most consistent signs that have been reported are fever, lethargy, anorexia, ocular and nasal discharges, and respiratory distress. Neurologic signs include incoordination, circling, tremors, opisthotonus, convulsions, and paresis. Paresis is often associated with radiculitis and myositis. In dogs, toxoplasmosis may coexist with canine distemper and signs are, in any case, not sufficiently distinctive to allow ready differentiation. Immunosuppression by intercurrent distemper may activate latent *Toxoplasma* infection.

Systemic toxoplasmosis has been reported in most species of domestic animals. Pulmonary lesions are probably most consistently found, followed by central nervous system lesions. The lesions in the various organs are morphologically similar in most species, varying mainly in degree.

Macroscopic lesions in the lung vary from irregular, gray foci of necrosis on the pleural surface to a hemorrhagic pneumonia with confluent involvement of the ventral portions. Careful examination of the liver usually reveals either areas of focal necrosis or irregular mottling and edema of the gallbladder. The spleen is enlarged, as are lymph nodes, which are wet and frequently red. Pleural, pericardial, and peritoneal effusions occur irregularly. Pale areas may be evident in the myocardium and skeletal muscle. Occasionally, the pancreas is the most severely affected organ, in which case an acute hemorrhagic reaction may involve the entire organ. Yellow, small, superficial intestinal ulcers with a hyperemic border have been reported in piglets. Large pale areas of necrosis may be present in the renal cortices, mainly in goats and kittens. Chronic granulomatous toxoplasmosis may involve the intestine in older cats and produce annular areas of thickening. The mucosa overlying the granulomas may be ulcerated.

Microscopically, the early pulmonary lesions are characterized by diffuse interstitial pneumonia, and the alveolar septa are thickened due to a predominantly mononuclear inflammatory cell reaction with a few neutrophils and eosinophils. Large numbers of macrophages and fibrinous exudate fill the alveoli. Foci of necrosis involving the alveolar septa, bronchiolar epithelial cells, and blood vessels are scattered throughout the lobules. These lesions are soon followed by regenerative changes characterized by hyperplasia and hypertrophy of alveolar lining cells, mainly type II pneumocytes: so-called epithelialization of alveoli. In some areas this may be so marked as to give the affected areas an adenomatous appearance. Tachyzoites are usually evident in variable numbers in alveolar macrophages and may also be found in bronchiolar epithelial cells and the walls of blood vessels.

In the liver, irregular foci of coagulation necrosis are scattered at random throughout the lobules. There is usually little evidence of inflammation associated with the necrotic areas. Variable numbers of tachyzoites may be present in hepatocytes

and Kupffer cells, usually at the periphery of the lesions. A moderate lymphocytic reaction may be found in periportal areas and around central veins in cats. In this species, tachyzoites have also been observed in bile duct epithelial cells. If the pancreas is involved, there is extensive peripancreatic fat necrosis, with areas of coagulation necrosis in parenchyma. Numerous tachyzoites are usually evident in both ductal and acinar cells.

Lesions in lymph nodes are often associated with infection in the corresponding organ. They are characterized by irregular areas of coagulation necrosis, mainly in the cortex. A moderate inflammatory reaction may be evident at the periphery of the necrotic areas. There may be necrosis and depletion of lymphocytes in the follicles. In more chronic cases, the changes are those of nonspecific hyperplasia of lymphoid cells in cortical and paracortical areas, with a large macrophage population in the medullary sinusoids. Tachyzoites may be seen in phagocytic cells in sinusoids. Similar lesions may occur in the spleen. Necrotic areas are mainly located in the red pulp in this organ.

In the heart and skeletal muscle, foci of necrosis and mononuclear-cell inflammation may be part of toxoplasmosis. There is often some difficulty in distinguishing between tachyzoites and mineralization of mitochondria in myocytes, but at some distance from areas of acute reaction, inert cysts can usually be identified in healthy fibers.

The development of brain lesions is inconsistent. In the most fulminating cases, cerebral lesions may be relatively inconspicuous. They consist of a nonsuppurative meningoencephalitis with multifocal areas of necrosis and often malacia. There is swelling of endothelial cells, necrosis of vessel walls, and vasculitis. There may be marked perivascular edema and hyperplasia of perithelial cells. Tachyzoites and occasionally cysts may be found in vessel walls and in necrotic areas in both gray and white matter at all levels of the brain. If survival is prolonged, residual cerebral lesions consist of microglial nodules along with more extensive hyperplasia of perithelial cells and perivascular fibrosis, which tends to make the vessels very obvious. At this stage, tachyzoites are rare, and cysts 30 μm in diameter with a wall of amorphous acidophilic material ~1 μm thick, located in areas away from the lesions, may be the only form seen. Spinal cord lesions resemble those seen in the brain.

The placental and fetal lesions associated with *Toxoplasma* infection are described with the Female Genital System (Volume 3), and ocular lesions with the Eye and Ear (Volume 1).

The finding of tachyzoites and/or cysts in association with areas of coagulation necrosis in one or more organs is highly suggestive of toxoplasmosis. With the exception of the dormant cysts, which may be found in brain, the accidental discovery of *Toxoplasma* in routine sections is rare. The inference from this is that in spite of the ubiquity of the infection, when *Toxoplasma* is found in sections in association with lesions, it is probably significant. The encephalitic form of toxoplasmosis in pigs must be differentiated from pansystemic viral infections with brain lesions, such as pseudorabies, hog cholera, African swine fever, and viral encephalitides. These diseases are discussed elsewhere. In sheep and horses, lesions of the central nervous system due to *Toxoplasma*-like organisms must be differentiated from those due to *Sarcocystis*, which tend to be associated with vessels. The lung lesions in cats with toxoplasmosis resemble those of feline calicivirus infection (see the Respiratory System, this volume).

Serologic tests such as the Sabin–Feldman dye test and the indirect hemagglutination test are of limited value in the diagnosis of disease associated with *Toxoplasma gondii* infection. The fluorescent-antibody technique is available for application to infected tissues. Intraperitoneal inoculation of infected tissue into mice may be needed to differentiate toxoplasmosis from other protozoan infections, such as *Sarcocystis*.

***Hammondia*** species are obligatorily heteroxenous organisms, with the cat (*H. hammondi*) and dog (*H. heydorni*) as definitive hosts. They are also known as *Toxoplasma hammondi* and *Isospora bahiensis*, respectively. *Toxoplasma*-like oocysts are shed in the feces of the definitive host and are infectious to intermediate hosts, normally prey species. There, bradyzoites develop in cysts in striated muscle. Disease is not associated with infection of intermediate hosts; diarrhea may occur in heavily infected dogs.

***Sarcocystis*** is obligatorily heteroxenous. Sexual stages occur in the subepithelial lamina propria at the tips of villi in the small intestine of carnivores, and oocysts sporulate in tissue, producing two sporocysts within a thin oocyst wall. Sporocysts containing four sporozoites shed in feces are infective to intermediate hosts, in which several generations of schizogony occur in vascular endothelium, and a final cyst containing merozoites (bradyzoites) is formed in myocytes and, occasionally, other cells. Ingestion of tissue cysts containing bradyzoites initiates gametogony in the definitive host. There is apparently no resistance to the development of gamonts, and no disease is associated with them in the definitive host. Many species of *Sarcocystis* are recognized, based on prey–predator cycles. Gametogony of a given species usually occurs in only one species of carnivore. The number of vertebrates capable of acting as intermediate hosts may be narrow or wide, depending on the species of *Sarcocystis*.

*Sarcocystis* cysts in ovine muscle may be grossly visible, causing losses at meat inspection. It is unclear whether *Sarcocystis* is involved in the etiology of eosinophilic myositis in cattle. *Sarcocystis* infection in cattle, sheep, goats, and swine may cause chronic ill thrift or an acute fatal disease characterized by anemia and widespread hemorrhage. Both syndromes are initiated during the endothelial phase of the infection. Abortion occurs during this phase of infection in some species. Abortion associated with the acute disease in pregnant animals is the result of the systemic illness, and the fetus usually is not infected. In cattle, however, some abortions, seen in otherwise clinically normal animals, are associated with schizonts of *Sarcocystis* in the vascular endothelium of the fetus, especially in the brain, and with nonsuppurative encephalitis. Encephalitis is occasionally associated with *Sarcocystis* infection in sheep, and in horses, *Sarcocystis* is the cause of protozoal myeloencephalitis.

***Besnoitia*** is also obligatorily heteroxenous. Some stages of merogony, and gametogony, occur in the intestine of the definitive host, cats, where they are not known to be pathogenic. Oocysts are shed unsporulated. When sporulated, they are *Isospora*-like, and so-called large forms of *I. bigemina* are probably *Besnoitia* spp. Meronts in the intermediate host develop in mesenchymal cells, probably fibroblasts, which become massively

hypertrophic, forming cysts containing many clusters of merozoites (bradyzoites) in the host-cell cytoplasm. Among domestic animals, cysts of *B. besnoiti* may assume some significance in the skin of cattle (see the Skin and Appendages, Volume 1).

CRYPTOSPORIDIOSIS. *Cryptosporidium* is a small apicomplexan protozoan parasite found on the surface of epithelium in the gastrointestinal (Fig. 1.49E) and respiratory tracts of mammals, birds, reptiles, and fish. Respiratory infection seems most significant in birds. Disease in mammals is enteric. *Cryptosporidium* has a typical coccidian life cycle, with merogony, gametogony, and sporogony occurring in the brush border of infected epithelial cells. The organisms are within a vacuole formed by apposition of two unit membranes of the host cell, probably caused by inversion of a microvillus by the infecting sporozoite or merozoite. A specialized "feeder" organelle is often present at the attachment zone in the base of the vacuole, between the infecting organism and the cytoplasm of the host cell. Developmental stages are small, in most cases about 2–6 μm in diameter. Undifferentiated meronts and gamonts are recognized as small basophilic trophozoites. Mature schizonts contain small, falciform merozoites. Macrogamonts are ~5 μm in diameter and contain small granules. Oocysts in tissue sections often are collapsed into a crescent shape. The various stages may be recognized in wax- or plastic-embedded sections under the light microscope but are best studied with the electron microscope. Oocysts may be demonstrated by fecal flotation or in fecal smears stained with Giemsa, by a modified Ziehl–Neelsen technique, or with auramine O and examined with fluorescent light.

The number of generations of schizogony and the significance of possible autoinfection by oocysts sporulated in the intestine of the host are unclear. The massive number of organisms that may be present in clinically affected animals suggests that extensive proliferation may take place within the host following ingestion of oocysts.

Although most coccidia are considered host specific, *Cryptosporidium* is not. Experimental cross-infection using cryptosporidia recovered from humans and a variety of mammals has been accomplished, with other species of mammals, and sometimes birds, susceptible to infection. Some strain variations may exist, however, reflected in the relative host susceptibility and site of proliferation. Cryptosporidiosis is a zoonosis, some human cases being associated with exposure to infected animals.

The pathogenicity of cryptosporidia was not recognized for a long time, and the mechanism by which disease is induced is unclear. In some hosts, infection appears always to be asymptomatic. However, neonatal ruminants seem particularly susceptible to disease induced by cryptosporidia. Diarrhea, anorexia, and depression in calves occur usually between about 1 and 3 or 4 weeks of age, and in lambs about 5–14 days old. Cryptosporidiosis is incriminated sporadically as a cause of diarrhea in other species, including piglets and cats. In humans, immunosuppression may be contributory to the development of cryptosporidiosis, and heavy infections have occurred in Arabian foals with combined immunodeficiency. However, severe immunodeficiency does not appear to be a necessary concomitant of infection. Cryptosporidia frequently occur concurrently with enterotoxic *E. coli,* rotavirus, or coronavirus infection in neonatal ruminants, but it is clear from experimental work that *Cryptosporidium* can be a primary pathogen.

In all species, intestinal cryptosporidiosis is associated with villus atrophy of varying severity, with blunting and some fusion of villi and hypertrophy of crypts of Lieberkühn (Fig. 1.50A,C). Surface epithelium is usually cuboidal, rounded, or low columnar, and sometimes exfoliating or forming irregular projections at tips of villi. Large numbers of cryptosporidia are usually visible in the microvillus border of cells on the villi (Fig. 1.50B) and not in crypts of Lieberkühn, although occasionally the reverse is true. Organisms are most heavily distributed in the distal half of the small intestine, especially in the ileum. They may occur in the cecum and colon, however, where they infect cells on the surface and occasionally in glands. In heavily infected large bowel, some attenuation of surface epithelium and dilation of crypts with necrotic debris may be evident. Mild proprial infiltrates of neutrophils and mixed mononuclear cells are present in both small and large intestine.

Diarrhea in cryptosporidiosis may be related to malabsorption associated with villus atrophy, and perhaps to the occupation of a large proportion of the surface area of absorptive cells in the distal small bowel by cryptosporidia. Mucosal lactase activity in infected calves is significantly reduced, even at uninfected or lightly infected sites in the anterior small intestine. This suggests that the effects on mucosal digestion and absorption are not solely related to physical alteration of villi or microvilli and associated loss of functional surface area.

Cryptosporidiosis is most significant in calves, as a cause of undifferentiated neonatal diarrhea, in which it must be differentiated particularly from coronavirus and rotavirus infection. Frequently it is concurrent with other agents causing this syndrome. A similar situation occurs in lambs, though disease does not appear to be as common or well recognized in that species. It is a sporadic or minor cause of fatal diarrhea in other species, usually but not always occurring in the neonatal age group. Though cryptosporidiosis can be induced experimentally in piglets, it is a relatively rare cause of spontaneous disease in them. The pathologic diagnosis is based on the presence of large numbers of cryptosporidia in sections of freshly fixed lower small intestine. Examination of smears of ileal mucosa stained with Giemsa may allow a more rapid answer or permit a diagnosis on tissue from an animal dead for some hours. In neonatal animals, other infectious causes of diarrhea should be sought at the same time.

### *Other Protozoa*

AMOEBIASIS. *Entamoeba histolytica* is the cause of amoebiasis in humans, nonhuman primates, and occasionally in other species, including dogs and cattle; cats are susceptible to experimental infection. Among domestic animals, spontaneous amoebiasis occurs with any frequency only in dogs. Even then, it is uncommon or rare in most areas. Infection in dogs appears to have a low prevalence, and most cases are sporadic, probably acquired by exposure to cysts in feces from infected people. Dogs tend not to pass encysted amoebae; hence it has been suggested that they present little public health hazard and are unlikely to support spread from dog to dog. Under some circumstances, however, cysts may be shed, and fecal material contain-

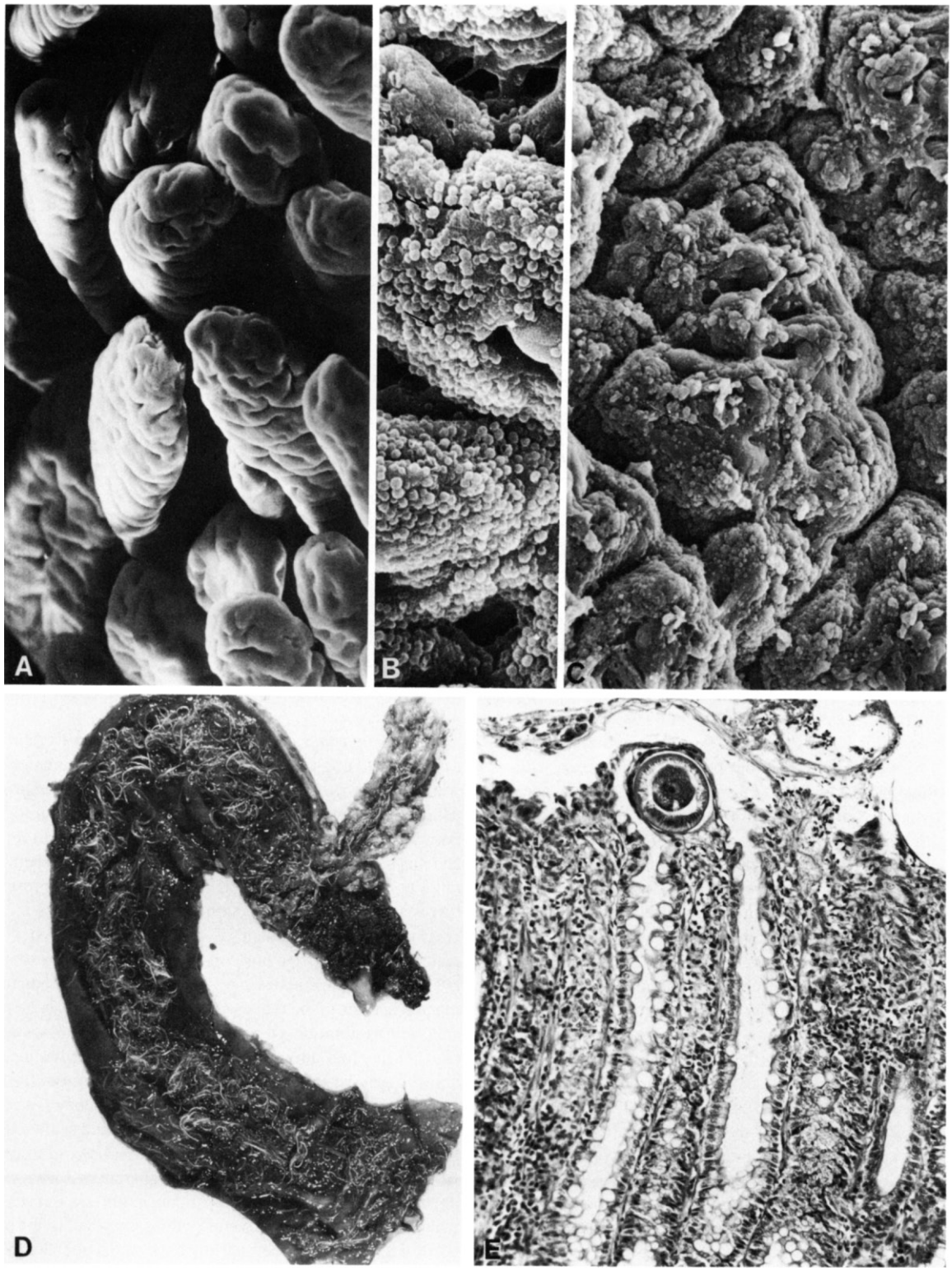


**Fig. 1.50.** (**A**–**C**) Scanning electron micrographs. (Courtesy of S. Tzipori.) (**A**) Normal villi. (**B**) Detail showing cryptosporidia (arrows). (**C**) Villus atrophy associated with cryptosporidiosis. Cryptosporidia are visible as minute spheres on the mucosal surface. (**D**) *Trichuris vulpis* typhlocolitis. Dog. (**E**) Mild erosive colitis. *Trichuris vulpis*. Dog. Anterior end of nematode is in tunnel in surface epithelium. There is exfoliation of epithelium, and effusion of neutrophils and fibrin from the surface.

ing motile trophozoites has been used to transmit infection orally to dogs.

Amoebae usually are nonpathogenic inhabitants of the lumen of the large bowel, but sometimes they cause colitis. The diet and immune status of the host and virulence attributes of various strains of the organism seem to influence pathogenicity. Large forms of *Entamoeba histolytica* are potentially invasive, and pathogenic strains are erythrophagocytic. Amoebiasis in dogs is associated with diarrheic or mucoid feces, perhaps with some blood, or with dysentery. Erosive mucosal colitis or ulcerative colitis occurs in dogs with amoebiasis, and disease seems more common or severe in animals with concomitant *Trichuris* or *Ancylostoma* infection.

Early lesions in human amoebiasis seem to be a diffuse acute mucosal colitis, with focal erosions or ulcerations. Amoebae, though scarce, may be found in mucus on the colonic surface but are most numerous in the fibrinocellular exudate over erosions or superficial ulcers. Ulcers advance as an area of necrosis and predominantly neutrophilic infiltrate, causing loss of glands, and extend for the full depth of the mucosa. Established ulcerative amoebic colitis classically has a flask-shaped ulcer, the narrow neck through the mucosa, and the broad base in the submucosa. There amoebae, and necrosis, expand laterally, apparently less constrained by the architecture of the tissue. The ragged mucosal margin of the ulcer overhangs the excavation in the submucosa. The muscularis is rarely invaded. Amoebae may attain the deeper tissue via mucosal blood vessels or lymphatics. A mixed inflammatory reaction is present about the periphery of areas of necrosis. Amoebae may be present, commonly in small clusters, in necrotic debris or in adjacent viable tissue, often not involved in an inflammatory reaction. Amoebae in tissue, often surrounded by a clear halo, may be spherical or irregular, with extended pseudopodia, and are about 6 to 40 or 50 μm in diameter. The nucleus has a central dense karyosome and peripheral chromatin clumps. The cytoplasm may appear foamy, can contain remnants of erythrocytes in phagolysosomes, and contains glycogen, which makes the cytoplasm PAS-positive. The lesions of established amoebiasis in the colon of dogs resemble those in humans, as may the early lesions.

Although dissemination of amoebae, with localization in other organs, especially liver, lung, and brain, is a relatively common complication in humans, it seems rare in dogs. One such case occurred in an animal with canine distemper.

*GIARDIA* AND OTHER FLAGELLATES. *Giardia* species are flagellate protozoa that inhibit the small intestine of a wide range of vertebrates. The taxonomy of the genus is confused. In the past, species status has been conferred on *Giardia* found in various hosts. Now it appears that a relatively small number of species exists, however, each with a relatively wide host range. *Giardia* infection is common in humans and is associated with disease in a proportion of them. *Giardia* from people are infective for a wide range of mammals, and there is circumstantial evidence that giardiasis in humans may be zoonotic in some cases. *Giardia* occurs in dogs, cats, cattle, sheep, and horses and has been associated with disease, with varying degrees of credibility, in each of these hosts.

*Giardia* trophozoites are pyriform in outline, about 10 to 20 μm long by 5 to 15 μm wide and 2 to 4 μm thick, and convex on the dorsal surface. The concave ventral surface is modified by the presence of an adhesive disk, which functions in attachment. Nutrient absorption seems to occur through the dorsal surface. A pair of nuclei, two axonemes, two medial bodies, and four pairs of flagella are present. The organisms apply their ventral aspect to the microvillous surface of enterocytes (Fig. 1.49D), usually between villi, in folds on the villous surface, or occasionally in crypts of Lieberkühn. *Giardia* has been demonstrated in the mucosa, but this is an unusual and probably aberrant location. Relatively resistant oval cysts are passed in the feces, and transmission is by the fecal–oral route.

The significance of *Giardia* as a pathogen in humans and other species has been controversial, since asymptomatic infection is the rule. There now seems little doubt that under some circumstances *Giardia* may cause disease. How the host–parasite relationship is modified to cause disease, and the pathogenesis of disease, are still unclear. In young dogs and cats, in which the disease is most important, though still uncommon, the main sign is intermittent or chronic diarrhea, which may persist for several months. The stool is soft, pale, mucoid, and greasy. Though appetite is not usually impaired, there may be a reduced growth rate or weight loss, suggesting malabsorption. A poor hair coat is attributed to deficiency of fat-soluble vitamins. Gastrointestinal dysfunction has not been extensively documented in animals. Some people with *Giardia* infection have malabsorption of *d*-xylose and vitamin $B_{12}$, and steatorrhea and hypocarotinemia. Excess fecal fat has been found in infected cats, but *d*-xylose malabsorption was not demonstrated in one dog with giardiasis.

Several mechanisms have been proposed to explain these findings. Although villous atrophy may occur in human patients with giardiasis, this usually occurs mainly in a subgroup of patients with hypogammaglobulinemia. Marked histologic abnormality is not found in many cases of giardiasis in humans, and this seems also to be true for dogs and cats. In experimental murine giardiasis, infection is associated with hypertrophy of crypts and increased production of cells, combined with an increased rate of movement of enterocytes along villi. Intraepithelial lymphocytes are common in infected intestine, and altered epithelial kinetics may be related to cell-mediated immune reactions in the mucosa. Atrophy of villi has been associated with restoration of cell-mediated immune competence in *Giardia*-infected athymic mice, suggesting that immune phenomena may be involved in the pathogenesis of giardiasis.

Selective deficiencies in some brush-border enzymes occur in people with giardiasis. Possibly these are related to altered villus transit times or to the direct effects of *Giardia* on microvilli, which may be deformed adjacent to adherent organisms. *Giardia* may also inhibit the activity of pancreatic lipase, causing fat malabsorption. Bacterial overgrowth of the small intestine may occur with *Giardia* infection, however, and associated bile salt deconjugation could explain steatorrhea in giardiasis. Possibly, *Giardia* is capable of deconjugating bile salts.

Giardiasis is usually diagnosed clinically on the basis of typical cysts in fecal flotations, or trophozoites in intestinal aspirates or fecal smears, coupled with remission of clinical signs following therapy and an inability to identify other potential

causes of the signs. A diagnosis is sometimes based on findings in biopsies of small intestine, or at autopsy. In dogs and cats, morphologic changes in the mucosa are not well defined. The mucosa may appear normal, but there may be equivocal blunting of villi, perhaps associated with a moderate infiltrate of mononuclear cells into the core of the villus, or a heavy population of intraepithelial lymphocytes. *Giardia* should be sought in animals with malabsorption syndromes. They lie between villi and are usually evident as crescent shapes, applied by their concave surface to the brush border of epithelial cells. In favorable sections through the level of the nuclei, they may appear to have a pair of "eyes." Trophozoites oriented along the plane of section may look as they do in smears, the paired nuclei giving the organism a facelike appearance. An abnormal number of bacteria, suggestive of overgrowth, may be present in the mucus and content in the vicinity, in symptomatic animals. A diagnosis of giardiasis should always be reserved for those cases in which no other explanation for the syndrome can be identified. Giardiasis has been associated with mucosal colitis in dogs, but the association is probably coincidental.

Among animals other than dogs and cats, *Giardia* seems most convincingly to be associated with enteric signs in cattle. However, the significance of infection in that and other species is very poorly defined.

*Trichomonas,* or similar flagellates, are sometimes encountered in the feces of horses, dogs, cats, and cattle with diarrhea, but there is no established causal association between the organisms and disease. The association of trichomonads with diarrhea in horses is discussed briefly with typhlocolitis in horses.

*BALANTIDIUM.* *Balantidium* is a large, oval protozoan about 50–60 μm or more long, with a macronucleus and micronucleus and covered by many cilia arrayed in rows along its surface. *Balantidium coli* occurs in the large bowel of swine, humans, and nonhuman primates. It is very common in pigs, and many infected people live in close contact with swine. It has also been reported from several dogs with access to swine yards, as a complication of trichurosis.

*Balantidium* is normally present as a commensal in the lumen of the cecum and colon but is capable of opportunistic invasion of tissues injured by other diseases. Its capacity to invade may be related to production of hyaluronidase. In swine, where the organisms are most commonly encountered by veterinary pathologists (Fig. 1.49C), *Balantidium* may be found at the leading edge of the necrotizing or ulcerative lesions of the large intestine that develop secondarily to intestinal adenomatosis, swine dysentery, or perhaps salmonellosis. Likely, *Balantidium* interacts with the anaerobic colonic flora in perpetuating and advancing the necrotizing lesions that are themselves complications of the primary bacterial infection. *Balantidium* is recognized in tissue by large size, ovoid shape, the dense, curved or kidney-shaped macronucleus, and the presence of cilia (which may be accentuated by silver stains) on the surface.

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