Neuro-Ophthalmology
A Practical Text

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PREFACE

The visual sense is of paramount importance for most people; nearly a third of all afferent sensory input is visual. If the neural processes concerned with the control of eye movements are included, close to eighty percent of the brain is occupied with vision and related functions.

This book attempts to explore neuro-ophthalmology in a reasonably complete manner. It is a pragmatic clinical guide to neuro-ophthalmic disorders presented with a framework of basic scientific information. No attempt has been made to be exhaustive. The book is liberally laced with decision trees, tables, and bibliographic references so that, given a patient's complaint, symptoms, or findings, the reader may quickly move to the differential diagnosis, office and laboratory evaluation, and then treatment of the patient.

This work is intended to provide the basis for the highest quality care of the patient with a neuro-ophthalmic problem and/or medical problem that presents in a neuro-ophthalmic context. The bibliography for each chapter has been chosen to complement the text with references to more inclusive works (which will provide more complete bibliographic references), recent, especially pertinent or substantive citations, and a few particularly thoughtful or provocative titles. For details, please consult these works (to which the author is indebted also).

Even a single-authored volume is really dependent on the help and support of many "significant others," and for their contributions and unfailing support I gratefully thank: my parents, family, and friends; my mentors—Arthur Jampolsky, who pointed out the fascination of neuro-ophthalmology to a premed student at a time when barely a half dozen people considered themselves neuro-ophthalmologists, and Bernard Becker, Andy Gay, and the incomparable William F. Hoyt—all of whom provided sterling examples and intellectual challenge; my many colleagues for their comments and suggestions that helped to make this book better than it otherwise might have been*; my residents and staff, especially ophthalmic technicians, Alita Soon, Mary Wu, and Kathy Jones, and ophthalmic photographers Mary Federico and Michael Coppinger, who helped me continue to learn from my patients; my patients and their doctors who referred them to me; my editors; and, very specially, my secretary, Frank Collier, without whom this book would never have been finished.

* Again, especially William F. Hoyt, Dick Mills, Dick Sogg, Neil Miller, and Stephen Geiser; also, Bob Nelson, David Rodgers, John Heckenlively, Jim Corbett, David Zee, Mort Goldberg, Creig Hoyt, Klara Landau, Wayne Cornblauth, and Dick Weleber.

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CHAPTER 1

THE VISUAL AFFERENT PATHWAYS

ANATOMIC CONSIDERATIONS

The eye is the paramount sense organ of the body, detecting the first threat of danger, the first stirring of the quarry, a veritable window on the world, open to information from afar, discerning the tiniest motes dancing in a sunbeam, discriminating the transient hues of a fleeting rainbow. Safe in their deep bony orbits, reposing on a cushion of fat, protected by the curtaining eyelids and moistened by glistening tears, the eyeballs move in conjunction, each with six slender muscles directing the intent gaze upon the object of suspicion or curiosity.

Lockhart

The eye develops as an outpouching of the brain (Fig. 1–1). Its pathology and physiology are like those of the central nervous system; it is one of the primary sense organs and the retina is its primary sensory element. The other ocular structures are the supportive and nutritive elements necessary for maintenance and function of the retina. The sclera is a structural and protective coating; the pigment epithelium, vascular choroid, and blood vessels are nutritive; the cornea, lens, and their accessory structures are the optics; and the aqueous and vitreous provide protective support, flux of nutrients, and optical access.

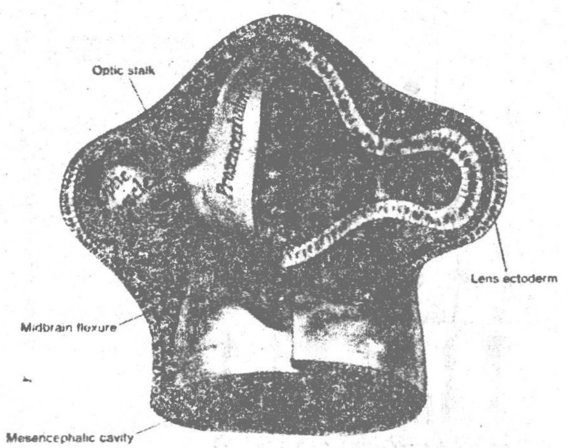

Figure 1–1. The eye forms as an outpouching of the central nervous system. (The formation of the optic vesicle and cup in a 4-mm human embryo.) (*From Miller N, ed.* Walsh and Hoyt's Clinical Neuro-ophthalmology. *4th ed. Baltimore: Williams & Wilkins, 1982; 1; with permission.*)

THE VISUAL PROCESS

The visual process begins as light rays enter the eye through the cornea; pass through the aqueous, lens, and vitreous; and strike the retina. The optical system, primarily the lens and cornea, acts to focus the image as does the lens of a camera. The focused image is reversed on the retina, both right to left and up to down (Fig. 1–2). If the eye is too long for its focusing power, the images form anterior to the retina and the patient is nearsighted (myopic); if too short, the image is focused behind the retina and the patient is farsighted (hyperopic). If the cornea is not perfectly spherical, light is refracted differently in various meridians, causing astigmatism.

THE RETINA

Classically, the retina is said to have 10 layers (Fig. 1–3). From innermost to outermost, they are the (1) internal limiting membrane, (2) nerve fiber layer, (3) ganglion cell layer, (4) inner plexiform layer, (5) inner nuclear layer, (6) outer plexiform layer, (7) outer nuclear layer, (8) external limiting membrane, (9) receptor elements (rods and cones), and (10) retinal pigment epithelium.

The three nuclear layers (3, 5, and 7) contain cell bodies, whereas most synapses occur in the plexiform layers (4 and 6). The retinal pigment epithelium is critical in the catabolic metabolism of the

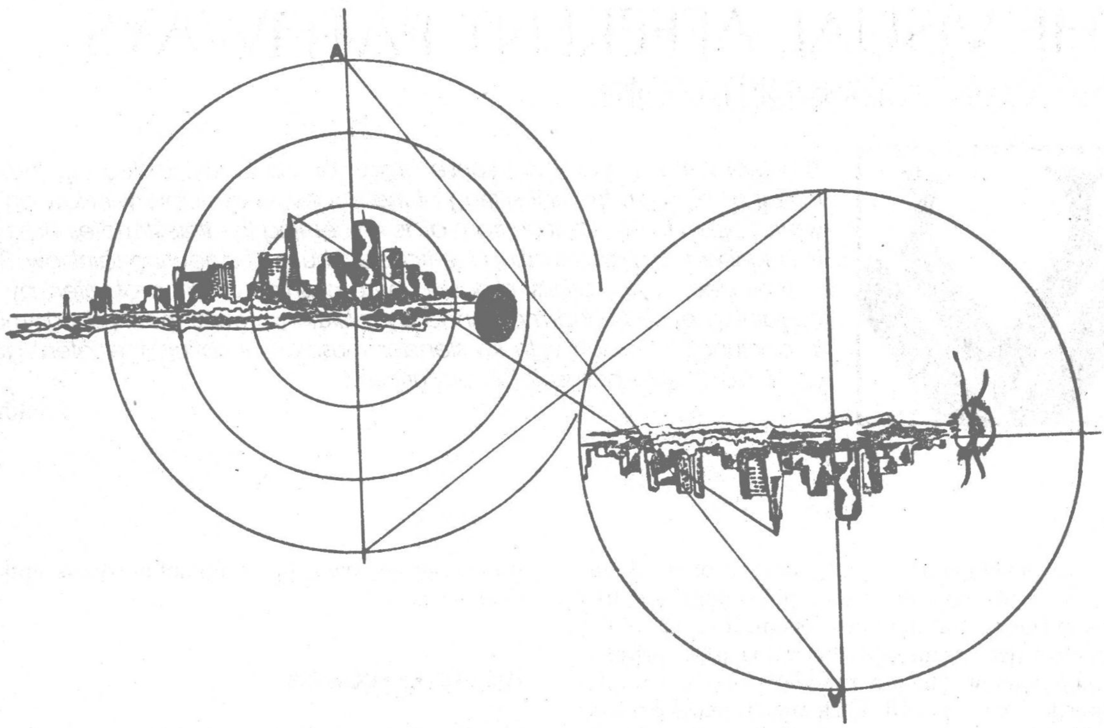

Figure 1–2. Diagrammatic portrayal of how the optics of the eye project the scene viewed onto the retina (reversed and upside-down).

photoreceptors; it ingests and disposes of their shed outer segments and facilitates their continued renewal. Uniquely, the glial Müller cells traverse the entire retina from the internal limiting membrane to the external limiting membrane. They provide the architectural skeleton and physiologic support of the neural cells.

The **receptors** (rods and cones) absorb much of the incident light that transverses the retina. The subsequent bleaching and isomerization of the receptor visual pigments, rhodopsin (rods) and iodopsin (cones), is the first step in the transduction of light energy into the electric energy of neural excitation. The receptor mechanism is exquisitely sensitive, responding to only a few quanta of light. As sensory organs, the rods and cones are analogous to the peripheral sensory endings (eg, pacinian corpuscles) of the other sensory pathways.

The *cones*, color- and light-sensitive receptors, are located primarily in the central retina, outnumbering rods in the macula and exclusively occupying the fovea. They are small and tightly organized, providing for a high order of visual discrimination. Because they are small in size and contain minimal

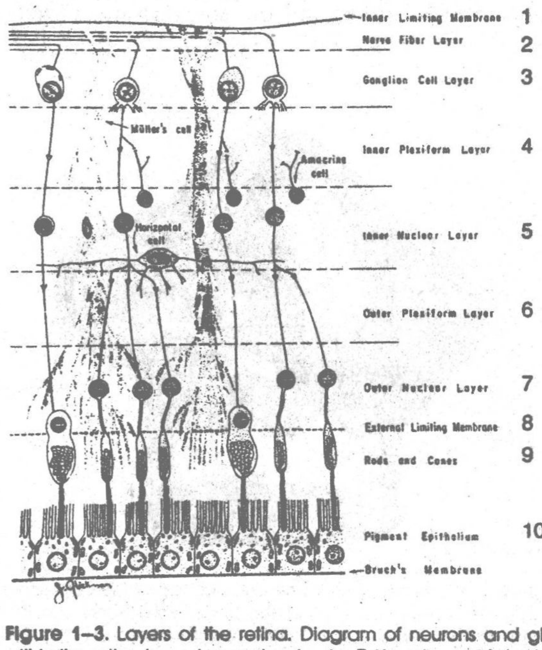

Figure 1–3. Layers of the retina. Diagram of neurons and glia within the retina based on a drawing by T. Kuwabara. (*Adapted from Cogan D.* Neurology of the Visual System. *Springfield, IL: Thomas, 1967, with permission.*)

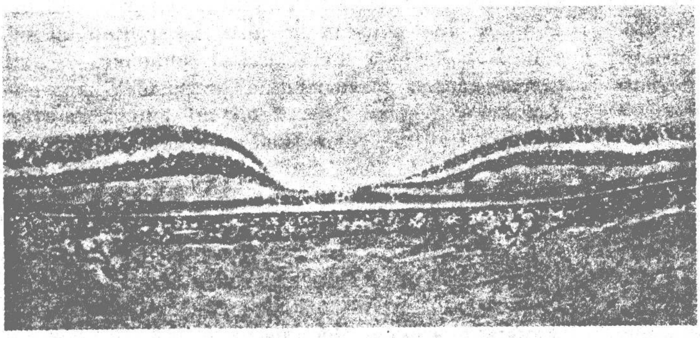

Figure 1–4. Cross section at the posterior pole of the eye including the macular and paramacular regions of the retina. Noteworthy is the attenuation of all the retinal layers, except the photoreceptors, in the center of the macula. (*From Cogan D.* Ophthalmic Manifestations of Systemic Vascular Disease, *Vol 2 In: Smith LH, ed.* Major Problems in Internal Medicine. *Philadelphia: Saunders, 1974, with permission.*)

visual pigment, however, they have a high threshold to stimulation. *Rods* are more important in peripheral vision and in low illumination. Because rods have a large amount of visual pigment relative to cones and many intracellular connections, they are more sensitive. Thus, the cones yield high visual acuity under photopic (well lit) conditions; the rods are more sensitive in scotopic (dimly lit) conditions, but discriminate poorly.

Many types of retinal cells, for example the A2 cell, which received input from both rods and cones, are being newly investigated and characterized. Their functional organization and roles are incompletely understood.

The **ganglion cells** form a layer with maximal thickness and density (8 to 10 layers) in the parafoveal macula, but are absent from the fovea itself (Fig. 1–4). This facilitates acute vision as the light rays traverse fewer retinal layers. With increased distance from the fovea, ganglion cell density decreases and dendritic field size increases.

Morphologically, the *ganglion cells fall into three categories.* The largest group (80%) are cells with small bodies that usually give rise to one dendrite (but occasionally yield two or three). These cells project to the dorsal layers, the parvocellular layers, of the lateral geniculate body (layers 1 to 4). These ganglion cells respond linearly to appropriate stimulation and show high resolution and color sensitivity. They have been termed P-beta or B cells in primates (somewhat analogous to X cells in cats), and are thought to participate in tasks requiring fine discrimination.

Another group of small-bodied ganglion cells is the group called P-gamma, C, or W cells, which constitutes 10% of the ganglion cells and which projects to the superior colliculus (SC) with a collateral projection to the lateral geniculate body. These cells have slow conduction velocities and sluggish responses.

TABLE 1–1. MAJOR SUBDIVISIONS AND CONNECTIONS OF THE PRIMATE GENICULOCORTICAL VISUAL SYSTEM

Retina	B-ganglion cells		A-ganglion cells
LGN	Parvocellular	Interlaminar	Magnocellular
Area 17	4cβ		4Cα
	Interblobs	Blobs	4B
Area 18	Pale stripes	Thin stripes	Thick stripes
Higher visual areas	?V3,?V4	V4	MT
Property			
Color	Yes/no[a]	Yes	No
Contrast sensitivity	Low	High[b]	High
Spatial resolution	High	Low	Low
Orientation selectivity	Yes	No	Yes
Movement sensitivity	Yes	No	Yes
Directionality	No[c]	No	Yes[d]
Stereopsis	No[e]	No	Yes

[a] Cells beyond 4Cβ do respond to color-contrast borders but are not overtly color-coded.
[b] By deoxyglucose.
[c] At least it is not prominent.
[d] Rare in thick stripes in area 18 but very common in layer 4B of area 17 and in MT.
[e] In anesthetized animals, we have seen only a few stereotuned cells in upper layer area 17. In attentive animals, cells coded for stereoscopic depth have been reported both above and below layer 4C of area 17, but are especially concentrated in layer 4B. We do not understand these differences in results, but one possibility is that the stereo mechanisms are built up in 18, and the stereotuning in 17 is the result of a back projection that is suppressed by anesthesia.
From Livingstone M, Hubel D. J. Neurosci. *1987;7:3420, with permission.*

The third group of ganglion cells, also forming about 10% of the total population, is the group called M or A cells in primates (roughly analogous to Y cells in cats). These cells have large cell bodies and project to the magnocellular layers of the lateral geniculate body (layers 5 and 6); some also project to the superior colliculus. These cells give fast, short-lasting, nonlinear, broad-based, achromatic responses. They are very sensitive to low contrast and flicker; they have low acuity in contrast to P-beta (B, X) cells and are thought to encode movement.

Each ganglion cell type seems to have its own pattern of projection via parallel visual channels, each relaying information about different aspects of vision (see Table 1–1).

The **retinal nerve fiber layer** consists of ganglion cell axons that course radially toward the optic disc (Fig. 1–5). These are the tertiary neurons of the visual pathway. Bundles of axons pass toward the optic nerve within tunnels formed by the processes of the Müller cells and astrocytes (Fig. 1–6). As the retinal nerve fiber layer and optic disc, the anterior visual pathway is visible to the examiner as is no other part of the central nervous system (CNS).

Axonal Transport. Within neurons, retrograde and anterograde axoplasmic flow transports materials to and from the cell bodies. As all cellular proteins are produced in the cell body, this bidirectional traffic furnishes nutrition and building blocks to the far-flung cell processes, the axons and dendrites. Transmitter substances, viruses, cell organelles, and poisons are also transported by axonal flow. In fact, the access of some viruses and toxins (herpes, polio, tetanus) to the CNS is by retrograde axoplasmic flow. Some substances are even transported transsynaptically. When disease or mechanical factors slow axoplasmic flow, the dammed-up axoplasm causes neuronal swelling on either side of the damaged area. In the retina, these swollen cells show microscopically as cytoid bodies. Larger areas of axoplasmic stasis appear ophthalmoscopically as cotton-wool spots, confluent retinal whitening, and papilledema.

The Fovea and Macula

The fovea and macula are specialized retinal areas aligned with the optic axis of the eye; they subserve the finest visual acuity of any part of the eye. The discriminating capacity of the fovea determines the best possible visual acuity. The retina is thinnest at the fovea, where no blood vessels or ganglion cells overlie the photoreceptors (Figs. 1–7 and 1–4).

THE OPTIC DISC AND OPTIC NERVE

The fibers of the ganglion cells exit the globe at the optic disc (optic papilla, optic nerve head) to form the optic nerve. The optic nerve consists of four parts: (1) the ocular portion (1.5 mm), which transverses the sclera; (2) the orbital portion (40

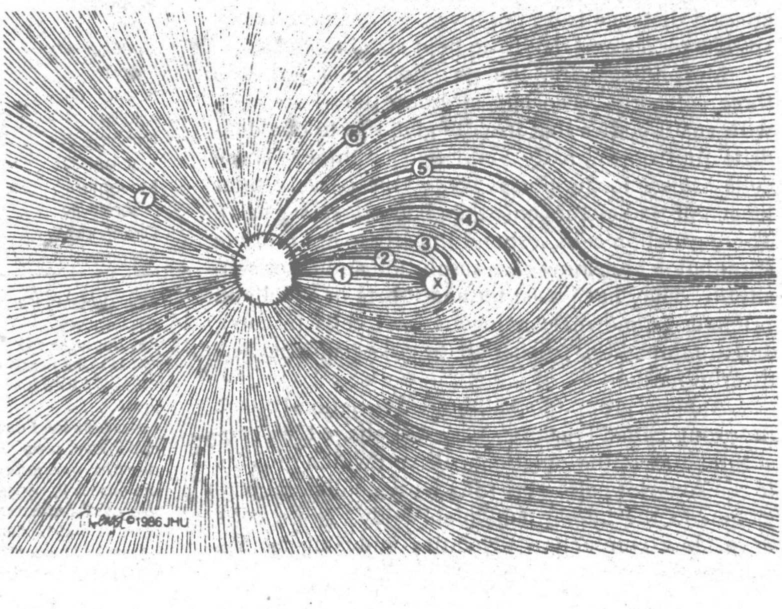

Figure 1–5. Schematic drawing of the pattern of nerve fibers in the retina. The **X** indicates the location of the fovea. Representative fiber pathways are highlighted with bold lines. 1. Nasal macular fiber originating near the horizontal meridian. 2. Nasal macular fiber originating a short distance above the horizontal meridian. 3. Perpendicular fiber. 4. Oblique fiber. 5. Fiber originating in the peripheral retina temporal to the fovea near the horizontal meridian (temporal raphé). 6. Fiber originating in the peripheral retina temporal to the fovea away from the horizontal meridian. 7. Fiber originating nasal to the optic disc. (*From Miller N, Pollock SC. The retinal nerve fiber layer. In: Beck R, ed.* Int Ophthalmol Clin. *1986;26:207, with permission.*)

mm), which leads to (3) the canalicular portion, which passes through the optic canal; and (4) the intracranial portion, which joins its counterpart from the opposite side to form the optic chiasm. Within the orbit, the optic nerve is not tethered. Thus, because its length exceeds the distance from the optic canal to the eyeball, it has a sinuous course that allows for considerable excursion as the globe moves.

Because the eye is an embryologic outpouching of the forebrain, in reality the **optic nerve** is an externalized white-matter tract of the CNS. As it exits the globe, it becomes myelinated and is invested with vaginal sheaths, which through the optic canal are continuous with the meninges of the CNS (Fig. 1–8). The optic nerve sheaths similarly are composed of pia, arachnoid, and dura. The dura is continuous with the periorbita in the orbital apex. At the globe, it splays out to insert onto the sclera surrounding the optic nerve. The pia invests the optic nerve itself. Characteristic mesodermal septa of pia carry an intricate supply of blood vessels into the tissues of the optic nerve. The arachnoid ends at the sclera. It contains the cerebrospinal fluid, which is in continuity with that of the CNS. This relationship is important in the effects of intracranial pressure on the optic nerve head.

The nerve itself contains two tissue compartments: the **neuroectodermal compartment,** with the nerve tissue proper, neurons, and neuroglia; and the **mesodermal compartment,** with the supporting and nourishing tissues—the blood vessels, fibroblasts, and meningothelial cells. These form orderly layers in which the neural elements are completely embedded in a glial cover; the glia in turn contacts the mesodermal elements that surround and form the blood vessels (Fig. 1–9).

At the optic disc, nerve fibers make up 90% of the optic nerve tissue; more posteriorly, nerve fibers still form the largest contribution to the optic nerve, but they are joined by a larger proportion of astrocytes. At the level of the sclera, the nerve fibers run through the collagenous tissue sheets of the lamina cribrosa.

The **lamina cribrosa** is a specialized, sieve-like region of scleral trabeculae through which the nerve fibers exit the eye (Fig. 1–10). Although these scleral trabeculae are relatively inert, many relationships critical to the integrity of the nerve occur in this region:

1. The nerve leaves the eye and its intraocular pressure and becomes invested with myelin and vaginal sheaths.
2. As the fibers acquire myelin, the nerve doubles in size from 1.5 to 3 mm (occasionally the myelin continues through the lamina as myelinated nerve fibers in the retina—see page 100).
3. In the orbit, the nerve is subject to the combined influences of orbital pressure and intracranial pressure (transmitted through the optic nerve sheaths).

With increased intraocular pressure, the lamina becomes physically distorted and bowed backwards,

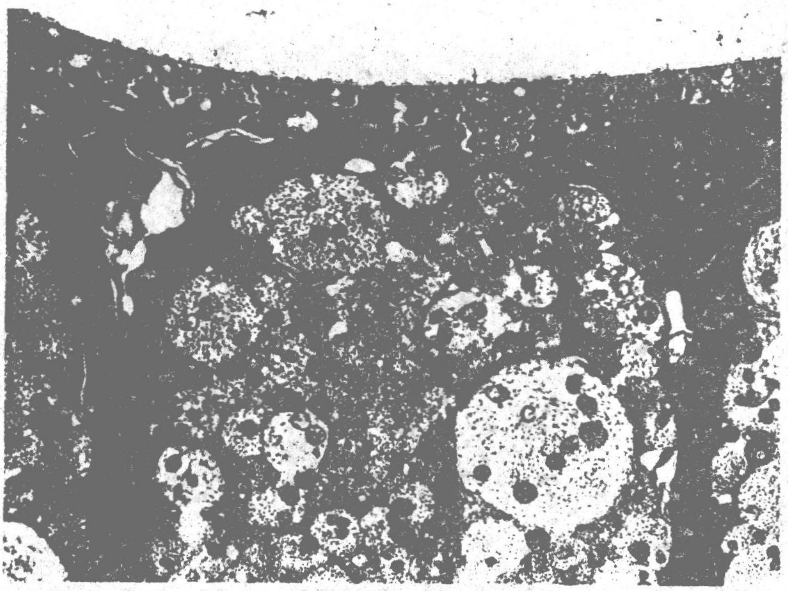

Figure 1–6. Nerve fiber layer of the retina. Two Müller cells (*top corners*) partly form the inner limiting membrane. Their radial fibers enclose bundles of nerves (×4000). (*From Hogan M, Alvarado J, Waddell J.* Histology of the Human Eye: An Atlas and Textbook. *Philadelphia: Saunders, 1971, with permission.*)

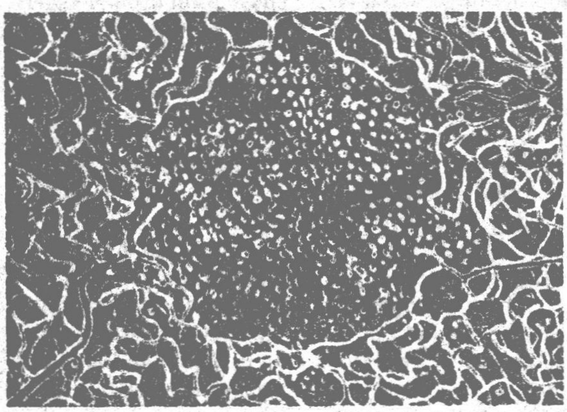

Figure 1–7. Retinal vascular organization in the fovea. Scanning electron micrograph shows the capillary-free zone of the foveola. (*From Miller N, ed.* Walsh and Hoyt's Clinical Neuro-ophthalmology. *4th ed. Baltimore: Williams & Wilkins, 1982; 1; with permission.*)

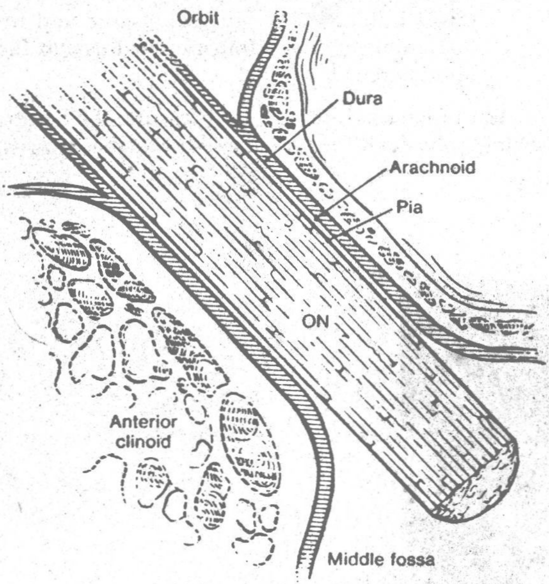

Figure 1–8. Schematic drawing of the optic nerve sheaths showing their relationship to the optic nerve (*ON*) and to the surrounding sphenoid bone. The dura is tightly adherent to the bone within the optic canal. Within the orbit it divides into two layers, one of which remains as the outer sheath of the optic nerve, and the other becomes the orbital periosteum (*periorbita*). Intracranially, the dura leaves the optic nerve to become the periosteum of the sphenoid bone. (*From Miller N, ed.* Walsh and Hoyt's Clinical Neuro-ophthalmology. *4th ed. Baltimore: Williams & Wilkins, 1982; 1; with permission.*)

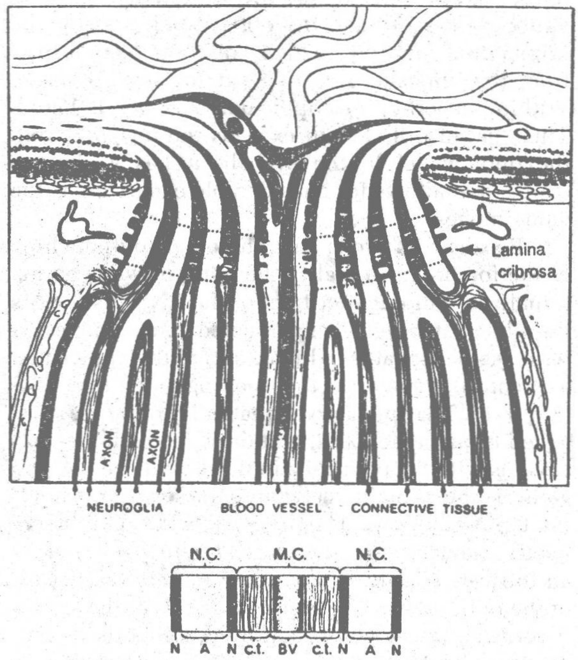

Figure 1–9. Layers of optic nerve. The intraorbital optic nerve is divided into two tissue compartments, neuroectodermal and mesodermal. In the neuroectodermal (*NC*) compartment, the axons (*A*) are surrounded by neuroglia (*N*). The neuroglial cells are in contact with the mesodermal compartment (*MC*) in which connective tissue (*ct*) surrounds the blood vessels (*BV*). (*From Newman NM.* The Prechiasmal Visual Afferent Pathways. *In:* Clinical Neuro-ophthalmology: the Afferent Visual System. *Karpe, J. and Burde, RM* (eds.) *Boston: Little, Brown, 1977, with permission.*)

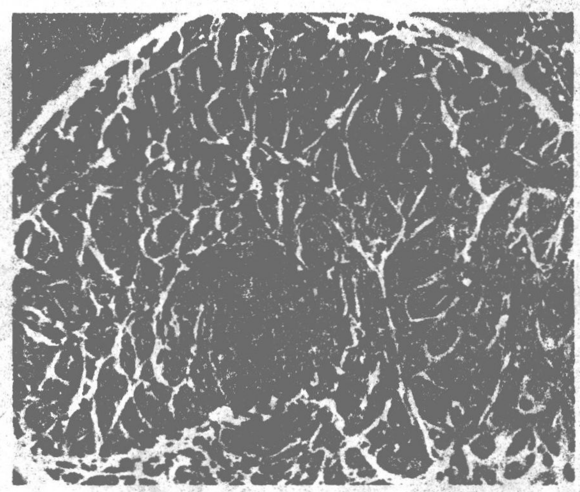

Figure 1–10. Scanning electron micrograph of the scleral laminar region viewed from the vitreous cavity. (*From Miller N, ed.* Walsh and Hoyt's Clinical Neuro-ophthalmology. *4th ed. Baltimore: Williams & Wilkins, 1982; 1; with permission.*)