SECOND EDITION

CLINICOPATHOLOGIC CORRELATION OF OCULAR DISEASE

a text and stereoscopic atlas

DAVID J. APPLE • MAURICE F. RABB

CLINICOPATHOLOGIC CORRELATION OF OCULAR DISEASE

a text and stereoscopic atlas

DAVID J. APPLE, M.D.

Associate in Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, Iowa;
Formerly, Associate Professor of Ophthalmology and Pathology,
Director, Theobald Laboratory of Ocular Pathology,
University of Illinois Eye and Ear Infirmary,
Abraham Lincoln School of Medicine, Chicago, Illinois

MAURICE F. RABB, M.D.

Professor of Clinical Ophthalmology, University of Illinois Eye and Ear Infirmary,
Abraham Lincoln School of Medicine; Director of Fluorescein Angiography Service,
Michael Reese Hospital; Chief of Ophthalmology, Mercy Hospital,
Chicago, Illinois

SECOND EDITION

with 758 illustrations and 112 stereoscopic views
in full color on 16 View-Master® reels

THE C. V. MOSBY COMPANY

Saint Louis 1978

SECOND EDITION

Printed in the United States of America

The C. V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63141

Library of Congress Cataloging in Publication Data

Apple, David J., 1941-
Clinicopathologic correlation of ocular disease.

Includes bibliographies and index.
1. Eye—Diseases and defects. 2. Eye—Diseases and defects—Atlases. I. Rabb, Maurice F., joint author. II. Title. [DNLM: 1. Eye diseases—Pathology. 2. Eye diseases—Pathology—Atlases. WW100.3 A648c]
RE46.A66 1978 617.7'1 78-15635
ISBN 0-8016-0272-6

GW/U/B 9 8 7 6 5 4 3 2 1

To Professors

GOTTFRIED O. H. NAUMANN and PETER C. KRONFELD

our first teachers in clinical ophthalmology

FOREWORD
to second edition

It is indeed a pleasure to write a foreword to a book that has proven to be so successful and valuable. The fact that within a few years a second edition has become necessary speaks for the demand that has existed for such a book.

This atlas presents a superb correlation of clinical and pathologic findings of many aspects of ophthalmic pathology. This is indeed a unique combination of excellent clinical pictures (many of them in stereo) with their pathologic substrates. The clinical part of this book illustrates beautifully the most important aspects of ophthalmic diseases. The pathologic part gives an up-to-date explanation of the underlying morphologic processes precipitating the same diseases. The book illustrates the importance of anatomic clinical correlation as one of the main foundations of scientific ophthalmology.

We are fortunate to have in this country a few eminent physicians who are trained in both pathologic anatomy and clinical ophthalmology. The senior author of this book is one of this elite corps. With an eminent clinician as coauthor, the result has been a text that should be of value for anybody who would like to know more about the underlying pathologic processes of the most important ocular diseases.

F. C. BLODI, M.D.

FOREWORD
to first edition

He from thick films shall purge the visual ray,
and on the sightless eyeball pour the day.

ALEXANDER POPE

By reading this book, we become the beneficiaries of the professional skills and avocations of two dedicated eye physicians. For years, Maurice Rabb has perseveringly recorded by stereophotography the incredible variety of human ocular disease. Similarly, David Apple has documented, utilizing similar stereoscopic techniques, the appearance of gross pathologic specimens and has carefully studied the diseased eye with the techniques and perspective of the general pathologist. Utilizing the resources of the University of Illinois Eye and Ear Infirmary, these authors have successfully blended their interests and skills with their ophthalmic knowledge. The result is a book with widespread appeal. Practicing ophthalmologists will enjoy the stereoscopic presentation of clinical and gross pathologic specimens. Pathologists will enhance their knowledge of eye disease. Medical students will marvel at the diversity of ways in which the human eye manifests abnormal processes. Most important, ophthalmology resident physicians will have available a readable introductory text with highly informative illustrations.

MORTON F. GOLDBERG, M.D.

PREFACE

Our major goal is to provide a didactic, illustrated overview of ophthalmic pathology. Approximately 400 new clinical photographs and photomicrographs, most previously unpublished, have been added. There are 50 new color stereophotographs. Most of the stereoreels from the first edition have been retained as black and white illustrations.

There is a new chapter on the optic nerve, and the chapters on the lens and glaucoma and the section on retinal detachment have been expanded.

We have reproduced several original line drawings and photomicrographs of historical interest, many dating from the nineteenth century. These provide interesting correlations of original or early descriptions of ocular diseases with modern information regarding the histopathology of these conditions.

Portions of this book were written during a period of sabbatical leave by one of us (D. J. A.) at the Ocular Pathology Laboratory of the University Eye Clinic, Tübingen, West Germany. We are especially grateful to Professor Dr. med. G. O. H. Naumann, Professor of Ophthalmology in Tübingen, for his support, advice, and instruction in preparing many portions of this text. Financial support was provided by a grant from the Alexander von Humboldt–Stiftung, Jean-Paul-Strasse 12, D-5300 Bonn-Bad Godesberg, West Germany, and United States Public Health Service Grant #24-14. During this period a comprehensive textbook of ocular pathology in the German language was also completed (see Naumann and Apple, reference 40, Chapter 1).

In addition to the many individuals cited in the preface to the first edition or who are individually cited in the tables and legends in this text, we would like especially to thank the following individuals, who have provided us with abundant illustrative materials.

Dr. Frederick Blodi provided complete access to the photographic files of the Department of Ophthalmology, University of Iowa, as well as to the slide collection in his laboratory of ophthalmic pathology.

Dr. Basil Daicker, ophthalmic pathologist at the University Eye Clinic in Basel, Switzerland, has generously furnished stereophotographs from his magnificent collection that have particularly enriched the chapter on retinal diseases. We also thank Dr. Ernst Martin Meyner, formerly of the University Eye Clinic, Tübingen, West Germany, for permitting us to use several anterior segment stereophotographs from his outstanding collection. Dr. Michael Goldbaum, Department of Ophthalmology, University of California at San Diego, provided source material and tables for the section on retinal detachment.

Drs. Steven Miller and Frank Judisch, University of Iowa, kindly reviewed portions of the manuscript. Ms. Joan Snyder, ophthalmic assistant at the University of Iowa, provided invaluable assistance in preparation of the manuscript. Dr. Steven Vermillion, resident in ophthalmology at the University of Iowa and a talented artist, prepared most of the new artist's drawings and sketches. Paul Montague and Louis Facto prepared the new clinical photographs and photomicrographs. Ms. Debbie Varney and Ms. Pam Gilcrest spent many hours typing the manuscript.

Special thanks go to Drs. David Gieser, Nancy Hamming, and George Wyhinny, former medical students and ophthalmology residents who worked with us in the Theobald Laboratory of Ocular Pathology at the University of Illinois, whose diligent efforts were responsible for the creation of significant portions of the text and many of the illustrations in both editions.

DAVID J. APPLE
MAURICE F. RABB

CLINICOPATHOLOGIC CORRELATION OF OCULAR DISEASE

a text and stereoscopic atlas

CONTENTS

Chapter 1

INTRODUCTION

BASIC OCULAR STRUCTURE*

The eye is composed of three primary layers (Fig. 1-1).

The outer† tunic, the tunica fibrosa, is composed primarily of collagen-elastic tissue and provides a protective outer wall. The cornea forms the anterior one sixth of this layer, and the sclera forms the posterior five sixths. The sclera is white and opaque due to the random, irregular layering of its collagen fibers. In contrast the corneal collagen lamellae are arranged in a parallel fashion and therefore exhibit a geometrically regular appearance. This renders the cornea transparent to incoming light.

The uvea, or tunica vasculosa, is the middle layer of the eye and lies immediately interior to the sclera. This richly vascular and pigmented tissue consists of three parts: the iris, the ciliary body, and the choroid. When the uveal tissues are separated from the other layers of the eye and examined grossly, they reveal a purple color and rounded contour that resembles a grape; hence the name uvea, which is derived from the Greek word for grape. The most important function of the uvea is the vascular supply to the eye, particularly to the outer portion of the sensory retina.

The inner layer of the eye, the tunica nervosa, composed of sensory retina, pigment epithelium, and the optic nerve, develops embryologically as an anteriorly protruding portion of the brain. This tunic is derived from the two-layered neuroectodermal optic cup. In the posterior aspect of the eye the original inner layer of the optic cup forms the sensory retina, and the outer layer develops the retinal pigment epithelium. The space between these layers, the original cavity of the optic vesicle, forms the subretinal space in the adult eye. In the adult it is normally only a potential space and reappears only in cases of pathologic retinal detachment. The anterior aspect of the tunica nervosa develops into the two-layered epithelia of the iris and ciliary body.

TECHNIQUES OF EXAMINATION

Gross examination of the eye (Reel I-1)

The eye is a sphere that measures roughly 24 to 25 mm in each diameter (Figs. 1-1 to 1-3, Reel I-1). The cornea, which occupies approximately the anterior one sixth of the globe, has a lesser radius of curvature than the sclera. The anterior aspect of the globe contains the refractive media and accessory structures of the visual apparatus. The perceptive tissues and nervous elements are largely confined to the posterior aspect.

Identification of major landmarks on the exterior of the unopened enucleated globe allows the pathologist to differentiate the right from the left eye, determine the horizontal-vertical orientation of the globe, and define the site of clinically observed intraocular lesions. These determinations are necessary to ensure proper sectioning of the globe (Fig. 1-4).

The adult cornea normally measures approximately 12 by 11 mm. It is actually round but appears oval because the superior and inferior conjunctiva at the limbus partly overlie the cornea at these sites. Because the apparently long axis lies in the horizontal plane, the shape of the cornea readily identifies the horizontal axis.

Examination of the posterior aspect of the eye

*General references in ocular embryology and anatomy,[1-26] pathology,[27-51] and selected general ophthalmology textbooks that pertain to these subjects[52-76] are listed at the end of this chapter.

†Following conventional terminology, the term *outer* signifies the outside of the globe, and *inner* refers to the center of the globe toward the vitreous. In all subsequent photomicrographs involving structures of the ocular fundus, the outer scleral aspect is at the bottom of the photograph; the inner aspect is toward the top.

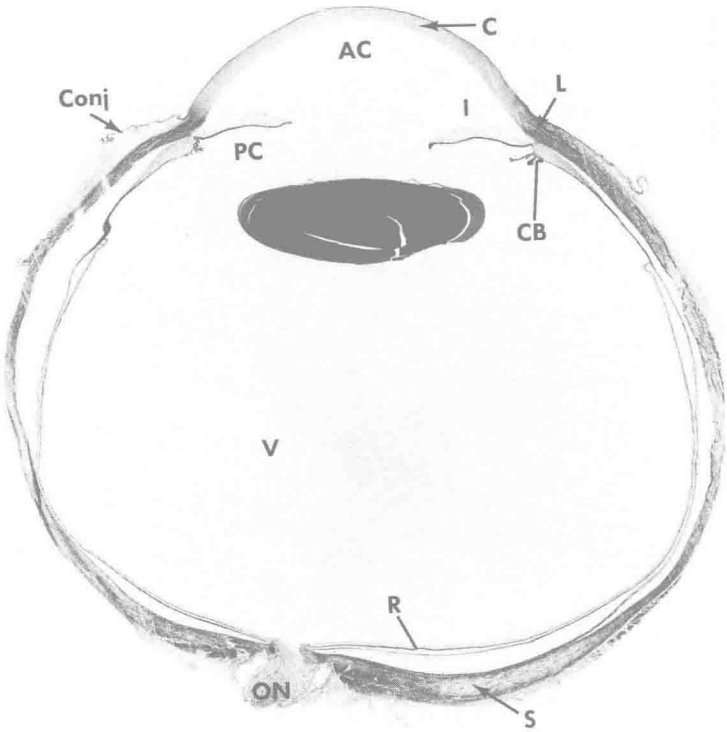

Fig. 1-1. Histologic section through a child's globe demonstrating the three major tunics. The outer fibrous tunic consists of the cornea *(C)*, which is continuous with the sclera *(S)* at the limbus *(L)*. The bulbar conjunctival epithelium *(Conj)* is continuous with the corneal epithelium. The middle (uveal) tunic consists of the iris *(I)*, ciliary body *(CB)*, and choroid. The sensory retinal *(R)* fibers enter the optic nerve *(ON)* posteriorly. *AC*, anterior chamber; *PC*, posterior chamber; *V*, vitreous. (H & E stain; ×6.)

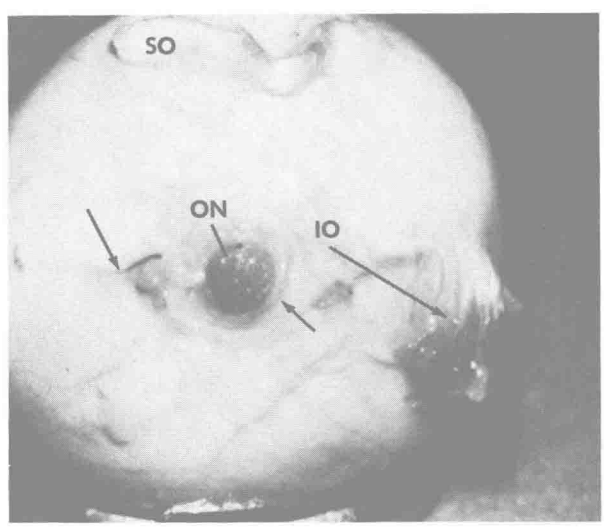

Fig. 1-2 (Reel I-1). Posterior aspect of an enucleated right eye. Note prominent nasal long posterior ciliary vessel *(arrow)*. The superior oblique *(SO)* muscle insertion is tendinous; the fleshy inferior oblique *(IO)* muscle inserts directly onto the temporal sclera. *ON*, optic nerve; *small arrow*, dural sheath of the nerve.

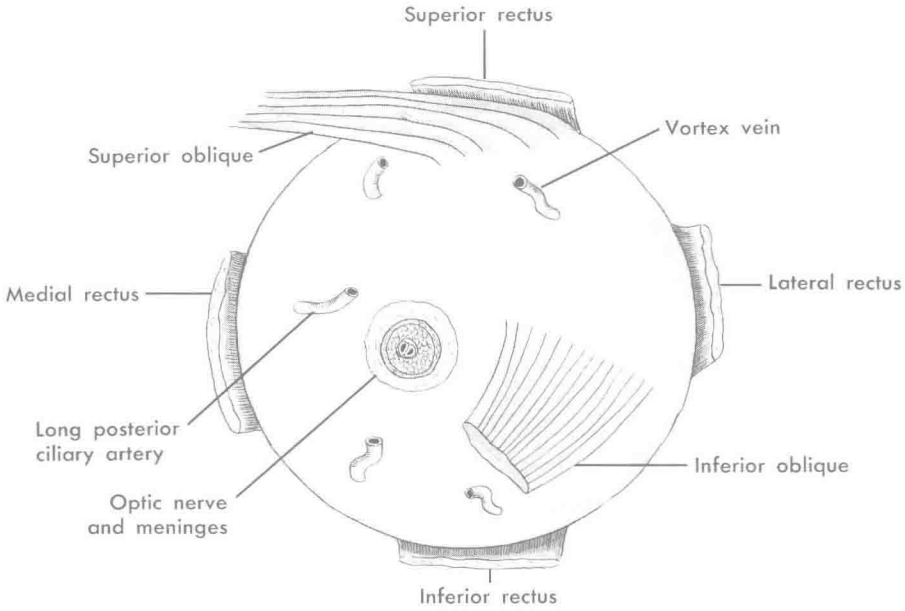

Fig. 1-3. Normal right globe, posterior external aspect.

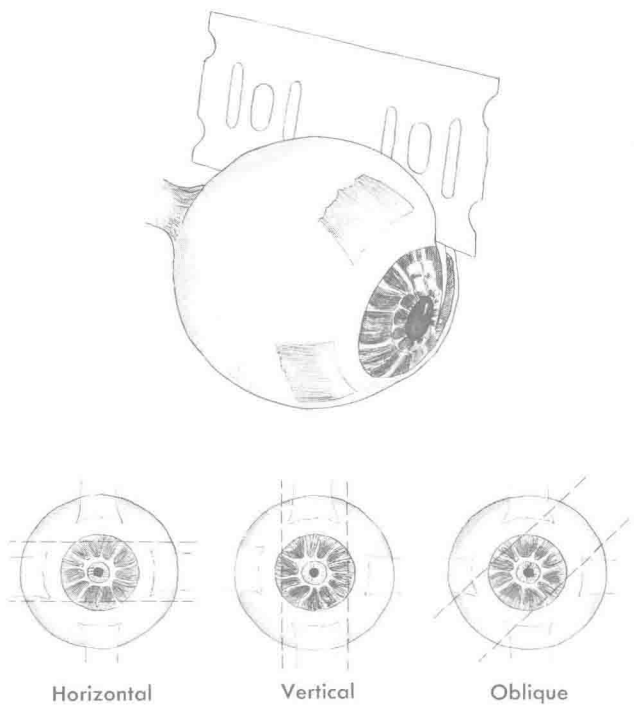

Fig. 1-4. Technique of gross sectioning of the globe. (From Naumann, G., and Apple, D.: Handbuch der speziellen pathologischen Anatomie, Band Auge, edited by Doerr, W., Seifert, G., Uehlinger, E., Heidelberg, Berlin, New York, to be published [1979], Springer Verlag; modified and redrawn by Dr. Steve Vermillion, University of Iowa.)

(Fig. 1-2, Reels I-1 and I-3) confirms the direction of the horizontal plane. At least one of the two long posterior ciliary vessels is visible as they course horizontally, emanating from the lateral aspect of the optic nerve. *The nasal one is almost always more prominent than the temporal,* which aids in determining the globe's nasal aspect.

The inferior oblique muscle has a muscular rather than a tendinous insertion into the sclera. It is identifiable at a point just temporal to the optic disc, overlying the macula. Observation of this muscle, with its thick, fleshy appearance, and the superior oblique muscle, which is in the superotemporal quadrant and has a tendinous insertion, allows differentiation of the right and left globes.

Histologic stains

Specific staining techniques make possible the recognition of characteristic structures within the eye and are invaluable for complete evaluation of certain disease entities. The theory of special staining is quite simple: the various cellular components have an affinity for certain stains so that each structure under study can be identified by the color imparted by the stain (which is essentially a tissue dye). Because reference is commonly made to these various techniques in the literature, it is useful to be aware of the major categories of stains available to the ophthalmic pathologist.

For routine histopathologic examination of ocular tissue, specimens are cut from a paraffin block and stained by the hematoxylin and eosin technique. *Hematoxylin imparts a basophilic (blue) stain to nuclear elements and structures containing nucleic acid; most cytoplasmic organelles are rendered light pink by eosin.*

Tissue prepared for electron microscopy is not normally embedded in paraffin; it must be embedded in special plastics in order to achieve satisfactory preservation for ultrastructural analysis. This type of embedding is advantageous both for light microscopy and thin-section electron microscopy. Cellular organelles are much better preserved by this method (compare Figs. 7-3 and 7-5); however, the adaptability of special staining techniques is sharply limited. For plastic-embedded tissue, most laboratories use dyes that give a blue color to the tissue (hence the names toluidine blue, methylene blue, or Mallory blue, which appear frequently in the literature). Plastic-embedding techniques are mainly utilized when electron microscopy is to be carried out or when special details in the tissue must be critically studied without artifact; the technique is too tedious for routine usage.

If plastic-embedded tissue is further processed for thin-section electron microscopy, it is usually fixed and stained utilizing three agents: osmium tetroxide, uranyl acetate, and lead citrate. These compounds contain heavy metals that have an affinity for membranes of cells and cell organelles; thus, contrast of cell structures is attained because most cell organelles are derived from such unit membranes (Fig. 9-4).

The most important special stain used by ophthalmic pathologists is the periodic acid–Schiff (PAS) stain. This stain has an affinity for certain mucopolysaccharides and glycoproteins and is especially useful in demonstrating ocular basement membranes. Such structures stain a brilliant red and are quite visible in contrast to the poorly staining background tissue. The important basement membranes in the eye include Descemet's membrane (Figs. 3-2 and 3-4), the lens capsule (the thickest basement membrane in the body; Fig. 4-6), the basement membrane of the ciliary processes, the internal limiting membrane of the retina, Bruch's membrane, and the basement membrane of all vessels, that is, the basement membrane of intraocular vascular endothelial cells and pericytes (Fig. 7-12, *A*).

The trichrome stain of Masson or a similar trichrome technique devised by Gomori is invaluable for identifying intraocular structures of different compositions. For example, collagenous tissues such as sclera and cornea stain blue, whereas smooth muscle such as that in the ciliary muscle assumes a dull red hue (Fig. 5-3). Pathologic deposits seen in some diseases, for example, granular corneal dystrophy (Fig. 3-46, *B*), have an affinity for components of this stain. This contrast in tissue staining improves visualization and differentiation of diverse tissues.

Numerous stains assist in the differentiation of several groups of mucopolysaccharides. They generally exhibit a blue color when positive. Such stains are important in analyzing the deposits of mucopolysaccharide in specific disease states, such as macular corneal dystrophy or the systemic mucopolysaccharidoses. Hyaluronic acid, the normal substance present in the vitreous, is stained positively with this type of procedure. The commonly used stains include the alcian blue technique and the colloidal iron method.

The Prussian blue stain for iron is invaluable for differentiation of intraocular pigments. The presence of iron, as observed in intraocular siderosis (Fig. 3-60) and in the various corneal iron lines or as occurs following hemorrhage, contrasts readily with normal intraocular melanin pigment. Melanin granules may resemble iron in routinely stained sections, but the blue color imparted to iron particles in this staining reaction ensures easy identification in most cases.

The various stains for myelin are useful in assessing the degree of optic nerve disease or atrophy (Figs.

9-23 and 9-24). The more commonly used stains include the luxol-fast blue stains and the Weigert stain. These stains are taken up by normal myelin. A defect in stain uptake is created at a site of demyelinization as in multiple sclerosis (Fig. 9-27).

Lipid structures normally do not stain in routinely prepared hematoxylin and eosin sections because the lipid is removed during technical processing through paraffin. Lipid can be demonstrated on freshly frozen tissue by using special stains, the most important of which are the sudan stains and the oil-red-O technique. Such techniques are important in evaluating disease states involving lipid-secreting tissues such as the meibomian gland (Fig. 10-64).

Important stains for amyloid are available; the best known is the Congo red technique. Histopathologic diagnosis of lattice corneal dystrophy (p. 101) is readily accomplished by utilization of amyloid stains.

Certain structures possess a molecular structure that, when stained and viewed through polarizing lenses, appears to glow. Major examples are amyloid (Fig. 3-49, *B*) and numerous types of foreign material, for example, wood (Fig. 3-58).

ORIGIN AND DEVELOPMENT OF THE EYE

The three layers of the globe exist and function in close connection with the adnexal structures of the eye as well as the central visual tracts and the cortical receptive areas in the brain. These structures are characterized by a very complicated embryonic developmental process caused by intricate interactions of the various germ layers. A knowledge of the embryology of the eye is necessary to understand the structure of the normal adult eye and to explain the pathogenesis of the numerous congenital defects and anomalies that may occur because of defective embryogenesis (Chapter 2).

This section describes the origin and early development of the eye as a whole. Detailed embryology and histology of the individual ocular tissues are described in the following chapters: sclera and cornea, Chapter 3; lens, Chapter 4; anterior segment and angle, Chapter 5; uvea, Chapter 6; retina, pigment epithelium, and vitreous, Chapter 7; optic nerve, Chapter 9; and conjunctiva and cornea, Chapter 10.

Optic vesicle and optic cup

The eye forms directly from the anlage of the brain by means of an outgrowth of the anterolateral part of the embryonic neural tube at the diencephalic level (Fig. 1-5). The neuroectodermal parts of the eye, the future retina and pigment epithelium, develop from the primitive neural tube ependyma at a very early period—within the first two to three

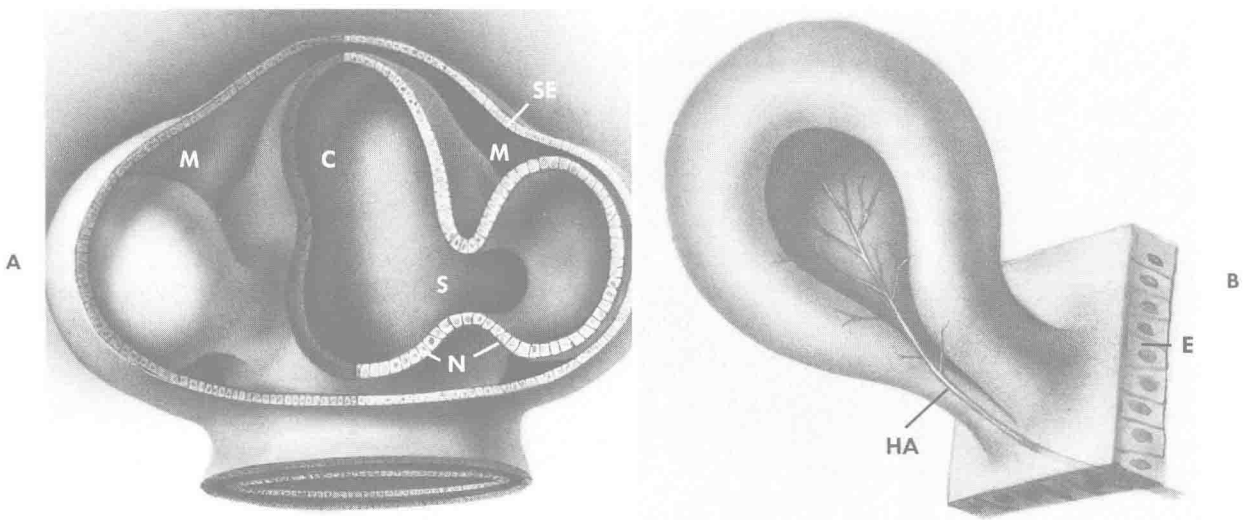

Fig. 1-5. A, Schematic illustration of the forebrain with formation of the optic vesicle in the first month of gestation. Note two lateral outpouchings of neuroectoderm to form the vesicles. *SE*, surface ectoderm lining the embryo. *N*, neuroectoderm derived from the neural tube forming an ependymal lining of the forebrain and primitive eye. Mesoderm *(M)* fills the space between the two. *C*, cavity of the forebrain, which is continuous with the cavity of the optic vesicle through the optic stalk *(S)*. **B,** Schematic illustration of the optic cup. The hyaloid artery *(HA)* enters the cup through the inferior embryonic ocular fissure. *E*, ependymal lining of the diencephalon.

weeks. At this time the apical (anterior) neural tube has not yet closed.

The very first evidence of eye development occurs as two anterolateral depressions of the neural plate, the optic grooves. They enlarge rapidly to form the optic vesicles (Fig. 1-5, *A*). The cavity of the evaginated optic vesicle is originally in broad communication with the lumen of the diencephalon. However the connection between the brain and vesicle eventually contracts to form the optic stalk, the anlage of the future optic nerve (Fig. 1-5, *B*). The distal (anterior) wall of the optic vesicle is destined to form the sensory retina. The proximal (posterior) wall represents the primordia of the future retinal, ciliary, and iris pigment epithelia.

At approximately the end of the first month the distal (anterior) wall of the optic vesicle makes contact with the outer epithelial lining of the embryo, the surface ectoderm. The primordium of the future lens develops from cells of this surface layer at the point of contact (see Fig. 4-1). Not only does the lens develop from this single layer of surface epithelium, but the future epithelia of the cornea, conjunctiva, and the entire integument are derived from this source.

The neuroectodermal anlage of the eye is in all stages of its development completely surrounded by several layers of mesoderm or mesectoderm (Fig. 1-5, *A*). This is the "middle tissue," situated between the core of neuroectoderm and the outer lining of surface ectoderm. The anterior portion of the mesoderm forms the future cornea (with the exception of the corneal epithelium), the stroma of the iris and ciliary body, as well as the structures of the anterior

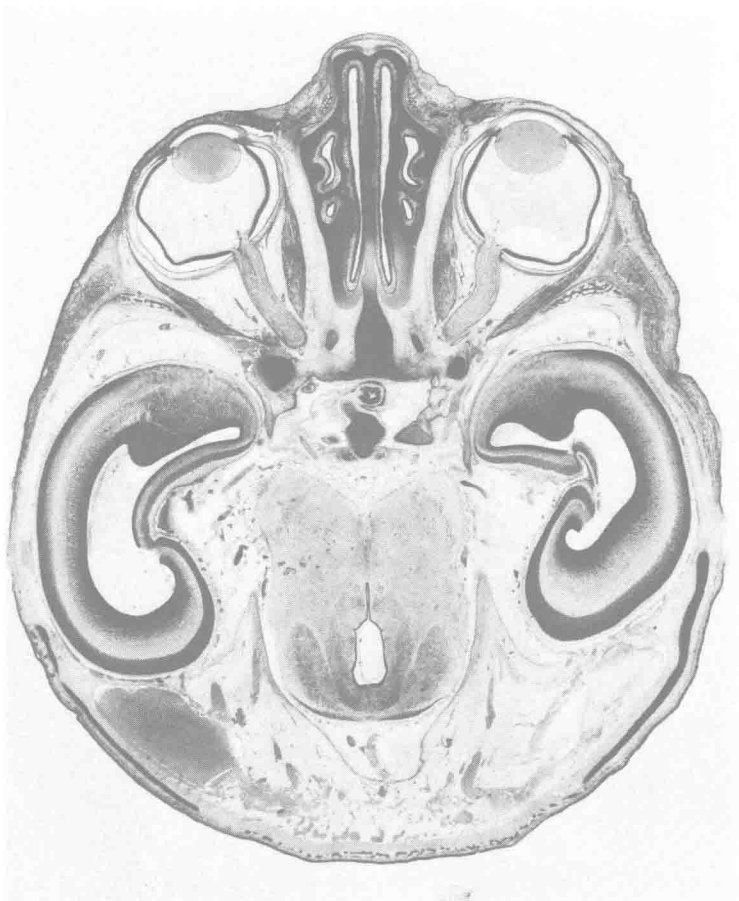

Fig. 1-6. Horizontal section through fetal head showing advanced development of optic cups. From the collection of Professor Wolfgang Stock, Tübingen, West Germany. (H & E stain; ×5.) (From Naumann, G., and Apple, D.: Handbuch der speziellen pathologischen Anatomie, Band Auge, edited by Doerr, W., Seifert, G., Uehlinger, E., Heidelberg, Berlin, New York, to be published [1979], Springer Verlag.)

chamber filtration apparatus. Important structures to develop from the mesoderm posteriorly are the stroma and vessels of the choroid, the sclera, and the bulk of the orbital tissues.

The primary optic vesicle is transformed into the optic cup between the fourth and seventh weeks of gestation (Figs. 1-5, *B* to 1-9). The optic cup forms by an invagination of the anterior (distal) and inferior wall of the optic vesicle. This epithelium folds posteriorly in the direction of the cavity of the optic vesicle and immediately begins to increase in thickness to form the sensory retina. The invagination extends from the anterior aspect of the cup all the way posteriorly to the optic stalk, forming a cleft, the embryonic ocular fissure, along the inferior margin of the eye (Figs. 1-5, *B*, 1-8, and 2-7). The fissure owes its existence to the fact that the invagination that transforms the vesicle into the cup occurs not only in an anteroposterior direction but also from underneath or ventral to the optic vesicle.

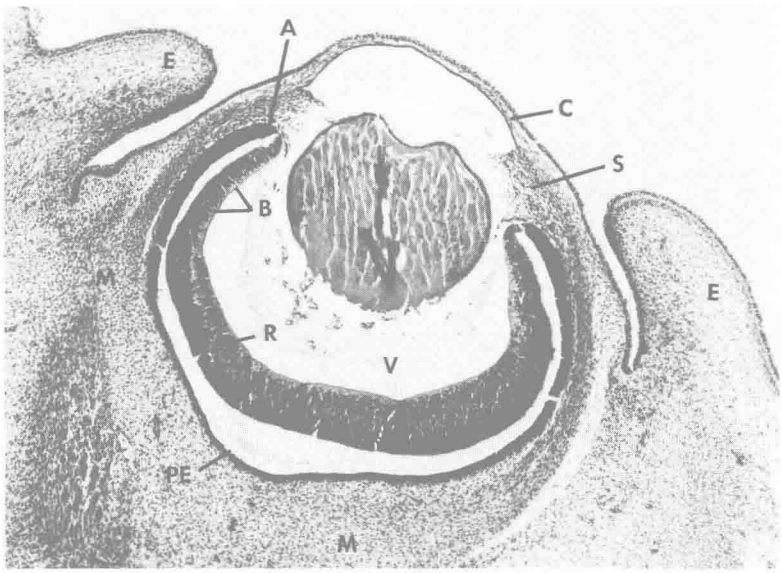

Fig. 1-7. Human embryonic eye at the 23 mm stage (approximately 7 weeks' gestation). *Area A*, anterior margin of the two-layered cup, the future iris. *Area B*, site of the future epithelium of the ciliary body. Posteriorly, the inner layer forms the sensory retina *(R)*, and the outer layer forms the retinal pigment epithelium *(PE)*. *C*, cornea; *E*, eyelid buds; *S*, stroma of future iris and ciliary body; *V*, primary vitreous; *M*, mesoderm surrounding the cup. This differentiates toward the choroid and sclera. (H & E stain; ×40.)

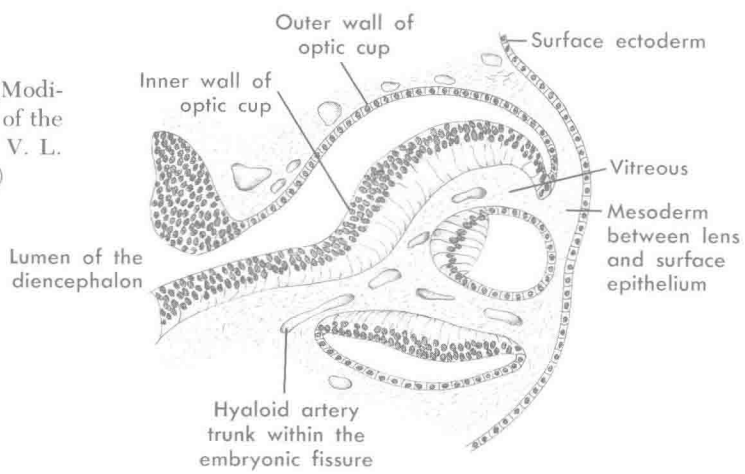

Fig. 1-8. Drawing of sagitally sectioned optic cup. (Modified from Salzmann, M.: The anatomy and histology of the human eyeball in the normal state, translated by E. V. L. Brown, Chicago, 1912, University of Chicago Press.)