ORAL PATHOLOGY

Oral Pathology

Edited by

RICHARD W. TIECKE, B.S., D.D.S., M.S., F.A.C.D.

Diplomate, American Board of Oral Pathology; Assistant Secretary, Council on Dental Therapeutics, American Dental Association; and Professor of Oral Pathology, College of Dentistry, University of Illinois

With 31 Contributors

The Blakiston Division

McGRAW-HILL BOOK COMPANY

NEW YORK TORONTO SYDNEY LONDON

ORAL PATHOLOGY

Library of Congress Catalog Card Number: 63-21888

64600

Contributors

Hazen J. Baron, D.D.S., Ph.D., Research Division, Warner-Lambert Laboratories, Morris Plains, New Jersey

Joseph L. Bernier, D.D.S., M.S., F.A.C.D., F.I.C.D., F.D.S., R.C.S. (Eng.), Diplomate, American Board of Oral Pathology, American Board of Oral Medicine, and American Board of Periodontology; Major General, U.S. Army Dental Corps; Assistant Surgeon General and Chief, Army Dental Corps

Surindar N. Bhaskar, B.D.S., D.D.S., M.S., Ph.D., Diplomate, American Board of Oral Pathology; Lieut. Colonel, U.S. Army Dental Corps; Chief, Department of Dental and Oral Pathology, U.S. Army Institute of Dental Research, Walter Reed Army Medical Center, Washington, D.C.

George W. Burnett, D.D.S., Ph.D., Colonel, U.S. Army Dental Corps; Chief, Department of Oral Biology, U.S. Army Institute of Dental Research, Washington, D.C.

Lester R. Cahn, D.D.S., Sc.D., F.R.C.S., F.D.S., R.C.S. (Eng.), Diplomate, American Board of Oral Pathology; Associate Professor of Oral Pathology, Columbia University, New York, New York

D. Walter Cohen, D.D.S., Diplomate, American Board of Periodontology; Professor and Chairman, Department of Periodontics, University of Pennsylvania, Philadelphia, Pennsylvania

Daniel A. Collins, D.D.S., M.S.D., Diplomate, American Board of Oral Pathology; Oral Pathologist, Mount Zion Hospital, San Francisco, California

Leon C. Edwards, M.D., Diplomate, American Board of Surgery; Major, U.S. Army Medical Corps

Harold M. Fullmer, D.D.S., Diplomate, American Board of Oral Pathology; Dental Director, Laboratory of Histology and Pathology, National Institute of Dental Research, Bethesda, Maryland

Benjamin J. Gans, D.D.S., M.S., F.A.C.D., Associate Professor of Oral Surgery, Northwestern University School of Dentistry, Chicago, Illinois; Chief of Oral Surgery, Michael Reese Hospital, Chicago, Illinois

Robert A. Goepp, B.S., D.D.S., M.S., Diplomate, American Board of Oral Pathology; Assistant Professor of Oral Pathology, Walter G. Zoller Memorial Dental Clinic and Department of Pathology, University of Chicago Hospitals and Clinics, Chicago, Illinois

Robert J. Gorlin, D.D.S., M.S., Diplomate, American Board of Oral Pathology; Chairman and Professor, Department of Oral Pathology, University of Minnesota, Minneapolis, Minnesota

George W. Greene, Jr., B.S., D.D.S., Diplomate, American Board of Oral Pathology; Chairman and Professor, Department of

Oral Pathology, University of Buffalo, Buffalo, New York

Louis S. Hansen, B.S., D.D.S., M.S., F.A.C.D., F.I.C.D., Captain, U.S. Naval Dental Corps; Diplomate, American Board of Oral Pathology; Head, Officer Education, Department of U.S. Naval Dental School, Bethesda, Maryland; Associate Clinical Professor of Pathology, George Washington University School of Medicine, Washington, D.C.; Lecturer in Pathology, The Graduate School and School of Dentistry, Georgetown University, Washington, D.C.

Francis V. Howell, A.B., D.D.S., M.S., Diplomate, American Board of Oral Pathology; Associate Clinical Professor of Pathology, University of Southern California Medical School, Los Angeles, California

A. C. W. Hutchinson, D.D.S., M.D.S., F.D.S., F.R.S.E., Former Dean of the University of Edinburgh, Edinburgh, Scotland; Visiting Professor in Diagnosis and Chairman of Curriculum Committee, Northwestern University Dental School, Chicago, Illinois

Viktors Kalnins, D.M.Sc., M.D., D.D.D., L.D.S., D.D.S., Associate Professor of Oral Pathology, Western Reserve University, Cleveland, Ohio

Nelson D. Large, D.D.S., M.S., Diplomate, American Board of Oral Pathology; Veterans Administration Hospital, Richmond, Virginia, and Assistant Professor of Oral Pathology, Medical College of Virginia, Richmond, Virginia

Jens J. Pindborg, D.D.S., Doctor of Odontology, Professor and Chairman, Oral Pathology, Royal Dental College, Copenhagen, Denmark; Chief, Dental Department, University Hospital, Copenhagen, Denmark

Norman H. Rickles, D.D.S., M.S., Diplomate, American Board of Oral Pathology; Professor and Head, Department of Pathology, University of Oregon Dental School, Portland, Oregon

Henry H. Scofield, B.S., M.S., D.D.S., F.A.C.D., Diplomate, American Board of Oral Pathology; Captain, Dental Corps, United States Navy; Chief, Dental and Oral Pathology Division, Armed Forces Institute of Pathology, Washington, D.C.

William G. Shafer, D.D.S., M.S., Diplomate, American Board of Oral Pathology; Chairman and Professor, Department of Oral Pathology, Indiana University School of Dentistry, Indianapolis, Indiana

Milton Siskin, B.A., D.D.S., F.A.C.D., Diplomate, American Board of Oral Medicine and American Board of Endodontics; Fellow of the American Academy of Oral Pathology; Professor, Department of Oral Diagnosis, College of Dentistry, University of Tennessee, Memphis, Tennessee

William G. Sprague, B.S., D.D.S., Diplomate, American Board of Oral Pathology; Lieut. Colonel, U.S. Air Force Dental Corps; Chief, Oral Pathology Division, U.S.A.F. Hospital, Lackland, Lackland Air Force Base, Texas

S. Miles Standish, D.D.S., Diplomate, American Board of Oral Pathology; Associate Professor of Oral Pathology, and Chairman, Division of Clinical Oral Pathology, Indiana University School of Dentistry, Indianapolis, Indiana

Harold R. Stanley, D.D.S., B.S., M.S., Chief, Oral Medicine and Surgery Branch, National Institute of Dental Research, Bethesda, Maryland; Diplomate, American Board of Oral Pathology,

Honorary Professor of the Odontologic Faculty, San Carlos University, Guatemala

Orion H. Stuteville, D.D.S., M.S., M.D., Diplomate, American Board of Oral Surgery and American Board of Plastic Surgery; Chairman, Department of Maxillofacial Surgery and Oral Surgery, Northwestern University Dental School, Chicago, Illinois

Richard W. Tiecke, B.S., D.D.S., M.S., F.A.C.D., Diplomate, American Board of Oral Pathology; Assistant Secretary, Council on Dental Therapeutics, American Dental Association; Professor, Department of Oral Pathology, University of Illinois, Chicago, Illinois

Charles A. Waldron, D.D.S., M.S.D., Diplomate, American Board of Oral Pathology; Chairman and Professor, Department of Pathology, Emory University School of Dentistry, Atlanta, Georgia

Mark C. Wheelock, M.D., Diplomate, American Board of Pathology; Chief of Pathology, Passavant Memorial Hospital, Chicago, Illinois

Carl J. Witkop, Jr., D.D.S., M.S., Diplomate, American Board of Oral Pathology; Chief, Human Genetics Section, Clinical Investigations Branch, National Institute of Dental Research, Bethesda, Maryland

Preface

Oral pathology is of the greatest importance to dentistry and forms the basis of all oral examinations and subsequent treatment. Dentistry cannot be practiced effectively without a broad background in the basic sciences, especially pathology. An understanding of this science is also necessary for comprehensive research activities.

This textbook covers the various aspects of oral disease including clinical features and histopathology. Pathologists and students must remember that the patient has symptoms and that these must always be considered in the interpretation of the histopathology.

Twenty-four plates of color are included. The majority of these show clinical features of various conditions and are used to give this area emphasis. But a number of plates are devoted to histochemistry, inasmuch as this is the first time a chapter of this type has been presented in an oral pathology textbook.

Oral Pathology has been written by 31 authors, all of whom are outstanding in their special fields. In every instance the author has written on a phase of pathology which holds particular interest for him and in which he is especially knowledgeable. While the text is directed chiefly to the undergraduate and graduate student it is also written in such a manner as to be useful to the practicing dentist.

A number of subjects not found before in an oral pathology textbook have been included as chapters because of their close relationship and ever-increasing importance to the field. In addition, several of these gather together material that has heretofore been available only as reports in widely scattered publications. Given more than usual attention are caries; pain sensation; oral syndromes; physical, chemical, and radiation changes; histochemistry; and genetic disease. It should also be noted that the chapter "Inflammation and Healing of Oral Wounds" represents an approach in depth; the subject is discussed in its many parameters. Cytology, an important adjunct to the early detection of oral cancer, is presented in all aspects and is placed in its true position with regard to dentistry.

It will be noted that in some instances there is overlap. A specific lesion may appear in more than one chapter and, on occasion, a minor difference of opinion among authors may be evident. These features are intentional and were included in order to place emphasis and to stimulate.

The editor wishes to thank all the contributors and others who assisted him for their time and patience. The majority of these are extremely busy and yet contributed generously and uncomplainingly of their time and material. Without them this text could not have become a reality.

Richard W. Tiecke

Contents

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Inflammation and Healing of Oral Wounds

Thirty-two kinds of inflammation are listed in one standard medical dictionary, and the processes of tissue repair are described with almost equal diversity. The numerous kinds of inflammation and healing commonly described reflect the variety of patterns that can be produced by the common processes of inflammation and healing in surviving tissues. From the moment of nonspecific injury, however, the behavior of the surviving tissue constitutes one of the most specific reactions of mammalian biology. The numerous varieties of reaction and repair are more apparent than real. An increasing knowledge of the fine structure and performance of injured tissue discloses important features common to all kinds of inflammation and healing. For this reason, much of the material presented here is drawn from studies which seek a basic understanding of inflammation and wound healing. Only rudiments of this knowledge are now available, but they are sufficient to give new and useful meaning to the varieties of inflammation and healing found in a particular species, such as man, or in a special region, such as the oral cavity.

ACUTE INFLAMMATION

The Anatomy of Inflammation

Acute inflammation affects tissues of every kind, but only the connective tissues, which bind the parts of the body together and support its organs with a tough and vascular stroma, can be described in classical terms as being inflamed. The microanatomy of inflammation in fibrous tissue involves five structural components principally. These are the cells (fibroblasts, histiocytes, and white blood cells), blood capillaries, lymph capillaries, the fibers (collagen, reticulin, elastin, and oxytalan), and the ubiquitous ground substance. These are briefly described below.

The Cells. The cells affected by inflammation include all types of cells found in the injured tissue. Evidence of profound changes within the parenchymal cells of organs and the epithelial cells of investing layers is striking, but little is known about the details of impaired metabolism of injured cells. Reliable ways to appraise degrees of cellular injury and recovery remain to be devised.[43] In spite of this, knowledge in this area will reach deeper into the cell in the next decades, and a synoptic account of the current status of certain important subcellular structures is therefore warranted.

Forty years ago an acceptable diagram of a typical cell depicted the cytoplasm containing vacuoles and centrosomes and a central nucleus with its nucleolus and scattered chromatin. A modern diagram of a typical cell is seen in Fig. 1-1. Certain features of its subcellular structures are summarized below.

Cell Membrane. Roughly 100 A thick, the cell membrane is a complex lipoprotein-carbohydrate capable of selective absorption and active transport of ions and small molecules; it acts by pinocytosis and phagocytosis to transfer larger particles to the interior of the cell.

Endoplasmic Reticulum. This many-folded internal membrane appears as numerous canaliculi by electron microscopy, possibly continuous with both the cell and the nuclear membranes; it affords enormous increase in effective membrane surface.

Ribosomes. These minute granules line the endoplasmic reticulum and are centers of protein synthesis rich in ribonucleic acid (RNA).

Mitochondria. These rodlike cytoplasmic bodies account for the oxidative reactions of the cell and provide it with energy.

Centrosomes. These minute paired bodies outside the nucleus—each consisting of numerous tubular structures seen only in electron micrograms—migrate apart and form polar bodies during cell division.

Lysosomes. These irregular packets in the cytoplasm are thought to contain digestive enzymes, since their rupture leads rapidly to the death of the cell.

Vacuoles. These clear spaces are the result of phagocytosis or pinocytosis following ingestion of particles or fluid from the environment; they are lined by a spherule of pinched-off cell membrane.

Nuclear Membrane. This double membrane separates the primary genetic material of the cell from the cytoplasmic sea around it; it has highly selective properties of metabolic transfer.

Chromatin. These nuclear filaments contain all the cell's deoxyribonucleic acid (DNA) and constitute the chromosomes when tightly coiled for division; they are the main genetic determinants.

Nucleolus. This spherical organelle of the nucleus contains minute granules rich in RNA and resembles the ribosomes; it contains active centers of protein and RNA synthesis.

Reference to certain changes in subcellular organelles during inflammation and repair follow. They are included here not so much because of their present importance but rather because of important developments to come in the study of inflammation.

Although all types of cells are affected by inflammation, the cells regarded as inflammatory are in a class of their own. Their classification, however, is far from settled in strict generic terms, and the identification by type and origin of the cells of an inflammatory exudate is sometimes impossible. The cells accumulate in the region of injury in numbers, forms, and proportions determined by both the nature of the injurious agent and the availability of cell types. The inflammatory response of a densely populated reticuloendothelial tissue, such as the tonsil, is remarkably different in cellular profile from that of ordinary fibrous connective tissue, where tissue macrophages and lymphocytes are scarce by comparison. Listed below are the principal inflammatory cells with their common synonyms and certain characteristics. All these cells can travel by means of ameboid movement.

Neutrophil (Polymorphonuclear Leukocyte, Pus Cell). The neutrophil is the most prevalent of the white blood cells in adults and also has the shortest life. It is ordinarily the first and the most numerous migrant to an acute inflammatory nidus. These cells, which are primarily phagocytic, also perform the important function of disintegrating and releasing into their environment digestive enzymes which assist in liquefying tissue detritus. Unlike the mononuclear cells, neutrophils do not reproduce themselves.

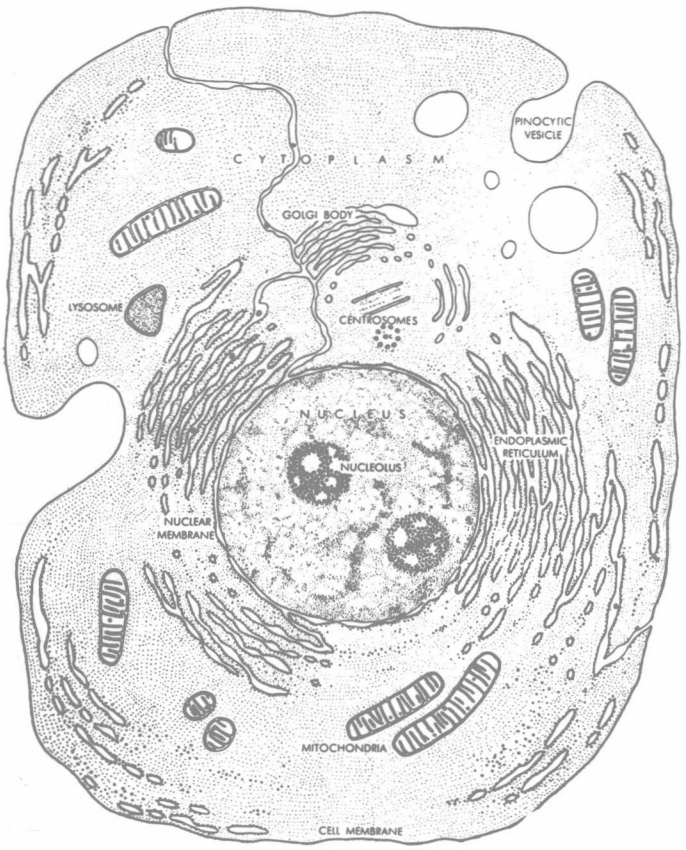

Fig. 1-1. Modern diagram of a typical cell. (*Courtesy of Scientific American.*)

Lymphocyte. The lymphocytes, the second most abundant of the white blood cells in adults, sooner or later outnumber the neutrophils in an inflammatory focus. Small lymphocytes, which have slight phagocytic ability, synthesize antibody. Inflammatory lymphocytes are capable of rapid growth and metamorphosis, and because of this they are thought by some[67] but not all authorities[27] to be the most important source of macrophages among the white blood cells.

Monocyte. This is the largest of the white blood cells which retains its form and primarily phagocytic function as an inflammatory cell.

Mast Cell. This cell is recognized by its dense cytoplasmic content of basophilic granules in the blood and is distinguished by its production of histamine, heparin, and 5-hydroxytryptamine. This cell is not always recognized in an inflammatory exudate because of the rapid discharge of its granules in the presence of injurious stimuli.

Eosinophil. The eosinophil is recognized by its cytoplasmic content of acidophilic granules. The presence of this cell in an inflamed tissue is inconstant except when incited by an allergic or immune reaction or by certain parasites or, as recently shown, in newborn infants 2 to 21 days old.[28]

Histiocyte (Tissue Macrophage, Clasmatocyte, Polyblast, Reticuloendothelial Cell). This large mononuclear fixed or wandering phagocyte belongs to the tissue. The origin is uncertain, and it becomes indistinguishable from other macrophages of inflamed tissue.

Plasma Cell (Plasmocyte). This oval cell with a characteristically eccentric nucleus is an antibody producer. Its participation in the inflammatory response is also inconstant.

Giant Cell. This multinucleated cell appears to arise from the confluence of a number of mononuclear cells, particularly in response to the presence of a foreign body and certain granulomatous infections. It tends to isolate the irritating agent and modifies inflammation of the involved tissue accordingly.

Fibroblast (Fibrocyte). The origin of this stellate, spindle, or round primary mesenchymal cell is disputed,[2] but evidence now available points to an autogenous cell line which is sustained by a constant reservoir of primitive fibroblasts which multiply, produce both fibrous and certain amorphous components of the matrix, and mature into fibrocytes.[46,47,87] The fibrocyte continues to maintain fibrous connective tissue by synthesizing its needs at a slow rate, but its blast potential, according to present evidence, vanishes.[25,63]

The fibroblast does not properly belong to the inflammatory cells, which are wholly engaged in defense, demolition, and disposal. Activation of its synthetic and mitotic machinery occurs in the earliest stages of inflammation however,[14,32] and it migrates from surrounding areolar tissue with the first macrophages to be drawn to the scene of experimental microtrauma. Obscured at first by the inflammatory cells infiltrating the field of more severe injury, the fibroblast initiates the processes of repair much sooner than is usually appreciated and shortly outnumbers the inflammatory cells in the regenerating connective tissue of uncomplicated healing.

The Blood Capillaries. The blood capillaries in connective tissue, separated by 10 to 20 diameters of a red blood cell, have a wall with four distinct elements. Two elements, the endothelial cells and intercellular cementing substance, form a tubular pavement which separates a coating of proteinaceous material within the lumen from a condensed pericapillary sheath which is continuous with the ground substance on the outside. With much to be learned, enough is known already to assign to those elements important roles in the capillary response to injury.

The Lymph Capillaries. The lymph capillaries are structurally similar to the blood capillaries, but with modifications which are reflected in their function. The interendothelial cementing substance appears to be weaker and more permeable than the corresponding material in blood capillaries, and the terminal lymphatics (less than 30 to 50 μ) appear to lack a pericapillary sheath. Where a sheath does exist, Zweifach[96] has observed a thin space which contains a clear fluid between it and the lymphatic endothelium in living tissue. In contrast to blood capillaries, the lymphatics offer easy access to macromolecular and fine particulate material in the ground substance.

The ground substance is the product and the mediator of metabolic interchange between the blood stream and cells. The lymph capillaries act as a siphon which guards the tissue against a lack of precision and full reciprocity of this metabolic interaction. The fluid left over from this interchange, which is not conveniently handled by either the cells or the blood capillaries and which must be drained off by other channels, is lymph. The composition of lymph from different regions is well established, but its fuller meaning as an interregnum fluid product of the main metabolic stream between the blood and the tissue cells is just now appearing.[90] Alterations in the delicately balanced relations of the capillaries, the ground substance, and the lymphatics are chiefly responsi-

ble for the swelling, redness, heat, and pain classically associated with acute inflammation.

The Fibers. The two common fibers of connective tissue are collagen and elastin. Both are proteins of macromolecular dimensions. *Collagen* fibers seen by light microscopy are composed of bundles of smaller fibrils with a characteristic 640 A banded appearance, seen only by electron microscopy. The microfibrils are made up of more elementary filaments which are produced by aggregation of fundamental collagen particles, tropocollagen.[40] The tensile strength of collagen fibers ranges from 50 to 100 kg per sq mm.[72] Collagen is characterized chemically by its unique amino acid composition. It is the only mammalian protein that contains hydroxyproline, which is important both for its contribution to the physical and chemical properties of the fibers and for its use as a measure of the collagen content of a tissue upon chemical analysis. Collagen contains high percentages of hydroxyproline, proline, and glycine and little or none of the aromatic or sulfated amino acids, such as tyrosine and methionine. The strength of most connective tissues, including bone, is related to its content of collagen. The arrangement and density of the fibers depend largely upon tensile forces acting upon them. The dense, linear orientation of fibers in a tendon, the random, dense mesh found in most of the dermis, and the loose reticular network of areolar tissue are all patterns which illustrate this.

Elastin is less abundant in most tissues than collagen, from which it is distinguished by its extreme insolubility and a different amino acid composition. It has little importance as a product of wound healing, but can be prominently affected by inflammatory conditions in structures possessing elastic membranes, such as arteries.

Reticulin consists of fine fibers distinguished by an affinity for silver salts which render them black in microscopic sections. Such fibers are found in basement membranes as compact lamellas and early in healing wounds as diffusely scattered fibrils. In both situations the fibrous protein has been identified as collagen in firm association with lipid and carbohydrate substances. Two different reticulins have been distinguished by contrasting the properties of the substances associated with the basic collagenous microfibril. The reticulin of the healing wound can be regarded as immature fibrous collagen.[46]

The *oxytalan* fiber, so called because of its resistance to acid hydrolysis and because of features which distinguish it from collagen, reticulin, and elastin, has recently been described. It has been found normally only in the periodontal membrane and adjacent gingiva and pathologically in dental granulomas and radicular cysts.[31] Although oxytalan fibers are more closely related histochemically to elastin, they are most commonly found in the ground substance between collagen fiber bundles.

The Ground Substance. The ground substance, which is the least structured part of connective tissue, was also the last to be recognized. The very existence of an intercellular, interfibrillar material was disputed less than 30 years ago, and its properties are still far from fully known. The ground substance was originally identified as an amorphous material separating the cells, fibers, and capillaries of connective tissue, requiring special techniques for its demonstration. One of the earliest of these remains one of the most graphic. Bensley[10] observed that paramecia injected with a drop of saline solution into connective tissue swam freely about the central portion of the bulla created. At the periphery, however, it was evident that the small creatures were butting repeatedly against a barrier invisible through the microscope. With special stains and the recent use of electron microscopy, this barrier of ground substance has achieved some degree of morphologic differentiation.[87] It is subdivided into regions much smaller than originally supposed by a lattice of solitary microfibrils of collagen, invisible by light microscopy. Chemical[45] and morphologic studies indicate that the ground substance serves both cementing and transport functions, that two phases—one colloid rich and water poor, and the other water rich and colloid poor—probably coexist[15] and that gel-sol changes in the mucinous ground substance are vital to its functions of cementing,[45] metabolic transport,[29,33,48] and defense against injury. The ground substance has a small molecular and ionic composition resembling plasma and usually contains plasma mucoproteins, glycoproteins, and lipids in small amounts. Proteins and carbohydrates constitute the macromolecular fabric of the ground substance and are found in both conjugated and free forms. In addition, soluble molecular collagen is present, providing building blocks for fibers and rendering rigidity and stability that the ground substance would not otherwise possess. Disaggregation or depolymerization of the macromolecules of the ground substance and their restitution during inflammation and healing have acquired increasing recognition and importance in recent years.[14]

As outlined above, the anatomy of inflammation is restricted chiefly by the limit of visibility of light microscopy, which is about 0.0001 mm. Below this level of visibility, in the range of 1 to 1,000 A, the

vital macromolecular machinery of life and of its defense and repair, with its flux of finer particles, constitutes a realm in which chemistry and anatomy are the same.

Injury and Acute Inflammation

Benjamin Zweifach describes the events following microinjury of a living connective tissue membrane as follows:

> . . . it is almost impossible to induce a local injury, even on a micro-scale, without involving some cellular elements. In such circumscribed lesions in the mesentery, the ground substance shifts from a gel to a sol state, the area then becoming surrounded by cellular elements (within 30 to 120 minutes). Thereafter, the liquid ground substance seems to gelate again and is invaded by cellular elements (macrophages and fibroblasts). After two to three hours the injured site begins to resume a normal appearance, although the abnormal accumulation of cellular elements persists for at least six hours.

Zweifach[95] also shows that when the microinjury is made near a true capillary, several minutes elapse before visible changes in the vessel follow those already in progress in the ground substance. This suggests that a diffusible substance released at the site of injury affects distant cells and structures.

Menkin[58] defined inflammation as the result of severe cellular injury in vertebrates and isolated from cellular exudates materials which he identified as specific inflammatory agents and named them according to their functions. He named leukotaxine and necrosin as the locally acting factors, pyrexin as the leukocytosis-promoting factor, and leukopenin as the local product of inflammation with distant actions. The purity and specificity of these materials are uncertain, and their codification by Menkin is widely disputed. It is evident from the studies of Zweifach, cited above, and many others dating back to Metchnikoff, that an injury causing inflammation is not necessarily severe or cellular, nor is it confined to vertebrates. The roles of other, better-characterized substances such as histamine, serotonin (5-hydroxytryptamine), hyaluronidase, and certain globulins in inflammation remain to be clarified. A detailed discussion of these controversial substances is beyond the scope of this chapter, but certain important features of their actions are included.

The earliest detectable change in acute microinflammation is the liquefaction of the *ground substance* and the uptake of water. Carbon particles, which ordinarily remain stationary after introduction by micropipette, are seen to diffuse widely into the ground substance of inflamed tissue, where they display Brownian movement. Electrometric[14,29] and histochemical studies[14,32] indicate depolymerization or disaggregation of molecular colloids (mucopolysaccharides, mucoproteins) of the ground substance, a marked increase in water solubility, and a loss of negative colloid charge density, with altered binding of electrolytes. Similar effects are produced by microinjection of hyaluronidase, trypsin, and a number of bacterial and other biologic toxins, but not by histamine or heparin.[96] These changes in the ground substance cause it to revert, in many ways, toward its embryonal state; many of these changes are found in the stroma of rapidly growing tumors,[32] in uninjured connective tissue in scurvy,[64] and in connective tissue damaged by rheumatic fever.[32] The ground substance not only changes in the direction of its embryonal state in acute inflammation, but far surpasses it in the extent to which colloidal disaggregation, permeability, and solubility are increased. The inflammatory reaction in avascular fetal connective tissue proceeds in much the same way as the lytic phase of inflammation in mature tissue described above.[18] In a tissue with effective blood and lymph circulation, inflammation takes on the features that have colored it since antiquity and have dominated its investigation in this century. Rubor, tumor, calor, dolor, and functio laesa stem mainly from the vascular reactions to injury.

Ehrich[27] looks upon the hyperemia and increased permeability of *blood capillaries* in inflamed tissue as an auxiliary mechanism which delivers plasma and white blood cells to the site of injury and speeds up the removal of the inciting agent and tissue debris. This view is supported by studies of inflammation in avascular invertebrates, in the young fetus, and in the mature cornea, where traumatic inflammation arises, resolves, and heals as a mesenchymal process without the benefit of intrinsic blood circulation. Although the primacy of mesenchymal reactions in inflammation and healing is established, the independence of the mesenchyme is not. Beyond the early fetal stage, a mammalian tissue deprived of its blood supply dies. Infarction or severe ischemia, whether in the oral cavity or elsewhere in the body, produces an abortive kind of inflammation which rapidly assumes the character of necrosis or gangrene. If the organism survives, there develops in the tissue adjacent to the infarction (the paravulneral region of a wound) an acute inflammatory response which spreads outward with diminishing intensity. Its successful conclusion in healing depends in large measure upon the vascular reactions of the inflamed tissue.

The earliest visible evidence of direct mild mechanical injury of a capillary is an increased adhesiveness between certain blood elements and the endothelial lining. Platelets and leukocytes adhere to the capillary wall, at first downstream in the venous capillaries and, with more intense irritation, in the region of trauma.[95] Following this, evidence of increased capillary permeability, with transudation of plasma, appears. The greatest change in the capillary wall appears to be a softening and increased porosity of the interendothelial cement. It is generally accepted that the intercellular cement, representing about 0.2 per cent of the area of the capillary bed, accounts for virtually all transfer of cells and colloids from the blood stream. During the inflammatory reaction, the capillaries, normally of fixed caliber, dilate and the number with active circulation increases greatly. More severe microinjury, according to Zweifach,[95] results in the rapid accumulation of white blood cells and platelets beneath the site of injury, with plugging and stasis of the injured capillary. Capillaries, as well as arterioles and venules which are cleanly transected, empty their contents and promptly retract in a way which closes them. As in the response to microtrauma described above, this is followed by a secondary hemostatic reaction, plugging by fibrin, platelets, and white cells and clotting of all elements of the blood farther inside the affected vessel.

The net effect of the complex neural and humoral control of the arterioles and venules[97] seen in the inflammatory response is a profound loss of tonic activity, and consequent dilation of the terminal vascular bed, resulting in the plethoric circulation of the inflamed region.

Unlike the blood capillary subjected to direct injury, the ruptured *lymph capillary* may not become sealed for several days, during which time fluid and cells flow freely between the vessel and the tissue. Intact lymphatics react to injury at first with dilatation and increased flow. The endothelial cells of both lymph and blood capillaries in the affected region imbibe water, swell, and manifest accelerated metabolism.[96] Although these necessary conditions prevail and even increase at the periphery of the injury if it is to be sustained, the lymphatics more severely affected become occluded by plugs of fibrin,[58] and the stage is set for inflammatory edema and a crowded cast of cells already assembling.

Holmberg,[43] reviewing the strides made in recent years in identifying dying *cells*, has highlighted the paucity of information concerning cell injury which is reversible. It might be argued that a cell cannot be injured by degrees in the same way that a complex tissue can, but that the activities of a cell subjected to injury can merely be depressed or stimulated, with an excess of either resulting in death of the cell. Increasing evidence[22] indicates, however, that cells, in their own way, are subject to injury by degrees and that recovery can proceed by degrees and end short of completion. Nothing about homeostasis is static, and least static of all are the little-known subcellular events attendant upon tissue damage.

At what point the activities of cells and subcellular organelles change from health to disease, from regenerative to degenerative cannot be said. The same changes at certain stages of the reaction to injury can lead, in fact, to opposite conclusions. The entire spectrum of cell changes can be seen within a short time after injury, ranging from cell death centrally to the least detectable changes at the periphery of the wound. It is generally accepted that the cells act both in vitro and in vivo as osmometers, and increasing data support the same view of the subcellular structures.

On the basis of many studies, the following composite view of the cell reacting to injury is ventured; the events described do not apply to a particular cell type or set of circumstances, both of which can modify the details of the proposed sequence of events. Among the earliest effects of anoxic injury are swelling and staining alterations of the lysozymes and mitochondria, accompanied by swelling of the cell. This does not at first or necessarily reflect a derangement of membrane function, but rather alterations in osmotic relations of the cell with its extracellular environment and of the subcells with their intracellular environment. Evidence of increased respiration and metabolism appears. Motion of the cell membrane is increased, with heightened pinocytosis, phagocytosis, and ameboid movement. An increase in the number of cytoplasmic granules indicates stepped-up synthesis.[32] Alterations in the endoplasmic reticulin appear and vary according to whether the cells are engaged primarily in movement or synthesis and division. A period of intensive protein synthesis precedes mitosis in the cell stimulated to divide. The effects of nearby injury upon this cell are clearly salutory, and the products of its accelerated metabolism diffuse easily outward through the liquefied ground substance, stimulating neighboring cells to similar activity. In a mild enough injury, no more striking changes than those represented above occur. Stationary cells resume their customary habits and habitus, and migrants deploy to enjoy the remainder of a normally short life.

It is upon the cells stimulated to heightened activity, not those subjected to a more injurious stimulus, that the burden of reaction and repair rests in the inflamed tissue. The effects of focal injury disseminate and decline in severity until such a population of cells, capable of accelerated migration, division, synthesis, and secretion, is reached.

Between the cells which are stimulated and those irreparably damaged lies a sparsely documented but clearly important and populous zone in which cell damage is evident, metabolism and respiration are depressed, membrane motion and cell mobility cease, and swelling is excessive without reaching lethal proportions. An influx of sodium accompanies that of water, and potassium along with other cell constituents is lost. Acid-base balance, consisting of a normally steep hydrogen ion gradient between cell and ground substance and between subcell and cytoplasm, is reduced and imperiled. Enormous numbers of cells, perhaps affected in these ways, and certainly in a host of other ways unknown at present, may survive the injury of illness and trauma and resume normal or modified functions.

The irreversibly damaged cell swells and rounds up; both the nuclear and cell membrane become permeable to dyes such as trypan blue and lissamine green.[43] Disorganization and loss of subcellular structures become evident, and with the damage already done, disruption of its membrane and extrusion of the cytoplasm of a cultured cell follow as a sort of biologic anticlimax.

The nature and effects of the products of cell destruction are difficult to dissect with any certainty. Locally, but only for a time, the effects of the initial injury are enhanced and disseminated in a spreading reaction of disaggregation and hydration in the ground substance, extravasation of plasma and blood elements, and more cell damage. Cellular diapedesis is dominated at first by polymorphonuclear leukocytes which migrate in sacrificial profusion into the injured region, adding cellular debris and digestive enzymes to the pool of breakdown products. As the inflammatory focus becomes increasingly acidic, lymphocytes and other mononuclear cells, better able to withstand the lower pH, replace the neutrophils. Plasma proteins diffuse through the watery ground substance, and fibrinogen precipitates shortly as fibrin.

The importance of fibrin, long recognized in blood clotting, is increasingly evident in the localization of acute inflammation. Thuerer and Angevine[84] have demonstrated a failure of bacterial infections to localize in animals treated with Dicumarol in doses sufficient to interfere seriously with fibrin formation. Menkin[58] has shown lymphatic occlusion by fibrin clots in acutely inflamed tissue, and Day[17] demonstrated a marked reduction in connective tissue permeability after perfusion of the membrane with a plasma-thrombin clotting mixture. Permeability is restored somewhat by hyaluronidase treatment, and altogether by streptokinase. Day concludes that the occlusive effect is the result of fibrin impaction in the interstices of the predominantly protein fabric of the ground substance.

Lymphatic and interstitial blockade of an inflamed tissue, except in coagulating thermal injury, is less prompt than has been appreciated. A phase of lysis and enhanced dissemination of both the agents[93] and the products of injury precedes localization. Hours to days may elapse before effective barriers, such as those described, develop.[7] Accompanying the occlusive and localizing reactions in the ground substance and lymphatics, disruption and thrombosis of the most severely involved blood vessels occur and complete a partial but biologically important isolation of the acutely inflamed region from the rest of the body. In bacterial infection, the localizing reactions are overcome in the absence of leukocyte infiltration of the region. Animals rendered severely neutropenic fail to respond to focal infection with the expected, intensely localized inflammation. Instead, the infection disseminates widely from the point of inoculation and can become rapidly lethal. In response to chemical and thermal injury, tissues of such animals display the usual inflammatory changes except for diminution or absence of leukocyte infiltration. An important result of cellular exudation in bacterial infection, apart from destruction of the pathogen present, is the intensification of the inflammatory response, presumably by products of cell destruction.

If an agent is intensely destructive, but the action is momentary such as the sweep of a scalpel, cell destruction is confined to a narrow zone resulting from direct contact with the knife and from exposure to air. If such a wound is closed without bacterial contamination, it does not become, by clinical criteria, inflamed. This impression is a tribute to the speed of dissemination of the effects of cell destruction and the speed of the reactions which confine the most damaging of these effects close to their origin. Microscopic appraisal of the same wound reveals a central path of destruction with intense inflammatory changes, surrounded to a depth that deceives the unaided eye by milder inflammatory changes affecting a cell population

capable of assuming the complex tasks of disposal and repair.

A milder but more persistent irritant, such as a subcuticular catgut suture, produces in the course of a few days a serpentine sterile abscess which is often associated with visible erythema and swelling more striking than that caused by the wound.

An irritant which is both intensely destructive and persistent, such as quartz, croton oil, or *Staphyloccus aureus* bacteria, produces a necrotizing inflammatory reaction which progresses until a barrier sufficient to confine the injurious agent develops. Experimentally, this may take hours to days, depending to a great extent upon the quantity of irritant applied. The additional biologic properties of growth and invasiveness of bacteria and the immune reactions of the host can decisively affect the course of a microbial lesion. The immune reaction to a microorganism, like the less specific reaction of intense inflammation described above, is uniformly and often dramatically localizing in net effect.[68] The advantages to the body as a whole are evident. The advantages of early localization of injury to the surviving local cell population are equally important. The number of healthy tissue cells affected by the inflammatory reaction about a minute center of necrosis is very much greater than the number of cells destroyed. This advantage is lost precipitously and almost geometrically as a necrotizing spherical lesion expands.

Fibers and fiber bundles swell, fragment, and become separated in acutely inflamed tissue to an extent controlled by their density and random interlocking. The dense, parallel fibers of ligaments and tendons, with great linear strength, are easily separated by lateral forces. The collagen fabric of the dermis or gingiva, on the other hand, is dense and interlocking and yields appreciably in any direction only to forces which disrupt the fibrous protein itself. The reaction of fibers during inflammation is largely due to changes in the cementing substances which bind microfibrils into fibrils and fibrils into fibers and bundles. Once precipitated as a fibrous material, collagen is remarkably inert and has a biologic half-life beyond measurement by ordinary isotopic techniques. The cementing substances and the other elements of the ground substance are vulnerable to lytic influences, however, which can be swiftly loosening. In addition, the sulfated mucopolysaccharides, which are thought to provide interfibrillary cementing, have half-lives measured in days and are therefore subject to rapid alteration by attrition alone. In acute inflammation, easy splitting and displacement of fibers which depend upon interfibrillary cementing for coherence occur. More direct injury of collagen fibers is marked by changes in tinctoral properties microscopically, gelatinization and eventual hydrolysis chemically. Collagenase participation in the disposal of injured fibers is unlikely and unessential; disaggregation renders collagen molecules susceptible to ordinary proteolytic digestion.

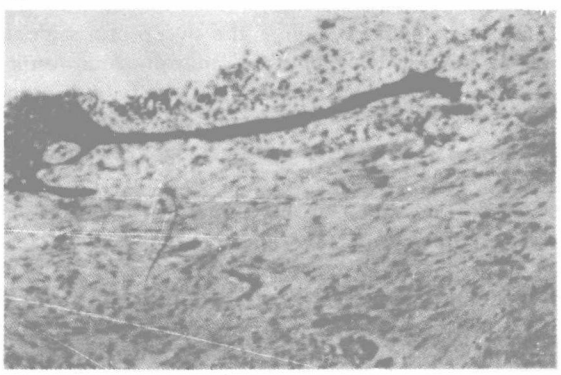

Fig. 1-2. Advancing pavement of epithelium undermines the tissue debris at the surface of the wound.

Collagen everywhere does not share the inert features described above. In the involuting uterus[42] and the ossifying fracture callous clinically, and in the carrageenin granuloma experimentally,[91] collagen is dismantled, digested, and absorbed with a rapidity that has as yet no sure explanation, but requires collagenase-like activity.

Elastic fibers are less susceptible to chemical attack but incur physical damage more easily, perhaps, than collagen. This can be seen particularly well in arterial injury, where the elastic membranes become fragmented well in advance of any visible disturbance of the adjacent collagen fibers.[82]

Basement membranes consist of surprisingly numerous and densely packed layers of collagen fibers and cementing substances, usually interposed between glandular or investing epithelium and stromal connective tissue. Gersh[32] interprets thickening and fraying of injured basement membranes as a part of the generalized depolymerization of mucopolysaccharides of the ground substance. If the injury is severe enough, the basement membrane rapidly loses its grip on the overlying epithelium and desquamation occurs, followed by loss of the membrane itself.

The *investing epithelium* of the oral cavity in man resembles epidermal rather than intestinal epithelium, except for a lightly keratinized layer rather than a well-formed heavy layer of keratin. The lack of a tough and stable waterproofing layer renders oral epithelium, like the rest of the alimentary tract, especially vulnerable to certain kinds