OCULAR PATHOLOGY

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Second edition

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PREFACE TO THE SECOND EDITION

In order to bring the subject matter of the 1st Edition up to date, approximately one-third of the text has been re-written and additions and amendments have been made throughout.

A new chapter on the more commonly encountered diseases of the eyelids has been added while the chapter on the conjunctiva has been re-written and expanded to include a more detailed account of viral keratoconjunctivitis and descriptions of corneal ulcers, degenerations and dystrophies. The subject of melanotic lesions of the conjunctiva and lids is presented in a new way which it is hoped will clarify this often confusing topic. By judicious revision of the text, the length of the book has been kept substantially the same as that of its predecessor despite the inclusion of much new material.

PREFACE TO FIRST EDITION

This book is for ophthalmologists and those training as ophthalmologists. It is based on the author's course of instruction in ocular pathology for the Diploma of Ophthalmology of Melbourne University and for the Fellowship in Ophthalmology of the Royal Australasian College of Surgeons.

The book makes no claim to be an exhaustive account of its subject but is an attempt to present, in brief but not synoptic form, most of what the post-graduate student should know about ocular pathology in order to face his examiners with confidence. Its more general but no less important aim is to emphasise the pathological basis of the signs and symptoms of ophthalmic diseases.

In selecting topics for inclusion, preference has been given to those which students find difficult to grasp and to material which, by reason of its dispersal in books, and journals, is not always readily available.

ACKNOWLEDGMENTS

It is a great pleasure to acknowledge the continued help and interest of ophthalmologists throughout Australia and South-East Asia who have supplied material for study.

I am overwhelmingly indebted to the following source books which for convenience are listed once here rather than repeatedly in the references at the ends of chapters and sections. The reader should consult them freely for further details, alternative viewpoints and for their valuable reference lists.

Ophthalmic Pathology
M. H. HOGAN & L. E. ZIMMERMAN (Saunders, London, 1962)

Pathology of Tumours
R. A. WILLIS (Butterworth, London, 4th Edition, 1967)

System of Opthalmology
S. DUKE-ELDER (Kimpton, London)

Tumors of the Eye
A. B. REESE (Hoeber, New York, 2nd Ed., 1963)

Systemic Pathology
EDITORS—G. PAYLING WRIGHT & W. ST. C. SYMMERS (Longmans, London, 1966)

Grateful acknowledgment is also made to the authors of the many journal articles consulted. Of these, a small number of particular interest appear as recommended reading at the ends of sections.

Many of the illustrations are new and for help with these I am indebted to Senior Technologist, C. Lebeckis and Clinical Photographer, T. Cottier of The Royal Victorian Eye & Ear Hospital. Figs. 4.1, 7.8, 7.10, 9.1, 9.2, and 12.7 are by kind permission of Professor Norman Ashton; Figs. 7.9 and 7.11 are by courtesy of the Editor, *Proceedings of The Royal Society of Medicine*; Fig. 2.5 by courtesy of the Editor, *Transactions of The Ophthalmological Society of the United Kingdom*; Fig. 10.4 by courtesy of Dr. J. McBride-White; Fig. 10.5 by courtesy of the Editor, *American Journal of Ophthalmology*; Fig. 11.10 by courtesy of the Editor, *Archives of Ophthalmology*.

I am especially grateful to Dr Edward Ryan for encouragement and constructive criticism.

To my Publishers I am again profoundly thankful for their courtesy and consideration.

C. H. GREER

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CHAPTER I

INFLAMMATION AND REPAIR WITH PARTICULAR REFERENCE TO THE EYE

Inflammation may be very simply defined as the immediate vascular and exudative reaction of living tissue to injury (Willis). The injury initiating the inflammatory response may be inflicted by living or non-living agents:

Injury by living organisms: In this case the injurious agent is self-reproducing, and continuously produces toxins which damage the tissues. The inflammatory response continues as long as the organisms survive and proliferate in the tissues and may therefore be of short or long duration.

Injury by physical agents: Injury by physical agents, such as mechanical trauma, heat, chemicals, etc., is inflicted once and then ceases. The resulting inflammation is excited by the products of tissue destruction and when these have been removed, inflammation subsides and repair proceeds.

ACUTE INFLAMMATION

Acute inflammation is a rapidly developing reaction to swiftly acting noxious agents, e.g. pyogenic cocci, and is non-specific in that it is chiefly invoked by the products of tissue destruction rather than by the injurious agents themselves. Acute inflammation often subsides relatively quickly and repair tends to be a fairly distinct process.

In acute inflammation the fluid exudate is serous, fibrinous or haemorrhagic or a mixture of these elements. In the majority of acute inflammations, the cellular response is mainly polymorphonuclear. Sometimes, however, clinically or experimentally acute inflammatory reactions are characterised by a mononuclear response.

The immediate response to the injurious stimulus is dilatation of the local arterioles, venules and capillaries. This results in a rise of hydrostatic pressure in the affected vessels along which the blood flows at an accelerated rate.

During the next few hours, vascular dilatation continues and capillaries previously closed, or conducting only a minimal flow, open up. Despite this,

blood flow progressively slackens and may eventually cease (vascular stasis).

As this occurs, protein-rich fluid escapes from the vessels into the surrounding tissues (formation of exudate). In acute inflammation this exudate approximates in constitution to blood plasma. Meanwhile leucocytes begin to adhere to the vascular endothelium as a preliminary to migration through the vessel walls (emigration of leucocytes). The cause and outcome of these changes will now be briefly considered.

ARTERIOLAR DILATATION

Initial dilatation is mainly due to axon reflexes. Thus the stimulation of local sensory nerve endings cause impulses to travel, not only along the sensory nerves to the central nervous system, but also by vaso-dilator branch fibres to local arterioles. *Prolonged* arteriolar dilatation on the other hand is possibly mediated chemically by locally formed vaso-active peptides released by injured cells.

CAPILLARY DILATATION

May be regarded as the initial phase of a reaction ultimately leading to increased capillary permeability to protein. Both phases of the reaction are brought about by the same substances, e.g. histamine, although higher concentrations of such substances are needed to increase permeability than to cause dilatation.

VASCULAR STASIS

The progressive slowing of the circulation and its stagnation are due mainly to increased viscosity of the blood consequent upon the escape of blood fluid into the tissues. Thus, as the concentration of red cells increases, blood viscosity rises sharply and the consequent resistance to onward flow causes a rise of pressure within the vessel which promotes further exudation of fluid. This cycle may end in complete circulatory stasis in the inflamed area with the capillaries obstructed by immobile trains of closely packed red cells.

THE FORMATION OF EXUDATE

The endothelium of normal small blood vessels is freely permeable to water, salts, amino acids and other substances of small molecular size but almost impermeable to the larger molecules of the plasma proteins which, therefore, exert osmotic pressure across the vessel wall. Normally a rough balance of forces is achieved between the hydrostatic pressure of the blood stream

tending to force fluid out of the vessel and the osmotic pressure of plasma proteins tending to draw fluid back into the vessel.

In inflammation the capillary wall becomes more permeable than normal to plasma proteins which are therefore lost into the tissue fluids. In addition, the capillary hydrostatic pressure is increased as a result of vaso-dilatation. The normal balance of forces is thus deranged, with the result that protein-rich fluid accumulates in the tissues and is retained there. Increased capillary permeability to protein is therefore a prime factor in the formation of exudate. Although we customarily speak of increased 'capillary' permeability, recent electron microscopic studies suggest that the actual site of increased permeability to protein and of leucocytic emigration during inflammation is the venules.

Of the many substances known to increase permeability, histamine and certain peptides seem to be principally active in the inflammatory reaction. Much of the body's histamine is contained in the granules of the ubiquitous mast cells; some is also present in blood platelets and basophil leucocytes. How histamine is released when tissues are injured is not known but it has been postulated that transiently active enzymes in the injured area attack the mast cells and disrupt their envelopes. It appears that the inflammatory dilatation and increased permeability of small vessels is diminished by cortisone.

EMIGRATION OF WHITE CELLS

When blood is flowing normally through small vessels, its cells occupy an axial stream leaving a clear, cell free, peripheral plasmatic zone. As blood flow slackens, this axial stream of cells becomes broader at the expense of the plasmatic zone. The red blood cells temporarily adhere to one another forming rouleaux-like masses much larger than individual white cells which are consequently displaced into the plasmatic zone where they adhere to the vascular endothelium preparatory to migrating through the vessel wall. It is not known how or why the leucocytes adhere to the endothelium. The white cells escape by forcing their way between the vascular endothelial cells and then through the basement membrane of the vessel and its peri-vascular sheath. Before the exit hole is sealed, a few red cells may also escape but this passive diapedesis is usually only of minor degree.

Once outside the vessel, leucocytes are chemotactically attracted by bacteria. Many bacterial species attract leucocytes in this way even although, as often happens, the bacterial toxins kill the leucocytes when they approach too closely. Neutrophils are also powerfully attracted by substances formed when antigen–antibody complexes react with complement.

PHAGOCYTOSIS

In man the important wandering phagocytes are the neutrophil (microphage) and the monocyte (macrophage), both of which migrate into the tissues from the blood. In acute inflammations neutrophils arrive first, and in the early stages greatly outnumber the monocytes.

The ability of neutrophils to phagocytose bacteria is greatly enhanced by serum opsonins. These are proteins which coat the bacterial surface and render the organism more easily ingestible. The best opsonins are antibodies specific for the bacteria and able to form a firm union with their surface antigens.

Phagocytes ingest both dead and living bacteria. The former they digest, the latter they kill if they can, but precisely how this is achieved is far from clear. It is suggested that the ingestion of foreign particles by neutrophils provokes increased glycolysis which increases lactic acid production, and that the increasing intracellular acidity releases bactericidal phagocytin and digestive enzymes from the cell granules. The lysozyme in tears, nasal secretions, saliva, etc., is able to lyse living bacteria but acts mainly against non-pathogenic organisms.

Virulent staphylococci taken up by neutrophils can resist digestion and may actively multiply inside the cells leading to their death. Neutrophils have only a short life and, as they die and break up, are phagocytosed by macrophages. Macrophages have a much longer life and can carry carbon particles and melanin granules for many months. Their wanderings with ingested living tubercle bacilli sometimes help to disseminate the infection.

PUS FORMATION

Suppuration is the natural result of the invasion of the tissues by pyogenic organisms. The inflammatory reaction brings to the infected area a large force of neutrophils to combat the invading bacteria. In the ensuing struggle bacteria are ingested and killed while tissue cells and polymorphs die from the effects of bacterial toxins. Enzymes liberated from dead cells, particularly from neutrophils, digest the dead cells, collagen fibres and serum, etc. to form pus which thus contains products of protein breakdown, nucleoproteins, lipids and fluid exudate together with both living and dead polymorphs and bacteria. Suppuration can also be induced in the absence of bacteria by the injection of bacterial proteins, turpentine, silver nitrate and other substances which cause an accumulation of neutrophils and necrosis of tissue cells.

In the eye, pus is commonly found as a dense yellowish blob suspended in the vitreous (vitreous abscess) or as a yellowish-white sediment in the

lower anterior chamber (hypopyon). In sections, pus is recognisable as a dense purplish mass composed mainly of polymorphs in various stages of disintegration.

CHRONIC INFLAMMATION

Chronic inflammation is the response to slowly acting, persistent injurious agents and may be a seriously destructive process. It develops slowly and is prolonged and the inflammatory changes are commonly accompanied by those of synchronous repair.

Exudation of fluid occurs but is usually less marked than in acute inflammation. The cells which enter the inflamed area are chiefly mononuclears, i.e. monocytes, lymphocytes and plasma cells. These migrant cells may be reinforced by the proliferation of tissue cells (histiocytes) native to the connective tissue of the part. Epithelioid cells and giant cells may be a prominent feature and eosinophils are sometimes also present in considerable numbers.

Chronic inflammations are sometimes granulomatous in character. This implies the formation of nodules of granulation tissue infiltrated with inflammatory cells predominantly of mononuclear type. In the pathology of nonsuppurative intraocular inflammation, granulomatous inflammation has come to have a rather limited connotation and implies an inflammation dominated by macrophages and their epithelioid-cell and giant-cell derivatives which are often, but not invariably, aggregated into nests.

HEALING AND REPAIR

The processes of healing and repair vary in complexity according to the following factors:

1. The amount of tissue damage sustained.
2. The means by which injury is inflicted, whether by micro-organisms, physical agents or nutritional or vascular insufficiency.
3. The persistence of noxious agents, especially micro-organisms, in the damaged area.
4. The nature of the injured tissue.

Despite these variables, the repair of all kinds of destructive injury is essentially similar and can be resolved into two chief components, namely new vessel formation and fibrosis, evidence of which is seen in different

proportions in the repair of both bacteria-free surgical incisions and ragged accidental wounds, in the healing of ulcers, abscesses and inflammatory foci and in the organisation of blood clot, etc.

NEW VESSEL FORMATION

While the damaged area is being cleared by phagocytes of dead cells, blood, fibrin, etc., new vessels begin to enter from adjacent tissue. These vessels are at first solid sprouts of new endothelial cells derived from the endothelium of existing vessels. The sprouts soon canalise and join others to form loops and networks. At first the new vessels consist only of endothelium and are abnormally permeable to red cells and plasma. Later they differentiate into fully formed capillaries, veins and arteries. Lymphatic vessels are reconstituted in the same way.

FIBROSIS

Fibroblasts, which migrate into the damaged area at about the same time as the newly formed vessels, are derived from fibrocytes in the adjacent tissues and possibly from macrophages. As the fibroblasts advance they are seen as stellate or bipolar cells with fine processes and cytoplasmic granules containing mucopolysaccharides. Fibroblasts are centres of collagen fibre formation but the fibres are not extensions of the fibroblast cytoplasm—rather they seem to form at the cell surface and to be shed into the intercellular ground substance. It is probable that ascorbic acid is necessary for normal collagen fibril formation.

Ground substance is a gelatinous or semi-solid matrix consisting in part of extracellular fluid largely derived from blood plasma. In addition, it contains abundant mucopolysaccharides, chiefly hyaluronic acid and chondroitin sulphate, and mucopolysaccharide–protein complexes (glycoproteins). Mucopolysaccharides in ground substance are possibly partly derived from fibroblasts and mast cells.

GRANULATION TISSUE

The resulting complex of fibroblasts and new capillary vessels is termed granulation tissue from the granular or cobbled appearance imparted to its surface by the capillary loops. In bacteria-free surgical wounds with close apposition of the edges, the formation of granulation tissue is minimal but whenever there is a gap in the tissues, as in ragged wounds or ulcers, the defect is filled by an abundance of granulation tissue.

In time, most of the blood vessels in granulation tissues close down and disappear. More and more collagen fibres are formed and the original

fibroblasts die or revert to a quiescent state (fibrocytes). Later the collagen fibres may fuse into a structureless glassy mass (hyalinisation).

GLIOSIS

Scarring also occurs in the retina and optic nerve following damage to these structures. When neurones are destroyed their necrotic remains are removed by microglial phagocytes and the resulting defect is filled by proliferation of the supporting glial cells more especially the robust fibrous astrocytes. This process of gliosis, which results in permanent glial scars, is analogous to collagenous fibrosis and scarring in connective tissues. In severe acute insults such as sudden occlusion of the central retinal artery, the neuroglial cells may be destroyed along with the neurones. In this case no reactive gliosis follows and the retina later collapses and shrinks to a few surviving glial fibres.

THE FORM AND FUNCTION OF INFLAMMATORY CELLS

A brief description of the form, origin and function of the cells encountered in inflammation is necessary to render intelligible any histological study of this process. The following description refers to the cells as seen in sections stained with haematoxylin and eosin.

NEUTROPHILS (neutrophilic polymorphonuclear leucocytes, microphages, pus cells)

Neutrophils originate in the bone marrow and are the most abundant of the circulating granulocytes. The cells, which measure 10–15 μ in diameter and have multilobed nuclei, are motile and actively phagocytic, especially for cocci. They enter acutely inflamed tissues from the blood stream by migrating through the vessel walls and are a major constituent of pus, e.g. vitreous abscess, hypopyon. When they die they release powerful proteolytic enzymes. In phacoanaphylactic endophthalmitis they are seen in the van of the phagocytes which invade the lens. Marked local suppuration induces increased production of neutrophils in the bone marrow with a consequent increase in their numbers in the circulating blood (neutrophilia).

EOSINOPHILS (eosinophilic leucocytes)

Eosinophils, which are also derived from the marrow are sluggishly motile and weakly phagocytic. They are recognisable by their bilobed nuclei and

numerous brightly eosinophilic granules. Since these granules contain an antihistamine substance it is possible that one function of eosinophils is to neutralise histamine when this is liberated in quantity in the tissues, e.g. in allergic reactions. Eosinophils are a variable component of the cellular infiltration of the uvea in sympathetic ophthalmitis and lens induced uveitis. They accumulate in great numbers around chronic gastric ulcers, in areas of subacute and chronic inflammation and in the respiratory mucosa in asthma and allergic rhinitis. In parasitic infestations, e.g. with nematodes or cestodes, eosinophils are concentrated around any parasites in the tissues and the number of eosinophils in the circulating blood may be considerably increased above the normal 400 per mm^3 (eosinophilia). Injections of ACTH produce a sharp fall in the number of circulating eosinophils, provided the adrenals are capable of responding.

MACROPHAGES

Macrophages in action are large round mononuclear phagocytes ranging from 15 to 40 μ in diameter with round, oval or reniform, often eccentric nuclei and abundant cytoplasm containing scavenged matter such as cell debris, bacteria, protozoa or fungi, particulate foreign matter, melanin granules, soft lens matter or blood derivatives. Macrophages distended with lipid droplets are known as foam cells or lipophages (Fig. 1.1). Macrophages unlike microphages are able to reproduce in the tissues.

Considered collectively, macrophages form a body-wide system of phagocytic cells with the following main components:

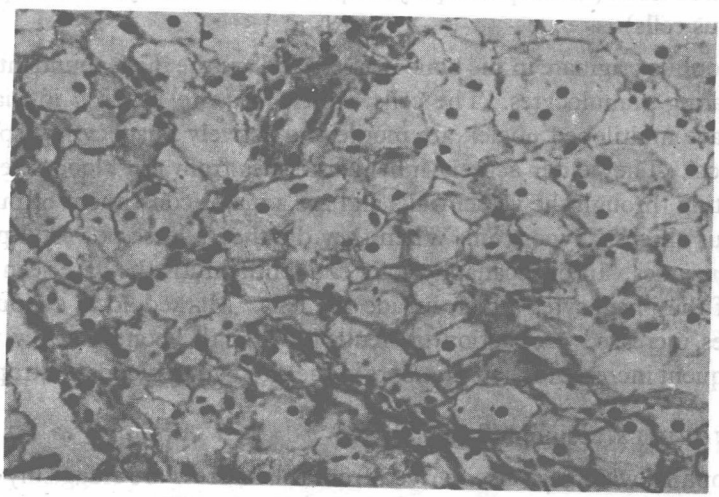

FIG. 1.1. Lipophages in xanthelasma.

Histiocytes: These are branching tissue cells which normally lie scattered either singly or in microscopic clumps throughout the connective tissues in a resting state from which they can be roused to phagocytic activity. Unfortunately the terms histiocyte and macrophage are often used synonymously.

Blood monocytes: These cells migrate through vessel walls as the occasion demands. Monocytes entering the eye often escape into the ocular chambers and the majority leave the eye in the aqueous stream via Schlemm's canal. However, monocytes sometimes settle in the connective tissues where they are transformed into histiocytes.

Sinus-lining (*littoral*) *cells* of the blood sinuses in liver, spleen, bone marrow and adrenal cortex and of the lymph sinuses in lymph nodes. These fixed macrophages are flat in the resting stage but thicken up and protrude into the sinus lumen after taking up foreign matter.

Microglial cells (*cerebral histiocytes*) of the central nervous system, including the optic nerve and retina. In areas of brain damage these normally small inconspicuous branched cells become greatly distended with lipid (compound granular corpuscles).

Perimacular circinate exudates, the exudates which form macular stars and many of the retinal exudates in Coats' disease, are aggregates of macrophages loaded with lipid which they have scavenged from pools of extravascular serum or plasma and from necrotic retinal cells.

Macrophages can be readily studied in the following conditions:

Coats' disease: In addition to those in the retina, numerous macrophages distended with lipid and pigment rods derived from the retinal pigment epithelium are found in the cholesterol-rich subretinal effusion. There is a tenaceous belief that macrophages found in subretinal effusions are mobilised retinal pigment epithelial cells which have assumed phagocytic functions. Histological appearances sometimes seem to support the possibility of such a transformation and no substantial proof has been offered that it cannot occur. However, it seems more likely that these subretinal macrophages are retinal microglial cells and monocytes.

Granulomatous iridocyclitis: Blood monocytes escape from the vessels into the inflamed tissues of the ciliary body and iris and thence into the posterior and anterior chambers and the vitreous. Large agglutinated aggregates of these cells adhering to the corneal endothelium form lardaceous or mutton-fat K.P.

Phacolytic glaucoma: Blood monocytes migrate into the eye in response to degraded lens matter and develop into spherical macrophages loaded with granular lens protein. They are found round the lens, in the anterior