Cell Pathology

SECOND EDITION

Norman F. Cheville,

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Preface

Cell Pathology was written for the professional person who must deal medically with sick animals. While this description encompasses zoologists caring for wild species and physicians interested in comparative medicine, the text was developed to conform with the discipline of pathology as it exists within the field of veterinary medicine.

The book was begun to provide an introduction to the ultrastructural aspects of anatomical pathology. The goal was to bridge the gap between what is seen in the electron microscope by the experimental pathologist and what the prosector encounters in the postmortem room. During the initial assembly of candidate micrographs, it became obvious that an atlas could not provide the intended message. Thereupon, the manuscript evolved into an interpretation of general pathology as it applied to the vertebrate species, with emphasis on the pathologic changes in cell ultrastructure. Diseases such as uremia, diabetes, leukemia, influenza, tuberculosis, and others that involve fundamental abnormalities have been used repeatedly to explain disease processes.

The subject matter of *Cell Pathology* represents lesions of nonhuman vertebrate animals. The animal kingdom is divided into the lower animals (up to the phylum Chordata) and the higher animals, which include the cyclostomes, bony and cartilaginous fishes, amphibians, reptiles, birds, and mammals. The second category is the realm and the responsibility of the veterinary pathologist. The constant need to compare the biology of one species with another imparts a distinguishing character to veterinarians and zoologists; that character is an underlying principle of this book.

In the text, I have tried to avoid becoming an urbane purveyor of scientific data and to get down on paper the substance of what I believe to be true. In dealing with controversial evidence, I have tried to avoid experiments that do not satisfy the traditional canons of scientific research and have resisted using in vitro studies when in vivo experiments or naturally occurring diseases are available. Human models of animal disease are occasionally used in clarification of certain mechanisms. Medical eponyms have been avoided. These silly and often outlandish designations are generally not used in the veterinary and zoological literature and should not be transferred to animal diseases from what appears to be their human counterpart. I have not avoided the use of such words as "normal," "identical," and "injection," whose meaning in relation to disease is usually relative to many variants. To those readers who develop aggressive and nervous tendencies over such words, I recommend that good judgment be applied.

It is hoped that the book will find use in undergraduate studies. There will be students (and I fear some academicians) who insist that a knowledge of ultrastructure is not necessary to the practicing biomedical professional person. Possibly. But against that logic can be cited the difference between the scientific and the technical faces of biomedicine. Acceptance of the title "doctor" is acceptance of the responsibility for understanding disease, not merely knowing how to deal with it technically. One cannot condone those planners of curricula who, while insisting on rigorous preprofessional courses in mathematics and physics, willingly constrict the courses that provide the very foundation of medical knowledge.

To those who will use this text in reference to the analysis of postmortem material, it must be emphasized that appropriate sampling is the important factor preceding the examination of tissue. The application of careless tissue sampling and unscientific examination results in useless, and sometimes harmful, information. Biologists who utilize microscopy in that fashion are the very ones who criticize the static nature of histology as not being "scientific" and who often thereupon proceed to draw lines between points of equally dubious physiologic samplings. The anatomical pathologist should not be cornered into intellectual paranoia by such nonsense. Those experimentalists who, conditioned by their familiarity with biochemical reactions, bypass entirely the fundamental changes in cell structure should be appropriately reprimanded. A quotation from Huxley is pertinent: "All progress in . . . biology involves straight description, comparative observation and analysis, and experiment, with a constant interplay between them all."

Acknowledgments

To THE MANY COLLEAGUES who have contributed to the inception and development of this book, I am deeply grateful. I must acknowledge indebtedness to those friends and graduate students who have used portions of my rough manuscript and contributed to its completion; T. Bertram, F. Coignoul, R. Cutlip, and H. Moon have so contributed. I am grateful to the staff of the Iowa State University Press who have done a patient and thorough job of editing the manuscript.

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I have come to realize that it is through the forbearance, over long periods of ill temper, of those closest to one that books are written. In final words, therefore, I offer thanks to my wife, Beth, who made this writing endurable, to my parents who made it possible, and to my children who make it all worthwhile.

Contents

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Introduction to Cell Pathology

PATHOLOGY, in the broadest sense, is abnormal biology. As a biological science, it encompasses all abnormalities of structure and function. It involves the study of pathologic cells, tissues, and organs and is the link between the basic sciences and clinical studies in the biomedical curriculum. In practice, animal pathology is partitioned into three distinct disciplines: *invertebrate pathology,* concerned with the lower animals; *medical pathology,* concerned with diseases of humans; and *veterinary* (or comparative) *pathology,* concerned with the disease processes of the vertebrate species of animal life.

Pathology is essentially the search for and the study of *lesions:* abnormal structural and functional changes. Their detection requires the techniques used in the study of anatomy and physiology. Pathologists tend to divide their approach to pathology along these lines, specializing in either anatomical or clinical pathology. This text is biased toward the anatomical, particularly toward changes in cell ultrastructure. The reader is cautioned that the separation between pathologic structure and function is an artificial one. Some lesions are detectable only by microscopy and others only by biochemical methods; for every chemical change in a cell, however, there is a corresponding structural change. The challenge to the anatomical pathologist lies in finding it.

Students not adept at dealing with normal biologic variance will find pathology exceedingly confusing. Disease produces great exaggerations in the spectrum of structural and functional cell responses considered normal. As animals age, limits of normality become increasingly vague. Vascular lesions are usually present in aged animals, and although they are pathologic, they may be considered part of the normal aging process by some. For example, the regression of the thymus in young adults is a "normal" process, yet it involves degeneration and death of cells.

Phylogeny, the evolution of a group of animals, is a basic concern of the student of veterinary or comparative pathology. It is impossible to develop a practical approach to pathobiology without an awareness of the differences (and similarities) among species. There is an intriguing tendency for closely related species to suffer similar metabolic, neoplastic, and infectious diseases. Specific pathogenic microorganisms generally will also infect animals close, in the phylogenic scheme, to the original host.

Animals have evolved fascinating and complex mechanisms for sustaining life in the face of severe environmental conditions. The kangaroo rat can go an entire lifetime without taking a single drink. The pupfish, which lives in hot desert springs, can tolerate water much saltier than the sea. Tadpole shrimp eggs can survive broiling heat and freezing cold for years if necessary until fresh rains hatch them. The study of these mechanisms, significant in its own right, also provides valuable insight into the ways in which cells respond in the injured animal.

In this text we deal with diseases of vertebrate species. These are considered the "higher animals" in contrast to the lower, nonvertebrate species. Occasionally disease processes in the latter will be considered where they provide useful models for a basic disease process. The spontaneous diseases that occur in these species are not mirrors of their counterparts in vertebrates. The biological processes, however, are similar and at the level of the cell may even be identical. One of the most exciting eras of pathology was begun by observations of the inflammatory response of the water flea.

PATHOGENESIS OF DISEASE.

Pathogenesis is the development of disease. To understand pathogenesis, both causal agent and host response must be identified. Determination of cause and tissue reaction must be followed by interpretation of their significance in the disease process. That is, are they primary causes and lesions or are they epiphenomena masking a subtler process that remains hidden?

Causes of Disease.

Studies of pathogenesis begin with the *etiology* or cause of disease. A sim-

ple classification of external etiologic agents is a division into physical, chemical, and microbiologic types (Table 1.1). Some of these agents directly and consistently cause a pathologic reaction and a predictable series of consequences. Cyanide stops mitochondrial function and will kill an animal regardless of nutritional and immune status. Rabies virus, once established as an infection, replicates in neurons, invariably producing neuronal degeneration, inflammation of the brain, and death. The only determinants of disease for these dangerous agents are the total dose received by the host and the portal of entry.

It is rarely sufficient, however, to explain disease in terms of single causes and unremitting, step-by-step progress. With most agents, production of disease is not uniform. The tubercle bacillus causes tuberculosis, yet only a small fraction of infected animals develop the disease. Feline leukemia virus infects large numbers of kittens but will induce lymphosarcoma or leukemia in only a few. In these diseases, pathogenesis involves a balance of agent viability and host defense. The genetic, nutritional, immunologic, and environmental characters of the host animal determine, in large part, the development and extent of disease. Thus the pathologist must seek multiple factors as "causes" of disease, searching for patterns of lesions and groups of lesions that combine to produce the clinical manifestation of disease.

TABLE 1.1. External Factors Causing Cell Degeneration

Agent	Examples
Physical	
Mechanical trauma	Cutting objects, blows, compression
Electrical trauma	Lightning, high frequency electric current
Heat	Heatstroke, sunstroke, fever, burns
Cold	Local freezing, cold shock
Radiant energy	Ultraviolet light, X-irradiation, cosmic radiation
Pressure	Mountain sickness, caisson disease
Chemical	
Biologic toxins	Bacterial toxins, fungal toxins, mushroom toxins, arthropod venoms, snake and amphibian venoms
Pesticides	Organophosphates (parathion), organochlorine (DDT), botanical insecticides
Herbicides	Chlorophenoxy compounds (2, 4-D), dinitrophenols, paraquat
Environment	Metals, polychlorinated biphenyls, nitrates
Biologic	
Viruses	Viruses causing acute cytopathic disease (many viruses)
	Viruses causing chronic disease (canine distemper variants, visna-maedi virus of sheep, scrapie)
	Viruses causing neoplasia (retroviruses, some herpesviruses)
Bacteria	Mycoplasma, rickettsia, true bacteria, actinomycetes, spirochetes
Fungi	
Protozoa	
Metazoa	

The relation of cause and effect may be masked by antemortem disappearance of the causal factor. Physical causes of disease such as heat and cold are often determined only by the pattern of tissue injury they produce. Drugs may be catabolized after lesions are produced in the liver but before death occurs. Microbial agents may be destroyed by host defenses between the times of infection and death. Commonly, clinical treatment obliterates the cause. Bacteria may be killed by antibiotics and cannot be cultured from even severe inflammatory foci in treated animals. In rare infections, antibiotic treatment may even promote death; in anthrax, treatment kills the circulating bacteria, but the host may die from the ensuing massive liberation of bacterial toxins.

One of the most misleading aspects of the examination of pathologic tissues involves *multiplicity of causation.* Two or more agents may be involved in tissue injury. Viruses may induce a respiratory disease of little importance, yet in so doing predispose the lung to severe secondary bacterial infection. When two or more processes such as these are combined, they must be differentiated and the dominant causal factor of the lesion determined. Isolation of a microorganism from tissue does not necessarily mean that it has caused the lesion in question.

Host Response. Disease occurs as a reaction of cells and supporting tissues to injury. Gross and microscopic examination of lesions establishes that basic tissue response and provides clues to diagnosis and, in biopsy specimens, to prognosis. It is traditional to begin the study of pathology by examining basic categories of tissue response; cell degeneration and necrosis, inflammation, disturbances of growth and development, and neoplasia. In examining abnormal tissue then, the first step is to answer the question, What is the basic process?

In many cases, processes are clearly distinct. Traumatic wounds to the body surface produce acute inflammation. Discrete cutting of nerve supply to muscle causes atrophy, a growth disturbance. The solid, directionless lobulations of a brain neoplasm are not easily mistaken for the wet and swollen brain with its surface dotted by inflammatory exudates (Fig. 1.1). Frequently, however, two patterns of disease are present in the same lesion. Deep burns produce degeneration and necrosis followed by intense inflammation. Tumors often ulcerate through epithelium and become infected.

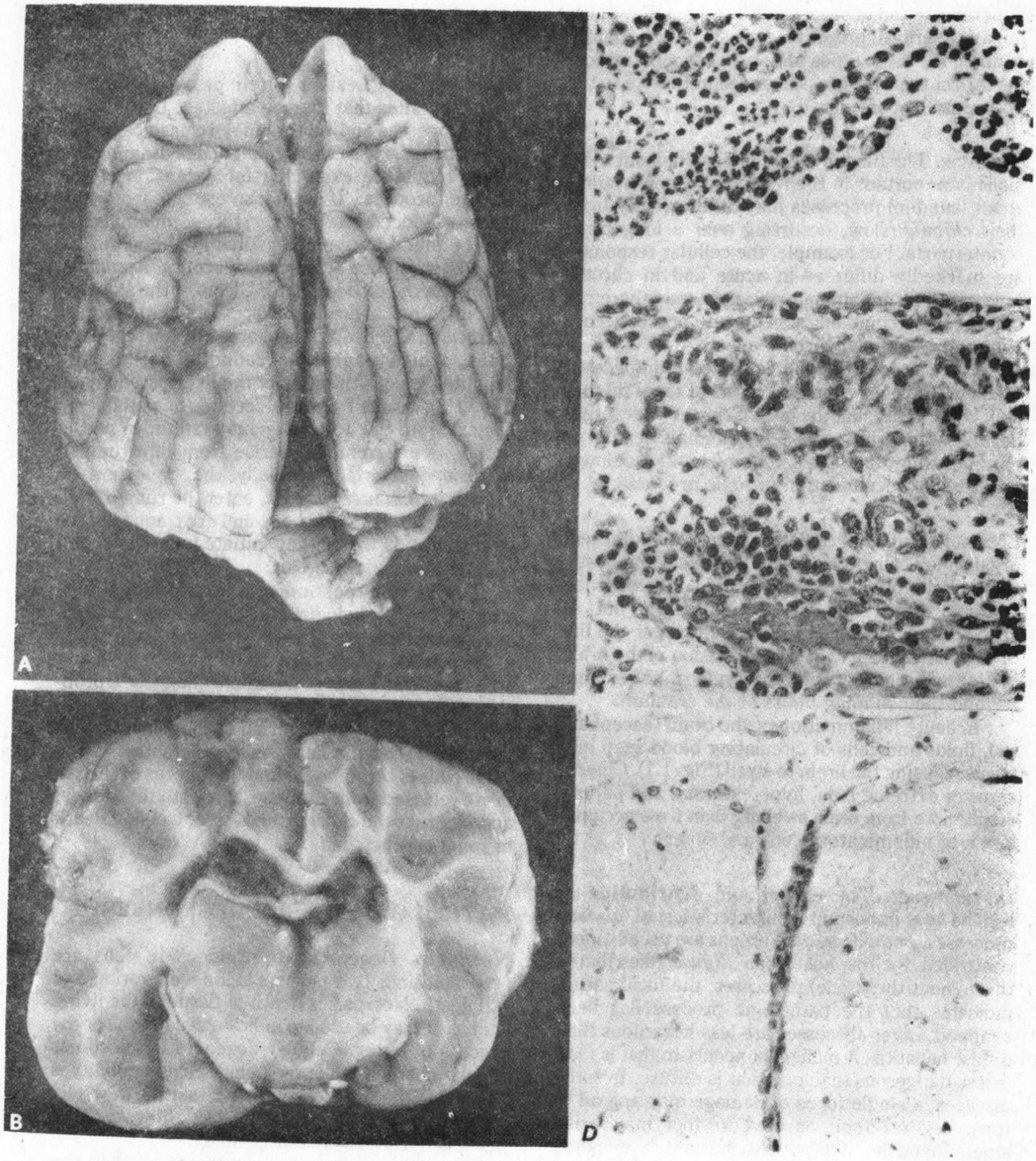

Fig. 1.1. Acute purulent encephalitis, young dog. *Escherichia coli* and anaerobic streptococci isolated from pus. *A.* Asymmetry due to brain swelling, affected left side of brain swollen (note rounded gyri) compared with right side; surface of purulent tract extending deep into neuropil is seen in center left cortex. *B.* Asymmetry in cross section with expansion of ventricles and purulent material in choroid plexus. *C.* Exudate of neutrophils and macrophages free in ventricle lumen (*top*); gliosis and inflammatory cell infiltrates in neuropil (*bottom*). *D.* Severe edema of brain several cm distant from purulent foci. Fluid spaces distort meningeal blood vessels and leave halos surrounding glia.

Superimposition of severe inflammation may mask the more serious, primary neoplastic lesion. Before defining the basic types of tissue response, factors that affect their progress in and significance to the host must be considered.

DURATION. The time involved in development of lesions is important in their structural appearance. *Acute* (sudden) processes may differ greatly from their *chronic* (slow, occurring over a long time) counterparts. For example, the cellular responses are markedly different in acute and in chronic inflammation. Inflammatory lesions may therefore be especially confusing when acute processes are superimposed upon chronic ones.

Acute processes tend to be less complicated than chronic ones. Acute necrosis of renal tubules may cause death, but the body lacks the widespread degenerative processes seen in animals dead from chronic kidney damage and uremia with its slowly progressive accumulation of toxic products.

LOCATION. Similar pathologic processes in different organs may cause differences in clinical manifestations. Foci of acute and chronic inflammation confined within subcutis are often painful but, as space-occupying lesions, do not endanger the life of the animal. The same type of lesion in the brain is life threatening, for brain tissue cannot expand beyond the confining limits of the cranium.

In acute inflammation of the brain (encephalitis), fluids and cells of circulating blood seep into tissue, causing the brain to swell (Fig. 1.1). Clinical signs of extreme pain, hyperesthesia, and paresis result more from brain swelling than from accumulation of inflammatory cells and fever.

DISTRIBUTION. The extent and distribution of lesions are important characteristics of disease processes. *Focal* (localized) lesions are usually more controlled by the host than *diffuse* (distributed throughout the tissue) processes; the focal nature indicates that the pathologic process has been confined. Liver abscesses are less hazardous than diffuse hepatitis. A malignant neoplasm that is focal is less dangerous than one that is diffuse. In some diseases, a single focus of damage may spread to form several foci, or several foci may arise simultaneously. These distributions are called *multifocal*.

To prevent spread of processes such as inflammation, necrosis, and neoplasia, biological mechanisms have evolved to sequester causal agents in foci of initial contact. For example, as some parasites attach to gastrointestinal mucosa they produce small foci of necrosis and ulceration (Fig. 1.2). These foci become underlined first by acute and then by chronic inflammatory tissue. Opportunistic bacteria attach to the site of damage, but this threat is largely neutralized by invasion of the tissue by plasmacytes that produce and release bacteria-killing antibodies.

DISSEMINATION. Lesions often provide clues to secondary sites that may be affected. Local infectious processes and tumors may release cells into *lymphatic vessels*, so that lymph nodes draining the lesion should be examined for extension of the disease process. If bacteria escape from the parasite-induced gastric ulcer, foci of inflammation may be found in the mediastinal lymph node.

Dissemination commonly occurs *hematogenously* (via the bloodstream). Ulcers of the stomach and intestine are often associated with foci of necrosis in the liver. These areas of dead hepatocytes, which appear as round, pale, sharply delimited lesions throughout the liver parenchyma (Fig. 1.3), result from the seeding of pathogenic bacteria into the portal venous system. In cattle, rumen ulcers commonly arise from intraruminal acidosis. Bacteria, especially the opportunistic *Fusobacterium necrophorum*, enter the rumen wall, pass through the portal vein, and are trapped in the liver sinusoids where they initiate foci of liver cell degeneration and necrosis.

During the postmortem examination (necropsy), the pathologist must make associations among combinations of lesions. The findings of pus in the uterus, friable growths on heart valves, and areas of tissue death in the kidney suggest a probable pathogenesis. A primary bacterial uterine infection has released bacteria into the bloodstream that localize on the heart valves. Infection of the valve causes thrombosis; and tiny pieces of thrombi are released from the heart, travel to the kidney, and obstruct the renal arterial tree, causing death of renal parenchyma.

PATHOLOGIC TISSUE RESPONSES

Necrosis. Degenerative reactions in cells are separated into two phases: cell degeneration and cell death. Necrosis is death of tissue in the living animal. It may be used to indicate dead tissue or the process of dying. Cellular degeneration becomes cellular necrosis when the point of irreversibility is reached in the degenerative process. Like the exact moment of death in the animal itself, however, that point is not precisely discernible.

Necrotic cells are shrunken and their intercellular attachments are broken. Their structural appearance depends not only on the type of degeneration but also on the time elapsing between injury and fixation for microscopic study. Sufficient time must elapse for pathologic changes to occur. Foci of necrosis are usually complicated by hemorrhage and peripheral zones of acute inflammation.

In histologic preparations, necrotic cells appear distorted, smudged, and homogeneous. Nuclei are contracted; they may be *pyknotic* (shrunken and

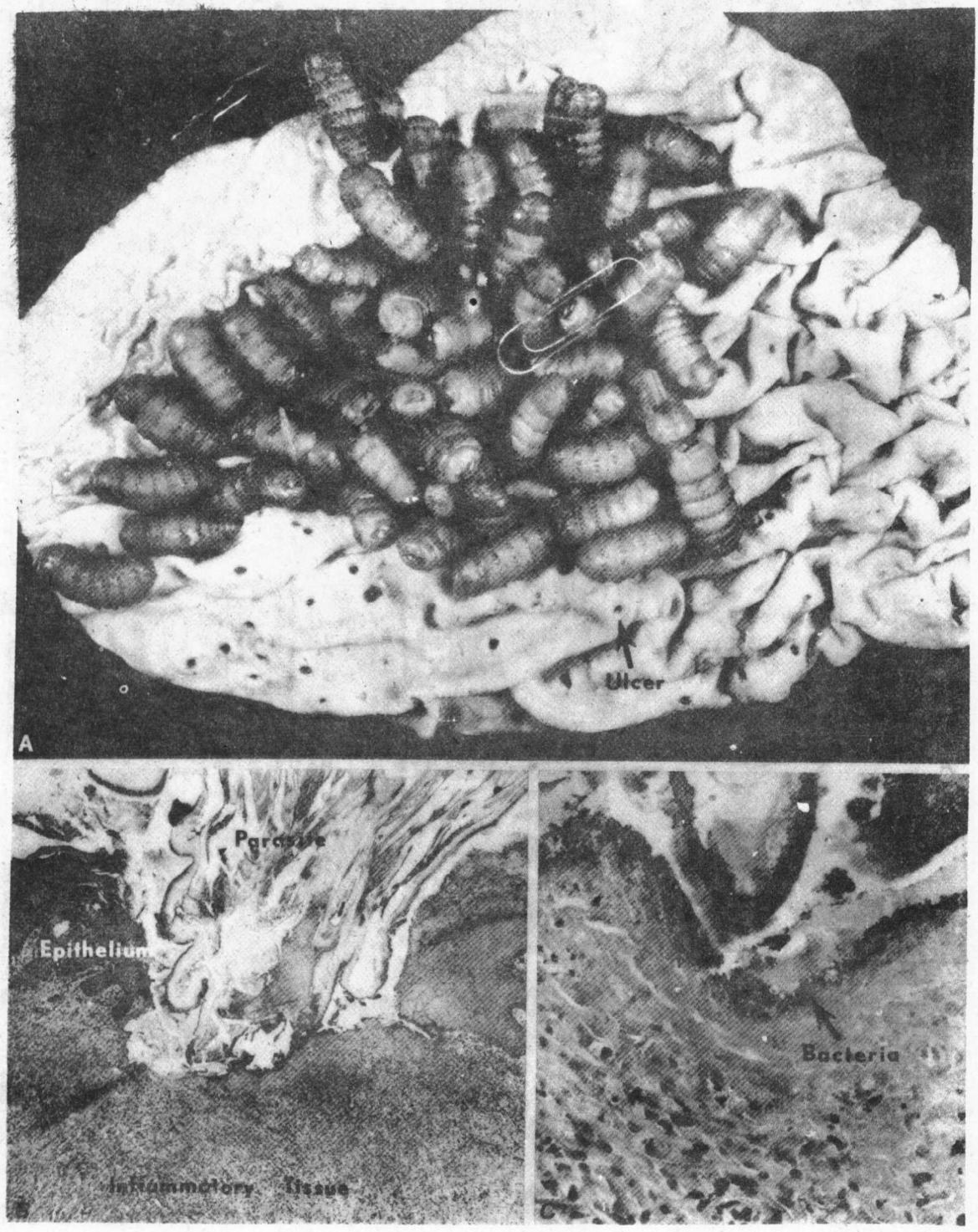

Fig. 1.2. *A. Gasterophilus intestinalis* larvae ("bots") on gastric epithelium, horse. *B.* Chitinous oral hooks of parasite produce erosions and ulcers. Hyperplastic squamous epithelium and chronic fibrosing gastritis with many plasma cells characterize lesion. *C.* Surface of pit contains many aerobic and anaerobic bacteria.

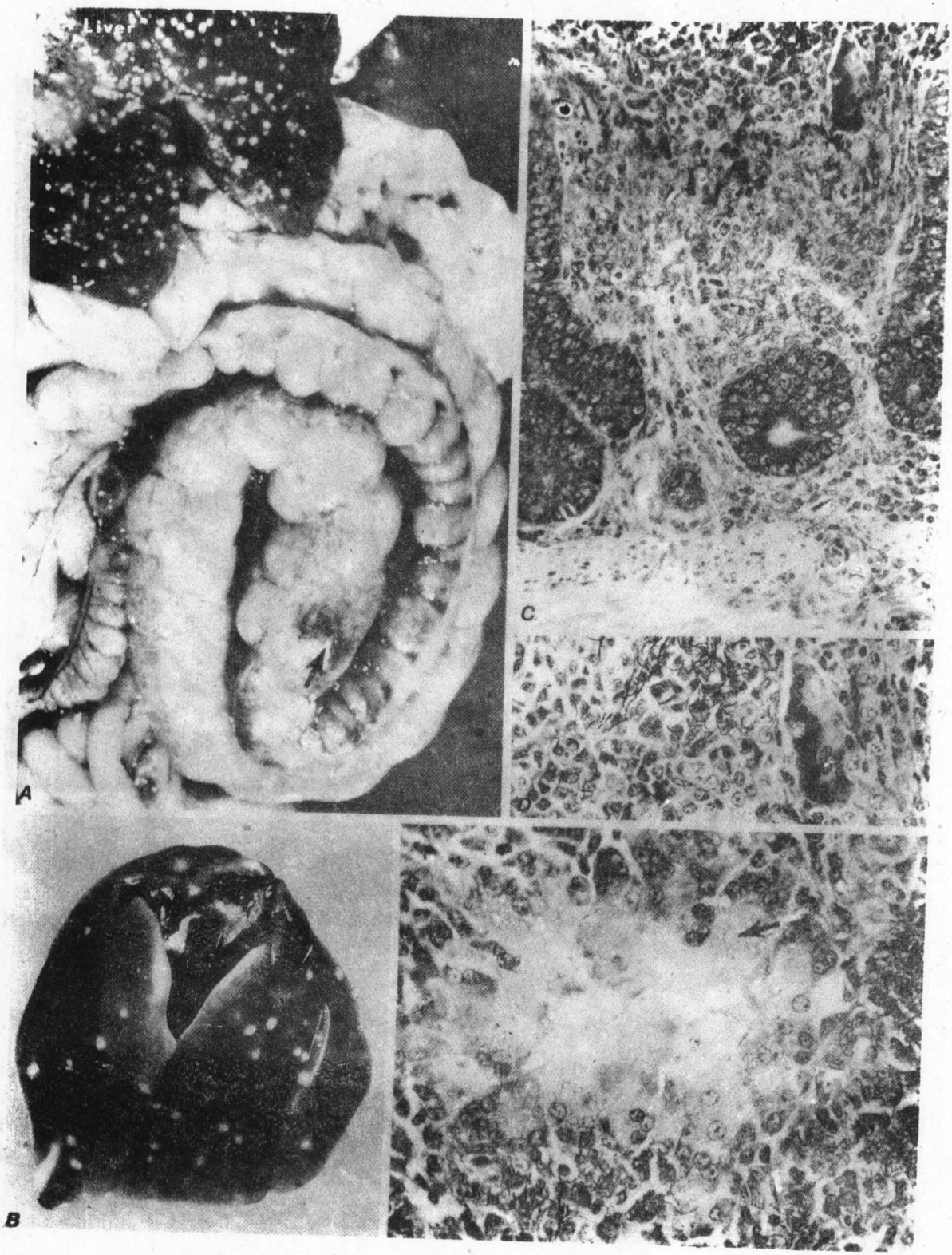

Fig. 1.3. Association of intestinal ulcers and focal liver necrosis. *A.* Tyzzer's disease (*Bacillus piliformis*), rabbit. "Paintbrush" hemorrhages on serosal surface of colon overlying ulcer (*arrow*). *B–E. Eubacterium* sp., turkey. *C.* Intestine, edges of mucosal ulcer (*top*) bounded by inflammatory cells and tangled filamentous bacteria. *D.* High power of *Eubacterium* sp., macrophages and giant cell. *E.* Focus of liver necrosis surrounded by zone of macrophages. *Eubacterium* sp. are associated with peripheral macrophages. Tiny cocci (*Staphylococcus aureus*) have superinfected necrotic tissue (*arrow*) (Micrographs, L. Arp).

dense with irregularities in the nuclear membrane), *karyorrhectic* (nuclear membrane ruptured, with fragmentation and release of nuclear contents), or *karyolytic* (complete dissolution of the nucleus with loss of chromatin material). If necrosis is recent, cells may stain deeply with eosin; but if autolysis (dissolution by their own enzymes) has occurred, cells take up little stain.

PATTERNS OF NECROSIS. Foci of necrosis in tissue often have characteristics that lead the pathologist in certain directions regarding etiology. Some of the patterns that can be recognized and vary according to the nature of the destructive agent are listed below.

In *coagulation necrosis,* the cell is homogeneous and opaque because of coagulation of protein. The coagulated cell persists after cell detail has disappeared. Interruptions in the arterial supply, bacterial toxins, or severe febrile illnesses may be responsible. The affected area of necrotic tissue is sharply delimited from surrounding normal tissue.

Rapid enzymatic dissolution of the cell that results in complete destruction is called *liquefactive necrosis.* It is seen in bacterial infection leading to pus formation in which proteolytic enzymes are released from leukocytes. The brain responds to anoxic injury with rapid enzymic digestion and foci of dissolution.

Caseation necrosis occurs when dead cells are converted into a granular friable mass resembling cottage cheese. It is present in diseases such as tuberculosis and tularemia. The presence of special lipids and the chronicity of the cellular reaction prevent liquefaction.

In *enzymic necrosis of fat,* lipases split the neutral fat in adipose cells, releasing the lipid and imparting a granular eosinophilic appearance to the fat cell. This type of necrosis is seen in trauma of adipose tissue and commonly accompanies pancreatic injury. Unidentified enzymes released from damaged pancreatic acinar cells free lipases in adipose cells, which cause autodigestion of triglycerides (Panabok'ke 1958). Fat, free in connective tissues, incites inflammation and phagocytosis, which separate enzymic necrosis from autolysis. Cholesterol clefts, giant cells, and calcium are often present.

The superimposition of growth of saprophytic bacteria upon necrosis results in a histologic pattern that is a mixture of coagulation and liquefactive necrosis. This *gangrenous necrosis* may occur because of bacterial invasion of an infarct or as a result of restriction of blood supply in an established bacterial infection caused by collection of fluid and intravascular clotting.

Gangrene is also applied to necrosis of tissues in an extremity wherein vascular occlusion has resulted in coagulation necrosis. When bacterial infection does not occur, the tissue mummifies and the condition is referred to as *dry gangrene.* Affected tissue is cool, dry, and discolored. There is a sharp demarcation of inflammatory tissue, preventing systemic infection. When organisms invade, the combination of ischemia and infection produces putrefactive, foul-smelling tissues, a lesion called *moist gangrene.*

NECROBIOSIS. In necrobiosis, cell death is programmed, and the cytopathic changes evolve in orderly and reproducible sequences. Necrobiosis occurs in adult animals as a part of normal cell turnover, such as the loss of cornified squamous cells of skin. Keratinocytes become filled with keratin, nuclei degenerate, and plasma membranes no longer adhere. As desmosomes disintegrate, cells desquamate from the skin surface (Fig. 1.4). Necrobiosis is also seen in erythrocytes, which die when their hemoglobin molecules begin to precipitate and new hemoglobin cannot be resynthesized. In erythrocytes the process actually begins immediately after maturation when nuclei degenerate. Their genome is no longer required for protein synthesis and, in mammals, they are shed from the cell. Cell death occurs without sequelae because cell function has been fulfilled and the cells have been replaced with new erythrocytes.

Necrobiosis is a prominent feature of embryonic development and histogenesis (O'Connor and Wyttenbach 1974). An intriguing model for study has been the tail breakdown in tadpole amphibians during metamorphosis. The tail regresses because of a thyroxin-dependent autolysis initiated in the myocyte. Early cytoplasmic changes include folding of myofibrils and loss of striation; these develop before gross signs of tail atrophy occur. Degeneration of mitochondria is also an early change and is followed by disorganization and disintegration of sarcoplasmic reticulum and the development of lysosomes. Macrophages replace and destroy the myocytes. An earlier erroneous interpretation stated that rupture of lysosomes with liberation of hydrolizing enzymes was the initiating reaction in destruction of tail tissue. It has been demonstrated, however, that lysosomes appear in response to autolysis of the myocytes. While they may release hydrolytic enzymes within the cell, lysosomes do not initiate the necrobiotic process (Weber 1964; Fox 1973).

POSTMORTEM DEGENERATION. The interpretation of lesions is often clouded by degeneration that has taken place between the time of death and necropsy. Postmortem changes vary in the rapidity with which they occur, depending on environmental temperature and humidity (Table 1.2) and the condition of the animal (layers of fat, hair, or feathers act as insulators against heat loss after death).

Postmortem degeneration is due to total diffuse anoxia. Autolytic changes mimic early ischemic change and in fact have a hypoxic basis. Organelles degenerate according to their oxygen requirements,

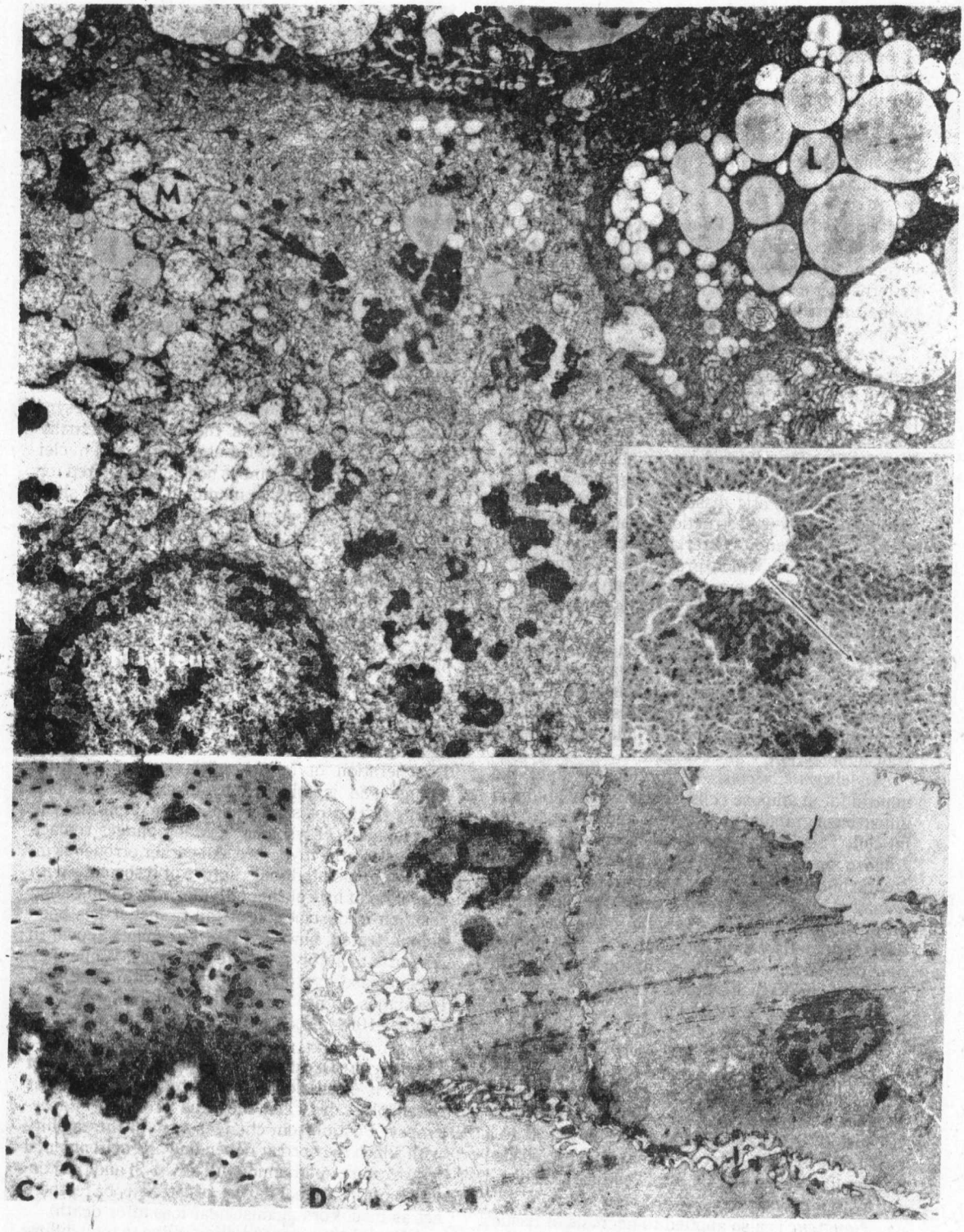

Fig. 1.4. Necrosis and necrobiosis. *A.* Necrosis of hepatocyte in CCl_4 poisoning, rat. Note mitochondria (*M*), lipid globules (*L*), and bile pigment (*arrow*). *B.* Histology: centrolobular necrosis; arrow traverses blood flow from portal triad to central vein. *C.* Necrobiosis in stratified squamous cells of normal esophagus. *D.* Ultrastructure: squamous cell nuclei degenerate, cell junctions separated, and cytoplasm homogeneous lacking organelles.