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—◆—
Opthalmology

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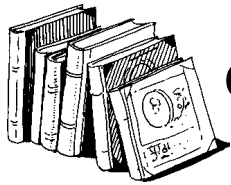
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Commentaries

Medical History

In my medical school training taking a comprehensive medical history was sacrosanct. We had to memorize a huge list of symptoms for each organ system and ask every patient about every symptom in the specified order. As a resident in a medical specialty I still had to fill out a form, but it was less complete.

Houston Merritt, MD, sole author of *Merritt's Textbook of Neurology*, and one of the great clinicians of the twentieth century, on the downside of his prowess, but still teaching third-year medical students in a weekly conference when I was a student, was renowned for his ability to extract, like Sherlock Holmes, the important nuggets of a case, leaving the chaff behind as needless, confusing facts. His style of listening to a case presentation, then tapping a reflex, or asking one question, or checking the eye movements, then pronouncing the solution, was legendary.

"Giant basilar artery," he proclaimed.

"A giant basilar artery aneurysm?" he was asked.

"What else could it be?" was his response, in the era before CT and MRI imaging made such questions irrelevant.

When I moved to Rhode Island I met an excellent dermatologist who told me that he didn't like to listen to the medical history. I laughed. This was inconceivable. He said it was usually a waste of time. "When I tell the residents that I don't want to hear the history, they think I'm joking. It takes them a while to realize that I'm serious. If I want to know something I'll ask. Otherwise I just want to see the lesions."

In my area of neurology, Parkinson's disease and movement disorders, unlike the case for epilepsy or cerebrovascular disease, the history generally isn't very useful either. Sometimes it is, of course, and I am still a diligent taker of historical data.

In the November issue of *Mayo Clinic Proceedings*, an article was published which, to me was a landmark for creativity and utility (Newman-Toker DE et al. Imprecision in Patient Reports of Dizziness. . . *Mayo Clin Proc* 2007;82:1329) It was like a step into another dimension, a sort of meta-medical analysis.

This article examined the value of the medical history in the evaluation of the dizzy patient and concluded that it was relatively useless ("the quality of the patient's dizziness symptoms should be given less diagnostic weight than it currently receives.").

This groundbreaking report evaluated ER patients at a Johns Hopkins-affiliated Hospital complaining of "dizziness." Dizziness, is, of course, a common problem in the ER, and a challenge to the clinician because of its many meanings. It is generally subdivided into four classifications: vertigo, hypotension, disequilibrium, and "nonspecific." It is so poorly defined that I do not allow housestaff or students to use the term unless quoting the patient, since the term doesn't even point to an organ system at fault (inner ear, cardiovascular, gait instability, peripheral neuropathy, metabolic or drug effect, etc). The goal of the study was to learn how to classify the symptom. Their findings were as follows. Patients used poorly localizing adjectives like "woozy" and "empty." They generally used more than one term to describe their sensation, endorsing symptoms from different subtypes in the classification into etiologies. Of those "who did not identify vertigo, spinning, or motion" when asked to choose from a list of symptoms, 70%...endorsed a sense of room spinning..." Most impressive to me was a test for reliability in which patients were asked, after a mean time delay of only six minutes, the same questions about their symptoms and only 52% were consistent.

In the same month, an article in *Neurology*, the largest circulation American neurology journal, compared patient self-report for seizures, and actual seizures, measured with complete observation in a seizure ward, and found that patients underestimated their spells, missing 80% of certain types of seizures (complex partial seizures).

Twenty years ago I worked part-time at Rhode Island's Institute for Mental Health (now the psychiatric branch of Eleanor Slater Hospital) as the neurology consultant for hospitalized psychiatric patients. I did this because of my interest in studying drug-induced move-

ment disorders, one of which was akathisia, the syndrome of motor restlessness. It may seem obvious to the reader, but wasn't to

me at the time, that studying a subjective phenomenon in people who were seriously mentally ill, taking medications that slowed their thought processes, was not going to be a very productive experience. And it wasn't, so I gave it up. People who were restless one minute weren't the next and even reported that they never had been restless. And what did I mean by restless?

There are three points in this essay. The first is the importance of Humpty Dumpty's time-honored declamation, that "Words mean exactly what I want them to mean, nothing more, nothing less." The second is that the medical history needs to be taken for what it's worth which is often not face value, sometimes valuable, sometimes irrelevant or even obfuscatory. While it is an error to discount the reports of the patient and family, it can be equally counterproductive to base too great a reliance on it. Thirdly, there is a need for studies of the process of medical practice. We need to better understand when the history is useful, and when not; when to rely on objective (usually expensive) tests, and when to let our judgment be our guide (medical, not legal). There is a reason that certain symptom complexes are more challenging than others. It is because people are not machines, and we experience our aches and pains in different ways.

There are reasons that computers will never take over from doctors. Dizziness is one of them.

— JOSEPH H. FRIEDMAN, MD

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Can Privacy Survive In the Brave New World?

Privacy is an old word describing the condition of being withdrawn from the company of others or, alternatively, portraying a place of concealment and seclusion. These past definitions have now given way to a broader meaning: to define a personal form of human liberty. And there are few liberties more fervently, more deeply held by Americans—or protected more assertively—than their right of privacy. The privilege of insulating one's thoughts, one's living space, one's beliefs and apostasies, one's integrity, one's body, one's very individuality represents, for many, the bedrock of fundamental freedom. And yet words such as privacy and individuality are nowhere encountered either in the Declaration of Independence or in the Preamble and first ten Amendments of the US Constitution. Synonyms such as "liberty", "freedom of speech" and "the right of the people to be secure in their persons" abound but privacy, as the innermost sanctuary of liberty, is not expressly mentioned.

Privacy must be distinguished from secrecy. Privacy is the nourishing of one's inner thoughts to make them worthy of guarding. Secrecy is the building of a protective wall to keep outsiders from intruding—whether or not that which is guarded is worth guarding.

Of man's many possessions, his personal thoughts must have a protected sanctuary called privacy. Privacy by itself is meaningless if it doesn't hold something to be held private; empty privacy, like an empty vault, holds nothing worth protecting. Privacy must safeguard something of substance and it then represents the culmination of a lengthy process. Before there is freedom of speech, for example, there must be freedom of thought. For unencumbered thought to be defensible it must incubate over time, like a defenseless babe, until it can uphold itself. And thinking one's independent thoughts, some perhaps novel or nonconforming, represents hard labor since it is unaided by the comforting ideas of the majority. Even the problem with heresy requires that one has to think out, without help, one's own unorthodoxies.

Some nations cherish the traits of privacy, individuality and nonconformity. Santayana observed that England was a paradise of individuality, eccentricity, heresy, anomalies, hobbies and humors. And while the oft-quoted line, "For a man's home is his castle," was originally professed in Latin, it was first uttered as policy in England in 1644. Other nations, however, find privacy a deeply suspicious, alien quirk, with the cult of individuality to be suppressed rather than sheltered.

Three ancient professions—clergy, law and medicine—intrude upon the privacy of their constituents. But in each instance there is a solemn pledge to honor the secrecy of that which is disclosed whether it be in the act of confession, the discussions between an attorney and client or the many personal secrets that a patient will share with his physician.

In medicine the bond of secrecy harkens back 2,400 years when novitiates in the Aesclepians, the ancient guild of Greek physicians, took a solemn pledge prior to membership, a covenant now called the Hippocratic Oath. Beyond mere moral sanction, it was a binding oath upon its members. The following statement appears in this brief pledge: "And whatsoever I shall

see or hear in the course of my profession, as well as outside my dealings with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets." It bound physicians to protect the right of privacy, but it also frowned upon gossip in a non-medical context.

To this day, newly graduating physicians take this solemn oath [or some revised oath] bearing the same promise to uphold privacy. Yet some promises give way to what society calls "practicality." In decades past, there was just the patient, the attending physician and an unstated, shared bond of secrecy. Today, there are many intruders into this partnership-of-secrecy including clinical laboratories, imaging facilities, electrophysiological centers, countless accountants and clerical personnel—and hovering over all, are the insurance companies who pay for all of these diverse clinical resources. Thus, instead of a private compact between two, there is an Orwellian nightmare with a participating cast of thousands despite the desperate efforts of all concerned to protect the tattered remnants of patient-privacy.

The forensic sciences have accelerated the drive to diminish privacy and positively identify each person's DNA and fingerprints, innocent or not. Some have suggested that the poetry engraved on the base of the Statue of Liberty now be appended to: "Give me your tired, your poor, your fingerprints." And the future may hold only a life of increased transparency with succeeding generations deploring their kinship with the goldfishes.

The diversity of views on the merit of privacy is reflected in the many, often conflicting, meanings imparted by the word "privacy." In classical usage—as seen in cognate words such as privy and privilege—privacy meant a highborn, empowering status surviving in entities such as the Privy Council. Somewhere in the middle are newer words such as privatization. And at the lower end of the spectrum are such derivative words as privation suggesting a divestment of something rather than an act of addition or strengthening. And in modern armies, indeed, is there any rank lower than private ?

— STANLEY M. ARONSON, MD

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CORRESPONDENCE

e-mail: SMAMD@cox.net



New Strategies for Common Eye Diseases

Elliot M. Perlman, MD

This edition of *Medicine & Health/Rhode Island* deals with several recent advances in ophthalmology. I proposed these topics to Joe Friedman, the editor, and then solicited two of my colleagues to add their input. My purpose was twofold:

1. I was inspired by the contributions of time and effort that our colleagues have been making to this journal. With the ever-increasing pile of unread eye journals accumulating on my desk, I still manage to peruse *Medicine & Health/Rhode Island*. The articles are appropriately geared to the Rhode Island physician readership and serve to enlighten me about the progress in other fields of medicine. In one of the monthly editorials the editor noted that, "We receive some unsolicited material, but not a lot. We encourage these." I was encouraged and decided to put together this issue.
2. The practice of ophthalmology has drifted farther and farther from the practice of mainstream medicine, not just in what we do, but also where we practice. Our specialty is virtually all outpatient-based. With most of us operating in ambulatory surgicenters and seeing patients only in our private offices, our physical presence in a hospital corridor is becoming a rarity. We don't interact regularly with our non-ophthalmology colleagues. Consequently, I was hoping to bridge the gap a little and let other physicians know how far we've come in ophthalmology. The topics I've chosen are those that I believe other physicians will find helpful in relating to their patients with common eye problems.

Presbyopic Intraocular Lenses discusses the exciting developments in what undoubtedly will become the standard of care in cataract surgery. *Endothelial Keratoplasty* highlights a technique of corneal transplant that is already replacing the method we have been using since 1905! *The Quest to Conquer Age-related Macular Degeneration* by Richard G. Bryan, MD, discusses how far we've come in averting blindness in our burgeoning elderly population. Lastly, *Clinical Update on Optic Neuritis and Multiple Sclerosis* by Marjorie A. Murphy, MD, discusses new management strategies in dealing with a common, often devastating disease in young people.

Elliot M. Perlman, MD, is Clinical Associate Professor of Surgery (Ophthalmology), at the Warren Alpert Medical School at Brown University.

CORRESPONDENCE

Elliot M. Perlman, MD
Rhode Island Eye Institute
150 East Manning St.
Providence, RI 02906
Phone: 401-272-2020
E-mail: elliottperlman@cox.net

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The guest editor and author has no financial interests to disclose.



Endothelial Keratoplasty

Elliot M. Perlman, MD

There are about 40,000 full-thickness (also called **penetrating**) **corneal transplants (PKP)** performed in the United States each year; 68% are done because of failure of a single cell layer: the corneal endothelium.¹ (Figure 1)

The cornea at birth has about 400 000 hexagonal-shaped endothelial cells forming a monolayer lining the posterior cornea. Like cells in the central nervous system, the endothelium cannot undergo cell division; thus, there is a slow loss of endothelial cells throughout life.² Certain diseases, most notably Fuchs' endothelial dystrophy, cause a premature loss of endothelial cells. Ocular trauma, especially cataract surgery, can also be responsible for significant loss of endothelial cells.

The function of the endothelium is to maintain the clarity of the corneal stroma. The normal corneal stroma is clear, compact, and contains very little water (78% water vs. 98% water for the opaque sclera). Collagen fibrils run limbus-to-limbus in the stroma and are stacked in a very regular fashion (Figure 2a). The fibrils are surrounded by an extracellular matrix of hydrophilic glycosaminoglycans. This structure gives the cornea its unique optical clarity. The normal endothelial cells are connected to each other only by focal tight junctions and thus form a "leaky" barrier to aqueous humor percolation into the stroma. The endothelial cells are highly metabolic. They utilize Na⁺/K⁺ ATPase ion pumps to pump solutes out of the stroma; the water leaves the cornea following along the osmotic gradient.²

When endothelial cell function is compromised, the corneal stroma becomes edematous and thickened. The evenly packed collagen fibrils spread apart and incoming light is scattered. (Figure 2b) Visual acuity drops. The only solution is to replace the endothelial cells. A reasonable question to ask is: why do we need to transplant all the layers of the cornea just to replace a single cell layer? The answer is that PKP has several advantages: it is relatively easy to do; it works for all types of corneal disease (not just endothelial disease); and it has the potential to produce very good visual results.

Traditional PKP is done by punching out a full-thickness corneal button from donor tissue, typically about 7.5 to 8.5 mm in diameter. A similar full-thickness trephination is done on the patient's cornea, and the donor button is sutured into the opening using 10-0 monofilament nylon. The sutures can be running, interrupted or a combination of these.

There are, however, significant problems with PKP. It typically takes 6 months to a year to obtain optimal vision after PKP. Sutures are usually removed selectively to improve vision over the course of multiple visits during this period. Not only is the optical clarity of the grafted cornea necessary, but also its con-

tour is important. The cornea does two-thirds of the refraction of the eye. If the cornea is excessively steep, the eye becomes myopic; if it is excessively flat, hyperopia results. If the contour is anything but perfectly spherical, astigmatism will be present. Thus, a grafted eye can be very myopic or hyperopic, as well as have excessive astigmatism. Despite careful attention to these details, as many as 10% of patients cannot see well after PKP—even with a perfectly clear graft—because the required glasses would be too thick and incompatible with the spectacle lens needed for the unoperated eye.

More serious problems can develop from suture-related problems: suture

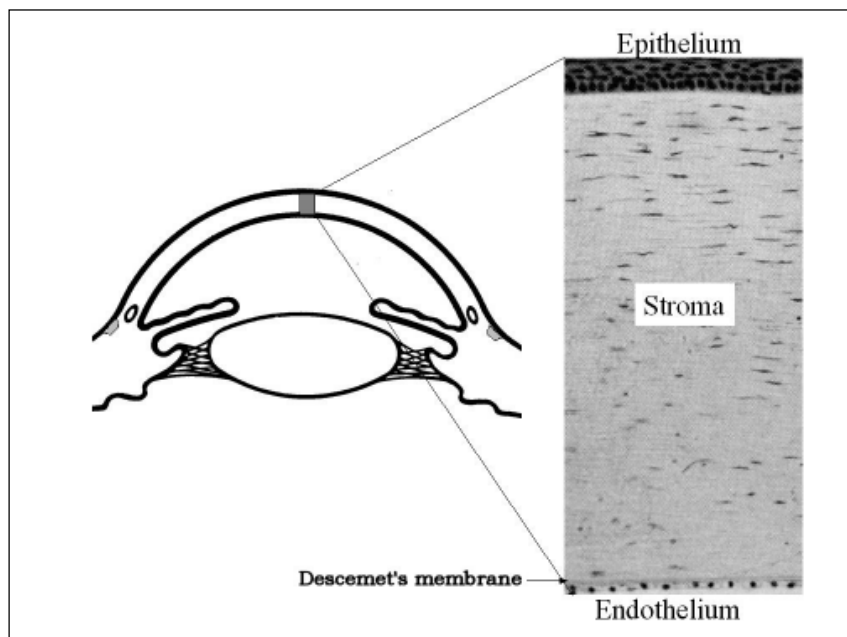


Figure 1. Corneal anatomy.

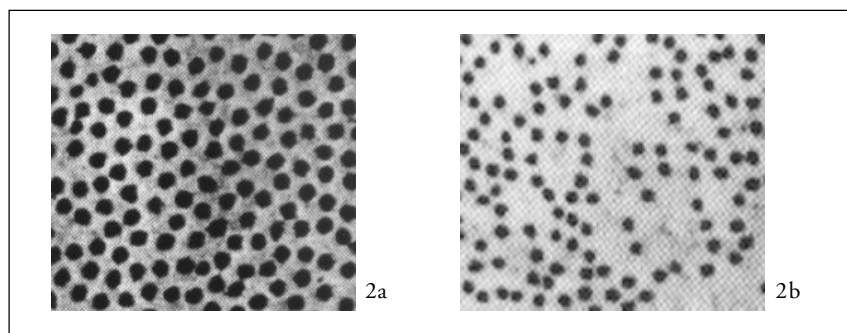


Figure 2a. Cross-section of collagen fibrils in normal corneal stroma (original magnification x51800). Figure 2b. Cross-section of collagen fibrils in an edematous cornea (original magnification x46700).

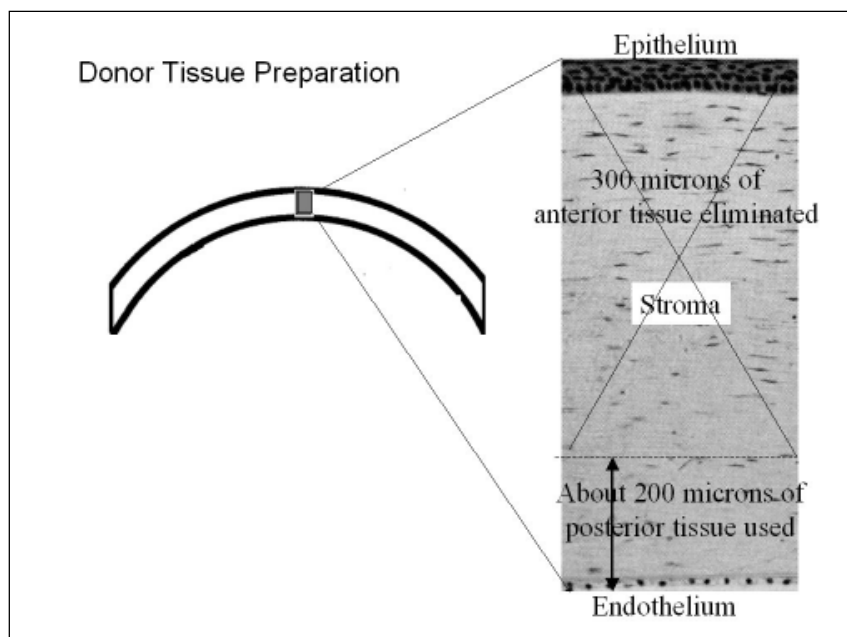


Figure 3. DSEK: donor tissue preparation.

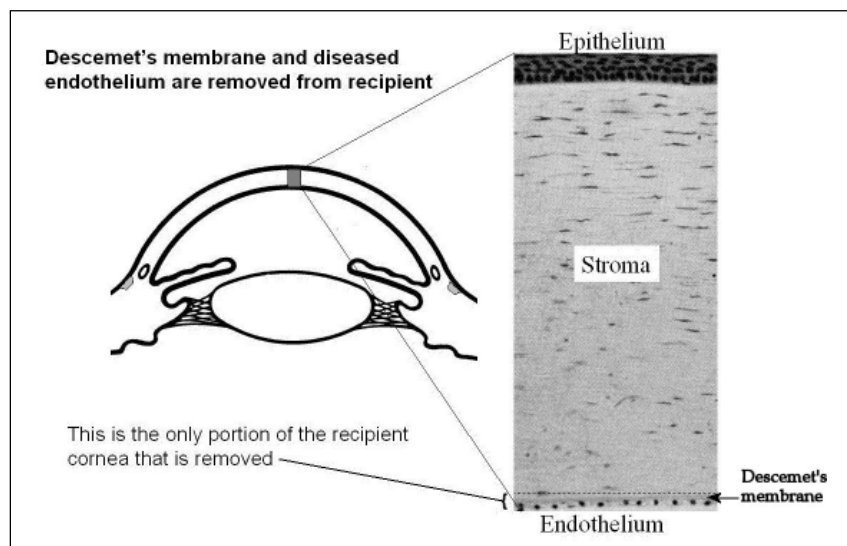


Figure 4. DSEK: recipient cornea preparation.

breakage causes discomfort and patients need to have them removed, leading to many unscheduled office visits. Sutures can become infected, leading to corneal abscess and even endophthalmitis with profound loss of vision. Another serious issue with PKP is that full-thickness grafts

permanently weaken the cornea. Blunt trauma to the eye can lead to wound rupture, even years after the transplant. The intraocular contents (iris, lens etc) can prolapse out of the eye if the rupture is large enough, leading to permanent loss of vision.

In the past several years, recognizing the inherent problems with PKP, corneal surgeons have been working on techniques to transplant only the deeper layers of the cornea. Called collectively endothelial keratoplasty, these procedures replace only the innermost portion of the cornea (posterior stroma, Descemet's membrane and the endothelium).

A variation of endothelial keratoplasty is called DSEK (**Descemet's Stripping Endothelial Keratoplasty**).³ In DSEK, the donor tissue is prepared by placing the donor cornea in an artificial anterior chamber and securing it in place. A rapidly oscillating blade called a keratome is used to remove the top 60-70% of the donor cornea (epithelium and 60-70% of the stroma), which is discarded. (Figure 3) The remaining 30-40% of the cornea is placed in a curved Teflon block and a large disk is punched (typically 8.5 to 9.0 mm diameter).

DSEK is done with IV sedation, either with a peribulbar injection of anesthetic or topical anesthesia. A small incision is made at the limbus of the patient's cornea, and a small hook-like instrument is used to strip off and remove the diseased Descemet's membrane and endothelium. (Figure 4) Then, another 4 to 5 mm incision is made at the limbus. The donor cornea is folded like a taco and inserted into the anterior chamber of the patient. (Figure 5a,b) The incision is closed with 2 10-0 nylon sutures. An air bubble is injected between the leaves of the taco to unfold it and force it into position apposing the patient's stromal tissue. The air bubble is left in this position for 10-60 minutes to allow adherence of the donor tissue to the recipient stroma. Finally most of the air is removed (Figure 5c) and the patient is discharged home.

Over the course of the next several weeks, vision improves as the grafted endothelium begins clearing the edema

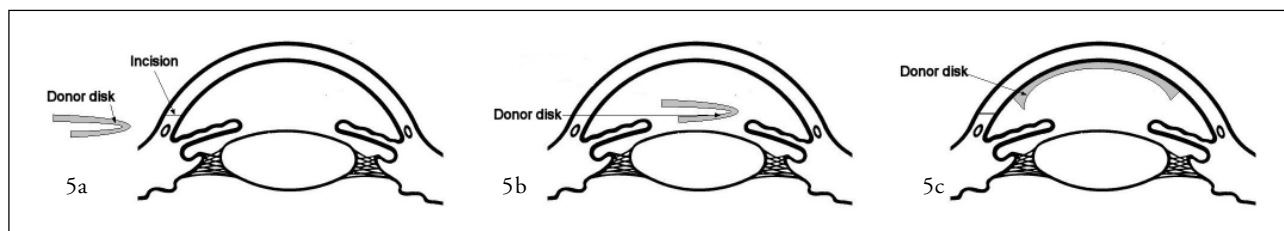


Figure 5a. DSEK: Folded donor disk outside anterior chamber. Figure 5b. DSEK: Folded donor disk inside anterior chamber. Figure 5c. DSEK: Donor disk adhering to recipient stroma.

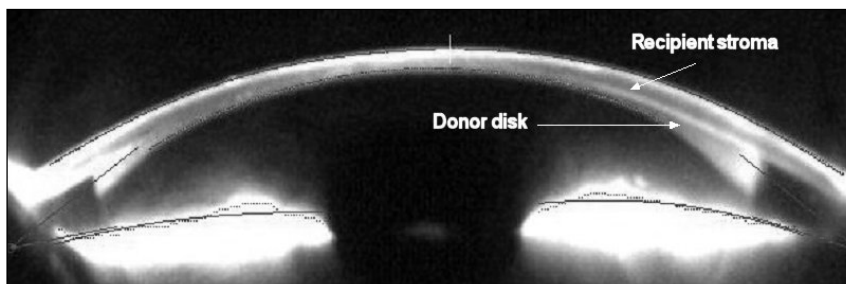


Figure 6. *In vivo* imaging of eye after DSEK.

from the recipient cornea. The 2 sutures are removed at 6 weeks. Visual recovery can come as soon as 1 month, but typically takes several months. This is still considerably faster than after PKP.

Because the incision is small and is located at the limbus—not directly in the cornea—the refractive status of the eye is similar to what it was before the cornea became edematous³. Not infrequently, the DSEK patient can see well without any glasses—a distinctly unusual event after PKP. DSEK essentially eliminates suture problems. Because the corneal incision is small and peripheral, the corneal mechanical strength is nearly normal, and the threat from blunt trauma is much less.⁴ The donor disk in DSEK has a larger diameter than a typical PKP graft, so the number of endothelial cells transplanted by DSEK is 15%-26% higher. Another intriguing possibility is that the location of the DSEK disk (in the anterior chamber) is farther from the limbal host cells that are involved in graft rejection. A recent study showed a lower graft rejection rate in DSEK patients compared to PKP patients (7.5% vs. 13% after 2 years).⁵

As the procedure is relatively new, there are still post-operative problems. The donor disk may not stay adherent to the host stroma, and an air bubble might have to be placed back into the anterior chamber as an office procedure. Also, perhaps because of the extra manipulation of the donor tissue, there is a higher incidence of primary graft failure (the donor disk fails to clear the edematous cornea, and a re-operation would be required). Another concern with DSEK is that it is difficult to end up with a perfect “20/20” result. This mild limitation may be due to the fact that there is an interface present (between the host stroma and the donor stroma) (Figure 6) or that the recipient’s stroma may not be

totally transparent, even after the excess hydration is gone.⁶ Lastly, the long-term results of endothelial keratoplasty—and whether the grafted endothelium survives at least as well as with PKP—must still be evaluated.

Endothelial keratoplasty has revolutionized corneal transplantation. It is already replacing PKP in the treatment of corneal endothelial disease. Some corneal surgeons are making the incisions small enough that they do not require sutures. Others have been working on transferring just Descemet’s membrane and the endothelium, a process hampered by the fragility of this thin tissue preparation. The first report of a successful transplant of this type was recently published.⁷ Lastly, laboratory research on endothelial cell regeneration may some day allow removal of a recipient’s remaining endothelial cells, increase the cell density *in vitro* and then re-transplant them back into the recipient, thereby avoiding graft rejection.⁴

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Elliot M. Perlman, MD, is Clinical Associate Professor of Surgery (Ophthalmology), at the Warren Alpert Medical School at Brown University.

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Presbyopic Intraocular Lenses

Elliot M. Perlman, MD

"Now, thanks to ReZoom...I've got my zoom back!"

– Gary Player,
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Although this sounds more like an ad for Viagra®, it refers to one of the new FDA-approved **intraocular lenses (IOLs)** which correct presbyopia.

In the not-too-distant past (the late 70s), during my ophthalmology residency, we waited until cataracts got "ripe" before we operated. The reason was not related to the technical difficulty of the surgery, but rather because the visual result was so poor that a patient would be better off with moderately dense cataracts than coke-bottle-like aphakic spectacles. These thick lenses would distort and magnify the image as well as cause such peripheral vision problems that even walking with them was dangerous!

We have come a long way since, not just in the technique of cataract surgery, but also in the method we use for visual correction afterward. IOL implantation at the time of cataract surgery has become the standard of care for the past 25 years. Advances in these lenses were prompted by advances in the techniques used for cataract surgery itself. Initially the lenses were not flexible, requiring a large incision for insertion. At that time, prior to the widespread use of phacoemulsification for cataract surgery, cataract incisions had to be much larger (5 to 7 mm) to allow removal of the intact nucleus (center) of the cataract.

Modern cataract surgery utilizes phacoemulsification. In phacoemulsification, a small titanium or steel tip on a hand piece

is inserted into the anterior chamber through a small incision (2.2 to 2.75 mm) in the peripheral cornea. The tip vibrates at ultrasonic speeds to break up the cataract into very fine pieces, which are aspirated out of the anterior chamber, usually through a port in the same hand piece. Because phacoemulsification cataract surgery can be done through a very small incision, intraocular lens manufacturers began developing foldable intraocular lenses. First introduced about 15 years ago, they are made of a plastic polymer, such as silicone or acrylic.

A typical cataract operation today is done under topical anesthetic with IV sedation as needed. There is usually no need to stop any anticoagulants or anti-platelet medication. After the peripheral corneal incision is made, the surgeon creates a circular opening in the anterior capsule of the lens (capsulorhexis) to allow access to the cataractous portion of the lens. While the surgeon is viewing the procedure through an operating microscope, the cataract is broken up and removed using a phacoemulsifying hand piece.

Cataract surgery removes most of the natural lens of the eye. (Figure 1a) What remains is the posterior capsule of the lens and part of the anterior capsule, a configuration which resembles a bag, often called the capsular bag. (Figure 1b) To correct the vision after cataract surgery, the foldable IOL is placed into the capsular bag. (Figure 1c). To replace the convex natural lens, the IOL has a convex shape. The thicker the IOL is, the more converging power the lens has. Until recently, this lens has been a monofocal lens, meaning that it has only one power and focuses in only one plane. The portion of the IOL that does the focusing is called the optic, which is usually circular and about 6 mm in diameter. The IOL is placed into an inserter resembling a small peashooter, which is used to position the lens into the capsular bag. The IOL does not have to be sutured into place. Because of the small incision size, suturing of the incision is not generally required either. The entire cataract operation with IOL implant takes about 20 minutes.

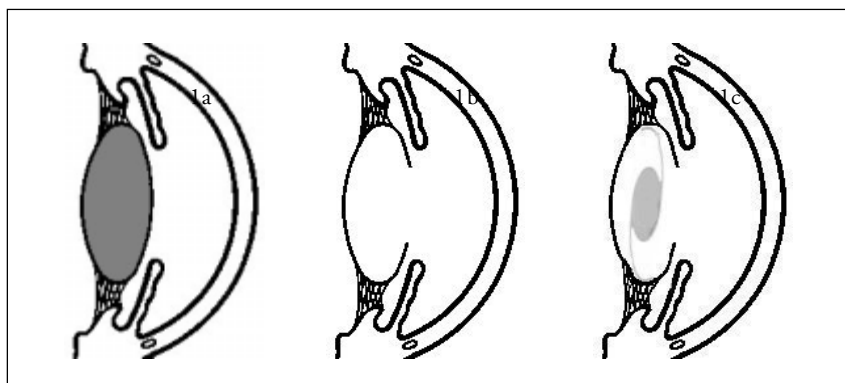


Figure 1a. Eye with a cataract.

Figure 1b. Eye after cataract surgery, showing capsular bag (C-shaped structure).

Figure 1c. Eye after cataract surgery with intraocular lens.

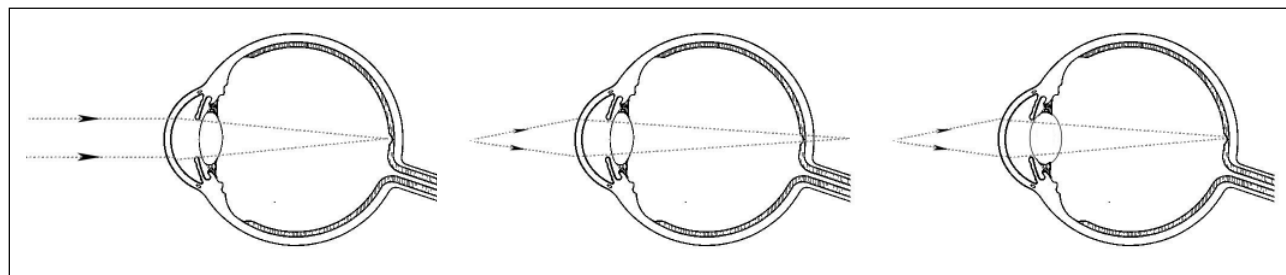


Figure 2a. Distance vision in the emmetropic eye. Figure 2b. Near vision without accommodation.

Figure 2c. Near vision with accommodation.

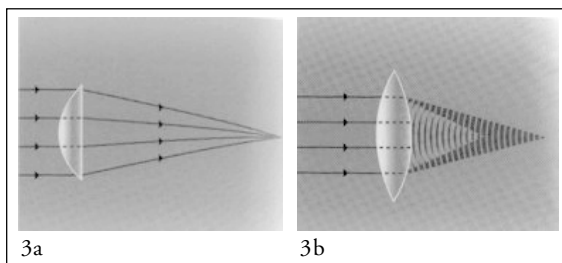


Figure 3a. Monofocal lens focusing.
Figure 3b. Multifocal lens focusing.

Part of what makes modern cataract surgery so successful is the accurate determination of the IOL power needed to permit the pseudophakic patient (a patient who has had a cataract operation and IOL implant) to see well in the distance with little or no spectacle correction (emmetropia). When the natural lens of the eye is removed, the only converging lens in the eye is the cornea. The steeper the cornea is, the more powerful is its converging power. There are a number of instruments that can very accurately measure the curvature (and thus the power) of the cornea. The only other parameter we need to determine the correct IOL power to implant is the axial length of the eye (the length of the eye from the front surface of the cornea to the retina). We also know how far the IOL will be from the retina. With this information, it is a straightforward calculation to determine the exact power the IOL must be to achieve emmetropia.

It should be apparent from the above discussion that we can select the correct IOL power to eliminate myopia at the time of cataract surgery. And, indeed, this is the case.

Modern cataract surgery is a form of refractive surgery, and many previously existing refractive errors can be corrected at the time of cataract surgery. If patients have significant astigmatism preoperatively (the cornea is shaped more like the surface of a spoon rather than a sphere), they would still need

glasses in the distance, despite perfectly correct monofocal lens placement. Many ophthalmic surgeons use incisions in the periphery of the cornea (limbal relaxing incisions) at the time of cataract surgery (or after the surgery) to minimize the astigmatism.

Implantation of a monofocal IOL at the time of cataract surgery can allow the elderly eye with a cataract to have the visual quality of a middle-aged (presbyopic) eye without a cataract. The remaining issue is that presbyopia still exists, and virtually all patients who have had cataract surgery and see well in the distance without glasses will still need reading glasses.

To understand how presbyopic IOLs work, it is necessary to review some basic optics in the normal eye.² In the emmetropic eye, the incoming rays from a distant object are parallel and are focused by the cornea and natural lens to a point on the surface of the retina. Both the cornea and lens act as converging lenses. (Figure 2a) When the same emmetropic eye views a near object, the incoming rays from the near object are actually diverging when they strike

the surface of the cornea and lens. Without the effort of accommodation, the rays would focus somewhere behind the retina and the object would appear blurry. (Figure 2b) Accommodation involves constriction of the ciliary muscle, which allows the lens to become thicker (more powerful) and thus cause more convergence of the rays. With the proper amount of convergence, the rays will be focused as a point on the retina. (Figure 2c)

As we age, the lens of the eye becomes more rigid. Thus, accommodative effort becomes less effective. This progressive loss of accommodation—like death and taxes—is almost universal. It is called presbyopia (“old eyes”). By the time most of us are 55 years old, we’ve lost it all, and reading glasses are a necessity.

The monofocal IOL has made cataract surgery one of the most successful and satisfying operations in all of surgery. In the past several years, however, with the introduction of presbyopic IOLs, cataract surgery results have taken another quantum leap forward, making the pseudophakic eye even more like the eye of a young phakic person.

The Food and Drug Administration (FDA) has approved 3 presbyopic lenses: The *ReZoom* Lens by AMO; the *ReStor* Lens by Alcon and the *crystalens* by eyeonics. The *ReZoom* and *ReStor* lenses are multifocal IOLs; the *crystalens* is an accommodating IOL. In contrast to a monofocal lens (Figure 3a), which focuses light at one plane, a multifocal lens focuses light at more than one plane simultaneously. (Figure 3b) The *ReZoom* Lens has a series of 5 concentric rings, some of which focus at near (14” from the eye) and some of which focus in the distance. The central 2.5 mm of the lens focuses for distance. (Figure 4) The *ReStor* Lens has an “apodized diffractive center”. This lens utilizes sophisticated diffractive optics in its central 3.6 mm to cause light to focus in the distance and quite close simultaneously (about 10” away from the eye). (Figure 5)

I believe a more accurate description of these 2 multifocal lenses would be the term “bifocal lens”, since the lenses actually have only 2 focal points (distance and near). At any given time, some of the light passing through a multifocal lens will be coming from distant objects, and some will be coming from near objects. Which object the eye sees clearly is partially dependent on the size of the pupil at the time. For instance, in a bright light, the

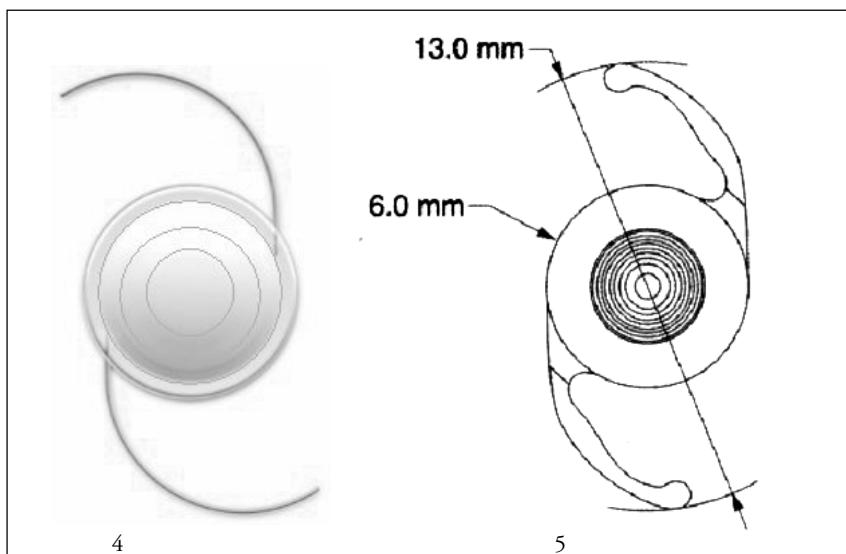


Figure 4. *ReZoom* multifocal intraocular lens.
Figure 5. *ReStor* multifocal intraocular lens.

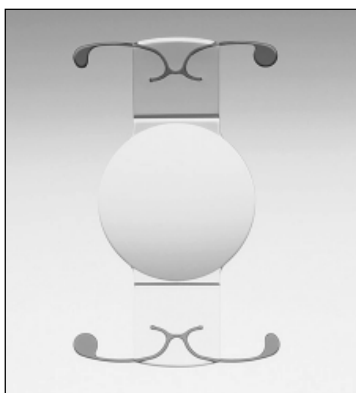
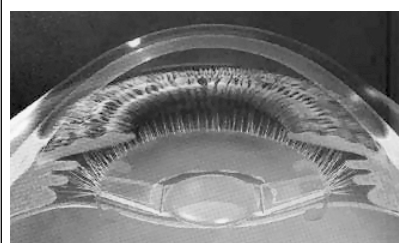


Figure 6. crystalens accommodating intraocular lens.

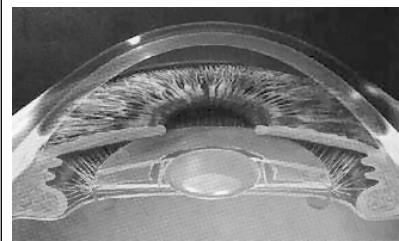
pupil will be constricted (e.g. less than 2.5 mm). The ReZoom lens will be seeing mostly a distant object in that lighting, since the central 2.5 mm of that lens focuses for distance. The ReStor lens could be seeing both distance and near with that pupil size^{3,4}.

An interesting aspect of these multifocal lenses is that the brain must be “trained” to sort out distance and near objects. This learning process, which can take several months, is greatly aided when both eyes have multifocal lenses implanted; hence, bilateral cataract surgery is preferred when these lenses are used^{3,4}. According to Alcon’s studies,⁵ 80% of patients with bilateral ReStor lenses never need glasses.

One of the difficulties with multifocal lenses is that glare and haloes may be noticeable under subdued lighting (e.g. night driving). Under those circumstances, the pupil



7a



7b

Figure 7a. crystalens in a non-accommodating eye.

Figure 7b. crystalens in an accommodating eye.

is large, and both distance and near components of the multifocal lenses are functioning. In addition, since the lenses are set for either distance or near, patients may have trouble with intermediate range objects (e.g. 20”-30” away, such as computer screens, grocery store shelves, or music stands).

The crystalens, the accommodating presbyopic IOL, has a 5 mm optic and 2 haptics (“arms”). (Figure 6) The haptics each have a horizontal hinged area, which is readily flexed. The crystalens more closely resembles the accommodation of the natural lens. When the eye containing the crystalens is not accommodating, the lens focuses in the distance, similar to a monofocal lens. (Figure 7a) When the eye accommodates (when the ciliary muscle contracts), the crystalens is actually pushed forward a small amount. This movement makes the lens transiently more powerful. In addition, the whole front surface of the crystalens flexes and becomes more convex. Both these actions allow focusing on a near object. (Figure 7b)

Like the multifocal lenses, the crystalens also takes some “training” so that the patient gets used to accommodating the correct amount. It also is helpful if crystalenses have been implanted bilaterally. While accommodating IOLs may not have as much multifocal IOL problems such as glare and haloes, these lenses may not fully accommodate, and the patient may still require some form of reading glasses.

The entire cost of traditional monofocal IOLs (about \$50-\$150) is covered by Medicare (and other insurance carriers) as a part of the facility fee, and the patient has no financial responsibility. The cost of presbyopic IOLs is about \$900 per lens and is not covered by Medicare and other carriers. In addition to this cost, the ophthalmic surgeon charges an additional fee for these lenses. Although they are not technically more difficult to insert than monofocal lenses, all measurements to determine lens power must be exceedingly accurate, the ocular health must be perfect, and the cataract surgery must be flawless. Also, if patients have even a small amount of astigmatism, presbyopic lenses may not work well. Post-operative management can also be more time-consuming and may require additional refractive procedures. Patient expectations, as in patients who have LASIK (elective refractive surgery), can be extremely high.

The total cost borne by the patient for the use of these lenses is typically \$2000 to

\$2500 per eye. Medicare and other insurance carriers consider presbyopic lenses “cosmetic” and do not pay for them. Thus, the patient – for the first time in many years – has a fair amount of out-of-pocket cost to have bilateral cataract surgery with presbyopic lenses implanted. As I alluded to in the beginning of this article, presbyopic IOL companies are pitching their ads to the Viagra®-age consumers: the baby boomers. According to the presbyopic IOL companies,⁶ 78 million Americans were born between 1946 and 1964. Every 7 seconds, a boomer reaches age 50, the average age. There is a high overlap between this age group and the appearance of cataracts: 33% of the population between the age of 45 and 64 already have formation of early cataracts or about 13 million people in the US. Favoring the potential wide-spread use of presbyopic IOLs are financial statistics regarding this age group: baby boomers account for more than half of US spending, and people over the age of 50 account for more than half of all health care spending⁵.

Presbyopic IOLs can give the cataract patient vision similar to someone under 40 years old and, indeed, patients can “get their zoom back.” The same cataract operation and presbyopic lenses are even being used in patients without cataracts (so-called “clear lensectomy”) to correct refractive errors as well as presbyopia. With many new presbyopic lenses being developed, it is possible that the use of these lenses may supplant LASIK as the predominant refractive procedure, even in patients without cataracts.

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Elliot M. Perlman, MD, is Clinical Associate Professor of Surgery (Ophthalmology), at the Warren Alpert Medical School at Brown University.

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Elliot M. Perlman, MD, has no financial interests to disclose.

The Quest To Conquer Age-Related Macular Degeneration

Richard G. Bryan, MD

A new era has dawned in the treatment of the leading cause of irreversible vision loss in elderly patients: **age-related macular degeneration (AMD)**, a disease afflicting at least 1.75 million people in this country. That number is likely to double by 2030. Until recently, our treatments were palliative at best, but we now have the capacity to stabilize and even reverse vision loss in many patients.

AMD affects the macula, the part of the retina responsible for sharp central vision. There are two forms: dry or non-exudative AMD and wet or exudative AMD. Overall, 90% of patients have the dry type, characterized by the accumulation of submacular deposits called drusen. (Figure 1) Typically, the drusen may be consistent with good vision but are precursors to vision loss. About 10% of patients will lose vision, most commonly from conversion from dry AMD to wet AMD. The characteristics of the drusen determine the risk of progression: from <5% risk over 5 years for smaller low-risk drusen to 50% over 5 years for large, high-risk drusen with pigmentary changes.

DRY AMD

Most patients with dry AMD have fairly good vision, although there are often subtle defects such as the loss of contrast sensitivity, blank spots in the vision, or slight distortion. Despite efforts to eliminate the drusen with a light laser treatment or drugs, no interventions have been shown to be useful as a treatment. However, much focus has been placed on diet and supplements as a preventative for vision loss.

The best study to date is the **Age Related Eye Disease Study (AREDS)**¹ published in 2001. This large multi-center randomized trial sponsored by the National Eye Institute was designed to address the issue of diet and antioxidant supplements for AMD. This study showed that supplementation with antioxidants in high doses slows down the risk of conversion to wet AMD by about 25%. The vitamins used were beta-carotene 15mg, vitamin C 500mg, vitamin

E 400IU, and Zinc 80mg (with 2mg of copper to prevent zinc toxicity). The vitamins were well tolerated with the exception of some GI upset. The AREDS II study is now in the recruitment phase to look at the role of lutein and omega-3 fatty acid supplementation in preventing advanced AMD.

The patients in the AREDS study filled out a dietary and lifestyle questionnaire. This information, along with other studies, has given us a picture of patients at higher risk for advanced AMD. Overall, a diet rich in fish and green leafy vegetables, such as spinach or kale, was relatively protective against vision loss. Risk factors included a diet high in saturated fats and smoking. Indeed, smokers have the highest relative risk for advanced AMD. Of course, these conclusions are just statistical associations, not shown to be causally related.

MECHANISMS FOR VISION LOSS IN AMD

Wet AMD is characterized by neovascularization in the macula, leading to hemorrhage and leakage. (Figure 2) The

mechanism of neovascularization remains unclear, but is presumably multifactorial. Most agree that several factors are important. First, there is an ischemic environment in the macula, resulting in the release of cytokines such as **Vascular Endothelial Growth Factor (VEGF)** and **Platelet-derived Growth Factor (PDGF)** that promote neovascularization. This may be due to the thickened Bruch's membrane (the innermost layer of the choroid) that prevents efficient transport of oxygen from the choroid to the retina or changes in choroidal circulation. Second, there is an inflammatory component to the neovascular membrane in histopathologic studies. This may contribute to cytokine production and further growth of the neovascularization. Its role has been validated by the effective adjunctive role that steroids play in treatment of AMD. In most cases, the neovascularization consists of fragile, abnormal blood vessels growing through breaks in the choroid and then under the retina. Because of its characteristic appearance in a fluorescein angiogram, the neovascularization is often called a neovascular membrane.

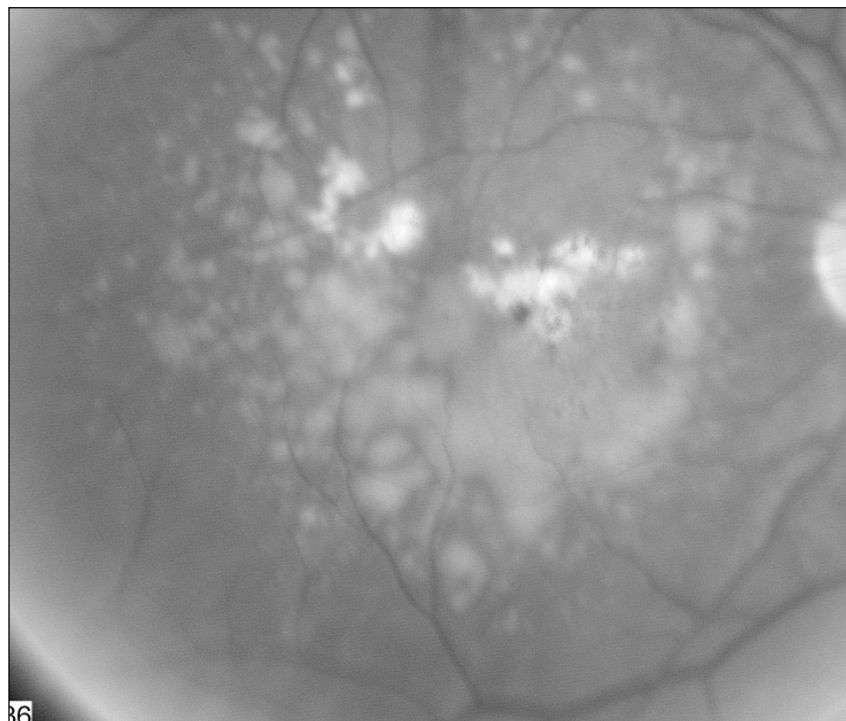


Figure 1. Eye with dry AMD



Figure 2. Eye with wet AMD

Another less common reason for vision loss is a more advanced form of dry AMD: geographic atrophy. In this case, the subretinal drusen give way to loss of the overlying retinal pigment epithelium. This is a progressive process that typically starts off-center (often without symptoms) then slowly expands to involve the central macula. This is responsible for about 10% of dry AMD patients with severe vision loss. Unfortunately, nothing can be done today to slow down or reverse the process, so I will not discuss the topic further.

EVOLUTION OF AMD TREATMENTS

Effective treatment for most patients with choroidal neovascularization was not available until recently. Destructive laser photocoagulation of the neovascular lesions was the only widely accepted treatment available until 2001, as demonstrated in the **Macular Photocoagulation Study (MPS)**. Even though the study recommended treating all well-defined neovascular membranes, laser photocoagulation was only widely used for treatment of lesions where the central macula (the fovea) was spared. This group constitutes only about 17% of newly diagnosed patients. Even with a successful treatment, the recurrence rate was at least 50%. Today, laser photoco-

agulation is still used, but only for lesions well away from the macular center.

...anti-VEGF monotherapy will probably remain the mainstay of treatment for most patients.

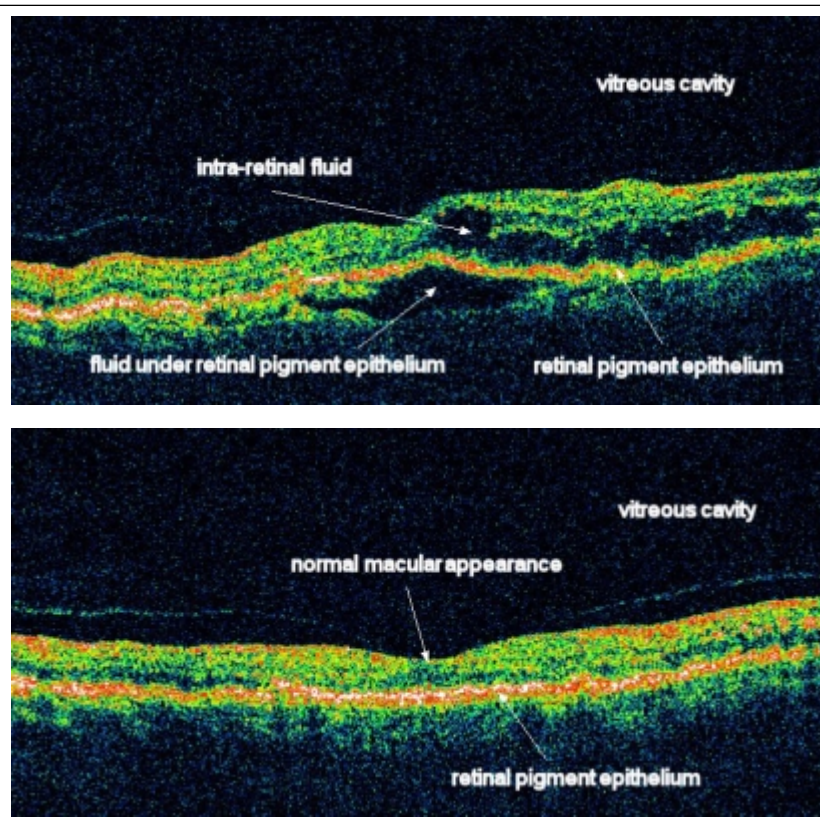
The first treatment with widespread acceptance for subfoveal lesions began in 2001 with the introduction of **photodynamic therapy (PDT)**² with verteporfin (Visudyne). This treatment involved intravenous infusion of Visudyne, a drug that selectively accumulates in leaky neovascular tissue, followed by treatment with a non-destructive laser that selectively activates the dye. The result was endothelial cell damage and subsequent closing of the neovascular complex. The treatment was somewhat disappointing, because it only slowed down vision loss rather than reversed it. A number of factors were responsible for this. First, recurrent leakage appeared in 80% of patients, requiring multiple retreatments. Second, normal choroidal circulation is also affected by the treatment, as evi-

denced by the general choroidal hypoperfusion on fluorescein angiography. After a few years of disappointing results, many retina specialists combined this treatment with an intravitreal triamcinolone injection to get a longer lasting effect (see discussion below).

The second effective treatment for subfoveal lesions was introduced in 2004. Pegaptanib (*Macugen*, OSI [Eyetech] and Pfizer Pharmaceuticals) is an aptamer that selectively blocks the 165 isoform of VEGF, the isoform most linked to pathologic neovascularization in the eye.³ This treatment takes advantage of VEGF's important role in both neovascularization and vascular permeability. It is given as an intravitreal injection every 6 weeks to chronically suppress VEGF, as the neovascular lesions have a tendency to come back once the medication is gone. (Intravitreal injection is an in-office procedure, done using topical anesthetic under sterile conditions.) The results from the Macugen trial were similar to that seen with Visudyne, leaving retina specialists dissatisfied.

A turning point was reached with the widespread off-label use of bevacizumab (*Avastin*, Genentech) in mid-late 2005 and later ranibizumab (*Lucentis*, Genentech) that was approved by the **Food and Drug Administration (FDA)** in August, 2006.⁴ These compounds are humanized monoclonal antibodies (*Avastin*) or an affinity-matured Fab fragment (*Lucentis*) that block all isoforms of VEGF. They are administered by intravitreal injection on a monthly basis for up to 2 years, chronically suppressing VEGF in the eye. With either drug, the exudation from the neovascular complex usually dries up within a month or two, leaving a smaller dry scar. For the first time, patients maintained stable vision in more than 90% and substantial improvement of vision in about 40%. It has been a remarkable advance. (Figure 3)

Because elderly patients with AMD often have cardiovascular disease, there is some concern about the safety of chronic VEGF suppression. VEGF plays a crucial role in normal vascular and neuronal maintenance. Among patients over 65 receiving standard chemotherapy and high dose *Avastin* intravenously every 2 weeks for its FDA-approved indication—metastatic colon cancer—8.5% of them



(Top) Figure 3a. Optical Coherence Tomography (OCT) showing cross-section of macula with wet AMD before treatment with intra-vitreous Avastin.

(Bottom) Figure 3b. OCT showing dramatic recovery of normal macular appearance 1 month after treatment with Avastin.

had vascular events, compared to 2.9% vascular events in patients on chemotherapy alone. These vascular events included myocardial infarction, cerebrovascular accident, accelerated hypertension, venous thrombosis, and severe hemorrhaging. Fortunately we use a much smaller dose as an intravitreal injection, in theory limiting the systemic exposure.

There are several reasons to believe that there may be a systemic risk to intravitreal injection of Avastin and Lucentis. First, systemic levels of Avastin (22 day half life) and Lucentis (half life of several hours) have been identified after intravitreal injection at usual doses. Second, VEGF is well known as an important mediator of repair of ischemic and damaged tissue.

Very little reliable data exist as to the complication rate of Avastin, as this is an off-label use that was widely adopted after a few very compelling case series were reported. A large randomized study is now in the recruitment phase to determine the level of risk, but it will be years

before data are available. Combined data from the ANCHOR and MARINA trials did not show any statistically significant increase in vascular events with Lucentis use, although this was a small study powered to determine efficacy and not uncommon complications. There was a safety signal in these trials consisting of a few more cerebrovascular events, but these did not reach the level of statistical significance. The actual risk may only come out during the post-marketing surveillance period.

Many questions remain unanswered. First, how should a patient's systemic health influence the use of Avastin and Lucentis? For example, how should a patient be treated who had a recent stroke or myocardial infarction? How about unstable angina? Since there is a documented effect of bevacizumab on wound healing, should the treatment be withheld in the peri-operative period of major surgery? Second, what is the role of the internist or cardiologist for patients who are being treated? Is there any utility to preventative therapies such as anti-

coagulation or more intensive cardiovascular monitoring in at-risk patients?

ALTERNATE TREATMENT STRATEGIES

Although the need for treatment of exudative AMD is obvious, the questions about risk necessitate long discussions with the patient and families. Most patients wish to proceed with the treatment, but some are afraid. Even those with significant cardiovascular risk factors have demanded treatment on the premise that they would rather be dead than blind. In my own practice, I am treating a retired physician with cardiovascular risk factors who had a minor stroke during a course of Avastin treatments. Even when told that I would withhold treatment due to the serious potential extra risk, he absolutely demanded that I continue. Fortunately, nothing further has happened.

An important pricing issue has recently surfaced regarding the use of Lucentis and Avastin (both Genentech products). The off-label use of Avastin by ophthalmologists has required compounding pharmacies to prepare small sterile aliquots of the 4-ml vials. The cost of a single intravitreal injection is about \$40. However, Lucentis costs about \$2000 for a single intravitreal injection. In October, 2007, Genentech sent a letter to all retinal surgeons, indicating that it planned to stop distributing Avastin to compounding pharmacies. The company cited FDA concerns about the particulate level of this intravenous product when used for intraocular injection. Also Genentech noted that Lucentis was developed and FDA-approved specifically for ocular use. This ongoing controversy may limit the availability of the much less expensive product.

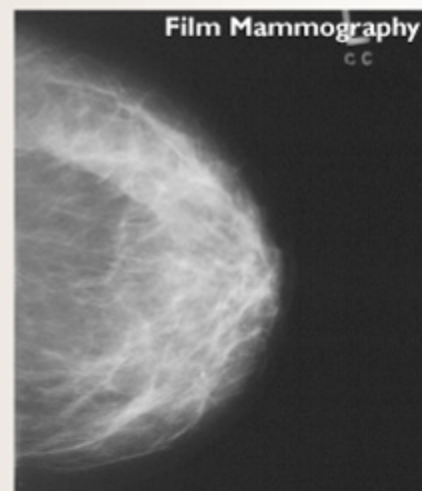
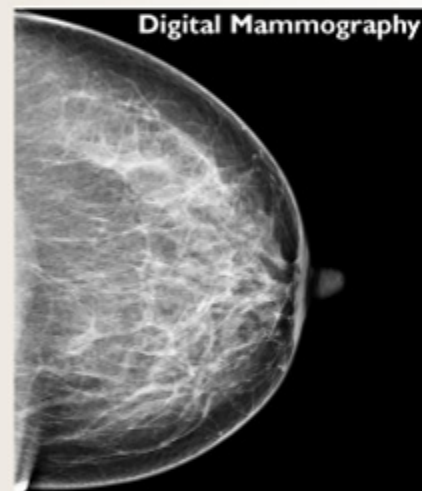
Besides systemic risks and pricing issues, there are other disincentives to Lucentis/Avastin treatment as currently recommended. The procedure itself only takes a few minutes and is minimally painful, but it must be done monthly. Each time, the patient must deal with wait times for dilation, imaging, and the procedure that may reach an hour or two. They often have to bring a family member or friend to drive them. These frequent injections are not only a tremendous burden on the patient but also on our practices. Patients we used to see a



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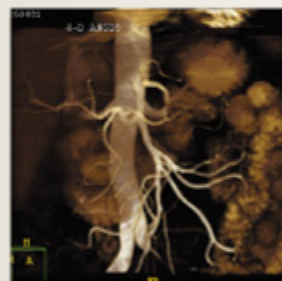
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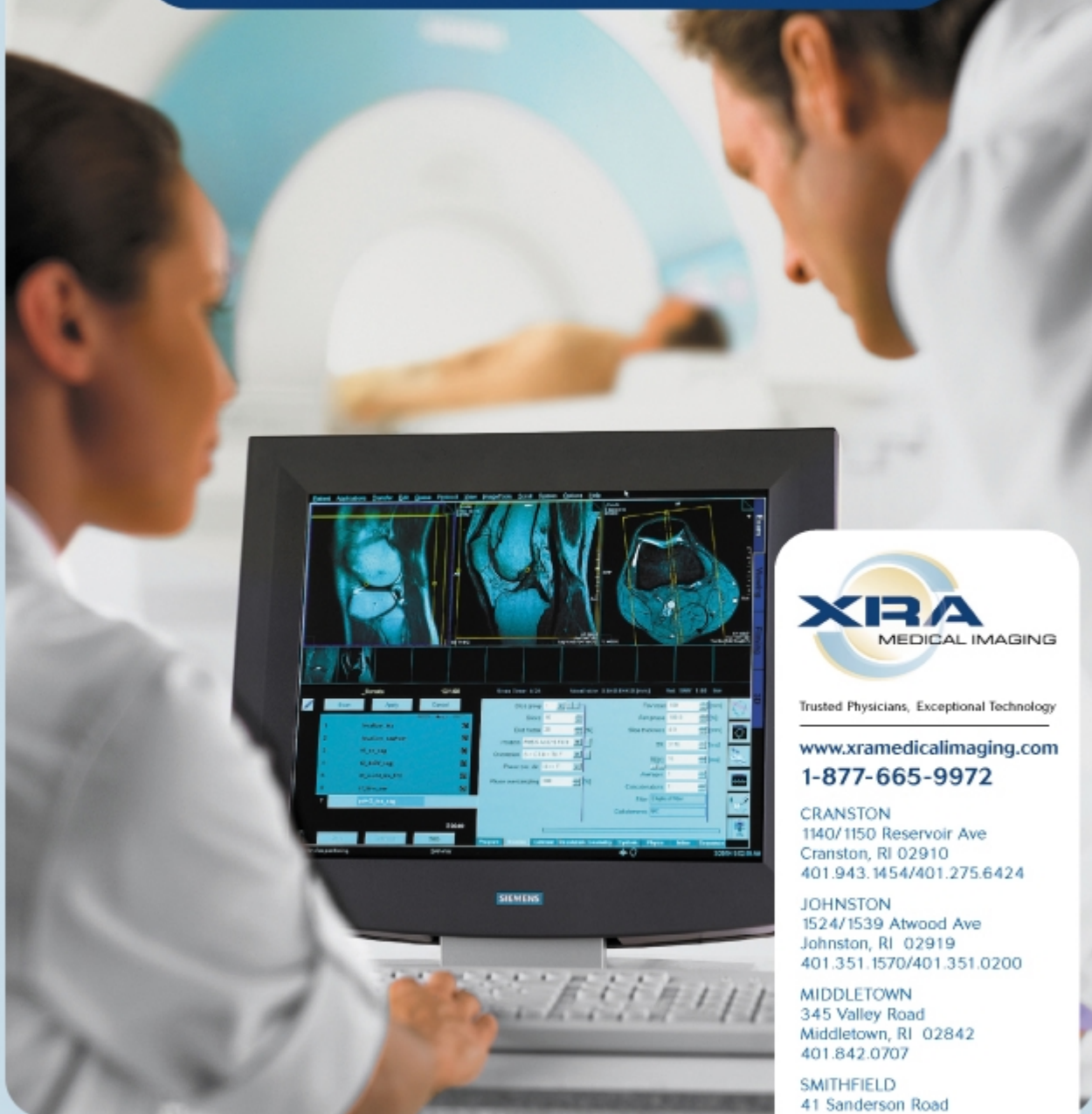
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couple of times a year now require monthly visits and procedures, clogging up our schedules. Therefore, much recent investigation has focused on alternative treatment strategies or new medications to reduce the burden.

One strategy is to reduce the dosing schedule. The PIER study sponsored by Genentech was meant to address this question by using Lucentis every three months instead of monthly. Unfortunately, the patients did not do as well as with the monthly treatments, even though it was still better than photodynamic therapy or Macugen. Another strategy is the PRONTO protocol. This involves an induction period of monthly injections to dry up the lesion, followed by close follow-up. If any recurrent exudation appears and/or vision loss occurs, another injection is given. This strategy was shown in a relatively small trial to have similar visual results to the ANCHOR and MARINA phase III trials with half the injections on average. Of course, the patients still must come to the office monthly, even if they do not receive an injection.

Yet another strategy is to use combination treatments, usually involving some combination of photodynamic therapy and another agent. The theory is to use the vasculo-occlusive properties of the PDT with a vasculostatic agent such as steroids or anti-VEGF agents. The first attempt at this was the use of intravitreal triamcinolone acetate (Kenalog) to treat the inflammatory component in combination with PDT. This was proposed early after the introduction of PDT in

response to the disappointing results of PDT alone. Although this combination was initially superior to PDT, the results were more disappointing in long-term follow-up. Additionally, the ocular side effects of Kenalog are significant, including glaucoma and cataract.

Today, most studies use an anti-VEGF agent and PDT with or without intravitreal steroid. Only a few trials have been done, but these combinations have been effective at reducing the need for repeated treatments while still improving vision. At the same time, they reduce theoretical ocular side effects and reduce the exposure to anti-VEGF agents.

To further address the safety and efficacy problems, other more potent anti-VEGF products are in development. One promising agent is the VEGF trap, which is just entering phase III trials. This is a humanized soluble decoy VEGF receptor, which binds strongly to VEGF, thereby preventing VEGF from binding to the cell receptor site. It appears that this drug may require less frequent injections, up to every 3 months. However, the VEGF trap will not be available for a few years.

Many retina specialists have not settled on a single treatment protocol for their patients with exudative AMD. Indeed, there are many permutations of available treatments. I expect that a more rational and individualized approach to our AMD patients will arise over the next few years, probably involving various combination treatments. Until then, anti-VEGF monotherapy will probably remain the mainstay of treatment for most patients.

SUMMARY

AMD causes irreversible blindness in the elderly. For years, treatment has been non-existent or ineffective. With the advent of anti-VEGF agents, ophthalmologists can stabilize and even improve visual function in these patients.

To accomplish this, however, requires frequent intraocular injections and follow-up, costly in time and money to the patient and the health-care system. In the near future, it is likely that newer strategies and newer drugs will make the treatment of AMD easier, more effective, and more affordable.

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Richard G. Bryan, MD, is Clinical Assistant Professor of Surgery (Ophthalmology), at the Warren Alpert Medical School at Brown University.

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Discussion of Investigational or Off-Label Use of Product

bevacizumab triamcinolone acetate (Kenalog)

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CORRESPONDENCE

Richard G. Bryan, MD
Rhode Island Eye Institute
150 East Manning St.
Providence, RI 02906
Phone: 401-272-2020
E-mail: rgbryan@alumni.duke.edu



Clinical Update on Optic Neuritis and Multiple Sclerosis

Marjorie A. Murphy, MD

Acute idiopathic optic neuritis is the most common cause of optic neuropathy in young patients. It is an isolated inflammatory optic neuropathy secondary to demyelination and is one of the clinically isolated syndromes suggestive of **multiple sclerosis (MS)**.¹ Optic neuritis is often the heralding manifestation of MS, and many patients with MS develop optic neuritis at some point during the course of their disease.

The **Optic Neuritis Treatment Trial (ONTT)**² has provided the best prospective data regarding the clinical presentation, outcome with respect to treatment, and development of MS in patients with optic neuritis. This multi-centered study enrolled 448 patients who were treated either with oral placebo, IV steroids followed by an oral placebo taper, or oral steroids alone. Patients were followed for visual outcome as well as for the development of clinically definite MS.

DEMOGRAPHICS

Patients with optic neuritis are typically young, with a peak incidence in the third and fourth decade, and more women than men are affected.³ In the ONTT, 77% of the patients were women, 85% were Caucasian, and the mean age was 32. The annual incidence of optic neuritis in the US is approximately 5 cases per 100,000 and the prevalence is 115 cases per 100,000.⁴

SYMPTOMS

Visual loss generally occurs over a period of hours to a few days, and may progress over 7 to 10 days. Progressive deterioration of vision beyond 2 weeks is highly uncharacteristic of optic neuritis.⁵ Reduced color vision is common, and patients frequently report a darkening of vision or desaturation of color. Pain, usually exacerbated by eye movement, is present in more than 90% of cases³ and may precede or coincide with visual loss. Uhthoff's phenomenon (transient worsening of vision with elevation of body temperature such as after exercise or a hot shower) may be seen, though it is nonspecific and is also noted with other optic neuropathies.

SIGNS

Patients typically have reduced visual acuity ranging from nearly normal to **no light perception (NLP)**. In the ONTT, 10% of the patients were 20/20, 25% were between 20/25 and 20/40, 29% were 20/50 to 20/

190, and 36% were 20/200 to NLP.^{2,3} Dyschromatopsia can usually be identified by testing with Ishihara pseudoisochromatic color plates and noting asymmetry between eyes. The typical visual field defect is a central scotoma but can be of any type. The optic nerve appears normal in the acute phase in about two thirds of cases (retrobulbar optic neuritis) and is swollen in about one third of cases (optic papillitis).² In both cases, temporal pallor of the disc often develops after 4 to 6 weeks from onset of visual loss. Peripapillary hemorrhages and retinal exudates are uncommon findings.³

DIAGNOSIS

The diagnosis of optic neuritis is primarily a clinical one. The ONTT showed that routine blood tests, including ANA, ACE, FTA-ABS, and chest x-ray are of no value in typical cases (young patients with subacute vision loss and pain on eye movement).⁶ A more thorough assessment should be considered when atypical features of optic neuritis are present, including a very swollen optic nerve, retinal exudates, absence of pain, and absence of any recovery within 30 days.⁷

An MRI of the brain with gadolinium should be obtained in all patients with optic neuritis. This study is essential to evaluate the risk of MS, and it may be repeated over time because the most recent criteria for the diagnosis of MS incorporate the presence of MRI findings.⁸ In the ONTT, 59% of patients with a previously normal neurologic history had clinically silent white matter lesions.⁹ The most typical findings are small T2-hyperintense lesions in the periventricular white matter, subcortical white matter, and pons.¹⁰ Enhancement of the lesions on T1-imaging indicates active plaques. Both **short-term inversion recovery (STIR)** and **fluid-attenuated inversion recovery (FLAIR)** sequences increase the sensitivity of detecting these white matter lesions.¹¹

Spinal cord imaging is usually not helpful in patients with clinically isolated optic neuritis.¹² Dedicated orbital views (thin sections with fat suppression and gadolinium administration) are only necessary in atypical optic neuritis, as the documentation of optic nerve enhancement is not necessary in most typical cases.^{1,14}

CSF analysis was found by the ONTT to be unnecessary in the initial evaluation of patients with typical isolated optic neu-

ritis because it neither changed the diagnosis nor added information to that obtained from MRI in predicting future development of MS.¹³ A lumbar puncture should only be performed in selected atypical cases of optic neuritis, especially for bilateral cases, in childhood, or when an infectious or inflammatory disorder is suspected.¹³

Visual evoked potentials (VEPs) are only an extension of the ophthalmologic examination and should not be used to make a diagnosis of acute optic neuritis in the setting of unexplained visual loss.¹⁵ As the diagnosis of acute optic neuritis is clinical, ophthalmologists do not recommend VEPs in the routine diagnosis or management of acute optic neuropathies.

An MRI of the brain is therefore the only requisite test in typical cases of optic neuritis. Criteria for atypical optic neuritis include: 1) marked optic disc swelling, 2) vitritis, 3) evidence of orbital inflammation or infiltration 4) progressive visual loss after 2 weeks, 5) lack of partial recovery within 4 weeks of onset of visual loss, and 6) persistent pain.^{15,18} An MRI of the orbits with fat suppression and administration of gadolinium will exclude compressive lesions, and a laboratory workup (RPR, FTA-ABS, Lyme titers, ACE, ESR, ANA, B12, c-ANCA, p-ANCA, and mitochondrial analysis) and lumbar puncture may be obtained.

VISUAL PROGNOSIS

The ONTT confirmed that spontaneous visual recovery begins rapidly (within 3 weeks) in approximately 80% of patients with idiopathic acute optic neuritis and continues to improve for up to 1 year.^{16,17} At one-year follow-up, at least 95% of patients had visual acuity better than 20/40 in the affected eye. Although 50% of patients had a visual acuity of 20/20 in the affected eye, a majority of patients complained of permanent visual dysfunction such as impaired contrast sensitivity, decreased color vision, difficulty with motion perception, and diminished intensity of light. At 10 years, visual acuity was > 20/20 in 74% of patients and > 20/40 in 92%, with only 3% worse than 20/200.¹⁷

Optic neuritis not uncommonly recurs in either the same or fellow eye. In the ONTT, 28% of patients developed recurrence within 5 years¹⁶ and 35% at 10 years.¹⁷ Recurrent

episodes were more frequent in patients who eventually developed MS and in those who received treatment with oral prednisone alone.

The ONTT provided documentation of the effect of corticosteroid therapy on visual outcome in optic neuritis. **Intravenous methylprednisolone (IVMP)** at a dose of 250 mg four times a day for 3 days, followed by 11 days of oral prednisone at 1 mg/kg/d resulted in increased rates of visual recovery during the 15 days after vision loss. At successive follow-up examinations, however, this effect diminished. By 6 months, there was minimal difference between treated and placebo groups, and by 1 year and thereafter, there was no significant long-term benefit for visual function.^{2,17} Hence, treatment with IVMP may speed recovery of vision in the first few weeks after onset but provides no long-term benefit.

Oral prednisone alone at doses administered in the ONTT (1 mg/kg/d) produced no visual benefit, either for speeding recovery or for long-term visual function. Furthermore, it was associated with a significantly higher rate of recurrence in the affected or fellow eye (27% vs. 13% in the IVMP and placebo groups) at 6 months, an effect that was borne out through 10 years of follow-up.¹⁷ The continuing recommendation from the ONTT and the standard of practice in the US neuro-ophthalmology community is not to treat idiopathic optic neuritis with oral prednisone.¹⁸

RISK OF DEVELOPING MS

In the ONTT, the overall risk for the development of **clinically definite MS (CDMS)** after an initial isolated episode of idiopathic optic neuritis was 30% at 5-year and 38% at 10-year follow-up.¹⁷ Numerous studies have shown that brain MRI is the most powerful predictor of future development MS in patients with acute idiopathic optic neuritis. This is in accordance with the recent modification of MS diagnostic criteria, which now include MRI changes.⁸

Although the presence of white matter abnormalities (demyelinating lesions) is not sufficient to make the diagnosis of CDMS, it does provide evidence of multifocal brain involvement, and in the clinical setting of optic neuritis, raises the risk significantly. In the ONTT, the 5-year risk for CDMS was 16% with a normal brain MRI (no lesions), compared with 37% with one or two lesions and 51% with three or more lesions.¹⁹ At 10 years, the increased risk of CDMS with the presence of white matter lesions was sustained, but the only statistically significant difference was between no lesions (22% risk) and one or more lesions

(56% risk); the gradually progressive risk with increasing volume load of lesions seen at 5 years was not continued at 10 years.²⁰

The ONTT did not show any demographic or clinical features of optic neuritis predictive of developing MS in patients with abnormal baseline MRI. However, in patients with normal baseline MRI, the risk of developing MS was three times lower for men than for women.²⁰ The risk was also lower for those who had optic nerve head edema. MS did not develop in any patient with a normal MRI at 10-year follow-up who had 1) painless visual loss, 2) absence of light perception in the affected eye, 3) severe optic disc edema, 4) peripapillary hemorrhage, or 5) macular exudates.²⁰ These findings emphasize the importance of a dilated fundoscopic examination by an ophthalmologist in all patients with acute optic neuritis, as these findings should help identify a group of patients with a very low risk of MS.⁷

...the standard of practice...is not to treat idiopathic optic neuritis with oral prednisone.

BENEFITS OF THERAPY

Corticosteroids

At 2-year follow-up in the ONTT (in patients with two or more white matter lesions), the IVMP treatment group was found to show a significantly decreased risk for the development of MS. However, the beneficial effect was not maintained for 3 years.²¹ The lack of a significant difference between the treatment groups in the subsequent development of MS was apparent regardless of the number of MRI abnormalities. This lack of benefit was borne out in subsequent 5- and 10-year follow-up studies.²⁰

Immunomodulation Therapy

Three types of **immunomodulation agents (IMAs)** are available for the treatment of **relapsing-remitting multiple sclerosis (RRMS)**: interferon beta-1b (Betaseron), interferon beta-1a (Avonex, Rebif), and the synthetic copolymer glatiramer acetate (Copaxone). Several large-scale phase III multi-center clinical trials have established that these agents are beneficial in reducing disability progression, acute demyelinating inflammation (active white matter lesions on T1-weighted MRI), total disease burden (cumu-

lative white matter lesions on T2-weighted MRI), and brain atrophy (overall parenchymal volume and "black holes" of focal atrophy) in patients with established relapsing disease.²²⁻²⁵ In 1998, the National MS Society in a consensus statement recommended that IMA therapy be initiated immediately upon establishing a diagnosis of RRMS.²⁶

More recent studies have addressed IMAs' effectiveness in reducing the risk of developing MS after a single demyelinating episode. The **Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS)**²⁷ was designed to evaluate the effect of Avonex in lowering the rate of developing MS after a single demyelinating event (optic neuritis, incomplete transverse myelitis, or brain-stem/cerebellar syndrome). Half of the patients enrolled had isolated optic neuritis as this initial event. All subjects had two or more white matter lesions on brain MRI, and all received IVMP followed by corticosteroid therapy within 14 days of onset. They were then randomized to weekly injections with either intramuscular Avonex or placebo.

At 3 years after the onset of treatment, the cumulative probability of CDMS was 35% in the Avonex group and 50% in the placebo group.²⁷ In addition, Avonex was associated with a significant reduction of new MRI T2 lesions, gadolinium-enhanced lesions, and T2 lesion volume. New clinically silent MRI signal abnormalities appeared within 18 months in 82% of the placebo-treated patients.²⁷ Hence, this finding indicated that a large number of such high-risk patients had ongoing silent demyelination.^{28,29} The follow-up study, the **Controlled High Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance (CHAMPIONS)**, showed that these results were sustained at 5 years. It also suggested that there may be modest beneficial effects of immediate treatment with Avonex compared with delayed initiation of treatment.³⁰

Subsequent trials were conducted with the early use of other immunomodulatory drugs. The **Early Treatment of MS (ETOMS)**³¹ study evaluated therapy with Rebif in patients with a first neurologic episode consistent with MS, assessing the effect on lowering the risk of subsequent CDMS. The study differed from the CHAMPS with regard to a number of features including the inconsistent initial use of IVMP and a lower incidence of optic neuritis as the initial event (35% vs. 50%). However, the results confirmed the findings of the CHAMPS: the risk of subsequent CDMS was reduced at 2-year follow-up from 45% with placebo to 34% with treatment.^{31,32} In addition, the

number of new T2-MRI lesions and the increase in lesion burden were significantly lower with active treatment. Similar findings were noted in the **Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT)** study,³³ in which 28% of patients in the Betaseron-treated group developed clinically definite MS, compared with 45% in the placebo group.

MANAGEMENT OF OPTIC NEURITIS

Initial therapeutic options

Acute treatment options for idiopathic optic neuritis include intravenous methylprednisolone or observation alone. IVMP hastens visual recovery but has no effect on the final visual outcome. The decision to use IVMP should be individualized, considering such factors as the patient's visual function, results of brain MRI, and side effects.⁷ With regard to visual function, this regimen is only considered for those patients requiring faster recovery, such as monocular patients, those with severe bilateral visual loss, or those with vocational requirements for a high level of visual acuity or depth perception.¹⁸ Although the ONTT protocol involved daily IVMP in divided doses, pulse therapy is now commonly administered as a single daily outpatient dose of methylprednisolone, 1 gram daily for 3 days. The subsequent oral prednisone taper (1 mg/kg daily for 11 days with a 4-day taper thereafter) is still used by many but not all ophthalmologists. Oral prednisone alone should not be used in the treatment of idiopathic acute optic neuritis.

Long-term therapeutic options

MS has traditionally been considered a disease in which early inflammatory events injured myelin but spared axons, with the cumulative effects of multiple episodes producing axonal damage and permanent neurologic disability only late in the course of the disease.¹⁸ However, recent pathological and MRI studies suggest that axonal damage occurs early in MS.³⁴⁻³⁷ Once this axonal damage occurs, permanent neurological deficits may result. The issue of axonal damage is at the center of an ongoing debate over whether to intervene early with disease IMAs in patients with clinically isolated syndromes,^{38,39} especially those predicted at high risk for the subsequent development of MS. Results of the CHAMPS²⁷⁻²⁹ and ETOMS^{31,32} studies suggest that patients with optic neuritis and abnormal baseline MRI ("high risk patients") should be considered for interferon beta-1a therapy. Moreover, the CHAMPIONS study³⁰ suggested that such treatment should be initiated early after the

first demyelinating event. In addition, the results of the BENEFIT study³³ suggest that interferon beta-1b should be considered to delay progression to definite MS in patients with a first clinically isolated syndrome, including acute idiopathic optic neuritis.

All patients presenting with idiopathic demyelinating optic neuritis and a high-risk brain MRI should be informed of the therapeutic option of IMAs for reducing the risk of MS.¹⁸ The data on the benefits of IMAs apply only to patients with at least two typical MRI white matter lesions; in those with lower risk based on MRI, the benefits of IMAs are unproved. Additional considerations include the high cost of therapy, commitment to long-term weekly injections with associated side effects, and the possibility that therapy in any individual may be unnecessary.^{5,18} At 10-year follow-up in the ONTT, 44% of patients were disease-free without therapy, and there is evidence that the clinical course of MS that develops after optic neuritis may be less severe than other cases of MS.⁴⁰ There is no consensus on this issue: expert recommendations range from treatment in all cases, to treatment only in cases with at least two MRI lesions, to treatment only for those who, on repeat MRI (3 to 6 months), show newly active lesions, suggesting ongoing demyelinating activity.^{7,18,38,39} The decision to initiate IMA therapy after initially isolated optic neuritis should be individualized and requires a careful discussion of all aspects of therapy.

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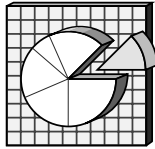
Marjorie A Murphy, MD, is a Clinical Associate Professor in the Department of Ophthalmology, Rhode Island Hospital/The Warren Alpert Medical School at Brown University, and Director of Neuro-Ophthalmology at Rhode Island Hospital.

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CORRESPONDENCE

Marjorie A. Murphy, MD
Department of Ophthalmology
Rhode Island Hospital
APC 7
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-4669
E-mail: margiemurphy@cox.net



Eye Injuries Treated in Rhode Island Hospitals

Edward F. Donnelly, RN, MPH, and Jay S. Buechner, PhD

Eye injuries are an important cause of visual impairment.¹ The reported population-based rate of the incidence of eye injury varies depending on the data source and on the definition of eye injury. One recent study reports an estimated national rate of eye injuries treated in hospital emergency departments of 3.15 per 1000 population in 2000.²

Information on the incidence of eye injuries among Rhode Island residents comes primarily from the data on **inpatient (IP)** discharges and **emergency department (ED)** visits reported regularly to the Rhode Island Department of Health by the state's acute-care general hospitals since 1989 (IP) and 2005 (ED). Recent analyses of all injury and trauma treated in hospital inpatient settings³ and hospital emergency departments⁴ did not specifically address eye injuries. This analysis presents Rhode Island data on ED patients treated for eye injuries during 2005 and on hospital inpatients treated for eye injuries during the five-year period 2002-2006, aggregated because of small annual numbers.

METHODS

Under licensure regulations, the eleven acute-care general hospitals in Rhode Island have reported to the Department of Health's Center for Health Data and Analysis a defined set of data items on each IP discharge beginning January 1, 1989, and on each ED visit beginning January 1, 2005. The data reported include patient-level demographic and clinical information. This analysis covers IP discharges occurring January 1, 2002 – December 31, 2006, (including admissions from all sources, not just the ED) and ED visits occurring January 1 – December 31, 2005 (including only those ED visits where the patient received treatment in the ED and was not admitted as an inpatient). Due to ongoing investigations into the manner in which hospitals report their utilization data, these data are provisional and subject to change.

Cases of eye injury were identified by searching all twenty-five fields for diagnostic codes provided in hospital IP records and all eleven fields for diagnostic codes provided in records of ED visits. Cases with an eye injury reported anywhere in the record were divided into those with a principal diagnosis of eye injury and those with an additional

diagnosis of eye injury. In the latter group, the principal diagnosis could be either another injury or a condition other than injury.

The included codes and code ranges, from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM)⁵, were grouped as follows:

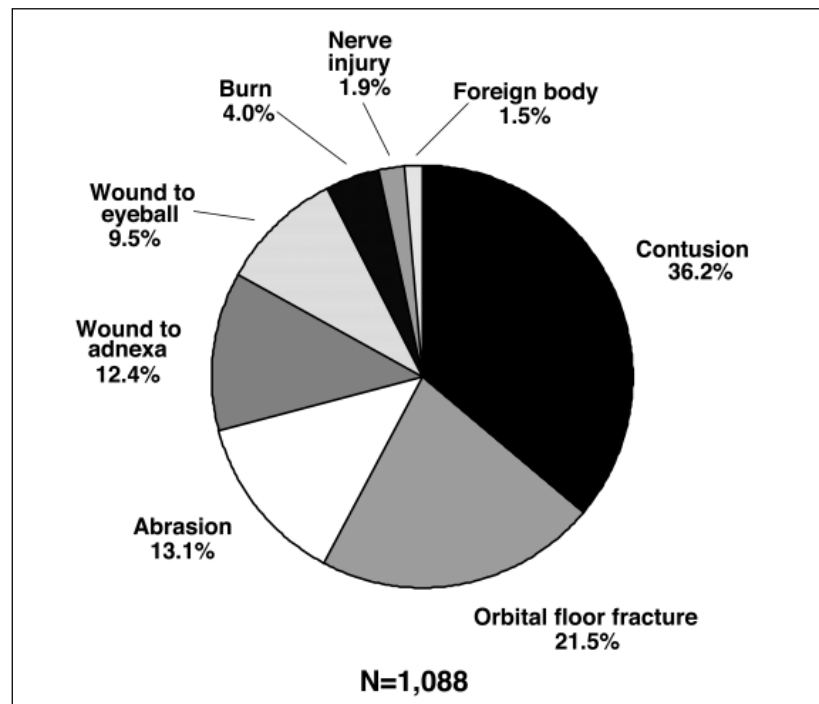


Figure 1. Hospital inpatient discharges with a diagnosis of eye injury, by type of injury, Rhode Island, 2002-2006.

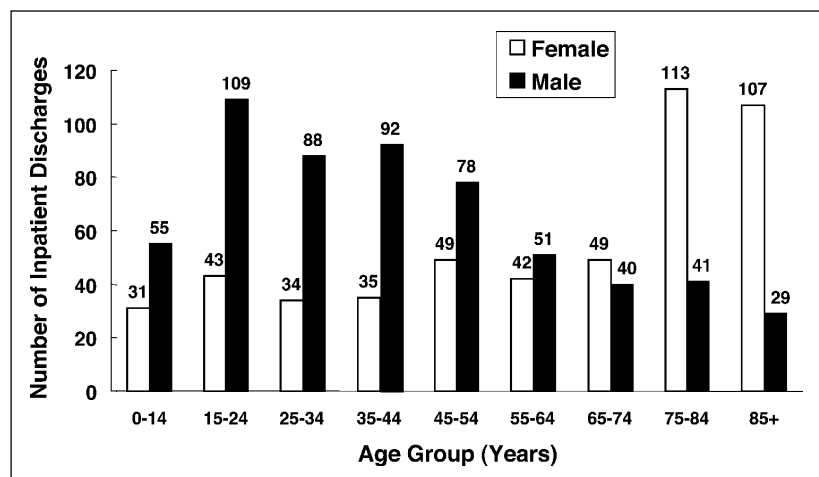


Figure 2. Hospital inpatient discharges with a diagnosis of eye injury, by age group and sex, Rhode Island, 2002-2006

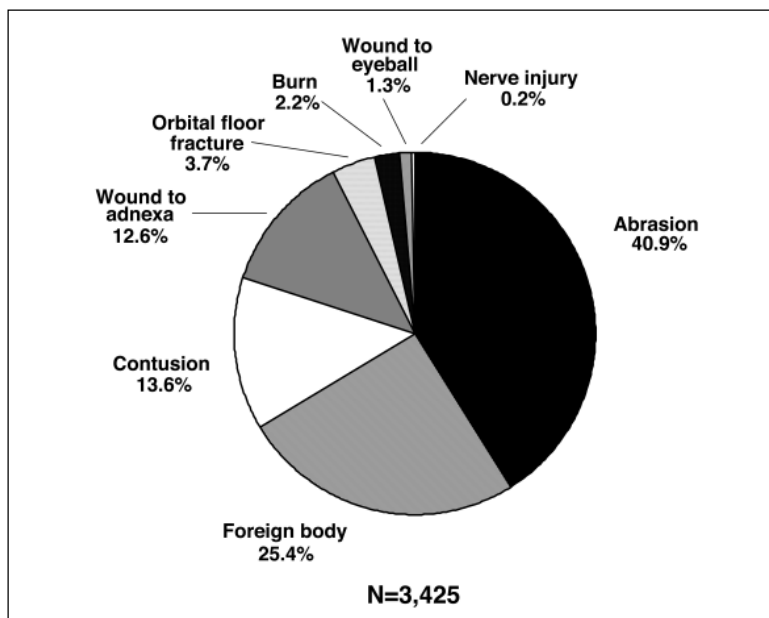


Figure 3. Hospital emergency department visits with a diagnosis of eye injury, by type of injury, Rhode Island, 2005.

- Blowout fracture of the orbital floor [ICD-9-CM 802.6, 802.7]
- Open wound to the adnexa [870]
- Open wound to the eyeball [871]
- Superficial injury (abrasion) to the eyeball and adnexa [918]
- Contusions of the eyeball and adnexa [921]
- Burn of the eye [940; 941 with 5th digit of '2']
- Injury to nerves involved in vision and movement of the eyes [950, 951.0, 951.1, 951.3]
- Foreign body on external eye [930]

Groupings were based on those used in the Barell Injury Diagnosis Matrix⁶ augmented to be comparable with a recent national study.¹ The mechanism and intentionality of eye injuries were examined using the ICD-9-CM external cause of in-

jury codes (E-codes) reported in both the IP and ED databases.⁷

RESULTS

In the five-year period 2002-2006 there were 1,088 hospital discharges with either a principal diagnosis or an additional diagnosis for eye injuries. Eye injuries were the principal discharge diagnosis in 200 of these cases. Open wounds to the eyeball were the most often cited (39.5%) as a principal diagnosis, with orbital floor fractures second (29.0%). Among all cases, contusions (36.2%) were the most commonly reported eye-injury diagnoses in inpatient records. (Figure 1)

Eye injuries resulting in an inpatient hospitalization occurred throughout the age span but followed very different patterns by sex. (Figure 2) Males predominated in the age groups through age 54, as is common with injury hospitalizations. Female and male numbers were about equal in the age groups 55-74. In persons 75 years of age and older who were hospitalized with eye injuries, females make up most of the cases (75.9%). The median age among IP hospitalizations was 39 for males and 68 for females.

By mechanism of injury, eye injuries among inpatients were caused primarily by falls (34.6%), motor vehicle crashes (21.6%), and being struck by an object or person (10.6%). Only 5% of hospital IP records reporting eye injuries lacked an external cause of injury code.

There were 3,425 visits to Rhode Island hospital EDs in 2005 with diagnoses of eye injuries. For eye injuries for which medical care in the ED was sought, very few (3.5%) were admitted for an overnight stay in the hospital. (There are no data on how many of these injuries were referred for subsequent inpatient treatment at the same or a different hospital.) Most of the eye injuries seen in the ED were classified as unintentional (85.8%) with a much smaller number due to assault (6.3%). Slightly more ED visits lacked a code for external cause (7.1%) than was true for inpatient discharges.

Among reported ED visits for eye injury in 2005, abrasions (40.9%), foreign bodies on the external eye (25.4%), and contusions (13.6%) predominated. (Figure 3) Open wounds to the adnexa (12.6%) were common but not often admitted, while eye-injury patients with open wounds to the eyeball and blowout fracture of the orbital floor were those most likely to be admitted.

In 2005, males accounted for 64.2% of hospital ED visits involving an eye injury and made up the majority of visits in age categories through age 74. (Figure 4) Seven percent of males and 5% of females reported assault as the cause of the injury. ED visits for eye injuries were concentrated among children and younger adults, with the number generally declining with increasing age.

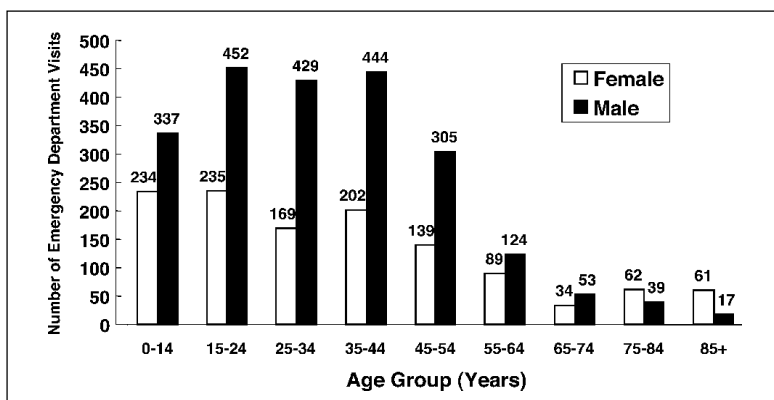


Figure 4. Hospital emergency department visits with a diagnosis of eye injury, by age group and sex, Rhode Island, 2005

DISCUSSION

Although the number of eye injuries treated in hospitals in Rhode Island annually reaches into the thousands, relatively few require immediate hospitalization as an inpatient. Nevertheless, the consequences of eye injuries to the patient can be substantial, as well as the costs to society, if lasting visual impairment results. The recent availability of data on ED visits for eye injuries in Rhode Island will support investigations into the types of injuries, their causes, and the affected populations, data that can guide public health efforts to prevent and control such injuries in our population.

Edward F. Donnelly, RN, MPH, is Senior Public Health Epidemiologist, Center for Health Data and Analysis, and Clinical Teaching Associate, Department of Community Health, Warren Alpert Medical School of Brown University.

Jay S. Buechner, PhD, is Chief, Center for Health Data and Analysis, and Clinical Assistant Professor of Community Health, Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests

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Images In Medicine

Incarcerated Inguinal Hernia As the Presenting Feature of Carcinoma of Unknown Primary Site

Samantha Nazareth, Yasmin Metz, MD, Samir A. Shah MD, and Edward Feller, MD

A 73-year-old man presented to his physician three weeks after discovery of a painless right groin mass. On examination, he was afebrile and a hard, smooth mobile, 4 cm, non-tender, irreducible mass was palpated above the right external ring. Abdominal CT confirmed an incarcerated right inguinal hernia (figure). Laparoscopic herniorrhaphy revealed that the mass was indurated omentum. Pathological exam of the specimen with special stains revealed a metastatic adenocarcinoma of presumed GI origin. Review of his CT showed no evidence of possible primary site. CT of the chest without contrast revealed no mass or adenopathy. Laboratory investigation revealed a slight, non-specific elevation of cancer associated antigen (CA 19-9) = 43.6 U/mL (normal to 37 U/mL with metastatic disease generally having values > 1000 U/mL); carcinoembryonic antigen (CEA) = normal. CA19-9 and CEA are tumor markers commonly elevated in intra-abdominal malignancies. UGI endoscopy and colonoscopy were normal, MRI of the abdomen and pelvis revealed omentum with some nodular studing. The patient remained asymptomatic, declined empiric treatment, and died of disseminated, undiagnosed malignancy 6 months post-diagnosis.

DISCUSSION

Malignancy is a rare cause of incarcerated hernia, reported in 15 of 22,816 (0.07%) of cases in one large review. Similarly, incarcerated inguinal hernia is a very rare initial manifestation of carcinoma of unknown primary. Adenocarcinoma found in inguinal hernia sacs is most commonly gastrointestinal, ovarian, prostatic or due to tumors associated with ascites. Unusual benign lesions, including pancreatic pseudocysts or abdominal abscesses may also present as a groin hernia. A new, irreducible, rapidly expanding inguinal hernia or a long-standing hernia that becomes acutely incarcerated may, exceptionally, be due to malignancy. Our patient's non-specific presentation did not suggest malignancy. Physicians should be aware of incarcerated inguinal hernia as the initial manifestation of cancer, including carcinoma of unknown primary site, a malignancy that commonly eludes specific diagnosis, as in our patient.



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Samantha Nazareth is a 4th year student at The Warren Alpert Medical School of Brown University.

Yasmin Metz, a Brown MD, is a resident in Internal Medicine at New York Hospital-Presbyterian Medical Center.

Samir A. Shah, MD, is Clinical Associate Professor of Medicine at the Warren Alpert Medical School at Brown University.

Edward Feller, MD, is Clinical Professor of Medicine at The Warren Alpert Medical School at Brown University, and Director, Division of Gastroenterology at Miriam Hospital.

Disclosure of Financial Interests

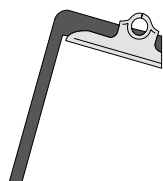
Samantha Nazareth, Yasmin Metz, MD, and Edward Feller, MD, have no financial interests to disclose.

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CORRESPONDENCE

Edward Feller, MD

e-mail: Edward_Feller@brown.edu



The Rhode Island Survey of Physician EMR Adoption

Jay S. Buechner, PhD, Rosa R. Baier, MPH, and David R. Gifford, MD, MPH

The widespread adoption of electronic medical records (EMR) systems by physicians has the potential to reduce the incidence of medical errors and increase the likelihood that patients with acute and chronic conditions will receive care that meets recommended standards. Because of this potential, President Bush has established the goal that a majority of Americans will have access to electronic health records by 2014.¹ The American Health Information Community, an advisory body to the US Department of Health and Human Services, has identified the adoption of EMRs by physicians as the highest priority in meeting that goal.² As of 2006, an estimated 29.2% of physicians in office-based practice reported using an EMR that was partly or fully electronic and 12.4% reported using a “comprehensive EMR” including four minimum features: computerized orders for prescriptions, computerized orders for tests, test results (laboratory and/or imaging), and clinical notes.³ Governor Carcieri has also made the adoption of EMRs part of his health care platform.

In Rhode Island, legislation passed in 2006 mandated that the Department of Health collect and make public indicators of the quality of care provided by individual licensed health care practitioners, building on similar legislation passed in 1998 covering licensed health care facilities.⁴ After consultation with stakeholder groups, the Department’s Health Care Quality Program recommended that measures of the adoption and use of EMRs be collected and reported for physicians, and the Program’s Steering Committee endorsed that recommendation in July 2007.

The survey, currently collecting physician responses through February 29, 2008, has several innovative features. To identify the appropriate survey population, the Department’s licensure database was accessed to identify physicians (MDs and DOs) who reported that they provided any direct patient care when they last renewed their license. Of 4,573 licensed physicians on December 19, 2007, 2,125 (46%) reported they provide direct patient care; they formed the base survey population. The initial contact for most physicians was by e-mail (96.7% of the population provided an e-mail address on their re-licensure application), and the survey is administered through a web-based survey system. Physicians who previously opted out of receiving communication from the web-based survey system were excluded from the e-mail distribution. The survey content draws from similar efforts in Massachusetts⁵ and at the national level³ and covers physician practice arrangements, EMR system characteristics, and physician use of selected EMR system features. An option available to physicians who participate in Blue Cross of Rhode Island is to generate a printout of their responses that can be submitted to Blue Cross and may qualify them for increased reimbursement rates. Because of the usefulness of this feature to their reimbursement incentive program, Blue Cross is a co-

sponsor of the EMR survey.

As the Department of Health’s licensure database may not have the most current information on physicians’ e-mail addresses, mailing addresses, or practice status, some practicing physicians may not have been included in the initial survey mailings. Physicians who believe they should have been included may participate by accessing the survey through the Department of Health’s website (www.health.ri.gov) by clicking on the link “Physician EMR Survey” appearing on the website’s home page.

After the data collection period concludes on February 29, 2008, the Health Care Quality Program will treat the survey data as a pilot round, as it has for other settings. The data will be examined and reported in aggregate and evaluated for possible improvements in later iterations of the survey. Information at the level of the individual physician will not be publicly reported on the HEALTH website, but will be shared with each reporting physician. Later iterations of data collection will be publicly reported at the physician level, thereby satisfying the 2006 legislative requirement placed on the Health Care Quality Program by the Rhode Island General Assembly.

Jay S. Buechner, PhD, is Chief, Center for Health Data and Analysis, and Clinical Assistant Professor of Community Health, The Warren Alpert Medical School of Brown University.

Rosa R. Baier, MPH, is Associate Scientist at Quality Partners of Rhode Island.

David R. Gifford, MD, MPH, is Director of Health, Rhode Island Department of Health, and Clinical Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.

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Disclosure of Financial Interests

The authors have no financial interests to disclose.



Nutrition in the Older Adult

Timothy Farrell, MD, and Ana Tuya, MD

Mrs. N is a 93 year-old woman with no significant past medical history who presents to the office with her daughter for her annual visit. She has never been hospitalized, takes no routine medications except for a multi-vitamin, and has no active medical problems. Mrs. N lives in an apartment in her daughter and son-in-law's home and is entirely independent. She no longer drives due to visual impairment, and ambulates with a cane, but is otherwise independent in all activities of daily living. Her daughter takes her to the grocery store and all appointments. Mrs. N prepares her own meals, does her own housework and only needs help with laundry because it is in the main house. Her daughter is concerned because of Mrs. N's recent weight loss, about 5 pounds over six months. The patient says she's not concerned and that she's eating to her satisfaction and feels well. Her average intake consists of toast with jam in the morning; tea, half of a sandwich or salad for lunch, usually with one slice of luncheon meat; and dinner, which usually consists of some meat or fish, vegetable, and rice or potato, though she frequently only picks at her plate. She will have an occasional sweet. She does not drink any alcohol.

Although many clinicians would readily identify the term "failure to thrive" with the pediatric population, this term also applies to the elderly population. Failure to thrive, often due to undernutrition, is defined by weight loss and associated loss of functional status, muscle loss, and cachexia. There is a lack of consensus regarding the extent and rapidity of weight loss that constitute failure to thrive; however, an unintentional weight loss of greater than 10 pounds over 1 year, or a body mass index (BMI) <18.5 kg/m², is often used in clinical practice. The rate of weight loss and the absolute change from the patient's self-reported ideal body weight should be considered as well. The characteristic weight loss in failure to thrive usually has a multi-factorial etiology, and is often associated with depression or dementia. It is thought that a chronic inflammatory state and lack of physiologic reserve may contribute to failure to thrive.

Protein and calorie malnutrition are common in elders, especially over age 75 and in the presence of chronic disease. Unintentional weight loss is found in 13% of community-dwelling elders, and 30-80% of nursing home residents. Age-related physiologic changes lead to decreased appetite due to changes in the appearance, smell, taste, and texture of food. Delays in resumption of normal eating after illness and diminished thirst perception (and ability to access fluids) reflect altered

regulation of food and fluid intake, respectively. Older patients require fewer calories to meet energy requirements due to a decrease in lean body mass. A daily multivitamin will meet requirements for almost all vitamins, except vitamin B12 and vitamin D (see table below for nutritional requirements).

The diagnostic approach to failure to thrive in elders should be tailored to the individual patient, but a thorough history (including a dietary history) and physical examination, calorie count, and consultation with a nutritionist or dietician are invaluable. The initial workup usually includes a complete blood count with differential, glucose, electrolytes, liver function tests, thyroid function test, and urinalysis. Albumin and prealbumin are both negative acute phase reactants which limits their clinical utility, although the shorter half-life of prealbumin (2-3 days versus 3 weeks for albumin) favors the use of prealbumin to monitor the response to nutritional interventions. Serum cholesterol less than 160 mg/dL, as well as hypoalbuminemia have been linked to poor clinical outcomes, but neither test is highly sensitive or specific for undernutrition. Screening tests, such as the Mini-Nutritional Assessment and Subjective Global Assessment, have not been studied extensively or adopted in clinical practice.

The treatment of failure to thrive should begin, as in most geriatric syndromes, with a consideration of non-pharmacological approaches. The physician should encourage the patient to participate in activities that promote socialization, es-

Daily Nutritional Requirements: Younger vs. Older Adults

	<i>Younger adult (age 18-65)</i>	<i>Elderly population</i>
Total calories	25-40 kcal/kg/day	25-30 kcal/kg/day
% calories from fat	<30%	25-30%
% calories from carbohydrates	≥55%	50%
Protein	0.6 g/kg/day	1.0-1.25 g/kg/day (increased to 1.5 g/kg/day in stress states)
Water	1.8-2.8 L/day	1.5-2.0 L/day
Sodium	1.5-2.3 g/day (<2 g/day in CHF)	3.5 g/day (<2 gm/day in CHF)
Fiber	28-34 g/day	25-35 g/day
Calcium	1000-1200 mg/day	1200 mg/day
Vitamin D	200 IU/day	400-800 IU/day
Vitamin B12	1.3 mg/day	2.4 mg/day
Folate	400 mg/day	400 mg/day

pecially in relation to meals, and to increase physical activity if possible. Impediments to socialization and activity, including limited mobility, financial problems, and depression, should be addressed. Dental care should be updated, and dysphagia or odynophagia should be addressed if present. High-density oral caloric supplements, such as Boost and Ensure, are most likely to be consumed when offered between meals. Meal presentation should be as attractive as possible; for example, meals should be served at the proper temperature to maximize palatability in the context of decreased overall gustatory sensation in older adults. Medications which might decrease taste (e.g., HCTZ) or olfaction (e.g., enalapril) should be discontinued if possible.

The pharmacological armamentarium for the treatment of undernutrition is limited, but mirtazapine (an antagonist of the 5-HT₃ receptor) is generally the first agent chosen in such instances. A typical starting dose of mirtazapine, whose appetite-stimulating and sedative effects are inversely proportional to increasing dosage, is 7.5 mg po at bedtime for older persons. Megestrol, a progesterone derivative which increases adipose tissue but not muscle mass, should be avoided in patients with thromboembolic disease; a typical starting dose is 625 mg po daily. Dronabinol and androgen therapy are generally not well tolerated by older adults. Agents that target the proposed inflammatory mechanism in failure to thrive, such as anti-TNF drugs, remain experimental. A discussion of feeding tubes and parenteral nutrition is beyond the scope of this article, but unless a true, reversible cause of undernutrition is found, these are generally not indicated.

Mrs. N is followed for 6 months, during which time she continues to have gradual weight loss. Medical causes are investigated, but all studies are negative for a reversible cause of anorexia and weight loss. She continues to report only decreased appetite, without focal symptoms of any other problems. Gradually she becomes weaker and begins to rely on her daughter for help with meal preparation and house cleaning, starts to use her husband's old walker for support, and can no longer shower without becoming fatigued. She moves into the main house with her daughter, who helps her with activities of daily living. She begins to appear more cachectic and debilitated on examination. Yet, no obviously treatable cause is found. A family meeting is held with the daughter and Mrs. N to discuss the options for pursuing further workup of her continued anorexia and weight loss. The patient is fully oriented and able to make her own decisions, but she looks to her daughter for support and is open to her opinions, and wanted her present for the meeting. The patient stated that she has lived a good life, and is satisfied with her current quality of life. She is not excited to pursue additional testing and is unsure if she would pursue treatment if a disease were found. She is satisfied with taking the multivitamins, and would like to continue with the supplements and dietary recommendations. Her daughter understands her perspective and agrees that they would not want to pursue surgery, chemotherapy, or other aggressive treatments, should a malignancy be found upon workup of her anorexia. This has been a chronic and slowly progressive problem, and they prefer to focus on the quality of her life for the time she has left. These wishes coincide with the patient's pre-

viously outlined living will. If the patient continues to decline they would pursue palliative, comfort-focused care.

On the next follow-up visit in 3 months, Mrs. N, after continuing to get weaker, is referred to hospice and is cared for at home until her death 15 weeks later.

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Timothy Farrell, MD, is a Geriatric Fellow, The Warren Alpert School of Medicine at Brown University.

Ana Tuya, MD, is Assistant Professor, The Warren Alpert School of Medicine at Brown University.

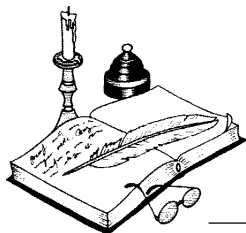
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Physician's Lexicon

Forty Days in Limbo

The English medical vocabulary owes a great debt to the Italian language for many of its words including lazaretto, anemia, malaria, marijuana, influenza, belladonna, dengue and quarantine.

The word, *quarantina*, derived from the Italian term for forty [days], echoes man's lengthy preoccupation with the numeral forty. The Bible is replete with forties. For example, the reign of Solomon [I Kings 11:42] was forty years, as were the reigns of his predecessors, Saul and David [II Samuel 5:4]. Noah's flood lasted forty days and Moses, at age 40, climbed Mount Sinai and remained isolated for forty days before resuming his leadership of the wandering Israelites. The periodic faithlessness of these nomadic Israelites forced them to wander for forty years in the vast deserts of the

Middle East before reaching their promised land.

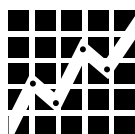
Jesus endured forty days in the wilderness, emerging victorious over temptation [Matthew 4:2] and then preached for forty months. Both Muhammad and Buddha began their separate evangelic missions at age forty. The number forty appears in many of the funerary rituals of the Fulani of Africa. In many African tribes, the final mourning taboos are lifted after forty days of grieving. In certain Asiatic tribes, a widow may seek a new husband but only after forty days of celibate mourning.

Forty, some anthropologists believe, represents an interval for the preparation of an inspired task or, alternatively, a cycle of days marking the end of one living event and the beginning of another. And,

of course, there is the medical student's aphorism of those most likely to be victimized by gall bladder disease: "female, fair, fat and forty."

A *lazaretto* was the name given to hospices for the care of those with leprosy, the first bearing this name was established in Venice in 1403. The Bible [Luke 16:20] describes a certain beggar, with many sores, named Lazarus, who was apparently afflicted with leprosy. Though hungry, he was not fed by a rich man at whose gates Lazarus dwelt. The beggar died and "was carried by the angels into Abraham's bosom." Thus medieval sanctuaries for the lepers—and later, for patients with any contagious pestilence—were often called lazarettos.

—STANLEY M. ARONSON, MD



RHODE ISLAND DEPARTMENT OF HEALTH
DAVID GIFFORD, MD, MPH
DIRECTOR OF HEALTH

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

VITAL STATISTICS

EDITED BY COLLEEN FONTANA, STATE REGISTRAR

Underlying Cause of Death	Reporting Period			
	February 2007	12 Months Ending with February 2007		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	262	2,795	261.3	3,614.0
Malignant Neoplasms	182	2,299	214.9	6,100.0
Cerebrovascular Diseases	35	385	36.0	492.0
Injuries (Accidents/Suicide/Homicide)	41	542	50.7	8,251.0
COPD	52	479	44.8	452.5

Vital Events	Reporting Period		
	August 2007	12 Months Ending with August 2007	
	Number	Number	Rates
Live Births	1,179	13,664	12.8*
Deaths	779	10,018	9.4*
Infant Deaths	(7)	(105)	7.7#
Neonatal Deaths	(5)	(74)	5.4#
Marriages	865	6,972	6.5*
Divorces	252	3,128	2.9*
Induced Terminations	326	4,699	343.9#
Spontaneous Fetal Deaths	55	1,017	74.4#
Under 20 weeks gestation	(48)	(937)	68.6#
20+ weeks gestation	(7)	(80)	5.9#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,067,610

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population

Rates per 1,000 live births

NINETY YEARS AGO, FEBRUARY 1918

William Benham Snow, MD, in "Poliomyelitis, Anterior, Pathology, Symptoms, Indications and Treatment," noted: "Recent investigations have demonstrated it to be infectious in character, of varying intensity, not in all cases causing paralysis, and sometimes manifesting congestions of the mucous membranes of the nose and fauces, with involvement of the gastrointestinal tract. The identify of the particular germ of the disease and its origin and method of transmission are still unsettled questions." Dr. Snow cited statistics from the recent epidemic in New York to show that foreign-born were most affected: 3825 people born in the United States; 5,180 born elsewhere. Furthermore, many of the native-born had foreign-born parents. These data stand in contrast to a 1912 Treasury Department Public Health Bulletin: "poverty and unsanitary conditions... seem to have little if any influence in determining infection."

Marion R. Durfee, from the Providence School of Lip Reading, contributed "The Value of Speech-Reading for the Adult Deaf." The author asserted that the United States was "a trifle backward" in its endorsement of lip reading.

An Editorial, "The Laboratory in War," exhorted: "The bacteria of disease are to be defeated by methods no less highly specialized than are the other procedures of modern warfare."

FIFTY YEARS AGO, FEBRUARY 1958

Johannes Virkes, MD, in "Barbituate Poisoning," estimated, from national data, that Rhode Island had 70 cases per year. For treatment, there were "two opposing schools of thought: one advocated "an active expectant attitude relying on supportive treatment only;" the other relied on "potent analeptics."

A.A. Savastano, MD, in "Use of Hydrocortisone in Office Practice," discussed the use among his orthopedic patients. He followed 1072 patients (with arthritis, Osgood Schlatter's disease, tendinitis, etc.) for at least 3 months. Of the patients with arthritis, 25% "improved so much after 1 to 3 injections that no further treatment became necessary for 3 months or longer."

The Division of Vital Statistics of the Rhode Island Department of Health submitted "A Special Report: Influenza Epidemic and 1957 Mortality in Rhode Island." In 1950, the state recorded 16 deaths; in 1951, 16 deaths; in 1956, 5 deaths; in 1957, 8 deaths. The authors urged Rhode Islanders to be vaccinated.

TWENTY-FIVE YEARS, FEBRUARY 1983

W. Christopher Ehmann, MD, and Tom J. Wachtel, MD, contributed "Acute Gastric Dilation Associated with Viral Hepatitis." They discussed a 52 year-old man, living in a group home, where no other residents were ill. They concluded: "Treatment of gastric dilation associated with medical disorders is simple and effective."

John P. Fulton, PhD, Steven A. Wartman, MD, PhD, Tom J. Wachtel, MD, Albert F. Wessen, PhD, Herbert Constantine, MD, and David B. Reuben, contributed "Problem of Vague Academic Evaluations in Selection of Residents: A Case Study." Using multiple regression analysis, they concluded: "Medical school grades when available and national board Part II results provide the best criteria for evaluation."

David A. Rochefort, MD, Donald C. Williams, MA, Bruce C. Kelley, PhD, David M. Gute, PhD, MPH, and James K. Jackson discussed "Rhode Island's Aging Population and The Use of Medical Care, 1980-2020."



The Name of Choice in MRI



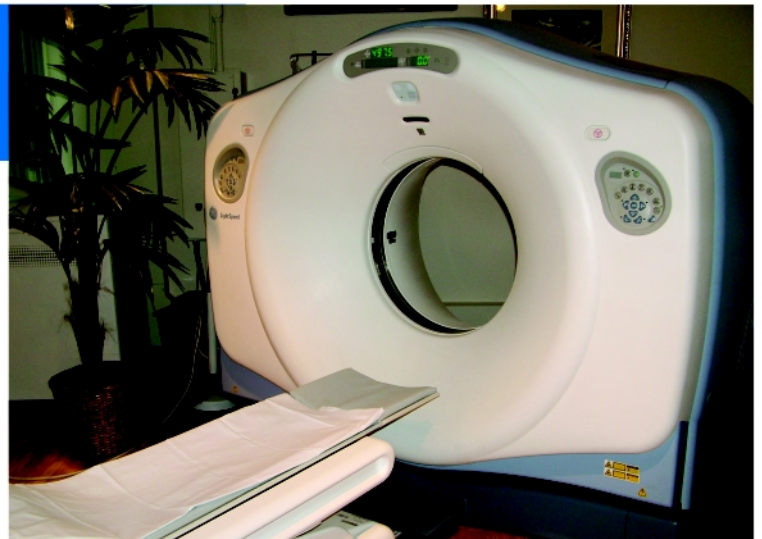
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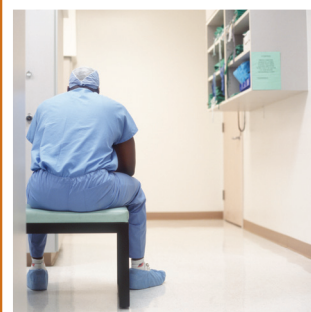
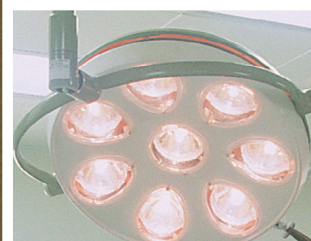
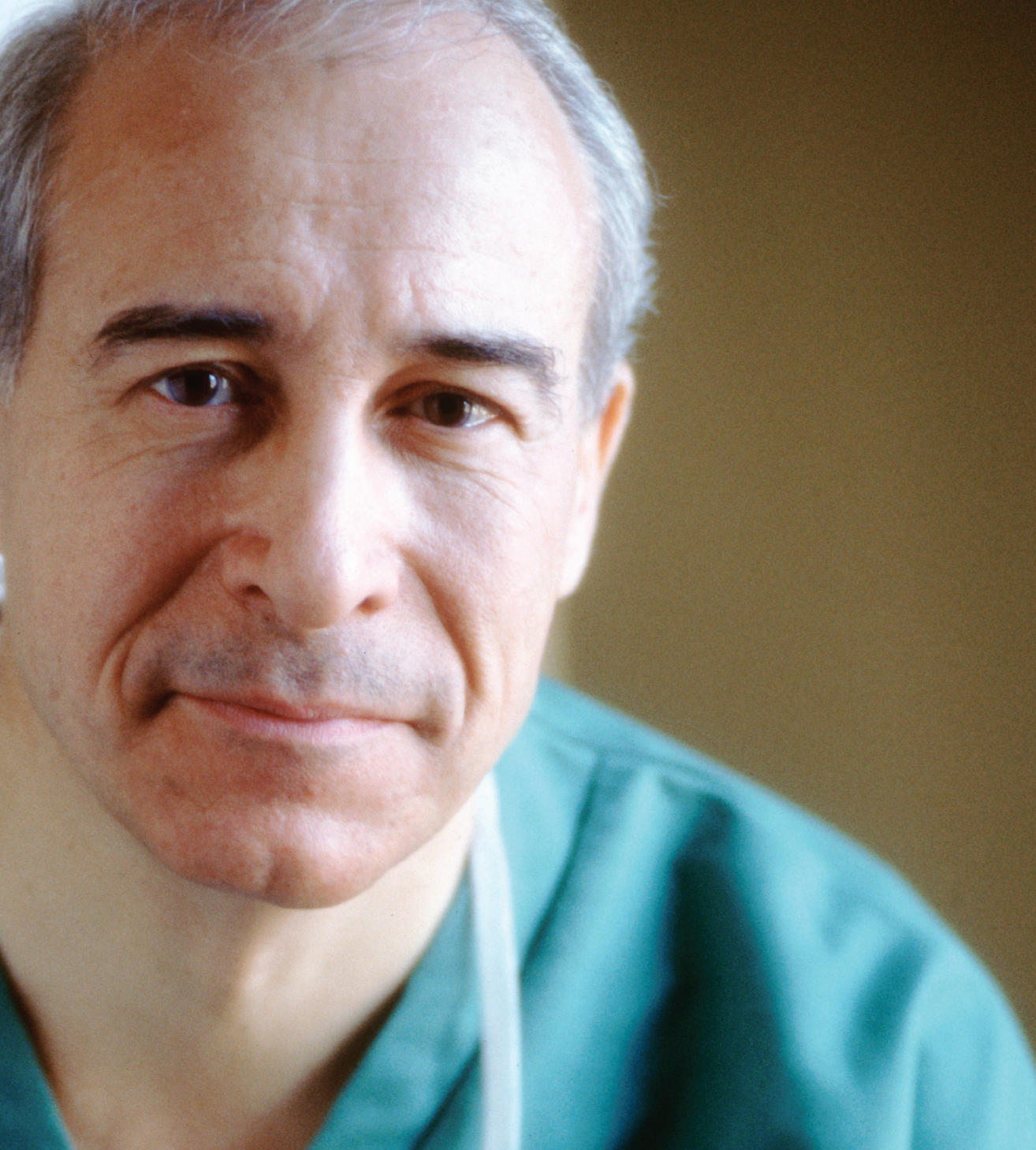
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