OPHTHALMIC PATHOLOGY

AN ATLAS AND TEXTBOOK

AMERICAN ACADEMY
OF
OPHTHALMOLOGY AND OTOLARYNGOLOGY
AND THE
ARMED FORCES INSTITUTE OF PATHOLOGY

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FOREWORD

The value of a Registry of Pathology as an educational medium could have no better exemplification than this Atlas and Textbook of Ophthalmic Pathology. It presents a clear and comprehensive coverage of the morphologic pathology of the eye and an exposition of the physiologic processes that pertain to ocular change. The text, written by outstanding investigators in the field of ophthalmology, represents the most advanced thought on the pathologic considerations of this specialty and furnishes a solid foundation for the interpretation of clinical manifestations of ocular disease.

The Registry of Ophthalmic Pathology is the oldest component of the American Registry of Pathology. The contribution of specimens and records by ophthalmologists over a period of thirty years has built up an outstanding collection of material in this Registry. During these years this valuable material has been coordinated for greater usefulness in study and research by analysis and interpretation carried on by members of the staff of the Armed Forces Institute of Pathology, both present and past. Thus, this Atlas is the product of a great collaboration in which, in a sense, all who have contributed material to the Registry are partners.

We are gratified to have been in a position to stimulate and participate in the preparation of this unique work. It is something new in the way of an atlas in that it includes the discussion of physiologic mechanisms that influence pathologic change, and it still retains the best features of the older atlases in its magnificent illustrations. This volume is indeed an achievement in which both the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology can justly take pride.

ELBERT DECOURSEY
Brigadier General, MC, USA

PREFACE

The Atlas and Textbook of Ophthalmic Pathology is an outgrowth of the Atlas of Ophthalmic Pathology by DeCoursey and Ash, which was based on material in the Registry of Ophthalmic Pathology, produced by the Army Medical Museum, and sponsored by the American Academy of Ophthalmology and Otolaryngology. Its preparation was instigated by the educational committees of the Academy, inspired by the success of the earlier Atlases. The aim of these committees was to provide a text embodying the requirements in histopathology for Board certification, to further the instruction of residents in hospitals with limited teaching and laboratory facilities, and to furnish a convenient source for the ophthalmologist pursuing study in the pathology of his specialty.

As the task of revision progressed, it was proposed that Friedenwald's "Pathology of the Eye" be used as a basis for the text, that relevant physiologic data be included, and that the photomicrographs be arranged to illustrate subjects corresponding to the chapter headings rather than specific cases. It was realized that while this procedure involved considerable change in the character of the Atlas, it would add materially to its usefulness. Although this volume is intended as a teaching aid rather than a reference, it logically carries the added text, which has been written to give the most widely accepted concepts of pathology as they are now understood and taught in the leading medical colleges.

The purpose of the Academy in sponsoring the publication of this Atlas and the Atlas of Otolaryngic Pathology remains unchanged since Dr. Ralph A. Fenton suggested in 1937 that they be made a part of its educational activity. The first edition of the Atlas of Ophthalmic Pathology appeared in 1938 under the joint authorship of Captain Elbert DeCoursey, Pathologist to the Registry, and Lieutenant Colonel James E. Ash, Curator of the Army Medical Museum, with credits to Helenor C. Wilder, Roy M. Reeve, and Lawrence P. Ambrogi. The second edition in 1939 and the third edition in 1942 were products of the same collaboration. Later in the war years, revision toward a more comprehensive text was projected, and this work was begun while Colonel Ash was Director of the Army Institute of Pathology, as the Army Medical Museum had by then been designated. The writing of the text was undertaken by a group of authors headed by Dr. Jonas S. Friedenwald, and this book is the fruit of that collaboration.

To facilitate administration of the project, Dr. Brittain F. Payne was selected in 1945 as Chairman of the Committee for Revision of Pathologic Atlases. He appointed as members of that Committee a number of teachers of eye, ear, nose and throat pathology. Every ophthalmologist of that group contributed in one way or another to the preparation of the Atlas in his field. In 1946 the Academy Committees on Pathology were merged into an Advisory Committee charged with the supervision of the selection of material and the production of the Atlases.

The debt of the Academy to Colonel Ash for his deep interest in the Atlases and for his enthusiastic cooperation in their preparation is gratefully acknowledged. Brigadier General Raymond O. Dart, who succeeded him as Director, continued the traditional cooperation with the Academy. Dr. Hugh G. Grady, who became Scientific Director of the American Registry of Pathology during this period, has been most helpful in matters concerned with publication. It is particularly fitting that the Atlas and Textbook of Ophthalmic Pathology should become an accomplished fact when Brigadier General DeCoursey, who contributed so generously to the three early editions, is Director of the Armed Forces Institute of Pathology.

The American Academy of Ophthalmology and Otolaryngology gratefully acknowledges the contributions of Dr. Brittain F. Payne, who has guided the Committee on Revision of the Atlases; Dr. Jonas S. Friedenwald, who has written much of the text and revised and

unified all of it; Helenor Campbell Wilder, who not only contributed to the text but also bore the entire responsibility for the illustrations; Dr. A. Edward Maumenee, who is to be credited with a large share of the authorship; Dr. Theodore E. Sanders, Dr. John E. L. Keyes, Dr. Michael J. Hogan, who wrote or collaborated on one or several chapters; Drs. William C. and Ella U. Owens, who contributed text and illustrations on retrolental fibroplasia; Dr. Frederick H. Verhoeff, Colonel James E. Ash, Dr. Georgiana Dvorak Theobald, Dr. Algernon B. Reese and Dr. John S. McGavic, who acted as consultants, reviewing the manuscripts and suggesting revisions and additions; Dr. Benjamin Rones, who organized and took part in the conferences of the authors and in the critical review; and Helen Knight Steward, who edited the manuscript and prepared it for press in addition to her regular assignment in the Armed Forces Institute of Pathology. With no thought of reward other than that of seeing a much-needed work well done, the members of the Committee on Revision of the Atlases, the authors, and the contributors of time and material to the production of the Atlas and Textbook of Ophthalmic Pathology have exemplified to the highest degree the spirit of unselfish cooperation that so typically distinguishes the medical profession and its devotion to the cause of education.

WILLIAM L. BENEDICT, M.D.

CONTENTS

INTRODUCTION: ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The anatomy and physiology of the eye have attracted the attention of scientific investigators since the dawn of medicine. A list of the contributors to the present knowledge of its structure and function includes the names of many who stand in the front ranks of the natural sciences. The seeming isolation and completeness of the eye permit the study of certain phases of structure and function as detached problems. Although this may be the case in regard to ocular anatomy and physiology, the problems of ocular pathology are in no sense isolated. Disease in so specialized an organ as the eye is manifested by a degradation in function. The more intense the disease, the more the eye behaves like less highly differentiated parts of the body.

The purpose of this book is to present a brief description of the pathogenesis and morphologic pathology of diseases of the eye. Much of the content on pathogenesis has been taken from *The Pathology of the Eye* by Jonas S. Friedenwald. The material on morphologic pathology is in part a continuation and expansion of *The Atlas of Ophthalmic Pathology* by DeCoursey and Ash. The aim is to form a bridge leading from general pathology to this special field, so that the student will not find himself lost in a maze of seemingly strange and unrelated facts. The general laws of pathology hold quite as rigorously for the eye as they do for any other organ. Diseases of the eye, as well as of every other organ, produce lesions which are modified in varying degree by the special structure and function of the organ.

In the history of the development of pathology the eye occupies a notable position. Much of the early work on inflammation by Cohnheim and others was accomplished through experimentation on the eye. The absence of blood vessels in the cornea, for instance, made it possible to differentiate the cellular from the vascular factors in inflammation, and the transparency of the cornea facilitated the study of early lesions in living tissue.

It is such local anatomic and physiologic peculiarities as the avascularity and transparency of the cornea that justify the study of the pathology of the eye as a special branch of systemic pathology.

LIDS

The lids are essentially two movable folds of skin which protect the eye. This skin, while particularly thin, is like the skin elsewhere in the body, except for minor variations which make it more suitable for the organ it covers. It contains only a few fine hairs and little subcutaneous fat. The looseness of the subcutaneous connective tissue of the lids probably explains their disposition to edema, though some peculiarities of the structure of the capillaries and venules may play a part. The vasomotor control of the circulation in the lids and conjunctiva seems to be more labile than that in other organs; witness the congestion of these parts commonly associated with eye strain or general fatigue, and the dilatation of the deeper-lying veins of the lids, responsible for the dark rings seen about the eyes under a variety of circumstances. The junction of the skin and mucous membrane, like similar junctions elsewhere, is a favorite site for the development of epitheliomas.

CONJUNCTIVA

The epithelium of the conjunctiva is unkeratinized but readily forms a horny layer on drying and in other conditions. This is seen clinically in cases of lagophthalmos, total absence of the lacrimal gland and keratitis sicca.

The constant flow of tears from the lacrimal glands through the excretory tubules, across

the conjunctival sac, and into the lacrimal canaliculi not only protects the conjunctiva from drying, but also plays an important role in defending it against bacterial infection. The ciliated epithelium lining the lacrimal ducts actively aids the downward passage of the tears and of such debris as they may carry with them. In the conjunctival sac the flow of the tears is furthered by the blinking motion of the lids. While the total secretion of tears under normal circumstances is probably not more than one or two cubic centimeters a day, the fluid is spread in so thin a layer and the total volume within the conjunctival sac at any moment is so small that the conjunctiva is continually being washed clean.

In addition to this purely mechanical function, the tears possess a definite bacteriolytic property, and even *in vitro* can be shown to inhibit the growth of certain bacteria. One active principle in this antibacterial process has been isolated and is known to be a mucolytic enzyme named "lysozyme." This substance, first described by Fleming[1] in 1922, has been demonstrated in the tears, saliva, nasal secretions, blood plasma and leukocytes, also in egg white and certain vegetable juices. It is noticeably absent in the cerebrospinal fluid, aqueous and normal urine. It is chemically similar to avidin but may be differentiated from avidin by its greater solubility.[2] Lysis of bacteria by this enzyme is caused by hydrolyzing a substance of mucoid nature in the bacterial membrane.[3] This action of lysozyme on bacteria has been confirmed by observations with the electron microscope and has been compared with the action of bacteriophage and sulfonamides.[4] The titre of lysozyme in normal tears is fairly high, but with increased lacrimation from almost any cause the lysozyme titre is reduced,[5] as is also the protein concentration, so that with the advantages of increased flow are associated the disadvantages of decreased bactericidal activity and even of definite, though slight, irritation to the conjunctiva. A similar alteration in the character of the tears may be responsible for some cases of chronic simple conjunctivitis.

Lysozyme is probably not the only bacteriolytic agent in tears, for it is primarily effective against saprophytes and causes little if any destruction of pathogenic organisms. Fleming[1] and Ridley[5] have shown that tears are capable of lysing pathogenic bacteria. Recently, Thompson and Gallardo[6] have shown that boiling the tears in acid solution destroys their lytic action on *Staphylococcus albus* and *Staph. aureus* without changing their lysozyme content. Meyer, Smyth and Dawson[7] found that lysozyme withstood similar treatment without inactivation. Thus it would seem that the tears have more than one bacteriolytic enzyme.

The mechanical cleansing and bacteriolytic action of tears accounts for the paucity of organisms in the conjunctiva as compared with other exposed portions of the body. In addition, the film of mucus which normally covers the conjunctiva may act in part as a protective coat. However, these mechanisms are not totally effective, as may be deduced from the frequency of bacterial and viral conjunctivitis. In rare instances the conjunctiva may act as portal of entry for systemic infections such as tuberculosis, tularemia, meningococcus meningitis and syphilis.

CORNEA

Transparency of the Cornea. The extraordinary transparency of the cornea has long been of profound interest to ophthalmologists. It depends on the optical homogeneity of the tissue, but the exact mechanism whereby this property is maintained is still debated. The factors which contribute to its clarity may be divided into two categories: (1) the physical arrangement of the tissues, which will be described in Chapter II, and (2) their state of hydration. The anterior surface of the normal cornea is extremely smooth because of the wetting effect of the thin film of tears with which it is constantly covered, the unusual regularity of the epithelium and the absence of cornified cells. The cell membranes are in such excellent apposition that there is scarcely any intercellular fluid.

As to the state of hydration of the cornea, Fischer[8] has demonstrated that its transparency and that of the sclera are dependent in part on the water content. He showed that the sclera could be clarified to a semitranslucent state by reducing the water content 30 per cent or by increasing it 20 per cent, and that the cornea loses its clarity when the fluid content is increased. This is observed clinically in endothelial dystrophies of the cornea, or it can readily be demonstrated in vitro by placing pieces of cornea in physiologic solution of sodium chloride. Cogan and his co-workers[9] demonstrated that the cornea is capable of imbibing fluid regardless of the tonicity of the solution, within a considerable range of variation of the hydrogen ion concentra-

tion. They stated that the property of normal deturgescence distinguishes the cornea from other tissues. Even though the water content of the cornea is normally much higher than that of the sclera, pieces of sclera will swell little or not at all in solutions in which pieces of cornea swell several hundred per cent. Cogan and his co-workers have shown that the cornea acts as a semipermeable membrane. The boundary between epithelium and stroma is relatively impermeable to water-soluble, lipoid-insoluble substances (water is the exception to this rule). The stroma, on the other hand, is impermeable to lipoid-soluble, water-insoluble substances. With the exception of water, substances that readily penetrate the cornea have characteristically biphasic solubilities. Weak organic electrolytes are soluble in both fat and water in proportion to their degree of dissociation. Thus weak organic bases become progressively less dissociated (salts to free bases) and more fat-soluble in decreasing hydrogen ion concentrations, whereas weak acids are less dissociated in increasing hydrogen ion concentrations. The alkaloids and topical anesthetics used in the eye are biphasically soluble in the pH of the tears (pH 7.0 to 7.4).

Cogan and Kinsey[9] assume that water is constantly passing from the cornea into the tears and perhaps also into the aqueous, these two fluids being hypertonic with respect to the interstitial fluid of the cornea which is in a steady state with the fluid in the limbal capillaries. The same authors, among others, have found that the corneal stroma denuded of epithelium and endothelium will swell to several times its normal thickness in salt solutions of tonicity comparable to that of tears, and ascribe the lack of swelling in the intact cornea to the loss of water into the tears and aqueous humor. It is obvious that the maintenance of the normal deturgescence of the cornea requires energy for the removal of water. This energy may be provided by the mechanism responsible for the secretion of tears and also by evaporation on the epithelial side of the cornea and by secretion (presumably of solutes) into the aqueous humor.

The experiments of Cogan and Kinsey demonstrate that the corneal collagen fibers in their normal state are not fully hydrated, that is, they are capable of rapidly imbibing large volumes of water when exposed to physiologically isotonic salt solutions. It follows that in this normal state of corneal deturgescence there can be no appreciable volume of interstitial fluid. In the sclera, where no such mechanism of deturgescence operates, interstitial fluid is present. The index of refraction of such interstitial fluid is much less than that of the collagen fibers with their high protein content. Consequently, in the sclera at each boundary between fiber and interstitial fluid there is an abrupt change in refractive index. At these surfaces, then, light is scattered and reflected. In the cornea the relative absence of interstitial fluid together with the diminished protein concentration in the relatively more watery corneal collagen fibers contributes in a major degree to the optical homogeneity of this tissue.

A third factor may eventually prove to be of great significance in maintaining the transparency of the cornea. The chemical composition of the cornea and sclera are almost exactly the same except for their mucoids. Meyer and Chaffee[10] have shown that the sclera contains very little mucoid and that which it contains is chiefly chondroitin-sulfuric acid, whereas the cornea contains large amounts of hyaluronosulfuric acid. These authors have suggested that the corneal mucoid is in some way connected with the transparency of the cornea, and in support of their argument have demonstrated that the mucoid is not present in corneas opaque from many causes.

In summary, the cornea is transparent because of the regular arrangement of its elements and its state of deturgescence. The exact mechanism for maintaining this deturgescence is not known.

The clarity of the cornea is also influenced by the sensory fibers of the fifth cranial nerve. It has been observed that sectioning of the fifth nerve or alcohol injections into the gasserian ganglion produced changes in the cornea (neuroparalytic keratitis). Tagawa,[11] in experimental studies on rabbits, has shown that the initial changes in the epithelium are due to edema. The mechanism of this edematous change following sectioning of the sensory nerves to the eye is not understood.

Any local change in the index of refraction leads to turbidity of the cornea, with the result that extremely minute changes may produce opacities which are easily recognized in the living state, but which may give little or no histologic evidence of their presence. Corneal scars, for instance, which are readily visible clinically, may be disclosed on microscopic examination only by slight irregularities in the arrangement of corneal fibers. Routine his-

tologic stains do not differentiate between the chondroitin-sulfuric acid of fibrous tissue and the hyaluronosulfuric acid of normal cornea; moreover, any new form of connective tissue in the cornea has a tendency to take on gradually the characteristics of the normal corneal stroma. The fibers become thicker, their arrangement more regular, and eventually even a certain degree of transparency may be regained. Such complete regeneration of tissue is, of course, rare. In order that a corneal scar may disappear completely the initial injury must be slight, it must be incurred in childhood or infancy, and considerable time must have elapsed since the injury.

Each layer of the corneal stroma forms a fairly continuous sheet, and if the lamellae have not been disorganized, invading cells find the journey easiest if they remain between the layers where they gained entrance. It is one of the characteristics of corneal inflammation that wandering cells and new-formed vessels can be traced across the cornea confined almost entirely between the same layers as the lesions which are responsible for their presence.

Bowman's membrane is a basement membrane similar to that between the epithelium and connective tissue in many organs, particularly in the skin and convoluted renal tubules. These membranes are thought to be a condensation of the underlying connective tissue. Bowman's membrane apparently possesses the same chemical composition as the substantia propria, consisting chiefly of collagen. A common pathologic characteristic of these membranes is their tendency to become calcified in various local diseases and also in some general disturbances of calcium metabolism.

Descemet's membrane is a tough, so-called elastic membrane on the posterior surface of the corneal stroma. Its chemical and physical properties and histologic staining reactions are like those of the capsular membrane of the lens and Bruch's membrane, which separates the choroid from the pigment epithelium of the retina. These membranes resemble certain basement membranes between the epithelium and connective tissue and the elastic membranes in arteries in that they are composed in part of mucoproteins. The lens capsule and the cuticular portion of Bruch's membrane are apparently of epithelial origin, being formed by the subcapsular epithelium of the lens and the pigment epithelium of the retina, respectively; but Descemet's membrane is entirely mesodermal, for it lies upon the corneal stroma and is covered with a layer of hexagonal endothelial cells.

Descemet's membrane is composed of two layers. These are less clearly marked than those of Bruch's membrane of the choroid, which consist of an extremely thin, outer elastic layer, a continuation of the elastic tissue of the choriocapillaris, and an inner, thicker cuticular layer that is thought to be an excretion of the pigment epithelium of the retina. It is probable that an important element of the function of such membranes as Descemet's and Bruch's is their permeability to various diffusing substances. The nutrition of the lens is wholly dependent on the interchange of dissolved substances across the lens capsule, and the rods, cones and pigment epithelium of the retina are separated from their chief source of nutrition, the choriocapillaris, by Bruch's membrane.

Metabolism of the Cornea. Recent studies on the metabolism of the cornea have thrown new light on its functional properties. In the past the assumption that this tissue was sluggish and inert has been supported by the observation that its oxygen uptake, when computed per milligram wet weight, is small compared to that of many active tissues. Nine-tenths of the oxygen uptake of the cornea, however, is consumed by the epithelium, and when the respiration of the corneal epithelium alone is computed, it is found that this is among the tissues with high metabolic rates.

It has been shown (Herrmann and Hickman[12]) that the carbohydrate metabolism of the corneal epithelium is similar to that of many other tissues. It has a cyanide-sensitive oxygen uptake and contains cytochrome oxidase. It consumes glucose, glycogen, lactate, and pyruvate. Under aerobic conditions and adequate supply of carbohydrate, the oxygen uptake equals that required for complete combustion of the carbohydrate consumed. Under anaerobic conditions, lactate is produced in amounts equivalent to the glucose and glycogen lost. Glycolysis is inhibited by fluoride and iodo-acetate, and under these circumstances phosphate esters accumulate, indicating that the glycolytic system follows the usual pathways. In the absence of adequate carbohydrates the oxygen uptake remains normal or rises, but without an associated increase in nonprotein nitrogen. Consequently, the alternative metabolites are probably fats.

In contrast with the conventional metabolic pattern of the epithelium, the stroma has no oxygen uptake and can utilize neither lactate nor pyruvate. Nevertheless it is capable of utilizing glucose at a rate per cell about twice that of the epithelium. Lactate is produced by the stroma but cannot be consumed by it. In the isolated cornea the lactate produced by the stroma is utilized by the epithelium and constitutes an appreciable fraction (perhaps 25 per cent) of the total carbohydrate supply of the epithelium. Moreover, the aerobic glucose consumption of the stroma with the epithelium in place appears to be somewhat less than in the freshly denuded stroma, indicating a control of glucolysis in the stroma by the oxidative metabolism of the adjacent epithelium analogous to the familiar intracellular Pasteur effect.

The denuded corneal stroma, however, rapidly loses its ability to utilize glucose, and an examination of the distribution of phosphate esters in the tissues suggests that the failure in glucose consumption is due to an exhaustion of the capacity of the tissue to transfer phosphate from glycerophosphate to hexoses. It may be concluded, therefore, that the epithelium normally assists the stroma in maintaining a supply of carriers for energy-rich phosphate transfers.

There is, then, a complex metabolic exchange between the corneal stroma and epithelium. It seems most likely that the cornea is not unique in this respect, and that complex metabolic interactions may be present in many tissues where adjacent cells of different structural and functional types are components of a highly organized integrated structure. Studies in this field have been carried further in respect to the cornea than to many other tissues. The significance of such interactions is obvious in pathologic processes in which the death or disease of some cells results in changes in their neighbors.

The origin of the nutritional fluid in the cornea has received considerable attention. It is probable that this fluid enters the cornea from several sources. Gruber,[13] in 1894, produced rust spots in the corneas of cats with pieces of iron wire and, by subsequently injecting potassium ferrocyanide into the circulation, caused the spots to turn blue from the periphery to the center while the aqueous remained uncolored. This diffusion from the vessels had been previously observed by Leber[14] in 1873. Laqueur,[15] in 1872, had demonstrated that a similar passage of substances from the aqueous, entering the periphery and diffusing towards the center of the cornea, could occur when ferrocyanide was injected into the anterior chamber. The work of Cogan and his co-workers strengthened the evidence that the cornea probably receives the greater part of its nutritional fluid from the limbal vascular plexus. The tears, which contain approximately 50 milligrams of glucose per 100 cc., may also contribute to the nutrition of the cornea. Herrmann and Hickman[12] have shown that in vitro the cornea is capable of imbibing glucose when the epithelial surface is irrigated with a solution of this material. It is possible also that the cornea, at least under unusual circumstances, may receive some nutritional components from the aqueous. Evidence for this is the continued viability of corneal grafts, with over half of the cornea replaced, when the donor cornea is connected with the recipient only by a fibrinous clot for two or three days after operation. Further indirect evidence of the continued survival of the stromal cells has been supplied by the experiments of Gunderson[16] with free-floating implants of the cornea in the anterior chamber.

Fischer[17] has shown that the cornea takes up oxygen from the outside air and discharges carbon dioxide. Friedenwald and Pierce[18] confirmed his finding that carbon dioxide normally escapes from the aqueous via the cornea, but they were unable to show that the oxygen passed from the outside air through the cornea into the aqueous at the normally existing partial pressures of oxygen in the aqueous and in air. This in no way contradicts the evidence for direct uptake of oxygen by the corneal epithelium for its own endogenous respiration. On the other hand, it is well known clinically that some patients can wear contact glasses for as long as sixteen or eighteen hours without apparent damage to the cornea. Contact lenses do not prevent the cornea from obtaining oxygen from the external source, although they probably reduce the rate of supply. It would seem, therefore, that the corneal epithelium normally utilizes the oxygen from the air but may be able to accommodate itself to a diminished oxygen supply for periods of many hours. Factors affecting the efficiency of this accommodation may influence the ease with which different individuals tolerate the contact glass.

Innervation of the Cornea. The cornea, because of the simplicity of its structure, is an

excellent tissue in which to study terminal nerve endings. Its only nerve endings are plexiform ramifications with free nerve terminals, except around the sclerocorneal junction where both Krause's end-bulbs and endings for cold sensation are also present. Tower[19] has shown that the nerve endings of one afferent fiber are represented by terminal ramifications which extend over a quadrant or more of the cornea and may spread onto adjacent sclera and conjunctiva. She has also pointed out that while pain is usually the only response to any form of stimulus in the central portion of the cornea, the evidence is convincing that beneath the pain there is also a feeling of touch or pressure, not as a separate modality but as a second aspect of one sensory experience. This can be demonstrated clinically by instilling topical anesthetics and testing sensation before complete anesthesia occurs. It can also be demonstrated after sectioning of the descending root of the fifth nerve in the medulla for the relief of trigeminal neuralgia (Walsh[20]). The avascular cornea is also an excellent site for initiating the axon vascular reflex in the conjunctiva.[21] In this reflex the impulse is thought to pass up a sensory fiber and then down (i.e., antidromically) a collateral branch supplying an arteriole. This reflex is blocked by the application of topical anesthetics, but it is not blocked after sectioning of the fifth nerve if the cornea is stimulated before degeneration of the sensory fibers takes place.

SCLERA

The sclera comprises five-sixths of the fibrous tunic of the eye. It is modified anteriorly to form the cornea and is interrupted posteriorly by the optic nerve. It forms a continuous covering for the globe, broken only by the emissaria for the perforating nerves, arteries and veins. The sclera is almost avascular and does not contain true lymphatics. The episcleral tissue is relatively vascular. The sclera is penetrated only with great difficulty by cellular elements, such as wandering cells and tumor cells, because of the comparatively uninterrupted course and density of the connective tissue. Those cells that make their way into or out of the eye generally do so either through the blood stream or along the perivascular and perineural spaces about the perforating vessels and nerves. It is not unusual in cases of focal infection within the eye to find the perivascular spaces at some distance from the lesion choked with cells, and the presence of such perivascular infiltrates is no reason to assume that syphilis or tuberculosis is the etiologic factor. In regard to the perivascular tissue spaces, an analogy may be drawn between the eye and the brain, for the brain, too, has no lymphatics, and inflammations of the brain in general are also characterized by the presence of perivascular infiltrates at some distance from the lesion.

The sclera is an almost avascular inert fibrous structure. Diseases affecting it are, therefore, comparatively rare and their pathology relatively simple. Unfortunately, for the same reason, they are usually chronic in character and extremely resistant to treatment. The general pattern of the inflammatory reaction and the etiologic factors are essentially the same as those of tendons and tendon sheaths elsewhere in the body, e.g., gout, rheumatic fever, tuberculosis and syphilis. Brawny scleritis and scleromalacia perforans represent unusual degeneration of the collagen fibers of the sclera. The histopathologic pictures suggest that they might be caused by a sensitization of the body to these fibers (Rich[22]). Lacerations and perforating lesions of the sclera are for the most part repaired by migration of fibroblasts from the episcleral or choroidal tissues.

The rigidity of the sclera is an important factor in measuring the ocular tension. The rigidity varies considerably and is usually increased in scleritis, uveitis and old age.

INTRAOCULAR FLUID CIRCULATION

A discussion of this subject will be found in Chapter XII. The role of the intraocular fluid currents influencing the pattern of intraocular inflammatory reaction is discussed in the chapters dealing with intraocular inflammations. For the present it will suffice to point out that the intraocular fluid represents a common pool for all the tissues which it bathes. Through this pool metabolic exchanges occur, humoral effects may be transmitted, and toxic and irritating substances arising in one tissue may affect another. It is this common pool which after a fashion links together the many parts of the eye into an organic whole, and which is therefore an important vehicle in the local spread of many disease processes.

LENS

The lens is described in Chapter II, *Histology*, and its physiologic and pathologic characteristics are detailed in Chapter XI, *Diseases of the Lens*.

VITREOUS

Normally there are no living cells in the vitreous, but large flat wandering cells can easily be found on the outer surface of the vitreous, especially in the posterior part of the globe, when the retina is examined in flat preparations. The vitreous has no active metabolism, so the changes which occur in it in disease are of a passive nature and are largely determined by the cells and cellular products which enter it from adjacent structures. It does provide an excellent culture medium for bacteria, however, and because of its avascular structure such infections do not respond satisfactorily to antibiotics given systemically. Occasionally the vitreous becomes saturated with products of metabolism of the neighboring tissues, such as cholesterol or calcium soaps, which precipitate or crystallize out, forming opaque masses, synchysis scintillans and, more often, asteroid hyalitis. These are beautiful to observe but disagreeable to own because of the moving shadows which they sometimes cast.

The reflection of light at the anterior surface of the retina, seen with the ophthalmoscope, is probably due to a difference in the index of refraction between the vitreous and the anterior surface of the retina. A higher protein content of the retina gives a slightly greater refraction index to this structure. Several hypotheses have been advanced to explain the reduction of this reflection with age. The only one which is more than speculative is supported by histologic observation. The vitreous sheets on the surface of the retina often become condensed in the aged. Such a zone of condensation could abolish the normal abrupt transition in index of refraction at the boundary between retina and vitreous and replace it with a zone of continuously varying refractive index, thus suppressing the normal light reflection at the boundary. Changes of this type are to be expected, particularly if the vitreous has become fluid or semifluid.

Condensation of the vitreous sheets through simple collapse and packing together of these structures can occur, not merely in the neighborhood of the retinal surface but also at any point within the vitreous cavity. Faintly opaque bands and strings can be seen with the slit ultramicroscope in the excised vitreous that has been subjected to very slight mechanical trauma. Presumably similar condensations and agglutinations of the vitreous sheets would account for many of the common floating opacities. Other, usually denser, opacities result from serous, hemorrhagic and cellular effusions.

It may well be asked, Why does the vitreous exist? What is its function? The vitreous is frequently replaced by aqueous in elderly patients and following degenerative or inflammatory lesions in the eye; also it can be replaced operatively by saline solution or cerebrospinal fluid without causing apparent damage to the function of the eye.

IRIS

The iris appears as a thin diaphragm in the anterior segment of the eye, with its root attached to the anterior surface of the ciliary body and its free margin forming the circular pupil. Its physical structure is well suited to its physiologic function. Its loose fibrous tissue allows free movement during contraction and dilation of the pupil. The rapidly acting contractor and dilator muscles under the control of the vegetative nervous system function as a shutter system to control the amount of light entering the eye. The layer of pigmented epithelium on the posterior surface provides a barrier to the penetration of light. The vascular bed is an excellent source of macrophages and immune bodies when they are needed to combat inflammation of the anterior segment or following introduction of foreign material into the eye.

The efficiency with which the reticuloendothelial system of the iris functions can be demonstrated by injections of colloidal dyes or India ink into the anterior chamber. Frequently as much as 80 per cent of such material is removed from the aqueous within an hour after it has been injected. On histologic examination the foreign material can be seen adherent to and contained in the endothelial cells on the anterior surface of the iris. During the next few hours numerous heavily laden phagocytic cells can be found migrating through the stroma to the blood vessels. True lymphatics are not present in the iris, but a delicate perivascular membrane becomes visible when wandering cells enter or leave the eye in great numbers. Following injections of small amounts of bacteria into the anterior chamber, cultures of the aqueous are frequently sterile at the end of one or two hours but become positive in from six to ten hours. This indicates that the bacteria had been phagocytized by the reticuloendothelial system of the iris but were able to overcome this protective mechanism and escape into the aque-

ous after a period of multiplication. This phagocytic action of the iris is responsible in part for the difference in severity of inflammations following penetrating injuries of the anterior chamber and those involving the lens or vitreous.

The formation of adhesions between the iris and lens is well known clinically and is analogous to the formation of intra-abdominal or intrapleural adhesions. When first formed as the result of inflammatory processes, the adhesions are only fibrinous; later they are organized and may become very tough. The mechanism by which the root of the iris becomes adherent to the back of the cornea in glaucoma is somewhat different and will be discussed in Chapter XII. Much has been written about the migration of pigment-bearing cells and free pigment granules from the iris and also from the ciliary body. The attempt has been made to find in these migrations a fundamental factor in the etiology of glaucoma. The prevailing opinion, however, is that this pigment migration is a normal phenomenon increasing with age and with any disease which interferes with the nutrition of the anterior segment of the globe.

Although the iris performs only a minor role in the normal production and absorption of the aqueous, it is a source of plasmoid or secondary aqueous. Scheie, Moore and Adler[23] have shown, by complete removal of the iris in cats, that a large percentage of the protein in the secondary aqueous comes from the iris vessels. Thus, these vessels are probably the source of antibodies in inflammatory reactions in the anterior segment of the eye.

The fibrous tissue in the iris differs from that found elsewhere in the body in that it seldom responds to trauma by proliferation. Keloids of the iris are never seen, even in Negroes, following iridectomy. Inflammatory membranes are observed on the anterior surface or extending from the edges of the iris following prolonged irritation, but simple uninfected wounds of the iris do not, in general, close by fibrous proliferation.

CILIARY BODY

The ciliary body consists of smooth muscle, some rather loose connective tissue, and blood vessels. The double layer of epithelium which covers it is, however, rather highly differentiated tissue with some peculiar reactions. The role of this tissue in the secretion of the aqueous will be discussed in Chapter XII. In long-standing, severe intraocular inflammations this epithelium is sometimes stimulated to massive proliferation, growing out in strands along the fibers of the zonula (suspensory ligament of the lens). In some cases, especially if the ciliary body has been injured, an exudate arises from the ciliary body and extends across the posterior surface of the lens. With the growth of epithelium, blood vessels and connective tissue, this exudate becomes organized into a dense membrane, which contracts to pull the retina from its moorings, eventually leading to shrinkage and disorganization of the whole globe. The ciliary processes, which consist of loose folds of the epithelial layer enclosing a very vascular connective tissue, are normally supported by the fibers of the zonula between which they hang. They have no internal support and tend to prolapse into operative or traumatic wounds of the neighboring sclera.

In many respects the ciliary processes resemble the choroid plexus of the cerebral ventricles, but they differ in having a double rather than a single layer of epithelium. Nevertheless, their functional similarity is striking, and the composition of the aqueous is much like that of the spinal fluid.

The capillaries of the ciliary processes are extremely large and relatively numerous. Many have an internal diameter of 30 or 40 microns. As has been shown by Friedenwald and Stiehler,[24] their walls are far more permeable to dyes than are those of the iris or retina. Presumably the nutritional and respiratory exchanges which they can furnish operate with unusual efficiency. Correspondingly, it has been shown that the ciliary epithelium has an unusually high rate of respiration. Moreover, the cells of the ciliary stroma, which have long been considered relatively inert and functionless, also have a high metabolic rate.

CHOROID

The choroid is composed primarily of blood vessels and connective tissue, some of which contains pigment. The choroidal vascular bed has been thought to act as erectile tissue and because of this property to play some role in acute congestive glaucoma. It is certainly true that the choroid is at least three times as thick in some histologic specimens obtained at autopsy as in others, depending on the position of the head at the time of, or immediately after, death. It has also been shown that when the eye is enucleated or the blood supply to the eye is interrupted, the tension falls immedi-