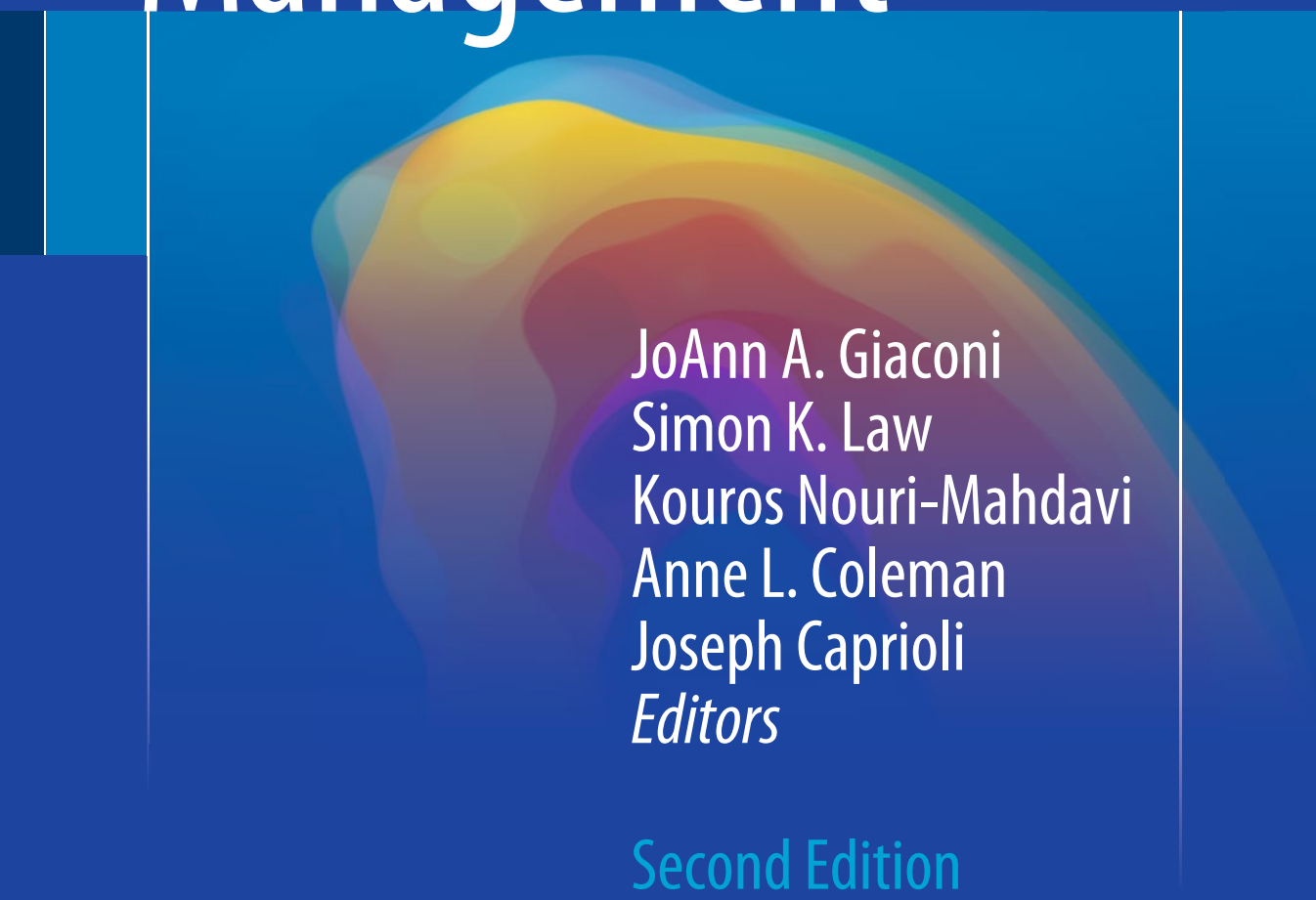
Pearls of Glaucoma Management



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Editors

Second Edition

Springer

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Foreword

If you have ever uttered the commonly expressed lament, "Glaucoma is so confusing!" then this text is for you. You will no longer be bewildered.

Why practitioners may be confused about how to be of help to patients with glaucoma—in its many incarnations and reincarnations—is easily understood. The issue seems to be overwhelming when one considers that the already massive population of those with glaucoma is increasing rapidly as the world's population increases and ages.

During the past 50 years the fundamental definition of glaucoma has changed almost 180°, and the indications for treatment have become more variable and controversial, some advising early therapy and others strongly cautioning against such an approach: Various diagnostic tests have come and gone and are interpreted in such different ways that there seems to be no consensus; surgical techniques come in and out of fashion in perplexing ways. There seems to be a constantly shifting, sandy foundation on which are built unsteady schools of ever-varying advice. Why practitioners, patients, and the public are often bewildered is understandable.

The current text was designed to be relevant, scientific, and practical. The editors have accomplished their objective well. The authors chosen to share their wisdom are expert practitioners who recognize the dangers of basing treatment on theory. They, the leaders in their fields, create an understanding of glaucoma and conditions related to glaucoma that is sound, scientific, and effective. The editors clearly instructed their contributors to avoid speculation, to be practical, and to insist on evidence, not opinion (and where good evidence was lacking, to indicate such a lack). The result is a cohesive picture that should be of immense help to all those trying to make sense of what to many seems to be confusing.

It is perhaps not surprising that this text accomplishes its objective so admirably. The senior editor is a vastly experienced physician, equally at home in the clinic, the operating room, the classroom, and in a basic research laboratory. The contributing authors come from many different institutions and cultures; some are younger and others older. The current text, however, does not present information that must be sifted by a discerning reader in order to come up with appropriate advice. Rather, the authors simplify, clarify, organize, and explain practically and scientifically. Those wanting to know how to approach patients with glaucoma or those many, many patients in whom it is not clear whether glaucoma is present or not will find this a treasure trove of sound science blended with critical experience.

The need for this intellectually vigorous, practical approach to caring for patients with conditions related to intraocular pressure and optic nerve disease is great. There is probably truth in the belief that all persons will eventually develop glaucoma if they live long enough. As the world population ages and increases, as resources become ever more precious, and as cost considerations become more confining, there is increasing urgency for guidelines that concentrate on the essentials and that will help achieve the goal of caring for the sick and for the well, specifically, the greatest good for the greatest number, while still addressing the needs and wants of each individual person.

Currently there is much interest in "translational research." This book is highly successful in translating vast amounts of disparate, sometimes disconcerting information into understandable sentences, paragraphs, and illustrations that will result in more effective and more relevant care.

Philadelphia, PA, USA George Spaeth

Preface

This book was developed based on the questions that clinicians, fellows, and residents taking care of glaucoma patients have asked us as consultants. Most textbooks on glaucoma provide a broad overview of the clinical and basic science literature, which is very useful to students learning about glaucoma. However, these textbooks may leave many questions unanswered for the clinician searching for advice on how to manage a specific problem. This book asks and answers those questions. Additionally, it covers topics that are not always included in traditional textbooks but that are being discussed at national and international meetings.

In addition to asking the questions that frequently arise in managing patients with glaucoma, a goal of this textbook was to have the authors who are familiar with the world literature digest that information in the context of their own clinical experience. We asked authors to answer questions the way they might answer a physician's questions over the phone. We asked them to state their opinions on how they like to manage clinical situations, where appropriate, and to also point out that their preferred management is not the only way to manage the problem if other acceptable means are available. The questions are organized by topic and cover diagnostic testing and interpretation, risk factors, medical treatment, procedural treatments, various glaucoma subtypes, and complications.

We must thank all the consulting physicians, students, residents, and fellows who we have encountered and who inspired this textbook. As well, we thank Ms. Minn Oh for administrative help with the second edition of this book.

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Optic Nerve: The Glaucomatous Optic Nerve

1

Claude F. Burgoyne

Core Messages

- The principle insult in glaucoma occurs within the neural, cellular, and connective tissues of the optic nerve head (ONH).
- Intraocular pressure at all levels has biomechanical effects on the optic nerve tissues.
- Clinical cupping is one manifestation of the pathophysiology of glaucomatous damage, but is not the pathophysiology itself.
- The variable appearance of the ONH in all optic neuropathies is the predictable result of ONH tissue biomechanics.
- As our clinical tools for characterizing ONH biomechanics improve, so too will our ability to understand normal ONH aging and its contributions to the clinical behavior and susceptibility of the ONH.

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1.1 Why Is the Optic Nerve Important in the Diagnosis and Management of Glaucoma?

Glaucoma is an optic neuropathy. Although there are several pathophysiologies that must be managed in the clinical care of the glaucoma patient, what defines all forms of glaucoma is an optic neuropathy that demonstrates classic and recognizably variable [1–6] structural and functional behaviors.

1.1.1 The Optic Nerve Head Is the Principal Site of Glaucomatous Damage to the Visual System

Although glaucomatous damage likely encompasses important pathophysiology within the retinal ganglion cell (RGC) stroma [7–12], photoreceptors [13–17], lateral geniculate body [18–20], and visual cortex [20], strong evidence suggests that damage to the RGC axons within the lamina cribrosa of the optic nerve head (ONH) [21–26] is the central pathophysiology underlying glaucomatous vision loss. Recent studies in monkeys [25–30], rats [31–33], and mice [34] support the importance of the ONH in glaucoma by describing profound alterations at

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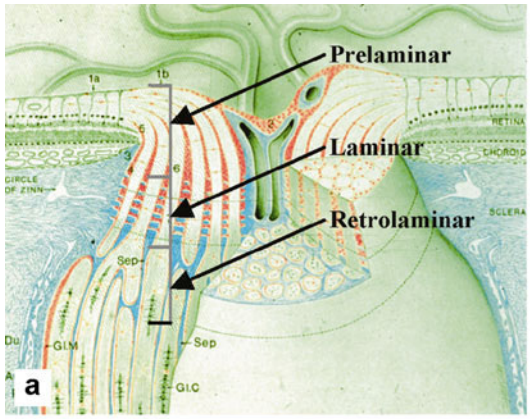
the earliest detectable stage of the disease within the prelaminar, laminar, and peripapillary scleral tissues of the ONH.

The ONH tissues make up a dynamic environment wherein 1.2–2.0 million RGC axons converge, turn, and exit the eye through the inner (Bruch's membrane opening) and outer (scleral) portions of the neural canal (Fig. 1.1). Within the scleral portion of the canal, the bundled axons pass through a three-dimensional meshwork of astrocyte-covered, capillary-containing connective tissue beams known as the lamina cribrosa (Fig. 1.1). Within the lamina, axonal nutrition is dependant upon the movement of oxygen and nutrients from the laminar capillaries, through the laminar beam extracellular matrix (ECM), into the laminar astrocyte processes within the beam, finally reaching the peripheral and central axons of each bundle, via cell processes [35].

The connective tissue beams of the lamina cribrosa are anchored via the neural canal wall to a circumferential ring of collagen and elastin fibers within the peripapillary sclera [36–38] and are presumed to bear the forces generated by intraocular pressure (IOP) (Fig. 1.1). IOP-related stress (force/cross-sectional area of the tissue experiencing that force) and strain (a measure of local deformation of a tissue induced by applied stress) within the load-bearing tissues of the ONH influence the physiology and pathophysiology of all three ONH tissue types (Table 1.1): (1) the connective tissues, (2) the neural tissues, and (3) the cells that exist alone or in contact with both (1) and (2) [39–41].

While the pathophysiology of glaucomatous damage to the ONH tissues remains controversial, we have proposed that it is multifactorial and is influenced by at least three etiologies (Table 1.2)—IOP-related connective tissue stress and strain [21–24], blood flow/nutrient diffusion/ischemia within the laminar and prelaminar tissues [42–45], and the autoimmune and/or inflammatory state of the tissues [46–51] (Fig. 1.2, top). The interplay between the pathophysiology of ONH neural and connective tissue damage and the clinical appearance and behavior of the neuropathy are discussed in Figs. 1.2 and 1.3 and the sections that follow.

Fig. 1.1 The optic nerve head (ONH) is centrally influenced by IOP-related stress and strain. The ONH is made up of prelaminar, laminar, and retrolaminar regions (**a**). Within the clinically visible surface of the normal ONH (referred to as the optic disc) (**b**), central retinal vessels enter the eye and retinal ganglion cell (RGC) axons appear *pink* because of their capillaries (which are principally supplied by branches from the posterior ciliary arteries (PCA) in (**c**). The primary site of RGC axon insult in Glaucoma is within the lamina cribrosa (schematically depicted with axon bundles) in (**d**), isolated by trypsin digest in a scanning electron micrograph in (**e**) and drawn with stippled extracellular matrix (ECM), central capillary (*red*), and surrounding astrocytes (*yellow* with basement membranes in *black*) (**f**). Blood flow within the ONH, while controlled by autoregulation, can be affected by non-IOP-related effects such as systemic blood pressure fluctuation and vasospasm within the retrobulbar portion of the PCAs. Additional IOP-induced effects may include compression of PCA branches within the peripapillary sclera (due to scleral stress and strain) and compression of laminar beam capillaries reducing laminar capillary volume flow (**c**, **f**) [43]. There is no direct blood supply to the axons within the laminar region. Axonal nutrition within the lamina (**f**) requires diffusion of nutrients from the laminar capillaries, across the endothelial and pericyte basement membranes, through the ECM of the laminar beam, into astrocyte processes within the beam, through the astrocyte processes into the adjacent axons (*vertical lines*). Chronic age-related changes in the endothelial cell and astrocyte basement membranes, as well as IOP-induced changes in the laminar ECM and astrocyte basement membranes may diminish nutrient diffusion to the axons in the presence of a stable level of laminar capillary volume flow. The clinical manifestation of IOP-induced damage to the ONH is most commonly "deep cupping" (**g**), but in some eyes cupping can be shallower accompanied by pallor (**h**). *Z-H* circle of Zinn-Haller; *PCA* posterior ciliary arteries; *NFL* nerve fiber layer; *PLC* prelaminar region; *LC* lamina cribrosa; *RLC* retrolaminar region; *ON* optic nerve; *CRA* central retinal artery. (**a**) Reproduced with permission of Arch Ophthalmol. Copyright 1969 American Medical Association. All Rights reserved [35]. (**b**, **g**, **h**) Reprinted with permission from J Glaucoma. Copyright 2008 [83]. (**c**) Reprinted with permission from Elsevier. Copyright 1996. This article was published in The Glaucomas. Edited by Ritch R, Shields MB, Krupin T. Mosby, St. Louis; Cioffi GA, Van Buskirk EM: Vasculature of the anterior optic nerve and peripapillary choroid. Pg 177–197 [140]. (**d**) Courtesy of Harry A. Quigley and reprinted with permission from Kugler Publications, Amsterdam [141]. (**e**) Reproduced with permission of Arch Ophthalmol. Copyright 1990 American Medical Association. All Rights reserved. (**f**) Reproduced with permission of Arch Ophthalmol. Copyright 1989 American Medical Association. All Rights reserved [142]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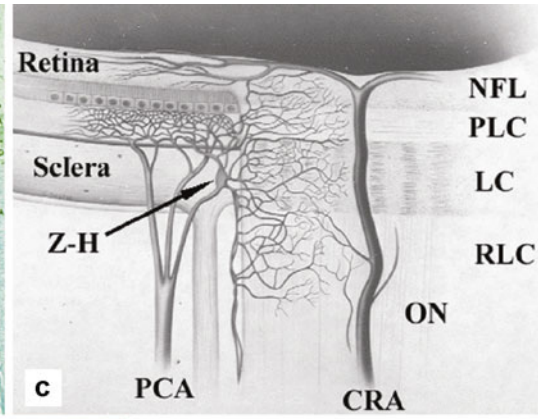
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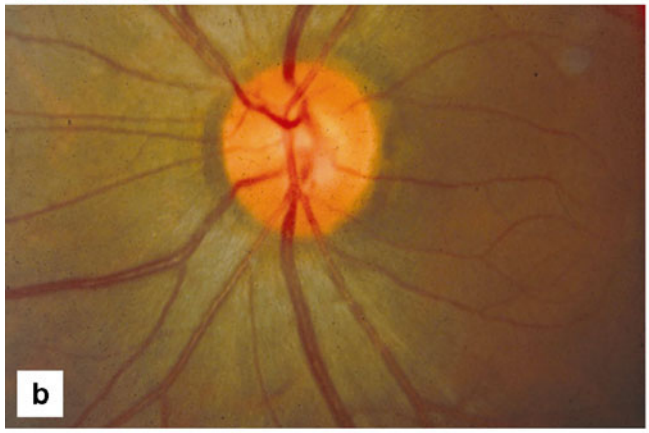
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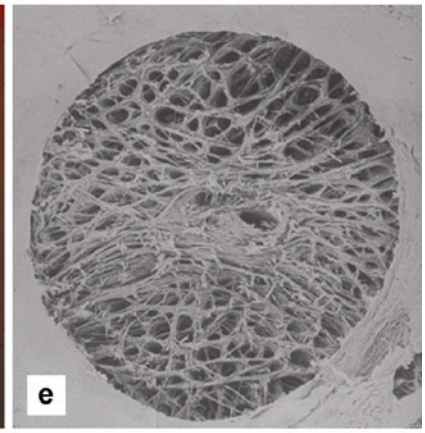
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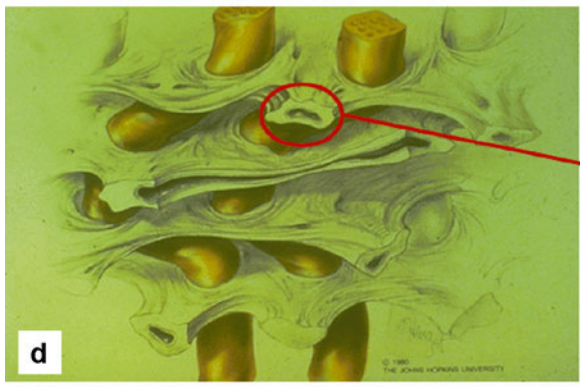
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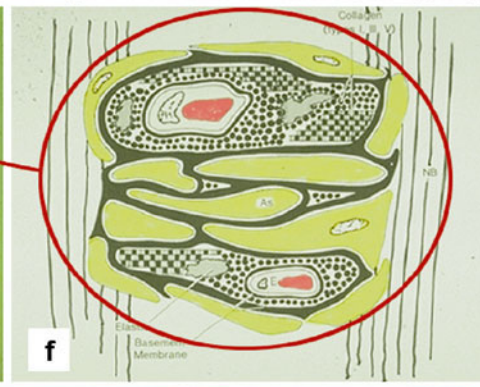
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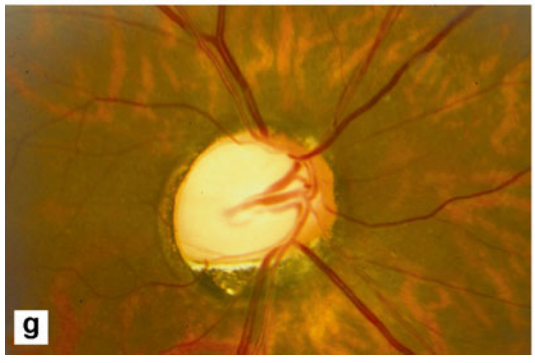
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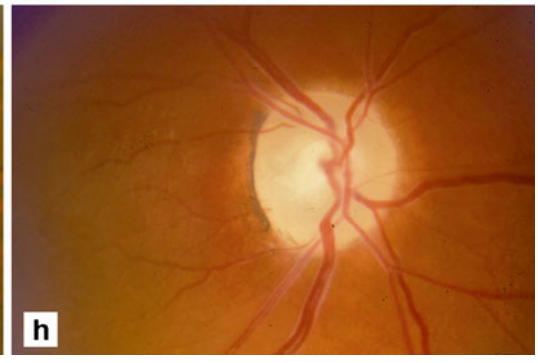
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Table 1.1 Optic nerve head tissue types

1.	Connective tissues
	Load-bearing connective tissues of the peripapillary sclera, scleral canal wall, and lamina cribrosa
2.	Neural tissues
	Retinal ganglion cell (RGC) axons
3.	Cells that exist alone or in contact with 1 and 2 above
	Astrocytes
	Glial cells
	Endothelial cells
	Pericytes
	Basement membranes (BM)

Table 1.2 Primary proposed etiologies glaucomatous damage to the ONH

IOP-related connective tissue stress and strain
Blood flow/nutrient diffusion and/or ischemia within the laminar and prelaminar tissues
Autoimmune and/or inflammatory mechanisms within the tissue

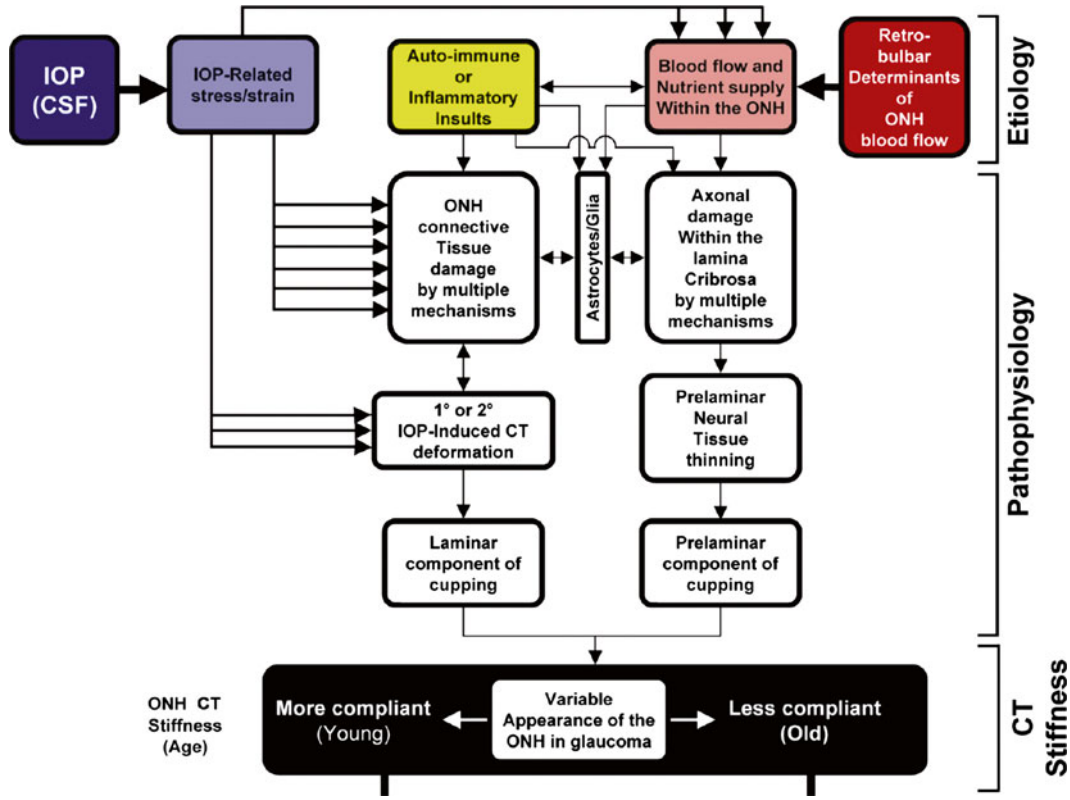

Fig. 1.2 While damage to the neural and connective tissues of the ONH is multifactorial, ONH appearance in the neuropathy is importantly influenced by connective tissue stiffness. In our biomechanical paradigm, IOP-related strain influences the ONH connective tissues and the volume flow of blood (primarily) and the delivery of nutrients (secondarily), through chronic alterations in connective tissue stiffness and diffusion properties (explained in Fig. 1.1). Non-IOP-related effects such as autoimmune or inflammatory insults (*yellow*) and retrobulbar determinants of ocular blood flow (*red*) can primarily damage the ONH connective tissues and/or axons, leaving them vulnerable to secondary damage by IOP-related mechanisms at normal or elevated levels of IOP. Once damaged, the ONH connective tissues can become more or less rigid depending upon lamina cribrosa astrocyte and glial response. If weakened, ONH connective tissues deform in a predictable manner, which underlies a laminar component of clinical cupping (Figs. 1.3 and 1.4). Reprinted with permission from J Glaucoma, copyright 2008 [83]

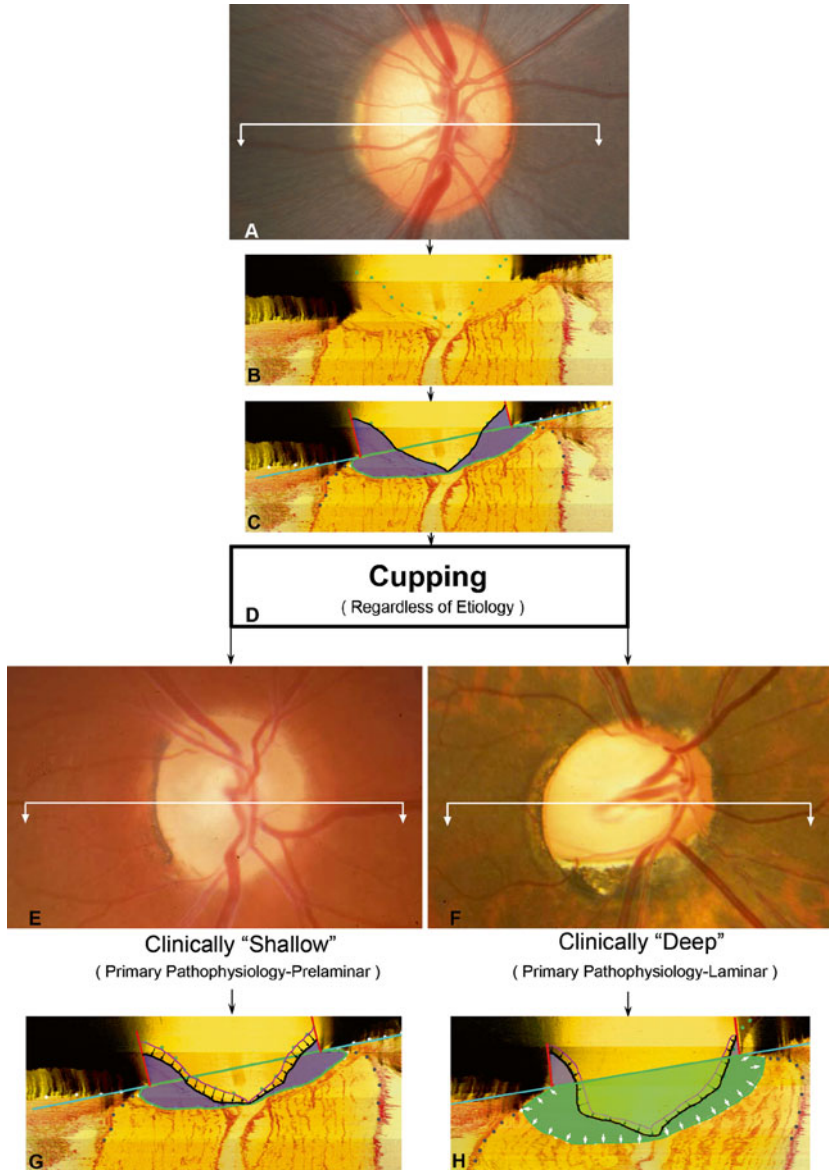

Fig. 1.3 All clinical cupping, regardless of etiology, is a manifestation of underlying "prelaminar" and "laminar" pathophysiologic components. (**a**) Normal ONH. To understand the two pathophysiologic components of clinical cupping, start with (**b**) a representative digital central horizontal section image from a postmortem 3D reconstruction of this same eye (*white section line* in (**a**))—vitreous top, orbital optic nerve bottom, lamina cribrosa between the sclera and internal limiting membrane (ILM) delineated with *green dots*. (**c**) The same section is delineated into principle surfaces and volumes (*black*—ILM; *purple*—prelaminar neural and vascular tissue; *cyan blue line*—bruchs membrane opening (BMO)-zero reference plane cut in section; *green outline*—post-BMO total prelaminar area or a measure of the space below BMO and the anterior laminar surface). (**d**) Regardless of the etiology, clinical cupping can be "shallow" (**e**) or "deep" (**f**) (these clinical photos are representative and are not of the eye in (**a**)). A prelaminar or "shallow" form of cupping (**g**, *black arrows*) is primarily due to loss (thinning) of prelaminar neural tissues without important laminar or ONH connective tissue involvement. Laminar or "deep" cupping (**h**, *small white arrows* depict expansion of the *green shaded space*) follows ONH connective tissue damage and deformation that manifests as expansion of the total area beneath BMO, but above the lamina. Notice in (**h**) that while a laminar component of cupping predominates (*white arrows*) there is a prelaminar component as well (*black arrows*). While prelaminar thinning is a manifestation of neural tissue damage alone, we propose that laminar deformation can only occur in the setting of ONH connective tissue damage followed by permanent (fixed) IOP-induced deformation (Reprinted with permission from [30]). Investigative Ophthalmology & Visual Science by Hongli Yang. Copyright 2007 by Investigative Ophthalmology & Visual Science. Reproduced with permission of Investigative Ophthalmology & Visual Science in the format Textbook via Copyright Clearance Center [30]

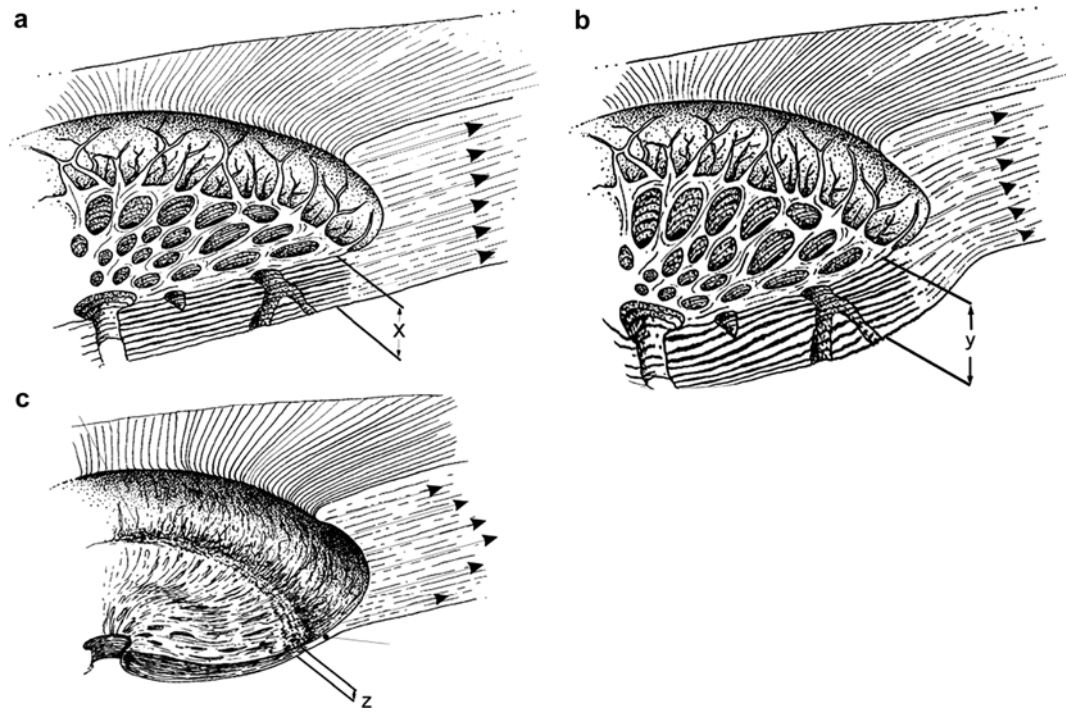

Fig. 1.4 Our central hypothesis regarding ONH connective tissue damage in "laminar" cupping. "Deep," "laminar," or "glaucomatous" cupping is a manifestation of ONH connective tissue damage, which can be caused by either IOP-related or non-IOP-related insults (see Fig. 1.5). However, regardless of the primary insult to the ONH connective tissues, their deformation (if present) is driven by IOP-related connective tissue stress and strain. Thus, the presence of ONH connective tissue deformation in any optic neuropathy is evidence that the level of IOP at which it occurred (whether normal or elevated) is too high for the connective tissues in their present condition. (**a**) Schematic of normal laminar thickness (*x*) within the scleral canal with scleral tensile forces acting on the scleral canal wall. (**b**) Early IOP-related damage in the monkey eye [25–30] includes posterior bowing of the lamina and peripapillary sclera accompanied by neural canal expansion (mostly within the posterior (outer) scleral portion) and thickening (not thinning) of the lamina (*y*). In our studies to date, this appears to represent mechanical yield (permanent stretching) rather than mechanical failure (physical disruption) of the laminar beams (**c**). Progression to end-stage damage includes profound scleral canal wall expansion (clinical excavation) and posterior deformation and thinning of the lamina (*z*) by mechanisms that are as yet uncharacterized [143, 144]. If all other aspects of the neuropathy are identical, the stiffer the lamina, the more resistant it will be to deformation. Whether this is better or worse for the adjacent axons is a separate question that remains to be determined. Reprinted from Prog Retin Eye Res:24. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT: The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage; pp. 39–73. Copyright (2005) with permission from Elsevier [41]

1.1.2 The Pathophysiology of Glaucomatous Damage Is Separate from the Clinical Phenomenon of "Cupping"

Cupping is a clinical term used to describe enlargement of the ONH cup in all forms of optic neuropathy [52–59]. However, *cupping* is also used as a synonym for the pathophysiology of glaucomatous damage to the ONH [24, 60–62]. Because the clinical and pathophysiologic contexts for *cupping* are seldom clarified, there is a confusing literature regarding the presence, importance, and meaning of *cupping* in a variety of optic neuropathies [2, 63–76].

We have previously proposed [30] that all optic neuropathies can demonstrate clinical cupping and that all forms of *clinical* cupping have two principal *pathophysiologic* components—prelaminar thinning and laminar deformation (Fig. 1.3). Prelaminar thinning results from net thinning of the prelaminar tissues due to physical compression and/or loss of RGC axons even in the presence of gliosis [77–80]. In this paradigm, prelaminar thinning results in a clinically shallow form of cupping [81, 82] (being limited to the prelaminar tissues) that occurs in all forms of RGC axon loss (including aging) and is therefore nonspecific. Laminar deformation results in a clinically deeper form of cupping that occurs only in those optic neuropathies in which damaged ONH connective tissues (lamina cribrosa and peripapillary scleral connective tissue) have become susceptible to permanent, IOP-induced deformation [25, 26, 28, 29, 41]. Whether the ONH connective tissues are primarily damaged by IOP or some other insult (ischemic, autoimmune, inflammatory, secondary astrocyte activation, or genetic predisposition [41]) (Fig. 1.4), if they deform they do so under the effects of IOP (normal or elevated) in a predictable way, and this deformation underlies laminar or deep or glaucomatous cupping (Figs. 1.3 and 1.4).

The previous paragraph contains two important ideas. First, it is possible for non-IOP-related processes to damage the ONH primarily and still end up with a nerve that looks and behaves in a manner we call *glaucomatous*. Second, IOP-related connective tissue stress and strain still drive the processes that cause the damaged tissues to deform, even if IOP is not the primary insult in the process and regardless of whether IOP is high or low.

1.1.3 The Clinical Appearance and Behavior of the ONH Holds Clues as to the Etiology of a Given Optic Neuropathy

When IOP is not elevated, and sometimes even when it is, the clinical challenge in the examination of the optic disc is not to recognize glaucoma, but rather to recognize the presence of an optic neuropathy and then separately determine the likelihood that IOP is playing a contributing role. The notions of laminar and prelaminar cupping suggest two important concepts to consider in the clinical assessment of an optic neuropathy.

First, detection of clinical cupping or its progression suggests the presence of an optic neuropathy, but it does not confirm that IOP is the etiologic agent. Regardless of clinical circumstances, but particularly when IOP is within normal limits, clinical cupping without clinically detectable connective tissue deformation should not be an absolute indication for IOP lowering. We have previously proposed that in patients with robust ONH connective tissues, IOP-related stress and strain can cause a prelaminar form of cupping in which pallor exceeds excavation by causing axonal degeneration without damage to the underlying connective tissues [41, 83]. Having proposed this concept, we now emphasize that without direct evidence of ONH connective tissue damage, the role of IOP in an individual optic neuropathy cannot be certain.

Second, in contrast to surface change detection, clinical detection of ONH connective tissue damage (i.e., a "laminar" contribution to cupping) is direct evidence of IOP involvement in the neuropathy and should become an absolute indication for IOP lowering, regardless of the level of IOP or the etiology of the primary connective tissue insult (ischemia, autoimmune, inflammatory, or IOP-related strain) [41, 83]. Thus, in all eyes, the presence of laminar cupping has diagnostic significance if we can develop the clinical tools to detect it.

1.1.4 The Aged ONH Holds Important Clues About Susceptibility

A variety of data suggest that the ONH becomes more susceptible to progressive glaucomatous damage as it ages, though this concept remains unproven through direct experimentation and it may not hold true for every aged eye. The data to

date can be summarized as follows. First, in most [84–88] but not all [89, 90] population-based studies, IOP does not increase with age, and in some studies where it does increase, the magnitude of increase is not likely to be clinically important. Thus, the fact that the prevalence of glaucoma increases with age [91–93] is likely explained by a greater susceptibility to IOP and other non-IOP-related risk factors, rather than to a higher prevalence of IOP elevation with increasing age. Second, in an extensive review of the literature, low-tension glaucoma is a disease of the elderly [94–99], with only a few reports regarding the onset and progression of normal tension glaucoma in infants, children, and young adults [100]. Third, age is an independent risk factor for both the prevalence [91–93] and progression of the neuropathy at all stages of damage [101–103].

1.1.5 How Age Influences the Susceptibility and Clinical Behavior of the ONH

Over a lifetime, the ONH connective tissues are exposed to substantial levels of IOP-related stress and strain at normal levels of IOP. This stress and strain increases as IOP increases and/or fluctuates (Fig. 1.5) [104–108]. Stresses and strains at a given level of IOP are physiologic or pathophysiologic depending upon the response of the tissues that experience them (Fig. 1.5). In this context, IOP is not so much normal as physiologic or pathophysiologic and what constitutes physiologic and pathophysiologic levels for IOP may change as they are influenced by associated systemic factors and aging.

Physiologic stress and strain induce a broad spectrum of changes in both the connective

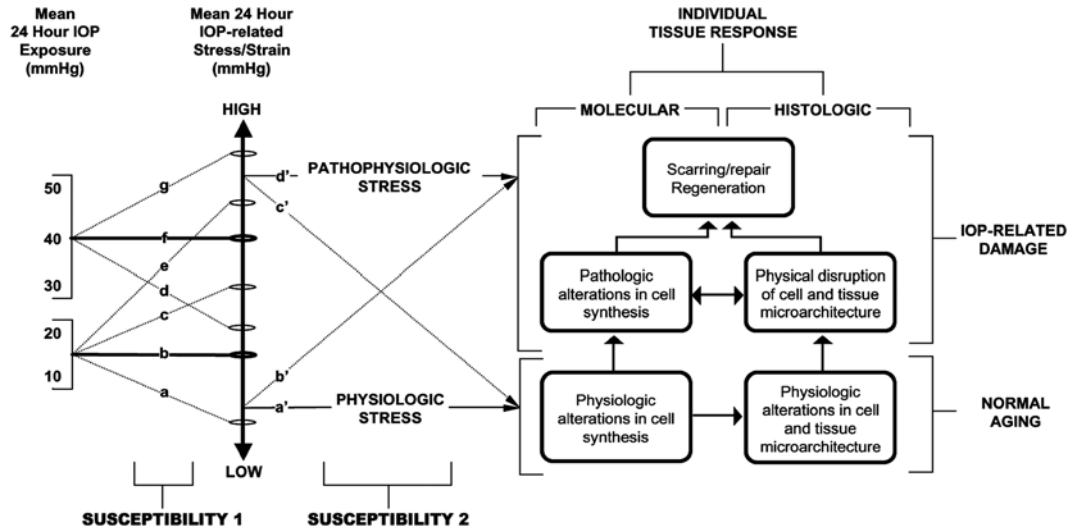

Fig. 1.5 Over the course of a lifetime, whether an eye demonstrates the "neuropathy of aging" or the neuropathy of glaucoma lies in ONH susceptibility. For a given ONH, IOP generates low or high levels of stress depending upon the 3D architecture of the ONH connective tissues (size and shape of the canal, thickness of the lamina and sclera—*susceptibility 1*). Some ONHs will have relatively low stress at high IOP (*d*). Others will have high stress at low IOP (*e*). Whether a given level of IOP-related stress is physiologic or pathophysiologic depends upon the ONH's microenvironment (*susceptibility 2*). Strong connective tissues, a robust blood supply, and stable astrocytes and glia increase the chance of normal ONH aging (*right*, *bottom*). While the existence of a neuropathy of aging is controversial, the difference between "normal" age-related axon loss (if it is shown to exist) and the development of glaucomatous damage is a matter of ONH susceptibility (Reprinted with permission from [41]). Reprinted from Prog Retin Eye Res:24. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT: The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage; pp. 39–73. Copyright (2005) with permission from Elsevier [41]

tissues and vasculature that are central to normal aging. While the concepts of age-related optic nerve axon loss [33, 109–114] and an optic neuropathy of aging [2, 55, 113–115] remain controversial, we believe that the range of physiologic stress and strain experienced within the ONH connective tissues over a lifetime are likely to be of central importance to both concepts.

Pathophysiologic stress and strain induce pathologic changes in cell synthesis and tissue microarchitecture (Fig. 1.5) that exceed the effects of aging. These changes underlie two governing pathophysiologies in glaucoma: (1) mechanical yield and/or failure of the load-bearing ONH connective tissues (Figs. 1.2, 1.3, and 1.4), and (2) progressive damage to the adjacent axons by a variety of mechanisms (Fig. 1.2).

The aged ONH is more likely to have stiff connective tissues [116–128] and a compromised blood supply [129, 130]. However, age-related increases in laminar beam thickness [117, 120, 122, 127, 131], laminar astrocyte basement membrane thickness [120, 131], and laminar ECM hardening [117, 120, 122, 131] should not only increase laminar beam stiffness, but should also diminish nutrient diffusion from the laminar capillaries into adjacent axons (Fig. 1.1). Thus, for a given magnitude of IOP insult, the aged ONH should demonstrate (1) less deformation due to the presence of a stiffer lamina and peripapillary sclera and (2) more pallor for a given amount of deformation because (a) the aged ONH may be more susceptible to axon loss and (b) pallor precedes deformation in the aged eye, while deformation precedes (or supersedes) pallor in the young eye.

Apart from the issue of ONH susceptibility, we predict that if all aspects of insult are equal (alterations in IOP, the volume flow of blood and nutrient transfer from the laminar capillary to the ONH astrocyte are all of the same magnitude, duration, and fluctuation), the aged eye will demonstrate clinical cupping that is on average shallow and pale (at all stages of field loss) compared with the eye of a child or a young adult. This clinical behavior in its most recognizable form is described as *senile sclerotic cupping* [1–6, 132].

We thus propose an overlap between the optic neuropathy of aging and the optic neuropathy of glaucoma in the aged eye and a biomechanical explanation for why the aged eye should demonstrate a shallow form of clinical cupping in which pallor more than deformation predominates.

1.1.6 Apart from the Aged ONH, Are There Some Nerves That Are Mechanically More Sensitive to Damage?

Although IOP [133–136] has been shown to play a causative role in glaucomatous ONH damage at all levels of IOP, many questions remain. There is no agreement on the effects of IOP within the tissues of the ONH; no data exist that would allow one to predict a safe level of IOP for a given ONH; and there are no accepted explanations for the varied clinical manifestations of glaucomatous damage [3], glaucomatous cupping, and glaucomatous visual field loss.

The principal ocular determinants of ONH susceptibility to a given level of IOP are likely to include (1) the IOP level (both the magnitude and variation); (2) the geometry and material properties of the ONH and peripapillary scleral connective tissues; (3) the volume flow and perfusion pressure of blood within the laminar capillaries; (4) nutrient diffusion to the astrocytes for a given level of blood volume and pressure; (5) the molecular response of astrocytes and glia to physical strain within their basement membrane and the presence of physiologic stress within their microenvironment (Fig. 1.2); (6) RGC factors that make its axon more susceptible to damage within the ONH, or its stroma more susceptible to apoptosis in response to axonal distress; (7) the immune environment of the ONH and retina; and (8) the number of remaining viable axons.

At present, we lack the means to directly assess any of the determinants listed above; however, the following features may soon be within the reach of a variety of new imaging strategies and may contribute to clinically derived engineering finite element models of individual

ONHs that we hope will one day underlie target pressure assignment: (1) the three-dimensional geometry and material properties of the lamina cribrosa, scleral flange, and peripapillary sclera [104–108]; (2) the difference in material properties between the peripapillary sclera and the lamina cribrosa [137, 138]; (3) the flow of blood and transport of nutrients across the basement membranes and ECM of the laminar beams; (4) the volume flow of blood through the intrascleral branches of the posterior ciliary arteries; and (5) the presence of peripapillary scleral posterior bowing and the distance between the anterior-most point of the subarachnoid space and the vitreous cavity [139].

Summary for the Clinician

- Glaucoma is an optic neuropathy in which the principal insult to the visual system is multifactorial and occurs within the neural, cellular, and connective tissues of the optic nerve head (ONH).
- IOP is a contributing risk factor to this pathophysiology at low, normal, and elevated levels because of its primary and secondary biomechanical effects on these tissues.
- Clinical cupping is one manifestation of the pathophysiology of glaucomatous damage, but is not the pathophysiology itself.
- A shallow form of cupping is nonspecific and can be expected to occur in all forms of optic neuropathy. Although the clinical appearance and behavior of the neuropathy of glaucoma can vary and include shallow forms of cupping, the pathophysiology of glaucomatous damage classically involves a deep form of cupping, which is a manifestation of ONH connective tissue damage and deformation. The variable appearance of the ONH in all optic neuropathies is the predictable result of ONH tissue biomechanics.
- As our clinical tools for characterizing ONH biomechanics improve, so too will our ability to understand normal ONH aging and its contributions to the clinical behavior and susceptibility of the ONH.

Acknowledgements Portions of this chapter and its figures appeared in the following article and are used with the permission of the *Journal of Glaucoma*:

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