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VOLUME XCIX

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2001

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In Memorium

DR NORMAN ASHTON, ELECTED 1989  
DR CARL CORDES JOHNSON, ELECTED 1961  
DR ALBERT M. POTTS, ELECTED 1962

**NORMAN HENRY ASHTON, MD**

BY *Lorenz E. Zimmerman, MD, DSC*



Last year began with the loss of a very dear friend and colleague as well as a world-class leader in ophthalmic pathology, Professor Norman H. Ashton of London. Of humble origin, young Norman left school at age 16 to begin working as a laboratory assistant in a West London hospital. Subsequently, the head of the laboratory further stimulated Ashton's interest in medicine suggesting that he train to be a doctor. According to Alec Garner, some initially considered that suggestion to have been made in jest, as Ashton's family had not been one of academics and "going to University wasn't something the Ashtons did."

Nevertheless, Ashton did "read-medicine" at Kings College London and Westminster Hospital Medical School. After qualifying by age 26, Ashton specialized in pathology and was appointed a pathologist to the Kent and Canterbury Hospital from 1941-1945. He then served in the Royal Army Medical Corps in West Africa and Egypt from 1945 to 1947.

When Ashton returned to London following the end of World War II, Sir Stewart Duke-Elder was completing his staffing of the new Institute of Ophthalmology at

Moorfields where he was director of research. Sir Stewart selected Norman Ashton as head of the pathology department despite his lack of any special training or experience in ophthalmic pathology. That was the insight of a genius "head-hunter"! Ashton began his tenure as the first director, Department of Pathology at the Institute of Ophthalmology in 1948. For over nearly a century before that, "the most exalted position in the English-speaking World for an ophthalmic pathologist" had been the joint position of pathologist curator and librarian at Moorfields Hospital held by such notable figures as Edward Treacher Collins, Sir J. Herbert Parsons, George Coats, and Edward Nettleship.<sup>2</sup> These gentlemen were clinical ophthalmologists who earned their living in their practice of ophthalmology while contributing their time and interest in ocular pathology to Moorfields Hospital on only a part time basis. The new full-time position occupied by Ashton as head of the Department of Pathology at the Institute of Ophthalmology was the first of its kind in England.<sup>1,2</sup> From the beginning of his tenure, Ashton provided a comprehensive service encompassing all the major pathology

disciplines required for diagnostic histopathology and research, including experimental pathology. Not only did his laboratory provide the clinical laboratory and anatomic pathology service for Moorfields Hospital, but also consultation service for all of the British Isles and, in fact, the entire British Empire, which afforded Ashton and his staff the opportunity to study ocular involvement in various exotic diseases. During his 30 year tenure before reaching the mandatory retirement age of 65, Ashton established his world-wide reputation as the leading experimentalist in ophthalmic pathology, with major contributions towards understanding the pathogenesis of the retinopathy of prematurity, diabetic and hypertensive retinopathy, the nature of "cotton wool spots," and the pathogenesis of primary open angle glaucoma. He attracted many well-trained general pathologists for prolonged periods of training in ophthalmic pathology, one of whom, Alec Garner, became Ashton's successor as Director of the Department of Pathology when he retired in 1978.

Ashton had no peers when it came to incorporating his remarkable talents in the arts with his professional activities in ophthalmic pathology. He became a talented painter in oils but also applied the same artistry to his research preparations. His command of the English language was awesome, putting him in as great demand for after-dinner speeches as for participation in national and international meetings of ophthalmologists and pathologists. The legendary Bob Hope added significantly to Ashton's luster in the after-dinner public speaking arena when they were the 2 banquet speakers at a dedication of a new research wing for the Wilmer Institute. Ashton spoke first and so delighted the audience with his wit, charm, and eloquence, that the prolonged applause prompted Bob Hope to complain that he had not been warned that he was to share the platform with a "funny eye doctor"! Many who witnessed that performance left uncertain as to which of the two had been the most entertaining performer! But, as Garner has stated, Ashton was much more than an entertainer on that occasion, as his speech stressed the importance of research and his disapproval of medical research that did not have an endpoint of relevance to patient care.<sup>1</sup>

According to the current Directors of the Institute of Ophthalmology (Sillito and Luthert),<sup>3</sup> Ashton's legacy comprises not only the results of his own research but also the structures he has left behind. His clear thinking was central to the creation of the current Institute of Ophthalmology building on a joint site with Moorfields Eye Hospital. And by pivotal contributions to the establishment and growth of the national charity, Fight for Sight, he ensured that the current generation of researchers are in a position to carry on where he left off. Garner expressed similar thoughts,<sup>1</sup> stating Ashton's

commitment to the Institute was total. Success in research is determined not only by ideas but the availability of resources to pursue them and Norman threw himself heart and soul into supplementing the Institute's research funds. He was a key element in creating and working for "Fight for Sight", a charity primarily devoted to supporting the research activities of the Institute. In this he was far from self-seeking, very little of the money he helped raise coming to his own department. This selfless commitment is further demonstrated in his taking up the chairmanship of the charity when, in 1978, he stepped down from the Chair of Pathology. His share in the part played by "Fight for Sight" in making it possible for the Institute to move to more adequate premises next to Moorfields Eye Hospital and then to extend them was recognized in naming the newest development, opened only last year, the "Ashton Wing."

In 1959 Norman Ashton had been the first European guest-of-honor at the annual meeting of the American Ophthalmic Pathology Club, and 2 years later Ry Anderson of Copenhagen, Denmark, was similarly honored. Both were greatly impressed and stimulated by several of the unique features of this type of meeting, which had no counterpart in Europe. This led Ashton to propose, with the assistance of Anderson and Willem Manschot of the Netherlands, the development of a similar organization, the European Ophthalmic Pathology Society.<sup>4</sup> Despite the fact that at its first organizational meeting at the Royal College of Surgeons in London in 1962, many of the participants were unable to make their presentations in English, and some of the Founder Members had not previously met, all were in agreement that the meeting was a huge success and that Norman Ashton deserved special credit for making it possible. Accordingly, he was unanimously elected to the presidency for the period 1962-1965 and subsequently designated Life President in 1965.

Ashton was widely recognized and fittingly acclaimed. He received the Nettleship Prize (1955), Proctor Gold Medal (1957), Doyne Lecture Medal (1960), Bowman Lecture Medal (1965), Donders Lecture Medal (1967), William MacKenzie Memorial Lecture Medal (1967), Baron C Ver Heyden de Lancey Medical Art Society Prize (1978), Gonin Gold Medal (1978), and Jules Stein Award (1981). He was elected Fellow of the Royal Society of London (1971), Honorary Fellow of the Royal Society of Medicine (1979), Honorary Member of the American Ophthalmological Society (1989), and Honorary Fellow of the Royal College of Pathologists, London (1992). In 1976 Ashton was appointed by Her Majesty the Queen, as Commander of the Order of the British Empire.

Amazingly, Norman Ashton, who was a pathologist, not an ophthalmologist, was made President of the

Ophthalmological Societies of the United Kingdom, presiding over its Centenary Meeting of 1980. What an expression of affection as well as appreciation for what this great pathologist had done for ophthalmology! He was selected to be the Helen Keller Prize Laureate for 1998, awarded for vision research at a ceremony usually held at the annual meeting of the Association for Vision and Research, USA, but owing to Professor Ashton's deteriorating state of health, the Helen Keller Foundation arranged to have its presentation take place during the 1998 Oxford Ophthalmological Congress in Oxford, England.

In 1990 when the American Journal of Ophthalmology dedicated its November issue to me on the occasion of my 70th birthday, Professor Ashton contributed one of the "Letters of Tribute."<sup>5</sup> Long before that he had become widely recognized as the pre-eminent Dean of ophthalmic pathologists. I reprint some of his comments for several reasons. One is to document his generosity, keeping in mind that it was he who was generally regarded as the leading figure in ophthalmic pathology. Another is to illustrate some of his beautiful, clever way with words:

"It is a privilege to have this opportunity to congratulate Lorenz Zimmerman on his 70th birthday and to pay tribute to his outstanding achievements in ophthalmology. His career and mine have been so closely paralleled, even entwined, that I am in a special position to recognize his remarkable contributions to the study of eye disease, which when he entered the field in 1953 was limited in scope. With few exceptions, it was a histologic hobby, rigidly encapsulated in ophthalmology and so sealed off from general pathology; locked up, as it were, in a Pandora's Box of ocular ills, where-in a wealth of opportunities for original observations awaited the person with the right key. Zim had that key, made with the metal of his wide experience in general pathology, his tireless energy, and his inquiring mind. A glance at his formidable list of publications shows that before specializing in ophthalmic pathology...."

Just as Alec Garner pointed out in relation to Ashton's "duel" with Bob Hope, here again Ashton had an important message to offer all of us in ophthalmic pathology:

"It is difficult to overestimate the importance of Zim's work and he will always be an important figure in the evolution of eye pathology, but today the scene is shifting. New and highly complex techniques (littered with acronyms comprehensible only to the initiated) in molecular biology, genetics, and immunology are emerging, all of which are highly relevant to eye disease. No longer can one person hope to bestride the disciplines, and all the specialty of ophthalmic pathology must expand to include experts in these growing areas, or it will sink back into the deep freeze of conventional histology, a tendency that is unfortunately encouraged by ophthalmic pathology societies throughout the world."

And this clever way to end his tribute:

"Dear Zim, in this penultimate pleasant phase of our lives, spent happily poised between postmaturity and presentility, we can look back with satisfaction and claim that in our time we together covered ophthalmic pathology from A to Z (in that order because I preceded you by five years!) but on this special occasion I should say from Z to A. Congratulations on your birthday...."

Although Norman Ashton may not have been "born with a silver spoon in his mouth" as Alec Garner stated, his parents certainly endowed him with a remarkable set of genes, which he exploited in remarkable ways.

[Editor's note The obituary for Norman Ashton was modified from the obituary published in *Archives of Ophthalmology* 2001;119:1229-1230.]

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*Necrology*

CARL CORDES JOHNSON, MD

BY *Richard M. Robb*, MD

Carl C. Johnson died at the age of 88 on February 5, 2000 at his residence in Weston, MA. Carl was the son of Carl Henning Gothard Johnson and Olga Amelia Cordes. He was the husband for 62 years of Rosina Irving Biggerstaff Johnson. Born in 1911 in Schenectady, NY, Carl graduated from Union College in Schenectady in 1934 and from Harvard Medical School in 1938. He served an internship at Hartford Hospital, Hartford, CT from 1938 to 1940, and completed his residency in ophthalmology at the Massachusetts Eye and Ear Infirmary in 1942.

From 1942 to 1962 he was associated with Dr Paul Chandler in the private practice of ophthalmology in Boston. He then served as Associate Chief of Ophthalmology at the Massachusetts Eye and Ear Infirmary with Dr David Cogan from 1962 to 1968. He was an Associate Clinical Professor of Ophthalmology at Harvard Medical School from 1965 to 1981. Dr Johnson's special interest in ophthalmology was blepharoptosis, and his major clinical contributions were in the surgical correction of ptosis, the subject of his American Ophthalmological Society thesis in 1961. He became particularly interested in the syndrome of epicanthus inversus, blepharophimosis, and ptosis, about which he contributed several original papers. For the staff of the Massachusetts Eye and Ear Infirmary during his tenure,

he was the acknowledged authority on all matters concerning the eyelids. He shepherded many residents through their initial encounter with eyelid surgery, most often by helping them with his preferred external levator resection. From 1968 to 1983 he returned to private practice with Dr Roland Houle in Boston, and then moved his office to Weston, where he retired in 1991.

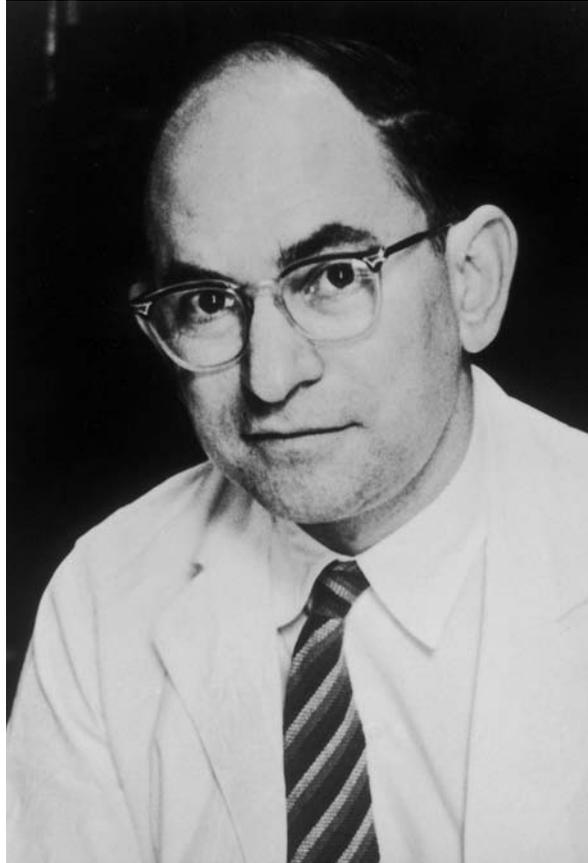
Dr Johnson's professional affiliations were with the American Academy of Ophthalmology, the American Board of Ophthalmology, and the American Ophthalmological Society. He was a past president of the New England Ophthalmological Society and a Fellow of the American College of Surgeons. He served as a medical advisor to the Massachusetts Society for the Prevention of Blindness, and was a member of the advisory board of the American Society of Ophthalmic Plastic and Reconstructive Surgery.

Carl was an accomplished equestrian. For some years he served as master of the Nashoba Valley Hunt. In his later years he spent much of his time in Spain with his daughter and son-in-law and their family. He is survived by his wife, his daughter, Carol (Countess Gael Balouzet) de Tigny; 2 granddaughters, Virginia de Tigny Fachini and Elisabeth de Tigny Mourrot; and two great grandsons, Massimiliano Carlo Fachini and Alexander Carl Mourrot.

*Necrology*

ALBERT M. POTTS, PHD, MD

BY *J. Terry Ernest*, MD, PHD



Albert Mintz Potts, professor of ophthalmology and pioneer in ophthalmic research, died of myofibrosis at the age of 86 at his home in Tucson, Arizona on February 7, 2001. Albert led a distinguished career characterized by a fascination with vision, a commitment to the highest standard of scientific research, and a creative integration of biochemistry and ophthalmology.

Born in Baltimore, Maryland in 1914, Bert attended Baltimore City College, a unique high school honors program, before earning a A.B. degree in chemistry at Johns Hopkins University at the ripe age of 20 years. Four years later, he received his PhD in Biochemistry from the University of Chicago and eventually a MD from Western Reserve University in 1948.

Much of his genius was his ability to make complex retinal biochemistry understandable and clinically relevant. Several years ago, I had the opportunity to review his PhD thesis and found it is less than 20 pages with only a few references. I asked him about its brevity, and he pointed out that he had discovered a new chemical reaction and there were no references.

During World War II, Bert worked on the Manhattan Project at the University of Chicago, exploring the potential health risks of radioactivity on humans, studying the effects of breathing radioactive particles, and designing equipment to protect workers from inhalation of radioactivity. Significantly, in 1946, he wrote a paper on the application of nuclear physics to biology and medicine. While he had the opportunity to move to Los Alamos with the Project, Bert decided to attend medical school and complete a residency in ophthalmology at Western Reserve. Simultaneously, he led pioneering research of radioactive isotopes studying biochemically active substances in the body and later, in the eye.

While on faculty at Western Reserve, Bert watched his very successful clinical practice and teaching commitments at University Hospitals eclipse time for research. Consequently, in 1959, he accepted a position at the University of Chicago as Professor of Ophthalmology and Director of Ophthalmic Research, and focused his research on ocular electrophysiology and the biochemistry of the retina.

## *Necrology*

Bert's insights into the pathogenesis of eye diseases were legendary at the University of Chicago, but it was his relationships with his students that will be remembered best. During his tenure, he mentored a number of residents who were earning their combined PhD/MD degrees and who were interested in vision research. He had a sympathetic ear and provided sage advice. Most importantly, he believed in all of us and no matter how far from the road we would diverge, he never judged, but simply helped us back onto the highway. A number of his students have become department heads of major universities.

I spent many years with Bert as my mentor and friend, and would be remiss if I did not share one story. Shortly after finishing my dissertation, Bert called me into his office and told me that my work was so wonderful and good, that he wanted me to do a little bit more. Needless to say, I did a little bit more, and in the end, felt good about it. In later years, I would send him birthday cards asking him to do a little bit more, which he naturally did, until the very end.

After leaving the University of Chicago, Bert served as chairman of the Department of Ophthalmology at the University of Louisville from 1975-83, and as acting head of the Department of Ophthalmology at the University of Arizona from 1984-85. After his "retirement," he began work on a project to organize his extensive ophthalmology slide library into a computerized diagnosis program for emergency room physicians. He was an active member of the International Society for Clinical Electrophysiology of Vision and served as Vice-President for the Western Hemisphere from 1978-84.

Over 200 articles and several books attest to his commitment to research and to the depth and breadth of his fascination with vision. I remember one study in particular in which he needed to know the number of fibers in the optic nerve. Their count had only been estimated before, but the data were important for his analysis of

optic nerve diseases. He quickly pointed out to me, when I asked him about how he would accomplish such an impossible task, that Alice would do it in a day. At that time, Alice was a very large image processing computer. When Professor Potts told you something, you knew you could build on it because it was basic, comprehensive, complete and correct.

He also explored vision from an anthropological perspective and his book, *The World's Eye*, examines the myths, meanings, and symbolism of the eye across cultures and throughout history. Bert's interests also included photography, astronomy, chess, jewelry-making, collecting ancient Greek and Roman coins, and collecting amulets against the evil eye from around the world.

Finally, it is important to remember Dr Potts as a superb ophthalmologist. He was able to bring his basic science knowledge to the clinic for the benefit of his patients and at the same time, show great compassion for their suffering. He would spend whatever time was required to explain clearly and precisely the patient's problem and his treatment plan. He showed us by example how to care for patients and how to integrate basic science and clinical care.

His wife of 62 years, Esther Potts, 3 children and 2 grandchildren survive him. He is also survived by Edith Goldman, who served as his secretary and office manager in Cleveland, Chicago and Louisville, and by Pin Chit Au, his lab assistant in Chicago, Louisville and Tucson.

The University of Chicago has established the Albert M. Potts Award for Pursuit of Research in Ophthalmology. The fund enables an outstanding ophthalmology resident with an interest in research to attend the annual Association for Research in Vision and Ophthalmology meeting.

Bert Potts, scholar, clinician, administrator and renaissance man, he will always be in our minds and in our hearts.

## MINUTES OF THE PROCEEDINGS



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*One Hundred and Thirty-Seventh Annual Meeting  
May 20-23, 2001*

The ONE HUNDRED AND THIRTY-SEVENTH ANNUAL MEETING of the American Ophthalmological Society was held at The Homestead in Hot Springs, Virginia on May 20-23, 2001. President Paul R. Lichter called the opening session to order at 7:30 AM on Monday morning, May 21. The following scientific program was presented:

1. "The Effects of Panretinal Photocoagulation on the Primary Visual Cortex of the Adult Monkey" by Joanne A. Matsubara, PhD (by invitation), Dawn Y. Lam, BSc (by invitation), Ronald E. Kalil, PhD (by invitation), B'ann T. Gabelt, MS (by invitation), T. Michael Nork, MD, Dan Hornan, MBBS (by invitation), and Paul L. Kaufman, MD
2. "Fibrous Congenital Iris Membranes With Pupillary Distortion" by Richard M. Robb, MD
3. "Strabismus due to Flap Tear of a Rectus Muscle" by Irene H. Ludwig, MD, and Mark S. Brown, MD (by invitation)
4. "Psychosocial Implications of Blepharoptosis and Dermatochalasis" by John D. Bullock, MD, MS, Ronald E. Warwar, MD, David G. Bienenfeld, MD, Sara L. Marciniszyn, MD, and Ronald J. Markert, PhD
5. "The Opportunity for International Ophthalmology in Treatable Blindness" by Bruce Spivey, MD
6. "Conductive Keratoplasty for the Correction of Hyperopia" by Penny A. Asbell, MD, Robert K. Maloney, MD (by invitation), Jonathan Davidorf, MD (by invitation), Peter Hersch, MD (by invitation), Marguerite McDonald, MD (by invitation), E. Manche, MD (by invitation), and the Conductive Keratoplasty Study Group (by invitation)
7. "The Ateleotic Macula: A Newly Recognized Developmental Anomaly" by M. Elaine De Pool, MD (by invitation), Hala El-Hileli, MD (by invitation), and Irene H. Maumenee, MD
8. "Complications of Cataract and Refractive Surgery: A Clinicopathological Documentation" by David J. Apple, MD, and (by invitation) and Liliana Werner, MD, PhD

## **Executive Session, May 21**

President Paul R. Lichter called the Annual Executive Session of the American Ophthalmological Society to order at 11:30 AM. He appointed Dr. John D. Bullock to be the parliamentarian.

A motion to approve the minutes of the 2000 Executive Session, which were published in Volume XCVIII of THE TRANSACTIONS OF THE AMERICAN OPHTHALMOLOGICAL SOCIETY, was made, seconded, and approved.

The following reports were submitted.

## **Secretary-Treasurer Report**

CHARLES P. WILKINSON, MD reported that the financial status of the American Ophthalmological Society was in order. He enthusiastically announced the establishment of the AOS Website, [www.aosonline.org](http://www.aosonline.org), and said the details would soon be mailed to the members.

## **Editor's Report**

J. BROOKS CRAWFORD, MD. The *Transactions of the American Ophthalmological Society*, Volume XCVIII, was mailed in January 2001. The mailing included copies to active members, honorary members and emeritus members who requested a copy, complimentary copies (primarily to the widows of deceased members listed in the Necrology), copies to libraries for the cost of shipping from a grant by The Charitable, Education, and Scientific Fund, and paid orders.

The height and width of the volume was increased to the size of major journals (*Archives of Ophthalmology*, *American Journal of Ophthalmology*, *Ophthalmology*) to reduce the thickness of the journal (546 pages compared to 1115 pages last year) and make it easier to bind. Reports from our members indicate a favorable response to this change. A few mistakes occurred and I apologize for them. Johnson Printing has purchased new color proofing equipment which will make it easier for authors and the editor to review the proofs in actual but not true color. This may help to eliminate mistakes associated with color printing.

The *Transactions* included the Minutes of the Proceedings of the Executive Session, 4 obituaries, 22 papers, 10 theses, and the Constitution and Bylaws of the

American Ophthalmological Society.

42 pages were in color. The first 2 pages of color prints for papers and the first 4 pages for theses were partially subsidized by the Charitable, Education, and Scientific Fund, costing the author \$50 a page instead of \$500 a page. To realize the full benefit of this it is important for authors to group the pictures they want reproduced in color and provide specific instructions to the Editor of how they wish them presented, i.e. how many per page and their organization on each page. The editor feels that some of the color photographs could have been combined on pages and that some of the graphs in color could have been easily converted to black and white, saving the author unnecessary expenses, but this decision ultimately rests with each individual author. Let me emphasize once again *that it is the responsibility of the author of each paper and thesis to communicate this information to both the editor and the printer (Johnson Printing) and be sure that this is correct in the galley proofs.*

We are grateful to Dr William Tasman for publishing the theses on Duane's CD ROM and to Drs Bradley Straatsma and Thomas Liesegang for publishing abstracts of the papers and theses in issues of the *American Journal of Ophthalmology*.

The Council has decided that only the first discussion of a paper and the author's response will be published in future TRANSACTIONS. Everyone is still welcome and encouraged to add to the discussion of a paper.

This concludes my report. Thank you Mr. President.

### Report of the Program Committee

STEPHEN S. FEYMAN, MD. The Program Committee consists of Stephen S. Feyman, MD, Chair, Paul R. Lichter, MD, and Charles P. Wilkinson, MD.

This year, there were 42 abstracts submitted for possible inclusion in the Annual Meeting. The committee members independently reviewed each abstract and assigned a grade on a scale between 1.0 and 5.0 to each one. Although abstracts of many superb papers were submitted, time constraints limited the number of papers that could be accepted for possible inclusion. A preliminary program was designed to include the 22 abstracts with the best mean grades. The final printed program was developed from information related to the order in which the papers were received and the specific audio-visual requirements of each presentation.

Of the papers scheduled for the program, there were 5 to be presented by new members, 5 by associate members, and 12 by the members.

The Program Committee wants to thank the members and their guests for their participation in the scientific

program of the Annual Meeting. In addition, I want to extend my personal thanks to Drs Lichter and Wilkinson for their aid in organizing the scientific meeting, arranging for the presentations, and for their help in inviting the primary discussants, and to Lisa Brown, the AOS Meeting Manager, for her great efforts on our behalf.

### Report of the Thesis Committee

LEE M. JAMPOL, MD. The members of the committee included Bruce Shields, Bronwyn Bateman, and myself. We anonymously reviewed 8 theses, 7 new ones and one revision. We recommended that 5 (4 of the new ones and the revision) be accepted, that one be revised, and that 2 be rejected.

### Report of the Photographer and Archivist

RALPH C. EAGLE, JR., MD. One hundred eighty-seven photographs were taken at the 2000 meeting of the American Ophthalmological Society at the Inn at Spanish Bay in Pebble Beach, California. Three were used as figures in volume XCVIII of the Transactions of the AOS. These included photos of President W. Banks Anderson and his wife Nancy, Howe Medalist William S. Tasman and his wife Alice Lea and a group photograph of 10 new members. The photos were taken with a Nikon 6006 camera using 35mm color print film. Two sets of color prints were prepared. Prints were distributed to all of the new members. In addition, all photos were digitized using the Kodak PhotoCD format. Figures for the Transactions were prepared from the digitized images using an Apple Macintosh™ PowerPC computer and Adobe Photoshop™ 5.0 and were submitted in digital format to the Johnson Publishing Co. on a 100MB Iomega Zip disk. Computer generated prints were also prepared for editorial review. The Society's digital photo archives now comprise 1131 images from the 1996, 1997, 1998, 1999 and 2000 meetings.

### Report of the Emeritus Committee

STANLEY M. TRUHLSEN, MD. The latest American Ophthalmological Society directory shows a membership of 108 emeritus members. I am sorry to report the loss of 2 of our members:

Carl Cordes Johnson (1961)

Albert M. Potts (1962)

Our membership continues to grow however, as 7 active members have applied for emeritus status in accordance with our constitution, which requires a 25 year membership, or age 70 or complete retirement from active practice, the recommendation of the Council and

an affirmative vote of three quarters of the members present at the Executive session. The new member applicants are:

Taylor Asbury (1966)  
Richard F. Brubaker (1982)  
Ronald E. Carr (1974)  
Rufus O. Howard (1977)  
Robert G. Small (1988)  
Barbara W. Streeten (1982)  
H. Stanley Thompson (1977)

The Emeritus membership received 2 newsletters this past year regarding this meeting and the annual luncheon which will be held in the Dominion Room immediately following this Executive session.

The growth of the Emeritus membership is an indication of the high regard and loyalty members have for this venerable old society, and by the number of members, spouses and friends who will gather to see old friends, socialize and spend a part of our meeting together, in addition to the other activities of this meeting.

A motion to accept the new applicants for Emeritus members was made, seconded and approved.

### **Report of the Foundation of the American Academy of Ophthalmology Museum Liaison**

JOHN D. BULLOCK, MD. The Museum Committee of the Foundation of the American Academy of Ophthalmology is chaired by Dr Norman Medow. The Museum was first organized in 1980 and is housed in the Academy headquarters in San Francisco. It is now named The Museum of Vision and is committed to educating people about the eye, vision, and ophthalmology through its collections, exhibitions, and public outreach programs.

It strives to improve science literacy among young people and their families raising their their awareness of ophthalmology's important relation to history, art, the humanities, mathematics, and other fields of science. The Museum of Vision has over ten thousand objects dating from the third century B.C. and is the premier ophthalmic collection in the United States.

The Museum of Vision is considered a "museum without walls" because it circulates its programs and exhibitions nationally. Two of the traveling exhibits, "Discover Your Eye-Q!" and "Art and Vision: Seeing in Three-D," emphasize a hands-on approach to the science of vision. The Academy's largest exhibit entitled "Animal Eyes" is an exhibition about human and animal vision. It was developed by the museum with generous support from the National Science Foundation and Lens Crafters. The exhibit recently won first place in the American Association of Museums national traveling exhibition competition and has been traveling throughout the

United States for the past several years. It is expected to reach an estimated 1.1 million visitors. This exhibit travels under the sponsorship of the Association of Sciences and Technology Centers and in the year 2001 will be or has been exhibited in Evansville Indiana, Sacramento California, Minneapolis Minnesota, and West Hartford Connecticut. It is accompanied by text available in Braille, large print and Spanish. The exhibition is currently being refurbished and will tour for another 3 years.

The museum has also developed a curriculum guide, Eye Openers-Exploring Optical Illusions, that can accompany the interactive exhibit "Discover Your Eye-Q!" which features optical illusions and activities related to vision.

By way of the Internet, the public can actually visit portions of the Museum's collection, online. This information can be accessed by (1) logging onto either (a) aao.org or (b) eyenet.org, and then, clicking onto (2) the Academy Foundation, and then clicking onto (3) the Museum of Vision. This website contains information about the museum, its educational programs, aspects of its collection, and information concerning ophthalmic history.

The Ophthalmic History Center presents a history of cataract surgery, a history of spectacles, a history of the invention of the ophthalmoscope by Hermann von Helmholtz and a history of the American Academy of Ophthalmology.

In its collections the museum has numerous artifacts including many types of ancient spectacles. The museum also owns the famous illustrated report of the first successful cataract extraction completed in about 1747 by Jacques Daviel, as well as early ophthalmic textbooks, many old instruments, anatomical specimens, eye cups, paintings, woodcuts, and other artistic artifacts.

During the year 2001 (as of May 1), the museum had answered a total of 65 inquiries from ophthalmologists and from the general public and added 175 highly desirable artifacts to its collection. The museum recently purchased a new collections management software package which will enable the museum to keep better track of its collection, as well as to aid in research and exhibit design purposes.

The superb former director of the museum is Licia Wells, who is now the promotion and marketing manager of the Clinical Education Products of the American Academy of Ophthalmology. The current collections manager is Tina Schmitz.

The museum presents an exhibit at the annual American Academy of Ophthalmology meeting. This year in New Orleans, the exhibit will focus on Chinese spectacles and spectacle cases.

The excellent work of the museum's staff and committee members, through their devotion and energies,

assures that the achievements and history of ophthalmology will be preserved and perpetuated far into the future. Thank you.

### **Report of the National Association for Biomedical Research Committee**

EDWARD A. JAEGER, MD. The AOS has been a member of the National Association for Biomedical Research (Nabr) for many years. Nabr is an association that tracks the activities of animal rights activists, as well as legislation associated with the use of animals in research. The dues are \$500 per year. Many members of the AOS have been involved in therapeutic trials and investigative studies involving the use of animals. Our organization promotes the ethical care and responsible treatment of laboratory animals. Many landmark breakthroughs in the diagnosis and treatment of diseases have been achieved through the use of laboratory animals. While alternative in vitro methods have been developed, few in the scientific community would question the continuing need for the use of animals in evaluating cancer treatments, the development of an AIDS vaccine and in many other diseases that result in significant human mortality and morbidity.

There were 2 important issues this year that weighed heavily on medical research facilities. The first was a partial resolution of the lawsuit *Alternatives Research and Development Foundation (ARDF) vs. The U.S. Department of Agriculture (USDA) and Glickman (Past-head of USDA)*. The purpose of this suit was to expand the definition of "animal" in the *Animal Welfare Act* to include rats, mice and birds. This enormously would increase the overhead costs to medical research facilities. Unfortunately, this suit was settled out of court in which the USDA agreed to expand the definition of "animal" much to the dismay of Nabr and the entire medical research community. However, the legislature denied funding for the administrative costs for implementing this change for a period of 1 year.

The second important issue was an attempt to define "pain and distress" in animals used in research. By necessity, a definition would include various levels of pain and distress along with appropriate relief to be instituted at each level. This would extend further the record keeping and reporting responsibilities of medical research facilities. However, to date, there have been no concrete proposals submitted in this regard although they may be anticipated.

There are a large number of animal rights and anti-research organizations along with extremist environmental groups which espouse militant and terrorist tactics to achieve their personal agenda. Cars, houses, genetic and medical research facilities and restaurants have been

damaged, all in the name of a perceived higher good. The FBI has labeled some of these organizations as "left wing extremist groups." This makes one wonder if there isn't an additional agenda behind the "higher good." This is illustrated by the "credits" attributed to the burning of the Republican headquarters in Bloomington, Indiana because the party had supported the construction of I-69 through Indiana. In the arsonist's mind, the highway was being built to "satisfy the greed of the multi-national corporations, as well as the lust of the working class for money."

Other attacks on society include the chastising of the Boy Scouts of America for having "fishing" and "fish and wildlife badges," the American Heart Association for its research practices, the *Survivor* TV series and the "Drink Beer not Milk" campaign. A prominent animal rights activist expressed the hope that "foot and mouth" cattle disease would spread to the U.S. This brings to mind the possibility that it could be intentionally spread.

There also have been many positives. A number of states have passed anti-terrorist legislation. Christopher Reeves and hockey player, Travis Roy, strongly have supported spinal cord research. The British government staunchly has refused to buckle under to the unreasonable demands and terrorist threats of militant animal rights and environmental groups. The Bush Administration has emphasized the need for more medical research and is expected to review the previous legislation with the possibility of redirecting priorities. The new head of the USDA is The Honorable Ann Veneman, a highly respected administrator with a ranching background.

Nabr is a necessary organization and worthy of our continued support. Barbara Rich is the Executive Vice President. She is a knowledgeable and vigorous proponent of the ethical and humane inclusion of animals in the on-going medical research effort to neutralize diseases in the human species.

### **Report of the American Ophthalmological Society Representative to the American College of Surgeons Board of Governors**

BARRETT G. HAIK, MD. At present, 2,839 ophthalmic surgeons are fellows of the American College of Surgeons. They represent six percent of the 48,880 active members. In 2001, 66 ophthalmic surgeons applied for fellowship. The College's Advisory Council for ophthalmic surgery is chaired by Lee R. Duffner. Members are Thomas A. Deutsch, A. Raymond Pilkerton, Jr., James W. Karesh, and Arysal S. Niffenegger, Barrett G. Haik, and Regent William H. Coles.

The American College of Surgeons Board of Governors met on Sunday, October 22, 2000, in Chicago, Illinois. Issues discussed by the Board include the com-

plexity and burdensome nature of coding surgical services for reimbursements. Many were greatly dissatisfied with “evaluation and management” (E&M) coding, stating that the methodology used to determine E&M procedure coding is flawed, and unnecessarily complex and that it inadequately compensates surgeons for their patient care services. It was suggested that the College should develop guidelines to assess MCO contracts, continue to offer practice management and coding workshops, and continue its efforts to support federal legislation that would establish a “patient’s bill of rights.”

The governors also expressed their concern regarding graduate medical education and the reductions in academic medical centers that may result in extreme challenges for the Centers in fulfilling their 3 missions—clinical care, education and research.

Professional liability, malpractice, and tort reform. The major concern of the Board relating to professional liability is the total lack of tort reform across the United States. It was suggested that the College should continue to serve as a “clearing-house” for information and assistance on professional liability issues and problems, and continue its efforts to support tort reform legislation at the state and federal levels.

With regard to professional development, recommendations included continued expansion of the College’s education and verification activities related to new surgical technology, equipment and devices; continued monitoring of the certification and recertification requirements of the ABMS boards to ensure that educational programs are meeting the needs of the fellows; and continued work with various specialty societies to develop and disseminate guidelines for education on and competency assessment for new and various surgical procedures.

The American College of Surgeons Oncology Group was established in 1998 with funding from the National Cancer Institute and was recently approved for 5 additional years of funding beginning May 2000. The Group is involved in ten cooperative clinical trials in the United States; however, there are no active trials presently in the ophthalmic oncologic field.

Representation of the American Ophthalmological Society on the Board of Governors and the Advisory Council for Ophthalmic Surgery of the American College of Surgeons fosters improved communication between ophthalmologists and other surgical subspecialists. The College welcomes increased input from the American Ophthalmological Society and its membership.

### **Report of the Joint Commission on Allied Health Personnel in Ophthalmology**

DONALD J. DOUGHMAN, MD. During the year 2000,

JCAHPO continued its leadership role in certification of Ophthalmic Medical Personnel. During the year, 1492 candidates were examined, 1214 of whom passed. At the level of Certified Ophthalmic Assistant, 1006 individuals became certified for the first time, 149 advanced in level of certification, and 32 received certification in a subspecialty for a total number of 14,384 current certified ophthalmic medical personnel.

The year 2000 was the 28th JCAHPO Annual Continuing Education Program of Ophthalmic Medical Personnel held in conjunction with the American Academy of Ophthalmology meeting in Dallas, TX, October 21-25. The number of registrants was 2,656. The program featured 258 course offerings by more than 350 volunteer faculty, including 26 new courses, 148 workshops, and 364 presentations. Bar-coded course tickets allowed JCAHPO to provide attendees with an acknowledgment of CE credits in a timely manner.

This past year saw a number of accomplishments including accreditation for 5 years by the National Commission for Certifying Agencies (NCCA). The JCAHPO Bookstore was successfully launched, the proceeds to be used for JCAHPO Education and Research Foundation for scholarships and travel grants. JCAHPO conducted 4 oversold regional CE programs and formed a partnership with American Society of Ophthalmic Administrators (ASOA) to present a 4-day program for clinical and surgical personnel. In addition, more than 4000 career videotapes were distributed to schools nationwide to market the profession of ophthalmic medical assisting. The alliance of JCAHPO and the Association of Technical Personnel in Ophthalmology (ATPO) continues to bring benefits to both organizations.

JCAHPO has been restructured for effective, efficient cost saving by reducing the number of commissioners to 2 from each member organization. (The one exception is ATPO which still has 3.) The commission now consists of 29 commissioners from 14 different member organizations who volunteer countless hours on 16 working committees which meet twice a year in the fall in conjunction with the American Academy of Ophthalmology and each spring in conjunction with ARVO. The American Glaucoma Society is in the second year of provisional membership.

The JCAHPO Education and Research Foundation was founded 10 years ago and has raised \$390,000 and given 308 scholarships to allied health personnel. New endowment funds honoring Virginia S Boyce, Harold Stein MD, and Bud Appelton MD have been established. Since 1991, more than \$1,000,000 has been raised by the foundation.

JCAHPO requests the continuation of active support from the American Ophthalmological Society, 1 of the 6

founding member organizations and further requests the reappointment of Dr. Donald J Doughman and Dr. Robert L Stamper as representatives of the American Ophthalmological Society.

### **Report of the American Orthoptic Council**

EDWARD L. RAAB, MD. The mission of the American Orthoptic Council is to develop standards for the education and training of orthoptists, to examine and certify candidates for the profession of orthoptics, to recertify orthoptists on the basis of continuing education and the maintenance of good standing, and to encourage and support this important health care profession. Ethical issues relating to orthoptic practice also are within the responsibilities of the AOC.

The Society's representatives during the past year have been Drs Thomas France, David Weakley, and Edward Raab. All have served in important Council, educational, and administrative positions.

Dr Weakley, who replaced Dr Albert Biglan as a Society representative, chairs the organization of an annual workshop indicating the contributions of orthoptics to the evaluation and treatment of often complex strabismus problems given at the annual meeting of the American Association for Pediatric Ophthalmology and Strabismus and attracting a large audience. He also serves on committees which accredit new and existing teaching programs and are developing additional programs, and on the Editorial Committee.

Dr France is Editor in Chief of the American Orthoptic Journal, which publishes the traditional and very popular Academy Sunday Night symposium presentations, the annual Scobee Memorial and John Pratt-Johnson lectures, and free papers and abstracts including those in non-English languages that are pertinent to strabismus and orthoptics. He represents the AOC on the Canadian Orthoptic Council and was the creator of this valuable collaboration of the 2 organizations. Dr France also is a member of the Bylaws, Long Range Planning, Public Relations and Nominating Committees.

Dr Raab is the Council's immediate Past President and continues to serve on its Executive Committee, which conducts the business of the AOC between annual meetings. He chairs the Nominating Committee, which proposes officers for the Council and potential new appointees for consideration by their respective sponsoring organizations, and the Bylaws Committee. These committees are now investigating important revisions of the committee structure and terms for officers. Dr Raab also serves on the Long Range Planning and Accreditation Committees.

In addition to the annual Academy Sunday Night

Symposium and the AAPOS workshop, both of which involve participation of orthoptists and pediatric ophthalmologists, the Council's activities also include an active presence on the Joint Commission for Allied Health Personnel in Ophthalmology, and an Internet web site shared with the American Association of Certified Orthoptists.

Action items for the Council are our requests for continuance of the American Ophthalmological Society as a represented sponsoring organization, and renewal of the Society's generous financial support.

### **Report of the Proceedings of the Council of the American Academy of Ophthalmology**

ALBERT W. BIGLAN, MD. The council of the American Academy of Ophthalmology met in Dallas, Texas, on October 21 and 22, 2000. The first day of the council consisted of hearings and development of the council advisory recommendations (CARS). On the second day, the council advisory recommendations were reviewed during the regional meetings. I was assigned to attend the regional meetings for my district, Metro East Delaware. New Jersey, New York and Pennsylvania gave reports. The meeting was presided over by Zoraida Fiol-Silva, MD.

There has been growth and strength in the Delaware State Society. Delaware currently shares services with their medical society and they have developed a much stronger infrastructure. There are still areas that need to be worked on.

In New York, the optometric group is beginning an aggressive campaign for hospital privileges. An interesting development is the application for a certificate of need for an ambulatory surgical center by a group of investor-funded optometrists. The New York contingent is actively engaged in the planning for our regional program. This will be a combined meeting for the four states' ophthalmology societies to be held in the year 2002.

Pennsylvania reported on the variation on payment for diagnosis reimbursement program. This program, the Adesso® proposal, was going to be implemented by the Highmark® insurance company. This would provide payments based on a diagnosis for ophthalmology, cardiology and orthopedics. This insurance company has approximately 65% of the business in Pennsylvania. A proactive campaign supported by ophthalmology, orthopedics, and cardiac surgery was able to cause this 20-million-dollar program to be put on hold. The insurance company countered with their need to find a way to control physicians who are "abusing" the system. Discussions are ongoing on how to identify outlying physicians who are "abusing the system." Ophthalmologists are currently working with the

insurance company to create a program that satisfies the needs of the ophthalmologist, the insurance company, but most importantly, the patients.

New Jersey is a very active state. They had legislation submitted by the optometrists to regulate chain dispensaries. The ophthalmologists in the state reviewed this legislation and added language to strengthen the ethical conduct of optometrists. The optometrists are confronted with a lobby by their own group against their own bill because of the additions made by the ophthalmologists.

The Metro East region is promoting the resident advocacy program. This program encourages residents to become involved with their state organizations. The program also promotes the development of ethical principles. The program is sponsored by the state society and the local ophthalmology training programs.

The Academy leadership school was considered to be successful. John Maher, M.D., president-elect of the Pennsylvania Society, is a graduate of this school. A member of the New York state society is also a recent graduate and has become active in their state leadership.

Eighteen council advisory recommendations were developed and refined at this council meeting. At the final session, they were individually approved by voice acclamation.

Guest speakers at the general sessions included H. Dunbar Hoskins, Jr. MD, the EVP of our Academy. William L. Rich, III, MD the Secretary for Federal Affairs, brought us up-to-date on the activities of the Washington office along with Cathy Cohen, our Vice President for Government Affairs.

The use of Verteporfin (Visudyne®) was approved with a 0-day global period. It was expressed with concern that this may cause re-evaluation of other retina codes.

Visual fields, E & M Codes, and examination under anesthesia codes were increased in their value. A complicated cataract code, which increases the value for these procedures, will be forthcoming at the first of the year.

Randal L. Johnston, MD the OPHTHPAC chair, gave an update on the PAC. Only 11% of the membership of the Academy contributes to this valuable resource. PAC money has been successfully used to lobby on our behalf. For example, it has reversed the increase in scope of practice initiatives in the states of Florida and Alaska.

Michael W. Brennan, MD gave an update for the State Affairs committee. Throughout the Academy, only 55% of Academy members are State Society members. This needs to be improved. Creative ways need to be developed to improve this percentage.

Michael R. Redmond, MD gave a report on the sub-specialty task force. This effort is to give more meaningful representation for the sub-specialty groups in the Academy and to have the ability to have a better dialog

with the Academy office in San Francisco.

George Blankenship, MD, our Academy president-elect, gave an inspirational speech at lunch and Samuel Masket, MD had an award ceremony for retiring counselors.

The mid-year forum was held in Washington, D.C. from April 18-22, 2001.

The congressional advocacy day was considered to be very successful. Members met with their representatives and discussed patient protection, regulatory relief and funding for low vision treatment.

Council regional meetings were conducted and I attended the sub-specialty society update, which was by invitation. Michael R. Redmond, MD, led a two-hour discussion between academy staff, leadership and representatives of sub-specialty societies. I was asked to present information about the recent Kentucky vision examination law that was passed and how the organization responded to that. We discussed ways of being more proactive for any additional similar legislation that may be submitted in any of the other states.

Humphrey Taylor, a trustee of the AAO board, gave an information-packed discussion on health care delivery.

The forum broke up into state section meetings and specialized interest section meetings. I attended the latter. The council advisory recommendations were reviewed and commented upon, and elections were held. Dr Malcolm Mazow was elected as council vice-chair 2002-2003.

The council convened in general session. Invited guest, Jim Carroll, talked about e-commerce and how eventually there would be cost savings through standardized systems by which medical and financial information is transferred electronically. This has not yet occurred. In fact, there is more paper generated in offices today than there was before computers.

J.C. Noreika, MD, MBA, gave some tips on how to integrate a computer and voice recognition into the daily practice of ophthalmology. Jay Wisniski discussed the use and abuse of e-mail with patient communication. Confidentiality issues were openly discussed. Ingrid Zimmer-Galler, MD discussed the use of telemedicine in ophthalmology.

Following this, the group broke out into 2 hearings. One on the RUC process was conducted by William L. Rich, III, MD. The other was a symposium on standards of care conducted by Richard L. Abbott, MD. I attended the standards of care symposium. This discussed the preferred practice patterns that had been generated by the academy. We discussed the need for keeping these updated, to keep them general yet specific, and to keep the language sufficiently vague so as not to generate litigation but rather to support and defend allegations against EYE MD's.

Dr H. Dunbar Hoskins, Jr., the executive vice-president for the AAO, brought the group up-to-date with a stimulating luncheon address.

On Saturday afternoon, a symposium considered marketing in medicine, addressing the medical legal issues, federal trade commission issues, and patient consumer issues, and how they relate to marketing. Following this, a symposium was held on the shortage of Wydase.

On Sunday, April 22, 2001, the final session addressed the never-ending battle for the scope of practice. This was conducted by Allen D. Jensen, MD. Mike Brennen, MD brought the group up-to-date on the strategic retreat. David Parke, II, MD discussed the importance of academic departments in supporting and our efforts in defining the scope of practice for optometry and to set examples regarding co-management.

Invited guest, Richard Cooper, MD, who is director of health policy at the Medical College of Wisconsin, gave an overview of non-physician's efforts to increase their scope of practice throughout medicine. This apparently affects ophthalmology and 2 other sub-specialties, pediatrics and family practice. The other sub-specialties do not seem to be impacted by this as much as these three sub-specialties. A debate over national standards of care versus setting standards at a state level was discussed. There was no pattern for legislation. Specifically, states that permitted expanded scope of practice for optometry were not approving similar legislation for other sub-specialties and vice-versa. The argument of limiting scope of practice for optometry would be supported by evidence that outcomes of care were better, that there were less errors, or that utilization was more appropriate when patients were seen by ophthalmologists. Paul Lee, MD, presented evidence that we are performing very successful procedures and the number of adverse outcomes is very small. To obtain such outcome statistics, studies of large populations to collect data would be required and would probably not be practical. The focus should be on utilization.

Mike Brennen appropriately summarized the scope of practice issues as a battle involving strategic retreat, mobilization of forces, and improvement of legislative support for all components necessary for a victory.

The meeting adjourned on Sunday morning.

### **Report of the Constitution and Bylaws Committee**

EDWARD L. RAAB, MD. Council appointed a Committee to draft suggested amendments to the Constitution and Bylaws intended to update and reflect the current structure and operations of the Society.

Members of the Committee were Drs Froncie Gutman, John Clarkson and Edward Raab. Dr Raab

served as Chairperson. Substantial assistance was provided by the Secretary, Dr Charles Wilkinson, and by the Administrator, Ms Lisa Brown.

Work began in November, 2000 and was completed in March, 2001, with the submission of the extensively revised documents for Council approval. This was obtained in April, and the documents were prepared for submission to the membership for its input, with final action to be taken at the Executive Session of the 2002 Annual meeting as required under the present Bylaws.

The principal effects of the proposed amendments are:

1. The category of Associate member is eliminated. Approved individuals would enter the Society as Members.
2. Future proposed amendments will be submitted to the membership thirty days prior to an Annual Meeting, and will be discussed and voted upon at the Executive Session of that Annual meeting.
3. In voting on proposed amendments, abstentions will no longer have the effect of a "nay" vote, but will be disregarded for the purpose of calculating whether there is a sufficient number of votes favorable for passage.
4. Decisions now stated to be those of the involved committee are now officially described as those of the Council.
5. To avoid the inconvenience and expense of filing future changes to the Constitution (Articles of Incorporation) with the State of Minnesota (the state of incorporation of the Society), several sections which are at least equally appropriate as sections of the Bylaws have been moved to the latter document. Provisions of the Bylaws dealing with policy, procedures or tradition have been removed entirely, with the present intent that they continue in force as resolutions of the Council or acts of the President.

No action is required at the 2001 Council meeting or Executive Session. When all input is received and any further refinements have been made, counsel for the Society should review the amended documents for legal correctness prior to enactment.

### **Report of the Chairman of the Council**

FRONCIE A. GUTMAN, MD. Mr. President and members, the Council met in Cleveland, Ohio on October 7-8, 2000 and here at the Homestead on May 20, 2001. At the Fall meeting, a review of the increase in costs of the annual AOS meeting caused the Council to make the following meeting fee recommendations. Emeritus members will be charged a full registration fee; spouses and guests will

be charged a \$100 guest fee; and guests who only attend the banquet will be charged a banquet fee of \$75.00.

The Council formally adopted the document entitled "Guidelines for the preparation of an AOS Thesis." This publication was initially prepared by Dr Hal Freeman and should be of great value to candidates for membership, the Thesis Committee, and all of our membership.

Through the work of the ad hoc Bylaws Review and Revision Committee, the Council was able to adopt a revised edition of the Constitution and Bylaws, which will have a so-called first reading in the form of a distribution of both old and suggested new items at this Executive Session. I want to thank Dr Edward Raab for his tireless efforts and leadership as the Chair of the Committee.

The Council approved the development of an AOS web site that should be operational within the next few months and the Council recommends that the Society's contributions for 2001 continue at the current levels.

The Council has accepted the report of the Committee on Theses and has approved the following candidates for Associate Membership in the American Ophthalmological Society:

- Louis B. Cantor, MD, Indianapolis, Indiana
- William V. Good, MD, San Francisco, California
- Mark S. Humayun, MD, Baltimore, Maryland
- Henry D. Jampel, MD, Baltimore, Maryland
- Robert N. Weinreb, MD, La Jolla, California

The AOS Herman Knapp Testimonial Fund reported that 8 fellowships for a second year of postgraduate study have been awarded for the 2001-2002 academic year. The annual stipend for each fellowship is \$20,000. The Knapp Fund and Research to Prevent Blindness are jointly continuing their support of a special two-year Ophthalmic Pathology Fellowship.

During the past 3 years, Council has continued to discuss and refine our Strategic Plan, which was developed and approved by the membership in 1998.

To provide for an expanded dialog on possible initiatives, a Strategic Planning Retreat was held in February 2001. The retreat participants included the Council members and 9 additional members of the AOS. The purpose of the retreat was to discuss and make recommendations regarding the mission and role of the AOS in the 21st century.

Our discussions addressed the current status and relevancy of the AOS mission; the role of the AOS within ophthalmology in the 21st century; the process and criteria for membership; the annual meeting; and publication policies for the transactions.

The Retreat participants recognized that although the AOS has played a significant, historical role, the society currently has no clear, identifiable role in American oph-

thalmology. Over the past 137 years, the AOS has become "marginalized" and has lost its former relevance. The absence of a clear mission is somewhat confusing to current members while diminishing the value of potential membership for non-members. Our discussions suggested that the AOS has an opportunity to become a hosting organization for forums on major health care issues that impact medicine, ophthalmology, and the public.

We all recognized that the AOS seeks the leaders and potential leaders in ophthalmology as its members. However, because thesis acceptance is an absolute requirement for membership, a number of distinguished, contributing, potential members have been denied membership. In addition, a significant percentage of individuals asked to write a thesis have not completed this portion of the application process. When coupled with a lack of a clear AOS mission, the current economic pressures in healthcare, the time demands involved in completing a thesis, the uncertainty of thesis acceptance and the requirements to publish the thesis in the AOS transactions, the enthusiasm for AOS membership may have lessened.

Following receipt of the Retreat recommendations, the Council has taken the following actions as provided for in the Strategic Plan.

An editorial revision of the mission statement provides an expanded purpose. The mission statement now reads as follows:

"The mission of the American Ophthalmological Society is to promote excellence in patient care, education, and research; to address essential issues in medicine; and to advance the art and science of ophthalmology."

This revision challenges the AOS to "address essential issues in medicine."

To pursue this goal, Council has approved the addition of a symposium devoted to a topic of national importance to ophthalmology, medicine, and the public as part of our annual meeting. The forum will feature presentations by nationally recognized experts and offer opportunities for open discussions with society members. An additional goal would be the publication of the deliberations in the form of monographs or position papers. If current plans can be executed, the first symposium will be held at the annual meeting in 2002. If planning permits us to proceed with a symposium in 2002, the annual meeting program will consist of a slightly reduced but significant number of papers plus the special symposium.

Another Council action concerns the meeting days for the annual meeting. To lessen the impact of "time out of the office," Council is accepting a recommendation to hold the meeting from Friday through Sunday. A survey

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of our membership reveals that these were the preferred days for our annual meeting. Implementation of new days will begin in approximately 2 to 3 years.

An additional important action charges the Council with reviewing the process and criteria for membership. A central element of this review would ensure that the process identifies ophthalmic leaders who have made significant contributions and ensure a review of their entire professional portfolio. A thesis continues to be one of the criteria for membership.

The Council makes the following appointments for officers and representatives of the Society. For president-elect Marilyn T. Miller, MD; for Secretary-Treasurer Charles P. Wilkinson, MD; for Editor of the AOS Transactions J. Brooks Crawford, MD. The Council extends the current appointment for 1 year of Julia Haller and John Gottsch as Co-Chairmen of the New Member Committee. The appointment of Suzanne Veronneau-Troutman is extended for 1 year as the AOS Representative to the Pan American Association of Ophthalmology. Ralph C. Eagle, Jr. is appointed to a second three-year term as our archivist and photographer. Albert Biglan is appointed as our American Academy Councilor. The Councilor appointment requires a yearly election and I make the motion to elect Dr Biglan as our Councilor and Dr Banks Anderson as the alternate.

(The motion was approved).

The following meeting dates are established

The Cloisters, Sea Island, Georgia, May 19-22, 2002

Four Seasons Biltmore, Santa Barbara, CA, May 17-20, 2003

It has been an honor for me to serve as your Council Chair. As Chair of the Council, I want to publicly thank all council members for the time and dedication they have given this year. On behalf of the Council, I want to thank the AOS members who participated in the retreat. On a personal note, I want to thank our Secretary-Treasurer, Pat Wilkinson, and Lisa Brown for their continuing extraordinary efforts in providing administrative support and guidance to the AOS.

I move approval for the Council Report and its recommendations.

(The Council Report was approved.)

**Report of the President**

PAUL R. LICHTER, MD. I wish to express my

appreciation to the American Ophthalmological Society for the opportunity to serve as your president. It has been a pleasure. I make the following presidential appointments:

Program Committee	Stephen S. Feyman
Thesis Committee	M. Bruce Shields, J. Bronwyn Bateman, Joel S. Mindel
American Orthoptic Council	Thomas D. France, Edward L. Raab, David R. Weakley
JCAHPO	Donald J. Doughman and Robert L. Stamper
Emeritus Committee National Association for Biomedical Research Committee on Prizes	Stanley M. Truhlsen  Edward A. Jaeger Robert R. Waller, Richard F. Brubaker, Bruce E. Spivey
AOS Council	Melvin L. Rubin, Daniel M. Albert, John C. Clarkson, Dan B. Jones, Susan H. Day

I wish to personally thank Pat Wilkinson for the extraordinary work he does as our Secretary-Treasurer and Lisa Brown for her valuable work in our behalf. I declare the Executive Session in recess until tomorrow evening.

**Tuesday Morning, May 22**

The scientific program continued with the following papers:

9. "Curvularia Keratitis" by Kirk R. Wilhelmus, MD, MPH, and Dan B. Jones, MD
10. "Primary Ocular Rhabdomyosarcoma in 33 Patients" by Carol L. Shields, MD, Jerry A. Shields, MD, Santosh G. Honavar, MD (by invitation), and Hakan Demirci, MD (by invitation)
11. "Evolutionary Attempts at Four Eyes in Vertebrates" by Ivan R. Schwab, MD, Viet Ho, BS (by invitation), Alan Roth, MD (by invitation), Thomas N. Blankenship, PhD (by invitation), and Paul G. Fitzgerald, PhD (by invitation)
12. "Surface Keratopathy After Penetrating Keratoplasty" by Vahid Feiz, MD (by invitation), Mark J. Mannis, MD, Ganesha Kandavel, MD (by invitation), Martin McCarthy, MD (by invitation),

Luis Izquierdo, MD (by invitation), Marianna Eckert, MD (by invitation), Ivan R. Schwab, MD, Sima Torabian, MD (by invitation), Jane Ling-Wang (by invitation), and Wei Wang (by invitation)

13. “The Negative ERG is Not Synonymous With Nightblindness” by Gerhard W. Cibis, MD and Kathleen M. Fitzgerald, PhD (by invitation)
14. “The Advanced Glaucoma Intervention Study (AGIS): 10. Variability Among Academic Glaucoma Subspecialists In Assessing Optic Disc Notching” by Douglas E. Gaasterland, MD, Beth Blackwell, ScD (by invitation), Leonard G. Dally, MSc (by invitation), Joseph Caprioli, MD, L. Jay Katz, MD (by invitation), Fred Ederer, MA, FACE (by invitation) and The AGIS Investigators (by invitation)
15. “Change on the Horizontal and Vertical Meridians of the Cornea After Cataract Surgery” by John C. Merriam, MD, Lei Zheng, MD (by invitation), Joanna Urbanowicz, MD, PhD (by invitation), and Marco Zaider, PhD (by invitation)
16. “The Reproducibility of Ophthalmic Utility Values\* by Gary C. Brown, MD, MBA, Melissa M. Brown, MD, MN, MBA (by invitation), Sanjay Sharma, MD, MSc, MBA (by invitation), George Beauchamp, MD, and Hussein Hollands, MSc (by invitation)
17. “Corneal Melts Associated With Topically Applied Nonsteroidal Anti-inflammatory Drugs” by Allan J. Flach, MD

### **Tuesday Evening Banquet, May 22**

FRONCIE A. GUTMAN, MD. As Chairman of the Council for the 137th meeting of the AOS, it is my pleasure to welcome all of you to this special evening. I can't tell you if this is the 137th banquet or not. I do know it is my only banquet as Chair of the Council and that alone makes it special for me.

More than any other organization, the AOS respects and honors its heritage. In recognition of our heritage, I ask all emeritus members and their spouses to stand. Please join me in a toast to our emeriti.

The demands of this years' activities have required an unusual amount of time from each member of the council. I can assure you that each has made a significant contribution. A “special thank you” to Dan Albert for focusing our attention on the future opportunities and needs of the AOS. Going forward, the council will be in good hands as Mel Rubin, a close friend for the past 36

years, assumes the Chairmanship. I can assure Mel that Pat Wilkinson, our Secretary-Treasurer, and Lisa Brown will provide any needed administrative support. It is impossible for me to fully express my appreciation and gratitude for the superb job both of them do on behalf of the AOS.

I would like the members of the Council and their spouses to stand and be recognized as I call their names—our President and his wife, Paul and Carolyn Lichter; our President-elect, Robert Drews; our Editor and his wife, Brooks and Chrissie Crawford; our Secretary-Treasurer and his wife, Pat and Alice Wilkinson; our Councilors, Mel and Lorna Rubin, Dan Albert, John and Diana Clarkson, Dan and Marilyn Jones; and the lovely lady who so loyally and unwaveringly supports me, Bonnie Gutman. Please be seated.

These are reflective times for the Council. We are all proud of the historical leadership and contributions of the AOS but recognize that our organization is being challenged to identify a relevant role within ophthalmology in this 21st century. The Council has accepted this challenge and is offering proposals for constructive change.

Being a member of the Council this year has been both interesting and challenging. I want to thank Stan Truhlsen, our 1996 President, for appointing me.

This evening, I have the privilege of introducing our President, Paul Lichter. Where do I start with such a gifted and accomplished individual—well, let's start at the beginning.

Paul was born in Detroit, Michigan. Although he is widely traveled and enjoys an international reputation, his educational training and professional career have tethered him in Ann Arbor, less than 20 miles from his birth place.

Paul attended Cranbrook High School in Bloomfield Hills, Michigan and started dating Carolyn, his wife to be, in his senior year. Between receipt of his undergraduate degree and the initiation of medical school at the



Officers and Council; left to right: Robert C. Drews, Melvin L. Rubin, J. Brooks Crawford, Paul R. Lichter, John G. Clarkson, Froncie A. Gutman, Charles P. Wilkinson

University of Michigan, Paul and Carolyn were married in 1960. Paul extended his Ann Arbor experience with residency training. He has been described by many as a futurist, a visionary. This was evident to one of Paul's fellow residents early on. One evening, during their residency, while sorting and organizing departmental teaching slides, Paul was talking about the tremendous potential and opportunities that he foresaw for their department in the years ahead, a vision for the future that Paul would transition into reality. Not the typical behavior or reflections for most residents.

Following completion of a glaucoma fellowship with Dr Robert Shaffer in San Francisco, and a tour of duty with the United States Navy, Paul returned to join the faculty of the ophthalmology department at the University of Michigan in 1971. In 1978 he became Chairman and has developed an internationally renowned program. Paul's incredible fund raising abilities have materially benefited his department. The W. K. Kellogg Eye Center embodies Paul's dreams, his standards, and his character in the same way a beautiful statue reflects the love, sensitivity, and skills of the sculptor.

What about Paul's personal interests? His hobbies include golf—which he took up at the age of 9 and still pursues passionately; Michigan athletics—he regularly attends the University of Michigan football and basketball games; and photography. He currently has an exhibition of his Galapagos islands photographs at the University Hospital in

Ann Arbor. Another little known fact concerns his theater career. Paul received an extraordinary review for his performance in the Ann Arbor Theater production of *Fiorello*.

I could spend the next hour or 2 reviewing Paul's professional career. I believe Paul has held every major leadership position in American ophthalmology. Rather than listing his accomplishments, I would like to share with you some observations and thoughts of his friends and colleagues. The comments used to describe Paul include: great leader; proud and supportive of his staff; we work with him, not for him; insatiable energy, never idle, always working on something; honest, ethical and fair; extremely well organized; strategic thinker; superb decision maker; great sense of humor; shrewd politician; great fund raiser. And the one I like best, "I send him my most difficult cases; I trust him."

As an alumnus of the University of Michigan Department of Ophthalmology, I take great pride in Paul's leadership, contributions, and accomplishments. On a personal note, I am honored to work with him as a colleague and to enjoy his friendship.

Please join me in a toast to Paul and Carolyn Lichter as we welcome Paul to the podium.

PRESIDENT PAUL R. LICHTER, MD. Thank you, Dr Gutman, for your warm and most generous introduction. The fact that you and I were trained in ophthalmology in the same program by the same chief, Dr Bruce Fralick, has given this year an even more special significance. Some of you may not know that your Council Chair was a football quarterback at Purdue University. Ophthalmology has benefited from the leadership skills that a quarterback must possess. Not only has Froncie distinguished himself in service to the AOS, but also he has served as President of the American Academy of Ophthalmology and as long-time Secretary of the Heed Foundation. It was Froncie's foresight and perseverance that found a home in the AOS for the Knapp Fund. The AOS Knapp Fund provides a stipend for a second year of ophthalmology fellowship training and has supported a number of very gifted young men and women. I hope their mentors will keep in mind the importance of proposing them as AOS candidates. Froncie, would you and Bonnie please stand and let us thank you for your outstanding work on behalf of the AOS.

Now, I would like to introduce the Athletic Chair, Dr Woody Van Meter, who will present the athletic awards.

### **Report of the Athletic Committee**

WOODFORD S. VAN METER, MD. The following are the athletic awards for this year's annual meeting. The winners of the athletic trophies are as follows:



Carolyn and Paul Lichter

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<u>Trophy</u>	<u>Event</u>	<u>Winner</u>			
			Ellsworth Trophy	Ladies' golf low gross	Dottie Truhlsen
Beetham-Bullock Trophy	Skeet shooting	Mylan Van Newkirk	Homestead Cup	Ladies' golf low net	Audrey Ing
McCaslin-Fralick-Kimura Trophy	Fly fishing	Barrett Katz	EVL Brown Bowl	Men's tennis winners	John Gottsch and Robert Yee
Mishima-Michaels Trophy	Men's golf low gross	Woody Van Meter	EVL Brown Bowl	Men's tennis runner's-up	Gerhard Cibis and Sloan Wilson
Canada-McCulloch Cup	Men's golf low net	Bruce Spivey	Perera Bowl	Ladies' tennis winners	Rosanne Raab and Alice Wilkinson
Truhlsen Trophy	Senior Man's Low Gross	Allan "Buzz" Kreiger	Hughes Bowl	Ladies' tennis runner's-up	Dorothy Van Meter and Ann Wilson
Knapp Memorial Trophy	Men's team golf	Paul Lichter and Bruce Spivey	Wong-McDonald Trophy	Mixed Doubles winners	cancelled because of rain
			Wilson Trophy	Mixed Doubles runner's-up	cancelled because of rain



Knapp Memorial Trophy winners for team golf: Paul Lichter and Bruce Spivey



Athletic Director Woody Van Meter presents Beetham-Bullock trophy to skeet shooting winner Mylan Van Newkirk

I wish to make some additional comments. In the skeet shooting, Frances Small, shooting for the first time, hit 2 clay pigeons with 1 shot.

The Truhlsen Trophy is a new trophy for senior (over age 65) men. Joe Flanagan was second by one shot; Dave Berler was third by 2 shots off the leader.

In golf, Paul Lichter had the longest drive; Dave Berler was the senior with the longest drive. Buzz Kreiger was the closest to the pin; Tuck Asbury was the senior closest to the pin. Pat Wilkinson holed out from 75 yards on one hole, the shot least likely to be reproduced.

PRESIDENT LICHTER. Many thanks, Woody. You've done a superb job this year in organizing the athletic events and we greatly appreciate your efforts.

In the absence of the New Members Committee Chair, the Secretary-Treasurer will read the list of new members.

C. P. WILKINSON, MD. We have a talented and distinguished group of new members this year. May I introduce them:

- Dr David J. Apple
- Dr Norman P. Blair
- Dr Mark J. Manis
- Dr T. Michael Nork
- Dr Leonard M. Parver
- Dr Paul E. Runge



New Members 2001

Left to right: Carol L. Shields, T. Michael Nork, Norman P. Blair, Andrew K. Vine, Oliver D. Shine, Leonard M. Parver, Mark J. Mannis, Kirk R. Wilhelmus, David J. Apple, Paul E. Runge

Dr Oliver D. Schein  
Dr Carol L. Schields  
Dr Andrew K. Vine  
Dr Kirk R. Wilhelmus

PRESIDENT LICHTER. Thank you, Dr Wilkinson. It is time for the highlight of the evening, the presentation of the Howe Medal. To make the presentation, I call upon Dr Robert Waller, a member of the Committee on Prizes, who is standing in for Dr Robert Kennedy, Chair of the Committee, and Dr Richard Brubaker, the third member of the Committee on Prizes.

### Report of the Committee on Prizes

ROBERT R. WALLER, MD. Dr Lichter, officers and councilors of the Society, members and guests. The Committee on Prizes, consisting of Drs Richard F. Brubaker, Robert E. Kennedy, and myself, has a most pleasant assignment tonight. It will be our honor and privilege to announce in the next few minutes the recipient of the Howe Medal for 2001, the most prestigious honor the American Ophthalmological Society bestows.

All members of the Committee on Prizes would like to thank the Society for allowing us to participate in this wonderful occasion. In addition, we would like to give special thanks tonight to Fred M. Wilson, the most recent chair of the Committee on Prizes with whom we reviewed committee deliberations of previous years. His advice and counsel regarding how best to complete our work was invaluable, and we thank him for his splendid assistance.

We are very excited to tell you about this year's most

outstanding and deserving recipient.

He is from the Midwest, born in Herman, Nebraska, just a few years before this photograph was taken.

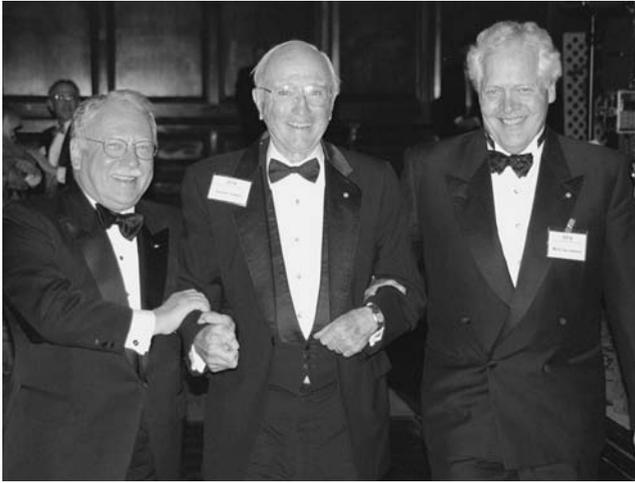
Much of his formal education was in the Midwest, including his medical school years. Our recipient then traveled to Albany, New York, for his internship, and then residency training in Pathology and Bacteriology. While in Albany, he developed an interest in how disease and trauma affect the human eyes, leading to his decision, fortunately for us here tonight and especially for his patients, to specialize in ophthalmology

This year's Howe medalist then entered the military service in 1946, and at the conclusion of his service in 1948, he began his residency training at Barnes Hospital in St. Louis. Our medalist was in the private practice of ophthalmology for 42 years. He rose to the rank of Professor of Ophthalmology at his university. He served with distinction as Editor of Ophthalmology, and then he became President of the American Academy of Ophthalmology

He has been a member and past president of:

The Nebraska Academy of Ophthalmology  
The Omaha Medical Society  
The Omaha Ophthalmological Society  
The Emmanuel Medical Staff  
The Eye Study Club  
The University of Nebraska Chapter of Alpha Omega Alpha  
The University of Nebraska College of Medicine Alumni Association

And for this beloved society Editor of the Transactions, Chairman of the Council, and President.



Bruce Spivey (left) and Mylan Van Newkirk (right) escort Howe Medal recipient, Stanley M. Truhlsen



Howe Medal Recipient, Stanley M. Truhlsen, and his wife Dottie

His community recognized our medalist with its finest honor, naming him the 91st King of AK-SAR-BEN.

Our recipient is a swimmer and he is to be found among these distinguished golfers of the American Ophthalmological Society.

This is but a glimpse into his professional life of some 50 years now. Service with kindness and compassion is his hallmark . . . for his patients, for his profession, for his community, for his family, which includes 4 wonderful children, and his lovely wife, Dottie, who is with us tonight.

None of what we have said tonight thus far really describes what is perhaps very important to emphasize. Our Howe medalist is a man of great integrity and honesty, one of our beloved profession's finest ambassadors and one of the nicest people on the planet.

Before presenting the medal, I would like to say that the Committee on Prizes would like to perpetuate the tradition of awarding to the spouse of this year's recipient a red and white corsage (the color of the Howe Medal). A red and white boutonniere could be given in the case of a male spouse.

Please escort to the stage our 2001 recipient of the Howe Medal, Dr Stan Truhlsen, and his lovely wife, Dottie.

**PRESIDENT LICHTER.** Clearly, the Committee on Prizes has made an outstanding selection for this year's Howe Medalist. Heartiest congratulations, Dr Truhlsen, for all you've done for ophthalmology and the AOS.

So far at this meeting, we have heard 17 papers given by colleagues from several of the subspecialties of our profession. We've heard the papers discussed by thoughtful members who added perspective to the presentations. So many of you have told me how much you have enjoyed these past 2 days and how much you value a meeting

where such a variety of topics is presented. And you've expressed how much you relish the chance to meet fellow members and their spouses and guests in a lovely setting where social and professional chitchat has a value well beyond the formal aspects of our scientific program.

The rich history and precepts of the AOS that have been passed along for 137 years is a special heritage that is our privilege to perpetuate. My hope is that the AOS will always be a beacon of what represents the best in medicine and ophthalmology. I could not be more proud to be a member. And to be chosen for this one year to be your President is an honor that I greatly cherish. Thank you for this privilege.

It was 1976 when I was elected to membership in the AOS. One member of my new member class of 1976 is here tonight and I would like to recognize Dr Bruce Spivey, a Past President of the AOS and past Howe Medalist. Dr Spivey, please stand.

I want to thank the same people who Dr Gutman thanked—the Council, our Editor, our Secretary-Treasurer, and our staff for their dedicated and effective efforts on behalf of the Society. Most significantly, I want to thank the most important person here tonight from my perspective, a person who has always been supportive of whatever I've agreed to do in my professional career and who has been as strong a supporter of the AOS as I have tried to be, my wife, Carolyn. Please stand.

Now it is my pleasure to call to the podium your President-Elect, Dr Robert Drews, to accept the symbolic transfer of the President's medal. Bob has served ophthalmology in many capacities and has been a loyal member of the AOS for many years. I've worked with him in several of these roles and I could not be more pleased to have him succeed me as AOS President. Bob's wife, Lorene, was unable to be here with us, but we express to

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both of you our congratulations and best wishes for your AOS Presidency.

PRESIDENT-ELECT ROBERT DREWS. Thank you Mr. President. It is a great honor for me to have been selected as your next President. I'm very grateful to the Society and I look forward to serving you in this next year. Please enjoy the rest of the evening and I declare this Business Meeting adjourned.

**Wednesday Morning, May 23**

The scientific meeting concluded with the following papers:

18. "Comparison of Contrast Sensitivity, Visual Acuity, and Humphrey Visual Field Testing in Patients With Glaucoma" by Jacob T. Wilensky, MD and (by invitation) Anjali Hawkins, MD, PhD.
19. "Intravitreal Injection of T-PA for Central Retinal Vein Occlusion" by Michael J. Elman, MD and (by invitation) Anita Carrigan
20. "Monitoring of Controlled Accommodative Esotropia" by Ed Raab, MD
21. "North Carolina Macular Dystrophy: Clinicopathologic Correlation" by Kent Small, MD and (by invitation) Irene Woo, Nitin Udar, Ben Glasgow, MD, and John Flannery, MD.

The following members were present and registered at the meeting.

Active	Albert, Daniel
Emeritus	Alper, Melvin
Active	Anderson Jr., W. Banks
Emeritus	Annesley Jr., William
Associate	Apple, David
Active	Apt, Leonard
Active	Asbell, Penny
Emeritus	Asbury, Taylor
Active	Bartley, George
Active	Beauchamp, George
Active	Berler, David
Active	Berrocal, Jose
Active	Biglan, Albert
Associate	Blair, Norman
Active	Blankenship, George
Active	Bobrow, James
Associate	Brown, Gary
Active	Bullock, John

Associate	Caldwell, Delmar
Active	Cibis, Gerhard
Active	Clarkson, John
Active	Coleman, D Jackson
Emeritus	Cox Jr., Morton
Active	Crawford, J. Brooks
Active	Drews, Robert
Active	Eagle Jr., Ralph
Active	Elman, Michael
Active	Farris, R. Linsy
Active	Feman, Stephen
Active	Ferris, Frederick
Active	Ferry, Andrew
Active	Flach, Allan
Active	Flanagan, Joseph
Active	France, Thomas
Active	Frank, Robert
Emeritus	Frayner, William
Active	Freeman, H. MacKenzie
Active	Frueh, Bartley
Active	Gaasterland, Douglas
Associate	Gardner, Thomas
Emeritus	Glew, William
Active	Godfrey, William
Active	Goldberg, Morton
Active	Gottsch, John
Active	Green, W. Richard
Active	Gutman, Froncie
Active	Guyton, David
Active	Haller, Julia
Emeritus	Hedges Jr., Thomas
Active	Illiff, Nicholas
Active	Illiff, W. Jackson
Active	Ing, Malcolm
Active	Jabs, Douglas
Active	Jaeger, Edward
Active	Jampol, Lee
Emeritus	Jarrett II, William
Active	Jones, Dan
Active	Kaiser-Kupfer, Muriel
Active	Kass, Michael
Active	Katz, Barrett
Active	Kaufman, Paul
Active	Kenyon, Kenneth
Active	Koch, Douglas
Active	Kreiger, Allan
Active	Kupfer, Carl
Active	Lemp, Michael
Active	Lewis, Richard
Active	Lichter, Paul
Active	Ludwig, Irene
Active	Luxenberg, Malcolm
Associate	Mannis, Mark

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Active	Maumenee, Irene	Active	Small, Kent
Active	Mazow, Malcolm	Active	Sommer, Alfred
Active	Merriam, John	Active	Spivey, Bruce
Active	Meyer, Roger	Active	Stager Sr., David
Active	Miller, Marilyn	Active	Steinert, Roger
Associate	Mills, Richard	Active	Tasman, William
Associate	Mitchell, Paul	Active	Townsend, William
Associate	Nork, T. Michael	Emeritus	Truhlsen, Stanley
Active	O'Day, Denis	Active	Tso, Mark
Associate	O'Neill, John	Active	Van Meter, Woodford
Emeritus	Parks, Marshall	Active	Van Newkirk, Mylan
Associate	Parver, Leonard	Associate	Vine, Andrew
Active	Payne, John	Active	Waller, Robert
Active	Raab, Edward	Active	Weakley Jr., David
Active	Ritch, Robert	Active	Welch, Robert
Active	Robb, Richard	Emeritus	Wetzig, Paul
Active	Robertson, Dennis	Active	Wilensky, Jacob
Active	Rubin, Melvin	Associate	Wilhelmus, Kirk
Associate	Runge, Paul	Active	Wilkinson, Charles
Associate	Schein, Oliver	Emeritus	Wilson, R. Sloan
Active	Schocket, Stanley	Emeritus	Wolff, Stewart
Emeritus	Schultz, Richard	Active	Wood, Thomas
Active	Schwab, Ivan	Active	Yee, Robert
Active	Sergott, Robert		
Associate	Shields, Carol	Professional Guest	Ridley, Miriam
Active	Shields, Jerry	Professional Guest	Werner, Liliana

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## PAPERS



# THE EFFECTS OF PANRETINAL PHOTOCOAGULATION ON THE PRIMARY VISUAL CORTEX OF THE ADULT MONKEY\*

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BY Joanne A. Matsubara, PhD (BY INVITATION), Dawn Y. Lam, BSc (BY INVITATION), Ronald E. Kalil, PhD (BY INVITATION), B'Ann T. Gabelt, MS (BY INVITATION), T. Michael Nork, MD, Dan Horman, MBBS (BY INVITATION), AND Paul L. Kaufman, MD

## ABSTRACT

**Purpose:** To determine the effects of panretinal photocoagulation (PRP) on the levels of cytochrome oxidase (CO), Zif268, synaptophysin, and growth-associated protein 43 (GAP-43) in the primary visual cortex of adult monkeys.

**Methods:** Ten adult primates underwent unilateral argon laser PRP with instrument settings at 300 to 500  $\mu\text{m}$  spot diameter, 200 to 500 mW power intensity, and 0.1 to 0.2 second duration, causing moderate to severe burns in the peripheral retina. At 20 hours, 12 days, 6 months, and 13 months after laser treatment, the visual cortex was assessed histologically for CO and immunohistochemically for Zif268, synaptophysin, and GAP-43.

**Results:** PRP resulted in transneuronal changes in the relative distributions of CO, Zif268, synaptophysin, and GAP-43 in the primary visual cortex. CO activity was relatively decreased in the lasered eye's ocular dominance columns at 12 days post-PRP, with recovery by 13 months post-PRP. The level of Zif268 was dramatically decreased in the lasered eye's ocular dominance columns at 20 hours post-PRP, with gradual recovery by 13 months post-PRP. Levels of synaptophysin and GAP-43 immunoreactivity were increased in both the lasered and the nonlasered eyes' ocular dominance columns at 6 months post-PRP.

**Conclusion:** PRP treatment results in metabolic activity changes in the visual cortex of the adult monkey. These changes are followed chronologically by spatial redistribution of synaptophysin and GAP-43, neurochemicals known to play a role in cortical plasticity. This study demonstrates, for the first time, that PRP as used in the treatment of diabetic retinopathy results in a redistribution of neurochemicals in the adult monkey visual cortex. Such changes may help explain the anomalous visual functional loss often reported by patients after PRP.

*Tr Am Ophth Soc* 2001;99:33-43

## INTRODUCTION

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Diabetic retinopathy is the leading cause of the onset of blindness among adults of working ages (20 to 74 years). Timely treatment with panretinal photocoagulation (PRP) has been found to stop or slow visual loss associated with diabetic retinopathy.<sup>1</sup> Although clinical trials have documented the efficacy of PRP, its mechanism is not clear. One theory proposes that PRP destroys some of the ischemic retina, thereby reducing its production of an angiogenic factor.<sup>2</sup> A second theory suggests that PRP improves oxygenation of the ischemic inner retina by destroying metabolically active photoreceptor cells and allowing diffusion of oxygen from the choriocapillaris to the inner retinal layers.<sup>3-7</sup>

\*From the Department of Ophthalmology, University of British Columbia, Vancouver, Canada (Dr Matsubara, Ms Lam, Mr Horman), and the Center for Neuroscience (Dr Kalil) and Department of Ophthalmology and Visual Science (Dr Kalil, Ms Gabelt, Dr Nork, Dr Kaufman), University of Wisconsin-Madison. Supported by grant EY02698 from the National Eye Institute and grant MT13363 from the Medical Research Council.

Although the exact mechanism underlying the efficacy of PRP is not understood, it is known that photoreceptors in the peripheral retina are destroyed by laser treatment, thus causing partial visual loss in the treated eye.<sup>8</sup> Visual deprivation—by lid suture, intraocular injection of tetrodotoxin (TTX), or enucleation—can cause significant changes in the neurochemistry and organization of the central visual pathways;<sup>9-12</sup> therefore, we were interested in elucidating the central consequences of visual loss associated with PRP. Given the frequency and importance of PRP for diabetic retinopathy, characterizing its effects on the visual cortex, and the consequences to visual function, is worthwhile.

This study focused on the consequences of unilateral PRP on the redistribution of several neurochemicals in the primary visual cortex of the adult monkey. Two metabolic activity markers, cytochrome oxidase (CO) and the immediate early gene product Zif268, were studied because both are down-regulated in response to visual deprivation.<sup>11-14</sup> Zif268 is down-regulated within hours of deprivation,<sup>14</sup> while changes in CO activity usually require days.<sup>11</sup> The effects of PRP on 2 plasticity markers that play

an important role in the formation and maintenance of new synapses in the nervous system, growth-associated protein 43 (GAP-43) and synaptophysin,<sup>15-17</sup> were also evaluated.

## METHODS

### PHOTOCOAGULATION

Ten adult cynomolgus (*Macaca fascicularis*) and rhesus (*M. mulatta*) monkeys were anesthetized with ketamine (10 mg/kg intramuscularly) followed by sodium pentobarbital (35 mg/kg intramuscularly). The pupils were dilated with 2.5% phenylephrine and 1% tropicamide. The animals were placed prone in a head holder, or held by an assistant, and argon laser light was delivered by a standard slit-lamp system (Coherent model 900 argon laser) through a one-, two- or three-mirror Goldmann-type contact lens, designed and fabricated especially for the monkey eye.<sup>18</sup> Senior retinal specialists T.M. Nork and I.H.L. Wallow performed PRP. One eye of each monkey received argon-green (514 nm) laser burns, analogous to the DRS/ETDRS protocol,<sup>1</sup> with instruments set at a 300 to 500  $\mu\text{m}$  spot diameter, 200 to 500 mW power, and 0.1 to 0.2 second duration. The lasered area extended 20° to 50° from the fovea. Complete PRP consisted of 650 to 1,050 argon lesions and was divided into 2 sessions. Intensity and topography were documented by fundus photography using a Zeiss fundus camera. Details of the PRP given to each animal are in Table I. All experiments were conducted in accordance with the ARVO statement for the use of animals in ophthalmic and vision research.

### TISSUE PREPARATION

At the designated post-PRP times (20 hours, 12 days, 6 months, and 13 months), animals were anesthetized with ketamine and surgical-depth sodium pentobarbital as

previously described. The eyes were removed and immersion-fixed in 4% paraformaldehyde in phosphate buffer (PB) or frozen in -80 °C isopentane. The retina from each immersion-fixed eye was dissected and a whole-mount preparation was photographed to document laser sites.<sup>19</sup> Next, the retina was embedded in O.C.T. and frozen in liquid nitrogen. Cryostat sections of 8- $\mu\text{m}$  thickness were stained with hematoxylin-eosin, and the sites of photocoagulation were assessed for the severity of damage to the neural retina at the light microscopic level (Fig 1).

After enucleation, animals were euthanized and perfused intracardially. Three animals (asterisks, Table I) underwent perfusion with Sorenson's buffer (0.1 M) in 0.9% saline solution. The brains were removed and the occipital lobes divided into blocks representing the fovea (block 1, opercular surface) and the peripheral field (blocks 2, 3, and 4) in the primary visual cortex (area V1) (Fig 2).<sup>20,21</sup> Cortical blocks were flattened between glass slides and frozen in isopentane at -80 °C. Tissue from these 3 animals was used for CO histochemistry and Zif268 immunohistochemistry. The other 7 animals (Table I) were perfused intracardially with PB (0.1 M, pH 7.2) followed by 4% paraformaldehyde in PB. The brains were then removed and stored in cold PB. Brain tissue was blocked and cryoprotected in 20% to 30% sucrose at 4 °C overnight. Tissue from these 7 animals was used for CO histochemistry and immunostaining for Zif268, GAP-43, and synaptophysin.

### CYTOCHROME OXIDASE (C)

The cytochrome oxidase histochemical protocol was based on previously documented methods.<sup>22,23</sup> Sections of tissue were incubated for 2 to 4 hours at 40 °C in a solution containing 20 to 25 mg of diaminobenzidine (DAB), 30 mg of cytochrome C, 20 mg of catalase, and 2 g of sucrose dissolved in 100 mL of 0.05 M phosphate buffer (pH, 7.2). The

TABLE I: DETAILS OF PRIMATE PANRETINAL PHOTOCOAGULATION (PRP)

ANIMAL ID	SPECIES	SEX	AGE (YR)	WEIGHT (KG)	SURVIVAL TIME (POST-PRP)	PRP (ARGON GREEN LASER)			
						POWER (MW)	DURATION (SECOND)	SPOT SIZE ( $\mu\text{M}$ )	NO. OF BURNS
RQ637°	<i>Macaca mulatta</i>	Male	6-8	6.2	20 hr	230-290	0.1	500	1016
AQ60°	<i>M. mulatta</i>	Male	6-8	5.35	20 hr	250-300	0.2	300	1016
AQ21	<i>M. mulatta</i>	Male	6-8	5.95	20 hr	250-400	0.2	300	1045
K420	<i>Macaca fascicularis</i>	Female	8-10	3.1	12 days	240-280	0.1	500	761
K429	<i>M. fascicularis</i>	Male	8-10	7.1	12 days	220-260	0.1	500	822
K367	<i>M. fascicularis</i>	Male	8-10	5.1	12 days	240	0.1	500	877
K374	<i>M. fascicularis</i>	Male	8-10	5	12 days	240	0.1	500	1021
K415°	<i>M. fascicularis</i>	Male	8-10	4.1	6 mo	250	0.2	500	660
K414	<i>M. fascicularis</i>	Male	8-10	4.2	6 mo	220-250	0.2	500	693
K413	<i>M. fascicularis</i>	Male	8-10	4.9	13 mo	280	0.1	500	706

° Animals that were perfused with Sorenson buffer. All other animals were perfused with 4% paraformaldehyde.

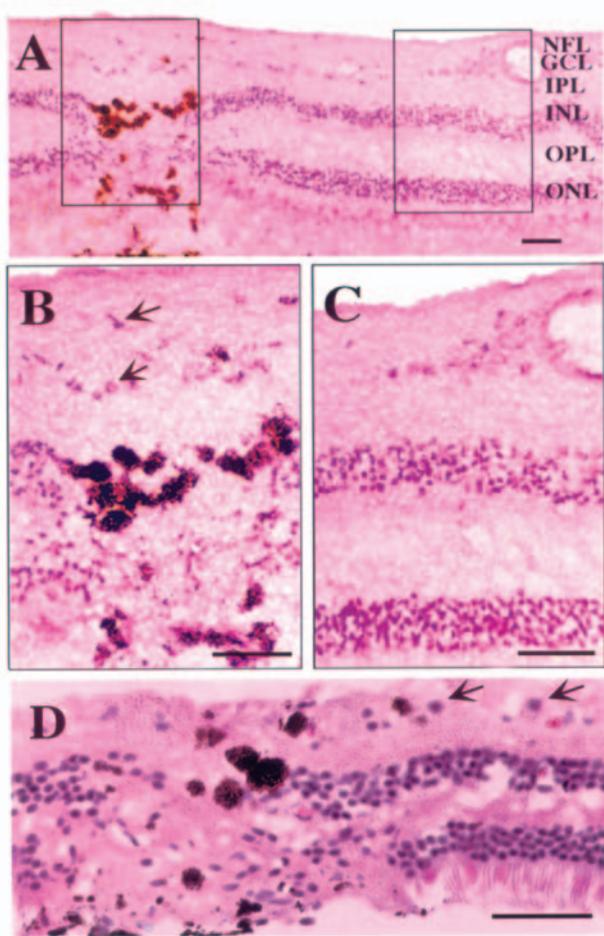


FIGURE 1

Cryostat cross section of retina stained with hematoxylin-eosin at 6 and 13 months post-PRP. A, Predominant damage due to PRP was a grade III burn. Outer retinal layers were severely disrupted with loss of photoreceptor cells. There was moderate disruption to inner nuclear layer with hyperpigmentation (left box). B, Enlargement of left box in A shows a laser site with significant sparing of retinal ganglion cells (arrowheads). C, Enlargement of right box in A shows an interlaser site with intact retinal anatomy. D, At 13 months post-PRP, predominant damage due to PRP was also a grade III burn. Outer retinal layers were severely disrupted with loss of photoreceptor cells. There was moderate disruption to inner nuclear layer with hyperpigmentation. Ganglion cells (arrowheads) were anatomically intact. NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer. Scale bars =0.1 mm.

reaction was intensified by the addition of 1% nickel ammonium sulfate (3 to 5 mL) and 1% cobalt chloride (3 to 5 mL).

#### ZIF268, GAP-43, AND SYNAPTOPHYSIN IMMUNOHISTOCHEMISTRY

Monoclonal antibodies against the phosphorylated and nonphosphorylated forms of GAP-43 and the 38 kDa band of synaptophysin were obtained from Sigma-Aldrich Co (St Louis, Mo). The polyclonal antibody against Zif268 was obtained from Dr R. Bravo. All cortical blocks were

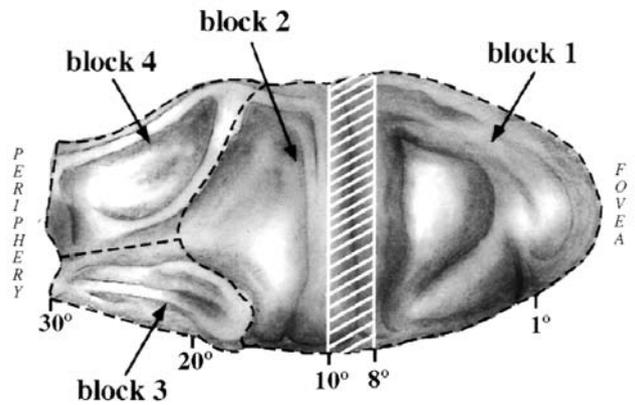


FIGURE 2

Schematic view of macaque's entire primary visual cortex from a flattened preparation,<sup>20,21</sup> identifying the boundaries of tissue blocks processed in this study. Block 1 is dorsal opercular surface, representing approximately the central 10° of visual field. Block 2 is roof of the calcarine sulcus, representing approximately 10° to 30° eccentricity. Hatched area between blocks 1 and 2 is the "hinge," where operculum folds into the calcarine sulcus, which in our preparation was not accessible. Blocks 3 and 4 are ventral and dorsal banks of the calcarine stem, respectively. Blocks 3 and 4 include peripheral visual field representation, approximately 15° to 60° eccentricity.<sup>21</sup>

frozen and cut at 50 μm tangential to the pial surface. Tissue sections were placed in a solution containing rabbit polyclonal antisera selective for Zif268, at a 1:10,000 dilution in PB with 3% normal goat serum, for at least 48 hours at 4°C.<sup>13</sup> The sections were then washed in PB containing 0.3% Triton X-100 and incubated for 2 hours at room temperature in a 1:1,000 dilution of biotinylated goat anti-rabbit secondary antibody in 0.3% Triton X-100 in PB. After washing with PB, the sections were incubated for 1 hour at room temperature in a solution of avidin-biotin conjugated horseradish peroxidase complex (Vector Labs, Burlington, Calif). Sections were then subjected to a nickel-enhanced DAB reaction.

Synaptophysin and GAP-43 immunohistochemistry was performed using a 1:1,000 dilution of antisera in PB with 0.1% Triton X-100 and 3% normal horse serum. Sections were incubated for 48 hours at 4°C, then washed 3 times with 0.3% Triton X-100 in PB and placed into a solution containing biotinylated horse anti-mouse secondary antibody at a dilution of 1:1,000 in 0.3% Triton X-100 and 3% normal horse serum in PB. Bound antibody was then visualized with the glucose oxidase-DAB reaction. All sections were mounted onto gelatinized slides, air-dried, and coverslipped. The primary antibody was absent in control sections, which were otherwise processed identically.

#### DATA ANALYSIS

##### Layer 4C

Video images of tissue sections processed for CO, Zif268, synaptophysin, and GAP-43 were captured with a COHU

CCD (4915) camera using a Macintosh IIfx-based analysis system with a Data Translation DT-2255 quick capture board. NIH Image 1.62 was used to obtain density profiles and to measure periodicity of ocular dominance columns. Optical density was measured in lasered and nonlasered eye ocular dominance domains. Because CO-stained tissues demonstrated a uniform staining pattern at 20 hours post-PRP, we identified ocular dominance columns by Zif268 immunoreactivity. For the other post-PRP time points, CO histochemistry was used to identify the lasered (light bands) and nonlasered (dark bands) eye columns. To demonstrate that the light and dark bands in synaptophysin and GAP-43 immunoreacted tissue coincided with lasered or nonlasered eye ocular dominance columns, tissue sections were co-aligned with alternate serial sections processed for CO or Zif268. For the 4 neurochemicals and at each post-PRP time point, 10 transects were taken in the lightly stained eye bands and also in the adjacent darkly stained bands. Density ratios between neighboring bands were calculated as the fraction of lasered over nonlasered eye band densities. Mean density ratio was calculated from 10 density ratios.

Estimates of baseline levels of synaptophysin and GAP 43 were obtained from densitometric measures of immunostaining in visual cortical block 1, the foveal representation, which appeared unaffected by PRP treatment (Table II).

Statistics were performed on density ratios using the *t* test and the analysis of variance (ANOVA) test. Lasered eye–nonlasered eye density ratios of 1, <1, or >1 were possible. Ratios of 1 represented uniform staining between adjacent ocular dominance bands. Ratios of <1

indicated that the lasered eye columns were less intensely stained than the adjacent, nonlasered eye columns, and the opposite was true for ratios of >1. A two-tailed *t* test compared the density ratio at each time point to the uniform staining intensity ratio of 1. The *P* value for the null hypothesis was set below 0.01. For each neurochemical marker, differences between mean density ratios for the 4 time points were evaluated by the ANOVA statistical test.

### Layer 2/3

In layer 2/3 CO blobs were captured and blob density was measured with the same video system and image program previously described. Optical density of neighboring CO blob rows was again compared as the fraction of lasered over nonlasered eye blob densities. Statistical analysis, as previously described, was used to compare blob density ratios to the uniform staining intensity ratio. In addition, ten transects that ran perpendicular to ocular dominance columns were used to measure blob periodicity.

## RESULTS

### RETINAL HISTOLOGY

The spot diameter, duration, power, and number of laser burns per case are given in Table I. The mean distance between laser sites was calculated to be 1.5 spot diameters (750  $\mu\text{m}$ ). It is estimated that about 20% of the retina was lasered during PRP. Figure 1 illustrates 8- $\mu\text{m}$  cryostat sections of the retina stained with hematoxylin-eosin at 6 months (Fig 1 A through C, case K414) and at 13 months (Fig 1D, case K413) post-PRP. Histopathological analysis revealed that the predominant damage to the retina from PRP was a mild to moderate grade III burn.<sup>8</sup> The lasered sites were characterized by hyperpigmentation and disruption of the retina, especially the inner nuclear layer, the outer plexiform layer, and the outer nuclear layer. The retinal ganglion cell layer was histologically intact (arrows, Figs 1B, 1D). The interlaser sites demonstrated normal retinal histology (Fig 1C).

### CO STAINING IN LAYER 4C OF THE VISUAL CORTEX

#### 20 Hours Post-PRP

CO staining appeared uniform throughout layer 4C at 20 hours post-PRP (Fig 3E). The optical density values of CO staining in lasered and nonlasered ocular dominance columns confirmed our qualitative observation that CO density was statistically similar in adjacent eye bands at 20 hours post-PRP (Fig 4A).

#### 12 Days and 6 Months Post-PRP

Stripe-like fluctuations in CO histochemistry of layer 4C were observed at 12 days and 6 months post-PRP

TABLE II: PERCENTAGE OF CORTICAL TISSUE EXHIBITING OCULAR DOMINANCE BANDS (ODB)

ANIMAL ID	SURVIVAL TIME	BLOCK NO	AREA WITH ODB (MM <sup>2</sup> )	TOTAL AREA (MM <sup>2</sup> )	% AREA WITH ODB
K429R	12 days (CO <sup>a</sup> )	1	0	262.6	0
		2	92.6	121.4	76.3
		3	50.2	119.7	42.0
		4	129.7	188.4	68.8
K420R	12 days (CO)	1	0	152.6	0
		2	51.5	69.1	74.5
		3	10.1	83.7	12.1
		4	106.5	139.8	76.1
K367R	12 days (CO)	1	0	377.9	0
		2	87.8	170.4	51.5
		3	13.6	190.9	7.1
		4	42.5	343.4	12.4
K414R	6 months (CO)	1	0	216	0
		2	66.7	101.9	65.4
		3	61.5	152.4	40.4
		4	194.8	265.5	73.4

<sup>a</sup>CO, cytochrome oxidase.

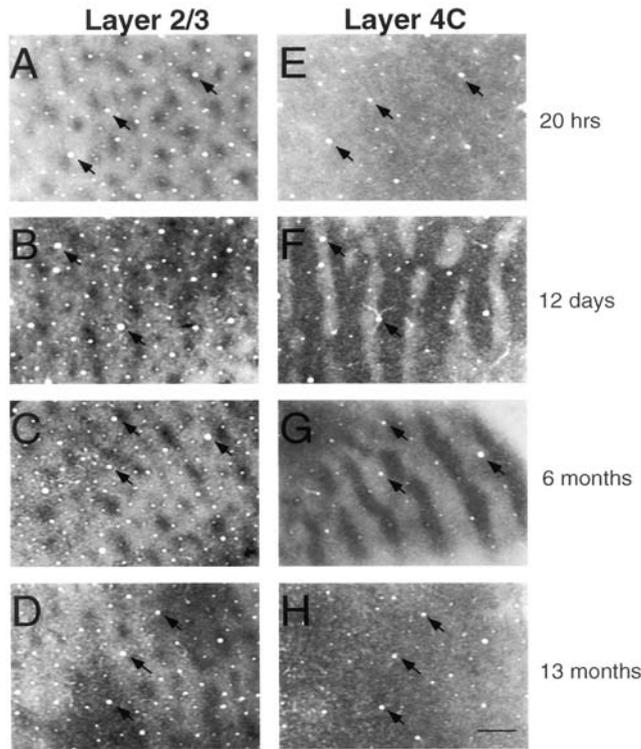


FIGURE 3

Cytochrome c oxidase-stained tangential sections through layers 2/3 and 4C at 20 hours, 12 days, 6 months, and 13 months post-PRP. A and E, 20 hours post-PRP. No visible effects of deprivation on CO staining of blobs (A) or in thalamic recipient zone in layer 4C (E). Mean density ratio (lasered/normal eye) of  $0.993 \pm 0.002$  SEM in layer 4C was not significantly different from a normal density ratio of uniform staining. B and F, 12 days post-PRP. Rows of shrunken blobs (B) were located overlying pale ocular dominance bands of layer 4C (F). Mean density ratio of CO blobs at 12 days post-PRP was  $0.70 \pm 0.11$ , significantly  $<1$ . Ocular dominance bands were visible in layer 4C of blocks 2, 3, and 4 but not in block 1. Mean density ratio in layer 4C for 12 days post-PRP was  $0.89 \pm 0.02$ , significantly  $<1$ . C and G, 6 months post-PRP. Shrunken rows of CO blobs (C) align with light ocular dominance bands (G). Mean density ratio in layer 4C for 6 months post-PRP was  $0.69 \pm 0.04$ , significantly  $<1$ . D and H, Density of neighboring rows of CO blobs at 13 months post-PRP was equivalent (D). At 13 months post-PRP, stripe-like fluctuations in CO staining between lasered and nonlasered eyes' ocular dominance bands in layer 4C were no longer present (H). In layer 4C, mean density ratio of  $0.98 \pm 0.09$  was not significantly different from a uniform density ratio of 1. Scale bar = 1 mm.

(Figs 3F, 3G). These fluctuations presumably represent ocular dominance columns, with the lightly stained CO area representing the lasered eye's cortical columns and the darkly stained CO area representing the nonlasered eye's cortical columns.<sup>11</sup> The fluctuating pattern of CO staining was only observed in cortical areas representing the peripheral visual fields (Table II, data for blocks 2, 3, and 4). Cortical areas representing central vision (Table II, data for block 1) exhibited uniform staining in layer 4C.

As the retina is topographically represented in visual cortex, metabolic activity changes caused by unilateral PRP deprivation should also demonstrate topographic

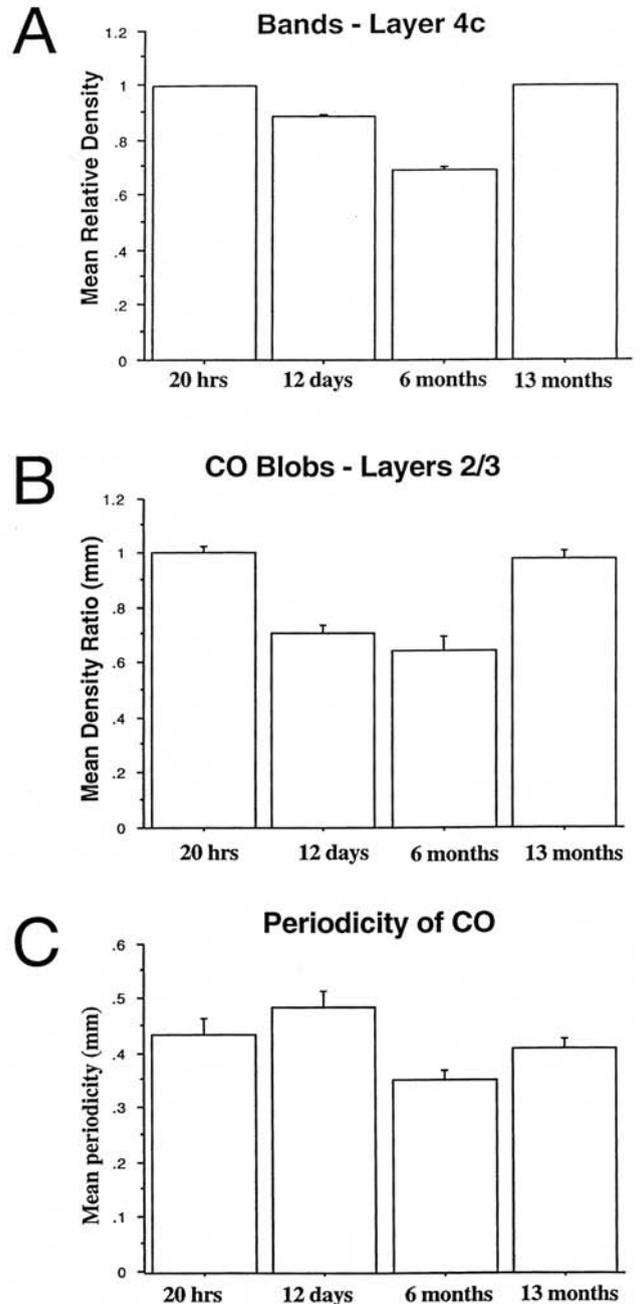


FIGURE 4

Summary graphs identifying time course of changes in density and periodicity levels of CO after PRP treatment. Data are mean density ratios (lasered eye/normal eye)  $\pm$  SEM. A, Gradual reduction in CO activity in lasered eye's ocular domains bands at 20 hours ( $1.00 \pm .01$ ), 12 days ( $.886 \pm .025$ ), and 6 months post-PRP ( $.693 \pm .041$ ), with recovery to baseline levels by 13 months post-PRP ( $1.00 \pm .01$ ). Effects of PRP on optical density and periodicity of CO blobs in layer 2/3 (B). Mean density ratios (lasered eye/normal eye) of CO blobs in layer 2/3. At 12 days and 6 months post-PRP, density of CO blobs was significantly  $<1$  ( $P < .01$ ). At 20 hours and 13 months post-PRP, density of CO blobs was not significant. C, Mean periodicity of CO blobs in layer 2/3 ranged from 0.35 to 0.48 mm.

registry. We calculated the area of visual cortex that exhibited light and dark CO columns at 12 days and 6 months post-PRP (Table II) to be greater than 50% of the lower peripheral visual fields (blocks 2, 4). In contrast, less than 50% of the upper peripheral visual field (block 3) exhibited CO fluctuations.

### 13 Months Post-PRP

No discernible fluctuation in CO staining was observed in layer 4C at 13 months post-PRP (Fig 3H). Figure 4A illustrates the time course of changes in CO density in layer 4C.

### CO STAINING IN LAYER 2/3

CO blobs at 20 hours post-PRP appeared uniform (Figs 3A and 5A). Note that in Fig 5B the density of neighboring rows of CO blobs at 20 hours is equivalent. At 12 days (Fig 3B) and 6 months post-PRP (Fig 3C), CO blobs centered over the lasered eye bands were both paler and smaller, compared with blobs centered over the non-lasered eye bands. Examples of transects used for measuring optical density and periodicity of CO blobs at 6 months post-PRP are shown in Figs 5C and 5D. By 13 months post-PRP, the density of neighboring rows of CO blobs was equivalent again (Fig 3D).

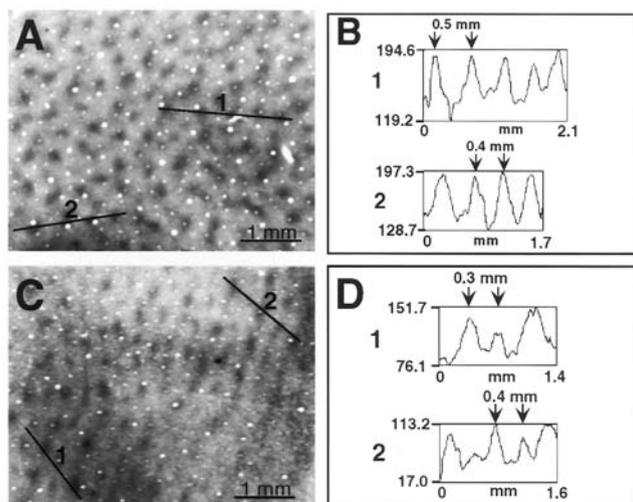


FIGURE 5

Density and periodicity of CO blobs in layer 2/3. Transects through several neighboring rows of CO blobs drawn perpendicular to ocular dominance band orientation as demonstrated by anti-Zif268 immunoreactivity for 20 hours post-PRP (A) or by CO histochemistry for 6 months post-PRP (C). Density values along transects (B, D). Arrows indicate an example of two neighboring blobs from each transect; value between arrows represents distance between blobs. A and B, 20 hours post-PRP. CO blobs of neighboring rows demonstrated uniform density, with a mean density ratio of  $1.00 \pm 0.08$ . Mean periodicity was  $0.44 \pm 0.10$  mm. C and D, 6 months post-PRP. CO blobs displayed nonuniform density; rows of pale CO blobs alternated with rows of dark CO blobs. Mean density ratio for 6 months post-PRP was  $0.65 \pm 0.16$ . Both values were significantly  $<1$  ( $P < .01$ ). Mean periodicity was  $0.35 \pm 0.07$  mm for 6 months post-PRP.

### ZIF268 IMMUNOHISTOCHEMISTRY

Figure 6 illustrates immunostaining for Zif268 in layer 4C at 4 time points post-PRP. Darkly immunoreactive nuclei, seen as punctate staining, form a banded pattern (asterisks, Figs 6A, 6B, 6C). Figure 6A demonstrates bands of reduced immunostaining, representing the lasered eye, interdigitated with bands of dark immunostaining (asterisks) from the nonlasered eye at 20 hours post-PRP. At 12 days post-PRP, Zif268 immunohistochemistry again revealed a fluctuating pattern of lightly and darkly immunostained bands, though the contrast was less distinct than at 20 hours post-PRP (Fig 6B). At 6 months post-PRP, the difference between light and dark bands was just visible (Fig 6C), and by 13 months post-PRP there were no detectable bands present (Fig 6D).

### SYNAPTOPHYSIN IMMUNOHISTOCHEMISTRY

Synaptophysin immunohistochemistry resulted in uniform staining in all cortical layers except layer 4C. Figure 7 illustrates results from layer 4C at 4 time points post-PRP. Bands in layer 4C stained for synaptophysin were observed only at 6 months post-PRP (Fig 7G). Comparisons with CO tissue (Fig 7C) revealed that the darkly stained synaptophysin bands (Fig 7F) coaligned with darkly stained CO bands, representing the non-lasered eye columns. While a relative difference in density was visible (Fig 7G), the density of both the lasered and the nonlasered eyes' columns was greater than that of visual cortex from block 1, which represented baseline levels of synaptophysin in this study. The area that demonstrated synaptophysin bands was calculated to be  $35 \text{ mm}^2$  or approximately 13% of the cortical area that demonstrated a deprivation effect (loss of CO activity associated with the lasered eye).

### GAP-43 IMMUNOHISTOCHEMISTRY

Immunostaining using an antibody against GAP-43 also demonstrated a similar laminar pattern of labeling and time course as synaptophysin. Figure 8 shows serial sections stained for Zif268 (Fig 8A), CO (Fig 8B, C, D), and GAP-43 (Fig 8E, 8F, 8G, 8H). We observed uniform GAP-43 immunostaining at 20 hours, 12 days, and 13 months post-PRP (Fig 8E, 8F, 8H). However, GAP-43 bands were seen at 6 months post-PRP (Fig 8G). Comparisons with CO tissue (Fig 8C) revealed that the darkly stained GAP-43 bands aligned with the darkly stained CO bands associated with the nonlasered eye. As seen for synaptophysin immunoreactivity, density levels in the lasered and nonlasered eye columns were both higher than seen in the visual cortex of block 1, representing the

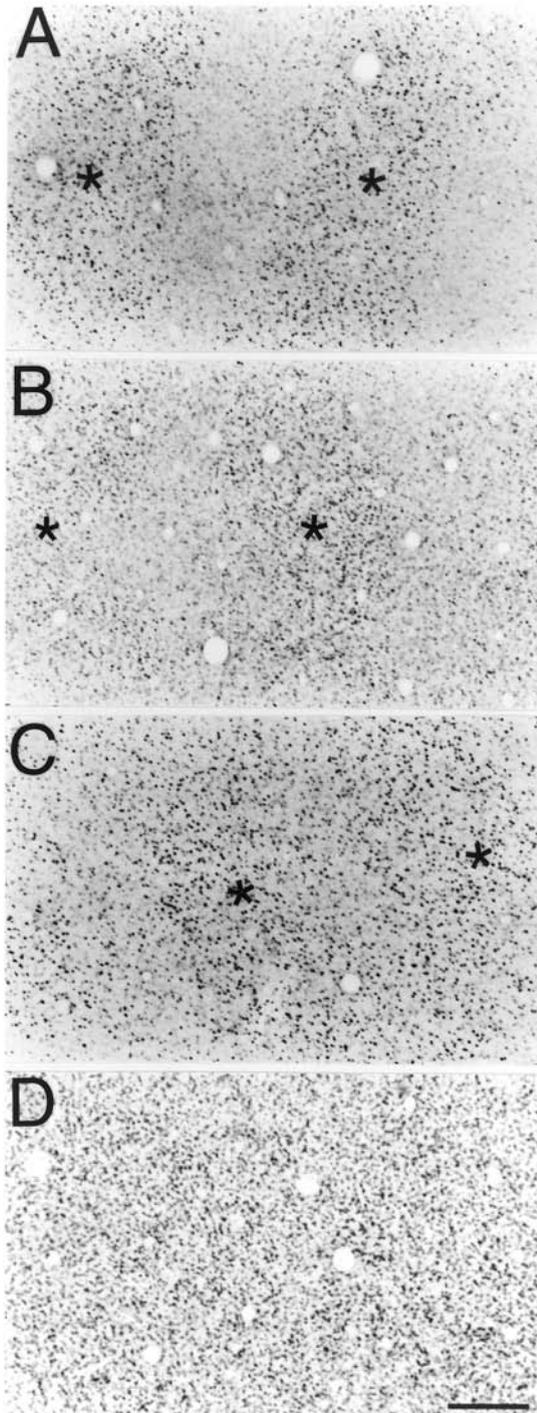


FIGURE 6

Comparisons of Zif268 immunoreactivity at 4 time points post-PRP. A, Anti-Zif268 immunostaining in layer 4C at 20 hours post-PRP demonstrates series of dark immunoreactive bands (asterisks), which represent ocular dominance bands of nonlasered eye, separated by light immunoreactive bands, which represent ocular dominance bands of lasered eye. B, Dark immunoreactive bands associated with nonlasered eye (asterisks) are still evident 12 days post-PRP. C, By 6 months post-PRP, contrast between dark and light bands is considerably less as immunostaining levels increase in lasered eye bands compared with nonlasered eye bands (asterisks). D, at 13 months post-PRP, uniform Zif268 immunoreactivity is present. Scale bar = 200  $\mu$ m.

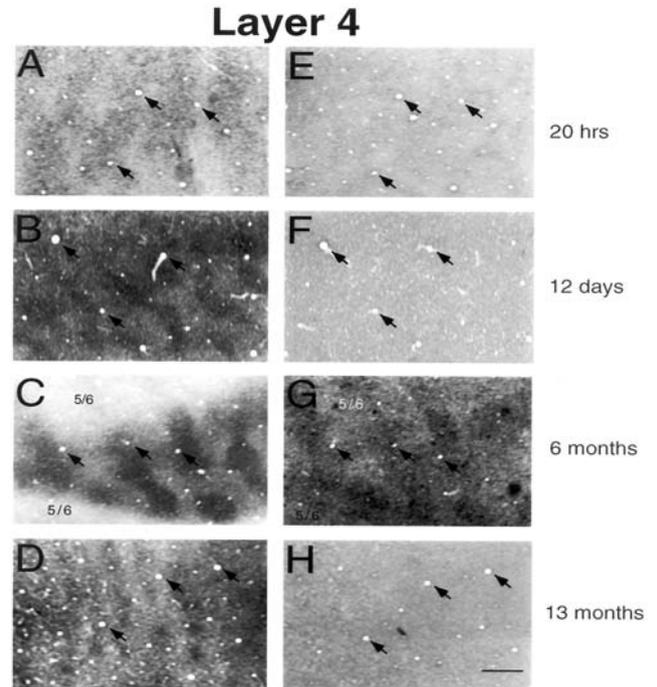


FIGURE 7

Comparisons of ocular dominance bands and synaptophysin immunoreactivity at 4 time points post-PRP. A, Anti-Zif268 immunostaining in layer 4C at 20 hours post-PRP. B and C, At 12 days and 6 months post-PRP, CO bands were evident through layer 4C. D, Rows of CO blobs in layer 2/3 identify orientation of ocular dominance bands at 13 months post-PRP. E, F, G, and H, Synaptophysin immunohistochemistry. At 20 hours (E), 12 days (F), and 13 months (H) post-PRP, there was no differential immunolabeling for synaptophysin between lasered and nonlasered eye columns. At 6 months post-PRP (G), a series of darkly staining synaptophysin immunoreactive bands was present in layer 4C. Mean density ratio of synaptophysin immunostaining at 6 months post-PRP ( $0.98 \pm 0.01$ ) was significantly different from a uniform density ratio of 1 ( $P < .01$ ) (Fig 8G). Alignment with sections stained for CO revealed that strongly immunoreactive bands co-localized with normal eye bands. Arrows identify cross sections of radially penetrating blood vessels used for alignment of serial sections. Scale bar = 1 mm.

fovea and thus unimpaired by PRP. The area that demonstrated GAP-43 bands was calculated to be 35 mm,<sup>2</sup> approximately 12% of the cortical area that demonstrated deprivation effect (loss of CO activity associated with the lasered eye).

## DISCUSSION

Previous studies have looked at the cortical changes arising after single central retinal laser lesions in the cat<sup>24-26</sup> and the primate.<sup>10</sup> This is the first study to look at the effects of multiple laser sites in the peripheral retina, as used in PRP therapy. This study focused on visual cortical changes in metabolic activity markers (CO and Zif268) and cortical plasticity markers (synaptophysin and GAP-43). We found that the levels changed in response to partial deafferentation by unilateral PRP. Of particular

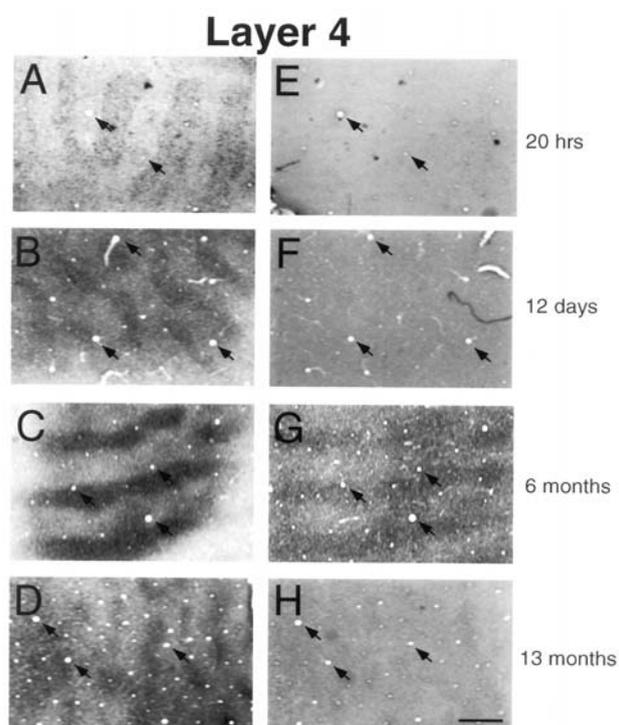


FIGURE 8

Comparisons of ocular dominance bands and GAP-43 immunoreactivity at 4 time points post-PRP. A, At 20 hours post-PRP, Zif268 immunostaining revealed a series of ocular dominance bands. At 12 days (B) and 6 months (C) post-PRP, CO histochemistry revealed ocular dominance bands in layer 4C. D, At 13 months post-PRP, rows of CO blobs in layer 2/3 identify direction of elongation of ocular dominance domains. At 20 hours (E), 12 days (F), and 13 months (H) post-PRP, uniform immunostaining for GAP 43 was observed across both lasered and normal eye ocular dominance domains. At 6 months post-PRP (G), a series of darkly staining GAP-43 immunoreactive bands was present in layer 4C of block 4, and mean density ratio of  $0.98 \pm 0.01$  was significant  $<1$  ( $P < .01$ ). Alignment with sections stained for CO revealed that strongly immunoreactive bands co-localized with normal ocular dominance bands. Arrows identify cross sections of radially penetrating blood vessels used for alignment of serial sections. Scale bar = 1 mm.

interest is the finding that synaptophysin and GAP-43 levels are greater in both the lasered and nonlasered eyes' ocular dominance columns at 6 months post-PRP, compared with baseline levels found in nondeprived visual cortex.

#### CO ACTIVITY

We found no change in CO activity at 20 hours post-PRP, in contrast with the study of Wong-Riley and associates,<sup>12</sup> which reported a reduction in CO activity as early as 14 hours after an intraocular TTX injection. It is likely that intraocular TTX injection silences all ganglion cells, whereas PRP may silence only ganglion cells within the laser sites, estimated at 20% of the retina. The difference in results is probably due to the more severe form of deprivation used in the study of Wong-Riley and associates. At 12 days and 6 months post-PRP, a gradual reduction in

CO staining in the lasered eye's ocular dominance columns (layer 4C) and in the overlying CO blobs (layer 2/3) was seen (Fig 4A, 4B). By 13 months post-PRP, the CO activity associated with the lasered eye's ocular dominance columns returned to levels equaling those of the non-lasered eye's ocular dominance columns (Fig 4A). The recovery of CO activity by 13 months post-PRP likely indicates a recovery of retinal ganglion cell metabolism, as our analysis revealed anatomically intact ganglion cells within the laser sites of the 13-month post-PRP eye (Fig 1D).

The reduction in CO activity in layer 4C of the 12-day and 6-month post-PRP cases covered the cortical representation of both laser and interlaser sites, as evidenced by the ocular dominance bands. Intuitively, this was surprising and suggests that laser photocoagulation may affect a visual field larger than that represented in the laser sites. Given that the histologic sections of the lasered retina showed that the interlaser sites were anatomically normal (Fig 1A, 1B), we can only speculate that the finding of reduced CO activity in the cortical representation of the interlaser sites is due to central mechanisms, consistent with Wong-Riley's earlier finding from the transition zone of a single focal laser lesion of retina.<sup>12</sup> Alternatively, reduced CO activity in the cortical representation of the interlaser sites may be due to a peripheral mechanism. It would be important to know whether the interlaser sites are visually responsive after PRP treatment. We do not know of any study that has attempted microperimetry of interlaser sites in patients post-PRP.

#### ZIF268

Zif268 is one of a family of immediate early gene products that were shown to be expressed in neurons in an activity-dependent manner.<sup>27,28</sup> In this study, it was used to identify ocular dominance bands at 20 hours post-PRP, a time point that did not demonstrate effects on CO activity. An earlier study from our laboratory<sup>13</sup> demonstrated that Zif268 immunoreactivity still delineates ocular dominance bands in the primate visual cortex after a 3-month unilateral enucleation. The resultant blurring of ocular dominance bands seen in the present study at 6 months and 13 months post-PRP is consistent with and extends our earlier findings<sup>13</sup> demonstrating that Zif268 levels recover to nondeprived levels between 6 and 13 months post-PRP. Whether this time frame of recovery holds for more severe forms of deprivation, such as enucleation or optic nerve transection, is not known.

#### CORTICAL PLASTICITY MARKERS

Synaptophysin is a presynaptic 38 kDa vesicle membrane glycoprotein<sup>29</sup> that is expressed during development and in parallel with the formation of new synapses.<sup>29-31</sup> GAP-43 is

expressed at high levels and transported to growth cones and immature synapses during neuronal development<sup>32,33</sup> and has been implicated in axonal growth, synaptic plasticity, and neuronal remodeling.<sup>34,35</sup> There is evidence that GAP-43 can be up-regulated in adult visual cortex after infusion of nerve growth factor in vivo.<sup>36</sup> In the present study, immunohistochemical localization of synaptophysin and GAP-43 at 6 months post-PRP revealed that the nonlasered eye bands were significantly darker than the lasered eye bands (Fig 8D). Further analysis revealed that the levels of synaptophysin and GAP-43 in both lasered and nonlasered bands were significantly higher than levels found in cortex representing the fovea, which is not targeted by PRP. These results suggest that there is an up-regulation of synaptophysin and GAP-43 within layer 4C of both the lasered and nonlasered eyes' ocular dominance columns at 6 months post-PRP.

#### CLINICAL RELEVANCE

A previous study<sup>37</sup> examined the aspects of visual function necessary in the everyday lives of diabetic patients and identified that tasks involving depth perception, judging distances, navigating stairs, and participating in sports were commonly cited as becoming more difficult since PRP treatment. The current clinical practice is to give PRP unilaterally in any given session. In patients who require bilateral PRP, the second eye is treated after a variable delay of 2 weeks to 2 months. Since our results show that unilateral PRP affects the levels of neurochemicals in the cortical representation of both lasered and nonlasered eyes, imbalances due to synaptic remodeling between eye domains may result in loss of peripheral visual function after PRP treatment. If this is indeed the case, it might be helpful, for those patients requiring bilateral treatment, to separate the PRP sessions between eyes by a week or less. Of course, clinical studies would have to be done to determine if changing the current PRP strategy might improve the quality of life for patients with proliferative diabetic retinopathy.

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## DISCUSSION

DR LEONARD M. PARVER. The authors have presented experimental results showing the consequences of PRP on the visual cortex. They investigated the effects of unilateral PRP on the distribution of several neurochemical markers in the primary visual cortex of the monkey eye at multiple time periods.

The results of their experiments demonstrate changes in the visual cortex following unilateral PRP. A number of their observations deserve further comment. To begin, their finding that the ocular dominance columns representing both the lasered and non-lasered eye show changes in synaptophysin and GAP-43 levels following unilateral PRP is left unexplained. Further, the authors

noted asymmetrical changes in the topographic representations in the visual cortex for the lower and upper visual fields even though presumably they received similar amounts of photocoagulation. The latter finding may be a consequence of sampling given the limited number of animals examined at any one point in time.

The authors also noted changes in the visual cortex representation for both lasered and interlasered sites. They speculate that the extent of the field changes seen at the visual cortex level is somehow greater than the site occupied by the laser burn. An alternate explanation is that the area of retina damaged during PRP is greater than the area represented by the visible retinal scars and represents the effects of indirect photochemical injury. Indirect photochemical damage to the macula of the monkey eye following PRP has been reported.<sup>1</sup> The changes observed were not visible on ophthalmoscopy or fluorescein angiography but were present on EM and confined to the RPE and outer photoreceptor layers. The authors examined the retina using only light microscopy. If there was evidence of photochemical injury, it may have been detectable only by EM. The authors did examine the region of the visual cortex representing the fovea and noted no changes using their neurochemical markers. One wonders whether this represents a threshold effect and whether the neurochemical markers require a certain level of damage to trigger changes in the topographic representation in the visual cortex.

The DRS and the ETDRS established the efficacy of PRP in the treatment of proliferative diabetic retinopathy. Subsequent clinical experience has proven these conclusions to be correct. As with any treatment, however, there are potential unwanted side effects. In the case of PRP, there was an unexplained loss in Snellen visual acuity first observed in the DRS and later confirmed in the ETDRS. Between 3% and 11% of patients suffer a loss of Snellen vision of 1 to 2 lines. Even in patients who do not demonstrate a loss of Snellen visual acuity, other more sensitive tests of visual function, such as contrast sensitivity, have uncovered visual abnormalities. The authors have proposed that their findings in the visual cortex following PRP may help explain this observed loss of Snellen visual acuity. While their findings could potentially support changes in peripheral vision following PRP, it is difficult to understand how changes solely in the topographic representation of peripheral retinal regions could effect central or macular visual tasks such as Snellen visual acuity, contrast sensitivity, or complex visual activities of daily living.

The authors have linked peripheral retinal damage produced by PRP with changes in the visual cortex. While questions remain, I encourage the authors to expand their observations.

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[Editors note] DR THOMAS R. HEDGES JR. wondered about the occasional recovery of central and peripheral vision in some patients after brain lesions. He pointed out that in the macula the cone projections are magnified between the eye and the visual cortex and asked if the authors could use markers to quantify the changes in these pathways and perhaps explain the extraordinary plasticity of the brain for recovery.

DR T. MICHAEL NORK. Dr Parver correctly points out a limitation of our study, namely that there could have been subtle changes in the levels of these neurochemicals in the

macular region of the visual cortex that were below the threshold of detection by the immunochemical and histochemical methods that were employed. Therefore, we cannot rule out the possibility that peripheral laser photocoagulation has an effect on this region of the cortex.

In response to Dr Thomas Hedges, Jr's suggestion that the central retinal pathways be further investigated by performing macular photocoagulation, we agree that an experiment such as this might be informative. We chose panretinal photocoagulation for this study because it is a commonly used treatment in humans to control retinal and iris neovascularization.



# FIBROUS CONGENITAL IRIS MEMBRANES WITH PUPILLARY DISTORTION\*

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BY *Richard M. Robb, MD*

## ABSTRACT

*Background:* In 1986 Cibis and associates<sup>1</sup> described 2 children with a new type of congenital pupillary-iris-lens membrane with goniodysgenesis that was unilateral, sporadic, and progressive. These membranes were different from the common congenital pupillary strands that extend from 1 portion of the iris collarette to another or from the iris collarette to a focal opacity on the anterior lens surface. They also differed from the stationary congenital hypertrophic pupillary membranes that partially occlude the pupil, originating from multiple sites on the iris collarette, but not attaching directly to the lens.

*Case Material:* The present report is an account of 7 additional infants with congenital iris membranes, similar to those reported by Cibis and associates, which caused pupillary distortion and were variably associated with adhesions to the lens, goniodysgenesis, and progressive occlusion or seclusion of the pupil. Six of the 7 patients required surgery to open their pupils for visual purposes or to abort angle closure glaucoma. A remarkable finding was that the lenses in the area of the newly created pupils were clear, allowing an unobstructed view of normal fundi.

*Conclusion:* This type of fibrous congenital iris membrane is important to recognize because of its impact on vision and its tendency to progress toward pupillary occlusion. Timely surgical intervention can abort this progressive course and allow vision to be preserved.

*Tr Am Ophth Soc* 2001;99:45-51

## INTRODUCTION

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In 1986 Cibis and associates<sup>1</sup> described a new type of congenital pupillary-iris-lens membrane with goniodysgenesis that was unilateral, sporadic, and progressive. One of their 2 cases developed a secluded pupil with iris bombe, requiring peripheral iridectomy. In 1994 Cibis and coworkers<sup>2</sup> reported an additional case in which the pupillary-iris-lens membrane was dissected from the lens surface at 3 months of age without cataract formation. As noted by the investigators, these membranes appeared to be different from the congenital pupillary strands that are occasionally seen to cross the pupil from one portion of the iris collarette to another or from the iris collarette to a focal opacity on the anterior lens surface. They also differed from the congenital hypertrophic pupillary membranes that partially occlude the pupil, originating from multiple sites on the iris collarette but not attaching directly to the lens.<sup>3-5</sup>

The present report is an account of 7 additional patients with unilateral congenital iris membranes that caused pupillary distortion and were variably associated with adhesions to the lens, goniodysgenesis, and progressive occlusion or seclusion of the pupil. These iris membranes are important because of their impact on vision and because timely surgical intervention may alter their progressive course. The Committee on Clinical

Investigation of Children's Hospital, Boston, approved this medical record review.

## CASE REPORTS

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### CASE 1

A 10-day-old full-term girl was noted by her pediatrician to have a white opacity in the left pupil. On ophthalmic examination at 11 days of age, she appeared to have a white plaque on the anterior surface of the left lens covering the nasal half of the pupil (Fig 1). The nasal portion of the pupillary margin was adherent to this membrane, but the temporal margin was free and there was a clear red fundus reflex in the temporal portion of the pupil. Both pupils constricted to light stimulus, and no afferent pupillary defect could be seen. There was a peripheral iris adhesion to clear cornea nasally at the 9-o'clock position. Retinoscopy revealed 2.50 diopters of hyperopia in each eye, and the fundi appeared normal by indirect ophthalmoscopy.

At 2 months of age, the infant had white plaque occupying three quarters of the pupillary area after dilation, and at 3½ months, less than 1 mm of clear pupil temporally. The child could now fix and follow well with the right eye but not with the left. The left fundus could no longer be seen. Examination of the infant under anesthesia revealed ocular pressures of 9 mm Hg in the right eye and 8 mm Hg in the left eye. The horizontal corneal diameters were 11.25 mm in each eye. On gonioscopy of the left eye,

\*From the Department of Ophthalmology, Children's Hospital and Harvard Medical School, Boston, Massachusetts.

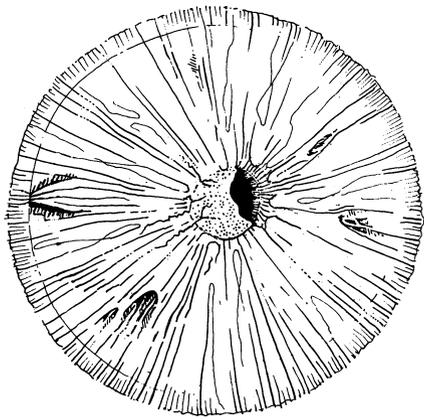


FIGURE 1

Case 1. Drawing of left iris showing white plaque covering nasal half of pupil and peripheral iris adhesion to clear cornea at 9-o'clock position.

the anterior chamber angle was open to the ciliary body band throughout, but there was a localized iris adhesion to Schwalbe's line at the 9-o'clock position. Radial iris vessels extended from the nasal iris onto the white pupillary plaque, which was in contact with the anterior lens surface.

With the infant under the same anesthesia, surgery was performed through a superior limbal incision. An attempt was made to cut the white plaque-like membrane with a Haab knife, but the membrane could not be cut or separated from the pupillary margin. An Ocutome tip was then inserted into the anterior chamber and passed through the small temporal pupillary opening. At this point, the membrane separated cleanly from the underlying anterior lens capsule, and the membrane and some of the adjacent iris were nibbled away to create a larger pupillary opening. A small crescent of iris pigment epithelium remained attached to the lens nasally, but elsewhere the lens was clear and has remained so postoperatively. Part-time patching of the right eye was undertaken between 4 and 9 months of age, and at the end of that time the preferential looking acuity was 20/130 in each eye. The eyes appeared straight and the ocular motility was full.

## CASE 2

A 4-month-old boy was referred because of an abnormal pupil in the right eye. A small, eccentric right pupil had been noted at 2 weeks of age, but initial ophthalmologic examination had led to no recommendations for treatment. The child was generally well, and there was no family history of eye disease. At 4 months of age, he fixed and followed visual targets well with the left eye but only poorly with the right eye. A preferential looking test revealed visual acuity of 20/400 in the right eye and 20/180 in the left eye. The eyes appeared straight, and the corneas were similar in size. The left pupil was normal in size and configuration and reacted well to light. The right pupil was 1 mm in diameter. It was

displaced nasally, and the nasal half of the pupil was occupied by a flat, white membrane that was adherent to the lens (Fig 2). A single iris strand extended from the white membrane above the surface of the iris to an attachment on Schwalbe's line, which could be seen through clear cornea, in the 2-o'clock meridian. A red fundus reflex could be seen through the temporal portion of the pupil, but this disap-

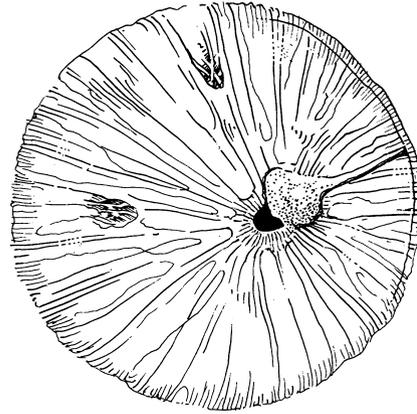


FIGURE 2

Case 2. Drawing of right iris showing nasal displacement of pupil by white membrane that was adherent to lens. A single iris strand extends from white membrane to an attachment to Schwalbe's line nasally.

peared when the pupil constricted to light.

When the infant was 4½ months of age, the pupil of the right eye was enlarged surgically with use of an Ocutome to nibble out the iris in an inferotemporal direction from the free pupillary margin. A pupil approximately 4 mm in diameter was created. The original iridolenticular adhesion remained intact, but the lens elsewhere was clear, and the fundus appeared to be normal. A peripheral iridectomy was performed at the 12-o'clock position.

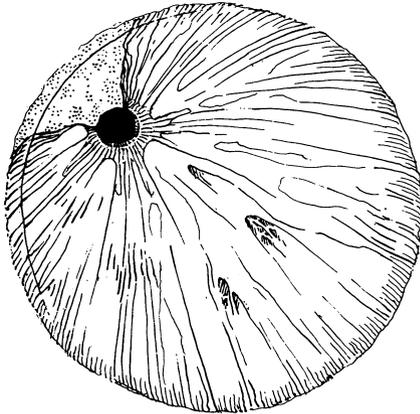
Preferential looking tests of visual acuity were equal in the 2 eyes postoperatively. Initially the infant's eyes appeared straight, but at 3 years of age a small-angle right esotropia became evident with near fixation. Part-time patching of the left eye was undertaken between the ages of 3½ and 5½ years. At age 6 years, glasses were prescribed as follows: right eye, +1.50 -0.50 x 180, and left eye, plano, with a bifocal add of +2.50 in each eye. The boy wore the glasses until age 9 years, at which time visual acuity was 20/25 in the right eye and 20/20 in the left eye with correction. A small-angle right esotropia with partial binocularity was still present. The right lens remained clear except at its original attachment to the nasal portion of the pupil.

## CASE 3

A 3-week-old boy was noted to have a "speck" on his left iris. On examination the speck was found to be a small ectopic pupil pulled toward the upper nasal quadrant by a white iris membrane that attached to a prominent

### *Fibrous Congenital Iris Membranes with Pupillary Distortion*

Schwalbe's line, visible through clear cornea between the 8- and 12-o'clock positions (Fig 3). A small red fundus reflex could be seen through the ectopic pupil, but the pupil dilated to only 1 mm with cycloplegic agents. The



**FIGURE 3**

Case 3. Drawing of left iris showing small pupil pulled eccentrically by an iris membrane that attached to Schwalbe's line, visible through clear cornea between 8- and 12-o'clock positions.

right pupil was normal in size and configuration, and the lens was clear. Preferential looking test acuities were 20/700 in the right eye and 20/2000 in the left eye.

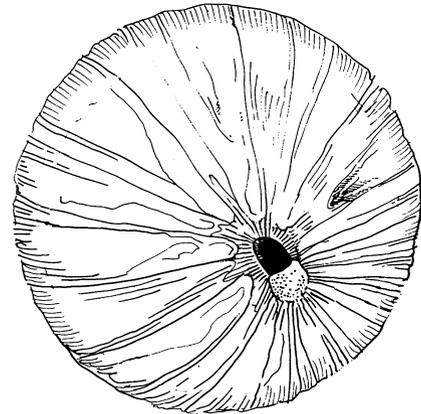
When the infant was 6 weeks of age, the left pupil was enlarged surgically. Gonioscopy revealed peripheral iris attachments to an anteriorly displaced Schwalbe's line between the 8- and 12-o'clock positions. The nasal pupillary margin was adherent to the lens. An Ocutome was used to extend the temporal margin of the pupil so that the horizontal pupillary diameter was approximately 6 mm. A peripheral iridectomy was performed at the 1-o'clock position. The lens was clear except at the point of the nasal iris adhesion, and the fundus was normal. At the time of surgery, the horizontal corneal diameters were 10.25 mm in the right eye and 9.50 mm in the left eye.

The left lens remained clear postoperatively. At 6 months of age, the preferential looking acuity was 20/88 in each eye. Mild myopia was noted when the infant was 2 years of age, but glasses were not prescribed until he was 7 years old, when refraction was -1.50 in the right eye and -0.50 -1.00 x 180 in the left eye. With this correction, the visual acuity with single letters was 16/16 in the right eye and 16/20 with single letters in the left eye. The eyes were straight, and the patient had binocular vision with stereopsis of 7 minutes of arc.

#### **CASE 4**

A 5-week-old girl was first seen because her left pupil was small and did not dilate. On examination she was able to fix and follow with each eye. The right iris and pupil were entirely normal. The left pupil was inferiorly displaced and

approximately 1 mm in diameter. A white membrane at the inferior margin of the pupil formed an attachment between the iris and the lens at that point (Fig 4). Under cycloplegia, the pupil dilated superonasally in an oblique, slit-like fash-



**FIGURE 4**

Case 4. Drawing of left iris showing inferior displacement of pupil by a white membrane that bound pupil to anterior lens surface.

ion. Retinoscopy through the slit opening revealed 1.25 diopters of hyperopia. The fundi appeared normal.

When the infant was 4 months of age, a preferential looking test revealed an acuity of 20/270 in each eye, but by 4½ months the left pupil had become smaller, the iris was convex, and the anterior chamber was shallow. On examination under anesthesia, the ocular pressures were 12 mm Hg in the right eye and 32 mm Hg in the left eye. Gonioscopy revealed a closed anterior chamber angle in the left eye. Surgery was performed through a limbal incision at the 10-o'clock position. A peripheral iridectomy was made, and the anterior chamber was deepened with Healon. With an Ocutome, an enlarged pupillary opening was created superior to the iris-lens adhesion. The lens was found to be clear in the area of the newly created pupil. Unfortunately, after this surgery fixation with the left eye was unsteady and wandering.

Subsequent examination under anesthesia when the infant was 5½ months of age revealed ocular pressures of 11 mm Hg in the right eye and 10 mm Hg in the left eye. The optic disc could be seen clearly in each eye, and in both eyes the cup-to-disc ratio was 0.4. The refractive error by retinoscopy under cycloplegia was +3.50 -1.00 x 180 in each eye. Part-time patching of the right eye was begun.

At 1 year of age, the infant had a definite left esotropia. Patching of the right eye proved to be very difficult. At 3 years of age, the visual acuity with picture cards was 16/30 in the right eye and 1/30 in the left eye. The left esotropia persisted.

#### **CASE 5**

A 3-week-old boy was noted by his pediatrician and a

local ophthalmologist to have a displaced pupil in his right eye. He was a full-term, otherwise healthy infant. On referral examination his corneas were found to be clear and symmetric. The left iris and pupil were normal in configuration and reaction to light. The right pupil was displaced superiorly. It was small and slit-like and appeared to be pulled toward the upper limbus by a white iris membrane that extended from the margin of the pupil to the anterior chamber angle (Fig 5). A red reflex could be seen

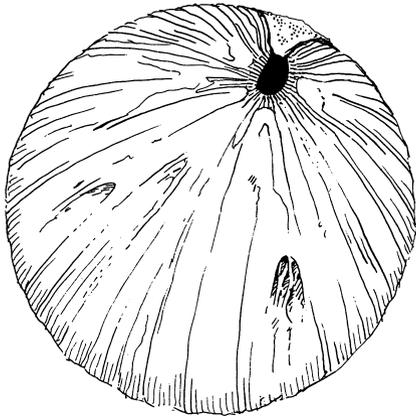


FIGURE 5

Case 5. Drawing of right iris showing displacement of pupil superiorly by a white iris membrane that extended from margin of pupil to anterior chamber angle.

through the slit pupil, and a small constriction to light was noted, but no view of the fundus could be obtained.

At 1 month of age, the child was examined while under anesthesia. The corneal diameters were 10 mm in the right eye and 10.5 mm in the left eye, and the ocular pressures were 10 mm Hg in both eyes. On gonioscopy, the right anterior chamber angle was normal except in the 1-o'clock meridian, where the iris was drawn up by a white membrane to the trabecular meshwork. A surgical incision was made at the 12-o'clock limbus, and with an Ocutome the pupil was enlarged in an inferior temporal direction. The underlying lens was clear, and through the enlarged pupil the fundus was seen to be normal.

Six weeks postoperatively, the child's preferential looking acuity was 20/1,000 in the right eye and 20/270 in the left eye. Part-time patching of the left eye was begun. By 4 months of age, the preferential looking acuity had improved to 20/180 in each eye, and at 7 months it was 20/130 in each eye. Patching was discontinued. The eyes appeared straight. A refraction at 14 months of age revealed mild hyperopic astigmatism, +2.50 -1.00 x 80 in the right eye and +2.00 -1.00 x 90 in the left eye. No glasses were prescribed. When the patient was last seen at age 7 years, the visual acuity was 20/25 in each eye. The eyes were straight, and there was binocular vision with stereopsis of 7 minutes of arc on the random dot E. The elliptical

pupil in the right eye showed only a slight constriction to light, but there was no relative afferent pupillary defect.

#### CASE 6

A 3-month-old boy was referred for ophthalmologic evaluation because of an irregular left pupil. He had been delivered with the aid of forceps, but at birth there were no forceps marks around the eyes. The left pupil was displaced temporally, and a strand of tissue extended from the pupil to the anterior chamber angle at the 3-o'clock position. Between the 2- and 4-o'clock positions, an anteriorly displaced Schwalbe's line could be seen through clear cornea. A small red fundus reflex could be seen through the oval eccentric pupil, but there was no view of the fundus and retinoscopy could not be performed. The anterior chamber was of average depth. The anterior segment and fundus of the right eye were normal. Ocular pressures were 15 mm Hg in each eye.

Because the left pupil appeared to be getting smaller with time, an examination of the infant under anesthesia was done at 6 months of age. The horizontal corneal diameters were found to be 11 mm in the right eye and 10.5 mm in the left eye. Gonioscopy revealed peripheral iris adherent to the anterior chamber angle from the 2- to 4-o'clock positions, a fibrous pupillary membrane, and a band extending from the membrane to Schwalbe's line temporally. Through a limbal incision, a full iridectomy was created with scissors from the 9- to 12-o'clock positions, extending centrally to the displaced pupil. In the area of the iridectomy, the lens was clear. The fundus was normal.

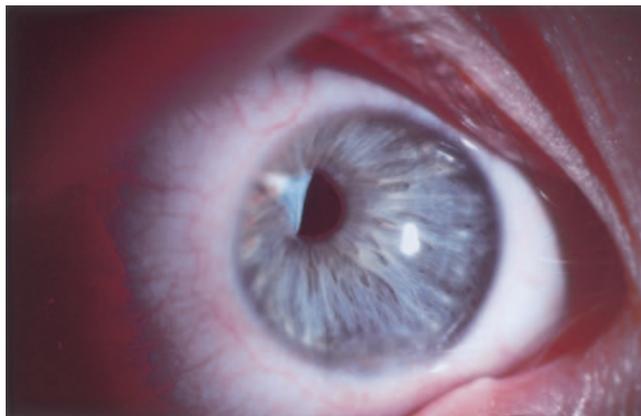
By 7 months of age the left eye was noted to be exotropic. Part-time patching of the right eye was begun. Initially the left eye was mildly hyperopic, but by age 1½ years, the refraction was plano in the right eye and -1.50 in the left eye. Glasses were prescribed, and efforts to patch the right eye were continued. By age 6 years, the left exotropia had increased to 40 prism diopters. The Snellen acuity with correction was 20/25 in the right eye and 20/50 in the left eye. Recession of the left lateral rectus muscle and resection of the left medial rectus were performed. Patching was not resumed postoperatively, and a small residual exotropia remained.

By age 15 years, myopic astigmatism had developed in both eyes: -3.25 -2.00 x 180 in the right eye and -3.25 -2.00 x 180 in the left eye. The corrected visual acuity was 20/20 in the right eye and 20/50 in the left eye. Ocular pressures were 17 mm Hg in both eyes. The patient chose to wear contact lenses, and when he was last seen at age 20, visual acuity was unchanged.

#### CASE 7

A 2-month-old girl was referred by her pediatrician and a

local ophthalmologist because of anterior segment abnormalities in the right eye. The child was a full-term healthy infant, and there was no family history of eye disease. On examination, the right cornea appeared slightly smaller than the left. A slightly elevated dermoid, 3 mm in diameter, at the inferior limbus extended only 1 mm onto clear cornea. The pupil was displaced toward the upper temporal quadrant, and from the 9- to 11-o'clock positions, the margin of the pupil was devoid of its pigmented layer and was attached to the lens by a white membrane (Fig 6). From this membrane a thin band of fibrous tissue extend-



**FIGURE 6**

Case 7. Photograph of right eye showing displacement of pupil toward upper temporal quadrant and a white membrane attaching iris to lens and extending peripherally to anterior chamber angle. Photograph was taken after a small inferior limbal dermoid had been removed. No iris surgery was performed.

ed peripherally above the surface of the iris to the anterior chamber angle. The portion of the pupil that was not bound to the lens could be dilated, and through the dilated pupil the lens appeared to be clear and the fundus normal. The anterior segment of the left eye was normal. The eyes were straight, and the child fixed and followed visual targets well.

At age 1 year, fixation with the right eye was noted to be reluctant, and a myopic retinoscopic reflex was seen in the right eye. Examination with the infant under anesthesia was therefore carried out. The corneal diameters were 11 mm in the right eye and 11.25 in the left eye. Ocular pressures were 9 mm Hg in the right eye and 11 mm Hg in the left eye. Cycloplegic retinoscopy revealed refractive errors of -4.00 in the right eye and +1.00 in the left eye. Gonioscopy confirmed that the anterior chamber angle of the right eye was open throughout its circumference except where the band extended from the iris surface to attach to the angle structures at the 10-o'clock position. On either side of the band the peripheral iris stroma was thinned, and several knuckles of the underlying pigmented iris could be seen. Both fundi were normal

except for a slightly less prominent foveal reflex in the myopic right eye.

After this examination the right pupil was kept dilated with atropine. Glasses were prescribed, and the left eye was patched part-time. This treatment was carried out with varying success until age 4 years. A right exotropia developed, and the myopia in the right eye increased to -6.00 diopters. Visual acuity at age 4 years was 3/30 in the right eye and 20/30 in the left eye with single picture cards. At this point, the limbal dermoid was excised from the inferior cornea. Despite efforts to continue with glasses and occlusion of the left eye, the visual acuity of the right eye at age 8 was only 20/300 with correction. Glasses were discontinued, and no further attempts at patching were made.

## **DISCUSSION**

The iris membranes described in these 7 cases are congenital, unilateral, and sporadic. They arise in the iris but not specifically from the iris collarette. They involve only a sector of the iris and create an attachment of the pupil to the anterior surface of the lens in that sector, distorting the pupil and pulling it into a variably eccentric position. The pupil may be small and slit-like, dilating only in that portion of its circumference not occupied by the membrane. A strand of the membrane often extends from the iris surface peripherally toward the anterior chamber angle, attaching to an anteriorly displaced segment of Schwalbe's line. In some cases, the membrane appears to be progressive. It may extend over the pupil (case 1) or may constrict the pupil (case 6) to the point that no useful optical path remains. In other cases, progression of the membrane leads to blockage of aqueous flow from the posterior chamber to the anterior chamber, and iris bombe results (case 4).

Pupillary dilatation may be useful in some patients to provide a better optical opening (case 7),<sup>6</sup> but more often surgical enlargement of the pupil has been necessary to restore vision or to treat angle closure glaucoma. Forceps and scissors may be used to perform the surgery (case 6),<sup>7</sup> but a suction-cutting instrument that can be inserted into the anterior chamber allows a more controlled iridectomy and protection of the underlying lens (cases 1 through 5).<sup>8</sup> Except for the point at which the membrane attaches to the lens, the lens has been clear in the area of the newly created pupil, and it has remained so. The fundi have been normal when viewed postoperatively. A small limbal dermoid in 1 patient (case 7) was the only other ocular abnormality found in our cases, except for a slightly smaller corneal diameter compared with the fellow eye (cases 3, 5, 6, and 7). No systemic disorders have been associated with the condition, nor have any abnormalities of pregnancy been identified.

The kind of iris membrane described in the cases presented here is different from what has been called a hyperplastic pupillary membrane.<sup>3,5</sup> The latter arises from the collarette of the iris and usually does not attach to the lens but covers the central pupil to a varying degree. Attachments to the anterior chamber angle are not found. These hyperplastic membranes are occasionally familial in nature.<sup>3</sup> Arguments for and against surgery for them have been advanced, but improvement of vision with surgery has been modest when preoperative and postoperative visual acuities have been available for comparison.<sup>4</sup> Another congenital pupillary abnormality, called congenital idiopathic microcoria by Lambert and associates,<sup>8</sup> is similar to but not identical with the abnormality in our patients. Their 5 patients had a unilateral white fibrous membrane present at the pupillary margin, and 4 of the 5 had eccentric pupils. The lenses, however, were reported to be uninvolved in the 4 patients who had pupil surgery, and no anterior chamber abnormalities were described. The investigators recommended early surgical treatment and vigorous occlusion therapy. Reynolds and colleagues<sup>7</sup> reported 2 patients with congenital pupillary membranes, the second of which had a white pupillary membrane, a tiny vertically eccentric pupil, and a filamentous adhesion to Schwalbe's line inferiorly. Surgery was performed in this case at 6 months of age, and the lens was described as clear postoperatively. Finally, the 3 cases described by Cibis and associates<sup>1,2</sup> with a congenital pupillary-iris-lens membrane with goniodysgenesis, and 1 additional case in the German literature<sup>9</sup> referred to by Cibis, all seem to have had the condition described in this paper. One of Cibis's patients had surgical removal of the membrane from the lens without cataract formation; another required a peripheral iridectomy for impending angle closure glaucoma.

The etiology and pathogenesis of the membranes described are uncertain. They are present at birth, but are unilateral and nonfamilial. Fluorescein angiography has shown vessels in the membrane and abnormal leakage over the membrane and at the pupillary margin.<sup>1</sup> The histology of 1 pupillary membrane revealed stromal fibroblasts, blood-bearing vessels, and perhaps aberrant smooth muscle, indicating that the tissue was derived from iris and not lens.<sup>2</sup> Cibis postulated disruption of the normal evolution of the embryonic pupillary membrane, possibly due to a vascular occlusion, as the cause of the abnormal membrane.<sup>2</sup> Mann<sup>10</sup> suggests that fetal iritis may lead to pupillary membranes that cause an attachment of the margin of the pupil (rather than the collarette) to the lens, but her illustrative cases do not resemble the cases described here. It does seem likely that some kind of aberrant persistence of the embryonic anterior tunica vasculosa lentis, other forms of which have been described by Goldberg in an account of persistent fetal vasculature in the eye,<sup>11</sup> is involved in the formation of this distinctive iris membrane.

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## CONCLUSION

The condition I have termed fibrous congenital iris membrane with pupillary distortion is an entity that has now been recognized by a number of investigators. It frequently interferes with the development of normal vision. Occasionally, it leads to seclusion of the pupil and angle closure glaucoma. In either circumstance, early surgery to create an enlarged pupil should be performed. Occlusion or seclusion of the pupil may be progressive in the early months, and cases in which the pupil can initially be dilated successfully should be observed closely for progression. An important feature of the condition is that the lens is clear except in the small area of iris-lens adhesion, and good vision can be obtained through a surgically enlarged pupil if amblyopia is not allowed to progress to an irretrievable level.

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## ACKNOWLEDGEMENTS

The author thanks Anne B. Fulton, MD, for contributing case 6 for this study, and Robert D. Gross, MD, for providing the photograph of case 7. Harriet R. Greenfield drew the illustrations for cases 1 through 5 using sketches and verbal descriptions from their medical records.

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## DISCUSSION

DR MORTON F. GOLDBERG. I, too, have seen patients with fibrous congenital iris membranes with pupillary distortion.

I believe that they are similar, and probably identical in pathogenesis, to the cases reported by Cibis and colleagues in 1986,<sup>1</sup> and to those reported by Dr. Robb. I do not believe, however, that this entity represents a new or unique disease. Rather, I believe it to be a manifestation of persistent fetal vasculature (PFV) in the anterior segment.

A review of ocular embryology shows that the key vascular structures in the anterior segment include the anterior tunica vasculosa lentis, the posterior tunica vasculosa lentis, and the intervening radial anastomoses between these two structures, known as iridohyaloid arteries.<sup>2</sup> Abnormal persistence of any of these vessels, causes well-known congenital anomalies such as persistent pupillary membrane, which may infrequently bleed and become scarred, or which may persist unchanged, or (usually) regress. Indeed, 30-95% of normal individuals have some persistence of the so-called pupillary membrane, a vascular remnant of fetal life, although visually disabling hyperplasia and scarring of this tissue are far less common. If these tissues do become scarred, a variety of physical signs may occur, including white membranes, posterior synechiae, and seclusion or occlusion of the pupil, leading, in some cases, to pupillary distortion or to secondary glaucoma of various types.

Clues to the underlying fetal and vascular origin include the radial configuration of the iris bands and associated posterior synechiae, as seen in several cases presented by Robb and Cibis et al., as well as the hairpin, recurving configuration of scar or vascular tissue around the sphincter of the pupil in any meridian. The presence of such congenital radial bands or scars implicates persistence of fetal vasculature, even if these structures are not confined or attached to the collarette of the iris.

Occasionally, additional clues include shorter axial lengths, smaller corneas, and asymmetries of the discs, maculas, or posterior poles. In fact, in Dr Robb's series, 4 of 7 cases showed such asymmetry in corneal diameters, a frequent finding in persistent fetal vasculature.

In summary:

1. I believe Dr Robb's observations are indeed similar to those of Dr Cibis and his colleagues.
2. Clues, such as congenital micro-cornea and vascular remnants of fetal life (which are often radially oriented), are helpful in making the correct diagnosis of persistent fetal vasculature that affects primarily, or only, the anterior segment.
3. Postnatal changes of a tertiary nature, such as scar tissue formation or remodeling, may occur, necessitating surgical intervention.
4. The presence of a clear lens is encouraging, but does not guarantee good visual results following anatomically successful anterior segment surgery, due to

associated PFV or other malformations in the posterior segment of the eye.

5. Finally, and perhaps most importantly, the simple presence of a defect in the eye at the time of birth does not necessarily relegate such an eye to permanently reduced vision. If surgery is done in a timely and uncomplicated fashion, and is followed by successful therapy of organic, anisometric, or strabismic amblyopia, good visual results may occur. Thus, Dr Robb has provided a useful service in stressing that these uncommon, late, tertiary events occasionally require surgery and that the surgery can be both anatomically and visually successful.

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[Editor's Note] DR GERHARD W. CIBIS feels that these cases are much more than persistence of primary fetal vasculature and in some cases may involve abnormalities of migration, proliferation, and regression of iris tissue; he showed cases to support this hypothesis.

DR RICHARD M. ROBB. Thank you, Dr Goldberg, for your careful reading of the manuscript and interpretation of how persistent fetal vasculature might be involved in the formation of these membranes. With regard to visual potential I would add that, so far, in the cases I have seen there have been no fundus abnormalities that I have recognized, except in 1 case where there was marked anisometropia and a flattened fovea in the more myopic eye. So I am still encouraged by the potential for good vision in these cases, and I agree with Dr Cibis that it is important to recognize the distinctive iris abnormality and to follow the patients carefully. Most congenital pupillary membranes that we see as pediatric ophthalmologists are looked at once and discounted. But these fibrous membranes are really different, and the fact that some of them are progressive means that you have to look repeatedly in the first weeks and months to be sure that you don't lose the opportunity to obtain a good visual result. These cases are uncommon, but the fact that several of us have seen them in some number, and that there are others reported in the literature, means that they are not rare. I believe many of you will encounter them. Thank you.



# STRABISMUS DUE TO FLAP TEAR OF A RECTUS MUSCLE\*

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BY Irene H. Ludwig, MD AND Mark S. Brown, MD (BY INVITATION)

## ABSTRACT

*Purpose:* To present a previously unreported avulsion-type injury of the rectus muscle, usually the inferior rectus, and detail its diagnosis and operative repair.

*Methods:* Thirty-five patients underwent repair of flap tears of 42 rectus muscles. The muscle abnormality was often subtle, with narrowing or thinning of the remaining attached global layer of muscle. The detached flap of external (orbital) muscle was found embedded in surrounding orbital fat and connective tissue. Retrieval and repair were performed in each case.

*Results:* Fourteen patients had orbital fractures, 7 had blunt trauma with no fracture, and 9 had suspected trauma but did not undergo computed tomographic scan. Five patients experienced this phenomenon following retinal detachment repair. Diagnostically, the predominant motility defect in 25 muscles was limitation toward the field of action of the muscle, presumably as a result of a tether created by the torn flap. These tethers simulated muscle palsy. Seventeen muscles were restricted away from their field of action, simulating entrapment. The direction taken by the flap during healing determined the resultant strabismus pattern. All patients presenting with gaze limitation toward an orbital fracture had flap tears. The worst results following flap tear repair were seen in patients who had undergone orbital fracture repair before presentation, patients who had undergone previous attempts at strabismus repair, and patients who experienced the longest intervals between the precipitating event and the repair. The best results were obtained in patients who underwent simultaneous fracture and strabismus repair or early strabismus repair alone.

*Conclusions:* Avulsion-type flap tears of the extraocular muscles are a common cause of strabismus after trauma, and after repair for retinal detachment. Early repair produces the best results, but improvement is possible despite long delay.

*Tr Am Ophth Soc* 2001;99:53-63

## INTRODUCTION

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Diplopia following head or facial trauma is usually attributed to palsy of a cranial nerve or its branch or to incarceration of an extraocular muscle in an orbital fracture site. Restriction of eye movement by adhesions to scar tissue is also reported to contribute to strabismus.<sup>1-4</sup> Generally, a lengthy delay (months) is advocated before strabismus surgery is undertaken.<sup>1-3,5-8</sup> Repair may consist of ipsilateral muscle surgery and/or a procedure to limit excursion in the nontraumatized contralateral eye<sup>9</sup> to balance the deficit in the injured one.

In a number of post-traumatic strabismus cases, a specific type of avulsion injury to the rectus muscle(s) has been identified and repaired. We propose a mechanism for the development of the flap tear, which is consistent

with recently reported anatomic and functional studies of the extraocular muscles.

## METHODS

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### SURGICAL APPEARANCE

Thirty-five patients underwent repair of avulsion-type injuries of one or more rectus muscles. The involved rectus muscle was approached through a standard fornix incision and placed on a muscle hook at its insertion into sclera. The presence of a flap tear was suggested by 3 different appearances:

1. A segment of muscle and tendon was missing, which narrowed the remaining portion of attached muscle (Fig 1).
2. The outer or orbital layer of muscle was missing, beginning at the musculotendinous junction and extending proximally (Fig 2). These muscles appeared thinned and lacked intact muscle capsule. The thinned area involved the entire width of the muscle in some and a smaller portion of muscle in others.

\*From the Department of Ophthalmology, LSU Eye Center, Louisiana State University Health Sciences Center, New Orleans (Dr Ludwig) and the Department of Ophthalmology, The University of South Alabama, Mobile (Dr Brown). Supported in part by an unrestricted departmental grant to the LSU Eye Center from Research to Prevent Blindness, Inc, New York, New York.

3. The muscle was encased in adherent orbital fat, requiring careful dissection before disclosure of the avulsion injury, which could appear as either of the two previously described abnormalities.

In each of the 3 presentations, the torn “flap” of tissue was found external to the muscle, scarred into surrounding orbital connective tissue and fat (Fig 3). Sometimes several smaller flaps of muscle were found.

Forced duction testing was performed before and during muscle repair in all cases. Restrictions both toward and away from the direction of the involved muscle’s action were often present. In some cases the forced duction abnormality was subtle, and it only became evident when the procedure was performed gently, with simultaneous comparison to the uninjured contralateral eye.

#### **SURGICAL REPAIR TECHNIQUE**

The flap was placed on a small muscle hook and dissected free from its orbital attachments at the distal end. A braided polyester suture was placed through the distal end of the flap, with standard strabismus locking bites (Fig 4). The flap was then attached to sclera at the original insertion, or back to the musculotendinous junction, as necessary to restore anatomy (Fig 5). The rent in overlying Tenon’s capsule, which was always present, was sutured with 6-0 polyglactin after the protruding orbital fat was repositioned through the rent.

If the capsule of the repaired muscle appeared complete, it was repaired directly with buried 6-0 or 7-0 polyglactin suture. In some cases, the capsule seemed partly damaged. In these cases, a free graft of Tenon’s capsule was sutured over the traumatized surface of the muscle with running 7-0 polyglactin (Fig 6). The Tenon’s graft was harvested from an uninvolved quadrant of the same eye, usually superotemporally.

Postoperatively no steroids were used. Patients were asked to exercise the muscle frequently by looking in and out of the field of muscle action to prevent adhesions from re-forming between the flap and surrounding orbital connective tissue.

#### **RESULTS**

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##### **PATIENT CHARACTERISTICS**

The mean age of the 35 patients at time of flap tear repair was 40 years (range, 6 to 82 years). The mean delay between the date of injury and repair was 67 months (range, 2 weeks to 46 years). Mean postoperative follow-up was 9 months (range, 1 to 68 months). The left inferior rectus muscle was most commonly involved (22 cases)

followed by the right inferior rectus muscle (12), the medial rectus (6), and the superior rectus (2) (Table I). The predominance of affected left inferior rectus muscles is presumed to be related to the right-handedness of assailants delivering the trauma in some cases.

#### **PRECIPITATING EVENT**

Fourteen patients had orbital fractures, and 6 had blunt trauma with documentation of the absence of fracture by computed tomographic (CT) scan. In 9 cases, the finding of flap tear was unexpected and orbital imaging was not undertaken. In most cases, a long time had elapsed between injury and repair. In 1 child, CT scan was obtained following development of downgaze deficiency 1 week after seemingly minor blunt trauma to the inferior orbital rim. There had been no external signs of the injury at the time. He had posterior orbital floor fracture and inferior rectus flap tear (Fig 7).

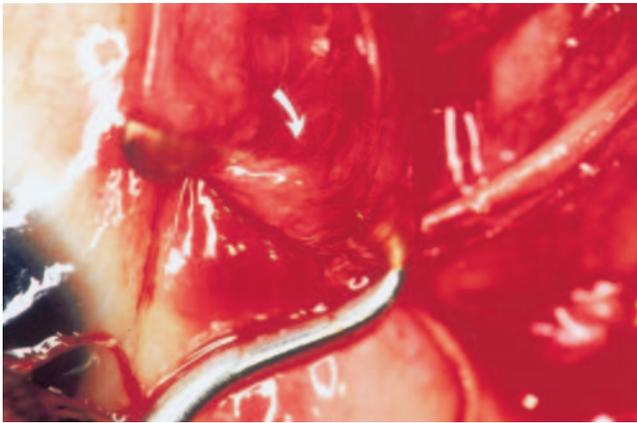
Two patients had no specific history of orbital trauma. One patient had a normal CT scan and questionable, remote history of trauma. Five patients developed flap tears after retinal detachment repair (Table II).

#### **DIAGNOSIS**

##### *Motility Defects*

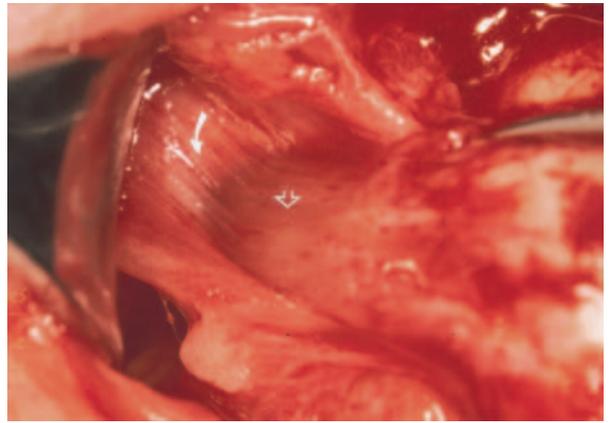
In 20 patients, the motility defect was toward the direction of action of the involved muscle, presumably as a result of a tether created by the flap. Twelve of these presented as downgaze deficiencies following documented orbital floor fracture. In 10 patients the presenting deficit was gaze restriction away from the field of action of the muscle, simulating persistent entrapment or muscle fibrosis. One had paradoxical esodeviation on attempted upgaze, along with limitation of elevation and depression after orbital floor fracture repair. One patient had 2 involved muscles in 1 eye. The torn medial rectus caused exotropia with adduction limitation owing to the tether effect, and the superior rectus tear led to hyperdeviation owing to a restrictive effect. Two patients had tears of both inferior rectus muscles and 1 medial rectus muscle each. The inferior rectus muscles caused asymmetric downgaze reduction owing to the tether effects, and the medial rectus muscle tears led to esotropia owing to restrictive effects. Another patient, with idiopathic etiology, had bilateral inferior rectus flap tears, with mild upgaze restriction in 1 eye, and downgaze restriction in the other. There was no difference in the appearance of the flap tear or the difficulty of repair in terms of the various types of motility patterns. Our impression was that an anterior attachment site of the flap led to a tether effect and a posterior flap position led to pseudo-entrapment.

*Strabismus Due To Flap Tear Of A Rectus Muscle*



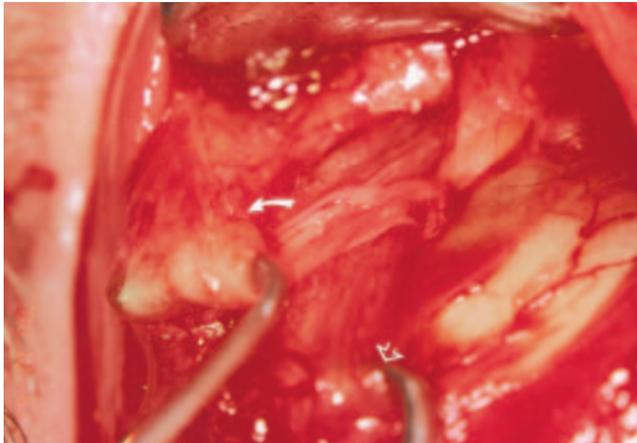
**FIGURE 1**

Flap tear of inferior rectus, narrowed type (same as in Fig 7A). Arrow indicates missing portion of muscle; hook is pulling on insertion of remaining attached portion of muscle.



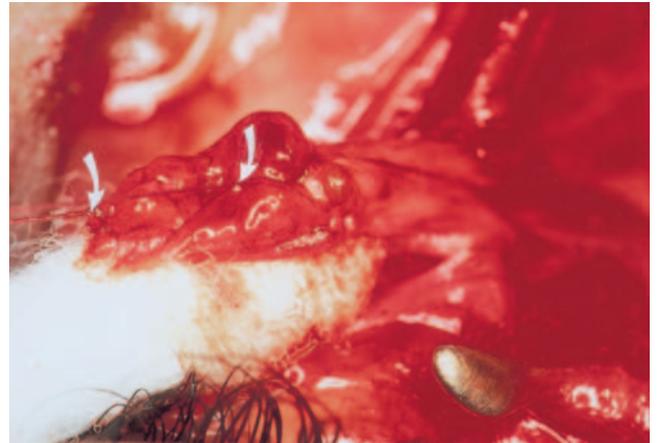
**FIGURE 2**

Flap tear of medial rectus, thinned type, 2 months after retinal detachment repair. Open arrow indicates thinned remaining portion of muscle, lacking capsule. Solid arrow points to flap, which is pulled outward by retractor.



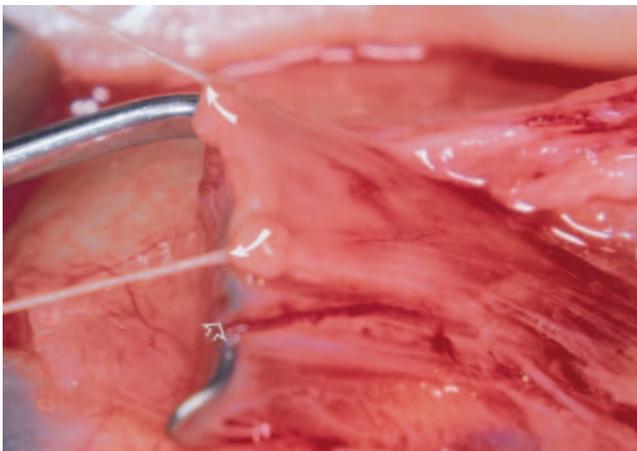
**FIGURE 3**

Flap tear of inferior rectus, 20 years after motorcycle accident. Attached portion of muscle is held by large hook (open arrow). Flap, held in small hook, is adherent to surrounding orbital tissue (solid arrow).



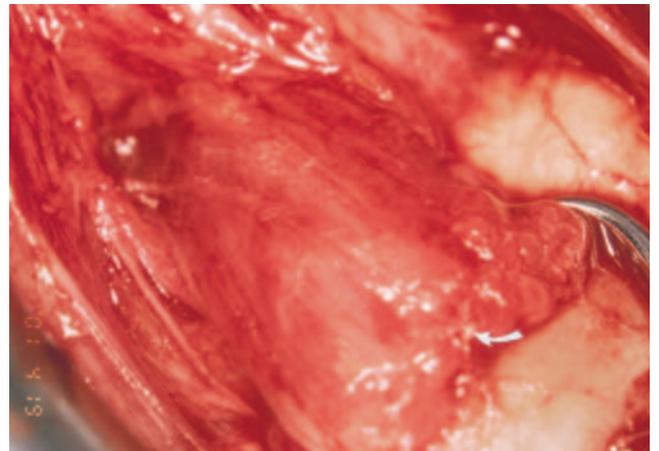
**FIGURE 4A**

Inferior rectus flap (same patient as in Figs 1, 6, and 7), dissected free, and placed on 6-0 braided polyester suture. Lock bites indicated by arrows.



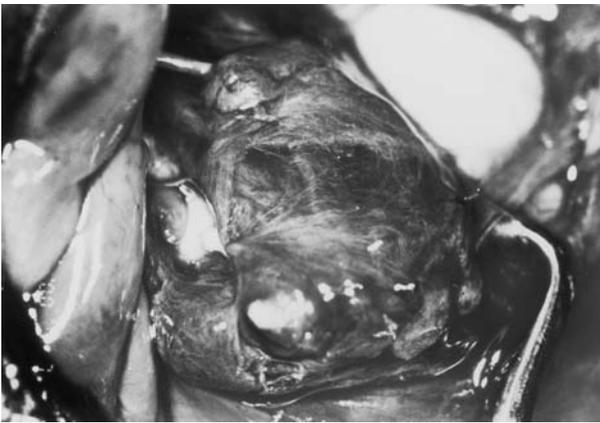
**FIGURE 4B**

Inferior rectus flap, thinned type. Flap is held on braided polyester suture (solid arrows). Hook (open arrow) holds attached, inner portion of muscle.



**FIGURE 5**

Medial rectus from Fig 2, after flap reattachment. Arrow indicates central knot in suture.



**FIGURE 6**

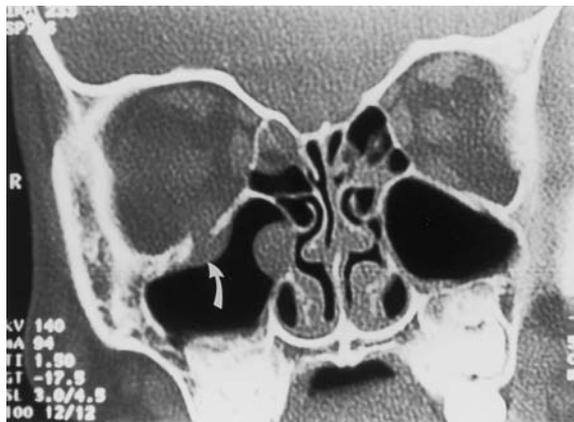
Repaired inferior rectus (same as in Figs 1 and 4a), with overlying Tenon's graft. Tenon's fibers are oriented 90° from muscle and tendon fibers.

**TABLE I: INVOLVED MUSCLES**

NO. OF MUSCLES INVOLVED	NO. OF PATIENTS	MUSCLE			
		LEFT INFERIOR RECTUS	RIGHT INFERIOR RECTUS	MEDIAL RECTUS	SUPERIOR RECTUS
1	30	19	8	2	1
2	3	1	2	2	1
3	2	2	2	2	0

*Preoperative Diagnosis*

Five patients were misdiagnosed preoperatively as having fourth cranial nerve palsy, 2 as having Brown's syndrome, and 1 as having sixth cranial nerve palsy. In the first patient treated (MC), a lost inferior rectus was suspected because of the absence of downgaze. Many of these patients would have qualified as having isolated palsy of



**FIGURE 7A**

CT scan showing posterior orbital fracture with inferior rectus entrapment (arrow). (Patient's inferior rectus is seen in Figs 1, 4a, and 6.)

**TABLE II: PRECIPITATING EVENT**

CAUSE OF STRABISMUS	NO. OF CASES
Orbital fracture	14
Blunt trauma, no fracture	5
Trauma, possible fracture	10
Retinal detachment	5
Idiopathic	1

the inferior rectus based on measurements alone.

Preoperative force generation testing was useful to rule out nerve palsy. Although restricted in excursion of movement, the involved muscles showed normal strength. Forced duction testing was usually performed immediately before surgery, with the patient under paralytic anesthesia.

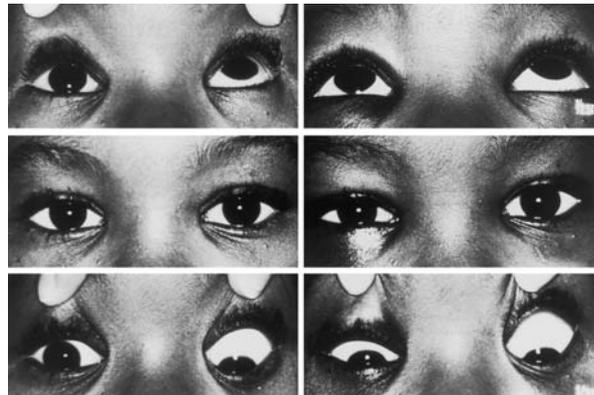
Since the first case was identified in 1994, every patient presenting to this practice with a preoperative diagnosis of orbital fracture together with limitation of motility toward the direction of the fracture was found to have a flap tear.

**SURGERY**

Sixteen patients underwent direct repair of the flap alone, with no other muscle surgery (Table III). Two of these required re-repair of the flap: 1 for a small residual flap segment that had been missed at the initial procedure,

**TABLE III: PRIMARY SURGERY**

	REPAIR OF FLAP ONLY	REPAIR OF FLAP PLUS RESECTION OR RESECTION OF SAME MUSCLE	SURGERY ON ADDITIONAL MUSCLES
Total cases	16	4	15
No. requiring second procedure	2	1	5



**FIGURE 7B**

Preoperative (left) and postoperative (right) motility of 6-year-old boy who underwent simultaneous repair of orbital floor fracture and inferior rectus (Figs 1, 4a, and 6) flap tear 2 months after minor blunt trauma.

Strabismus Due To Flap Tear Of A Rectus Muscle

TABLE IV: CLINICAL DATA OF ALL PATIENTS UNDERGOING REPAIR OF AVULSION-TYPE FLAP TEARS

PATIENT	AGE	DELAY (MO)	MUSCLE	?TETHER	CAUSE	?ADD'L MUSCLE	?2ND SURGERY	ALIGN PREOP	VERSIONS PREOP	ALIGN POSTOP	VERSIONS POSTOP	FOLLOW-UP
KB	12	1	LIR	no	football	no	no	RHT8	1-depr, 2-elev 3-elev OD	ortho	nl depr	10
EB	59	3	RIR	no	struck orbit in motorboat	recess RIR6, RLR4	no	LHT25		ortho	1-depr, 3-elev	19
DB	38	13	LIR	no	RD repair	LIR recessed 4	no	RHT25	2-elev OS	ortho	1-elev, depr OS	3
RB	42	252	LIR, LMR	yes	motorcycle accident	no	planned	LHT14/ET20	2-depr OS, 1-elev OD 2-abd OS 3-depr OS	LH(T)/2/ET20	2-elev, 2-depr OS	1
MC	24	13	LIR	yes	struck with fist	LSR rec 2/16/94	no	LHT4	3-depr OS	ortho	3-depr OS	68
BC	39	4.5	LIR, LMR	yes	MVA	reclMR6	reset LLR8, RMR5.5 LIR3	RHT10, ET55	4-abd OS, 1-depr OD, 2-elev OD	ortho	1-elevOU, 1-ad, abdOU	5
PD	29	8	LIR	no	orbit bumped by child's head	LLR, LMR inf transp	yes	ortho large RHT in upgaze RHT14	4-elev OS	ortho	3-elev, deprOS	1.5
BD	12	0.5	RIR	yes	bicycle handle	no	no	RHT10	4-depr OD	ortho	1-depr OD	2
TE	82	6	RIR	no	fell on pavement	RSO	no	LHT10	2-elev, depr OD	RHT5	?	1
BE	8	8	LIR	yes	bicycle handle	no	yes	LHT6	1-depr OS	LH2	nl depr	5.5
SE	39	204	LIR	no	RD repair	LLR5	adv LIR to orig insertion	RHT20	2-elev OS	RH2	2-elev OS	1
RG	79	10	LSR	yes	branch struck eye	LIRrec6	adv LIR, LSO	RHT20	4-elev OS	E12	3-elev OU	48
AG	20	228	RIR	no	unknown	RIR rec3	no	ortho, large LHT in upgaze XT10/ LHT10	4-elev OD	ortho	3-elev OD	3
SH	29	24	LSR, LMR	yes	struck with fist	LSR rec4	no		1-elev, deprOS	X2	1-elev OS	1
CH	42	8	RIR	yes	MVA	no	planned	RHT9	1-add OS	ortho	3-depr OD	3
WH	82	8	LIR	no	RD repair	LMR4	no	RHT5	4-depr OD	RHT10	4-elev OS	4
PJ	53 ?		LIR	yes	struck with fist	no	no	?	3-elev OS	ortho	3-depr OD	18
CJ	32	3	LIR	yes	struck with fist	LLR8	no	LHT35	?	LH(T)/4	3-depr OS	1
JK	68	24	RIR, LIR	yes	?blast concussion Korean War	no	no	ortho LHT6 in downgaze	1-depr OS, 1-elev OD	ortho all gaze	normal	1
SL	15	1.5	LIR	yes	football	no	no	2-elev	2-depr OS, ET on elev	ortho	2-elev OS	8

TABLE IV (CONTINUED): CLINICAL DATA OF ALL PATIENTS UNDERGOING REPAIR OF AVULSION-TYPE FLAP TEARS

PATIENT	AGE	DELAY (MO)	MUSCLE	?TETHER	CAUSE	?ADD'L MUSCLE	?2ND SURGERY	ALIGN PREOP	VERSIONS PREOP	ALIGN POSTOP	VERSIONS POSTOP	FOLLOW-UP
TL	24	87	LIR	yes elbow	struck with	s/p LIR rec	no	LHT10	3-depr OS	ortho	2-depr OS	3.5
JM	38	360	LIR	no	possible fist	LLR	yes	RHT30	1-elev OS	ortho	normal	5
KM	16	6	LIR	yes fist	struck with	no	yes	LHT16	2-depr OS	ortho	2-depr OS	36
SO	28	24	RIR	no	air bag	recSOOU	no	ET6/ RHT10	3+LSO	RHT4		0.1
RR	71	7	LIR	yes	MVA Resect LIR	SOOU adv	yes	LHT5	2-depr OS	ortho	1-depr OS	6
MS	51	552	LIR	yes playground	fell in	no	planned ET18	LHT18/ ET14	4-depr OS	LHT14/ ET14	4-depr OS	2
TS	8	2	RIR	yes	MVA	no	no	RHT6 2-elev OD	2-depr	ortho	1-elev OD	7
NS	33	264	RMR	no elbow	struck by	no	no	ET18 2-elev	1-ad, abd OD,	ET6	tr-abd OD	1
FS	56	3	LMR	yes in playground	struck with	LLR rec10	no	XT25	4-add OS	ortho	3-add OS	4
HV	49	12	LIR	yes tree branch	RD repair adv LSO4	recLMR4, res LMR3	res LIR3,5,	LHT25 1-abd OS, 3-LSO	3-depr;	X4 depr OS	3-elev;	8
BW	65	84	LIR	yes ladder	fell off	myot LMR	no	LHT10	2-depr OS	LH(T)3 1-add OS	2-depr;	1
BW	71	2 R	MR,RIR	no	RD repair	no	no	RET25 3-elev OD	2-abd,	RHT6 3-depr OD	2-abd,	0.2
HW	6	2	RIR	yes on bathtub edge	struck orbit	no	no	RHT16 depr OS	4-elev,	ortho 3-elev	1-depr OS	1.5
BW	36	3	LIR	yes pavement	fell on	no	no	E4(LHT)18	2-depr OS	ortho	normal	25
AW	29	3	LIR	yes bat	baseball LLR6	rec LSP5, LLR6	no	LHT25	4-depr OS	ortho	3-depr OS	2

and the other for a complete flap redetachment. The redetachment was thought to have occurred as a result of the child's failure to move the eye postoperatively, as well as damage to the muscle capsule and, possibly, loss of strength of the absorbable suture used to reattach the muscle. At reoperation, the flap was reattached with non-absorbable suture and a Tenon's graft was placed. The second repair was successful. Nonabsorbable suture has been used for flap reattachment in all subsequent cases.

Forced duction and spring-back testing<sup>10</sup> were used to determine whether flap tear repair alone relieved the gaze restriction and centered the eye. If not, additional surgery was undertaken.

#### *Additional Strabismus Surgery*

Fifteen patients underwent simultaneous surgery on other extraocular muscles, and 7 of these required a second strabismus procedure. Four patients exhibited residual restriction of motility away from the direction of action of the muscle with the flap repair, and they underwent simultaneous recession of that muscle alone during the initial surgical procedure. Surgery on additional muscles was needed more often when a longer time had elapsed between injury and repair. Secondary deviations were considered and corrected; the most common was ipsilateral lateral rectus recession for exotropia.

#### *Orbital Fracture Repair*

Six patients had undergone orbital fracture repair prior to flap tear repair, and 3 underwent repair of muscle and orbit on the same day by a strabismus surgeon (I.H.L.) and an ophthalmic plastic surgeon (M.S.B.). These 3 cases confirmed the impression that the flap tear is remote from the fracture site and is not the result of bony impingement on the muscle. Five patients with documented fractures did not undergo fracture repair.

#### **POSTOPERATIVE ALIGNMENT**

Preoperative and postoperative alignment data were not analyzed statistically for the group owing to the heterogeneous population of involved muscles and variety of additional muscle surgeries performed (Table IV). Of the 16 patients who underwent flap tear repair alone, all were improved, most achieved resolution of diplopia during regular activities, and 9 had normal alignment in all gaze positions.

The best results were achieved in those who underwent simultaneous repair of flap tear and orbital fracture and those who did not undergo fracture repair. The worst results occurred in those who had undergone previous orbital fracture repair (MC, CH, SL, TL, KM, AW) and/or strabismus surgery (RB, MC, TL, MS, FS). One patient

(CH) had undergone 2 orbital surgeries because of the persistent downgaze deficiency. He had severe motility restriction noted during subsequent flap tear repair, and although the primary position alignment was restored, motility remained poor.

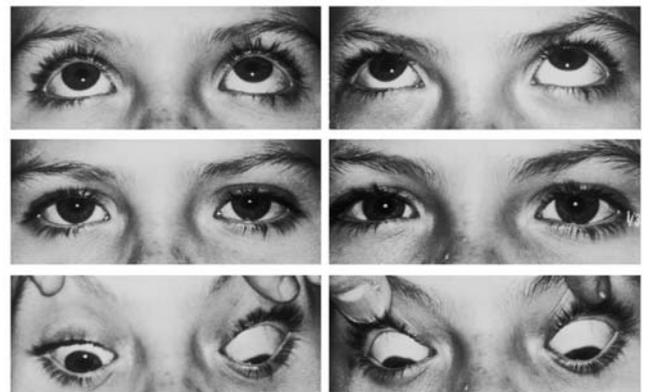
Long delay from injury to repair seemed to worsen the prognosis for some patients, but others did well despite the lapse of many years. Those with smaller flaps and smaller preoperative deviation of alignment had improved chance of resolution with flap-tear repair alone. Greater delay to treatment increased the likelihood of further surgery on additional muscles. No patient was worsened by flap tear repair (Table IV).

#### **CASE REPORTS**

##### *Case 1*

A 12-year-old boy developed diplopia after striking his right inferior orbital rim on the handle of a bicycle. In the primary position he had a right hyperdeviation of 14 prism diopters (D), which increased to 20D on downgaze. Elevation and depression of the right eye were markedly reduced (Fig 8, left). CT scan showed a narrow orbital floor fracture in the medial portion of the orbital floor, with entrapped orbital tissue and muscle. Orbital fracture and strabismus repairs were undertaken at the same time, 3 weeks after injury, by the authors.

Forced duction testing showed restriction to elevation and depression in the right eye. The fracture site was approached via standard transconjunctival incision. Significant herniated orbital fat and connective tissue were present, and entrapped inferior rectus tissue was identified in the posterior aspect of the fracture (Fig 9). After the tissues were lifted out of the fracture, repair was made with porous high-density polyethylene barrier sheet, and the wound was closed. The inferior rectus was then exposed through a standard inferotemporal fornx



**FIGURE 8**

Case 1. Preoperative (left) and postoperative (right) motility.



FIGURE 9

Case 1. Orbital fracture (arrow).

incision. The flap tear was identified by the narrowed appearance of the muscle (Fig 10) and repaired as already described (Fig 11), including free Tenon's graft. *The torn segment of muscle was markedly anterior to the entrapped portion and was clearly distinct and separate from the fracture site.* Postoperatively, downgaze gradually improved, and 6 weeks later motility was normal, with orthotropia in all directions of gaze (Fig 8, right).

#### Case 2

A 36-year-old policeman was hit on the back of the head and fell forward, striking his face on the pavement. He suffered a brief loss of consciousness. When he became aware of his surroundings in the hospital on the next day, he noticed vertical diplopia. An imaging study of the head was reported to be normal. Twelve days later he presented for strabismus evaluation. Alignment was esophoria of  $4\Delta$  in the primary position, and left hypertropia of  $16\Delta$  with esotropia  $4\Delta$  in downgaze. The hyperdeviation was absent on right head tilt, and  $6\Delta$  on left head tilt. Left fourth cranial nerve palsy was diagnosed by a strabismus surgeon (I.H.L.) as well as by a neuro-ophthalmologist. There was no improvement by 2 months after injury, and no torsion was found with subjective testing or fundus examination.

The patient recalled that the left lower lid was ecchymotic after the injury. High-resolution magnetic resonance imaging of the orbits and brain, with particular attention to the left inferior rectus, was obtained, but no abnormality could be detected. Nine weeks after injury, he underwent exploration of the left inferior rectus via an inferotemporal fornix incision. A flap tear was found, with thinning of the muscle proximal to the musculotendinous junction and absence of capsule. The repair included closure of the overlying rent in Tenon's capsule. One week after surgery, alignment was orthotropia in primary position with left hypertropia of  $10\Delta$  in downgaze. Five weeks

after surgery, the patient was orthotropic in all directions of gaze. Two years later he remains orthotropic in all directions.

## DISCUSSION

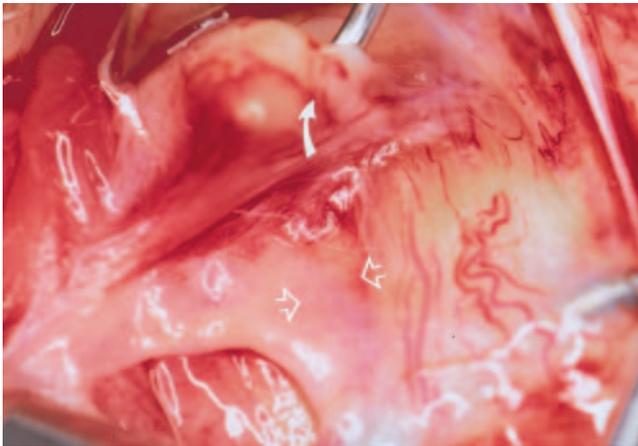
Orbital trauma has been associated with a range of severity of ocular injuries.<sup>11-13</sup> Posttraumatic strabismus has traditionally been attributed to direct muscle contusion by an orbital fracture site, orbital hematoma, or nerve damage.<sup>1-8</sup> Spontaneous improvement in diplopia has been reported,<sup>1,5,6,8,14</sup> and patients are usually asked to wait for some time before strabismus repair is considered.<sup>1-8</sup> Orbital surgery to relieve entrapment is usually undertaken if diplopia persists after 2 to 3 weeks.<sup>6,8</sup> Strabismus repair is then not considered before 4 to 6 months.<sup>1-8</sup> Strabismus procedures that have been advocated include ipsilateral rectus resection and recession,<sup>3</sup> contralateral superior oblique recession,<sup>3</sup> rectus muscle transposition procedures,<sup>8</sup> and the Faden operation to the contralateral eye.<sup>9</sup>

Since we observed the presence of flap tears without orbital fracture, as well as the findings in 3 cases in which orbital and muscle repairs were concurrent, we believe that the avulsion was a related, but separate, finding due to the original trauma.

Recent anatomic studies of the extraocular muscles have shown 2 distinct layers: (1) the global layer, adjacent to the globe, and (2) the orbital layer, which lies externally. The orbital layer has also been shown to be surrounded by dense connective tissue and penetrated by elastin, which effectively inserts the orbital layer of the rectus muscle into the orbital connective tissue.<sup>15</sup>

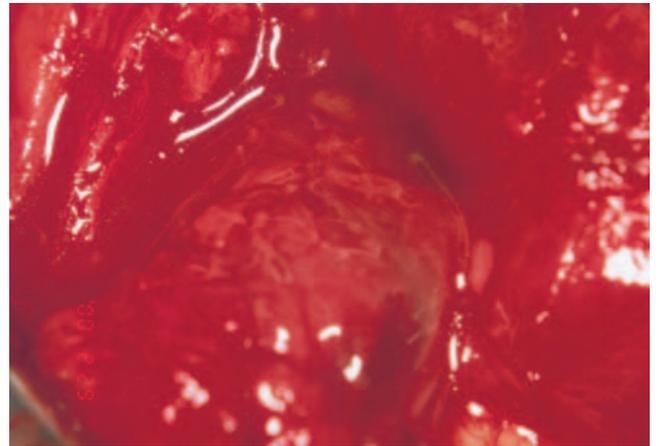
We hypothesize that the sudden downward force experienced by the orbital contents at the time of blunt trauma may exert traction on the connective tissue insertion into the orbital layer of the muscle, tearing the outer layer away from the inner, global layer (Fig 12). This mechanism could result in the thinned-type appearance of the flap-tear muscle. Other flap tears presented with a narrowed appearance of the muscle, with a full or partial thickness defect of the remaining attached portion of muscle. These may have experienced asymmetric avulsion force, leading to asymmetric flaps. The force might possibly be transmitted to the muscle from the side by the intermuscular septum, which would also produce flap asymmetry.

Perhaps the 2 muscle portions may reunite during healing; this would explain the cases of spontaneous improvement that have been reported.<sup>1-8</sup> Motility findings vary according to the healing pattern of the flap tear. If the flap heals anteriorly, creating a tether, the predominant defect would be a loss of function of the involved muscle (Fig 13). Tether-type motility defects are reported to occur in about one third of orbital floor fractures with



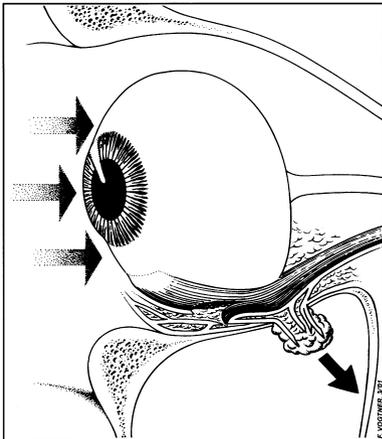
**FIGURE 10**

Case 1. Inferior rectus showing narrowed type of flap tear. Missing portion indicated by open arrows. Flap is held on small hook (solid arrow).



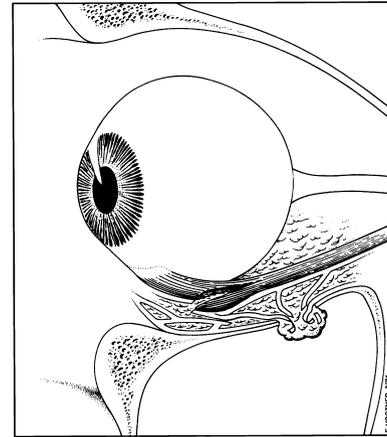
**FIGURE 11**

Case 1. Repaired inferior rectus, with Tenon's graft.



**FIGURE 12**

Drawing indicating hypothesized traction on inferior rectus outer layer due to orbital fracture, causing avulsion.



**FIGURE 13**

Drawing indicating anterior flap position after injury, which would create a tether.

vertical diplopia<sup>14</sup> and have also been reported with medial wall fractures.<sup>16</sup> A small tether effect of an inferior rectus flap tear could mimic ipsilateral fourth cranial nerve palsy. This was seen in 5 of our patients, and a similar motility pattern after floor fracture has been reported.<sup>11,17</sup> A posteriorly healed flap would lead to restriction of gaze away from the site of injury, which was also common. Restrictive strabismus was reported in two thirds of floor fracture patients with vertical diplopia.<sup>14</sup> An intermediate flap location could allow unimpeded motility. This is another possible explanation for spontaneous improvement of diplopia in some orbital fracture patients. Horizontal abnormalities resolved in several patients after flap tear alone, suggesting that horizontally directed adhesions might have contributed to the strabismus.

On the basis of our experience with this series of patients, we believe that a tether-type of motility defect is diagnostic of flap tear. Downgaze deficiency after orbital

floor fracture has been attributed to palsy of the inferior branch of the third cranial nerve,<sup>1,3</sup> but in our series all cases with downgaze deficiency after ipsilateral orbital floor trauma had flap tears. The unexpected finding of identical tears in patients with long-standing strabismus, some of whom remembered the trauma only after careful questioning, is of interest. The trauma was sometimes uneventful and not immediately apparent. After one learns to recognize the abnormally narrowed or thinned rectus muscle with missing capsule, the defect becomes readily apparent in many cases. A completely restored muscle capsule confirms that repair is complete. This was even possible in cases repaired many years after injury.

Five patients had flap tears after retinal detachment repair. Perhaps the retinal surgeon's practice of bluntly stripping connective tissue off the extraocular muscle may pull away a flap of muscle tissue and lead to postoperative strabismus.

Immediate and regular eye exercise postoperatively is important to prevent adhesions from re-forming between the muscle and orbital connective tissue. The free Tenon's graft and repair of the overlying rent in Tenon's capsule also may help to reduce adhesions. Nonabsorbable suture is always used to reattach or anchor the flap to sclera.

On the basis of the findings in these patients, it is recommended that all orbital fracture patients with diplopia who are to receive fracture repair undergo simultaneous exploration of the adjacent rectus muscle(s) through separate fornix incision(s), with minimal dissection. If an unrecognized flap is allowed to attach itself to or near the implant material, the motility defect becomes more difficult to treat later. If diplopia is due to flap tear, fracture repair may not be necessary, but if entrapment and flap tear coexist, as in 3 cases of this series, combined repair produces the best outcome.

#### ACKNOWLEDGEMENTS

The authors thank David S. Goldberg, MD; John Avallone, MD; David R. Stager Sr, MD; Robbin B. Sinatra, MD; Paula Gebhardt; Leonard Baham, COMT; and Maxine Haslauer for their assistance with this project.

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#### DISCUSSION

DR DAVID L. GUYTON. Dr Ludwig's description of "flap" tears of the extraocular muscles is both fascinating and convincing. Since the recent emphasis by Demer and colleagues<sup>1</sup> on the attachments between the orbital portions of the extraocular muscles and the surrounding connective tissue, strabismologists have been looking for practical applications of this knowledge. Drs Ludwig and Brown's flap tear mechanism appears to be consistent with this new view of connective tissue attachments.

Even before the connective tissue "pulley" concept, though, the so-called check ligaments, encountered at the time of surgery on the rectus muscles, have been well known to strabismus surgeons. Especially prominent are the dense attachments to the inferior rectus muscle, representing the origin of the retractors of the lower lid.<sup>2,3</sup> These particular attachments, also known as the capsulopalpebral head of the inferior rectus muscle, are very strong indeed. It is therefore not surprising that orbital trauma from an assailant, or from the cotton-tipped applicator of a retinal detachment surgeon, could tear portions of the inferior rectus muscle via these attachments, producing Dr Ludwig's "flap" tear. Indeed 87% of the involved muscles in her series were inferior rectus muscles.

How were the several medial rectus and superior rectus muscles involved? Their check ligaments are not very strong. Perhaps these cases were the result of locally directed trauma, actually shearing off or avulsing a portion of the muscle. Such injuries have been documented periodically in the literature. In a case of mine several months ago, the superior rectus muscle had been cleanly disinserted from the globe purely by trauma.

Dr Ludwig's contribution is more than just recognition of this "flap" tear mechanism. She has successfully repaired most of her cases. Because she has used several repair techniques, though, we still do not know which of these are necessary. For example, how important is the closing of rents in Tenon's capsule? How important is the free Tenon's tissue graft that she has used over the surgically repaired area? Should a non-reactive suture be used instead of an absorbable one? How important are range of movement exercises postoperatively, and do the

patients really do them?

I am confident that Dr Ludwig will continue to research these questions. I congratulate her and her co-author Mark Brown for an engaging and provocative presentation.

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[Editor's notes] DR EDWARD L. RABB asked why it was necessary to advance the torn flap. DR MALCOLM R. INC asked if an abrupt difference in muscle thickness suggesting a flap tear could be identified on a CT scan prior to surgical exploration.

DR IRENE H. LUDWIG. Regarding Dr Guyton's questions, I am not sure how important all these repairs are. My instinct is to fix a defect when I see it. I don't know if closing Tenon's capsule or employing a Tenon's graft is necessary. I did have 2 cases redetach when I didn't use the method of repair I described earlier. I had used absorbable sutures to reattach the flap, and I had not fully restored Tenon's capsule. Both of these cases were in children, who also did not exercise their motility postoperatively. I then repeated the surgeries the same as the initial repairs, but used non-absorbable sutures for flap reattachment, and free Tenon's graft over the muscles after repair. Their mothers increased the eye movement exercises. The second procedures worked.

Dr Guyton's suggestion of using a non-reactive suture to repair Tenon's capsule is an excellent idea. Perhaps a 7-0 polypropylene would serve well for this.

The patient's parents and/or spouses were charged with the importance of beginning the range of movement exercises immediately upon awakening. Several of those who admitted to poor compliance did not do well, but I do not have enough data to analyze this point. It is easy enough to recommend eye movement exercises, and it may be important.

To answer the question about imaging studies to preoperatively demonstrate a flap tear, I obtained no useful information from any of the preoperative CT and MRI scans I obtained. All were read as normal with respect to the extraocular muscles, excepting several with orbital fractures and posterior muscle entrapment. No anterior abnormality could be specifically identified. A few showed vague scar tissue or edema under the inferior rectus, but these had already undergone orbital fracture repair. One case (case 2 in the manuscript), had several repeat high resolution MRI scans performed of the suspect inferior rectus, with no abnormality seen by the radiologist, despite my insistence that something must be there. I talked myself into thinking the muscle capsule was irregular, but there was really no useful information obtained. His flap was small. The MRI scan would have deterred most from exploring the muscle. I now limit imaging to orbital CT scans to look for fractures.

To answer the question about why I advance the flap to the insertion, when some flaps originate a few millimeters posterior to the insertion, I do this when there is a tether limiting the action of the muscle. This tends to strengthen the muscle. In those muscles with restriction of gaze away from the muscle action, I leave the flap a little further back.



# PSYCHOSOCIAL IMPLICATIONS OF BLEPHAROPTOSIS AND DERMATOCHALASIS\*

BY John D. Bullock, MD, MS, Ronald E. Warwar, MD, David G. Bienenfeld, MD, Sara L. Marcinişzyn, MD,  
AND Ronald J. Markert, PhD

## ABSTRACT

*Purpose:* To investigate, for the first time, the psychosocial implications of blepharoptosis and dermatochalasis.

*Methods:* Two hundred ten individuals rated whole-face photographs of a series of patients on the basis of 11 different personal characteristics: intelligence, threat, friendliness, health, trustworthiness, hard work, mental illness, financial success, attractiveness, alcoholism, and happiness. Preoperative and postoperative photographs of both male and female patients with bilateral blepharoptosis and/or dermatochalasis were used. The paired *t* test was used to compare preoperative and postoperative ratings on the 11 characteristics.

*Results:* The preoperative photographs were rated more negatively than the postoperative photographs ( $P < .01 - P < .001$ ) on all 11 characteristics for both male and female patients by the 210 study subjects.

*Conclusions:* Members of society seem to view individuals with blepharoptosis and dermatochalasis negatively. These psychosocial attitudes may lead to unjust bias toward affected patients, and surgical correction likely provides benefits beyond improved visual function.

*Tr Am Ophth Soc* 2001;99:65-72

## INTRODUCTION

The functional visual deficits secondary to blepharoptosis have been well studied. Meyer and associates<sup>1</sup> quantified the amount of superior visual field loss observed with various degrees of ptosis by opacifying the superior portion of contact lenses to simulate different upper eyelid positions. Patipa<sup>2</sup> demonstrated and quantified the improvement in the superior visual field in primary and reading gaze after surgical correction of ptosis. Health-related quality-of-life issues associated with blepharoptosis have also been investigated. Battu and colleagues<sup>3</sup> used a questionnaire pertaining to vision-related activities and symptoms to study the effect of ptosis on patients' subjective perception of their visual function and quality of life prior to and following surgical correction. They found that postoperative patients perceived a significant improvement in their vision as well as their ability to perform tasks such as fine manual work, reading, and watching television. Using the same questionnaire with 100 different patients, Federici and coworkers<sup>4</sup> showed that the severity of the ptosis and the degree of perceived preoperative functional impairment correlated most strongly with the degree of perceived postoperative improvement. In both of these studies, patients reported improvement in self-image postop-

eratively as well.<sup>3,4</sup> While these studies have demonstrated the functional visual deficits and the health-related quality-of-life issues associated with blepharoptosis, we are not aware of any previous studies in which the psychosocial implications of blepharoptosis were examined. In the present study, we investigate, through the use of facial photographs and questionnaires, how members of society view individuals with blepharoptosis and dermatochalasis.

## METHODS

Four sets of 6 different whole-face color photographs were created. In each of the 4 sets, there was a male and female control (a 75-year-old white man and an 81-year-old white woman who did not have clinically significant blepharoptosis or dermatochalasis and who had never undergone eyelid surgery). In addition, there was a preoperative male (a man with clinically significant blepharoptosis and/or dermatochalasis prior to surgical correction), a different postoperative male (a different man who had undergone successful surgical correction of blepharoptosis and/or dermatochalasis), and a preoperative and a different postoperative female.

Four different men were used for the preoperative and postoperative male photographs; all were white and ranged in age from 55 to 75 years (mean, 68 years). One of the men underwent a bilateral upper eyelid blepharoplasty, one underwent a bilateral external aponeurotic ptosis repair with levator advancement, one underwent a bilateral upper eyelid blepharoplasty and external

\*From the Departments of Ophthalmology (Dr Bullock, Dr Warwar), Physiology and Biophysics (Dr Bullock), Psychiatry (Dr Bienenfeld), and Medicine (Dr Markert), Wright State University School of Medicine (Dr Marcinişzyn), Dayton, Ohio. Funded, in part, by contributions to the Wright State University Foundation, Dayton.

aponeurotic ptosis repair with levator advancement (Fig 1), and one underwent a bilateral Fasanella-Servat procedure.<sup>5</sup> Likewise, 4 different women were used for the preoperative and postoperative female photographs; all were white and ranged in age from 68 to 85 years (mean, 74 years). One of the women underwent a bilateral external aponeurotic ptosis repair with levator advancement, 1 underwent a bilateral upper eyelid blepharoplasty and Fasanella-Servat procedure<sup>5</sup> (Fig 2), and 2 underwent bilateral Fasanella-Servat procedures.<sup>5</sup>

In all patients preoperatively, the eyelids were symmetrical and the margin reflex distance ranged from 0 to 1.0 mm; in all patients postoperatively, the eyelids were symmetrical and the margin reflex distance ranged from 2.5 to 4.0 mm. Each of the 8 surgical patients used in the study had a preoperative photograph in 1 set and a postoperative photograph in another set. All of the surgical procedures were performed by one of the authors (J.D.B). Thus, each study subject viewed photographs of 6 different patients (no study subject viewed the same patient's preoperative and postoperative photographs).

Study subjects were recruited in suburban shopping malls and received \$2 for participating. The subjects were simply informed that they would participate in a study being conducted by Wright State University. The age and sex of each subject were recorded. Each subject was instructed to complete a questionnaire (designed by 3 of the authors [J.D.B., R.E.W., and D.G.B.]) according to their perceptions of each of the individuals in the set of photographs presented. The 6 photographs within each set were shuffled and presented to the subject 1 at a time in random order along with a questionnaire. In each questionnaire, the subjects were asked to rate the individual in the photograph on a scale of 1 to 5 on the following 11 personal characteristics:

1. intelligence (1 = not intelligent, 5 = very intelligent)
2. threat (1 = very threatening, 5 = not threatening)
3. friendliness (1 = not friendly, 5 = very friendly)
4. health (1 = not healthy, 5 = very healthy)
5. trustworthiness (1 = not trustworthy, 5 = very trustworthy)



FIGURE 1

Seventy-year-old man with bilateral upper eyelid dermatochalasis and blepharoptosis who underwent bilateral upper eyelid blepharoplasty and external aponeurotic ptosis repair with levator advancement. Left, Preoperative photograph. Right, 3 months after surgery.

6. hard work (1 = not hardworking, 5 = very hardworking)
7. mental illness (1 = very likely to be mentally ill, 5 = not likely to be mentally ill)
8. financial success (1 = not financially successful, 5 = very financially successful)
9. attractiveness (1 = not attractive, 5 = very attractive)
10. alcoholism (1 = very likely to be an alcoholic, 5 = not likely to be an alcoholic)
11. happiness (1 = not happy, 5 = very happy)

The scale was designed so that the higher rating represented the more positive aspect of each characteristic. To determine if there was a difference in the way preoperative versus postoperative photographs were judged, the paired *t* test was used for matched comparisons (ie, the mean rating of all 4 preoperative males versus the mean rating of all 4 postoperative males on each characteristic, the mean rating of all 4 preoperative females versus the mean rating of all 4 postoperative females on each characteristic, and the mean rating of all 8 [male and female]

preoperative patients versus the mean rating of all 8 postoperative patients on each characteristic). For example, the mean rating of the 4 preoperative males for the characteristic “intelligence” was 2.03 (scale: 1= not intelligent, 5 = very intelligent), and the mean rating of the 4 postoperative males for “intelligence” was 2.81. The paired *t* test was then used to compare the mean ratings (2.03 versus 2.81) to determine if there was a statistically significant difference in the way that the preoperative versus postoperative photographs were judged, and the probability (*P*) was < .001 that the difference in the ratings (2.81 – 2.03 = 0.78) was due to chance. Such comparisons were made for each of the 11 characteristics for both male and female patients

In addition to analysis of the preoperative versus postoperative comparisons of the male and female patients for all subjects, comparisons were broken down for (1) male subjects only, (2) female subjects only, (3) subjects under 21 years of age, (4) subjects 21 to 40 years of age, and (5) subjects over 40 years of age. Significance level (*alpha*) was set at 0.01.



**FIGURE 2**

Sixty-nine-year-old woman with bilateral upper eyelid dermatochalasis and blepharoptosis who underwent a bilateral upper eyelid blepharoplasty and Fasanella-Servat procedure.<sup>5</sup> Left, Preoperative photograph. Right, 4 months after surgery.

**RESULTS**

The results are summarized in Tables I and II. The study included 210 subjects, and the data was collected between January and March 1998. The mean age of the subjects was 33.9 years (range, 17 to 76 years); 98 (47%) were male and 112 (53%) were female. For all subjects (n=210) and all patients, the postoperative photographs were rated more positively than the preoperative photographs on all 11 characteristics ( $P < .001$  for all 11) (Table I). For all

11 characteristics for female patients were rated more positively postoperatively ( $P < .001$  for 13,  $P < .01$  for 5) (Table II).

**DISCUSSION**

While an old adage suggests that you can't judge a book by its cover, physical appearance, particularly of the face, eyes, and eyelids, can greatly influence one's impression of another individual.<sup>6,7</sup> Physiognomy is the determination of mental or moral character and qualities based on facial characteristics.<sup>5</sup> While most scientifically minded individuals would refute the argument that facial features correlate with personality traits, history is riddled with anecdotes of physiognomy put into practice. Aristotle devotes several chapters of his *Historia Animalium* to the study of facial appearance. On the subject of eyebrows, he declares, "Straight ones are a sign of soft disposition, those which bend in towards the nose, a sign of harshness, those which bend out towards the temples, of a mocking and dissimulating disposition." Concerning the eyelid canthi, he states, "If these are long, they are a sign of malicious disposition; if they have the part towards the nose fleshy, it is a sign of dishonesty."<sup>9</sup>

Pythagoras is reputed to have turned students away from his academy if he felt that their facial appearance was not suited to the study of mathematics.<sup>6(p3)</sup> The Bible, however, refutes the principle of physiognomy. In John 7:24, Jesus adminishes: "Judge not according to the appearance, but judge righteous judgment." Shakespeare also expressed his doubts about the validity of physiognomy when, in Act 1, Scene 4 of *Macbeth*, Duncan, the King of Scotland who had previously described the recently executed Thane of Cawdor as "deceit(ful)," proclaims:<sup>10</sup>

*There's no art  
To find the mind's construction in the face.  
He was a gentleman on whom I built  
An absolute trust.*

The philosophy of physiognomy gained popularity in the 19th century. In 1831, Charles Darwin almost lost his passage on the ship *HMS Beagle* because of the captain's impression of Darwin's nose. In his autobiography, Darwin relates, "He [Captain Fitz-Roy] was an ardent disciple of Lavater [the Swiss physiognomist Johann Caspar Lavater, author of *Essays on Physiognomy* (1772)<sup>12</sup>], . . . and he doubted whether anyone with my nose could possess sufficient energy and determination for the voyage."<sup>11</sup> Oscar Wilde seems also to have been a proponent of physiognomy. In 1885, he said to a new acquaintance, the French writer André Gide: "I don't like your lips. They are straight like those of someone who has never lied. I

**TABLE I: PREOPERATIVE VERSUS POSTOPERATIVE RATINGS OF PATIENTS WITH BLEPHAROPTOSIS AND/OR DERMATOCHALASIS ON 11 CHARACTERISTICS\***

CHARACTERISTIC	MEAN RATING		RATING CHANGE	P VALUE†
	PREOP	POSTOP		
Friendliness	1.85	2.72	0.87	<.001
Alcoholism	2.40	3.26	0.86	<.001
Happiness	1.81	2.63	0.82	<.001
Health	2.06	2.84	0.78	<.001
Mental illness	2.47	3.21	0.74	<.001
Intelligence	2.24	2.87	0.63	<.001
Financial success	2.13	2.74	0.61	<.001
Hard work	2.48	3.06	0.58	<.001
Attractiveness	1.53	2.06	0.53	<.001
Threat	2.89	3.36	0.47	<.001
Trustworthiness	2.53	2.94	0.41	<.001

\*Rating scale of 1 to 5. The scale was designed so that the higher rating represented the more positive aspect of each characteristic (eg, intelligence: 1= not intelligent, 5 = very intelligent; threat: 1 = not threatening, 5 = very threatening). 210 subjects completed questionnaires. †The paired *t* test was used for matched comparisons (ie, mean preoperative rating versus mean postoperative rating).

subjects (n=210) and male patients only, all 11 characteristics were rated more positively postoperatively ( $P < .001$  for all 11), and for female patients only, all 11 characteristics were rated more positively postoperatively as well ( $P < .001$  for 10, and  $P < .01$  for 1). For male subjects (n=98), 10 of 11 characteristics for male patients and 9 of 11 characteristics for female patients were rated more positively postoperatively ( $P < .001$  for 17,  $P < .01$  for 2). For female subjects (n=112), all 11 characteristics for male patients and all 11 characteristics for female patients were rated more positively postoperatively ( $P < .001$  for 18,  $P < .01$  for 4). For subjects under 21 years old (n=76), 9 of 11 characteristics for male patients and 6 of 11 characteristics for female patients were rated more positively postoperatively ( $P < .001$  for 10,  $P < .01$  for 5). For subjects 21 to 40 years old (n=62), all 11 characteristics for male patients and 9 of 11 characteristics for female patients were rated more positively postoperatively ( $P < .001$  for 16,  $P < .01$  for 4). For subjects over 40 years old (n=72), 9 of 11 characteristics for male patients and 9 of

TABLE II: PREOPERATIVE VERSUS POSTOPERATIVE RATINGS OF MALE AND FEMALE PATIENTS WITH BLEPHAROPTOSIS AND/OR DERMATOCHALASIS ON 11 CHARACTERISTICS

PATIENTS	SUBJECTS (N)		<21‡ (N=76)	RATING CHANGE (P VALUE)†		TOTAL (N=210)
	MALE (N=98)	FEMALE (N=112)		21-40‡ (N=62)	>40‡ (N=72)	
<b>MALE</b>						
Intelligence	0.78 (<.001)	0.80 (<.001)	0.75 (<.001)	1.05 (<.001)	0.60 (<.001)	0.78 (<.001)
Threat	0.57 (<.001)	0.56 (<.001)	0.54 (<.01)	0.76 (<.001)	0.41 (.012)	0.56 (<.001)
Friendliness	0.88 (<.001)	0.88 (<.001)	0.73 (<.001)	1.15 (<.001)	0.81 (<.001)	0.88 (<.001)
Health	0.87 (<.001)	0.86 (<.001)	0.78 (<.001)	1.23 (<.001)	0.67 (<.001)	0.87 (<.001)
Trustworthiness	0.32 (.13)	0.52 (<.001)	0.39 (.02)	0.48 (<.01)	0.26 (.06)	0.38 (<.001)
Hard work	0.64 (<.001)	0.78 (<.001)	0.76 (<.001)	0.82 (<.001)	0.57 (<.01)	0.72 (<.001)
Mental illness	0.67 (<.001)	1.05 (<.001)	0.95 (<.001)	1.18 (<.001)	0.54 (<.01)	0.87 (<.001)
Financial success	0.57 (<.001)	0.75 (<.001)	0.69 (<.001)	0.81 (<.001)	0.53 (<.01)	0.67 (<.001)
Attractiveness	0.78 (<.001)	0.41 (<.01)	0.32 (.02)	0.97 (<.001)	0.54 (<.001)	0.58 (<.001)
Alcoholism	0.99 (<.001)	0.89 (<.001)	0.89 (<.001)	1.08 (<.001)	0.88 (<.001)	0.94 (<.001)
Happiness	0.81 (<.001)	0.83 (<.001)	0.63 (<.001)	1.14 (<.001)	0.74 (<.001)	0.82 (<.001)
<b>FEMALE</b>						
Intelligence	0.45 (<.01)	0.51 (<.001)	0.30 (.07)	0.76 (<.001)	0.44 (<.01)	0.48 (<.001)
Threat	0.22 (.15)	0.51 (<.01)	0.40 (.15)	0.45 (<.01)	0.28 (.013)	0.38 (<.01)
Friendliness	0.68 (<.001)	1.02 (<.001)	0.85 (<.001)	0.97 (<.001)	0.80 (<.001)	0.87 (<.001)
Health	0.69 (<.001)	0.71 (<.001)	0.56 (<.01)	0.82 (<.001)	0.73 (<.001)	0.69 (<.001)
Trustworthiness	0.39 (<.01)	0.49 (<.001)	0.49 (<.01)	0.35 (.012)	0.47 (<.01)	0.44 (<.001)
Hard work	0.31 (.04)	0.55 (<.001)	0.57 (<.01)	0.42 (.014)	0.29 (.10)	0.43 (<.001)
Mental illness	0.67 (<.001)	0.54 (<.01)	0.20 (.33)	0.90 (<.001)	0.78 (<.001)	0.60 (<.001)
Financial success	0.59 (<.001)	0.51 (<.001)	0.45 (.013)	0.53 (<.01)	0.65 (<.001)	0.54 (<.001)
Attractiveness	0.63 (<.001)	0.35 (<.01)	0.28 (.09)	0.44 (<.01)	0.74 (<.001)	0.49 (<.001)
Alcoholism	0.56 (<.001)	0.98 (<.001)	0.83 (<.001)	0.84 (<.001)	0.68 (<.001)	0.78 (<.001)
Happiness	0.77 (<.001)	0.88 (<.001)	0.53 (<.01)	1.04 (<.001)	0.98 (<.001)	0.83 (<.001)

\*Rating scale of 1 to 5. The scale was designed so that the higher rating represented the more positive aspect of each characteristic (eg, intelligence: 1 = not intelligent, 5 = very intelligent; threat: 1 = not threatening, 5 = very threatening).

†The paired *t* test was used for matched comparisons (ie, preoperative male versus postoperative male, preoperative female versus postoperative female). In all comparisons, the mean postoperative rating was higher than the mean preoperative rating.

‡Age of study subjects in years.

want to teach you how to lie, so your lips become beautiful and twisted. . . .”<sup>13</sup>

The psychosocial impact of readily apparent strabismus on affected adults has been well studied. Using a self-report questionnaire, Satterfield and associates<sup>14</sup> found evidence to suggest that the presence of strabismus was perceived by affected patients to have a negative impact on many aspects of their lives, including self-image, securing employment, interpersonal relationships, school, and work. In another study, Burke and colleagues<sup>15</sup> had 16 adult patients who had recently undergone corrective strabismus surgery complete a self-reporting repertory grid concerning 15 personality traits with respect to themselves prior to and following the surgery. The investigators found that the patients scored themselves to be significantly more positive relative to the 15 traits after versus before surgery, and that the patients felt that others viewed them to be more positive relative to the traits after surgery as well. Coats and coworkers<sup>16</sup> showed study respondents mock resumes with photographs of men and women with a digitally generated

large-angle esotropia or exotropia and asked the respondents to rate the applicants on their perceived qualifications for a hypothetical job. They found that the presence of large-angle horizontal strabismus adversely affected perceived vocational qualifications for female applicants, but not for male applicants. In a study of similar design to the present study, Olitsky and associates<sup>17</sup> showed subjects a photograph of an orthotropic, esotropic, or exotropic individual, and asked the subjects to evaluate the person in the photograph with regard to 11 personality characteristics. When compared to the orthotropic photograph, the esotropic photograph was judged significantly more negatively with respect to intelligence, attentiveness, competency, humor, emotional stability, leadership ability, and communication and organizational skills, while the exotropic photograph was judged significantly more negatively only with regard to sincerity.

In addition to strabismus, the size of one’s pupils may affect how others view that person. Hess<sup>18</sup> showed male subjects photographs of 2 different women and asked them to compare the women with respect to various traits.

The photographs were identical except that in one, the pupils were retouched to make them larger, and in the other, they were retouched to make them smaller. The women with the larger pupils were viewed to be more “warm” and “soft,” whereas the same women with smaller pupils were viewed to be more “selfish” and “cold.”

In the present study, as a whole, both the male and female photographs with uncorrected blepharoptosis and dermatochalasis were viewed significantly more negatively on all 11 of our measured characteristics than the same patients’ postoperative photographs. Although small sample size precluded statistical analysis of preoperative versus postoperative ratings for each individual patient, each did show a higher mean postoperative rating on all 11 characteristics. While the mean postoperative ratings for all of the characteristics were higher within each of the analyzed subsets of study subjects, some characteristics did not show statistical improvement in certain subsets. It is possible that some of these comparisons would have been statistically significant if more subjects had been recruited. Worth noting is the subset of subjects under 21 years of age. This group found only 15 of 22 comparisons (11 characteristics for both male and female patients) to be significantly different (compared to the subset of female subjects, in which all 22 comparisons were found to be significantly different). Also, they were the only age-group not to rank the male or female patients significantly more attractive postoperatively. Perhaps the results for the subjects under 21 years of age would have been different if the patients in the photographs had been closer to those subjects’ ages. Also worth noting is that in the 55 comparisons for the male patients (11 characteristics and five subsets of subjects), only 5 did not show a significant improvement postoperatively; however, with the female patients, 11 of 55 failed to show a significant improvement postoperatively. This difference may be suggestive of a slightly more negative bias toward men (as opposed to women) with blepharoptosis.

There are some limitations to our study. The patients in the photographs (aged 55 to 85 years) are representative of an older population. Thus, the generalizability of the results to younger patients with ptosis is uncertain. We relied on paid volunteers as our study subjects, we did not determine the percentage of those approached who participated in the study, and the subjects were all recruited from similar suburban shopping malls (which may represent a skewed population). Our questionnaire was designed by 3 of the authors (J.D.B., R.E.W., and D.G.B.), was not based on any previous studies, and therefore does not represent an instrument of proven reliability and validity. The 11 study characteristics were chosen in an attempt to create a diverse yet succinct list of personal traits of interest to be studied. In order to mask

the purpose of the study, subjects did not view the same patient’s preoperative and postoperative photographs, and therefore preoperative and postoperative ratings of the same patient were performed by different study subjects. The purpose of the “control” male and female photographs was to further mask the intent of the study, and therefore they were not used in the statistical comparisons. In addition, the degree of ptosis required to elicit statistically significant results was not determined.

The indications for upper eyelid surgery have traditionally been based on functional deficits.<sup>19-21</sup> Previous studies have demonstrated that patients perceive an improvement in their quality of life following ptosis surgery.<sup>3,4</sup> Intuitively, this improvement may be attributed to the enlarged visual field resulting from proper surgery. However, the notion that the perceived improvement in quality of life may be due to as yet unexamined psychological factors produced by surgical correction of blepharoptosis has been suggested.<sup>22</sup> The results of the present study give credence to this concept. How we are viewed and treated by others is a large determinant of our perceived quality of life. While few people would intentionally practice physiognomy, the results of the present study indicate that most people, albeit unconsciously and perhaps innocently, are biased by certain facial features, namely, the presence of blepharoptosis and dermatochalasis. Thus, it is very likely that these biases affect the social and professional functioning of afflicted patients. Therefore, beyond the improvement in visual function, an equally or possibly even more significant outcome of surgical correction could be the reversal of the negative social implications associated with these eyelid conditions. This is a very important consideration for physicians and third-party insurers who strive to improve the functional, social, and psychological well-being of patients.

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## DISCUSSION

DR BARTLEY R. FRUEH. I thank the authors for providing me with their completed manuscript in a timely fashion. It is a fun paper to read. They have looked at a previously unstudied aspect of the common conditions, ptosis and dermatochalasis, approaching them from the viewpoint of how the lay public interprets the facies of people with these conditions in terms of intelligence, threat, friendliness, health, trustworthiness, hard-work, mental illness, financial success, attractiveness, alcoholism, and happiness. This is a polygenous grouping of traits found in no other study. I suspect the authors drained a few pints in a local establishment to come up with these 11 largely unconnected characteristics. However, the disparate nature of these categories adds value, interest, and charm to the study.

The study is well designed and executed. Since no subject sees the pre and postoperative photo of the same patient, the subject avoids the bias that might create. Their paired analysis is appropriate for the study. A minor criticism is that it would have been better to report the actual *P* value when it was between 0.01 and 0.001 rather than reporting as <0.01. I am sure they have these

numbers and it is a reporting style.

It would be reassuring to know that the pre and postoperative photographs were taken under identical conditions, including lighting, photographic exposure, hairstyle, spectacles, make-up, facial expression, and background. If patients were to look more glamorous in the postoperative photos due to any of these factors, that might become the predominate factor shaping the observer's opinion, instead of the effects of the surgery.

It is appropriate to question whether ptosis and dermatochalasis should have been combined for this study. Each could have been studied separately. The study provides no data to show whether the perception of these 2 conditions might differ.

Although control photographs of people without ptosis or dermatochalasis were used in the presentation of photos to subjects, the opinions on the controls were not utilized in the data analysis. There are 3 ways these data could be analyzed to yield new information. They could be compared with the ratings on the post-operative patients. If there were no difference, this would be evidence that the surgical procedures did restore these patients to normality. Secondly, they could be used in the analysis to adjust for any tendencies for the subjects who utilize less than the full 1-5 scale. For example, some might use only 2-4, others 1-3, and others 3-5. Thirdly, one could randomly allocate control ratings into 2 groups repeatedly, the so-called Monte Carlo simulation, and test for any differences as a way to demonstrate lack of bias in ratings, time of testing subjects, and location of testing.

Despite these queries, this is an excellent study that demonstrates that the public's perception of the facies of patients with ptosis and dermatochalasis is negative with respect to a number of important characteristics. So not only do ptosis and dermatochalasis impair the superior field of vision, the only element insurance companies care about, they probably negatively impact the patients navigations in our society. Surgical correction may well improve not only the patient's visual restriction and self-image, but their ability to interact with others.

[Editor's note] DR ROBERT D. YEE wondered if the questions asked brought attention to specific and selected characteristics and therefore introduced a bias into the study.

DR JOHN D. BULLOCK. I thank Drs Frueh and Yee for their insightful comments. Let me first address Dr Yee's question of bias due to the possible drawing of attention (presumably to the ptosis) by the questionnaire. I am not sure how else we could have done our study other than how we did it. One obviously has to show the group of subjects some patients who are pre-operative ptosis surgery

and other who are post-operative ptosis surgery. One obviously has to have photographs of these patients, and have a questionnaire to elicit the information that you want to obtain. I guess the only bias would come if the subjects realized that there were 2 patients in the group of 6 photographs who had ptosis and they somehow sensed that this was the purpose of the study. Short of that, I think we did our study in an as unbiased way as possible, under the circumstances. I do appreciate Dr Yee's comments.

I would now like to address Dr Frueh's comments and state before doing so that we really appreciate his thoughtful consideration of our paper. Firstly, he commented on the diverse group of traits that we studied. Our traits are diverse; we tried to "cover the waterfront" in terms of different aspects of one's personality. It should be noted that our co-investigator, Dr David G. Bienfeld, is the Vice Chair of the Department of Psychiatry at Wright State University School of Medicine; thus, we did have an excellent professional to help in selecting these characteristics. In the paper I cited by Burke, et al concerning adult patients who had recently undergone corrective strabismus surgery, these authors used a grid containing 15 different diverse personality traits, not unlike ours. Another minor criticism which Dr Frueh suggests is the reporting of the actual  $t$  values between .01 and .001. In my experience with statistics, it is most unusual to report statistics in the way suggested by Dr Frueh. Typically one does report them as we did ie., "less than .01" and "less than .001." It should also be noted that another of our co-investigators, Ronald J. Markert, PhD is a highly experienced biostatistician. Dr Frueh next commented about

the pre- and post-operative photographs being taken under identical conditions. In a retrospective clinical study, which ours was, this, of course, would be impossible. However, we did take the photographs under as closely similar conditions as practical in our office setting. There was certainly no attempt to make the post-operative patients look more "glamorous" than the pre-operative patients and, as a matter of fact, the group of photographs that we used were actually selected to be as similar as possible pre-operatively and post-operatively, other than for the presence or absence of ptosis. However, there were minor differences in the lighting, facial appearance, hair, and clothing between the pre and post-operative photographs as we indicated in our paper. He then questions whether or not the blepharoptosis should have been combined with dermatochalasis in our study. In fact, 7 of these 8 patients had blepharoptosis with or without dermatochalasis, and only 1 had dermatochalasis without blepharoptosis. Therefore, we are studying the effect of the abnormal appearance of the upper eyelids and did not study the public's perception of pure ptosis or pure dermatochalasis. He also questions the statistical use of the control photographs and the fact that their scores were not utilized in the data analysis. There are many ways to analyze data in any given study and our analysis was selected for simplicity and ease of analysis. In fact, our data showed that, as groups, the post-operative patients were rated much more favorably than the pre-operative patients to a very high statistically significant level. I again thank Dr Frueh for his thoughtful and thorough analysis of our paper.

# THE OPPORTUNITY FOR INTERNATIONAL OPHTHALMOLOGY IN TREATING BLINDNESS\*

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BY Bruce Spivey, MD

## ABSTRACT

As our worldview has become more pervasive, there has been a maturation of various international ophthalmological organizations. They have created several new initiatives that have the potential to dramatically affect preventable and treatable blindness, worldwide.

The first international ophthalmological organization (the International Council of Ophthalmology, established in 1927) evolved from the longest continuously held medical meeting in the world (the International Congress of Ophthalmology, first held in 1857). Subsequently, a number of supranational and international organizations have been created, and these groups are beginning to communicate with each other and with national ophthalmological societies in joint planning. The international nongovernmental organizations, lay ophthalmic international organizations (eg, International Agency for the Prevention of Blindness), and the World Health Organization have recently joined to create a proposal called *Vision 2020: The Right to Sight*. The International Council in partnership with Academia Ophthalmologica Internationalis has created a parallel and complementary plan, *Vision for the Future*.

The potential to alleviate or prevent blindness in over 150 million people requires our attention.

Understanding the seemingly complex interrelationships of these many organizations—often unfamiliar to American ophthalmology—is important for the uniquely strong ophthalmic organizations in the United States. American involvement can make a difference.

This presentation describes the background, relationships, and present plans, which, if implemented, will have a tremendous impact on treatable and preventable blindness and the level and quality of ophthalmic services throughout the world.

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## INTRODUCTION

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Over 2 million people each year go blind from treatable or preventable ocular disorders (Table I). The history and causes of blindness are well known. The magnitude of its incidence and prevalence is less well known. Two thirds of the over 160 million cases of blindness or serious visual impairment are avoidable. Cataract is the cause of three fourths of the cases of blindness. This paper describes the 150-year maturation process of international ophthalmology, its recent efforts and organizations, and 2 parallel and compatible efforts to confront blindness worldwide.

## WORLDWIDE COOPERATION

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Only since the latter half of the 20th century has it been possible to treat most forms of blinding conditions with consistently positive outcomes and to prevent blinding conditions such as vitamin A deficiency, trachoma, and onchocerciasis. For decades, there have been individuals and organizations dedicated to the alleviation of blindness in local, regional, and international purview.

\*From the Department of Ophthalmology, Weill Medical College of Cornell University and the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York, New York.

Coordination, however, has been sporadic. Given the maturity of international organizational structures and relationships, there are now several worldwide coordinated efforts, separate but parallel, distinct but intertwined, that are focusing on dramatically reducing worldwide blindness.

The prevention and treatment of blindness may be categorized under the public health sector (ie, prevention) and the ophthalmologic sector (ie, treatment solutions) (Table II). Governments and international nongovernmental organizations (INGOs), with the assistance of the World Health Organization (WHO), International Agency for the Prevention of Blindness (IAPB), World Bank, and other groups, are dedicated to prevention efforts. These same groups, along with ophthalmologists, are involved in treatment programs.

Substantial impact is now possible on account of a combination of advances in pharmacology and technology. First, medications for onchocerciasis, trachoma, and vitamin A deficiency are now widely available. Second, new technologies, sutures, and intraocular lenses in cost-affordable components are available in developing countries. Third, organizational maturity and focus, coupled with cooperative commitment by a variety of (and even competing) entities, have been linked in sufficient degree to create the momentum necessary to launch the

**TABLE I: STATISTICS RELATED TO BLINDNESS**

160+ million people have visual impairment  
 Two thirds of cases of blindness are avoidable  
 Three fourths of cases of blindness are due to cataract (30+ million people)  
 6+ million people are blind from glaucoma, 6+ million from trachoma  
 60% of cases of blindness are in India, China, and Sub-Saharan Africa  
 Blindness increases at an estimated rate of 2 million cases per year  
 The number of people over age 45 will double (to 1 billion) by 2020

**TABLE II: PREVENTABLE AND TREATABLE BLINDNESS**

**Preventable blindness:** Largely a public health solution

- Vitamin A deficiency
- Trachoma
- Onchocerciasis

**Treatable “blindness”:** Largely an ophthalmologic solution

- Cataract
- Diabetic retinopathy
- Glaucoma
- Congenital/heritable disorders (surgically amenable)
- Refractive errors

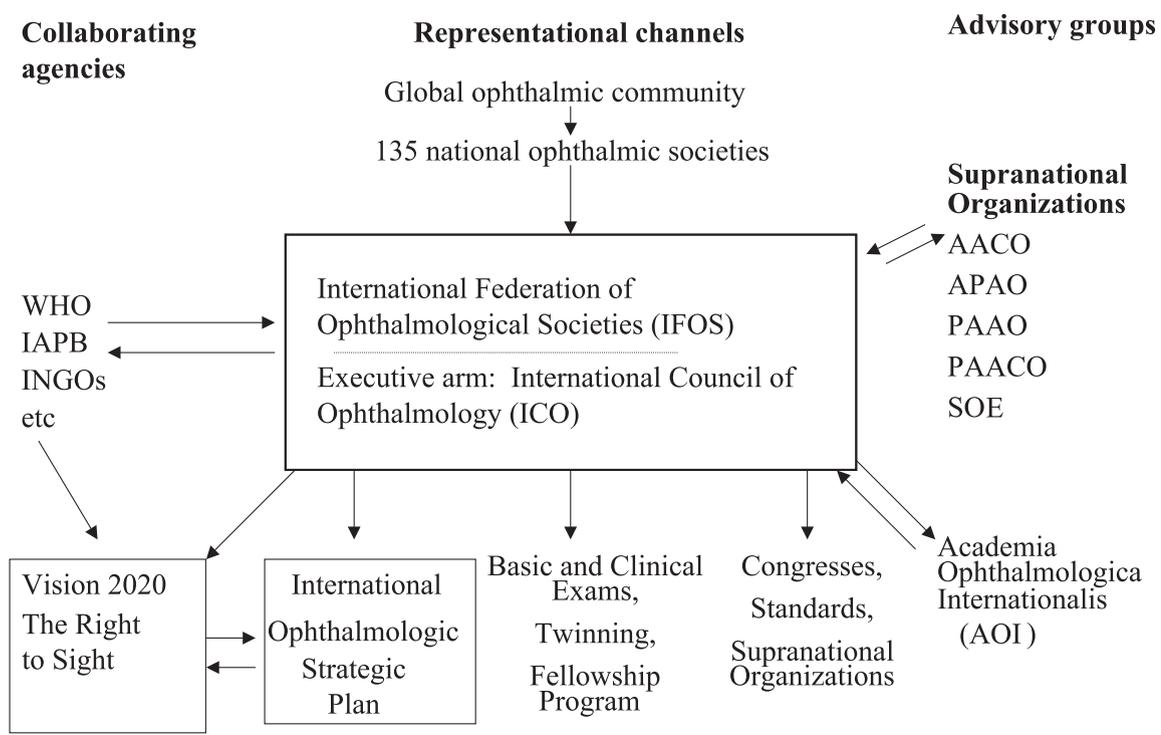
many in existence for over 100 years, are linked by the International Federation of Ophthalmological Societies (IFOS), established in 1933. The IAPB was established in 1975 by the ICO and the World Blind Union. Academia Ophthalmologica Internationalis (AOI) was also established in 1975. INGOs have evolved in the past 70 or more years. Also, over the past 50-plus years, supranational organizations have developed; these groups play regional roles in education and relationship building. Groups are the Pan-American Association of Ophthalmology (PAAO), established in 1939; the European Ophthalmological Society (SOE), established in 1956; the Asia-Pacific Academy of Ophthalmology (APAO), established in 1958; the Afro-Asian Council of Ophthalmology (AACO), established also in 1958; and the Pan-Arab African Council of Ophthalmology (PAACO), established in 1989. A large number of international subspecialty organizations are becoming more prominent.

**VISION 20/20 AND VISION FOR THE FUTURE**

worldwide challenge of alleviating blindness.

There are many international ophthalmic organizations. The International Council of Ophthalmology (ICO), established in 1927, evolved from the International Congresses of Ophthalmology, which date from 1857 (Fig 1). National ophthalmology societies,

Several years ago, the INGOs, IAPB, and WHO began to plan for an effort called *Vision 20/20: The Right to Sight*. The focus of this effort is to eradicate most preventable and treatable blindness by the year 2020. The program is now in an early implementation stage after having been publicly announced in early 1999.



**FIGURE I**

Components of international ophthalmology.

Earlier in 1999, international ophthalmology through the ICO and the AOI, along with a variety of consultants, began a planning effort concluded in early 2001. This effort, parallel to and supportive of *Vision 20/20*, is called *Vision for the Future*. It is to be implemented under the aegis of the ICO, and it focuses on the knowledge and skills particularly unique to or in the province of ophthalmology and ophthalmologists. The program is beginning to gain momentum.

The commitment and focus of ophthalmology's international efforts are directed toward developing countries, but the products and outcome of these efforts are applicable and useful in developed nations as well.

#### **GOALS**

*Vision for the Future* has 5 major goals:

1. Ophthalmologic education and training
  - A. To provide curricula for allied health, medical student, and residency education
  - B. To provide individual assessment of resident performance (basic and clinical science assessment programs)
2. Ophthalmology continuing education
  - A. To identify and disseminate appropriate curricular content
  - B. To disseminate educational materials
3. Eye care guidelines
  - A. To develop clinical guidelines that define appropriate care for existing capabilities
  - B. To disseminate and continue to develop guidelines for all ophthalmologists to ensure a basic international standard
4. Advocacy for the preservation and restoration of vision
  - A. To facilitate global initiatives for elimination of avoidable blindness (*Vision 20/20: The Right to Sight*)
  - B. To mobilize ophthalmologists and governments by their understanding of and interest in blinding disorders worldwide
5. Research in ophthalmology and vision
  - A. To facilitate basic and clinical science focused on global needs
  - B. To provide particular emphasis on the acquisition of clinical population and epidemiological research skills

Substantial progress has already been made in developing curricula and clinical guidelines. Continuing medical education surveys are complete. Advocacy and research are never-ending challenges that require substantial augmentation. Educational curricula and clinical guidelines are being made available through the ICO Web

site ([www.icoph.org](http://www.icoph.org)) and then through the various supranational and national ophthalmological organizations.

*Vision for the Future* includes commitments to the conditions of glaucoma and diabetic retinopathy that were not part of the initial *Vision 20/20*.

*Vision 20/20* has 3 major areas of focus.

1. Control of major causes of blindness
  - A. Cataract
  - B. Trachoma
  - C. Onchocerciasis
  - D. Childhood blindness (vitamin A deficiency and surgically treatable disorders)
  - E. Refractive errors and low vision
2. Human research development
  - A. Community workers
  - C. Secondary and tertiary professionals with emphasis directed toward Africa
3. Infrastructure and appropriate technology development
  - A. Infrastructure, including the structure itself, finances to support, and motivation to continue
  - B. Technology

*Vision 20/20* is to be developed and implemented by plans created in each country. Efforts are currently under way; the challenge is for multiple organizations to come together for the funding and functionality required. The various INGOs are continuing their plans and priorities, which are being considered as part of the overall *Vision 20/20* plan.

The immediate task is to closely link these 2 major efforts by building on the strengths of the parties involved. Ophthalmologists alone can create curricula, basic and continuing education materials, basic and clinic ophthalmic assessment examinations, clinical guidelines, and ophthalmic research. Once accomplished, especially in developing countries, these efforts will markedly facilitate eye care and, thus, *Vision 20/20*.

#### **CONCLUSION**

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Together with the WHO, IAPB, and INGOs, the international ophthalmic community can advocate for support to prevent and treat world blindness. Such an effort will require the cooperation of individual ophthalmologists, their organizations, and INGO-led and INGO-supported infrastructure to deal with cataract, diabetes, diabetic retinopathy, glaucoma, surgically treatable childhood blindness, and refractive errors.

The INGOs and IAPB, with support and curricula from ophthalmologists, can and must create the primary care human resources capability and infrastructure necessary to support the final implementation of blindness prevention and treatment.

The common good is obvious, and the tasks are clear but daunting. Close coordination, as well as sublimation of ego and the natural desire to control, will be required. Good will, thoughtful coordination, consistent communication, and persistence of commitment will be necessary for success.

Ophthalmologists in developed countries have a particular role and responsibility in the implementation of both *Vision 20/20* and *Vision for the Future*.

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## DISCUSSION

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DR ALFRED SOMMER, MD, MHS. Bruce Spivey's presentation could not be more timely. The dramatic advances in ophthalmic knowledge and surgical techniques of the past quarter century are matched, if largely disconnected from, the growing collaboration among nongovernmental organizations (NGOs) mounting a global campaign to prevent blindness.

The challenge laid out by Dr Spivey is quite simply: How can ophthalmologists and their professional societies best enhance the global initiative against avoidable blindness? The simple answer is, not easily! It is not that ophthalmology has too little to offer, but rather too much.

Individual ophthalmologists have played important roles in generating the global initiative:

- Barry Jones, Chan Dawson, Hugh Taylor, Allen Foster, myself, and others provided insights and energy into (public health) approaches that are reducing the burden of onchocerciasis, trachoma, and xerophthalmia.
- Venkataswamy, Ruit, Albrecht Hennig, and others have perfected high volume, low cost, efficient cataract surgery that has established a single, global standard for quality outcomes.
- Ed Maumenee joined with John Wilson in creating the International Agency for Prevention of Blindness (IAPB), (relinquishing the presidency of IAPB's forerunner, the International Association for the Prevention of Blindness, in the process).<sup>1</sup>

Success of public health prevention programs, and growth in the number of elderly, ensures that cataract and other surgically remedial conditions will increasingly account for the vast majority of unnecessary blindness in the world. By training, qualifications, and licensure, these conditions can only be dealt with by ophthalmologists.

The problem is that there are not enough ophthalmologists, performing enough surgery, in the places that most need them:<sup>2</sup>

- There is 1 ophthalmologist per 10,000 population in the US; 1 per 100,000 in India; and 1 per million in (urban) Sub-Saharan Africa.
- The average American ophthalmologist performs 10 times as many cataract operations a year as the average Chinese ophthalmologist.
- The average ophthalmologist is exquisitely responsive to market forces: Despite millions of cataract blind, Chinese ophthalmologists in Beijing, Shanghai, Guangzhou, Chengdu, and other large cities perform more refractive surgery than cataract surgery.

The problem is not purely of ophthalmology's making. Government policies determine the number of trained ophthalmic surgeons, and directly or indirectly influence their behavior. (The UK's National Health Service waiting list for cataract surgery is presently 6 months; for privately funded surgery it is less than 6 weeks).

NGOs, the World Health Organization, "summits," and "strategic plans" can quantify global blindness and launch valuable demonstration projects and initiatives. But none of this can solve the problem until incentives and market forces engage the broad ophthalmologic community in providing eye care to all who need it.

Dr Spivey, whose understanding of ophthalmologists, their organizations, and behavior is unmatched, has provided our profession another useful service. By introducing us to the magnitude and parameters of the global challenge, and the multitude of agencies that would be our allies, he has taken the first, vital step in engaging ophthalmology in a crusade that cannot succeed without it.

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DR BRUCE E. SPIVEY. I would like to thank all the discussants, particularly Dr Sommer who is universally acknowledged as a world leader in International Ophthalmology. His work on Vitamin A, with which I hope all of you are conversant, establishes a standard of treatment not only for the prevention of blindness but to protect life itself. Al

*The Opportunity for International Ophthalmology in Treating Blindness*

is being appropriately recognized for this dramatic breakthrough worldwide.

“Vision for the Future” and “Vision 2020” are huge endeavors and we are just getting started. Any of you who have ideas or interests let me or other members of the International Council know. AOS members, Brad Straatsma, Mark Tso and Paul Lichter, your President, are

also members of the International Council of Ophthalmology. I appreciate this opportunity to inform you about something with which you may not have been conversant. I look forward over the years to your involvement and to giving you updates about our progress. Thank you.



# CONDUCTIVE KERATOPLASTY FOR THE CORRECTION OF HYPEROPIA\*

BY Penny A. Asbell, MD, Robert K. Maloney, MD (BY INVITATION), Jonathan Davidorf, MD (BY INVITATION), Peter Hersh, MD (BY INVITATION), Marguerite McDonald, MD (BY INVITATION), Edward Manche, MD (BY INVITATION), AND the Conductive Keratoplasty Study Group (BY INVITATION)

## ABSTRACT

*Background/Purpose:* Conductive keratoplasty (CK) is a surgical technique that delivers radio frequency (350 kHz) current directly into the corneal stroma through a Keratoplast tip inserted into the peripheral cornea at 8 to 32 treatment points. A full circle of CK spots produces a cinching effect that increases the curvature of the central cornea, thereby decreasing hyperopia. We report here the 12-month results of a 2-year, prospective, multicenter US clinical trial conducted to evaluate the efficacy, safety, and stability of CK.

*Methods:* A total of 233 patients (401 eyes) with preoperative hyperopia of +0.75 to +3.00 D and  $\leq 0.75$  D of astigmatism (mean preoperative manifest refractive spherical equivalent =  $+1.76 \text{ D} \pm 0.60$ ) were enrolled into the study at 13 centers and underwent CK treatment.

*Results:* Twelve-month postoperative data are available on 203 eyes for safety and stability and 171 eyes for safety, stability, and efficacy. A total of 91% had uncorrected visual acuity (UCVA) of 20/40 or better, and 51% had UCVA of 20/20 or better. Manifest refractive spherical equivalent was within  $\pm 0.50$  D in 58%, within  $\pm 1.00$  D in 91%, and within  $\pm 2.00$  D in 99%. The mean change in residual refraction was  $0.26 \text{ D} \pm 0.49$  between 3 and 6 months,  $0.09 \text{ D} \pm 0.37$  between 6 and 9 months, and  $0.13 \text{ D} \pm 0.39$  between 9 and 12 months.

*Conclusions:* One-year data show safety and efficacy of CK in the treatment of hyperopia. Changes in residual refractive error after CK appeared to be small, suggesting that a stable refraction could be achieved by 6 months.

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## INTRODUCTION

Thermal techniques to correct hyperopia by steepening the central cornea date back to the work of Lans in the 19th century. Hot-wire thermokeratoplasty, a technique from the Soviet Union in which corneal spots were heated to 95% of corneal depth, produced unpredictable, unstable, and unsafe results.<sup>1-4</sup> Modern surgical procedures now include thermokeratoplasty-based techniques: pulsed, noncontact holmium:YAG laser keratoplasty (non-contact LTK, Hyperion System, Sunrise Technologies, Fremont, California);<sup>5-13</sup> contact Ho:YAG laser thermal keratoplasty (LTK) (Holmium 25, Technomed, Baesweiler, Germany);<sup>14-16</sup> diode laser thermal keratoplasty (DTK,

Rodenstock, ProLaser Medical Systems, Inc, Dusseldorf, Germany);<sup>17,18</sup> and conductive keratoplasty (Refractec, Inc, Irvine, California).<sup>19</sup> Excimer laser-based techniques include photorefractive keratectomy (PRK)<sup>20-25</sup> and laser in situ keratomileusis (LASIK).<sup>26-32</sup>

## THE CONDUCTIVE KERATOPLASTY PROCEDURE

The CK procedure performed with the ViewPoint CK System is designed to treat spherical, previously untreated hyperopia of +0.75 to +3.00 D. Treatment of presbyopia, astigmatism, and residual hyperopia following LASIK or other refractive procedures is another potential application.

Conductive keratoplasty (CK) delivers radiofrequency (350 kHz) current directly into the corneal stroma through a probe inserted into the peripheral cornea at eight or more treatment points. Localized heating of collagen is the result.<sup>26</sup> Increasing dehydration of collagen increases resistance to the flow of the current, making the process self-limiting. A thermal model predicts a cylindrical footprint approximately 150  $\mu\text{m}$  to 200  $\mu\text{m}$  wide by 500  $\mu\text{m}$  deep that extends to approximately 80% of the depth of the midperipheral cornea at each treated spot

\*From the Department of Ophthalmology, Mount Sinai Medical Center, New York, New York (Dr Asbell); Maloney Vision Institute, Los Angeles, California (Dr Maloney, Dr Davidorf); the Cornea and Laser Vision Center, Teaneck, New Jersey (Dr Hersh); the Refractive Surgery Center of the South, New Orleans, Louisiana (Dr McDonald); and Stanford University School of Medicine, Palo Alto, California (Dr Manche). Supported by Refractec, Inc, Irvine, California. Drs Asbell, Davidorf, Maloney, Manche, and Hersh participated as clinical investigators in this FDA phase III study sponsored by Refractec, Inc. Dr McDonald is a paid medical monitor for the US multicenter trial of Conductive Keratoplasty for Refractec, Inc.

(data on file, Refractec, Inc, Irvine, California). Striae form between the treated spots, creating a band of tightening that increases the curvature of the central cornea, thereby decreasing hyperopia.

This study reports the 1-year results of a 2-year, multicenter, prospective clinical trial to evaluate the safety, efficacy, and stability of CK to treat low to moderate hyperopia. Institutional Review Board approval was obtained at every study site prior to study inception.

## US CLINICAL TRIAL OF CONDUCTIVE KERATOPLASTY

### SYSTEM EQUIPMENT

The Viewpoint CK system consists of a radiofrequency energy-generating console (Fig 1); a handheld, reusable,



FIGURE 1

The ViewPoint conductive keratoplasty system: console, probe, and a choice of two lid specula that act as the electrical return path.

pen-shaped handpiece attached by a removable cable and connector; a speculum that provides a large surface for an electrical return path; and a foot pedal that controls release of radiofrequency energy. Attached to the handpiece is the Keratoplast tip, a single-use, sterile, disposable, stainless-steel, penetrating tip, 90  $\mu\text{m}$  in diameter and 450  $\mu\text{m}$  long, that delivers the current directly to the corneal stroma (Fig 2). At the very distal portion of the tip is a Teflon-coated stainless-steel stop (cuff) that assures correct depth of penetration (0.5 mm). The energy level default is 60% of 1 W and the exposure time default is 0.6 seconds. These parameters are set on the console so that each foot pedal excursion delivers the same level and duration of energy to the Keratoplast tip.

### PATIENT SELECTION

The nature of the procedure was explained to all partici-



FIGURE 2

The conductive keratoplasty Keratoplast tip (90  $\mu\text{m}$  wide, 450  $\mu\text{m}$  long) shown next to a 7-0 suture.

pating patients, and they signed informed consent forms prior to undergoing the procedure. Patients treated in the study had +0.75 to +3.00 D of spherical hyperopia,  $\leq 0.75$  D of refractive astigmatism, and a peripheral pachymetry reading at the 6 mm optical zone of not less than 560  $\mu\text{m}$ . Visual acuity was correctable to at least 20/40 in both eyes. Hard or rigid gas permeable lenses were discontinued for at least 3 weeks and soft lenses for at least 2 weeks prior to the preoperative evaluation. Hard contact lens wearers had 2 central keratometry readings and 2 manifest refractions taken at least 1 week apart. The manifest refraction measurements did not differ from the earlier measurements by more than 0.50 D in either meridian. Keratometry mires were regular.

Patients not eligible for CK treatment in the study were those with active ocular disease, corneal abnormality, progressive or unstable hyperopia, history of previous refractive surgery, or other significant ocular or physical history.

### EXAMINATIONS

Preoperative examinations included a manifest and cycloplegic refraction, uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) (distance and near), slit-lamp and fundoscopic examination, applanation tonometry, central keratometry, ultrasonic pachymetry, and computerized corneal topography. Postoperative examinations were performed on days 1 and 7 and on months 1, 3, 6, 9, and 12.

### TREATMENT

One drop of topical anesthetic was administered 2 or 3 times at 5-minute intervals, and the patient was monitored for degree of anesthesia. Pilocarpine was not administered. The CK lid speculum was inserted to provide corneal exposure and an electrical return path. Care was taken to ensure that the lid drape (if used) did not prevent direct contact of the lid speculum and eyelid, which would disrupt the electrical current return path. The fellow eye was

taped closed. The operating microscope was positioned over or in front of the eye to be treated.

The patient was reminded to fixate on the light from the microscope during corneal marking. The eight-intersection CK marker was dampened with gentian violet or rose bengal stain, and the marker's crosshair was centered over the center of the pupil. The marker makes a circular mark at the 7 mm optical zone, with hatch marks indicating the 6 and 8 mm optical zones. Light pressure was applied on the marker to mark the cornea. If gentian violet was used, the cornea was irrigated with balanced salt solution to remove excess ink. The surface of the cornea was dried thoroughly with a fiber-free sponge to avoid dissipation of applied energy by a wet surface.

The Keratoplast tip was examined under the microscope to ensure it was not damaged or bent prior to application. The appropriate treatment parameters were set on the console, and the eye was treated with the appropriate number of treatment spots, as specified in the nomogram (Fig 3). For example, to correct +1.00 D to +1.625 D of hyperopia, 16 treatment spots were placed: 8 at the 6 mm

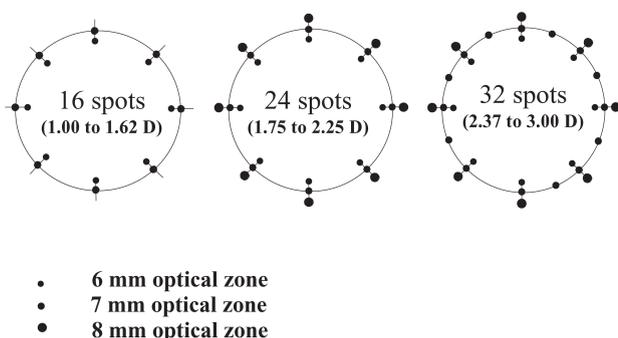


FIGURE 3

Nomogram showing number and location of treatment spots.

optical zone and another 8 at the 7 mm optical zone. When treating +0.75 D to +0.875 D (8 spots), treatment was applied only at the 7 mm optical zone.

To treat each spot, the tip of the delivery probe was placed at the treatment mark on the cornea, perpendicular to the corneal surface. Light pressure was applied until the tip penetrated the cornea down to the insulator stop. The foot pedal was depressed to apply the radio frequency energy. The tip was cleaned with a fiber-free sponge after each treatment spot to remove any tissue debris, taking care not to damage the tip. As specified by the study protocol, intraoperative keratometry was performed at the slit lamp to check for any induced cylinder.

**POSTOPERATIVE CARE**

One drop of a topical ophthalmic antibiotic solution and 1 drop of an ophthalmic nonsteroidal anti-inflammatory

drug were administered and continued for up to 3 days. Topical corticosteroids were not used.

**CLINICAL TRIAL RESULTS**

**PATIENT DATA**

The patients' demographic and baseline information is shown in Table I. A total of 361 eyes were treated with the

TABLE I: DEMOGRAPHIC AND BASELINE INFORMATION

Multicenter Study Investigators	20 surgeons at 13 centers in US
Refractive error treated	+0.75 D to + 3.00 D, ≤ 0.75 D cylinder
Intended refraction	Plano
Retreatments	None
Patients' characteristics	Age: 55 ± 6.4 years (range, 40 to 74) Female, 58%; male, 42% Caucasian, 81%
Mean preoperative MRSE	+1.82 ± 0.60 D
Range	+0.75 D to +3.00 D
Median MRSE	+1.75 D
Mean preoperative CRSE	+1.76 ± 0.60 D
Range	+0.75 D to +3.25 D

CK, conductive keratoplasty; CRSE, cycloplegic refractive spherical equivalent; MRSE, manifest refractive spherical equivalent.

current nomogram for CK (Fig 3), and an additional 29 were treated with an earlier nomogram that had a tendency to undercorrect. The 29 eyes treated with the earlier nomogram were excluded from analysis of efficacy variables. Thus data from 397 eyes were evaluated for efficacy, safety, and stability variables, and 401 were evaluated for stability and safety variables (Table II). Preoperatively, UCVA for distance was 20/40 or worse in 81% of the eyes, and UCVA for near was J5 or worse in 95%.

**EFFICACY**

Twelve months postoperatively, UCVA was 20/20 or better in 87 (51%) of 171 eyes, 20/25 or better in 125 (73%) of 171 eyes, and 20/40 or better in 156 (91%) of 171 eyes. Near UCVA increased an average of 6 Jaeger lines. Mean

TABLE II: ANALYSIS OF PATIENT DATA

EYES	NO.
Patients treated	233
Eyes treated	401
Total treated within protocol (no deviations)	397
Total treated prior to nomogram modification	29
Total treated with current nomogram	372
Evaluated for safety and stability variables	401
Evaluated for all variables (Efficacy, safety, stability)	397
Available at 12 months for stability and safety analyses	203
Available at 12 months for safety, efficacy, and stability analyses	171

manifest refractive spherical equivalent (MRSE) values showed 99 (58%) of 171 within  $\pm 0.50$  D of plano, 156 (91%) of 171 within  $\pm 1.00$  D, and 169 (99%) of 171 within  $\pm 2.00$  D (Fig 4). A summary of the efficacy results with conductive keratoplasty at 12 months is shown in Table III.

TABLE III: SUMMARY OF EFFICACY RESULTS WITH CONDUCTIVE KERATOPLASTY COMPARED WITH FDA GUIDELINES FOR REFRACTIVE SURGERY PROCEDURES

	FDA GUIDELINE	6 MONTHS (N=350)	9 MONTHS (N=340)	12 MONTHS (N=171)
UCVA $\leq 20/20$	50%	40%	50%	51%
UCVA $\leq 20/25$	Not stipulated	63%	74%	73%
UCVA $\leq 20/40$	85%	86%	93%	91%
MRSE $\pm 0.50$ D	50%	56%	64%	58%
MRSE $\pm 1.00$ D	75%	83%	87%	91%
MRSE $\pm 2.00$ D	Not stipulated	97%	99%	99%

FDA, Food and Drug Administration; MRSE, manifest refractive spherical equivalent; UCVA, uncorrected visual acuity.

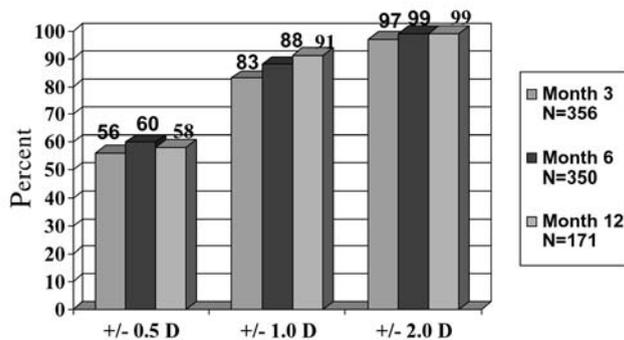


FIGURE 4

Accuracy of achieved refraction 3, 6, and 12 months following conductive keratoplasty treatment.

One hour after treatment, the opacities at each treatment spot were visible by slit lamp as small surface leukomas, with a band of striae connecting the treatment spots (Fig 5).

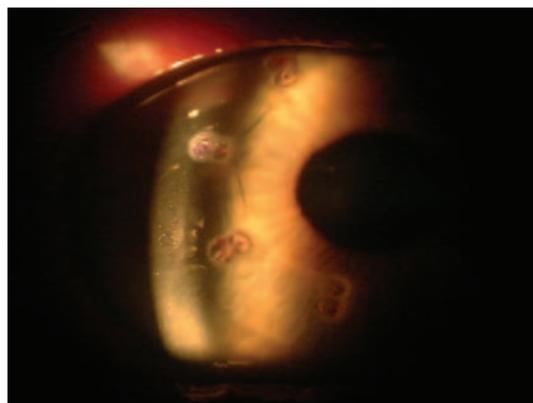


FIGURE 5

Leukoma visible by slit-lamp 1 hour following conductive keratoplasty treatment.

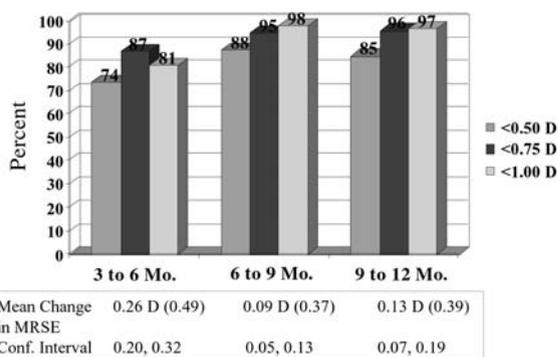


FIGURE 6

MRSE stability through 12 months in patients with consecutive visits.

### STABILITY

Postoperative MRSE values within  $\pm 0.50$ ,  $\pm 1.00$ , and  $\pm 2.00$  D of plano are shown in Fig 6. The mean change in residual refraction for eyes with all consecutive follow-up visits was  $0.26$  D  $\pm 0.49$  (CI = 0.20, 0.32) between 3 and 6 months;  $0.09$  D  $\pm 0.37$  (CI = 0.01, 0.17) between 6 and 9 months; and  $0.13$  D  $\pm 0.39$  (CI = 0.07, 0.19) between 9 and 12 months.

### SAFETY

No significant events occurred intraoperatively, and there were no treatment-related adverse events. No remarkable postoperative changes were seen in loss of BSCVA or induced cylinder (Table IV).

### DISCUSSION

Surgical correction of hyperopia has been a greater challenge to ophthalmology than surgical correction of myopia because of the impermanence of surgical effect

TABLE IV: SUMMARY OF SAFETY RESULTS WITH CONDUCTIVE KERATOPLASTY

CHANGE IN SAFETY VARIABLE	POSTOPERATIVE VISIT				
	1 MO (N=390)	3 MO (N=392)	6 MO (N=387)	9 MO (N=376)	12 MO (N=203)
2 Lines loss of BSCVA	6%	5%	4%	3%	0.50%
>2 Lines loss of BSCVA	2%	1%	0.50%	0.50%	0%
BSCVA worse than 20/40	0%	0%	0%	0%	0%
Increase >2.00 D cylinder	3%	2%	1%	<1%	0.50%
BSCVA <20/25 if better than 20/20 preoperatively	4%	2%	<1%	<1%	0%

BSCVA, best spectacle corrected visual acuity

(regression). Conductive keratoplasty is a new, nonablative method for the correction of mild to moderate hyperopia that uses electrical current to generate heat in the cornea. Stromal tissue provides resistance to the flow of the current, resulting in gentle, controlled tissue heating and collagen dehydration and contraction. The process is self-limiting, since resistance to the flow of current increases with increasing dehydration of collagen. Unlike Fyodorov's original "hot needle keratoplasty" technique, the CK delivery needle stays cool as collagen is heated.

Contraction of collagen following its dehydration has been shown to be a function of temperature and time.<sup>33</sup> Under steady-state laboratory conditions, collagen heated in the range of 55°C to 65°C dehydrates and contracts but can still regain its original configuration upon cooling. Above 75°C, collagen denatures completely. Thus the temperature "window" for collagen contraction without complete denaturation under steady-state conditions is approximately 65°C.<sup>33-35</sup>

However, because thermokeratoplasty is a dynamic (not steady-state) process, the state of collagen while undergoing thermokeratoplasty can be inferred, but not exactly defined, through these steady-state temperature studies. According to a thermal model, the CK targeted treatment zone reaches a temperature consistent with optimal shrinkage (65°C to 75°C) and produces a cylindrical footprint that has almost no axial gradient.<sup>33</sup>

Histologic studies have shown that the footprint extends to approximately 80% of the depth of the midperipheral cornea (data on file, Refractive, Inc, Irvine, California). Deep thermal penetration in the treatment zone (without damaging the endothelium) is desirable for permanent collagen shrinkage,<sup>34</sup> which is expected to reduce postoperative regression. Early ultrasound biomicroscopic (UBM) studies of patients following CK treatment have shown a consistent cylindrical footprint in the cornea 0.51 mm deep, a depth that would extend to 90% of the depth of most corneas (P. Asbell, preliminary UBM data, Mount Sinai School of Medicine, April 2001). In contrast to the CK technique, the Hyperion noncontact LTK technique generates the greatest amount of heat at the surface of the cornea because of the high absorption of light energy in water. The Ho:YAG beam is attenuated as it passes through the cornea so that the heat energy diffuses radially and axially into the tissue. The result is a cone-shaped collagen shrinkage zone (conical footprint),<sup>6</sup> with corneal denaturation decreasing from top to bottom. While studies have not been published on the depth of the LTK footprint, the penetration is believed to be more shallow. Deep penetration with a conical configuration could be expected to cause surface damage.

As a nonexcimer laser technique for correcting hyperopia, CK preserves the central cornea and does not induce

flap-related complications. The decreased complexity of the procedure compared with LASIK results in the need for fewer staff members. The range of correction, however, is limited to low hyperopia, and the surgeon must turn to LASIK, phakic IOL implantation, clear lens extraction, or other procedure for patients outside of the treatment range of CK.

In the multicenter clinical trial reported here, the efficacy results exceeded all Food and Drug Administration guidelines for performance of refractive surgery procedures. At 1 year after treatment, 51% of the study eyes showed 20/20 or better UCVA and 91% showed 20/40 or better. Regression following the CK procedure was low and decreased with time. Mean MRSE was within  $\pm 0.50$  D in 58% and within  $\pm 1.00$  D in 91%. During the last two intervals (6 to 9 months, 9 to 12 months), the MRSE refraction changed 0.09 D and 0.13 D, respectively. The refraction appeared to stabilize by 6 months. Since we performed no retreatments, our stability results reflect actual corneal refractive stability over the 1-year follow-up.

Leukomas visible by slit-lamp postoperatively were small because CK delivers energy deep into the stroma rather than on the surface. The striae between treatment zones remain visible at 3, 6, and 12 months, as reported by the United States CK clinical trial investigators, and suggest that the effect of treatment on the stroma is long-lasting.

The safety profile following CK was similar to that of LTK and is likely due to the preservation of the visual axis in both procedures. In comparison, hyperopic PRK<sup>20-25</sup> and hyperopic LASIK studies<sup>26-32,36</sup> have commonly demonstrated a two-line or greater loss of BSCVA of 5% to 6%.

## SUMMARY

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The refractive effect stabilized by approximately 6 months in this ongoing 2-year, prospective clinical study of the CK technique for correcting low to moderate spherical hyperopia. Postoperative visual acuity and predictability of refraction were excellent and met or exceeded the results reported for PRK or LASIK for low hyperopia. The stability results surpassed those reported with the noncontact LTK method. The CK technique spares the visual axis, has an excellent safety profile, and does not involve removal of any corneal tissue. The 2-year data from this ongoing trial should help to confirm current findings.

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## DISCUSSION

DR ROGER F. STEINERT. Until recently, refractive surgery procedures have concentrated on the correction of myopia and myopic astigmatism. However, the 1997 Baltimore Eye Study showed a distribution of refractive errors that approached a normal distribution, with as many hyperopic as myopic eyes in the range of +6D to -6D (Fig 1)<sup>1</sup>. In North America alone, 150 million potential patients are 40 or more years of age. Thirty-five percent of these patients are between +1 and +3.0D. Therefore, over 50 million individuals are potential candidates for one of the thermal approaches to correction of low hyperopia. In the USA today, techniques available for the correction of low hyperopia are photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK), capable of correcting both spherical and astigmatic errors; laser thermokeratoplasty, capable of correcting low

of first eye results is important.

In addition, the reported postoperative refractions are manifest refractions only. No cycloplegic refractive results are given. Residual accommodation may be present in patients under 55 years of age, especially when the residual hyperopia is relatively small.

I have attempted to compare the publicly available results from the pre-market approval submissions to the FDA by Sunrise Technology and Alcon Summit Autonomous Technology.

The demographics of the 3 groups appear similar, although the range of treatment in the LASIK group was considerably larger, up to +6D (Fig 2).

FIGURE 1

Distribution of refractive errors (adapted from reference 1)

spherical hyperopic errors utilizing the non-contact Sunrise Technology holmium laser; and clear lens extraction with implantation of an intraocular lens.

In PRK and LASIK, the excimer laser recontours the cornea by removing corneal stroma through the process of photoablation, in a pattern that is ideally equal and opposite to the refractive error of the eye. In non-contact holmium laser thermokeratoplasty, the patient typically receives 8 simultaneous laser applications as a ring of spots at 6.0 mm on the cornea, followed by 8 spots at 7.0 mm, with each spot consisting of 7 pulses delivered over 1.4 seconds.

Dr. Asbell has nicely summarized key results through 12 months of a different form of thermokeratoplasty. As



may be correlated between the 2 eyes, separate reporting

### Demographics

	CK	LTK	LASIK
MRSE	+1.76	+1.69	
Range	+0.5 to +3.25	+0.75 to +2.5	
CRSE	+1.82		+2.68
Range	+0.75 to +3.0		+1 to +6
Mean age	55	56.1	
Range	40-74	40-78	
Female	58.4%	59.6%	

FIGURE 2

Demographics of laser vision correction study eyes.

Looking solely at uncorrected visual acuity (UCVA) at 6 and 12 months, CK has the edge over LTK but not LASIK for 20/20 or better UCVA, despite the inclusion of higher hyperopic corrections in the LASIK group (Fig 3).

Curiously, predictability is comparable in the 3 procedures, however. Predictability usually closely correlates with UCVA unless irregular astigmatism is present (Fig 4).

Stability of hyperopic corrections, particularly thermal procedures, is a major concern. I could obtain somewhat comparable data for stability within 1 D over post-

### Effectiveness UCVA

	CK	LTK	LASIK
	6m	12m	6m
≥ 20/20	46%	55%	37%
≥ 20/25	65%	76%	69%
≥ 20/40	90%	91%	86%

FIGURE 3

Three uncorrected visual acuities (UCVA).

### Accuracy MRSE

	CK		LTK	LASIK
	6m	12m	12m	6m
+/- 0.5 D	60%	55%	57%	66%
+/- 1.0 D	88%	91%	83%	87%

**FIGURE 4**

Percentage of patients within 0.5 and 1.0 diopters of target manifest refraction spherical equivalent (MRSE).

operative intervals. Of note, CK and LTK look comparable after 3 months, while LASIK is more stable than LTK in the period from 1 to 3 months. CK data in this early interval are not given. One is left wondering whether LASIK is more stable in the first 3 months than either thermal procedure (Fig 5).

As the principal measure of safety, the thermokerato-

### Stability MRSE Change $\leq$ 1D

	CK	LTK	LASIK
1 to 3 months		82%	96.4%
3 to 6 months	96%	94.8%	
	94.2%		
9 to 12 months	97%		
6 to 12 months		94.3%	
12 to 18 months		96.8%	
18 to 24 months		100%	

**FIGURE 5**

Stability measured by percentage of patients with  $\leq$ 1 diopter change in manifest refraction spherical equivalent (MRSE) at postoperative intervals.

plasty procedures do, in the long run, have few patients who lose best spectacle-corrected visual acuity. Despite surgical creation of a flap, LASIK results seem comparable (Fig 6).

In summary, Dr Asbell and her coworkers have demonstrated preliminary efficacy, predictability and safety of the Refractec conductive keratoplasty device in a subset of eyes at 6 and 12 months. At these intervals, the results seem comparable to LASIK with the Autonomous scanning excimer laser and the Sunrise LTK procedure, with the exception of better UCVA at the 20/20 level for the CK and LASIK patients than the LTK patients. Early

### Safety Change in BSCVA

	CK		LTK	LASIK
	6m	12m		6m
Loss > -2 lines	1%	0	0	0
-2 lines	4%	0	0	4%
-1 line			0	21%
0			98.6%	54%
Gain +1line			0	17%
+2 lines			1.4%	3%
> +2 lines			0	1%

**FIGURE 6**

Change in best-spectacle corrected visual acuity (BSCVA) compared to preoperative value.

stability with LASIK appears better than with LTK; we don't have CK stability data before 6 months.

LASIK currently has a broader range of treatable hyperopic spherical correction, and also can treat simultaneous astigmatism. Another challenge to adoption of the CK procedure may be the large installed base of excimer lasers and microkeratome-trained surgeons.

Needless to say, good long-term results are fundamental to the success of any treatment modality. In refractive surgery today, however, the hearts and minds of patients are won by the vision on day 1, week 1 and, to some extent, at the first month after surgery. The results at these intervals are already collected in studies of these devices, but they are rarely reported because the emphasis of the FDA with its conventional reporting intervals has been on intermediate and longer term followup. However, our understanding of the clinical implications of refractive techniques also requires reporting of the key results in these early periods.

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[Editor's note] DR DOUGLAS D. KOCH questioned the assertion that the residual refractive error was stable after 6 to 9 months. He felt that regression may continue after that and pointed out that even a 20% regression was clinically significant in cases that were treated for only 1 to 2 diopters of hyperopia. He pointed out that one of the clinical photographs showed whitening and probable necrosis of the corneal epithelium. Similiar degrees of overheating in the stroma could produce necrosis of keratocytes and stimulate a wound healing response.

*Conductive Keratoplasty for the Correction of Hyperopia*

DR IVAN R. SCHWAB asked if endothelial cell damage or loss was studied.

DR PENNY A. ASBELL. I will try to answer the questions in order. Should the 2 eyes be analyzed separately? Generally device trials do not necessitate separate eye analyses as drug trials do since there is no drug-transfer effect. In the phase III multicenter study on conductive keratoplasty (CK), 12 month data from 401 eyes of 233 patients were combined for analysis. The FDA prior to the initiation of the study approved this method.

Why weren't cycloplegic refractions reported? For entry into the phase III CK study, patients were to have no more than 0.50 difference between their preoperative manifest and cycloplegic refractions. The patients (mean age of 55) were non-accommodating hyperopes, and the manifest and cycloplegic refractions were similar.

Should not residual refractions be reported as +/-0.50 diopters when small refractive corrections are being made? Results of the study were reported for +/-0.50 and +/-1.00 diopters of the intended plano correction.

In response to the question about the post-operative day 1 results and the "wow" effect, there is about a 0.75 diopter initial overshoot after the surgery so CK patients read J1 right away but don't immediately have 20/20 distant vision. Different refractive procedures have different advantages and disadvantages. Conductive keratoplasty has outcomes similar to those after LASIK, but unlike LASIK it spares the visual axis, does not cut corneal

nerves, and is an easier procedure to perform. Patients are not disappointed with the lack of the "wow" effect if the surgeon makes sure they understand what to expect and talks about the tradeoffs with them.

How many patients were lost to follow-up? One patient was discontinued because he was not treated. Accountability at follow-up visits ranged from 95% at month 12 to 98% at month 6. Lack of accountability at any visit was due to a missed visit, which occurred for less than 3% of the patients at any follow-up visit.

Does CK induce astigmatism? At 1 month following CK, the incidence of induced cylinder of 2.00 diopters or greater was 3%; at 1 year it was 0.5%. This is similar to induced cylinder data reported after Sunrise Hyperion laser thermal keratoplasty. Some level of induced cylinder is intrinsic into all hyperopia procedures since peripheral corneal flattening and central corneal steepening brings any peripheral irregularity to the center.

Is there data on CK treatment for astigmatism? Treatment of astigmatism with CK is now being studied. Data will be available in early 2002.

Is there information on wound healing following CK? I have presented photomicrographs of the bovine cornea following CK; they show good healing 1 week after surgery. A study reported to the American Society of Corneal and Refractive Surgery showed that the CK procedure did not significantly change endothelial cell counts in the central or peripheral cornea despite penetration of treatment to approximately 80% of the corneal depth.



# THE ATELIOTIC MACULA: A NEWLY RECOGNIZED DEVELOPMENTAL ANOMALY\*

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BY *M. Elaine De Pool, MD* (BY INVITATION), *Hala El-Hileli, MD* (BY INVITATION), AND *Irene H. Maumenee, MD*

## ABSTRACT

*Purpose:* We present a macular phenotype resulting from 1 or more abnormalities in the developmental pathway of the central retina.

*Methods:* We describe the clinical and genetic characteristics of 7 patients observed since shortly after birth with regard to visual acuity, refractive error, anterior segment status, retinal findings including foveal structure, and natural history.

*Results:* The patients varied in age from 18 months to 18 years. All patients were examined for the first time during their first year of life and by us at the age of 5 years or younger. The longest follow-up period was 16 years. The abnormal appearance of the macula consisted of thinning of the retina, rarefaction of the pigment epithelium with excess visibility of the large choroidal vessels, and absence of the foveal reflex. The visual acuities varied from 20/20 in the better eye to light perception. A retinal detachment was noted in 1 patient at age 2 1/2 years. The refractive errors varied from -2.50 to -16.50 diopters of spherical equivalent. The disease was limited to the retina in 4 patients. In 2 patients, however, developmental abnormalities of the anterior segment were also present; they consisted of malformation of the iris in 1 patient and Peters' anomaly in the other. The electroretinogram (ERG) showed reduced but not absent photopic responses and some reduction in scotopic responses.

*Conclusion:* The phenotype of ateliotic macula is being defined as characterized by an unfinished or primordial appearance. In the 7 patients studied, visual loss was noted shortly after birth. The visual outcome was variable with regard to visual acuity, but many patients showed improvement. There was no evidence of significant worsening of the disease with age except in 1 patient who had a retinal detachment. The ERG responses showed primarily photopic but also scotopic changes. The better-preserved ERG differentiates this disorder from Leber's congenital amaurosis.

*Tr Am Ophth Soc* 2001;99:89-94

## INTRODUCTION

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For lack of better knowledge, we typically categorize genetic retinal diseases by their phenotype and not by their genotype. We may use mode of inheritance as a modifying descriptor. The term *ateliotic* means unfinished, not reaching the goal; this term was chosen because of the primordial appearance of the macula. Terms such as retinitis pigmentosa continue to be used for historical reasons, even though this term is obsolete because of the implied inflammatory etiology of the disease and the identification of significant heterogeneity. By definition, retinitis pigmentosa is a progressive disorder, in contrast to Leber's congenital amaurosis (LCA), which commonly is stationary but rarely may be progressive. In retinitis pigmentosa, rod function is primarily involved; in LCA, both cone and rod function are absent. The ateliotic macula is characterized by primarily cone dysfunction, which is congenital and stationary; some patients may show

significant visual improvement with time. The genetic defect(s) for this phenotype remain(s) unknown.

## METHODS

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We studied 7 patients with regard to natural history, visual acuity, psychophysical testing, fundus appearance, and mode of inheritance. Visual fields, scanning laser ophthalmoscopy, Ocular Coherence Tomography (OCT), fluorescein angiography, and indocyanine green studies were performed in 1 older patient only.

## CASE 1

The patient was first examined at the age of 5 years. Visual acuity was 20/200 in each eye. Retinoscopic findings were -3.50 +1.25 x 85 and -3.75 +1.25 x 90. Pigmentary changes were seen in the macular area. The patient did not have nystagmus, but he had a red-green color defect. An electroretinogram (ERG) showed a normal scotopic response and a mildly reduced photopic b-wave. Funduscopy showed a staphyloma-like appear-

\*From The Johns Hopkins Center for Hereditary Eye Diseases, Baltimore, Maryland.

ance to the macular area and absence of macular reflex. The patient was last examined at the age of 17 years. At that time, visual acuities were 20/60 and 20/70 and retinoscopic findings were  $-2.25 +1.25 \times 60$  and  $-4.25 +1.00 \times 90$  (Figs 1A and 1B).

**CASE 2**

The patient was first examined shortly after birth, when she was given a diagnosis of Leber's congenital amaurosis. Results of an ERG performed by us were normal. The patient had a hypoplastic macular reflex in the right eye and an "ateliotic macula" on the left. Amblyopia therapy was instituted. At the age of 2 years her acuities were fix and follow in each eye with continued preference of fixation of the right eye. The appearance of the macula had not worsened in the left eye and was judged to be normal in the right (Figs 2A and 2B).

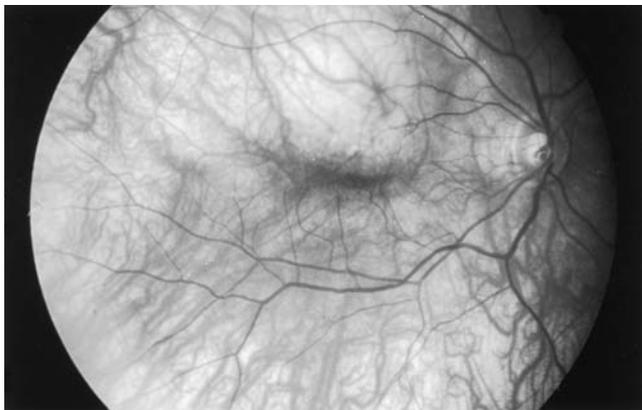
**CASE 3**

At examination at the age of 2 months, the patient would blink to light with both eyes. She had roving eye movements. Acuity was light perception only. We first exam-

ined the patient at age 11 months. Her fixation had become central and was not steady but maintained. There was a poor foveal reflex in each eye with pigment migration in the macular area and a dropout of normal structures in the peripheral retina temporal to fixation. Retinoscopic findings were  $-2.50$  and  $-11.50$ . When examined at 2 years of age, her visual acuity was 3/30 to the Allen cards in each eye. Refraction was  $-11.75 +1.75 \times 85$  and  $-13.00 +1.50 \times 85$ . Fundus evaluation showed continued coarse retinal pigment epithelial changes and a poor foveal reflex in each eye.

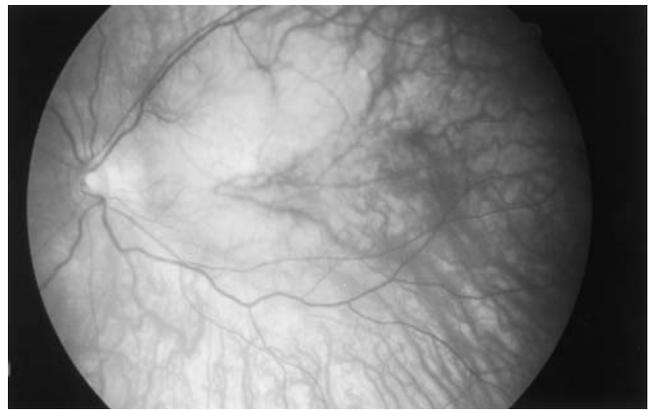
**CASES 4 AND 5**

These patients, the female children of healthy, first cousin Egyptian parents, were examined at 2 1/2 and 1 1/2 years of age on account of markedly reduced visual acuity since birth. The older sibling had a retinal detachment with a detached macula in the right eye. Refractive error in the left eye was  $-11.50$ . Bilateral atrophic patches were seen in the macular area. The patient underwent a retinal detachment procedure to the right eye. Her younger sister had nystagmus and bilateral atrophic patches in the



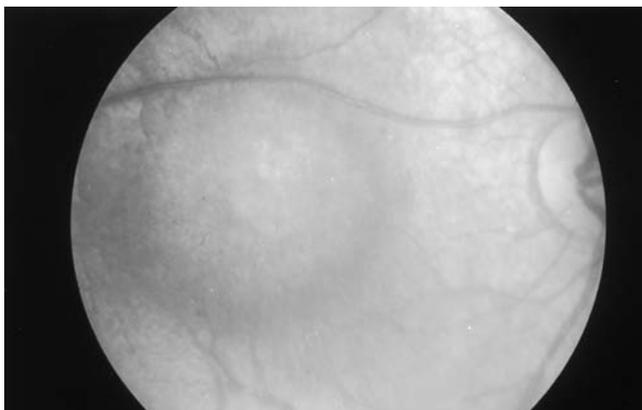
**FIGURE 1A**

Case 1. Right eye of patient with macular staphyloma OU.



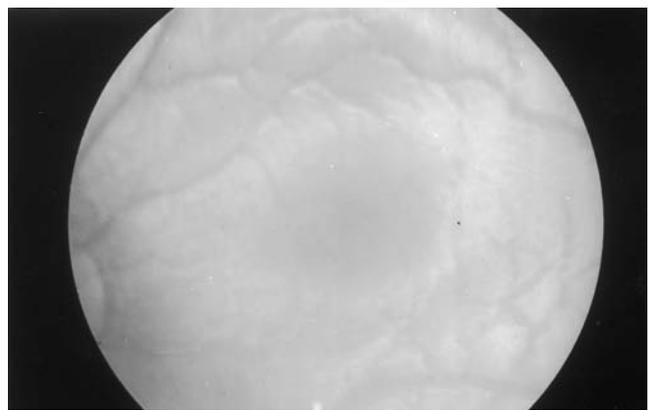
**FIGURE 1B**

Case 1. Left eye of patient with macular staphyloma OU.



**FIGURE 2A**

Case 2. Right eye of patient with asymmetric "ateliotic macula."



**FIGURE 2B**

Case 2. Left eye of patient with asymmetric "ateliotic macula."

macular area. Retinoscopic findings were -13.50 +5.00 x 110 and -11.50 +2.00 x 80.

#### CASE 6

At age 9 days the patient was noted to have a corneal opacity on the right. He underwent examination under anesthesia elsewhere. At that time, intraocular tension was normal in both eyes and no iridocorneal adhesions were noted. We began following the patient's clinical course when he was 3 weeks old. At 2 years of age, intraocular pressure increased and treatment with Timoptic was begun. Torch titers were negative, and a karyotype was normal. His gait was broad-based. He developed grand mal seizures, and a magnetic resonance imaging scan was performed. He was found to have hypoplasia of the cerebellar vermis, and a diagnosis of Joubert's syndrome was made. Refractive errors were -4.50 +5.00 x 135 and -14.50 +3.50 x 175. He had macular changes on the right that showed a bull's-eye appearance with pigment migration. He had a pit of the right optic nerve, which was tilted. In the left eye, involvement of the macular area was more significant, with large areas of depigmentation and rarefaction and hypoplasia of small choroidal vessels. Electroretinography revealed scotopic and photopic responses. Visual acuities at age 3 years were 5/30 and 1/30 with Allen cards (Figs 3A, 3B, and 3C).

#### CASE 7

The patient was first examined at age 6 months, when he had central steady and maintained fixation in the right eye. There was no obvious nystagmus. The anterior segment on the right was normal, and an eccentric minute pupillary opening measuring less than 1 mm was present on the left. An optical iridectomy was performed. The patient had a mild hypermetropic refractive error with anisometropia. He had bilateral macular changes consisting of a bull's-eye appearance. He was lost to follow-up until the age of 18 years. At that time, his visual acuities measured 20/20 in the right eye and finger counting in the left. Retinoscopic findings were plano in the right eye and -11.50 +7.00 x 130 in the left. No improvement was seen on manifest refraction. A fluorescein angiogram on the right showed a bull's-eye maculopathy. Results of an indocyanine green study were normal in both eyes. Findings on scanning laser ophthalmoscopy and focal ERG were normal as well (Figs 4A, 4B, and 4C).

#### RESULTS

The age and sex of the 7 patients in the study population are summarized in Table I. All cases of ateliotic macula were bilateral with significant variation in severity of the disease in the 2 eyes. Disease was characterized by congenital

onset. The disease was stationary and did not show progressive degenerative changes; rather, a slow improvement in visual function was observed in most patients.

Visual acuity ranged from normal to light perception only. The macula was characterized by a bull's-eye appearance to diffuse atrophic changes involving the whole posterior pole. There was excess visibility of the choroidal pattern with atrophy of the choriocapillaris and mild pigment migration in several of the affected patients. Color vision was affected. The refractive errors showed mild to very high myopia; anisometropia was common. One patient with high myopia was observed to have a retinal detachment at age 2 1/2 years. In this patient, no findings were suggestive of the Stickler or Knobloch syndromes.

Collagen XVIII, the gene involved in the Knobloch syndrome, was studied in all patients. No abnormality was found. In 1 patient, fluorescein angiography showed a bull's-eye appearance in the right eye, with a visual acuity of 20/20, and diffuse pigment displacement in the fellow eye, with a visual acuity of light perception only. Results of scanning laser ophthalmoscopy were normal in the right eye in spite of the bull's-eye appearance. The retinal thickness was at the lower limit of normal. An ERG showed a low normal response to the photopic flicker in the eye with normal acuity and 1/3 normal response in the fellow eye, which also had a reduction in rod response.

Patients showed a markedly reduced cone response and a variable reduction in rod response. Fundus appearance of the patients with high myopia was characterized by a disorganized macular area resembling the fundus appearance seen in patients with the Knobloch syndrome. There was a primordial appearance suggesting the term *ateliotic macula*. Ateliotic is derived from the Greek *telos*, meaning end or goal.

#### DISCUSSION

A large family with high myopia and a congenital macular anomaly was observed at St John's Hospital in Jerusalem by Iqbal and Jalili.<sup>1</sup> The parents were first cousins, and the mode of inheritance was clearly autosomal recessive. A similar, though smaller, family with recessive high myopia and macular changes is now being described by us. The family originated from Upper Egypt (patients 4 and 5). All other patients were identified and evaluated here in the United States. They were all isolated cases, and no definite identification of the mode of inheritance could be established. Both sexes were equally involved. Two patients had anterior segment malformations. The patient with unilateral partial corneal opacities had better retinal function in the affected eye. All patients had normal intelligence, and no other systemic abnormalities were noted except for 1 patient who had complex

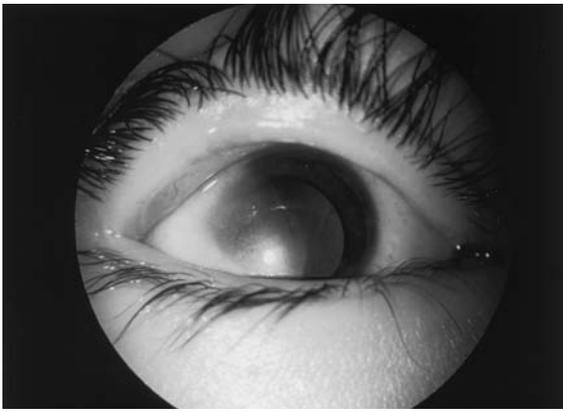


FIGURE 3A

Case 6. Anterior segment with Peters' anomaly.

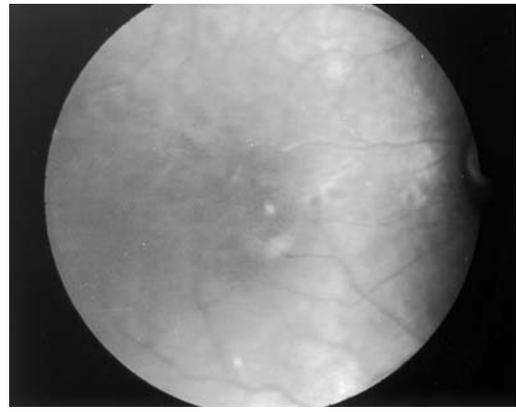


FIGURE 3B

Case 6. Right macular hypoplasia.

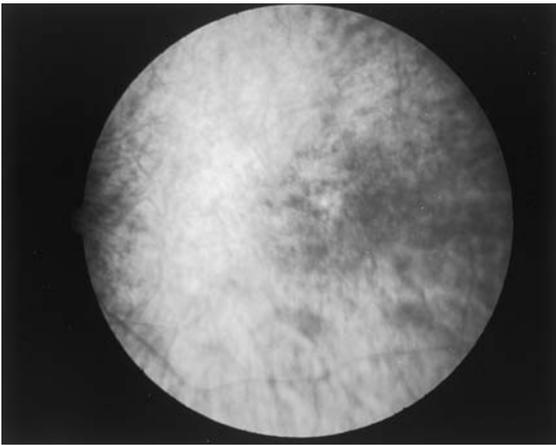


FIGURE 3C

Case 6. Left macular pigment migration.

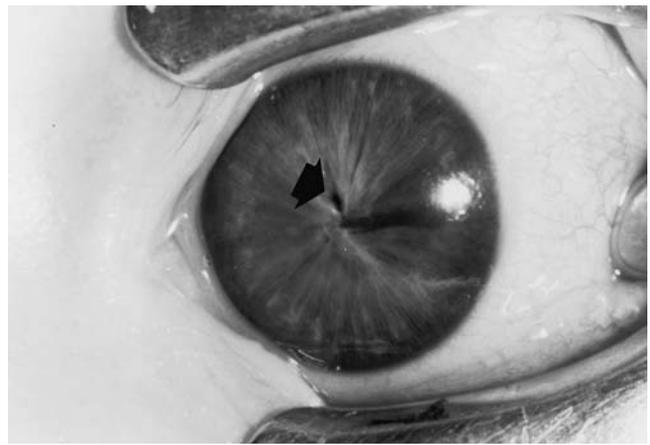


FIGURE 4A

Case 7. Left congenital malformation of the iris. Arrow indicates pupillary opening.

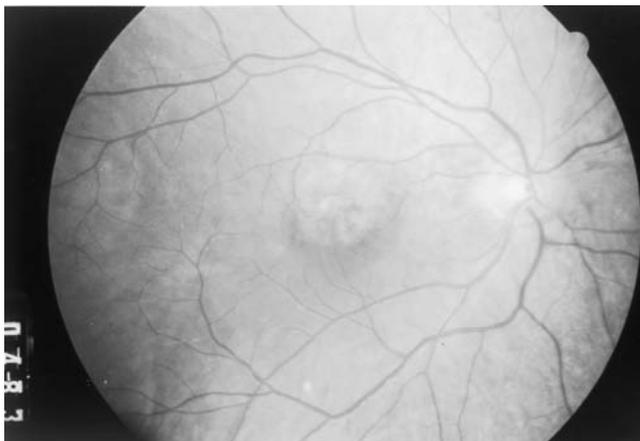


FIGURE 4B

Case 7. Right ateliotic macula with normal visual acuity.

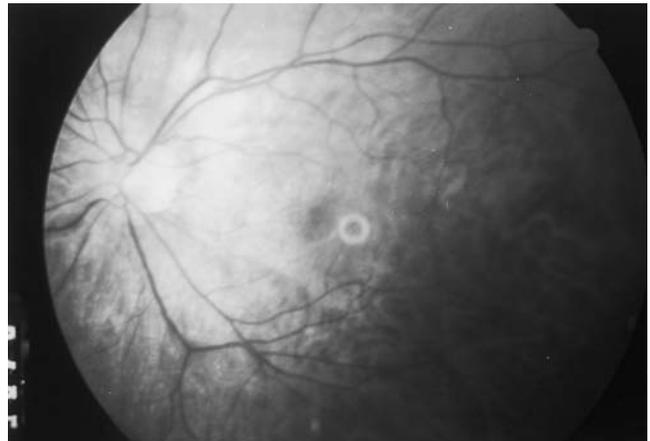


FIGURE 4C

Case 7. Ill-defined macula with pigment migration and chorioretinal atrophy.

malformations including hypoplasia of the vermis and an unexplained seizure disorder.

A variable macular phenotype of congenital onset with early poor visual acuity and an amorphous appearance to the macula is described. Parents typically consult in multiple

centers without receiving diagnostic confirmation or prognostic assessment. Classification certainly should serve the purpose of defining unique prognostic entities. It should similarly define entities that will benefit from the same treatment approach. The classification of patients under the

TABLE I:

PATIENT	AGE	SEX	ACUITY	REFRACTION	ANTERIOR SEGMENT	FUNDUS	ERG
1	17 yr	M	20/60 20/70	2.25+1.25 x 60 -4.25+1.00 x 89	Normal	Macular lesions OU	Normal scotopic, mildly reduced photopic
2	7 mo	F	F&F OU Prefers OS	-1.50+1.50 x 65 -1.00+1.50 x 90	Normal	Macular pigment changes OD, ateliotic macula OS	Normal for age
3	3 yr	F	CSM OU	-1.75+1.75 x 85 -13.00+1.50 x 85	Normal	Poor foveal reflexes chorioretinal dropout lesions, temporal to fixation	Present scotopic and photopic responses OU
4	2 ½ yr	F	Poor	OS -11.50 sph	Normal	Retinal Detachment OD; "colobomatous macula" OS	
5	1 ½ yr	F	Poor	-13.50+5.00 x 1.10 -11.50+2.00 x 80	Normal	Abnormal macula, myopic fundus OU	
6	3 yr	M	5/30 Poor fixation	-6.50 -16.50	Peters' anomaly	Macular lesion OU	Decreased scotopic and photopic amplitudes
7	18 yr	M	20/20 LP	Plano -11.50+7.00 x 130	Microcoria s/p sx OS	Atrophic macular area OU	Decreased photopic amplitude OS

CSM,; F & F, fix and follow; LP, light perception.

heading of ateliotic macula appears justified because they are united by the observation that the visual outcome appears much better than originally anticipated. The subgroup of patients with high myopia had the most primordial-looking macula. Their prognosis was also worse because of the development of a retinal detachment. It is unclear whether ocular findings in patients are worsened by their myopia or whether a separate gene defect is responsible for the families' combining macular dysplasia and high myopia. The studies by Anita Hendrickson and coworkers<sup>2-4</sup> have shown that the retinal photoreceptors develop in a centrifugal fashion with the origin in the macular area.

The genes involved in development of the fovea remain largely unexplored. Mutations in the CRX gene are known to cause a congenital anomaly of the macula. This gene has not been analyzed in these patients. The large Palestinian family with autosomal recessive inheritance should prove sufficiently large for successful linkage analysis and gene search. All isolated patients are probably best analyzed once mutation-specific diagnostic microchip analysis is possible.

Certainly previously named conditions such as North Carolina macular degeneration, progressive bifocal chorioretinal dystrophy, and Sorsby syndrome<sup>5</sup> are in the pathway of development of the macula. Several patients seen here had features reminiscent of the Knobloch syndrome.<sup>6</sup> No mutations were found in sequencing of that gene.

Understanding of the genes involved in macular development may become essential to treatment of macular degeneration in the elderly. It seems justified to create a new term to define developmental disorders of

the macula, beyond "hypoplastic macula," which defines absence of fine modeling of the macula.

## CONCLUSION

The understanding of developmental anomalies of the macula is integral to the understanding of cone function for potential repair and treatment. Large pedigrees need to be identified in order to isolate the genes responsible for the developmental disorders. Many patients present as isolated cases, and the prognosis and risk for recurrence need to be assessed on an individual basis; once the genes have been identified, a more accurate mutation-based assessment will become possible.

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## DISCUSSION

DR C. P. WILKINSON. Drs Maumenee, De Pool, and El-Hileli have described 7 patients with apparent macular hypoplasia, myopia, and additional isolated findings. They have employed the term “ateliotic” to refer to the macular changes that were present in these cases. They have demonstrated that these eyes were not associated with genetic abnormalities characteristic of the Knobloch syndrome. It is difficult to know if the ERG changes are consistent with high myopia or if they are representative of more severe diffuse retinal disease.

The term “ateliotic” is defined in Dorland’s medical dictionary<sup>1</sup> as: “characterized by incomplete or imperfect development.” This term seems to me to be consistent with the terms “dysplastic” and “hypoplastic”. Regardless of the precise wording that is employed, these macular changes are seen in a variety of syndromes, including systemic and ocular albinism, Knobloch syndrome, aniridia, PHPV, and incontinentia pigmenti. The findings also occur unassociated with apparent additional ocular or systemic problems. For instance, in 1976, Curran and Robb<sup>2</sup> described 9 patients with hypoplastic maculas and congenital nystagmus, and two-thirds of the patients were myopic. No additional problems were identified.

The Knobloch syndrome, named in honor of our own member, Bill Knobloch, was first described in 1971.<sup>3</sup> Subsequently, additional findings have been added to the syndrome, and most importantly, the site of the genetic defect has been identified.<sup>4</sup>

Regarding the 7 cases presented this morning, the precise category in which they belong is unclear. These obviously are not 7 examples of a similar macular morphology. Some appear to be similar to several of the cases described many years ago by Curran and Robb, whereas others do not appear to have classical hypoplasia of the macula, but rather changes ranging from apparent scarring at the level of the retinal pigment epithelium to an albinoid appearance.

I have 3 questions for the authors:

1. Why introduce the esoteric term “ateliotic” to replace the more widely used words “hypoplastic” or “dysplastic”, when the latter terms have been used for decades in referring to typical macular changes?
2. Were major Sticklers-like vitreous changes observed in these cases? An optically-empty vitreous cavity transversed by bands and sheets is frequently seen in eyes predisposed to retinal detachment, and many of these patients have systemic disorders associated with collagen production.
3. Finally, why do the authors believe that these 7 patients are particularly predisposed to retinal detachment?

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DR RICHARD A. LEWIS. I too was struck by the selection of the title and description of the “ateliotic macula”, in part for the substitution of the more common “macular hypoplasia”, in part for the adjectival prefix, and in part for the complexity of the admixture of Greek and Latin terms.

“Hypoplasia” is the fusion of the Greek preposition “υπο” (“hupo” or “hypo” meaning ‘under’ or ‘less than’) and the noun “πλασις” (“plasis”, the root noun for ‘molding’, ‘shaping’ or ‘conformation’ [from which we derive ‘plasma’, ‘plaster’, and ‘plastic’] and thereby ‘growth’), thus “defective formation, or incomplete development of a part.” Historically, hypoplasia has been applied to the failure to differentiate a normal fovea (ophthalmoscopically confined as the area of thickened retina confined by the elliptical foveal light reflex on the internal limiting membrane at the base of the slope of the thinning neuroepithelium and centered on the umbo), and classically associated with less than normal vision as in the albinisms, aniridia, and the like).

The macula is a larger ophthalmoscopic region confined by the major temporal vascular arcades, centered on the umbo, and extending temporally the same chord distance as in the umbo from the temporal edge of the sclerochoroidal rim. “Macula” is the Latin diminutive of “macus”, meaning ‘area’ or ‘spot’; thus “macula” is the ‘little spot’.

“Ateliotic” is derived from the Greek adjective “τελος” (“telos”), meaning “far” [thus the prefix in common English words like ‘telephone’ and ‘television’]. “ατελης” (“ateles”) (with the negative prefix “α”, roughly the equivalent of our “un-”) thus means “without end, unaccomplished, imperfect, or incomplete” and is the root for the scientific or medical term “ateliiosis” (adjectival form: ‘ateliotic’), meaning the “incomplete development of the body or any of its parts”.

However, it may be unnecessary to invoke a compound term for this failure of differentiation of the macula as Dr Maumenee has described this phenotype. In parallel to the derivation of Latin term, the Greek noun for “place” is “τοπος” (“topos”); the diminutive form would be “τοπιον” (“topion”), the ‘small place’, thus ‘the macula’. Absence of or a failure to develop the macula with purely Greek origin would be “atopion”.

# COMPLICATIONS OF CATARACT AND REFRACTIVE SURGERY: A CLINICOPATHOLOGICAL DOCUMENTATION\*

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BY David J. Apple, MD, AND (BY INVITATION) Liliana Werner, MD, PhD

## ABSTRACT

*Purpose:* To present selected complications of keratorefractive and phakic intraocular lens (IOL) surgery and a series of IOLs that required explantation because of various postimplantation opacification of the IOL optic.

*Methods:* Two specimens obtained after keratorefractive surgery, 2 phakic IOLs, and a total of 23 explanted IOLs from cases in which postimplantation opacification of the IOL optic had occurred were studied. These included 6 Bausch and Lomb (B&L) Hydroview H60M designs, 9 Medical Developmental Research (MDR) SC60B-OUV designs, and 24 IOLs with rigid PMMA optics that had been implanted in the 1980s and early 1990s. Of the latter, 8 required late explantation because of decreased visual acuity. Analyses performed included gross and light microscopic evaluation, histochemical staining, electron microscopy, and energy-dispersive spectroscopy.

*Results:* We provide examples of 3 postrefractive surgery complications: (1) fungal keratitis after LASIK, (2) post-LASIK corneal decompensation, and (3) cataract formation after implantation of phakic posterior chamber IOLs. Regarding the IOL optic opacities, classifications of 3 types are described: (1) a surface calcification of the B&L Hydroview IOL; (2) diffusion of calcium into the substance of the optic of the hydrophilic "acrylic" SC60B-OUV MDR foldable IOL design, sometimes leading to *total* opacification of the IOL optic and also its haptics; (3) a distinct pattern of intraoptical opacification with rigid PMMA designs that we term a snowflake degeneration. This term is based on the clinical and pathologic appearance of the individual lesions. Each snowflake lesion represents a focal breakdown of PMMA material as opposed to deposition of exogenous material.

*Conclusions:* Analysis of complications of refractive surgery represents a new field of ocular pathology. The clinicopathological reports presented here provide an overview of selected complications after refractive surgery. We also help define 3 newly recognized, clinically significant conditions based on postoperative IOL optic opacification. The calcification processes noted on the 2 modern foldable designs studied here (B&L and MDR lenses) need further review by the manufacturers in order to reassess production processes, especially in terms of polymer selection, manufacturing techniques, and other factors required to produce a safe and effective lens. Any lens not meeting today's high standards should not be marketed. The important fact in recognizing the snowflake complication of PMMA IOLs as described here is to alert surgeons about the nature of the lesion so that they will not alarm patients or require extensive and unnecessary testing in trying to determine its pathogenesis. There is no reason why successful explantation cannot be performed in cases where severe visual decrease or loss has occurred.

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## INTRODUCTION

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It has been purported by some that the modern cataract-intraocular lens (IOL) operation and various popular kerato-IOL refractive procedures are safe and free of complications in up to 99+% of cases. Some surgeons admit to having had no complications in their practices. It is indeed a fact that the incidence of most postoperative complications of anterior segment surgery has decreased. However, this has

led some individuals to become complacent and less vigilant regarding assessment and careful testing of new ocular prosthetics and surgical procedures. Despite the positive evolution of these anterior segment procedures, but concurrent with this era of decreased vigilance, we are unfortunately now identifying some serious problems, in some cases requiring explantation, corneal grafting, or other procedures. In this report, we provide a brief review of selected cases of refractive surgery complications associated with vision-threatening sequelae, and a clinicopathological correlative study of 3 newly recognized cataract-IOL related complications. To accomplish this, a series of explanted IOLs and excised surgical prostheses and corneas were studied by gross, light, and electron microscopic examination as well as energy dispersive spectroscopy.

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Our research center was founded in 1983 by the senior author (D.J.A.) and Randall Olson, MD, in Salt Lake City, Utah. The research and specimen analysis during this early period was almost totally focused on cataract-IOL surgery, hence the center was named the Center for IOL Research. Following David J. Apple's move to Charleston, South Carolina, in 1988, the scope of the work expanded, and we therefore changed the name to a more inclusive one, the Center for Research on Ocular Therapeutics and Biodevices.<sup>1</sup> Since its inception, the laboratory has been funded almost entirely by industry and private foundations. In 2000, thanks to a generous grant from the Magill Foundation, we expanded our oversight toward studying refractive surgery procedures and their complications. Therefore, in addition to the already established laboratory, a new center termed the Arthur and Holly Magill Research Center for Vision Correction, led by both of us and Dr Kerry Solomon, reflects this change. The 3 refractive cases briefly noted in this report represent examples of this new specialty of pathology of refractive surgery.

Since late 1982, we have received almost 17,000 specimens (Fig 1 top), both explanted IOLs and human eyes obtained postmortem with IOLs. One of the most important techniques used in the study of autopsy eyes is the Miyake-Apple technique, a modification of Miyake's 1982 postmortem videophotographic technique.<sup>2</sup> The information derived from this specimen database is the basis of the analysis of IOL opacification described in this paper. Especially significant is the recent addition of over 1,000 foldable IOLs (Fig 1 bottom) and refractive specimens to the database. All of these accessions have now provided material support to establish a new classification of postaphakic and phakic IOL opacifications, some of which are discussed in this study (Table I, No. 3, 5, 6, 7 and 8).

Today's cataract-IOL and refractive surgical procedures are not perfect. This is exemplified by the series of complications demonstrated in this study, many for the first time as of the time of this writing. These represent a microcosm of a

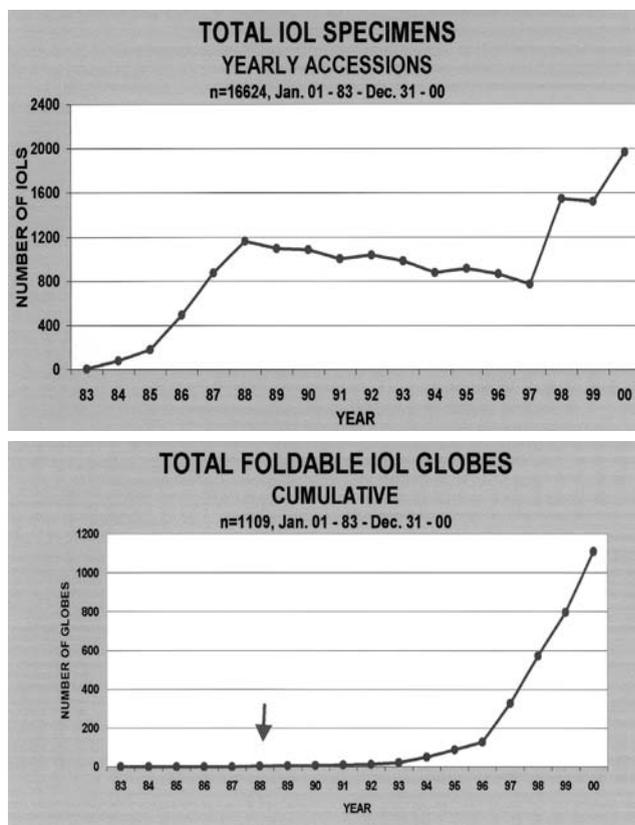


FIGURE 1

Accession of IOL-related specimens in Center for Research on Ocular Therapeutics and Biodevices, January 1983 through December 2000. Top, Total IOL specimens (n = 16,624). Bottom, Foldable IOLs in human globes obtained postmortem (n = 1,109). Arrow indicates transfer of our center to Charleston, SC, in 1988.

much larger clinical picture worldwide. We have correlated over the years that for every dozen or so specimens we receive in the laboratory, there are often thousands of patients suffering from these complications in the real world. Clinicians and governmental organizations should continue to closely scrutinize both established and newly marketed products and techniques so that unsafe products not be launched on the clinical market. This becomes problematic when the complications are only found after the fact, long after a product's introduction or launch, in patients who expected stellar results. We do not intend to be alarmist as we describe these various complications. However, the pathological specimens we present are clear, irrefutable evidence that these conditions exist and thus require our attention.

## I. A BRIEF PRESENTATION OF 3 SELECTED COMPLICATIONS OF MODERN KERATOREFRACTIVE AND IOL REFRACTIVE SURGERY

### FUNGAL KERATITIS AFTER LASIK AND DLK

Postoperative infection after laser in situ keratomileusis

TABLE I: POSTAPHAKIC AND PHAKIC IOL OPACIFICATIONS

1. Excessive anterior capsule opacification (ACO)
2. Silicone oil adherence to IOLs
3. Phakic posterior chamber IOL-induced cataract
4. Interlenticular opacification (ILO) of "piggyback" IOLs
5. Calcification on surface of optic of Bausch & Lomb Hydroview (B & L H60M)
6. Calcium deposits within optic of a hydrophilic "acrylic" IOL (MDR SC60B-OUV)
7. Snowflake opacification of PMMA IOL optic material 5 to 15 years postoperatively (an unexpected late degradation of PMMA)
8. Posterior capsule opacification (PCO)

IOL, intraocular lens; MDR, Medical Developmental Research; PMMA, poly(methyl methacrylate).

(LASIK) is relatively rare, partly because the corneal epithelial layer is kept relatively intact. However, when it occurs, it may be a serious and potentially sight-threatening complication. Post-LASIK infection can resemble or, as we note here, can evolve from diffuse lamellar keratitis (DLK), an idiopathic, presumed sterile inflammatory condition affecting the corneal interface after lamellar surgery. Accurate diagnosis is imperative because DLK and infectious keratitis require different treatment regimens.

We have recently reported cases of 3 patients who developed interface fungal infection following LASIK and DLK.<sup>3</sup> Culture and pathological analysis revealed *Candida albicans* in all 3 cases. Figure 2 shows a clinical photograph (Fig 2 top left), a light photomicrograph (Fig 2 top right), and an electron photomicrograph (Fig 2 middle) from the right eye of one of the patients, who had the corneal flap lifted, removed, and submitted to pathological analyses. Common features in all 3 cases were (1) early onset of DLK followed by intensive corticosteroid and

antibiotic treatment and (2) later onset of interface fungal infection. All cases resolved and good vision was restored after medical treatment with antifungal agents. It is difficult to determine whether the fungal infections were the result of original LASIK surgery, or whether they represented secondary superinfections associated with treatment of the nonspecific inflammatory response (DLK) with topical corticosteroid and antibiotic regimen, or both. It is very important that clinicians report their experience with DLK (and other complications) in the hope that definite causes can be detected and that prevention and cures can be attained.

#### FUCHS' DYSTROPHY AND LASIK

It has been speculated whether excimer laser treatment could lead to endothelial cell loss. Creation of long wavelength fluorescent radiation with absorption of energy by deep tissues, acoustic and shock waves generated by

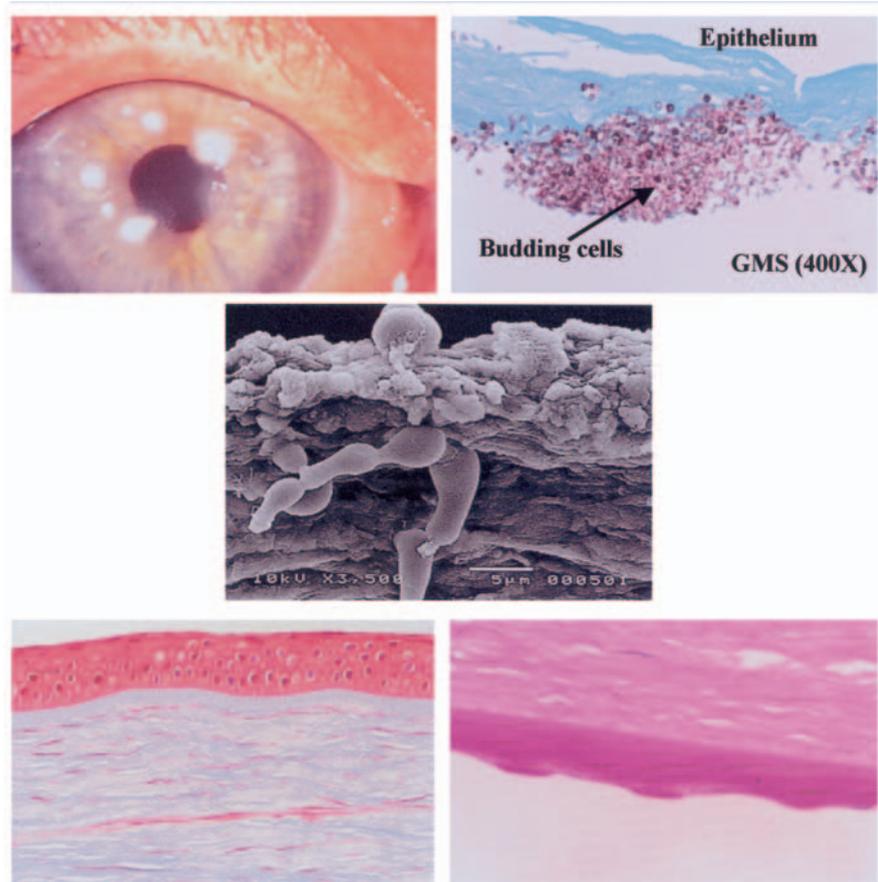


FIGURE 2

Complications after LASIK. Top left, Slit-lamp biomicroscopy 6 weeks post-LASIK, prior to surgical amputation of corneal flap from 1 of 3 patients with fungus keratitis. Dense infiltration with superficial ulceration of corneal flap was noted. Top right, Amputated flap of patient shown at left. Budding yeasts, hyphae, and pseudohyphae were confirmed (Grocott's methenamine–silver nitrate, original magnification x400). Middle, Scanning electron microscopic examination showing posterior surface of flap interface presented at top right reveals multiple budding and hyphae-forming cells (original magnification x75). Bottom left, Cornea of 48-year-old patient after LASIK. Red line shows normal flap interface (Masson's trichrome, original magnification x100). Bottom right, Cornea (same patient as in middle) showing severe endothelial cell loss with guttata formation (Fuchs' dystrophy) (PAS, original magnification x400).

ultra-short energy pulses, and resonance created by pulse repetition have all been implicated. In cases of LASIK, the role of the microkeratome and increased intraocular pressure must also be considered. Other factors that could influence the amount of damage include flap thickness, hyperopic versus myopic treatment, and type of beam or spot size. These factors affect the depth of tissue penetration and the location of energy application.

We recently reported a case of a 58-year-old woman who underwent LASIK in spite of a presurgical observation that she had moderate Fuchs' dystrophy.<sup>4</sup> Fourteen months postoperatively the patient had a corneal transplant because of visual loss in the left eye secondary to severe corneal decompensation. Histopathological evaluation of this corneal button revealed a slightly increased keratocyte population along the interface without significant new collagen formation (Fig 2 bottom left). The photomicrograph of Descemet's layer shows almost total endothelial cell degeneration, with an absolute decrease in number of endothelial cells (Fig 2 bottom right). The focal thickenings or excrescences of Descemet's membrane (guttata) are, of course, indicative of the preexisting Fuchs' dystrophy.

Regardless of the mechanism of injury, this case again elevates the question, still unanswered, about the possibility of endothelial damage after LASIK. A treatment as noted here may bring patients with Fuchs' dystrophy to the requirement for corneal transplantation earlier than otherwise might have been necessary, if at all. This should be considered when operating on eyes with even minimal or trace guttata.

#### CATARACT FORMATION AFTER PHAKIC POSTERIOR CHAMBER INTRAOCULAR LENS IMPLANTATION

The possibility of crystalline lens damage with subsequent formation of anterior subcapsular opacities probably represents the most controversial issue of phakic posterior chamber (PPC) IOL implantation.<sup>5-11</sup> The anterior subcapsular opacities that have been described with various PPC-IOLs are based on A-cell proliferation. The fibrotic response that may be caused by metaplasia of the anterior lens epithelium is what determines the degree of anterior capsular "thickening" following implantation of a PPC-IOL, which by definition rests in close proximity to (or on) the anterior surface of the crystalline lens.

We have had the opportunity to examine 3 Chiron-Adatomed silicone PPC lenses, all explanted because of late postoperative anterior subcapsular cataracts with visual loss.<sup>7</sup> Although these lenses have been withdrawn from the market, that study allowed us to clearly describe what *not* to do in the manufacture of PPC-IOLs. The lenses were well polished, but too thick, especially at the optic edge. We experimentally reimplanted one of the explanted IOLs in cadaver eyes and reviewed them from the anterior

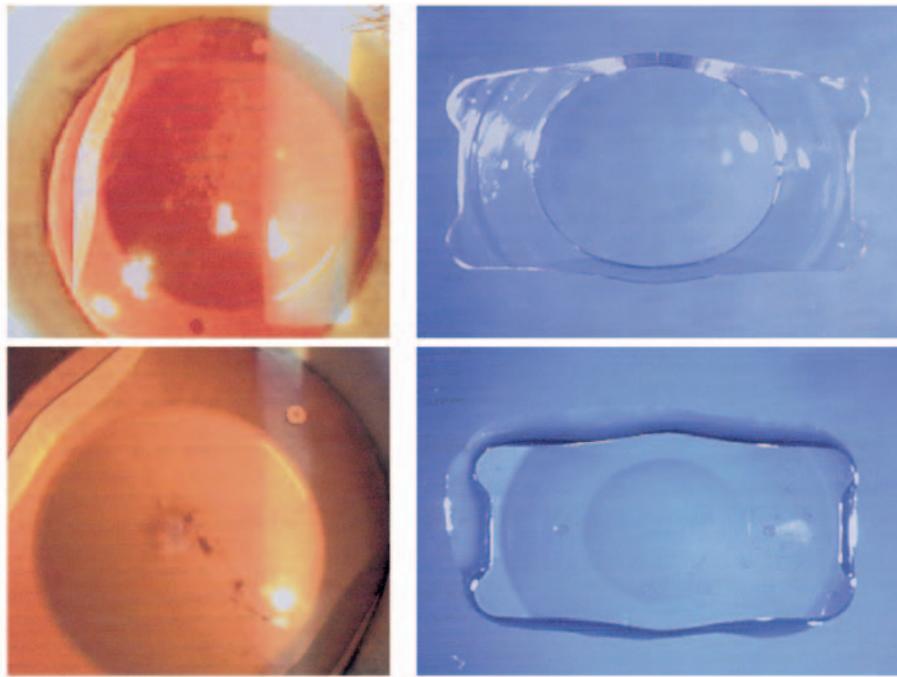
view (surgeon's perspective), from the posterior aspect (Miyake-Apple technique) as well as a side (sagittal) view. This lens had zonular fixation; it was virtually impossible to achieve true ciliary sulcus fixation as purported for this lens design. It was in contact with both the posterior surface of the iris and the anterior surface of the crystalline lens.

The modern Staar (Monrovia, California) PPC-IOL (the implantable contact lens, or ICL) seems not to be immune to this complication.<sup>9-11</sup> We have recently received a pair of these lenses, explanted by Dr Paul Koch (Warwick, Rhode Island) from a 47-year-old white woman.<sup>10</sup> The patient presented with anterior subcapsular opacities, as well as age-related cataract associated with decreased visual acuity and glare, requiring explantation 13 months after the primary procedure. Clinical and gross photographs of the explanted lenses relative to this case, are presented in Fig 3.

Several cases of cataract formation associated with PPC-IOLs have been well documented in the literature.<sup>5-11</sup> Most investigators have attributed this complication to the lack of enough space between the PPC-IOL and the crystalline lens. Nevertheless, other factors may be involved in the cataractogenesis process, such as surgical trauma and direct or indirect IOL-related factors, including continuous or intermittent contact between the phakic lens and the crystalline lens, and/or subclinical inflammation and metabolic disturbances of the crystalline lens. The incidence of cataract formation after PPC-IOL implantation varies considerably in the various reports available in the literature. Different studies cannot be compared because of many factors. First, great variation is observed regarding the age of the patients at implantation and the follow-up period. In many studies, the patients included were implanted with successive models of the same PPC-IOL design, as the previous models were considered obsolete.

PPC-IOL implantation appears to be an effective method for correcting moderate to high myopia, hyperopia, and also extreme myopia, when compared to methods such as LASIK (bioptic procedure).<sup>12-17</sup> Improvements in power calculation of the lenses are needed in order to increase the predictability of the refractive outcome. A method more accurate than the white-to-white distance is also required for determining the lens overall diameter. Adequate IOL sizing will help reduce the incidence of complications such as cataract and lens decentration. Although new PPC-IOL designs, such as the Staar ICL, seem to perform better in relation to cataract formation than the earlier Fyodorov and Chiron-Adatomed lenses, this still is an important issue with PPC-IOLs.<sup>6,8,9</sup> Long-term, standardized clinical studies will determine the safety of this technique for refractive correction.

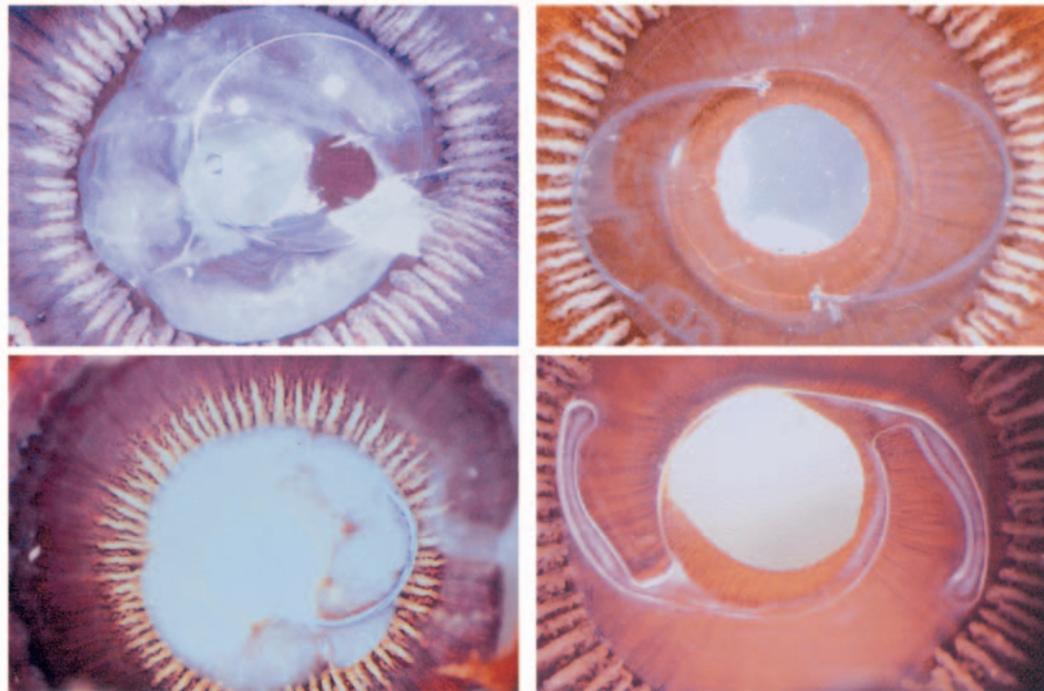
We would recommend that surgeons, when explanting these IOLs with associated cataract, save and submit not only the IOL, but also the capsulorhexis and any adjacent tissue from the crystalline lens behind it. There is



**FIGURE 3**

Top and bottom left, Retroillumination photographs from a bilateral case of anterior subcapsular cataract taken 13 months after ICL. Top and bottom right, Explanted ICLs currently being analyzed in our laboratory.

*Courtesy Paul Koch, MD, Koch Eye Surgicenter, Inc, Warwick, Rhode Island.*



**FIGURE 4**

Gross photographs of pseudophakic human globes obtained postmortem, taken from behind (Miyake-Apple posterior view), showing marked variation in posterior chamber IOLs implanted in early 1980s, as compared to present (2001). Top left, Three-piece PMMA posterior chamber IOL implanted in early 1980s. This J-loop IOL is asymmetrically implanted with 1 haptic in capsular bag and other extending back to pars plicata. Note marked decentration with edge of optic and a positioning hole within pupillary aperture. Also note extensive secondary cataract (PCO) that required posterior capsulotomy. Top right, Three-piece Alcon AcrySof IOL with excellent fixation, centration, and total clarity of media, an excellent result (circa year 2000). Bottom left, Three-piece PMMA posterior chamber IOL implanted in mid-1980s, with malfixation, marked decentration, and extensive peripheral and posterior capsule opacification. Bottom right, One-piece acrylic IOL showing excellent centration and clarity of media with perfect symmetric in-the-bag fixation. There is slight contact of iris at upper left edge of IOL optic, but otherwise this represents an excellent result.

virtually no available pathological information on the nature of the post-PPC-IOL-related anterior subcapsular cataract, and pathological studies would be very helpful, for example, in differentiating surgeon-induced versus IOL-induced secondary cataracts.

## 2. COMPLICATIONS OF INTRAOCULAR LENSES, WITH SPECIAL REFERENCE TO VARIOUS POSTOPERATIVE OPACIFICATIONS

### POSTERIOR CAPSULE OPACIFICATION

We recently reported the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy rate of 8 rigid and foldable IOL designs in a series of 5,416 pseudophakic human eyes obtained postmortem, accessioned in our Center between January 1988 and January 2000.<sup>15</sup> This study helped us identify factors that are instrumental in reducing the incidence of posterior capsule opacification (PCO, secondary cataract) and hence the need for Nd:YAG laser posterior capsulotomy (Table II).

TABLE II: 6 FACTORS TO REDUCE THE INCIDENCE OF PCO

#### SURGERY-RELATED FACTORS ("CAPSULAR" SURGERY)

1. Hydrodissection-enhanced cortical clean-up
2. In-the-bag fixation
3. Small CCC diameter slightly smaller than that of IOL optic. This places the CCC edge on anterior surface of optic and helps sequester capsular bag. This creates a "shrink wrap" of capsule around IOL optic.

#### IOL-RELATED FACTORS

1. Biocompatible IOL to reduce stimulation of cellular proliferation
2. Maximal IOL optic-posterior capsule contact, angulated haptic, "bioadhesive" biomaterial to create a "shrink wrap"
3. IOL optic geometry square, truncated edge

CCC, continuous curvilinear capsulorrhexis; IOL, intraocular lens; PCO, posterior capsule opacification.

The Miyake-Apple posterior photographic technique was used to identify the presence or absence of Nd:YAG laser capsulotomy orifice on the posterior capsule of each eye. The Nd:YAG laser posterior capsulotomy rate (%) as of January 2000 was documented.

Relatively high Nd:YAG laser posterior capsulotomy rates, ranging from 20.3% to 33.4%, were noted with 4 relatively older designs (high incidence of implantation between 1988 and the early 1990s). Four modern foldable IOLs manufactured from silicone and acrylic materials had significantly lower Nd:YAG posterior capsulotomy rates, ranging from 0.9% to 17.1%. The difference in Nd:YAG rates among the 8 IOL designs was found to be significant ( $P < .0001$ , chi-square test). Comparing foldable versus rigid designs, the foldable IOLs were associated with a much lower Nd:YAG laser posterior capsulotomy rate (14.1% versus 31.1%).

We have demonstrated that the noteworthy reduction of Nd:YAG rates toward single digits is possible if one follows basic principles being essential to PCO reduction, namely (1) to improve cellular-cortical removal, decreasing the incidence of Soemmering's ring formation, and (2) to ensure a barrier effect if residual and potentially migratory cells are still present. These principles are embodied in the 6 factors we have identified (Table II), 3 surgical factors and 3 IOL-related factors, the latter present in some modern lens designs (Fig 4). By use of the 6 factors identified in those analyses, we strongly believe that the overall incidence of PCO, and hence the incidence of Nd:YAG laser capsulotomy, is now available to bring these rates down to single digits. Careful application and use of these tools by surgeons can genuinely lead in the direction of virtual eradication of secondary cataract, the second most common cause of visual loss worldwide.<sup>19-26</sup>

### OPACIFICATION BASED ON CALCIFICATION ON OR WITHIN THE OPTIC OF 2 MODERN FOLDABLE IOL DESIGNS

#### *Bausch & Lomb Hydroview (H60M)*

Significant deposition of crystalline material on the surface of IOLs is uncommon. It has been reported to occur intraoperatively during cataract surgery with implantation of silicone IOLs, or in the early postoperative period after implantation of hydrogel IOLs. The deposits described in those studies were composed of calcium hydroxyapatite, and the hypothesized pathogenic mechanisms involved an oversupply of calcium/phosphate from intraocular solutions used during cataract surgery.<sup>27-31</sup>

We have recently received in our Center 6 explanted Hydroview lenses for pathological analyses.<sup>32-36</sup> The Bausch and Lomb Surgical (Rochester, New York) Hydroview IOL is a foldable hydrogel posterior chamber design that has been implanted for several years in international markets; over 400,000 have been implanted worldwide. However, although it was cleared for marketing in November 1999 by the US Food and Drug Administration (FDA), it has not yet been launched for general implantation in this country.

In each case, the lens has been explanted owing to deposition of crystalline material on its optical surfaces associated with decrease in visual acuity and glare, in the late postoperative period. The explanted lenses were sent to our Center for pathological, histochemical, and ultrastructural evaluation.

At the time of explantation, the age of the patients (2 women and 4 men) ranged from 70 to 85 years. Two patients were being treated for cardiovascular diseases, 2 were diabetic, and the other 2 were otherwise healthy. One of the lenses was explanted in Australia, 4 in Sweden, and 1 in Canada. All lenses were explanted at least 1 year

after the primary procedure owing to opacification observed at the level of the optics, associated with decrease in visual acuity and significant glare. The surgeons described the findings as a “brown granularity” or “small red corpuscles” present on both external optical surfaces of the lenses. In some cases, the optic of the lenses was almost completely covered by those structures, giving them a “frosty” and very reflective appearance. Nd:YAG laser was performed in all cases in an attempt to clean the optical surfaces, without success.

Once received in our Center, the IOLs were immediately placed in 4% formaldehyde in 0.1 M phosphate buffer, pH 7.4. Care was taken to avoid any manipulation of the IOLs’ optics with forceps or other grasping instruments. Some lenses were bisected for explantation, and only half of them were available to us.

Gross (macroscopic) analysis of the explanted IOLs was performed, and gross pictures were taken using a camera (Nikon N905 AF, Nikon Corporation, Tokyo, Japan) fitted to an operating microscope (Leica/Wild MZ-8 Zoom Stereomicroscope, Vashaw Scientific, Inc, Norcross, Georgia). The unstained lenses were then microscopically evaluated and photographed under a light microscope (Olympus Optical Co Ltd, Japan). They were then rinsed in distilled water, immersed in a 1% alizarin red solution (a special stain for calcium) for 2 minutes, rinsed again in distilled water, and reexamined under the light microscope.<sup>37</sup> Staining with alizarin red was also performed in 1 additional Hydroview, explanted owing to IOL malposition, to be used as a control.

We then performed full-thickness sections through the optic of 2 explanted Hydroview lenses and the control Hydroview explanted lens. The resultant cylindrical blocks were dehydrated and embedded in paraffin. Sagittal sections were performed and stained using the von Kossa method for calcium (staining with nitrate solution for 60 minutes; exposure to a 100-W lamp light; rinsing with distilled water; reaction with sodium thiosulfate solution for 2 minutes; rinsing with distilled water; counterstaining in nuclear fast red solution for 5 minutes). Calcium salts stain dark brown with this technique.

One lens was air-dried at room temperature for 7 days, sputter-coated with aluminum, and examined under a JEOL JSM 5410LV scanning electron microscope (SEM). This specimen was further analyzed by Dr. D. G. Dunkelberger (Electron Microscopy Center of the University of South Carolina, Columbia) under a Hitachi 2500 Delta SEM equipped with a Kevex x-ray detector with light element capabilities for energy dispersive x-ray analyses (EDS).

Gross and microscopic evaluations of all of the explanted Hydroview lenses had almost identical findings (Fig 5). By gross evaluation, the presence of the deposits

on their optical surfaces was noted to cause different degrees of IOL haze/opacification, directly proportional to the amount of deposits and the surface of the lenses covered by them.

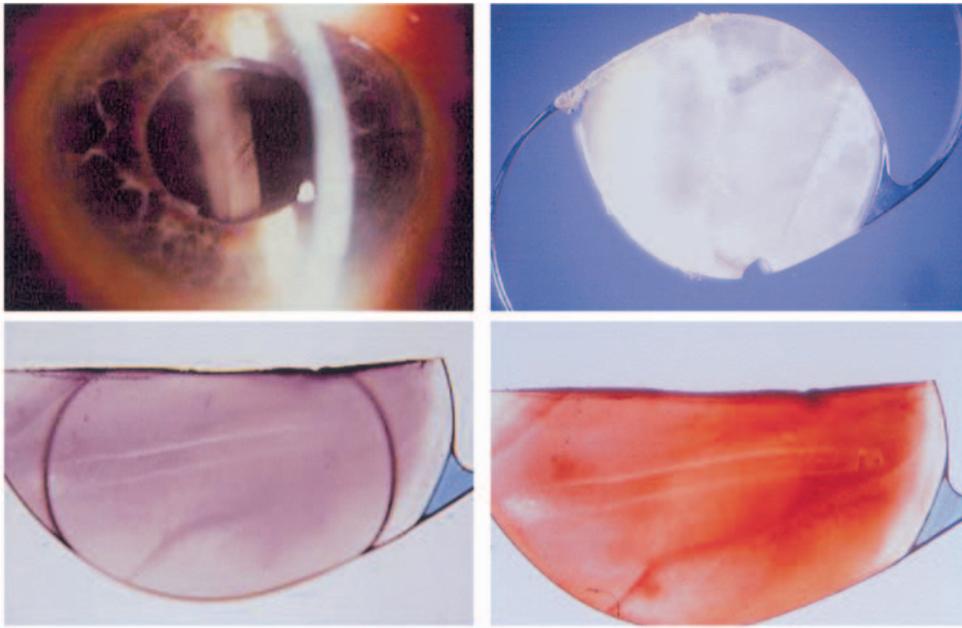
The surfaces of the unstained IOLs were covered by a layer of irregular granular deposits, composed of multiple fine, translucent spherical-ovoid granules. The deposits occurred on both anterior and posterior IOL optic surfaces, but not the haptics. In some cases, both surfaces were almost completely covered by a confluent granular layer, whereas in other cases some intervening clear areas were observed. Also, intervening clear areas, probably corresponding to marks caused by forceps during the folding process, were observed in all lenses. These areas were, however, not completely clear, and in high magnification they presented a layer of few, scattered, small round granules. Multiple pits related to Nd:YAG laser treatment were observed on the posterior surface of the IOLs in all cases. The deposits on the surfaces of the IOLs stained positive with alizarin red in all cases. In the areas presenting scattered, small granules, it was observed that only the deposits themselves stained red, while the IOL surface itself was not stained. No positive staining was observed on the haptics of the IOLs. Staining of the control Hydroview lens was also negative.

Sagittal histologic sections through the optic of 2 Hydroview lenses, stained using von Kossa’s method, showed a continuous layer of dark brown, irregular granules on the anterior and posterior optical surfaces and the edges of the lenses. Staining of the control Hydroview lens using the same method was negative. EDS performed on the deposits demonstrated the presence of peaks of calcium and phosphate.

After completion of these analyses, we received 7 other explanted Hydroview lenses in our Center, 3 from Dr. J. P. Gravel (Canada), 2 from Dr. A. Öhrström (Sweden), 1 from Dr. A. Apel (Australia), and 1 from Dr. J. Sher (Canada). The surgical, clinical, and pathological features of these cases were similar to those described above.

#### *Medical Developmental Research SC60B-OUV*

The other hydrophilic IOL (termed a hydrophilic acrylic IOL style) to be recently associated with clinically significant postoperative opacification within the optic is a one-piece design. The source of the polymer was Vista Optics, United Kingdom; the manufacturer and distributor is Medical Developmental Research (MDR Inc, Clearwater, Florida). Chang and associates<sup>38</sup> have reported 1 case of clouding and fogging of this IOL design. They noted an opacification associated with significant visual loss that occurred 7 months after uneventful lens implantation. This was a clinical report without explantation. Prior to



**FIGURE 5A**

Analyses of opacified Hydroview lenses. Top left, Slit-lamp photograph of patient implanted with Hydroview IOL showing a granularity present on anterior surface of lens. Imprints of folding/holding forceps can be observed (courtesy Arne Öhrström, MD, Vasteras, Sweden). Top right, Gross photograph showing 1 of the Hydroview IOLs explanted owing to optical opacification and accessioned in our Center. Bottom left, Photomicrograph of another Hydroview from our collection. Granular deposits can be observed covering optical surface of lens. Linear, parallel marks correspond to forceps imprints (original magnification x40). Bottom right, Photomicrograph (same case as in bottom left) showing deposits on surface of lens stained positive with alizarin red, indicating presence of calcium salts (alizarin red stain, original magnification x40).



**FIGURE 5B**

Analyses of opacified Hydroview lenses. Top left, Photomicrograph showing sagittal section of lens optic of opacified Hydroview. Lens material itself was dissolved during preparation for histological examination, but lens optic surface is delineated by a continuous layer of dark brown, irregular granules composed of calcium salts (von Kossa's stain, original magnification x200). Top right, Photomicrograph showing optic surface of another Hydroview lens covered with confluent layer of granules, while haptic (blue PMMA) is clear (original magnification x100). Bottom left, Scanning electron photomicrograph (SEM) from anterior optical surface of another Hydroview lens showing deposits, which are composed of multiple globules of variable sizes (Bar = 50  $\mu$ m). Bottom right, Energy dispersive x-ray (EDS) spectrum from Hydroview lens showed in bottom left. Note presence of important peaks of calcium and phosphate (arrows) at level of granular deposits.

our study, there have been no detailed clinicopathological analyses other than a brief preliminary report we recently published in a non-peer reviewed journal (Apple DJ, Werner L, Pandey SK. Opacification of hydrophilic acrylic intraocular lenses. *Eye World* 2000;5[9]:57).

We present the analyses of 9 explanted IOLs manufactured by MDR performed in our Center.<sup>39,40</sup> All of the accessioned lenses were model SC60B-OUV, the same model in Chang's report. It is a one-piece foldable design manufactured from a 28% hydrophilic material. All of the lenses were explanted because of late postoperative opacification of the lens optic associated with decreased visual function. We analyzed the clinical, pathological, histochemical, ultrastructural, and spectrographic features of these cases and tried to ascertain the nature of the intralenticular deposits.

All of the 9 lenses analyzed were implanted and explanted by the same surgeon, Mahmut Kaskaloglu, MD, from the Ege University, Alsancak Izmir, Turkey.<sup>39</sup> Two patients had diabetes, but the majority of patients did not have any known associated systemic or ocular conditions. In general, the patients returned around 24 months after the surgery complaining of a significant decrease in visual acuity (from 20/20 after the primary procedure to 20/50). The clinical characteristics of the SC60B-OUV lenses were different from the previously described "granularity" covering the optical surfaces of the Hydroview design. The clinical appearance of the SC60B-OUV lenses was that of a clouding similar to a "nuclear cataract." The lenses were explanted from 14 to 29 months postoperatively ( $24.42 \pm 5.12$ ). At the time of explantation, the ages of the patients ranged from 62 to 77 years ( $70.28 \pm 5.76$ ).

The analyses of the SC60B-OUV lenses followed the same protocol as described for the Hydroview lenses (Fig 6).<sup>32</sup> Gross and microscopic evaluations demonstrated that the optical surfaces and the haptics of the SC60B-OUV lenses were free of any deposits. However, there were multiple small structures initially noted to resemble "glistenings" within the central 5 mm of the IOL optical component. These were found to be the cause of each lens opacification. The edges of the optics and the haptics appeared clear. Alizarin red staining of the surfaces of all lenses was negative. This stain was likewise negative on the optical surfaces and haptics of the control IOLs.

Analysis of the cut sections (sagittal view) of the lens optics revealed multiple granules of variable sizes in a region beneath the external anterior and posterior surfaces of the IOLs. The granules were distributed in a line parallel to the anterior and posterior curvatures of the optics. They stained positive with alizarin red. Sagittal histological sections stained with the von Kossa method also confirmed the presence of multiple dark brown-black granules mostly concentrated in a region immediately

beneath the anterior and posterior optical surfaces.

SEM analysis of a cut section (sagittal view) of the IOL optic confirmed that the region immediately subjacent to the IOLs' outer surfaces, as well as the central area of the optical cut section, was free of deposits. This also revealed the presence of the granules in the intermediate region beneath the anterior and posterior surfaces. EDS performed precisely on the deposits in the same section revealed the presence of calcium peaks. The central area of the optical cut section where no granules were present served as a control, showing only peaks of carbon and oxygen.

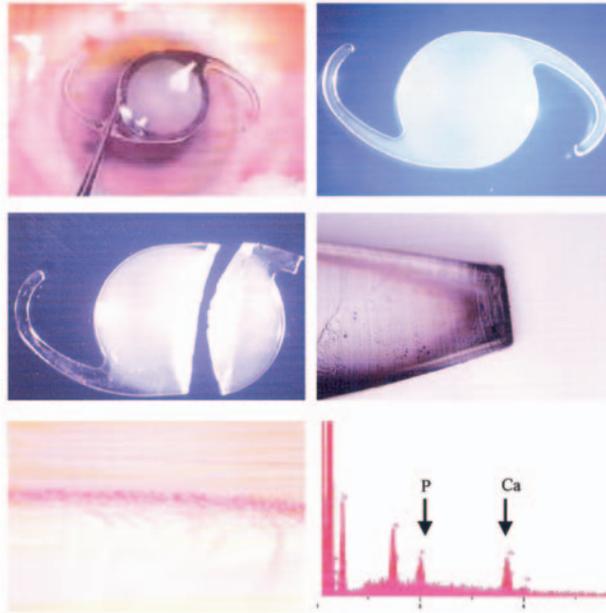
Burkhard Dick, MD, University of Mainz, Germany, has studied explants of this IOL model and has noted that the opacification within the optics may be related to the presence of unbound ultraviolet absorbers (monomers).<sup>41</sup> We have not yet done studies to verify Dick's findings that unbound UV-absorber monomers or any impurity causes opacification within the IOL optic. These findings and the calcification process demonstrated by us may be correlated, although our data does not allow us to make definitive conclusions.

### **3. SNOWFLAKE OR LATE DEGENERATION OF POLY(METHYL METHACRYLATE) POSTERIOR CHAMBER IOL OPTIC MATERIAL**

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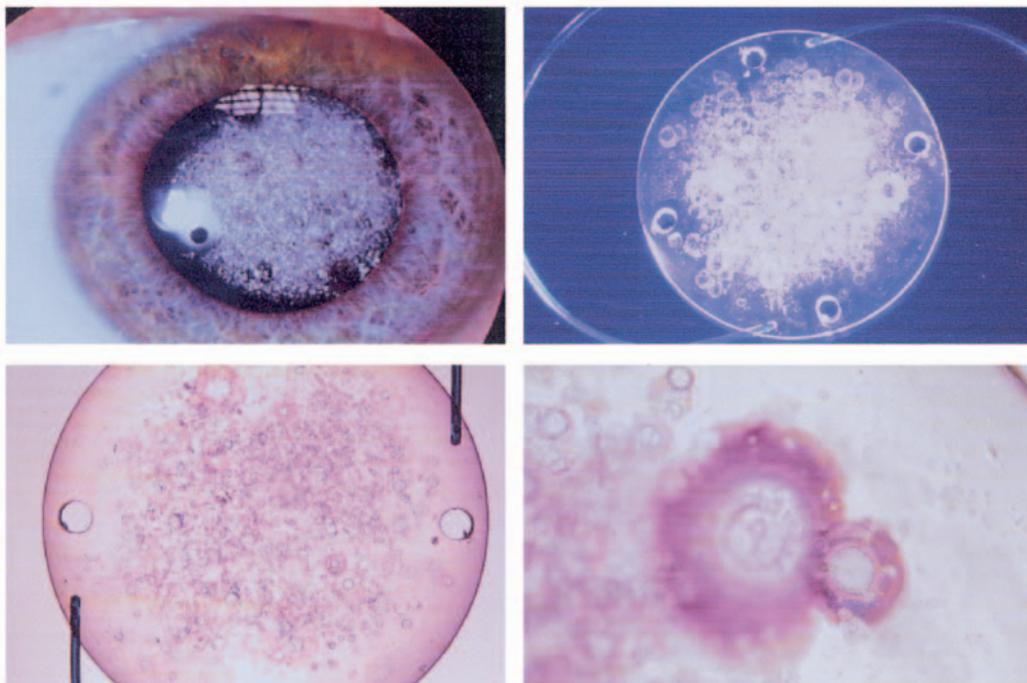
By the late 1980s most surgeons and researchers had not only concluded that poly(methyl methacrylate) (PMMA) was a safe biomaterial but also had confidence in the various manufacturing techniques required for lens fabrication.<sup>42,43</sup> Indeed, until recently, after examination of over 17,000 IOL-related specimens in our Center over a 19-year period from 1982 to the present, we had not documented any instances of PMMA-optic material alteration or breakdown. However, beginning with a gradual accumulation of anecdotal reports in the mid-1990s, culminating in a rapid accumulation of cases accessioned in our laboratory, we document in this report a series of cases characterized by a gradual and sometimes progressive late postoperative alteration or destruction of PMMA optic biomaterial.<sup>44</sup>

All of the 24 cases documented here are 3-piece PC-IOLs with rigid PMMA optical components and blue polypropylene or extruded PMMA haptics. The majority were IOPTEX and Surgidev models. Most had been implanted in the 1980s to early 1990s, and the clinical symptoms occurred late postoperatively, sometimes more than a decade after the implantation. Sixteen of the 24 cases were submitted as clinical histories and photographs. In 8 cases IOLs that had to be explanted because of visual aberrations or glare and progressive decrease in visual acuity were submitted with clinical histories and photographs provided by the explanting surgeons. These



**FIGURE 6**

Analyses of opacified SC60B-OUV lenses. Top left, Gross photograph taken immediately after lens explantation. Opacification is observed in central 5 mm of optic, while edge and haptics are transparent (courtesy Mahmut Kaskaloglu, MD, Ege University, Alsancak Izmir, Turkey). Top right, Gross photograph from another lens explanted by Dr Kaskaloglu showing total opacification. Middle left, Gross photograph from SC60B-OUV lens explanted by Dr Nitin Anand (Luton, United Kingdom). The opacified optic was bisected for pathological analysis. Middle right, Photomicrograph of 1 cut section of lens optic showing distribution of deposits within its substance (unstained, original magnification x40). Bottom left, Deposits shown in middle right stain positive with alizarin red (alizarin red stain, original magnification x200). Bottom right, Energy dispersive x-ray (EDS) spectrum from another opacified SC60B-OUV lens. Note presence of calcium (Ca) and phosphate (P) peaks (arrows) at level of granular deposits.



**FIGURE 7**

Examples of snowflake lesions within PMMA lenses. Top left, Clinical photograph of eye containing early PMMA IOL showing snowflake degradation. Top right, Gross photograph of rigid three-piece PMMA lens affected with snowflake degradation, demonstrating that most of involvement is within central core of lens optic, with sparing of outer periphery of optic. Bottom left, Three-dimensional light photomicrograph of another three-piece PMMA lens showing snowflake opacities. Bottom right, High-power three-dimensional light photomicrograph of same lens as in bottom left, showing individual snowflake lesions. There is an empty central space containing few particles of PMMA convoluted material (fragmented PMMA) surrounded by dense outer pseudocapsule.

lenses were also analyzed in our Center according to the protocol previously described.

The optics of the 8 explanted lenses had almost identical findings except for the degree of involvement (Fig 7). The common finding in all cases was the presence of the roughly spherical snowflake lesion, which we interpreted as foci of degenerated PMMA biomaterial. The amount of opacification corresponded proportionally to the number and density of lesions noted. Views of the cut edges of the bisected optic specimens prepared for scanning electron microscopy confirmed that the snowflake lesions were not surface deposits but rather were all situated within the substance of the optic. The snowflake lesions were clustered most commonly in the central and midperipheral zones of the IOL optics. The outer 0.5 to 1.0 mm peripheral (equatorial) rims of the lens optics were generally less involved or free of opacification. The lesions were usually focal and discrete, with intervening clear areas, but some did appear to coalesce. They generally involved the anterior one third of the optic's substance. Histochemical and spectroscopic analyses were negative, indicating no infiltration of exogenous material.

We suggest that manufacturing variations in some lenses fabricated in the 1980s to early 1990s, especially some made with a molding process (specifically, the cast molding process of the IOPTEx Research IOLs), may be responsible. It is highly likely that the late PMMA destructive process is facilitated by long-term ultraviolet (UV) exposure. This is supported by 2 pathologic observations. First, many opacities have been indeed clustered in the central zone of the optic, extending to the midperipheral portion but often leaving the distal peripheral rim free of opacities. Furthermore, the opacities are present most commonly and intensely within the anterior one third of the optic's substance stratum that is the first to be a recipient of UV radiation as it enters the lens. These observations would support the hypothesis that the slow and sometimes progressive lesion formation noted here might relate to the fact that the IOL's central optic is exposed to UV radiation over an extended period, whereas the peripheral optic may be protected by the iris. Since the anterior strata of the optic are the first to encounter the UV light, this might explain why the opacities are seen more frequently in this zone.

The emergence of this complication could have represented a true disaster, except for the fact that many of the patients implanted with these IOLs are now deceased. However, there are probably still sufficient numbers of patients living with varying stages of this complication. This necessitates that today's ophthalmologists be aware of, diagnose, and know when not to explant and/or exchange these lenses. It is important to know the nature of this syndrome in order to spare now-elderly patients and their doctors of unwarranted anxiety about the cause

of visual problems or loss and also to obviate request for unwarranted diagnostic testing.

## **DISCUSSION/CONCLUSION/SUMMARY**

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In spite of extensive hype, complications of modern kerato-IOL refractive surgery do exist. We provide examples of a new subdivision of ocular pathology: pathology of refractive surgery. Just as was done with IOL pathology, these studies will benefit patients undergoing these procedures.

In the 1980s, PC-IOLs came into vogue and underwent constant improvement; important research efforts were made to produce an "ideal" IOL to be "married" to the best possible surgical technique. During this period, we found that most IOL complications were in many ways related to problems with *fixation*.<sup>45-49</sup> Lenses and techniques designed to improve haptic fixation resulted from these efforts. Important elements of the surgical operation perfected during these early years were phacoemulsification, continuous curvilinear capsulorrhexis (CCC), and hydrodissection, among others.<sup>50</sup>

By the late 1990s, the cataract-IOL procedure had advanced to the high level that we enjoy today. Early problems caused by malfixation (eg, decentration) were almost eliminated. High-quality rigid and foldable IOLs had become available, the latter including those manufactured from silicone, acrylic, and hydrogel material.<sup>24</sup>

We believe the data related to the Nd:YAG laser posterior capsulotomy rates presented here are helpful in understanding how those 8 groups of lenses are performing in relation to PCO. To date, one cannot precisely determine the relative contribution of IOL design versus surgical techniques to the decrease of Nd:YAG rates, but this will be possible with continuing analysis, including annual updates, increasing number of pseudophakic cadaver eyes, and passage of time. The tools, surgical procedures and skills, and appropriate IOLs are now available to eradicate PCO. Continued motivation to apply the 6 factors we described will help diminish this final major complication of cataract-IOL surgery.

However, we have recently identified in 3 IOL groups new modalities of postoperative opacification after cataract surgery. Clinical details, incidence, epidemiology, and detailed case studies are described elsewhere.<sup>32,39,44</sup> The purpose of this report was to provide a clinicopathological overview of these 3 IOL groups, which represent 3 of the 8 conditions we have recently cited as causes of postaphakic and phakic IOL opacifications (Table I).

Bausch and Lomb has recently suggested that the Hydroview calcification might be attributed to problems with a silicone gasket in the packaging.<sup>35,36</sup> It has been postulated that minute amounts of silicone material may catalyze a reaction that will lead to deposition of calcium. We

have not studied this personally and await further verification and publication by the manufacturer. Because this condition takes at least 1 to 2 years to appear clinically, this amount of time must be allocated for clinical studies to truly verify whether this is the cause and its correction would be curative of this problem.

The MDR lens is manufactured in the United States in Clearwater, Florida, from polymer derived until recently from Vista Optics in the United Kingdom. To our knowledge the lens has been sold only outside of the United States, in Brazil, China, Egypt, France, Germany, Italy, and Turkey, among other countries.<sup>39,40</sup> Because this lens is apparently sold only outside of the United States, there is no possibility of the FDA oversight. However, since many countries depend on the FDA's opinion for introduction and use of such products, we feel it would be useful that changes in policy might be considered.

The third group of lenses, the rigid PMMA designs manufactured mostly in the 1980s and early in the 1990s, all represent a late postoperative complication, to our knowledge occurring mostly from 5 to 15 years after implantation. The lesions may be fairly nonprogressive, as we have noted with much of the Surgidev designs in the study, or are more progressive, leading to visual loss requiring explantation, as has been the case with some of the IOPTX lenses noted here as well as with other designs of an unknown source.<sup>44</sup> The main reason to publicize the existence of these problems now is to make the surgeon aware of this clinical pattern so that during long-term postoperative examination, one realizes what this process is. This knowledge would therefore save unneeded clinical diagnosis and testing and certainly spare the surgeon and the patient undue fear regarding these visually threatening lesions, which at first glance by clinical examination appear startling, and which in our experience present a unique appearance not described previously.

The snowflake lesions appear to be erupting now. We would suspect, on the basis of the age of these patients and the number of postoperative years, that the number of eruptions will increase and peak within the next 5 years. They will probably only recede as the patients die. It is important to emphasize that these probably represent a problem with IOL manufacture, in particular, specific molding processes used at that time, and should not represent a universal condemnation of PMMA optic biomaterial. It is also probable that some of these IOLs have been or continue to be sold to distributors in developing countries, and a knowledge of this condition will be useful to perhaps avoid this problem in some underprivileged countries.

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## DISCUSSION

DR ROBERT C. DREWS. Problems with low molecular weight PMMA have occurred before. Let me show some old slides.

In order to force PMMA molecules through a small aperture to injection mold IOLs, the chain length must be short, with a low molecular weight. Physical problems with such lenses have included warpage of one brand of injection molded intraocular lenses after they were implanted in the eye. The stress patterns inherent within injection molded lenses are easily revealed by placing the lenses between crossed Polaroid filters. Flashing and other edge finish problems have caused major chafing of the iris and other ocular tissues. Clinically, it was lenses that were injection molded from low molecular weight PMMA that first gave rise to epidemics of the UGH syndrome. Although UGH syndrome can occur with any intraocular lens, it was rare until injection molded intraocular lenses were introduced by American manufacturers

for mass production. Good finishes of this softer material were not achieved until tumble polishing was employed.

John Pearce first called attention to the myriad tiny refractile specks commonly visible by slit lamp in injection molded lenses placed in the posterior chamber. Like the specular corneal endothelial pattern, these are difficult to see at first; but, once seen, they are striking and easy to find. They are so tiny and the lighting requirements so strict to visualize them that I have never been able to photograph them. Like the "snowflakes", they absorb laser energy and make YAG capsulotomy difficult without injury to the IOL, and are one of the reasons I gave up using injection molded posterior chamber lenses, even when well finished.

The polymerization of methyl methacrylate into polymethyl methacrylate can yield chains of varying length and the final, commercial material can vary widely. The length of the PMMA chain turns out to be important. Perspex CQ (Clinical Quality), for example, has a molecular weight over 1.2 million. It is very pure and non-toxic. Its long chains are very stable, but cannot be forced through a small aperture for injection molding. It must be machined or compression molded. It is easily polished to a high finish. High molecular weight PMMA has a superb 50 year track record.

Now Drs Apple and Werner have alerted us to the appearance of "snowflakes" within the optics of IOLs presumably made from low molecular weight PMMA. They can become so dense that they make the lens opaque, another tragic long term complication. Because large numbers were exported, many eyes have been compromised.

I have 3 observations. 1) It used to be illegal to export non-FDA-approved drugs and devices. I assume it still is. 2) Whether all of these lenses were made of low molecular weight PMMA would be easy to verify by placing them between crossed polarized filters. 3) It would be interesting to look carefully in retrospect at some other injection molded PC IOLs to see whether the refractile specks found by John Pearce were early snowflakes.

I thank Drs Apple and Werner for a most interesting paper, and another cautionary lesson. The use of low molecular weight PMMA to make intraocular lenses has led to several, large scale tragedies.

[Editor's note] DR DOUGLAS D. KOCH was not as sanguine as Dr Apple that posterior capsule opacification is no longer a problem. He was involved in studies of some of the modern lenses. He found that capsule opacification may not occur for over 5 years, but it still occurs and is merely delayed. DR WOODFORD S. VANMETER asked whether modern equipment and techniques, such as low-flow, closed-circuit systems and the use of a continuous curvilinear capsulorhexis, both of which make cortical cleanup easier, might be a factor in the lower incidence of

posterior capsule opacification. DR JOHN C. MERRIAM was intrigued by the speculation that snowflake degeneration might be related to ultraviolet light exposure. He asked whether there was a difference in the number of these complications between northern and southern latitudes; he also asked if there was any experimental evidence as to what wavelengths of light were involved.

DR DAVID J. APPLE AND DR LILIANA WERNER. We thank Dr Drews for his remarks regarding our paper. His presentation makes us feel like we are the students lecturing our mentor. With the Society's permission, we would like to turn around our discussion and take this opportunity to thank Dr Drews for his efforts. Many of the achievements we have accomplished in our laboratory are based on the work by Dr Drews, who is one of the pioneers in the study of intraocular lens and cataract surgery complications, including the use of pathologic techniques and scanning electron microscopy. The studies date from as early as the late 1970's and 1980's and several are referenced here.<sup>1-14</sup>

Our work today on explants is based on the classic study of Dr Drews on explanted Barraquer implants. These lenses were implanted between 1954 and 1961 and Dr Drews reported on these in his Binkhorst Lecture of 1982 and published these in the Transactions of the American Academy of Ophthalmology 1982;89:386-393. This is the classic article on explants that we and others have taken as a model. The studies we present in this paper on various opacifications are based on these.

The poorly fabricated lenses using low molecular weight PMMA are largely things of the past, although scrutiny in areas without good oversight is still warranted to be sure that poor lenses are still not distributed. Today there should be absolutely zero tolerance with intraocular lenses, since research over the last several decades has been very thorough. Today's research is mostly one of "fine-tuning the technology;" the era of disastrous complications should be long past.

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## CURVULARIA KERATITIS\*

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BY Kirk R. Wilhelmus, MD, MPH, AND Dan B. Jones, MD

### ABSTRACT

**Purpose:** To determine the risk factors and clinical signs of *Curvularia* keratitis and to evaluate the management and outcome of this corneal phaeohyphomycosis.

**Methods:** We reviewed clinical and laboratory records from 1970 to 1999 to identify patients treated at our institution for culture-proven *Curvularia* keratitis. Descriptive statistics and regression models were used to identify variables associated with the length of antifungal therapy and with visual outcome. In vitro susceptibilities were compared to the clinical results obtained with topical natamycin.

**Results:** During the 30-year period, our laboratory isolated and identified *Curvularia* from 43 patients with keratitis, of whom 32 individuals were treated and followed up at our institute and whose data were analyzed. Trauma, usually with plants or dirt, was the risk factor in one half; and 69% occurred during the hot, humid summer months along the US Gulf Coast. Presenting signs varied from superficial, feathery infiltrates of the central cornea to suppurative ulceration of the peripheral cornea. A hypopyon was unusual, occurring in only 4 (12%) of the eyes but indicated a significantly ( $P = .01$ ) increased risk of subsequent complications. The sensitivity of stained smears of corneal scrapings was 78%. *Curvularia* could be detected by a panfungal polymerase chain reaction. Fungi were detected on blood or chocolate agar at or before the time that growth occurred on Sabouraud agar or in brain-heart infusion in 83% of cases, although colonies appeared only on the fungal media from the remaining 4 sets of specimens. *Curvularia* was the third most prevalent filamentous fungus among our corneal isolates and the most common dematiaceous mold. Corneal isolates included *C senegalensis*, *C lunata*, *C pallescens*, and *C prasadii*. All tested isolates were inhibited by 4  $\mu\text{g/mL}$  or less of natamycin. Topical natamycin was used for a median duration of 1 month, but a delay in diagnosis beyond 1 week doubled the average length of topical antifungal treatment ( $P = .005$ ). Visual acuity improved to 20/40 or better in 25 (78%) of the eyes.

**Conclusions:** *Curvularia* keratitis typically presented as superficial feathery infiltration, rarely with visible pigmentation, that gradually became focally suppurative. Smears of corneal scrapings often disclosed hyphae, and culture media showed dematiaceous fungal growth within 1 week. Natamycin had excellent in vitro activity and led to clinical resolution with good vision in most patients with corneal curvulariosis. Complications requiring surgery were not common but included exophytic inflammatory fungal sequestration, treated by superficial lamellar keratectomy, and corneal perforation, managed by penetrating keratoplasty.

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### INTRODUCTION

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Fungal infections of the eye are a growing threat that have substantial morbidity and cost.<sup>1</sup> *Aspergillus* and *Fusarium* are long recognized as ocular pathogens,<sup>2</sup> but the dematiaceous hyphomycetes have emerged as important opportunists.<sup>3-6</sup> Originally named for their tufted, floccose appearance in culture, dematiaceous fungi comprise those septate molds with melanin in their hyphae and conidia.<sup>7</sup>

\*From the Sid W. Richardson Ocular Microbiology Laboratory, Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas. Supported by a clinical investigator award (EY00377), cooperative agreement (EY09696), and core grant (EY02520) from the National Eye Institute; a senior scientific investigator award from the Research to Prevent Blindness, Inc; and the Sid Richardson Foundation.

*Curvularia* is a prevalent member of these darkly pigmented fungi that received its current name in 1933<sup>8</sup> and that is related to the sexual teleomorph *Cochliobolus*.

This genus of filamentous fungi colonizes soil and vegetation and spreads by airborne spores. Some of the 40 *Curvularia* species are phytopathogens. Plant diseases range from seedling failure to leaf blight,<sup>9</sup> including grass "fade out" during hot, humid weather. Curvularial growth on stored grain, thatch, and other dead plant material looks like smudges of blackish dust.

Several *Curvularia* species are zoopathogenic. Wound infection is the most common disease caused by *Curvularia* and ranges from onychomycosis to skin ulceration and subcutaneous mycetoma.<sup>10,11</sup> Other human *Curvularia* infections are invasive and allergic sinusitis and bronchopulmonary disease. Abscesses of the lung,

brain, liver, and connective tissue have occurred. Nosocomial infections include dialysis-related peritonitis and postsurgical endocarditis.<sup>12</sup>

Infection of the cornea, reported in 1959,<sup>13</sup> was the first human disease proved to be caused by *Curvularia*. Other ocular infections consist of conjunctivitis,<sup>14</sup> dacryocystitis,<sup>15,16</sup> sino-orbital cellulitis,<sup>17</sup> and endophthalmitis.<sup>14,18-20</sup> But the cornea is the most commonly infected site.<sup>2,3,13,14,21-88</sup> To describe the clinical spectrum and management of *Curvularia* keratitis, we reviewed our experience with this corneal phaeoophomycosis.

## METHODS

Cases of culture-positive *Curvularia* keratitis were identified by reviewing the records of our ocular microbiology laboratory for patients with keratomycosis. Patients evaluated for this study were treated and followed at the Cullen Eye Institute in Houston, Texas, between 1970 and 1999. At the initial examination, demographic and other data were recorded onto medical record forms. The diameter (d) of the stromal infiltrate was generally measured with a slit-beam reticule or eyepiece micrometer. The infiltrate area was then estimated by  $\pi d^2/4$ , rounding to the nearest 0.5 mm<sup>2</sup>. Additional information on risk factors, clinical features, laboratory data, interventions, and outcomes were collected from outpatient, hospital, photographic, microbiologic, and pathologic files and entered onto computerized spreadsheets.

Climatic information was downloaded from the online weather database provided by the National Climatic Data Center of the National Oceanic and Atmospheric Administration, US Department of Commerce. We averaged monthly data on temperatures recorded by 100 stations along the upper coast of Texas from 1970 through 1999.

Corneal scrapings were routinely smeared onto glass slides for gram, Giemsa, acridine orange, and/or calcofluor white staining and were inoculated directly onto culture media that typically included a blood agar plate, a chocolate agar plate, a thiol or thioglycolate liquid, an anaerobic medium such as *Brucella* or Schaedler agar (each incubated at 35°C), Sabouraud dextrose agar plate or slant, and brain-heart infusion (BHI) broth (both incubated at 25°C).<sup>89</sup> The minimal requirements for laboratory confirmation of *Curvularia* corneal infection were either a stained smear showing filamentous fungal elements with growth of *Curvularia* on at least 1 medium or isolation of *Curvularia* on at least 2 different primary media.

Dematiaceous fungal growth was recognized as pigmented colonies on C-streaks of primary culture media. *Curvularia* produced woolly olive-brown or black colonies, occasionally with a slate-blue sheen (Fig 1A and

1B). Rapidly growing mycelia often produced a central depression in the dark, matted colony. Slide culture showed the characteristic microscopic appearance of branched, septate, tawny hyphae and short, nodose, brown conidiophores bearing single and clustered septate conidia (Fig 1C). Speciation was based on the microscopic appearance of conidia.<sup>90,91</sup> The minimum inhibitory concentration (MIC) was determined for selected isolates with antibiotic-saturated paper discs in multiwell plates<sup>92</sup>



FIGURE 1A

Case 15. Dematiaceous fungal growth on blood agar from corneal scrapings.



FIGURE 1B

Case 15. Pigmented colonies on Sabouraud agar at several inoculation sites.



**FIGURE 1C**

Case 23. Septate hyphae and curved conidia on slide culture.

or by a broth-dilution technique.<sup>93</sup> The minimum fungicidal concentration (MFC) was determined by subcultures from the MIC microwells onto blood agar plates.

Logistic regression assessed correlations between exposure variables and both the visual outcome and the duration of antifungal treatment. Visual outcome was dichotomized based on final visual acuity better than 20/50 without surgical intervention. The breakpoint for dividing the duration of topical antifungal treatment into 2 groups was 30 days. Independent variables considered for inclusion in regression models were patient age, predisposing factor, prior corticosteroid or antibiotic use before diagnosis, duration until diagnostic evaluation, size of corneal infiltrate, and hypopyon status. Linear regression was used to explore the association of exposure variables on the duration of antifungal therapy. Regression models were performed using Stata 6.0 (College Station, Texas).

For molecular analysis, nucleic acid was extracted from culture specimen pellets with phenol:chloroform:isoamyl alcohol, precipitated with ethanol, and resuspended in tris-EDTA buffer. Fungal DNA was amplified using the polymerase chain reaction (PCR). The primer was based on the highly conserved 5.8s ribosomal RNA, internal transcribed sequence-2, and 25s rRNA regions.<sup>94</sup> Thermocycling was performed at 94°C, 58°C, and 72°C for 30 cycles. The PCR product was resolved on an agarose tris-borate-EDTA gel, visualized with ethidium bromide under ultraviolet light, and compared to positive and negative controls.

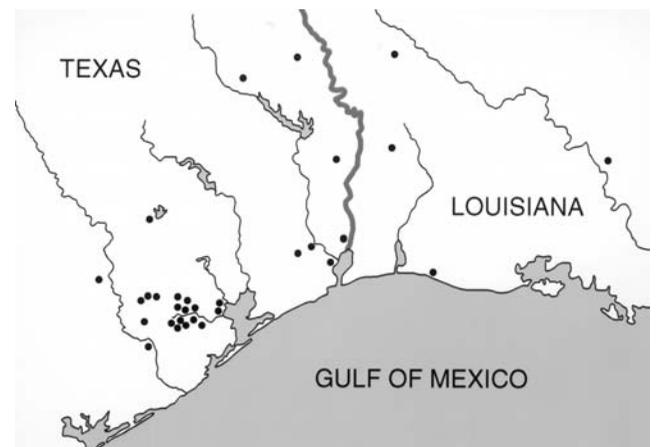
A murine model of *Curvularia* keratitis was attempted by scarifying the right cornea and applying a concen-

trated fungal inoculum using a protocol approved by our institutional animal care and use committee. Ten NIH Swiss female mice (Harlan Sprague Dawley, Indianapolis, Indiana) were used, of which 4 were pretreated with intramuscular methylprednisolone (Depo-Medrol, Pharmacia & Upjohn, Kalamazoo, Michigan) 100 mg/kg 4 days before inoculation. Following anesthesia with ketamine:xylazine:acepromazine, the cornea was scratched with a 25-gauge needle in a 6 x 6 linear grid pattern. A dark sludge of freshly grown *C lunata*, originally isolated from a human corneal infection (case 30), was prepared in phosphate-buffered saline to yield the spectrophotometric equivalent of either 10<sup>6</sup> or 10<sup>8</sup> cells per 5 mL. One of these inocula was applied to the corneal surface, and the eyelids were rubbed together. Eyes were observed daily to detect corneal inflammation and were examined histopathologically after euthanasia.

## RESULTS

### CLINICAL SUMMARY

Of 43 patients with *Curvularia* keratitis diagnosed by our laboratory, 32 were treated at our institute (Table I). All but 1 case began near the upper Texas or Louisiana coast (Fig 2). Average patient age was 43 ± 21 years, including 5 (16%) less than 12 years old. Thirty patients (94%) were males, and 20 cases (62.5%) occurred in left eyes. Sixteen (50%) involved injury with plant or dirt material. Twenty-two (69%) of the cases began during the hot, humid months of June, July, August, and September (Fig 3). Only 5 patients (16%) were correctly diagnosed as having fungal infection on their first examination. Twenty (62.5%) were initially thought to have bacterial keratitis; 2 were treated for herpes simplex virus keratitis; and 5 were first considered to have sterile or toxic inflammation. A



**FIGURE 2**

Regional map showing sites along US coast of the Gulf of Mexico where patients developed *Curvularia* keratitis.

TABLE 1: CLINICAL CHARACTERISTICS OF CASES CURVULARIA KERATITIS

CASE	YEAR	AGE	SEX	RACE	EYE	TRAUMA	INITIAL KERATITIS DIAGNOSIS	CORTICOSTEROID BEFORE DIAGNOSIS	ANTIBACTERIAL BEFORE DIAGNOSIS	DAYS UNTIL ANTIFUNGAL THERAPY	AREA (MM <sup>2</sup> ) OF CORNEAL INFILTRATE	HYPOPYON
1	1972	29	M	B	L	ND	Fungal	N	N	3	5	N
2	1973	68	M	W	L	Sawdust	Fungal	N	N	1	8	N
3	1973	48	M	W	L	Metal	Bacterial	N	Y	3	4	N
4	1973	49	M	W	L	Fingernail	Bacterial	N	Y	48	12	N
5	1974	11	M	W	R	Metal	Fungal	N	N	2	3	N
6	1976	8	M	W	R	None	Bacterial	N	Y	3	9.5	N
7	1976	24	M	H	R	Proptosis	Sterile	N	N	5	2.5	N
8	1977	8	M	W	L	Plant	Bacterial	Y	Y	9	5	N
9	1977	61	M	W	R	Sawdust	Bacterial	Y	Y	10	7.5	N
10	1977	63	M	W	L	Contact lens	Bacterial	Y	Y	14	9	N
11	1979	65	M	B	R	ND	Bacterial	N	Y	10	10	Y
12	1979	50	M	W	L	Chemical	Toxic	Y	Y	24	8	N
13	1981	50	M	H	R	Metal	Bacterial	N	Y	3	9	N
14	1981	52	M	W	L	Wood	Bacterial	N	Y	56	2	N
15	1982	51	M	B	L	Plant	Bacterial	N	Y	6	2	N
16	1984	6	F	W	L	Plant	Sterile	Y	Y	14	9	N
17	1987	26	M	B	R	Metal	Bacterial	Y	Y	3	8	N
18	1987	57	M	W	L	Dirt	Herpetic	N	Y	67	7	N
19	1987	30	M	H	R	Plant	Fungal	N	N	12	4	N
20	1988	10	M	W	R	Firecracker	Bacterial	N	Y	1	3.5	N
21	1988	57	M	W	L	Plant	Bacterial	Y	Y	10	5	N
22	1990	50	M	W	L	Radial keratotomy	Bacterial	N	Y	7	7	N
23	1990	35	M	W	L	Metal	Bacterial	Y	Y	4	9.5	Y
24	1992	62	M	W	R	Plant	Bacterial	N	Y	3	1	N
25	1992	15	M	W	L	Metal	Sterile	Y	N	2	2	Y
26	1993	60	M	W	L	Dirt	Herpetic	N	Y	10	8	N
27	1994	46	F	W	L	Metal	Bacterial	N	Y	12	9	N
28	1996	75	M	W	L	Sand	Fungal	N	N	2	16	N
29	1996	45	M	W	R	Wood	Bacterial	Y	Y	7	3.5	N
30	1998	69	M	W	R	Plant	Sterile	Y	Y	39	3	N
31	1998	33	M	H	L	Plant	Bacterial	N	Y	4	5	N
32	1999	71	M	W	L	Dirt	Bacterial	N	Y	11	27	Y

B, black; H, Hispanic; N, no; ND, not determined; Y, yes; W, white.

median of 2 days passed before patients obtained initial eye care following trauma or symptom onset, and a median of 7 days had elapsed when antifungal therapy was started. Patients with plant or dirt trauma were 4.8 (95% CI, 1.07 to 21.4) times more likely to have a delayed diagnosis greater than 1 week after onset ( $P = .04$ ). Before starting antifungal therapy, 24 patients (75%) were treated with one or more topical antibacterial agents, and 11 (34%) used a topical corticosteroid.

At the time of establishing fungal keratitis, the average  $\pm$  SD area of the corneal infiltrate was  $7 \text{ mm}^2 \pm 5 \text{ mm}^2$ . Four (12.5%) eyes had a hypopyon. Infection usually involved the center or lower half of the cornea (Fig 4). Early involvement typically presented as a feathery, superficial stromal infiltration with an epithelial defect (Fig 5). Two patients had brown pigmentation in the central portion of the infiltrate (Fig 6), although rust was a possibility in one. After the infection was established for longer than 1 week, focal necrotizing inflammation tended to

obscure the velvety edges (Fig 7). Chronic forms of *Curvularia* keratitis varied from suppurative ulceration to smoldering inflammation that seemed to be partially

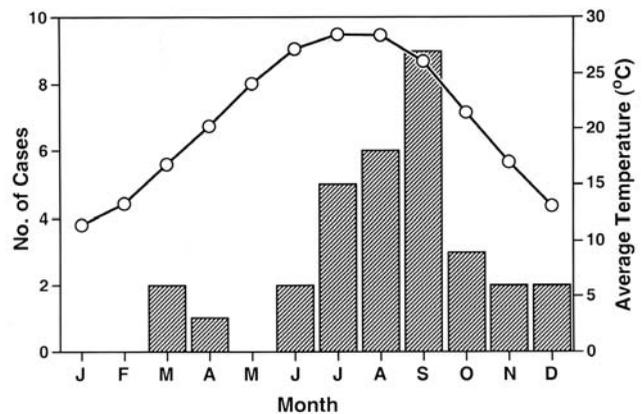
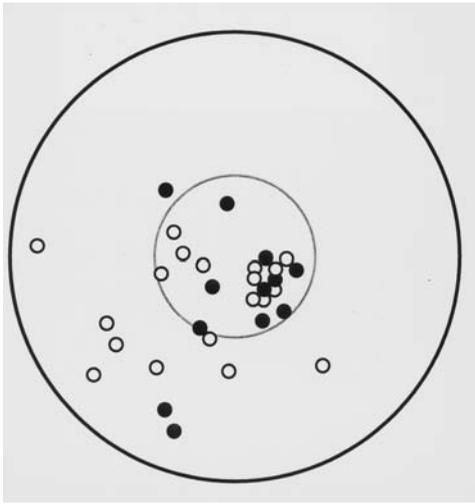
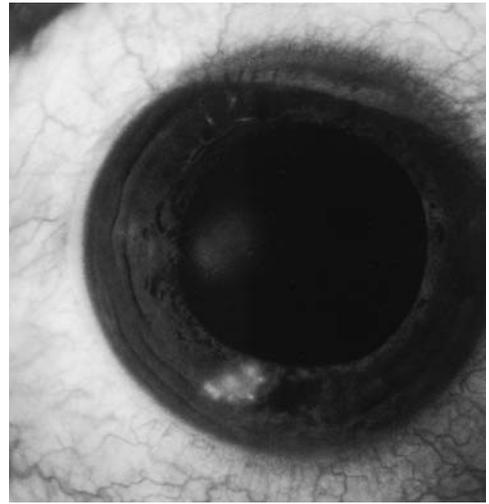


FIGURE 3 Seasonal distribution of onset of *Curvularia* keratitis (bars), compared to average temperatures of upper Texas coast (circles).



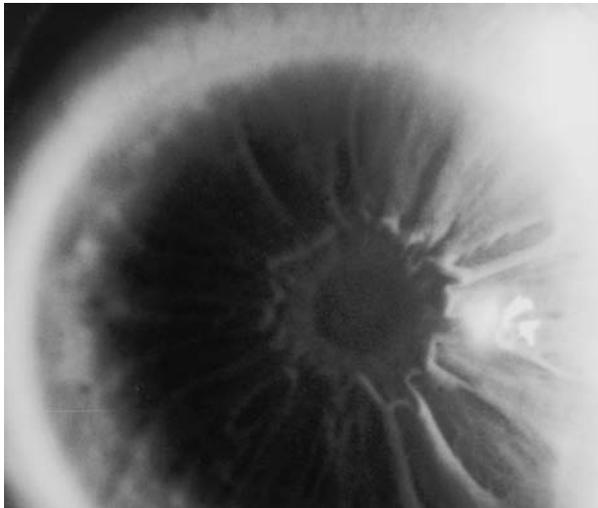
**FIGURE 4**

Topographic locations of stromal infiltrates' centers from patients with *Curvularia* keratitis. (Closed circles, right eyes; open circles, left eyes.)



**FIGURE 5A**

Case 7. *Curvularia pallescens* keratitis 5 days after onset of symptoms attributed to exposure from proptosis. (Compare Fig 5b-Fig 5g, all early infections occurring within first week of onset).



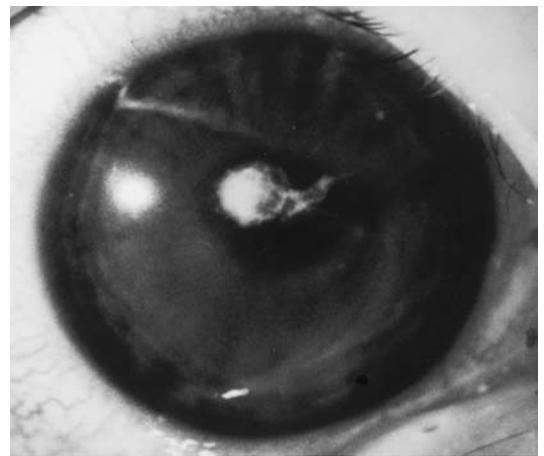
**FIGURE 5B**

Case 24. *Curvularia senegalensis* keratitis 3 days after injury to cornea while patient was using a lawn trimmer.

suppressed by topical antibacterial agents (Fig 8).

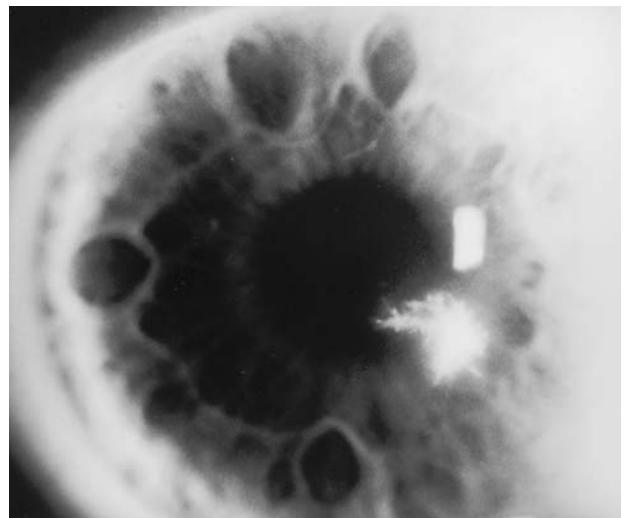
The median duration of topical antifungal therapy was 31.5 days (Table II), and the mean duration was 40 days. Topical natamycin 5% suspension was used in all but 1 patient who was treated with topical miconazole 1%. Adjunctive therapy included a second topical antifungal agent in 4 patients (3 with amphotericin B and 1 with miconazole) and oral antifungal therapy in 7 patients (4 with ketoconazole and 3 with fluconazole). A topical corticosteroid was used during antifungal therapy in 4 patients.

Corneal surgery was performed in 6 (19%) of the patients. A superficial keratectomy was performed on 3 eyes with an elevated or sequestered fibroinflammatory mass (Fig 9). Other complications included descemetocoele (Fig 10) and recrudescence from inadequate



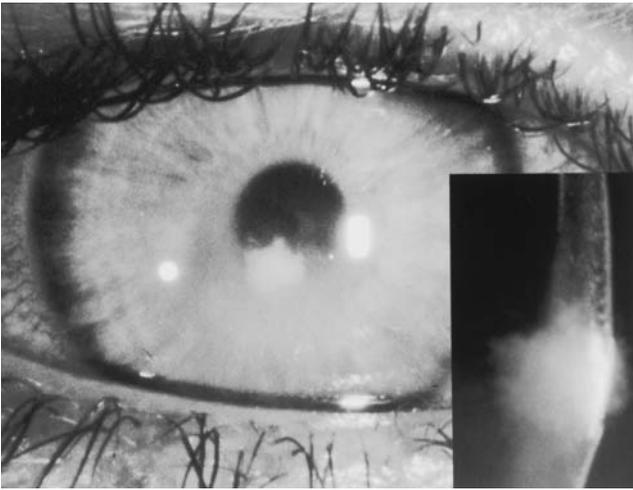
**FIGURE 5C**

Case 6. *Curvularia* keratitis 3 days after patient awoke with eye pain.



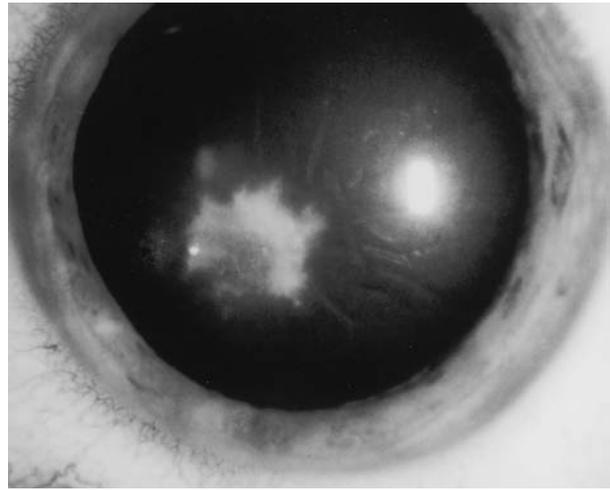
**FIGURE 5D**

Case 29. One week after onset of *Curvularia* keratitis due to a construction accident.



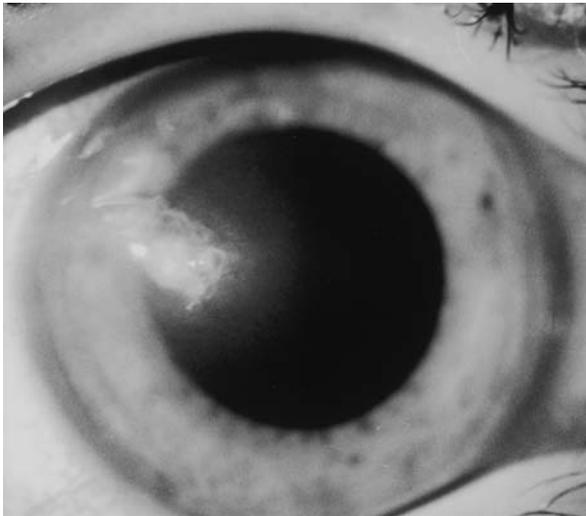
**FIGURE 5E**

Case 20. *Curvularia senegalensis* keratitis 2 days after firecracker injury.



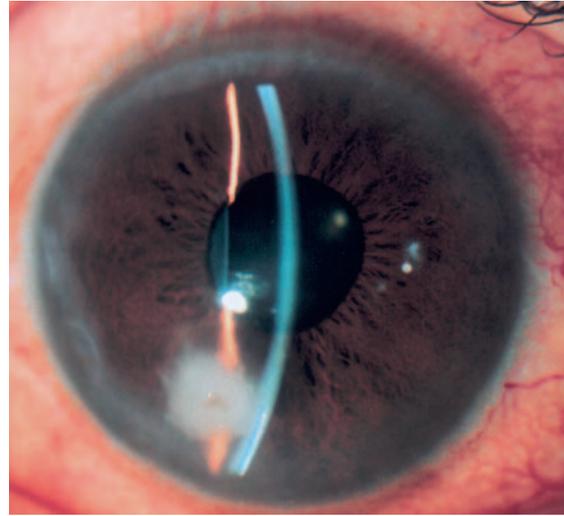
**FIGURE 5F**

Case 5. *Curvularia* keratitis 2 days after a screwdriver injury.



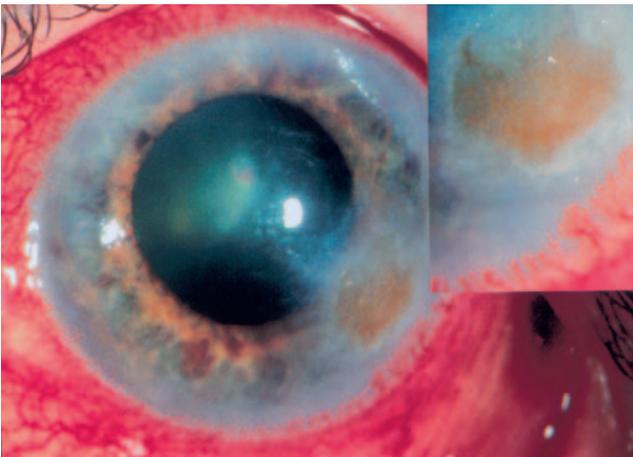
**FIGURE 5G**

Case 23. *Curvularia senegalensis* keratitis 4 days after a corneal metallic foreign-body injury that happened while patient was repairing a sewer.



**FIGURE 6A**

Case 13. Superficial stromal pigment in center of a focal infiltrate, 3 days after a corneal metallic foreign-body injury.



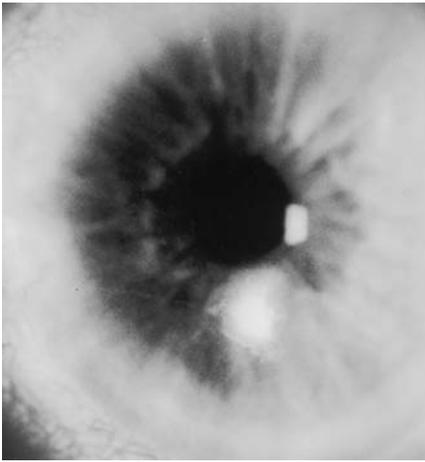
**FIGURE 6B**

Case 28. Brown pigmentation and persistent epithelial defect 3 weeks after patient got sand in eye.



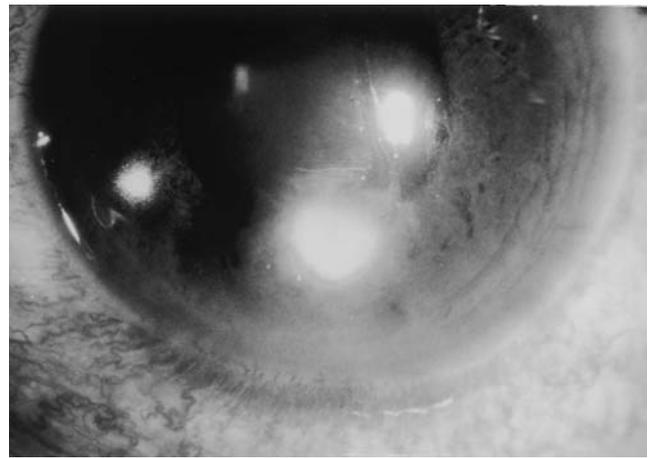
**FIGURE 7A**

Case 10. *Curvularia lunata* keratitis after 2 weeks of symptoms, treated for a soft contact lens-related infiltrate with fluorometholone, gentamicin, neomycin-polymyxin B, and chloramphenicol eyedrops. (Compare Fig 7b-Fig 5d, all established infections occurring 10 to 14 days after onset).



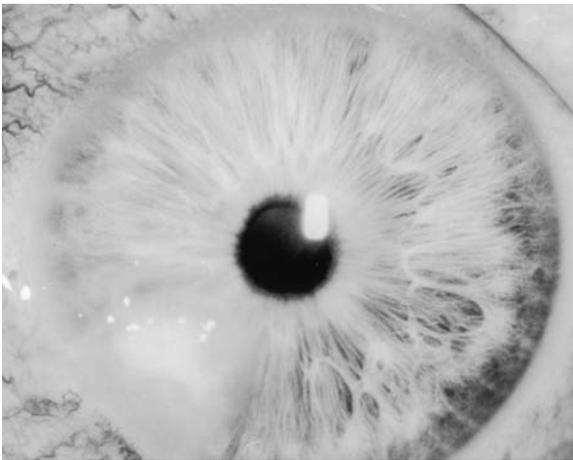
**FIGURE 7B**

Case 26. *Curvularia lunata* keratitis 10 days after onset, treated with trifluridine and tobramycin for presumed herpes simplex virus keratitis.



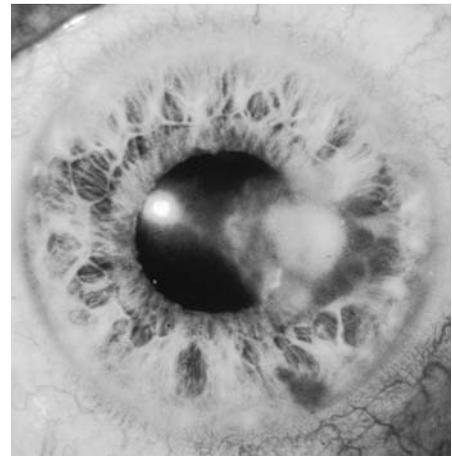
**FIGURE 7C**

Case 21. *Curvularia senegalensis* keratitis 10 days after a corneal abrasion caused by a lawn mower and treated with tobramycin-dexamethasone solution.



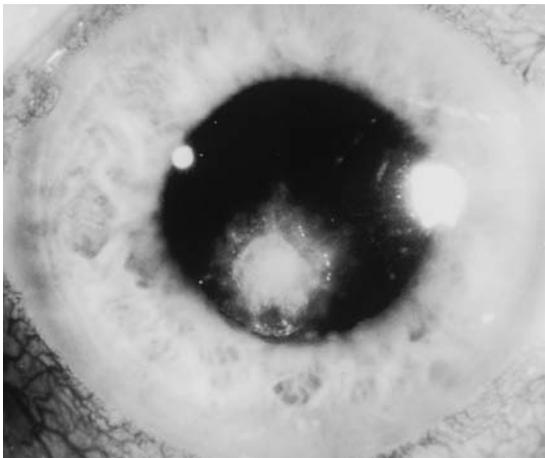
**FIGURE 7D**

Case 27. *Curvularia lunata* keratitis 12 days after abrading the cornea with a rusted wire and treated with ciprofloxacin and tobramycin eye-drops.



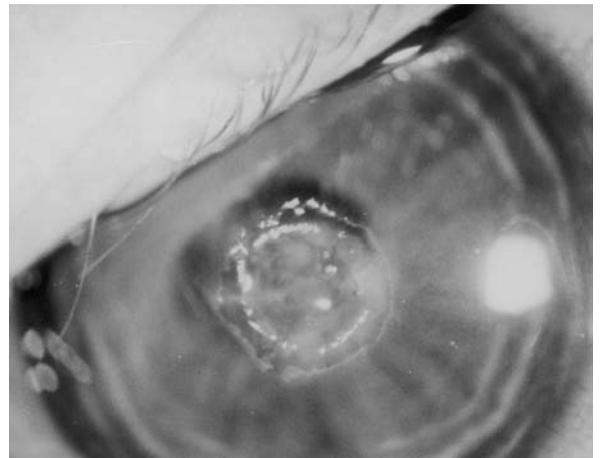
**FIGURE 8A**

Case 4. *Curvularia pallescens* keratitis 7 weeks after a fingernail-induced corneal injury. (Compare Fig 8b and Fig 8c, other chronic infections).



**FIGURE 8B**

Case 30. *Curvularia lunata* keratitis 5 weeks after a corneal injury that happened while patient was using a lawn mower. Infection was treated with neomycin-polymyxin B-dexamethasone solution.



**FIGURE 8C**

Case 16. *Curvularia prasadii* keratitis 2 weeks after patient scratched cornea on a yucca leaf; corneal signs were apparently suppressed by neomycin-dexamethasone eyedrops.

TABLE II: MICROBIOLOGIC AND TREATMENT RESULTS OF CASES OF CURVULARIA KERATITIS

CASE	HYPHAE ON SMEAR	CULTURE	OTHER CORNEAL ISOLATES	DAYS OF NATAMYCIN THERAPY	OTHER ANTIFUNGAL THERAPY	SURGERY	FINAL VISUAL ACUITY
1	N	<i>C senegalensis</i>	-	ND	N	N	ND
2	Y	<i>C lunata</i>	<i>Bacillus badius</i>	22	N	N	20/25
3	Y	<i>C senegalensis</i>	<i>Staphylococcus epidermidis</i> , <i>Geotrichum candidum</i>	17	N	N	20/20
4	Y	<i>C pallescens</i>	<i>S epidermidis</i>	33	Amphotericin B	N	20/25
5	Y	<i>Curvularia</i> sp	-	21	N	N	20/20
6	N	<i>Curvularia</i> sp	-	11	N	N	20/25
7	N	<i>C pallescens</i>	<i>S epidermidis</i>	ND	N	N	20/20
8	N	<i>Curvularia</i> sp	-	40	Amphotericin B	N	20/30
9	Y	<i>C senegalensis</i>	-	48*	Miconazole	N	20/20
10	Y	<i>C lunata</i>	-	60	N	N	20/20
11	Y	<i>C lunata</i> var <i>aeria</i>	<i>S epidermidis</i> , <i>Peptostreptococcus micros</i> , <i>Propionibacterium acnes</i>	ND	N	Keratectomy	20/50
12	Y	<i>C prasadii</i>	-	115	N	PKP	20/40
13	Y	<i>C senegalensis</i>	<i>P acnes</i>	23	N	N	20/20
14	Y	<i>C lunata</i>	<i>S epidermidis</i>	75	N	Keratectomy	20/20
15	Y	<i>C senegalensis</i>	-	14	N	N	20/40
16	Y	<i>C prasadii</i>	<i>Streptococcus morbillorum</i>	24	N	N	ND
17	Y	<i>C pallescens</i>	-	42	Amphotericin B	N	20/30
18	Y	<i>C senegalensis</i>	-	79	Miconazole, oral ketoconazole	Keratectomy	20/20
19	Y	<i>C pallescens</i>	-	50	Oral ketoconazole		20/30
20	Y	<i>C senegalensis</i>	-	19	N	N	20/70
21	Y	<i>C senegalensis</i>	-	47	N	N	20/40
22	Y	<i>C senegalensis</i>	<i>P acnes</i>	39	N	N	20/20
23	N	<i>C senegalensis</i>	<i>P acnes</i>	86	Oral ketoconazole	N	20/20
24	N	<i>C senegalensis</i>	-	30	N	N	20/20
25	Y	<i>C lunata</i>	-	12	Oral ketoconazole	PKP	20/400
26	Y	<i>C lunata</i>	<i>P acnes</i>	ND	N	N	20/30
27	Y	<i>C lunata</i>	-	78	Oral fluconazole	N	20/20
28	Y	<i>Curvularia</i> sp	-	35	Oral fluconazole	N	20/100
29	Y	<i>Curvularia</i> sp	-	24	N	N	20/30
30	N	<i>C lunata</i>	-	25	N	N	20/30
31	Y	<i>C lunata</i>	-	21	N	N	20/30
32	Y	<i>C lunata</i> var <i>aeria</i>	-	29	Oral fluconazole	PKP	20/125

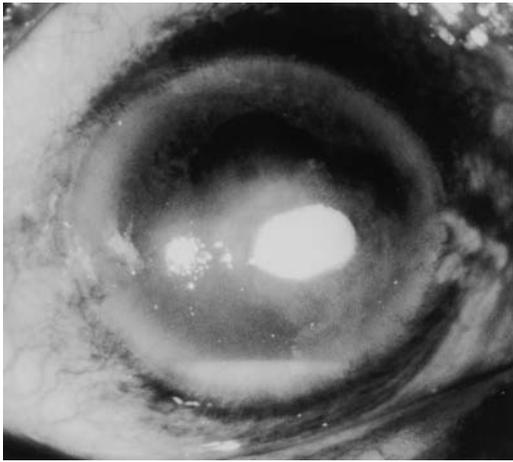
N, no; ND, not determined; PKP, penetrating keratoplasty; Y, yes.  
\*Only topical miconazole

therapy (Fig 11). Three patients underwent penetrating keratoplasty. Histopathological examination of 2 of these corneal buttons showed branching fungal elements (Fig 12). Despite these occurrences, 25 (78%) of all cases achieved visual acuity of 20/40 or better (Fig 13).

Logistic regression models assessing possible associations between initial clinical findings and either visual outcome or treatment duration are summarized in Table III. Multivariable modeling, selecting variables based on the likelihood ratio test, left only the presence of hypopyon in the final model with the visual acuity outcome. A similar model-building algorithm left only treatment delay in the final model with the treatment duration outcome. Linear

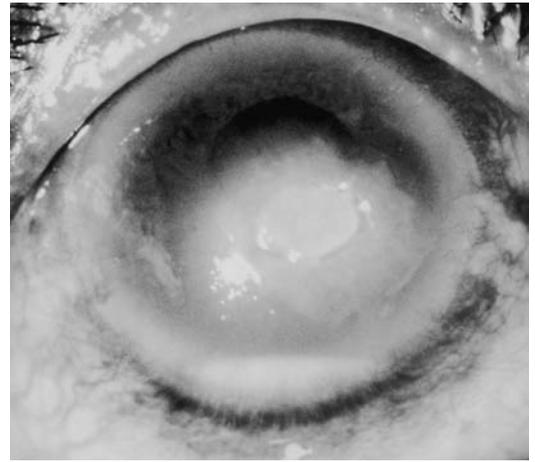
regression showed that, on average, patients experiencing a delay in diagnosis greater than 7 days had 1.95 (95% CI, 1.78 to 2.37) times the duration of topical antifungal treatment than those diagnosed within 1 week of onset ( $P = .005$ ), even after accounting for prior corneal trauma, prior corticosteroid therapy, infiltrate size, and hypopyon. Patients with a diagnostic delay greater than 1 week were treated for an average of 26 days (95% CI, 9 to 44 days) longer than those with a more rapid diagnosis.

Outcome was not convincingly correlated with natamycin's MIC ( $P = .6$ , using a breakpoint of 4  $\mu\text{g}/\text{mL}$ ) or MFC ( $P = .3$ , using a breakpoint of 16  $\mu\text{g}/\text{mL}$ ). The duration of topical natamycin was also not associated with



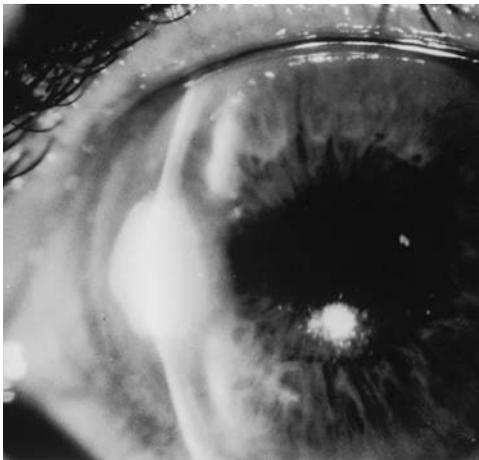
**FIGURE 9A**

Case 11. *Curvularia lunata* keratitis with dense white lesion extending above corneal surface.



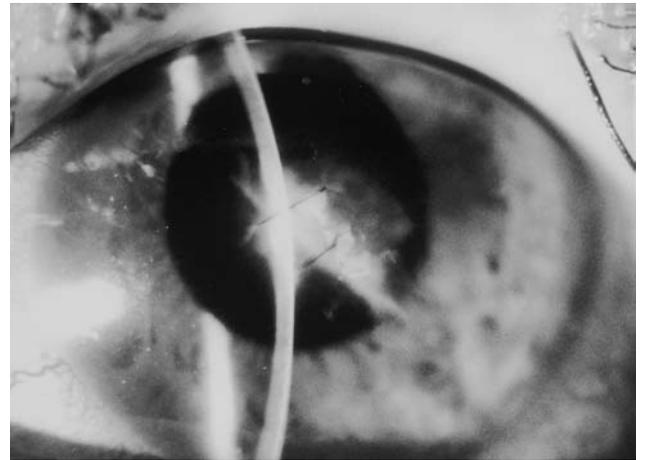
**FIGURE 9B**

Case 11. Three days after superficial keratectomy. (Compare Fig 9a).



**FIGURE 9C**

Case 14. *Curvularia lunata* keratitis 8 weeks after onset with inflammatory outgrowth.



**FIGURE 10**

Case 25. Progressive ulceration. Top, *Curvularia lunata* keratitis 2 days after onset of a corneal suture abscess, occurring 2 months after penetrating corneal injury due to hammering nail into a tree. Bottom, Descemetocoele 1 week later, after topical corticosteroid treatment every 2 hours was stopped and topical natamycin therapy was started (MIC = 2  $\mu\text{g/mL}$ ).



**FIGURE 9D**

Case 14. Superficial keratectomy performed 11 weeks after onset (compare Fig 9C). Corneal biopsy contained hyphae.

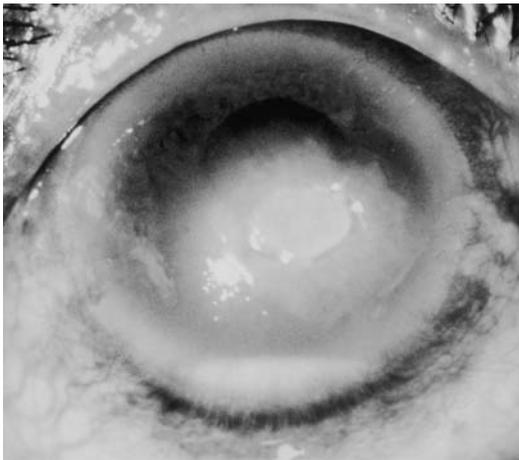
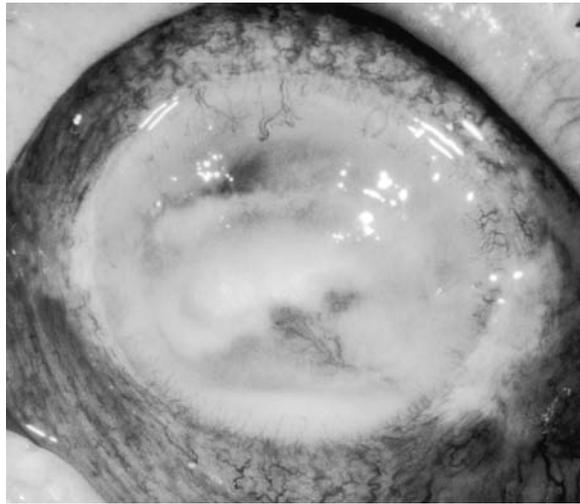
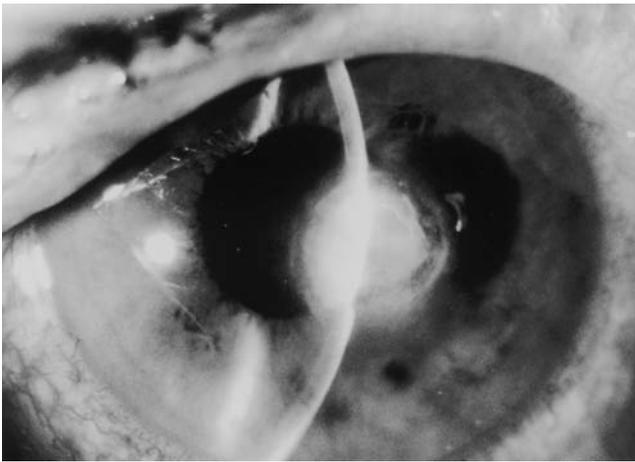


FIGURE 11

Case 18. Recrudescence of inflammation after premature discontinuation of antifungal therapy. Top, *C. senegalensis* keratitis at onset of antifungal therapy. Patient had scratched eye 2 months previously but was treated for herpes simplex virus dendritic keratitis, then stromal keratitis. Bottom, After near-resolution of inflammation with 6 weeks of topical natamycin therapy (MIC = 1 µg/mL), corneal infiltrate recurred 3 weeks after treatment was stopped. After 3 more weeks of natamycin, superficial keratectomy removed sequestered inflammation.

natamycin's MIC ( $P = .6$ ) or MFC ( $P = .3$ ), using similar breakpoints to define susceptibility. The different *Curvularia* species were not correlated with clinical severity, as assessed by infiltrate area or hypopyon, although the duration of topical therapy was significantly longer for patients with *C. prasadii* infection ( $P = .01$ ). The use of an adjunctive oral antifungal agent was not associated with visual outcome ( $P = .08$ ) or duration of topical antifungal therapy ( $P = .14$ ), but oral antifungals were used 5.5 (95% CI, 0.8 to 37.6) times more often among those with a poorer visual outcome and 2.3 (95% CI, 0.3 to 14.2) times more often in patients treated topically for more than 30 days.

**MYCOLOGICAL FINDINGS**

Dematiaceous hyphomycetes accounted for 22% of our fungal corneal isolates, and one third of these pigmented

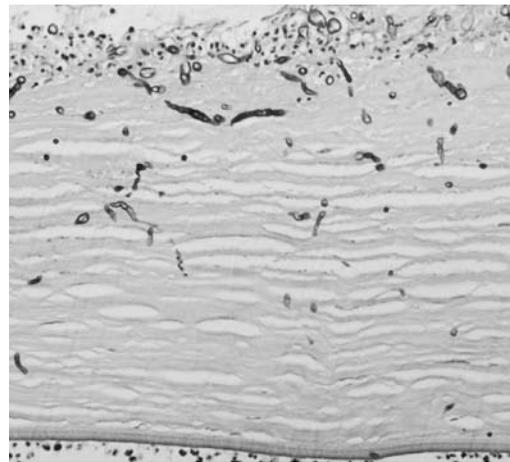
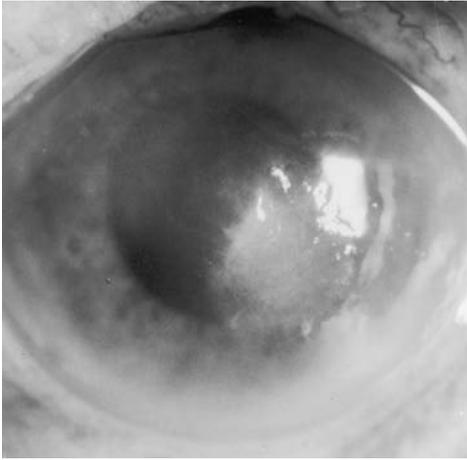


FIGURE 12

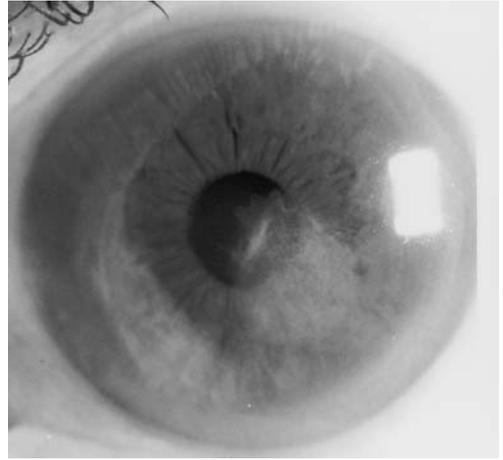
Case 32. Progressive *Curvularia* keratitis treated by therapeutic keratoplasty. Top, *Curvularia lunata* keratitis 10 days following corneal injury sustained while patient was cleaning his attic. Reconstructive keratoplasty occurred 1 week later. Center, Prominent neutrophilic infiltrate in stroma and anterior chamber, with PAS-positive filamentous fungi amongst necrotic lamellae (periodic acid-Schiff, x64). Bottom, Branching, septate filaments rooting into stroma and chlamydoconidia budding in superficial cornea (Gomori methanamine silver, x100).

*Curvularia Keratitis*



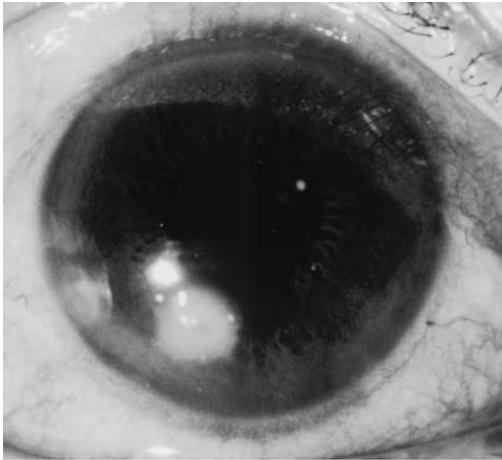
**FIGURE 13A**

Case 3. *Curvularia senegalensis* keratitis 3 days after corneal injury.



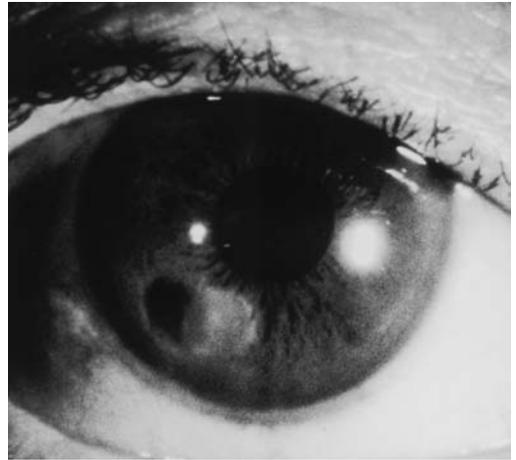
**FIGURE 13B**

Case 3. Four months later (compare Fig 13A) with faint corneal scar and 20/20 visual acuity.



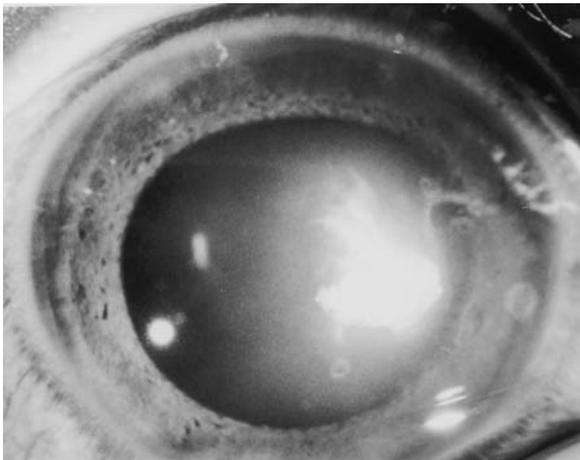
**FIGURE 13C**

Case 13. *Curvularia senegalensis* 3 days after onset.



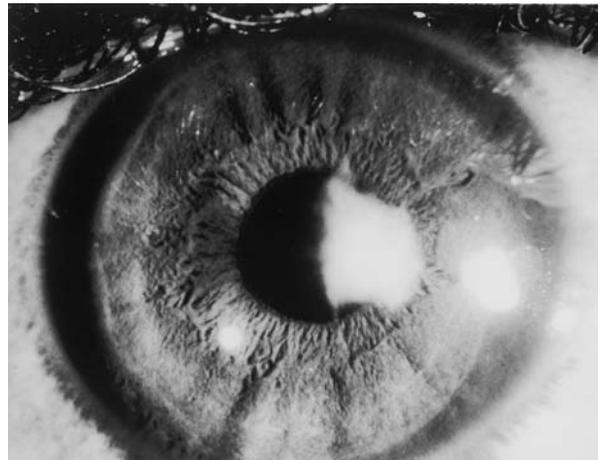
**FIGURE 13D**

Case 13. One month later (compare Fig 13C) with outcome of 20/20 visual acuity.



**FIGURE 13E**

Case 17. *Curvularia pallescens* keratitis 3 days after corneal injury.



**FIGURE 13F**

Case 17. Three months later (compare Fig 13E) with outcome of 20/30 visual acuity.

TABLE III: UNIVARIABLE ASSOCIATIONS WITH POOR VISUAL OUTCOME AND PROLONGED TREATMENT DURATION

CHARACTERISTIC	FINAL VISION WORSE THAN 20/50 OR CORNEAL SURGERY		DURATION OF TOPICAL ANTIFUNGAL THERAPY > 30 DAYS	
	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE
Age ≥ 50 yr	2.33 (0.36, 15.05)	.4	1.67 (0.41, 6.82)	.5
Plant or dirt trauma	0.50 (0.08, 3.22)	.5	0.80 (0.20, 3.25)	.8
Treatment delay > 7 days	1.17 (0.20, 6.89)	.9	7.33 (1.47, 36.66)	.015
Topical corticosteroid between onset and diagnosis	0.94 (0.14, 6.19)	.9	1.59 (0.36, 7.12)	.5
Topical antibiotic between onset and diagnosis	0.60 (0.09, 4.12)	.6	0.71 (0.14, 3.66)	.7
Stromal infiltrate > 9 mm <sup>2</sup>	7.67 (1.04, 56.77)	.05	2.25 (0.54, 9.45)	.3
Presence of hypopyon	25.0 (1.93, 324)	.01	0.75 (0.09, 6.11)	.8

isolates were *Curvularia*. *Curvularia* was the fourth most common isolate among our cases of fungal keratitis, following *Candida*, *Fusarium*, and *Aspergillus*. *Curvularia* accounted for 8% of 727 cases of human keratomycosis and for 4% of 95 specimens from oculomycoses in dogs, horses, and other animals processed by our laboratory over the last 30 years.

Hyphae were detected on stained smears of initial corneal scrapings from 25 (78%) of the 32 culture-confirmed patients with *Curvularia* keratitis in this series. Hyphal fragments were seen on 21 (72%) of gram-stained smears from 29 different patients, 6 (75%) of 8 acridine orange smears, 7 (70%) of 10 Giemsa smears, and 5 (83%) of 6 smears stained with calcofluor white. No significant difference was found among these 4 stains ( $\chi^2 = 0.4$ ,  $df = 3$ ). Fungal DNA was detected from 4 corneal isolates (including cases 23, 30, and 31) amplified by PCR (Fig 14).

Fungal growth was first detected at a median of 2 days for both blood and chocolate agar plates, 4 days for Sabouraud agar, and 5 days for BHI (Table IV). Of 23 cases where comparative information was recorded, fungal growth was detected on the blood or chocolate agar plates on the same day as on the Sabouraud or BHI media in 5 cases. In 10 cases, fungi grew more rapidly on blood and chocolate agars, appearing an average of 3 days (range, 1 to 6 days) before growth occurred on Sabouraud or BHI media. Fungal growth was detected on blood or chocolate agar plates but not on the Sabouraud agar plate or in BHI in 5 cases (2 *C. lunata*, 1 *C. senegalensis*, 1 *C. prasadii*, and 1 nonspeciati isolate). Fungi were found on Sabouraud or BHI media but not on blood or chocolate agar plates in 4 cases (2 *C. pallescens*, 1 *C. lunata*, and 1 *C. senegalensis*). Besides the *Curvularia* isolate, 11 (34%) of the cases had 1 or more other microorganisms isolated from the corneal scrapings (Table II). *Staphylococcus epidermidis* and *Propionibacterium acnes*

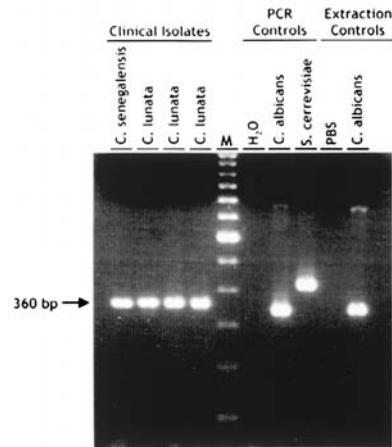


FIGURE 14

Fungal molecular analysis, electrophoretically analyzed on an agarose gel stained with ethidium bromide. Polymerase chain reaction (PCR) products of corneal cultures of 1 *Curvularia senegalensis* isolate (case 23) and 3 *Curvularia lunata* isolates (including cases 30 and 31) amplified consistently at predicted PCR product size of approximately 360 base pairs (bp). Other lanes show a base-pair ladder of size markers (M) and positive and negative controls for PCR reaction and extraction.

were the most common coisolates, although 1 case each of *Bacillus badius*, *Streptococcus morbillorum*, and *Geotrichum candidum* were found.

*Curvularia* species included *C. senegalensis* (11 cases), *C. lunata* (10 cases), *C. pallescens* (4 cases), and *C. prasadii* (2 cases). Five isolates were not speciated. Besides these 32 cases, our laboratory also identified *Curvularia* from 11 other patients with fungal keratitis using specimens sent to us by other treating ophthalmologists, comprising *C. senegalensis* (3), *C. lunata* (3), *C. inaequalis* (1), *C. leonensis* (1), and 3 nonspeciati strains.

The susceptibility pattern of the 14 tested isolates is shown in Table V. All of the *Curvularia* isolates were inhibited by ≤ 4 μg/mL natamycin, 86% by ≤ 1 μg/mL

TABLE IV: FUNGAL GROWTH FROM CORNEAL SCRAPINGS INOCULATED DIRECTLY ONTO CULTURE MEDIA

MEDIUM	MEDIAN DAYS (RANGE) OF FIRST DETECTABLE FUNGAL GROWTH	NO. WITH DETECTABLE FUNGAL GROWTH (NO. INOCULATED)	NO. OF CASES SHOWING GROWTH BEFORE OTHER SETS OF MEDIA <sup>a</sup>
Blood agar plate	2 (1 – 4)	17 (22)	15
Chocolate agar plate	2 (1 – 4)	19 (23)	15
Thioglycolate broth	3	2 (6)	0
Schaedler or Brucella agar plate	6 (1 – 7)	4 (5)	0
Sabouraud agar plate	4 (1 – 8)	15 (22)	4
Brain-heart infusion broth	5 (1 – 12)	12 (13)	4

<sup>a</sup>Fungal growth was identified on all media on same day for 4 specimens.

amphotericin B, 100% by  $\leq 8 \mu\text{g/mL}$  miconazole or ketoconazole, 86% by  $\leq .5 \mu\text{g/mL}$  itraconazole, and only 8% by  $\leq 16 \mu\text{g/mL}$  flucytosine. All species appeared similar in their susceptibility pattern (Table VI).

Our laboratory's initial attempt at establishing an experimental animal model of *Curvularia* keratitis was unsuccessful. Faint corneal haze was noted in a few animals on the first day following scarification. With periodic observation over 1 month, none of the inoculated mouse eyes developed clinical, histological, or molecular evidence of fungal keratitis.

## DISCUSSION

Human mycoses are caused by many mitosporic filamentous fungi. Most are classed as deuteromycetes, and these imperfect fungi include nonpigmented (hyaline or moniliceous) and pigmented (dematiaceous) groups. The histopathological recognition of dematiaceous hyphomycetes is based on seeing tissue invasion by pigmented hyphae, a condition sometimes called phaeohy-

phomycosis.<sup>95</sup> *Curvularia* is one of several genera of these "black fungi."<sup>96</sup>

## EPIDEMIOLOGY

Dematiaceous molds live and linger in the soil<sup>97</sup> and on plants<sup>98</sup> in warm climates. Probably because of their widespread presence in the subtropical environment, dematiaceous hyphomycetes caused 22% of our cases of fungal keratitis and 16% to 19% in other large series.<sup>36,42</sup> *Curvularia* is the most common dematiaceous fungal corneal isolate<sup>3,36,41,44,46,55,65</sup> and accounts for 4% to 9% of all fungi isolated from patients with mycotic keratitis in hot zones.<sup>41,46,65,70</sup>

One hundred ninety cases of *Curvularia* keratitis have been previously reported (Table VII). We identified 43 additional patients with corneal curvulariosis, including 32 treated at and followed up by our institute. The numbers of reported cases progressively increased during the last half of the 20th century (Fig 15). One fourth of the reports and one fourth of the total number of previously

TABLE V: SUSCEPTIBILITY OF CURVULARIA CORNEAL ISOLATES

ANTIFUNGAL	MINIMAL INHIBITORY CONCENTRATION (MIC)				MINIMAL FUNGICIDAL CONCENTRATION (MFC)			
	NO. TESTED	MIC RANGE	MIC <sub>50</sub> ( $\mu\text{G/ML}$ )	MIC <sub>90</sub> ( $\mu\text{G/ML}$ )	NO. TESTED	MFC RANGE	MFC <sub>50</sub> ( $\mu\text{G/ML}$ )	MFC <sub>90</sub> ( $\mu\text{G/ML}$ )
Natamycin	14	1 – 4	1	2	7	1 - >32	16	16
Amphotericin B	14	$\leq 0.125 - 4$	0.5	1	7	0.5 - >32	8	32
Clotrimazole	11	<0.25 – 8	1	4	7	1 - >32	8	>32
Miconazole	14	<0.25 – 2	1	1	7	0.5 - >32	4	32
Econazole	12	0.125 – 1	0.25	0.5	7	<0.25 – 32	1	16
Ketoconazole	9	<0.25 – 4	0.5	2	4	0.25 – 16	8	16
Butaconazole	6	$\leq 0.25 - 1$	0.5	1	1	0.5	0.5	-
Itraconazole	7	$\leq 0.25 - 1$	0.25	1	1	$\leq 0.25$	$\leq 0.25$	-
Fluconazole	3	>16	>16	>16	0	-	-	-
Saperconazole	3	$\leq 0.06 - 0.5$	0.125	0.5	0	-	-	-
Flucytosine	12	$\leq 0.25 - >32$	>32	>32	1	>32	>32	>32

TABLE VI: IN VITRO SUSCEPTIBILITIES (MIC<sub>50</sub>) OF DIFFERENT *CURVULARIA* SPECIES

SPECIES	NO. TESTED ISOLATES	NATAMYCIN	AMPHOTERICIN B	MICONAZOLE	KETOCONAZOLE	ITRACONAZOLE
<i>C lunata</i>	4	1	0.5	1	2	1
<i>C senegalensis</i>	5	2	1	1	0.25	0.25
<i>C pallescens</i>	2	1	0.5	1	0.5	≤0.25
<i>C prasadii</i>	1	4	<0.25	1	0.5	-

reported patients came from the United States. Nearly half of the reports and two thirds of the cases were from India and surrounding Asian nations. Besides India (n=109) and the United States (n=89, including our series), other regions reporting patients with *Curvularia* keratitis were Asia (n=24; from Bangladesh, Taiwan, Thailand, Nepal, Sri Lanka, Korea, Singapore, and the Philippines), Africa (n=6; from South Africa and Ghana), South America (n=4; from Argentina, Brazil, Paraguay, and Venezuela), and the Middle East (n=1; from Israel).

We averaged one patient per year with *Curvularia* keratitis, and the annual experience can be higher at eye clinics in India.<sup>36</sup> Two thirds of our cases began during the summer, when *Curvularia* airborne spores peak along the Texas coast of the Gulf of Mexico.<sup>99</sup> *Curvularia* species are among the most prevalent fungal spores in the air in many torrid climes. The amount of aerial *Curvularia* varies seasonally,<sup>70,100,101</sup> rising during and just after the warm, wet months.

Practically all of our patients developed their fungal keratitis after trauma, one half with plants or dirt. Others have also found the injured cornea to be open to opportunistic fungal infection.<sup>65</sup> Previous reports that mentioned predisposing factors indicated trauma in 72% of patients with *Curvularia* keratitis (Table VII, data not shown). Lawn-tool injuries in our region are common grounds for ocular<sup>30</sup> and cutaneous<sup>102</sup> *Curvularia* infections. Outdoor occupational or recreational injury may

explain why males accounted for 78% of all patients in our series and previous reports and why half were between 25 and 50 years of age (Fig 16). Children, however, are also at risk;<sup>54</sup> 16% of our patients were younger than 12 years of age.

Other predisposing factors include keratorefractive surgery,<sup>29</sup> corneal exposure, and climatic droplet keratopathy.<sup>27,72</sup> *Curvularia* keratitis is also a rare complication of soft contact lens wear,<sup>82</sup> possibly because this fungus is capable of contaminating contact lenses<sup>82,103</sup> and cosmetics.<sup>104</sup> *Curvularia* may be found on unwashed skin but colonizes less than 1% of normal human eyelids<sup>105</sup> and only 1% to 3% of healthy conjunctivæ.<sup>70,106-108</sup>

*Curvularia* keratitis has a slower course and less inflammation than some other fungal corneal infections.<sup>34</sup> Our patients often waited several days before seeking care, and half smoldered for more than a week before the diagnosis was made. An animal model of *Curvularia* keratitis also showed a gradually progressive evolution.<sup>21</sup> During its torpid course, fungal corneal infection allows an opportunity for bacteria, including staphylococci and anaerobes that are part of the ocular flora, to adhere to and possibly to infect the cornea. One third of our cases were polymicrobial infections, including one patient with polymycosis involving *Curvularia* and *Geotrichum*.

Similar to the 8% prevalence of *Curvularia* keratitis among human keratomycoses studied by our laboratory, we isolated *Curvularia* from 4% of all canine and equine

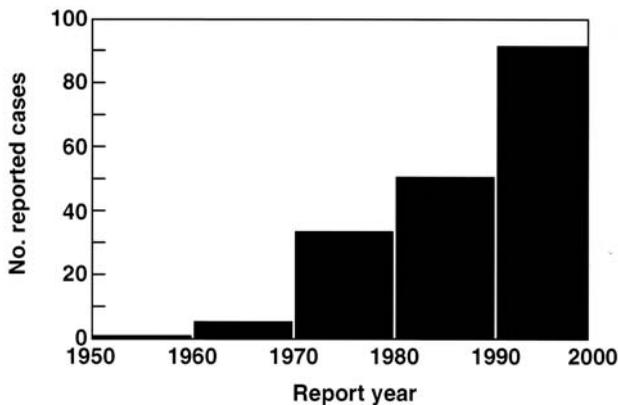


FIGURE 15

Time of literature publication of previously reported cases of *Curvularia* keratitis, by decade through the end of each reporting year.

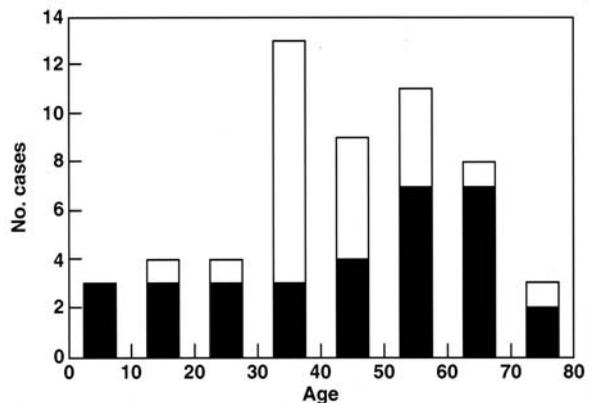


FIGURE 16

Age distribution of 32 patients with *Curvularia* keratitis in this series (black) and 23 previously reported cases with available demographic information (white).

*Curvularia Keratitis*

TABLE VII: PREVIOUSLY REPORTED HUMAN CASES OF *CURVULARIA KERATITIS*

REPORTING AUTHOR, YEAR	LOCALE	ISOLATE	NO.
Agrawal et al, 1982 <sup>21</sup> ; Shukla et al, 1984 <sup>22</sup>	India	<i>C lunata</i> var <i>aeria</i>	1
		<i>C geniculata</i>	1
Anderson et al, 1959 <sup>13</sup> ; Anderson and Chick, 1963 <sup>23</sup>	North Carolina, USA	<i>C lunata</i>	1
Arora et al, 1983 <sup>24</sup>	India	<i>Curvularia</i> sp	1
Berger et al, 1991 <sup>25</sup>	California, USA	<i>C lunata</i>	1
Brook and Frazier, 1999 <sup>26</sup>	Maryland, USA	<i>Curvularia</i> sp	1
Carmichael et al, 1985 <sup>27</sup>	South Africa	<i>C lunata</i>	2
Chander and Sharma, 1994 <sup>28</sup>	India	<i>Curvularia</i> sp	5
Chung et al, 2000 <sup>29</sup>	Florida, USA	<i>Curvularia</i> sp	1
Clinch et al, 1992 <sup>30</sup> ; Clinch et al, 1994 <sup>31</sup>	Louisiana, USA	<i>Curvularia</i> sp	2
Dasgupta et al, 1973 <sup>32</sup>	India	<i>Curvularia</i> sp	4
Dorey et al, 1997 <sup>33</sup>	Israel	<i>C lunata</i>	1
Dunlop et al, 1994 <sup>34</sup>	Bangladesh	<i>C fallax</i>	7
		<i>Curvularia</i> sp	2
Fitzsimons and Peters, 1986 <sup>35</sup>	South Africa	<i>Curvularia</i> sp	1
Garg et al, 2000 <sup>36</sup>	India	<i>Curvularia</i> sp	20
Grover et al, 1975 <sup>37</sup>	India	<i>Curvularia</i> sp	1
Guarro et al, 1999 <sup>38</sup>	Brazil	<i>C senegalensis</i>	1
Hagan et al, 1995 <sup>39</sup>	Ghana	<i>C fallax</i>	2
Imwidthaya, 1995 <sup>40</sup>	Thailand	<i>Curvularia</i> sp	3
Jan et al, 1992 <sup>41</sup>	Taiwan	<i>Curvularia</i> sp	4
Jones et al, 1969 <sup>3</sup> ; Forster et al, 1975 <sup>3</sup> ; Forster, 1994 <sup>42</sup> ; Forster and Rebell, 1975 <sup>43</sup> ; Liesegang and Forster, 1980 <sup>44</sup>	Florida, USA	<i>C senegalensis</i>	11
		<i>C verruculosa</i>	7
		<i>C pallescens</i>	1
		<i>Curvularia</i> sp	4
Kim et al, 2001 <sup>45</sup>	Korea	<i>Curvularia</i> sp	1
Lakshmi et al, 1989 <sup>46</sup>	India	<i>Curvularia</i> sp	18
Llamozas et al, 1966 <sup>47</sup>	Venezuela	<i>C lunata</i>	1
Luque et al, 1986 <sup>48</sup>	Argentina	<i>C lunata</i> var <i>aeria</i>	1
Mahajan, 1985 <sup>49</sup>	India	<i>Curvularia</i> sp	9
Marcus et al, 1992 <sup>50</sup>	South Africa	<i>C brachyspora</i>	1
Miño de Kaspar et al, 1991 <sup>51</sup>	Paraguay	<i>Curvularia</i> sp	1
Nityananda et al, 1962 <sup>52</sup>	Sri Lanka	<i>C lunata</i>	1
Nityananda et al, 1964 <sup>53</sup>	Sri Lanka	<i>C geniculata</i>	1
Panda et al, 1997 <sup>54</sup>	India	<i>Curvularia</i> sp	16
Poria et al, 1985 <sup>55</sup>	India	<i>Curvularia</i> sp	1
Prasad and Neva, 1982 <sup>56</sup> ; Nema, 1991 <sup>57</sup>	India	<i>C lunata</i>	3
Rahman et al, 1997 <sup>58</sup>	India	<i>Curvularia</i> sp	2
Rajasekaran et al, 1988 <sup>59</sup> ; Thomas et al, 1987 <sup>60</sup> ; Thomas et al, 1986 <sup>61</sup>	India	<i>C geniculata</i>	3
		<i>Curvularia</i> sp	5
Rajasekaran et al, 1987 <sup>62</sup> ; Thomas et al, 1988 <sup>63</sup> ; Thomas and Rajasekaran, 1988 <sup>64</sup>	India	<i>C geniculata</i>	1
Rosa et al, 1994 <sup>65</sup>	Florida, USA	<i>C senegalensis</i>	5
		<i>C verruculosa</i>	1
		<i>Curvularia</i> sp	5
Salceda et al, 1969 <sup>66</sup> ; Salceda, 1973 <sup>67</sup> ; Salceda, 1973 <sup>68</sup> ; Salceda et al, 1974 <sup>69</sup> ; Salceda, 1976 <sup>14</sup>	Philippines	<i>Curvularia</i> sp	1
Sandhu and Randhawa, 1979 <sup>70</sup>	India	<i>Curvularia</i> sp	5
Sanitato et al, 1984 <sup>71</sup>	Louisiana, USA	<i>Curvularia</i> sp	1
Sridhar et al, 2000 <sup>72</sup>	India	<i>C lunata</i>	1
Srinivasan et al, 1991 <sup>73</sup>	India	<i>Curvularia</i> sp	3
Srinivasan et al, 1997 <sup>74</sup>	India	<i>Curvularia</i> sp	5
Stern and Buttross, 1991 <sup>75</sup>	Florida, USA	<i>Curvularia</i> sp	1
Sundaram et al, 1989 <sup>76</sup>	India	<i>C lunata</i>	4
Upadhyay et al, 1991 <sup>77</sup> ; Upadhyay et al, 1992 <sup>78</sup>	Nepal	<i>C prasadii</i>	2
Warren, 1964 <sup>79</sup> ; Georg, 1964 <sup>80</sup>	Alabama, USA	<i>C geniculata</i>	1
Williams et al, 1991 <sup>81</sup>	Bangladesh	<i>Curvularia</i> sp	1
Wilson et al, 1986 <sup>82</sup>	Georgia, USA	<i>C lunata</i>	1
Wind and Polack, 1970 <sup>83</sup> ; Polack et al, 1971 <sup>84</sup> ; Polack, 1970 <sup>85</sup>	Florida, USA	<i>C lunata</i>	1
Wong et al, 1997 <sup>86</sup> ; Wong et al, 1997 <sup>87</sup>	Singapore	<i>Curvularia</i> sp	1
Wood and Turberville, 1985 <sup>88</sup>	Tennessee, USA	<i>Curvularia</i> sp	1

fungal corneal infections submitted to us by veterinarians. Others have also reported *Curvularia* keratitis in dogs<sup>109,110</sup> and horses,<sup>111</sup> even elephants.<sup>112</sup> *Curvularia* is part of the conjunctival flora of domestic mammals,<sup>113</sup> but zootic keratomycosis is probably largely due to corneal trauma from vegetation.

#### MYCOLOGY

Gram, calcofluor white, and other stains of corneal scrapings were equally sensitive in detecting hyphal elements from our patients with *Curvularia* keratitis. Gomori's methanamine-silver helped visualize fungal biomass in corneal sections, and the Fontana-Masson silver stain can highlight melanin in dematiaceous fungal cell walls. A panfungal PCR offers a rapid diagnostic option.

*Curvularia* matures fairly rapidly on semisynthetic media,<sup>114</sup> generally showing detectable colonies at a median of 2 days on blood and chocolate agar plates and at 4 days on Sabouraud agar or brain-heart infusion. Other media also support *Curvularia*.<sup>115</sup> The optimal temperature for culturing many *Curvularia* species is around 28°C,<sup>116,117</sup> although growth occurs in both 25°C and 35°C incubators.<sup>21</sup> Colonies of the septate, brown hyphae vary from dark green to brownish black. Conidiophores produce multicelled conidia that measure 18 to 40 μ long, depending upon species. The mitospores' characteristic lunate arc comes from a central or penultimate conidial cell that tends to be larger, darker, and curved.

Approximately 40 species of *Curvularia* are known, including some conidial anamorphs of *Cochliobolus*.<sup>118,119</sup> *C lunata* and *C senegalensis* account for 60% of the recorded known species causing *Curvularia* keratitis in humans (Table VIII).

#### PATHOGENESIS

Our cohort provides some insight into how fungal infection develops and progresses in the cornea. A dry, superficial infiltrate with feathery borders was the typical appearance of curvularial infections involving the central and paracentral cornea. Peripheral corneal disease tended toward ulcerative suppuration. Eyes with more severe ocular inflammation, such as a hypopyon at the time of initial diagnosis, had a more complicated course and resulted in poorer vision.

The pathophysiology of *Curvularia* keratitis remains speculative. Fungal antigens are implicated in allergic sinusitis,<sup>109</sup> and one or more of these proteins could be involved in corneal inflammation. Fungal components that suppress the innate immune response and that interfere with human cytokines<sup>120</sup> could contribute to indolent infection.

*Curvularia* produces several mycotoxins, such as the curvularins, brefeldins, and radicinin, that are cytotoxic<sup>121</sup> and that have antiviral activity. Other toxins are anthroquinones, curvapallides, cytochalasins, neocoprogen, pectinases, pyrenocenes, spirostaphylotrichins, triticones, and zaragozic acid. *Curvularia* produces lipid phosphatase, galactosidase, glucosidase, endoglucanase, chloroperoxidase, and cellulases<sup>122</sup> and has pathways for metabolizing steroids. The roles of curvularial enzymes and other toxins in fungal keratitis have not yet been studied. What accounts for ocular virulence among *Curvularia* species is unknown.<sup>123</sup>

Melanin in the cell walls of dematiaceous hyphae and conidia resists killing and could be involved in pathogenicity. Although melanin production by dematiaceous fungi is downregulated at body temperature,<sup>124</sup> superficial corneal pigmentation was visible in 2 patients. Like others,<sup>25,36,125</sup> we found macroscopic pigmentation of ulcerative keratitis to be an uncommon but distinguishing sign of dematiaceous fungal infection.

The use of topical corticosteroids, inappropriately given before diagnosis in one third of our patients, may affect the course of *Curvularia* keratitis.<sup>65</sup> An animal model of *Curvularia* keratitis suggested that the severity of corneal infection was worsened by topical corticosteroids in the absence of antifungal therapy,<sup>21</sup> although we were unsuccessful in establishing a murine model even with systemic immunosuppression. After starting antifungal therapy, few of our patients were treated with corticosteroids because of uncertain safety, efficacy, and need.

#### MANAGEMENT

The optimal selection and duration of antifungal therapy could not be determined from this retrospective cohort study. Previous case reports have suggested that topical amphotericin B<sup>13,50,79,86,88,126</sup> or miconazole<sup>35</sup> is sometimes effective, and our susceptibility data showed good in vitro activity with these agents. Topical natamycin 5% suspension, first successfully used for *Curvularia* keratitis in

TABLE VIII: REPORTED HUMAN CORNEAL ISOLATES OF *CURVULARIA*

SPECIES	NO.
<i>C lunata</i>	32
<i>C senegalensis</i>	31
<i>C fallax</i>	9
<i>C verruculosa</i>	8
<i>C geniculata</i>	7
<i>C pallescens</i>	5
<i>C prasadii</i>	4
<i>C brachyspora</i>	1
<i>C inaequalis</i>	1
<i>C leonensis</i>	1

1970,<sup>3,83</sup> is a preferred therapy.<sup>33</sup>

Our experience corroborates the benefit of topical natamycin for corneal curvulariosis. On average, our patients were treated with one month of topical natamycin when the diagnosis was made soon after onset. A delay in starting natamycin prolonged the length of therapy. In vitro susceptibility testing showed all tested isolates to be susceptible to 4 µg/mL of natamycin or less, a concentration achievable in the ulcerated cornea by topical administration.<sup>127</sup> Natamycin (formerly, pimaricin) has agricultural applications and is an approved fungicide on cheese and other foods to prevent mold spoilage;<sup>128</sup> only minimal resistance has occurred despite widespread industrial use.<sup>129</sup> Ocular curvularial isolates acquired from the environment remain largely susceptible to natamycin.

Other compounds capable of inhibiting *Curvularia* range from biocides, such as polyhexamethylene biguanide<sup>130</sup> and chlorhexidine gluconate,<sup>58</sup> to the imidazoles.<sup>131</sup> Most isolates of *Curvularia* are sensitive to ketoconazole and itraconazole,<sup>38</sup> and an oral triazole antifungal agent can cure *Curvularia* keratitis even without topical therapy.<sup>60,63</sup> Voriconazole, a derivative of fluconazole, has good in vitro activity against *C lunata*<sup>132,133</sup> and may prove useful for treating patients with fungal keratitis.

Surgical management of *Curvularia* keratitis includes lamellar keratectomy,<sup>71</sup> conjunctival flap,<sup>134</sup> and therapeutic keratoplasty.<sup>43,65</sup> We treated fibroinflammatory outgrowth with superficial keratectomy, and 9% of our cases underwent corneal transplantation. We obtained medical or surgical cure in all patients, and 78% achieved vision of 20/40 or better.

An astute ophthalmologist once commented that “each fungus...can cause its own disease that may differ in its clinical features and prognosis from all others.”<sup>135</sup> Our experience shows that *Curvularia* keratitis is a distinctive form of keratomycosis. By describing its characteristics and analyzing the clinical course, we aimed to learn more about how this fungus infects the cornea.

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## DISCUSSION

DR JOHN D. GOTTSCH. Drs Wilhelmus and Jones are to be commended for their comprehensive review of a 30 year experience with *Curvularia* keratitis. This is the largest series reported to date with this fungal corneal infection, a review all the more remarkable because the disease is less prevalent in the United States than in tropical countries. This series by Wilhelmus and Jones is possible because of their meticulous ocular microbiologic workups and data preservation over many years.

This study confirms several well known suspicions about this disease. First, keratomycosis is a rarely suspected diagnosis in presumed infectious keratitis. Only 5 of the patients were referred with fungal keratitis as the initial diagnostic impression. Secondly, fungal keratitis is more likely to develop with trauma, especially trauma that involves plants or soil. Only 3 patients did not have a history of trauma to the cornea, and half the patients in this study had sustained dirt or plant injuries. Thirdly, the disease is more likely to develop in hot humid environments. Seventy percent of cases in this study occurred along the Gulf Coast during the summer months. And lastly, topical steroid use likely facilitates the development of the disease as one third of the study patients had used topical steroids before referral.

What is most striking about this report is the recovery of vision that occurred in the majority of patients, with over half achieving 20/20-20/25 vision or better. Only 3 patients were 20/100 or worse, and only 3 required penetrating keratoplasties. This is in contrast to other literature reports concerning *Curvularia* fungal infections which record many failed grafts, eviscerations and lost eyes. In this group of 32 patients no eyes were lost.

To what does Dr Wilhelmus owe the successful treatment of these difficult corneal infections? Certainly as the data demonstrated, a delay in initiating treatment led to a greater length of antifungal therapy. Two of the grafted patients had a treatment delay of greater than 10 days. As the data also show, a delay in treatment in general led to a larger area of stromal infiltrate and presumably a deeper, more entrenched infection. Thus, time to diagnosis and treatment is of the essence. Initial smears revealed hyphal elements from nearly 80% of the affected patients, and culture results confirmed the diagnosis within days in all cases. Thus a diagnosis could be established on the same day as presentation in most cases and within a week in the others. The median time to starting antifungal therapy was only 7 days. Thus effective antifungal therapy, mostly with natamycin, was begun early in the course of disease.

Had these patients been empirically treated with a topical fluoroquinolone only, as some have advocated for the treatment of presumed corneal ulcers, all these

infections would have progressively worsened. The incidence of fungal ulcers in India has been reported to be as high as 37% and in tropical climates, smears and cultures are routine in patients who present with signs of infectious keratitis.<sup>1</sup> The incidence of fungal disease in the United States is less.<sup>2</sup> Even though fungal ulcers are rare in our practices, should we as a routine matter of course perform smears and cultures on patients with presumed infectious keratitis, particularly those patients with risk factors for fungal keratitis such as trauma, warmer climates, and previous steroid use? Steroid use after initiation of antifungal therapy is also a controversial issue. I would also like to ask Dr Wilhelmus whether topical steroids should be considered in the management of fungal keratitis. Lastly, is there a role for cyclosporine as an antifungal and anti-inflammatory drug for keratomycotic infections as has been advocated by some investigators?

I congratulate Dr Wilhelmus for this large study of *Curvularia* keratitis in the United States and providing us with a sound management strategy for this difficult disease.

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DR KIRK R. WILHELMUS. Dr Gottsch implies that we should treat fungal keratitis on a case-by-case basis. That's how some of us buy wine, and I agree that it's the best approach in external eye disease. Empirical diagnosis and hit-or-miss therapy are not the optimal ways to manage corneal infections. We attribute our successful treatment of keratomycosis to a decision making plan that uses the capabilities of the microbiology laboratory.

We are entering the era of molecular ophthalmology. In his Jackson Memorial Lecture, Professor Barrie Jones intuited that "each fungus...is in search of its own specific effective management." With new rapid diagnostic assays, we will soon be able to identify microorganisms and to examine their susceptibilities on the day of diagnosis. We must be prepared to use this information by learning how each microbe correlates with clinical findings and with outcome.

We also need an improved classification scheme for fungal keratitis. Dematiaceous fungi cause a spectrum of diseases: mycetoma, an infection with aggregated fungal granules; chromoblastomycosis, localized tissue inflammation with arrested fungal growth; and phaeohyphomycosis, tissue invasion by pigmented fungi. As suggested by McGinnis and Ajello in 1985, mycotic keratitis caused by *Curvularia* and other dematiaceous fungi is the

ophthalmic counterpart to cutaneous phaeohyphomycosis. Together, an ophthalmic pathologist and a clinical ophthalmologist could create an eye-specific nomenclature of ocular phaeohyphomycosis, hyalohyphomycosis, candidiasis, and zygomycosis.

Let me now address the 3 main issues raised during the discussion: the risk factors of keratomycosis, its antifungal treatment, and the role of corticosteroids.

First, our experience shows that fungal keratitis mirrors nature, and we cannot be myopic when looking at the cornea. The recent proposal to use a coca-attacking strain of *Fusarium oxysporum* as a mycoherbicide in the war on drugs may mean that fungal eye disease could become more widespread. Harvey Cushing said: "A physician is obligated to consider more than a diseased organ, more even than the whole man—he must view the man in the world." We shouldn't be too surprised that many microorganisms are capable of infecting the eye or that case prevalence depends partly on the weather, geography, and human activity. To paraphrase TS Eliot, it is not our patient's eyes that are diseased, but the world we have to live in. Using PCR, our laboratory is finding that about one third of people have fungi in their normal flora. Dematiaceous fungi known to infect the cornea (including not only *Curvularia* but also *Bipolaris/Drechslera*, *Alternaria*, *Phialophora*, *Exserohilum*, *Fonsecaea*, *Exophiala*, *Aureobasidium*, *Cladosporium*, *Colletotrichum*, *Epicoccum*, *Humicola*, *Lasiodiplodia*, *Phoma* and *Wangiella*) are common in nature. Microorganisms that we know as corneal pathogens are, by and large, opportunists.

Secondly, we're fortunate to be the only specialty in medicine to use natamycin, an antifungal whose main niche is the food industry. This fungicide can reduce fungal growth on stored grain, but its most popular use is to prevent mold on cheese. After dipping or spraying cheese with Delvocid or a similar product at a concentration of 200 to 300 ppm, natamycin crystallizes on the rind but, being insoluble in water, does not leech into the paste. For example, natamycin works on Italian blue cheese by suppressing surface mold without interfering with *Penicillium gorgonzola* inside the punch holes. Mutant strains resistant to natamycin have little or no ergosterol in their cell membrane, so these fungi grow slowly and cannot survive in nature or on the eye. Natamycin remains our preferred therapy for most keratomycoses caused by dematiaceous and hyaline filamentous fungi. Yet, we still need better antifungal agents and easier ways to select them.

Finally, Dr Gottsch's questions about the role of corticosteroids and cyclosporine in fungal keratitis are intriguing but hard to answer. Like *Richard II's* realm, the cornea is a "fortress built by Nature for herself against infection," with battalions of material and molecular defenses. But the cornea and her inflammatory

fortifications can self-destruct during microbial invasion. Although Drs Stern and O'Day wrote parallel articles 10 years ago that corticosteroids enhance fungal keratitis and are contraindicated, perhaps anti-inflammatory drugs do sometimes have an adjunctive role. Our laboratory and others have shown that cyclosporine has some intrinsic and synergistic antifungal activity and could prove worth-

while as a dual antifungal and anti-inflammatory agent. We have successfully used topical cyclosporine after reconstructive keratoplasty performed for fungal keratitis.

I appreciate the opportunity to present today. Many discoveries are yet to be made about fungal infections of the eye.

## PRIMARY OPHTHALMIC RHABDOMYOSARCOMA IN 33 PATIENTS\*

BY Carol L. Shields, MD, Jerry A. Shields, MD, Santosh G. Honavar, MD (BY INVITATION), AND Hakan Demirci, MD (BY INVITATION)

### ABSTRACT

**Purpose:** To review the findings, management, and outcome in 33 cases of primary ophthalmic rhabdomyosarcoma.

**Methods:** The records of 33 consecutive patients from a single ocular oncology center were analyzed retrospectively for outcomes of final visual acuity, local recurrence, and distant metastasis.

**Results:** Rhabdomyosarcoma was primarily located in the orbit in 25 cases (76%), conjunctiva in 4 (12%), eyelid in 1 (3%), and uveal tract in 3 (9%). Findings had been present for a mean of 5 weeks and included proptosis in 10 patients (30%), eyelid swelling in 7 (21%), and blepharoptosis in 6 (18%). The initial diagnoses before referral to us included primarily rhabdomyosarcoma in 8 cases (24%), conjunctivitis in 5 (15%), cellulitis in 5 (15%), and pseudotumor in 4 (12%). Tumors were classified according to the Intergroup Rhabdomyosarcoma Study Group staging and treatment protocols as group I in 4 cases (12%), group II in 12 (36%), group III in 16 (48%), and group IV in 1 case (3%). Treatment included surgical debulking, chemotherapy, and radiotherapy. Local tumor recurrence was detected in 6 patients (18%), lymph node spread in 2 (6%), and distant metastasis in 2 (6%). Long-term visual outcome of the 28 patients who maintained their globe was 20/20 to 20/40 in 11 patients (39%), 20/50 to 20/100 in 5 (18%), and 20/200 or worse in 12 (43%). Mean follow-up was 8.3 years; tumor-related death occurred in 1 patient (3%).

**Conclusions:** Rhabdomyosarcoma can present in the orbit, eyelid, conjunctiva, and uveal tract. Following treatment, local tumor recurrence occurs in 18% of cases, metastasis in 6%, and death in 3%.

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### INTRODUCTION

Over the past 25 years, the pediatric, oncologic, and radiologic literature has included several reports on the treatment and outcome of patients with rhabdomyosarcoma.<sup>1-14</sup> Through the collaborative efforts of the Intergroup Rhabdomyosarcoma Study Group, dramatic advances have been made in the understanding of the behavior and management of rhabdomyosarcoma.<sup>1-14</sup> The Intergroup Rhabdomyosarcoma Study Committee (as the group was originally known) was organized in 1972 to perform large collaborative randomized trials for treatment of rhabdomyosarcoma. Since the group's inception, 4 major trials (studies I through IV) have been done.<sup>1-14</sup> As a result of these trials, the survival rate following treatment of rhabdomyosarcoma at all sites has improved from 25% in 1970 to 70% in 1991.<sup>15</sup>

Orbital rhabdomyosarcoma has been recognized to have a better patient prognosis than rhabdomyosarcoma at other sites. Nearly 25 years ago, before the treatment

trials were done, the survival rate of patients with orbital rhabdomyosarcoma was poor (about 30%).<sup>16,17</sup> Treatment generally consisted of orbital exenteration and various chemotherapy regimens. Following trials I and II, improved treatment regimens with chemotherapy and radiotherapy, usually avoiding exenteration, were successful, and the prognosis of patients with orbital rhabdomyosarcoma strikingly improved to a survival rate of 93% at 3 years.<sup>13</sup>

The published reports of the Intergroup Rhabdomyosarcoma Study Group trials focused on patient life prognosis following various treatment regimens; little description was given to the clinical spectrum and diagnostic features of rhabdomyosarcoma in the ocular region. These important reports emanated from pediatric oncology centers and not ocular oncology centers; thus the clinical ophthalmologic details were scant. Additionally, all sites of rhabdomyosarcoma involvement, including the head and neck, genitourinary system, extremities, trunk, and others, were included in most of the analyses of outcome, and only brief details were provided on the subset of ophthalmic rhabdomyosarcoma.<sup>1-14</sup> It appeared that patients with rhabdomyosarcoma in the ocular region were classified under the general heading of "orbital rhabdomyosarcoma" regardless of exact site of origin, whether in the orbit, conjunctiva, or eyelid. Thus, the goal of this report is to describe and define the

\*From the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania. Supported by the Eye Tumor Research Foundation, Philadelphia (Dr C. Shields); the Macula Foundation, New York, New York (Dr C. Shields); the Paul Kayser International Award of Merit in Retina Research, Houston, Texas (Dr J. Shields); Orbis International, New York (Dr Honavar); and the Hyderabad Eye Research Foundation, Hyderabad, India (Dr Honavar).

clinical spectrum of ophthalmic rhabdomyosarcoma, giving particular emphasis to the various sites of origin, including the orbit, conjunctiva, eyelid, and globe.

## MATERIALS AND METHODS

The computerized files of the Ocular Oncology Service at Wills Eye Hospital were reviewed, and all patients with the diagnosis of primary rhabdomyosarcoma were identified. The patients' charts were reviewed, and data on the patient, eye, and tumor were collected. The patient data included age, race, male or female sex, symptoms, duration of symptoms, and initial diagnosis. Data regarding the affected eye and orbit included visual acuity, intraocular pressure, ocular motility and proptosis, and specific ocular structures involved (eyelids, conjunctiva, intraocular contents). Data regarding the tumor included its management before patient referral and its location, size, color, configuration, and appearance on computed tomography (CT) and magnetic resonance imaging (MRI). The tumor management and histopathology, staging and management according to the Intergroup Rhabdomyosarcoma Study Group, and response to treatment were recorded. Final ocular outcome, local tumor control, and systemic outcome were determined.

## RESULTS

Of more than 21,000 patients with ophthalmic tumors and pseudotumors evaluated on the Ocular Oncology Service at Wills Eye Hospital over the past 25 years, only 33 patients (0.2%) had primary ocular rhabdomyosarcoma. The mean patient age was 10 years (median, 7 years; range, 1 month to 68 years). At presentation, 8 patients (24%) were older than 10 years and 4 (12%) were older than 20 years. Twenty-three patients (70%) were male, and 10 (30%) were female; 27 (82%) were white, 4 (12%) were African American, 1 was Asian (3%), and 1 was Hispanic (3%). The right side was involved in 18 patients (55%) and the left in 15 (45%). The presenting clinical manifestations are listed in Table I. The mean duration of symptoms was 5 weeks (median, 4 weeks; range, 1 to 16 weeks). The initial diagnoses by the referring doctors are listed in Table II. Medical treatment of the lesion was performed in 12 cases prior to diagnosis of rhabdomyosarcoma; treatment included corticosteroids in 4 (12%), antibiotics in 7 (21%), and antihistamines in 1 (3%). Surgical biopsy was performed in 9 cases (27%) prior to referral to us.

Visual acuity at presentation was 20/20 to 20/50 in 23 patients (70%), 20/60 to 20/100 in 4 (12%), 20/200 or worse in none (0%), and "fix and follow vision" in the 6

TABLE I: MAIN PRESENTING FEATURE OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS

SYMPTOM	NO. (%)
Proptosis	10 (30)
Eyelid edema	7 (21)
Blepharoptosis	6 (18)
Conjunctival congestion	3 (9)
Visible mass	2 (6)
Blurred vision	2 (6)
Epistaxis	1 (3)
Nasal congestion	1 (3)
Leukocoria	1 (3)

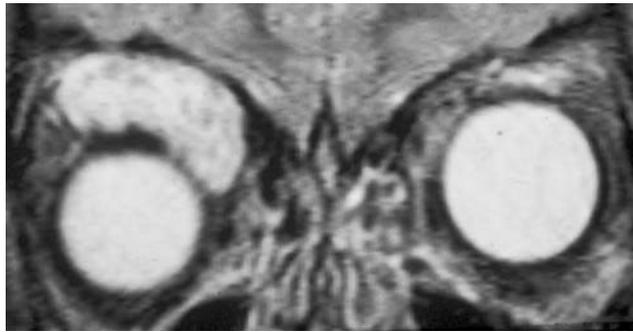
TABLE II: REFERRING DIAGNOSIS IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

DIAGNOSIS	NO. (%)
Rhabdomyosarcoma	8 (24)
Orbital cellulitis	5 (15)
Conjunctivitis	5 (15)
Idiopathic inflammatory orbital pseudotumor	4 (12)
Capillary hemangioma	1 (3)
Orbital cyst	1 (3)
Stye	1 (3)
Allergic edema	1 (3)
Insect bite	1 (3)
Merkle cell tumor	1 (3)
Conjunctival papilloma	1 (3)
Conjunctival cyst	1 (3)
Scleritis	1 (3)
Iris juvenile xanthogranuloma	1 (3)
Retinal detachment	1 (3)

preverbal children (18%). The mean intraocular pressure was 15 mm Hg (median, 14 mm Hg; range, 8 to 26 mm Hg).

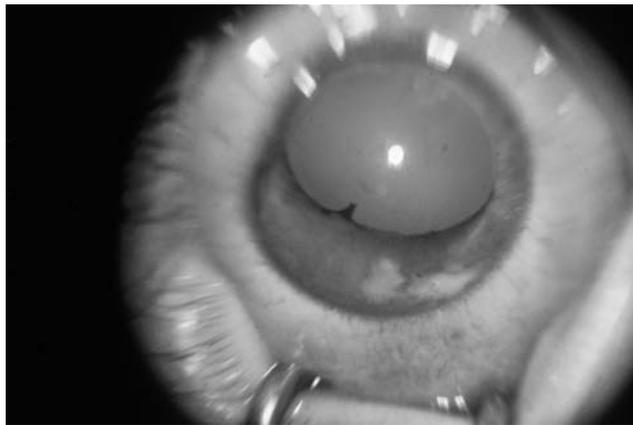
The primary tumor site was the orbit in 25 patients (76%), conjunctiva in 4 (12%), uveal tract in 3 (9%), and eyelid in 1 patient (3%) (Fig 1). The uveal tumors were located in the iris in 1 case and ciliary body in 2 cases (Table III). Of the 30 extraocular tumors, all had an orbital component, despite apparent tumor origin in the conjunctiva or eyelid, and the epicenter of orbital tumor location was superonasal in 11 cases (37%), superior in 10 (33%), inferonasal in 3 (10%), inferior in 3 (10%), nasal in 2 (7%), and inferotemporal in 1 (3%). No tumors were centered temporally or superotemporally in the orbit. Of the 4 conjunctival tumors, the location was upper fornix in 3 cases (75%) and lower fornix in 1 case (25%). No conjunctival tumors originated from the bulbar or limbal conjunctiva.

The ocular findings on presentation are listed in Table IV. The most common findings were proptosis (79%), paraxial globe displacement (79%), eyelid edema (64%), conjunctival congestion (61%), blepharoptosis



**FIGURE 1A**

Case 6. Top, Classic proptosis and eyelid edema from superonasal orbital rhabdomyosarcoma in 9-year-old boy. Bottom, MRI scan (T2-weighted image) demonstrating bright, moderately homogeneous signal of circumscribed superonasal tumor.



**FIGURE 1C**

Case 31. Fluffy white tumor in anterior chamber of 2-year-old child. At enucleation, tumor was confirmed to be intraocular rhabdomyosarcoma. Reprinted, with permission, from Elsas et al.<sup>34</sup>

(55%), dilated episcleral vessels (42%), and ocular motility restriction (42%).

The mean largest tumor dimension by CT or MRI was 25 mm (range, 10 to 60 mm). Excluding the 3 cases of uveal rhabdomyosarcoma, the tumor location in the orbital soft tissues was extraconal alone in 26 (87%), intraconal alone in none (0%), and both intraconal and extraconal in 4 (13%). Bone erosion was present in 10 patients (30%). No tumors caused bone expansion or hyperostosis. Sinus invasion by the orbital tumor was found in the maxillary sinus in 6 cases (20%) (with additional involvement in the



**FIGURE 1B**

Case 29. Pink subconjunctival rhabdomyosarcoma in superonasal fornix of 8-year-old child.

**TABLE III: PRIMARY TUMOR LOCATION IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA**

TUMOR LOCATION	NO. (%)
Orbit	25 (76)
Quadrant location*:	
Superior	10
Inferior	3
Nasal	2
Temporal	0
Superonasal	11
Superotemporal	0
Inferonasal	3
Inferotemporal	1
Anteroposterior location*:	
Anterior orbit	11
Mid orbit	13
Posterior orbit	6
Eyelid	1 (3)
Upper	1
Lower	0
Conjunctiva	4 (12)
Upper fornix	3
Lower fornix	1
Intraocular	3 (9)
Iris	1
Ciliary body	2

\*Total is 30 cases, including all orbital tumors, even those that arose primarily in the conjunctiva and eyelid and secondarily involved the orbit.

nasopharynx in 1 case and the ethmoid sinus in 1 case) and the nasal cavity in 1 case (3%). Intracranial invasion was found into the anterior cranium in 1 case (3%) and skull base in 1 case (3%). By imaging, the tumor was well defined in 21 cases (70%) and poorly defined in 9 (30%).

Orbital CT was available in 25 patients with orbital tumors and revealed a soft tissue, noncalcified mass with contrast enhancement of the tumor in all cases (100%), showing a pattern of generalized enhancement in 23 (92%) and peripheral "ring" enhancement in 2 (8%). The mass appeared cavitory in 2 cases (8%).<sup>18</sup> Orbital MRI was

TABLE IV: PRESENTING SIGNS IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

CLINICAL SIGN	NO. (%)
<b>Proptosis</b>	26 (79)
Displacement of eyeball	26 (79)
Superior	5 (15)
Inferior	8 (24)
Nasal	2 (6)
Temporal	3 (9)
Superonasal	1 (3)
Superotemporal	0
Inferonasal	1 (3)
Inferotemporal	6 (18)
Ocular motility restriction	14 (42)
Blepharoptosis	18 (55)
Edema	21 (64)
Both eyelids	8 (24)
Upper eyelid	12 (36)
Lower eyelid	1 (3)
Erythema	13 (39)
Both eyelids	4 (12)
Upper eyelid	8 (24)
Lower eyelid	1 (3)
Conjunctival congestion	20 (61)
Conjunctival chemosis	11 (41)
Dilated episcleral vessels	14 (42)
Retinal venous dilation	2 (6)
Retinal detachment	1 (3)
Choroidal folds	5 (15)
Disc edema	2 (6)

available in 10 cases, and T1-weighted images revealed a soft tissue mass with low signal in 4 cases (40%), intermediate signal in 5 (50%), and bright signal in 1 case (10%) (Fig 2). On T2-weighted images, the soft tissue mass showed low signal in 2 cases (20%), intermediate signal in 1 case (10%), and bright signal in 7 cases (70%). Gadolinium enhancement was documented in all 10 cases (100%); a pattern of generalized enhancement was shown in 9 cases and ring enhancement of the periphery in 1 case in which cavitory tumor was found<sup>18</sup> (Fig 3).

Histopathologically, the tumor cell type in the 30 cases of extraocular rhabdomyosarcoma was found to be embryonal in 27 cases (90%), alveolar in 3 cases (10%); no botryoid or pleomorphic types were found. The 3 intraocular tumors were too atypical to be classified into these groups. Frozen sections were performed in 15 cases and were found to be diagnostic in 13 (87%) and nondiagnostic in 2 (13%). Immunohistochemistry studies revealed immunoreactivity for desmin in all 16 cases (100%) in which it was performed. There was immunoreactivity for vimentin in 13 (94%) of the 14 cases in which it was performed. Immunoreactivity for myoglobin was detected in 6 (60%) of the 10 cases in which it was performed.

According to the Intergroup Rhabdomyosarcoma Study Group, the tumors were classified as group I in 4

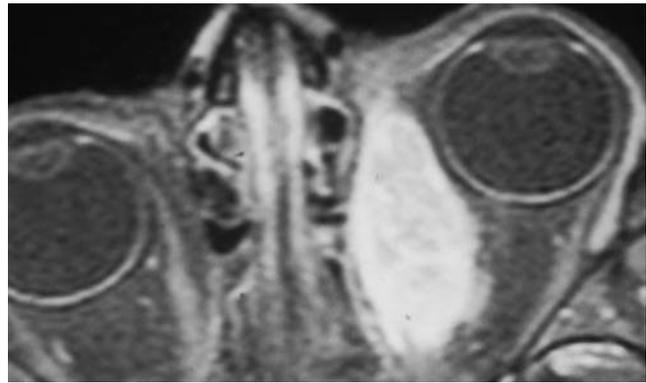


FIGURE 2A

Case 15. Orbital MRI scan (axial T1-weighted, fat suppression technique, gadolinium enhancement) showing fusiform moderately homogeneously enhancing rhabdomyosarcoma in superonasal orbit.

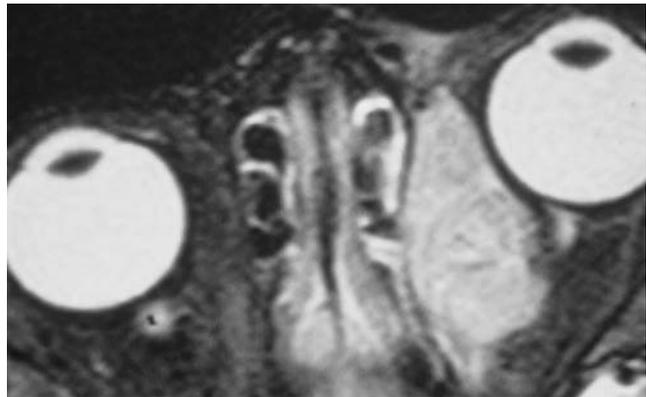


FIGURE 2B

Case 15. MRI scan (axial T2-weighted) showing bright signal of rhabdomyosarcoma with linear internal septations compared with orbital fat and normal muscle.



FIGURE 2C

Case 15. MRI (axial T1-weighted, fat suppression technique, gadolinium enhancement) performed 10 months after diagnosis and treatment of rhabdomyosarcoma, demonstrating lack of solid tumor and only mild enhancement at site of previous surgery.

cases (12%), group II in 12 (36%), group III in 16 (48%), and group IV in 1 case (3%) (Table V). Management was complex in these cases, involving various regimens of chemotherapy, radiotherapy, and even orbital exenteration

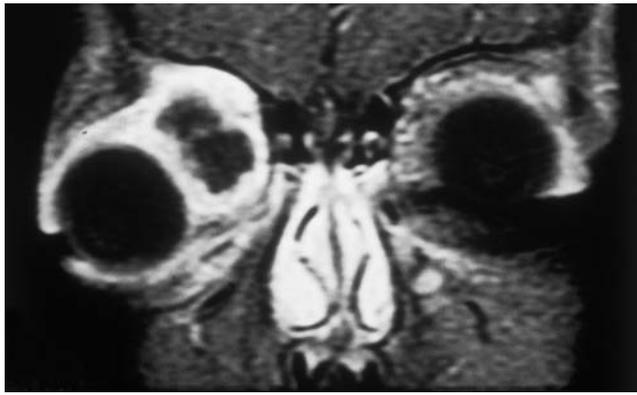


FIGURE 3

Case 17. Orbital MRI (axial T1-weighted, fat suppression technique, gadolinium enhancement) of atypical rhabdomyosarcoma, displaying central nonenhancing cavitation, simulating orbital lymphangioma.

Reprinted, with permission, from Fetkenhour et al.<sup>18</sup>

TABLE V: STAGING OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS ACCORDING TO THE INTERGROUP RHABDOMYOSARCOMA STUDY CLASSIFICATION

GROUP	DESCRIPTION	NO. (%)
I	Completely resected localized disease implying both gross impression resection and microscopic confirmation of complete resection and absence of regional lymph node involvement	4 (12)
Ia	Confined to muscle or organ of origin	4 (12)
Ib	Contiguous involvement outside muscle or organ of origin	0
II	Residual disease and/or regional lymph node involvement	12 (36)
IIa	Grossly resected localized tumor with microscopic residual disease and no evidence of gross residual tumor or regional lymph node involvement	11 (33)
IIb	Regional disease involving lymph nodes and completely resected*	1 (3)
IIc	Regional disease involving lymph nodes and grossly resected with microscopic residua*	0
III	Incomplete resection with biopsy or gross residual disease at site of origin or in regional lymph nodes	16 (48)
IV	Distant metastasis present at onset	1 (3)

\*Regional disease implies involvement of regional lymph nodes.

as per the Study Group protocol at the time of patient entry over the past years (Tables VI and VII). All patients were managed by pediatric oncologists as part of the Intergroup Rhabdomyosarcoma Study Trials. The 3 patients with intraocular rhabdomyosarcoma were managed with enucleation alone.

Complications of management, listed in Table VIII, most commonly included cataract in 18 patients (55%), dry eye in 12 (36%), and orbital hypoplasia in 8 (24%). The orbital, globe, and visual outcomes are listed in Table IX. Two patients (6%) required orbital exenteration, 3 (9%) required enucleation (all cases of uveal

TABLE VI: CURRENT RECOMMENDATIONS OF THE INTERGROUP RHABDOMYOSARCOMA STUDY GROUP IV FOR TREATMENT OF OCULAR RHABDOMYOSARCOMA (GROUPS I, II, AND III)

GROUP	RADIATION THERAPY*	CHEMOTHERAPY
I	None	VA x 32 weeks (regimen 44, VA)
II	4,140 cGy CFI	VA
III	5,040 cGy CFI or 5,940 cGy HFI	VA+C x 52 weeks (regimen 41, VAI) or VA+I x 52 weeks (regimen 42, VAC) or VI +E x 52 weeks (regimen 43, VIE)

CFI, conventional fractionated irradiation; HFI, hyperfractionated irradiation; V, vincristine; A, actinomycin D; C, cyclophosphamide; I, ifosfamide; E, etoposide.

\* Radiotherapy should begin at week 9.

Adapted from Lanzkowsky<sup>20</sup> and Wexler and Helman.<sup>21</sup>

TABLE VII: PRIMARY MANAGEMENT OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS

MANAGEMENT	NO. (%)
Surgical debulking + Chemotherapy + External beam radiotherapy*	28 (85)
Surgical debulking + Chemotherapy	1 (3)
Surgical debulking + External beam radiotherapy	1 (3)
Enucleation†	3 (9)

\* Proton beam radiotherapy was performed in 1 case.

† All were intraocular rhabdomyosarcoma.

TABLE VIII: COMPLICATIONS OF MANAGEMENT IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

COMPLICATION	NO. (%)
Orbit	
Orbital hypoplasia	8 (24)
Strabismus	1 (3)
Restriction of ocular motility	1 (3)
Diplopia	1 (3)
Eyelid	
Blepharoptosis	3 (9)
Ocular surface	
Dry eye	12 (36)
Radiation keratopathy	1 (3)
Intraocular	
Radiation cataract	18 (55)
Radiation retinopathy	3 (9)
Phthisis bulbi	1 (3)
Face	
Second malignant neoplasm	1 (3)

rhabdomyosarcoma), and 12 (36%) had poor visual outcome (20/200 or worse).

The local and systemic tumor outcomes are listed in Table X. Local recurrence was discovered in 6 patients (18%), regional lymph node metastasis in 2 (6%), and distant metastasis in 2 (6%); 1 patient (3%) died. The mean

**TABLE IX: OCULAR AND VISUAL OUTCOMES IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA**

OUTCOME	NO. (%)
Orbit	
No exenteration	31 (94)
Exenteration	2 (6)
Globe	
No enucleation	30 (91)
Enucleation	3 (9)
Visual acuity	
Good (20/20 – 20/40)	11 (33)
Intermediate (20/50 – 20/100)	5 (15)
Poor (20/200 or worse)	12 (36)
Enucleation or exenteration	5 (15)

**TABLE X: LOCAL AND SYSTEMIC TUMOR OUTCOMES IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA**

OUTCOME	NO. (%)
Local tumor outcome	
Regression	28 (85)
Recurrence <sup>°</sup>	6 (18)
Regional outcome	
No lymph node spread	31 (94)
Lymph node spread <sup>†</sup>	2 (6)
Systemic outcome	
No distant metastasis	31 (94)
Distant metastasis <sup>‡</sup>	2 (6)
Final status	
Alive	32 (97)
Dead of metastasis	1 (3)

<sup>°</sup>Local recurrence was managed successfully with debulking + chemotherapy in all 6 cases, with additional external beam radiotherapy in 1 case, gamma knife radiosurgery in 1 case, and exenteration in 2 cases.

<sup>†</sup>Lymph node spread was documented at presentation in 1 case and upon follow-up after therapy in 1 case. Lymph node spread was successfully managed with debulking + chemotherapy in both cases and additional radiotherapy in 1 case.

<sup>‡</sup>Distant metastasis was documented at presentation in 1 case and upon follow-up after therapy in 1 case. Metastasis was successfully treated with debulking + chemotherapy + radiotherapy in 1 case. One patient with overwhelming lung metastasis died despite chemotherapy.

time from diagnosis to local recurrence was 16 months (median, 15 months; range, 7 to 26 months). According to Kaplan-Meier estimates, local recurrence was detected in 10% of patients at 1 year follow-up, 19% at 2 years, and 23% at 5 years. Regional lymph node metastasis was discovered at initial examination in 1 patient and 1 month following institution of treatment in another patient. In the 2 patients with distant metastases, metastasis to the scapula was diagnosed at initial visit in one patient and metastases to the lung and long bones, leading to death, was diagnosed 6 years following treatment in the other patient. Second cancers were found in 2 patients (6%) and

consisted of nonfatal, completely resected facial basal cell carcinoma in the field of irradiation in 1 patient and fatal central nervous system glioblastoma occurring 10 years following complete control of orbital rhabdomyosarcoma in the other. In the 3 patients with uveal rhabdomyosarcoma, all of whom were treated with enucleation alone, no local recurrence, metastasis, or second cancer was found at mean follow-up of 29 months.

## DISCUSSION

Rhabdomyosarcoma is the most common soft tissue sarcoma arising in the pediatric population. It accounts for about 5% of all childhood cancers.<sup>6</sup> About 250 new cases of rhabdomyosarcoma are diagnosed each year in the United States.<sup>19</sup> It can occur in any anatomic location of the body where there is skeletal muscle as well as at sites without skeletal muscle, such as the urinary bladder, common bile duct, and soft tissues of the orbit.<sup>20,21</sup> The primary sites of rhabdomyosarcoma are the head and neck (40%), genitourinary tract (20%), extremities (20%), trunk (10%), and other locations (10%).<sup>20,21</sup> Rhabdomyosarcoma of the head and neck can be further subdivided by location within the orbit (10% of all rhabdomyosarcoma); in the parameningeal region, such as nasopharynx, middle ear, paranasal sinuses, and infratemporal and pterygopalatine fossae (20%); and at other sites, such as larynx, oropharynx, oral cavity, parotid gland, cheek, and scalp (10%).<sup>20,21</sup>

The diagnosis and management of rhabdomyosarcoma have been refined over the past half century. In the 1930s and 1940s, improved understanding of the histopathologic features allowed reclassification of tumors as rhabdomyosarcoma that had been previously grouped into “round cell or spindle cell sarcomas.”<sup>22</sup> Currently, rhabdomyosarcoma is classified into 4 major subtypes—embryonal (57%), alveolar (19%), botryoid (6%), and pleomorphic (1%)—with the remainder too undifferentiated (10%) or heterogeneous (7%) for specific classification.<sup>22</sup>

Over the past 30 years, several treatment trials by the Intergroup Rhabdomyosarcoma Study Group have stimulated interest in this tumor and provided important information regarding effective treatment regimens, leading to improved patient survival rates.<sup>1-14</sup> Currently, when all sites of rhabdomyosarcoma are considered, nearly 70% of patients survive.<sup>15</sup> Rhabdomyosarcoma shows a strong tendency for local invasion, local recurrence, and hematogenous and lymphatic metastases; thus treatment protocols involving both chemotherapy and radiotherapy have been used.<sup>1-14,23,24</sup> Patient survival from rhabdomyosarcoma at any site generally depends on several factors, including extent of disease at diagnosis (according to Intergroup

Rhabdomyosarcoma Study groups I through IV), tumor burden at diagnosis, primary tumor site, patient age, histopathologic and cytologic type, cellular DNA content (ploidy), and therapeutic response.<sup>20,21</sup>

With regard to tumor burden at diagnosis, survival rates are 90% for patients with clinical group I disease, 85% for group II disease, 70% for group III disease, and 40% for group IV disease. Smaller tumor burden (< 5 cm) carries improved survival compared with greater burden (> 5 cm), and younger patient age at presentation (1 year to 7 years) is more favorable than older age (> 7 years). With regard to primary tumor site, 5-year survival is 80% to 90% for those with rhabdomyosarcoma of the orbit, 71% for disease of the head and neck, 70% for parameningeal disease, 73% to 84% for genitourinary disease, 66% for disease of the extremity, and 60% for disease at other sites, such as retroperitoneum, trunk, pelvis, and paraspinal region.<sup>20,21</sup> Histopathologic features are important predictors of patient outcome; patients with embryonal cell type have the best prognosis, whereas those with alveolar cell type show the least favorable outcome. Additionally, prognosis is better with tumors whose DNA content is 1.5 times normal (hyperdiploid) than with those with normal diploid content. Finally, the most important prognostic variable is response to therapy: Patients who show a poor response or do not attain a complete pathologic response are less likely to survive.

In 1997, the Intergroup Rhabdomyosarcoma Study Group provided a comprehensive report on the subset of patients with orbital rhabdomyosarcoma.<sup>10</sup> Data were analyzed from 264 patients managed with treatment protocols from trials I, II, III, and IV. Tumor involvement was classified as group I in 3% of patients, group II in 20%, group III in 74%, and group IV in 3%. The tumor cell type proved to be embryonal in 80%, alveolar in 9%, botryoid in 4%, pleomorphic in 0%, undifferentiated in 4%, and other in 3%. Few details were given regarding patient clinical or imaging features because the report was focused on patient outcome. The average follow-up was 7.5 years. Overall, 18 patients (7%) died of rhabdomyosarcoma and 5 (2%) died of treatment-related complications. The 5-year survival rate was 74% for those with orbital alveolar rhabdomyosarcoma and 94% for those with embryonal rhabdomyosarcoma.

In our analysis of 33 patients with orbital rhabdomyosarcoma managed at an ocular oncology center in coordination with a major pediatric oncology center, we found similar results for tumor classification: group I in 12% of patients, group II in 36%, group III in 48%, and group IV in 3% (Table V). Likewise, we found a similar distribution of tumor cell type in the 30 tumors involving the extraocular structures: embryonal in 90%, alveolar in 10%, and botryoid or pleomorphic in none. Tumor-related death

occurred in 1 patient (3%), treatment-related complications leading to death in no patients, and death from second cancer in 1 patient (3%). Therefore, our results are similar to those of the Intergroup Rhabdomyosarcoma Study. The important addition from our observations, however, is the analysis of the clinical variations of this malignancy within the ocular tissues and the identification of a minor group of patients with rhabdomyosarcoma within the globe.

Ophthalmic involvement of rhabdomyosarcoma generally occurs in children at an average age of 10 years, but this malignancy can develop in adults. In our group, 24% of patients were older than age 10, and 12% were older than 20; the oldest patient was 68 years.<sup>25</sup> The most common presenting clinical features were proptosis (30%), eyelid edema (21%), and blepharoptosis (18%) (Table I). Nasal congestion and epistaxis were also manifestations of ophthalmic rhabdomyosarcoma. Those patients with tumors in the uveal tract had symptoms of blurred vision or leukocoria.

Rhabdomyosarcoma can affect several ocular tissues. In our series, the tumor developed in the orbit in 76% of cases, conjunctiva in 12%, eyelid in 3%, and within the globe in 9%. Some degree of orbital involvement was found in all 30 cases of extraocular tumor, despite apparent tumor origin in the conjunctiva or eyelid. Of those 30 extraocular tumors, the tumor location within the orbit was superonasal or superior in 70% of cases, usually in the anterior orbit (Table III). Thus, this tumor has a tendency to occur in the superonasal anterior aspect of the orbit.<sup>26</sup>

The most frequent clinical findings in patients with ophthalmic rhabdomyosarcoma are proptosis (79%), globe displacement (79%), eyelid edema (64%), and conjunctival congestion (61%). Thus, the differential diagnostic considerations include inflammatory lesions such as orbital cellulitis, idiopathic inflammatory orbital pseudotumor, conjunctivitis, and allergic edema, and other tumors such as orbital capillary hemangioma, lymphangioma, Langerhan's cell histiocytosis.<sup>27-31</sup> Most of these conditions can be differentiated by clinical history taking and examination, but orbital lymphangioma may prove to be more challenging to differentiate from rhabdomyosarcoma. Rhabdomyosarcoma occurs in patients of the same age-group as those with lymphangioma, and both diseases cause painless, noninflammatory proptosis, occurring over a short time. Differentiation by orbital imaging is usually helpful and shows a solid enhancing mass with rhabdomyosarcoma versus a multicystic nonenhancing mass with lymphangioma. However, in rare cases, rhabdomyosarcoma can display cavitation appearing similar to lymphangioma.<sup>15</sup>

Intraocular rhabdomyosarcoma is particularly rare.

Because of our interest in intraocular malignancies, we have seen a disproportionate number of patients with intraocular rhabdomyosarcoma, skewing the true incidence of patients with tumor in this location. Two of the cases in our series have been previously published.<sup>32,33</sup> In the third case, the eye of a 34-year-old African American woman was enucleated for a ciliary body tumor at another institution, and the rhabdomyosarcoma was discovered on histopathologic examination. According to our cases and a few reported cases, intraocular rhabdomyosarcoma has appeared in the iris as a circumscribed or fluffy mass at a median age of 4 years and has also presented in the ciliary body.<sup>32-35</sup> Iris rhabdomyosarcoma can resemble iris juvenile xanthogranuloma.<sup>33</sup> Enucleation has been performed in all of these cases. In the 4 published cases of intraocular rhabdomyosarcoma,<sup>32-35</sup> no patients had developed metastasis at 1-, 3-, 4-, and 20-year follow-up examinations.

Imaging of periocular rhabdomyosarcoma is critical in establishing the diagnosis, as well as the extent and location of the tumor, for surgical planning.<sup>36,37</sup> Mafee and associates<sup>36</sup> reviewed 11 cases of orbital rhabdomyosarcoma and found that these tumors on CT were isodense compared with normal muscles, generally with homogeneous internal qualities and well-defined margins, and lacking adjacent bone destruction. Moderate to marked enhancement with contrast agent was a feature of all tumors. However, larger tumors were less well defined, sometimes with bone destruction and heterogeneous internal qualities related to hemorrhage. Sohaib and coworkers<sup>37</sup> further refined these observations and noted that orbital rhabdomyosarcoma was intraconal in 40% and extraconal in 60%. Bone erosion was found in 17% and bone thinning in an additional 23%. MRI of orbital rhabdomyosarcoma demonstrated isointense or slightly hypointense signal compared with normal brain on T1-weighted images and increased signal on T2-weighted images.<sup>36</sup> All tumors showed enhancement with contrast agents. Areas of hemorrhage appeared as focal increased signal on T1- and T2-weighted images. In our series, similar features were found on imaging. All of the tumors in our series were extraconal, but some showed partial intraconal component. There were no tumors with intraconal involvement alone. The findings on MRI were more variable than those described by Sohaib and associates,<sup>15</sup> in that low or intermediate signal was found on T1-weighted images in 90% of cases and bright signal on T2-weighted images in 70% of cases. In 1 case, cavitory changes within the mass displayed ring enhancement.

Treatment protocols for rhabdomyosarcoma have evolved over the past 25 years according to the recommendations of the Intergroup Rhabdomyosarcoma Study Group.<sup>4,6,10,13,38</sup> Currently, according to the results of trial

IV, the recommended treatment includes both chemotherapy and radiotherapy as listed in Table VI, with the exception of completely resected orbital tumors, where only chemotherapy without radiotherapy is advised. Current management of group IV orbital rhabdomyosarcoma depends on the location and extent of disease and generally consists of combination chemotherapy and radiotherapy delivered to the orbit and all involved sites of tumor.<sup>20</sup> Recurrent tumors in the orbit usually are treated with orbital exenteration, sometimes supplemented with chemotherapy and radiotherapy.<sup>39</sup>

Several investigators have focused on late effects of therapy in orbital rhabdomyosarcoma in children.<sup>12,40,41</sup> In 2000, Raney and coworkers<sup>12</sup> reported on late effects of therapy in 94 patients with orbital rhabdomyosarcoma from the Intergroup Rhabdomyosarcoma Study III. Data were gathered by questionnaire from numerous oncology institutions involved in following the clinical course of the children. The investigators reported that exenteration or enucleation was necessary in 14% of patients for tumor control or treatment complications. Other late effects included cataract (82%), decreased visual acuity (70%), orbital hypoplasia (59%), dry eye (30%), chronic keratoconjunctivitis (27%), and retinopathy (6%). In our series, we were able to accurately record the late effects, since all patients were examined by our team of ocular oncologists. Overall, enucleation was necessary for all 3 patients with intraocular rhabdomyosarcoma, and orbital exenteration was performed for 2 (7%) of the 30 patients with extraocular rhabdomyosarcoma in order to achieve tumor control. Of the remaining 28 eyes, late effects included cataract (55%), dry eye (36%), orbital hypoplasia (24%), blepharoptosis (9%), and radiation retinopathy (9%), as listed in Table VIII. Consequently, current treatment of periocular rhabdomyosarcoma can lead to substantial local late effects.

In the late effects study, the visual acuity was reportedly decreased in 70% of patients, ranging from 20/30 to 20/400.<sup>12</sup> The details regarding visual outcome were not provided. We can add to these data and state that visual acuity following treatment in the 30 patients with periocular rhabdomyosarcoma was good at 20/20 to 20/40 in 37%, intermediate at 20/50 to 20/100 in 17%, and poor at 20/200 or worse in 47%. These results reflect primarily the long-term effects of radiation on the function of the eye.

The prognosis for patients with orbital rhabdomyosarcoma has greatly improved in recent years. Orbital rhabdomyosarcoma represents about 10% of all rhabdomyosarcoma cases, and it is recognized that patients with tumors at this site carry the best prognosis.<sup>12</sup> On the basis of Trials I, II, III, and IV, the survival rate of patients with orbital rhabdomyosarcoma is now 93%.

Tumor morphology is an important predictor of death: those patients with alveolar cell type have a 74% 5-year survival rate, whereas those with embryonal cell type demonstrate a 94% 5-year survival rate.<sup>10</sup> This favorable prognosis may be directly related to the tumor site and perhaps earlier detection with smaller tumor burden, but it could also be related to the fact that more orbital tumors display embryonal cell type (80%) when compared with rhabdomyosarcoma at any site (54%).<sup>10</sup> Despite the overall good prognosis, the seriousness of this malignancy should be realized. From another perspective, 44% of children who die of orbital rhabdomyosarcoma displayed alveolar cell type.<sup>10</sup> Even though age at diagnosis did not prove to be a predictor of tumor-related death, infants under 1 year of age with orbital rhabdomyosarcoma show particularly poor prognosis, with death in 46%.<sup>10</sup> The reason for more aggressive behavior of rhabdomyosarcoma in infancy is unknown.

Our results should be interpreted with caution. First, we maintain a tertiary referral practice, and some of our patients had initial biopsy or therapy elsewhere and were then referred to us following diagnosis or failure of treatment; thus, our series may represent cases with an expected worse prognosis. Second, tumors in the conjunctiva may be difficult to distinguish from those in the anterior orbit, leading to imprecision in pinpointing exact tumor origin in the periocular tissues. Additionally, the patient outcomes were gathered from data over 25 years with use of multiple treatment protocols. Our goal was to present details of the ocular spectrum of rhabdomyosarcoma, since this information was not available in the major reports from the Intergroup Rhabdomyosarcoma Study Group. We did not intend to compare one treatment with another, since this had already been accomplished by the previously mentioned studies.<sup>1-14</sup> Finally, our series represents only primary ocular rhabdomyosarcoma; secondary cases such as those that occur following radiotherapy for retinoblastoma were excluded.<sup>42</sup>

## SUMMARY

Primary rhabdomyosarcoma in the ophthalmic area can originate in the orbit, conjunctiva, or eyelid or within the globe. Most patients present with classic findings of proptosis, globe displacement, or eyelid edema. Orbital exenteration is necessary in 6% of patients for tumor control. Life prognosis is favorable, with a survival rate of greater than 90%.

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## DISCUSSION

DR GEORGE B. BARTLEY. I very much appreciate the opportunity to initiate the discussion of this fine paper by Dr Shields and her colleagues. The clinical features that they summarize complement those published by the Intergroup Rhabdomyosarcoma Study in 1997.<sup>1</sup> The clinical

outcomes are consistent with that report and confirm that orbital radiation therapy is cruel to the eye.<sup>2</sup> To frame your discussion of this tumor and its treatment, I'd like to summarize the 150-year story of rhabdomyosarcoma in approximately 150 seconds. It is a tale that includes raisins and bubble gum, tadpoles and FISH.

Although a case identifiable as a rhabdomyosarcoma was described by Weber<sup>3</sup> in 1854, the first notable descriptive series was not published for nearly another century, namely, Stout's<sup>4</sup> seminal paper in 1946. The lesions were included among the small blue round cell tumors primarily affecting children and initially were thought to develop from striated muscle. Soon, however, it was recognized that the tumor could originate from a more primitive, undifferentiated precursor and in 1958 the light microscopic categories that are now familiar to all of us were formally proposed by Horn and Enterline.<sup>5</sup>

The embryonal subtype constitutes about 60% of all newly diagnosed cases and accounts for more than 90% of orbital involvement. The histopathologic appearance has been memorably described by Dr Morton Smith as "raisins in bubble gum." Mature rhabdomyoblasts may resemble tennis racquets or tadpoles. About one-fifth of cases are categorized as alveolar because of a structural resemblance to pulmonary tissue. The remaining 20% demonstrate a pleomorphic or undifferentiated histiotype.

Diagnostic accuracy improved in the 1960s as immunohistochemical techniques to recognize myosin were used to complement light microscopy.<sup>6</sup> The prognosis for affected patients, however, remained nasty, brutish, and short. The momentum shifted in 1972 with the formation of the Intergroup Rhabdomyosarcoma Study Committee, whose collaborative recommendations now form the "standard of care" for the treatment of this rare tumor.

The future of rhabdomyosarcoma, in a sense, began in 1982, with the discovery that most alveolar tumors contain a translocation between chromosomes 2 and 13.<sup>7</sup> What results is the fusion of the PAX3 gene from chromosome 2 (band 2q35) with the FKHR gene from chromosome 13 (band 13q14). PAX3 is thought to be a transcriptional regulatory protein that contributes to the formation of myoblasts from mesenchymal precursors. Dysregulated cell growth and tumor transformation occur when the mutation's chimeric product (PAX3-FKHR) functions as an oncogene and activates PAX3's targets.<sup>8</sup>

Embryonal tumors do not demonstrate tumor-specific translocations, but they may show a loss of heterozygosity for several loci that are closely linked on the short arm of chromosome 11. This implies that a tumor suppressor gene, yet to be identified, is inactivated.

In addition to the *structural* genetic abnormalities that I've just described, *numerical* anomalies also have

been identified in rhabdomyosarcoma. For instance, some embryonal tumors with a hyperdiploid DNA content appear to be more sensitive to chemotherapy and radiation therapy than are tumors with a normal DNA content. The correlation, however, is inconsistent.

It is hoped that future studies, perhaps using fluorescence in situ hybridization (or FISH), will evince specific genetic abnormalities for each histologic subtype of rhabdomyosarcoma and suggest avenues for more precise means of therapy. This is important because neither vincristine nor actinomycin D is tumor-specific.<sup>9</sup> In the meantime, there is optimism that some patients may respond favorably to decreased doses of radiation therapy, shorter courses of chemotherapy, or possibly even to chemotherapy alone,<sup>10</sup> decreasing the treatment-related side effects noted in this paper and others. Thank you.

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DR CAROL L. SHIELDS. I would like to thank my discussant, Dr George Bartley. Dr Bartley made several important points regarding rhabdomyosarcoma, including tumor genetics, DNA ploidy, and radiotherapy complications.

With regard to tumor genetics, I agree that it is critical to evaluate fresh tumor tissue for genetic abnormalities, especially tumors that occur in children. It is our policy to save fresh tumor tissue on all patients with pediatric ocular cancers, whether it be rhabdomyosarcoma, retinoblastoma, or others. This tissue is immediately evaluated by genetic researchers or snap frozen for future research. Evaluation of tumor genetics can be useful for diagnostic and therapeutic reasons as well as for future genetic counseling.

With regard to DNA ploidy, it is recognized that rhabdomyosarcoma with hyperdiploid DNA content show different features and responses than those tumors with normal DNA content. In fact, DNA ploidy is a factor important in patient prognosis. Patients with hyperdiploid DNA content show more favorable prognosis than those with normal DNA content. However, there are several additional factors that affect prognosis in the patient with rhabdomyosarcoma including extent of disease at diagnosis as graded by Intergroup Rhabdomyosarcoma Study grouping I to IV, tumor burden at diagnosis, primary tumor site, patient age, histopathologic and cytologic type, and therapeutic response. Thus, the combination of these features with DNA ploidy is important for speculating on prognosis.

With regard to radiotherapy complications, there are efforts using newer methods of radiotherapy and lower doses to minimize treatment side effects. Even despite these therapeutic efforts radiation complications still occur but radiation-induced dry eye, cataract, and retinopathy are more effectively managed today than in the past.

In summary, we have come a long way with regard to tumor control of orbital rhabdomyosarcoma. Future efforts will focus on genetic investigations, therapeutic innovations, and minimizing side effects of treatment.



## SURFACE KERATOPATHY AFTER PENETRATING KERATOPLASTY\*

BY *Vahid Feiz, MD* (BY INVITATION), *Mark J. Mannis, MD*, *Ganesha Kandavel, MD* (BY INVITATION), *Martin McCarthy, MD* (BY INVITATION), *Luis Izquierdo, MD* (BY INVITATION), *Marianna Eckert,* (BY INVITATION), *Ivan R. Schwab, MD*, *Sima Torabian,* (BY INVITATION), *Jane-Ling Wang* (BY INVITATION), AND *Wei Wang* (BY INVITATION)

### ABSTRACT

**Purpose:** To determine the type and prevalence of epithelial abnormalities in the intermediate postoperative period after penetrating keratoplasty and to define the donor and recipient variables that influence the status of the graft epithelium.

**Design:** Prospective cohort study.

**Methods:** We prospectively followed the clinical course of 80 patients after penetrating keratoplasty. We monitored the status of the corneal epithelium for 3 months after surgery using slit-lamp biomicroscopy and fluorescein staining of the epithelium. Donor characteristics, recipient preoperative and postoperative variables, and postoperative medications were recorded. Epithelial abnormalities were analyzed against these variables by using univariate and combined statistical models to determine the impact of each variable on postoperative epithelial pathology. Main outcome measures included punctate keratopathy, macro-epithelial defects, hurricane keratopathy, rim defects, and filamentary keratopathy.

**Results:** Sixty-three percent of all patient visits demonstrated punctate epithelial keratopathy (PEK). Hurricane keratopathy (51%) and filamentary keratopathy (14%) constituted the next most commonly observed abnormalities. Older recipient age and the use of topical antibiotics were associated with a higher prevalence of punctate epithelial keratopathy. The odds ratio (OR) for a 1-year increase in age is 1.0276 (95% CI, 1.1013-1.0442), and the OR for using topical antibiotics is 6.9028 (95% CI, 3.1506-15.1239). Use of topical ofloxacin and increased time after surgery were associated with lower prevalence of punctate keratopathy; ORs were 0.9806 (95% CI, 0.9736-0.9876) and 0.3662 (95% CI, 0.1688-0.7943), respectively. Decreased corneal sensation and the presence of anterior blepharitis preoperatively were associated with an increase in hurricane keratopathy; ORs were 8.8265 (CI, 2.3837-32.6835) and 3.2815 (CI, 1.7388-6.1931), respectively. Total storage time for the donor material was also associated with an increased prevalence of hurricane keratopathy (OR, 1.0316; CI, 1.0052-1.0220). Patients with rim defects and macro-epithelial defects were more likely to have antibiotic and topical lubrication prescribed. No specific variable was found to have a significant association with filamentary keratopathy, except possibly for death-to-preservation time, which had a *P* value of .0587.

**Conclusions:** Surface keratopathy is one of the most common complications of keratoplasty. Our study demonstrates that older age, preoperative lid disease, and decreased preoperative corneal sensation appear to increase the probability of clinically significant epithelial surface abnormalities after keratoplasty. Recognition of these risk factors in advance of surgery will alert the surgeon to the need for appropriate management.

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### INTRODUCTION

Penetrating keratoplasty is the most common transplant procedure performed in North America.<sup>1,2</sup> A variety of fac-

tors affect graft survival and the visual rehabilitation of the corneal transplant recipient. Although endothelial rejection, infection, and disabling astigmatism are commonly considered the primary causes of physiologic or functional graft failure,<sup>3,4</sup> corneal surface disease can cause significant morbidity and delay in visual rehabilitation. Surface dysfunction may result in a poor refractive surface and can, in addition, cause significant discomfort to patients. Persistent macro-epithelial defects may predispose the graft to infectious keratitis and secondary failure. It is estimated that as many as 25% of grafts may fail on account of surface problems.<sup>5</sup>

In the first several weeks after corneal transplantation, the surface of a corneal graft undergoes enormous

\*From the Cornea Service, Department of Ophthalmology, University of California, Davis, School of Medicine (Dr Mannis, Dr Kandavel, Dr Izquierdo, Ms Eckert, Dr Schwab, and Ms Torabian); the Department of Ophthalmology, University of Arkansas Medical School/Harvey and Bernice Jones Eye Institute (Dr Feiz); the Division of Cornea and External Disease, Department of Ophthalmology, University of British Columbia (Dr McCarthy); and the Department of Statistics, University of California, Davis (J-L. Wang, W. Wang). Supported by grants to the Departments of Ophthalmology at the University of California, Davis, and the University of Arkansas from Research to Prevent Blindness, Inc, New York, New York.

changes, which frequently include total replacement of the donor epithelium by the recipient. The precise time for complete replacement of the donor epithelium is not known. However, studies of epithelial rejection<sup>4</sup> and sex chromatin in rabbits<sup>6</sup> have indicated that donor epithelium may persist for as long as 1 year after transplantation. Even after epithelial repair by mitosis, migration, and transformation of the host stem cell population, firm adhesion of the newly reconstituted epithelium to the underlying tissue requires production of new basal lamina and proper hemidesmosomal attachment. In a native cornea, this process requires several weeks.<sup>7</sup> In the transplant patient, this process is yet more complicated, since in the early postoperative period, there are the additional insults of the relative denervation of the cornea, poor lubrication, the instillation of frequent and often toxic topical medications, and an abnormal lid-cornea anatomical relationship.

Punctate erosions and vortex keratopathy, along with other types of epithelial abnormalities, are common after keratoplasty, especially in the early postoperative period.<sup>8,9</sup> If not appropriately managed, these ubiquitous problems can escalate into conditions that may threaten the health of the transplant. The critical period for stabilization of most surface problems is in the first 3 months.

In this study, we attempted to determine the prevalence and types of surface disease in the early and intermediate postoperative period as well as to study those donor and recipient factors that might influence the graft surface postoperatively. We followed a cohort of 80 patients prospectively after penetrating keratoplasty, and we systematically observed the status of the ocular surface for 3 months after surgery.

## METHODS

Between January 1998 and January 2000, a total of 121 patients were enrolled in this study, with the final analysis including 80 of the original 121 patients enrolled. We obtained an exemption from the Institutional Review Board at the University of California, Davis, since there was no alteration in the treatment regimen of patients whose data were included in this study. All patients underwent penetrating keratoplasty in the Cornea Service, Department of Ophthalmology, University of California, Davis. Surgeries were performed by one of the two faculty corneal surgeons (M.J.M., I.R.S.) or one of two cornea fellows under direct faculty supervision. The mean age of the patients enrolled in this study was 62.05 years (range, 13 to 88). The most common indications for penetrating keratoplasty were Fuchs' dystrophy (28.75%), aphakic or pseudophakic bullous keratopathy (15%), keratoconus (10%), herpes simplex virus (HSV) keratitis

(8.75%), and other indications (37.5%). The earliest recorded observation of the epithelium was at 4 days and the longest at 139 days postoperatively.

At initial examination, all patients underwent a complete anterior segment evaluation. This included notation of the status of the lids and lashes, Schirmer test I or basic tear secretion test, and corneal sensation. A Schirmer test value greater than 5 mm of tear advancement on a filter paper strip with anesthesia or 10 mm of tear advancement without anesthesia was considered normal. Corneal sensation was measured by using a Luneau (Cochet-Bonnet) esthesiometer. With this system, corneal sensation was graded from 0/6 (no corneal sensation) to 6/6 (full corneal sensation).

Data on the donor cornea were obtained from the eye bank of origin. These included the age and sex of the donor, death-to-preservation time (hours), preservation-to-surgery time (hours), and the eye bank evaluation of the epithelial status of the donor. Donor epithelial status was recorded as either good (minimal epithelial defect), mild (epithelial defect less than one-third area of the graft), moderate (epithelial defect less than two-thirds area), or severe (epithelial defect more than two-thirds area). Donor corneas were supplied as corneal-scleral buttons in Optisol medium.

## SURGICAL PROCEDURE

The host bed was prepared by making a deep partial-thickness trephination using either a disposable Weck™ handheld trephine mounted on an obturator or a suction trephination device (the Barron™ radial vacuum trephine or the Hanna-Moria™ trephine). The anterior chamber was then entered with a sharp blade, and the host button was removed using corneal scissors. The donor button was prepared by punching from endothelial surface against a Teflon block with a disposable Weck™ trephine mounted on an Iowa punch. The donor cornea was generally 0.25 or 0.5 mm larger than the recipient bed. The donor cornea was sutured to the host with 10-0 nylon suture either as 16 interrupted sutures or a combination of 12 interrupted and a single running suture, depending on the degree of vascularization of the recipient bed. Donor epithelium was not purposely removed. At the conclusion of each procedure, all patients received a subconjunctival injection of dexamethasone and either cefazolin or gentamicin. All eyes were patched and shielded overnight.

After removal of the patch on the morning after surgery, therapy was begun with ofloxacin drops, 4 times daily, and either prednisolone acetate 1% (Pred-Forte™) or prednisolone sodium phosphate 1% (Inflamase Forte™), 4 times daily. If a large epithelial defect (greater than one-third area of the graft) was present, therapy with

a lubricant ointment such as Refresh PM™ or erythromycin ointment at night was also started. After postoperative day 1, the status of the epithelium, the patient's topical medications, and dosage regimen were recorded for a minimum of 3 separate visits during a period of at least 10 weeks. At each visit, the corneal surface was carefully examined before and after application of fluorescein stain. Punctate keratitis was graded as 0-4, depending on the severity of staining, with 0 being minimal to no punctate staining and 4 being confluent punctate staining covering the entire graft surface. Punctate epithelial keratitis (PEK)—alternatively, punctate epithelial erosion (PEE)—was defined as localized or diffuse punctate microepithelial defects on the surface of the graft. Other epithelial irregularities, including hurricane (vortex) keratopathy, rim epithelial defects, filamentary keratitis, and macro-epithelial defects (>1 mm), if present, were recorded at each visit. Any postoperative complication such as wound leak, infectious keratitis, nonhealing epithelial defects, and graft rejection were recorded. Intraocular pressure was measured at each visit using a Tonopen™, and if pressure was elevated (>22 mm Hg), medical management was initiated.

Patients were excluded from the study for any of the following reasons: incomplete follow-up data (fewer than 3 postoperative visits or an observation period of fewer than 10 weeks), postoperative complications such as infectious keratitis, wound leak requiring the application of a contact lens, or lack of sufficient donor data. The total number of patients meeting the study criteria was 80, with a total of 332 documented visits.

#### STATISTICAL METHODS AND DATA ANALYSIS

Sixty-seven patients (269 visits) demonstrated differing degrees (0-4) of PEK as the only epithelial abnormality. Only these visits for each patient were analyzed to determine the significance of any associations with punctate keratitis. All 332 visits were used for statistical analysis of other epithelial abnormalities.

For PEK, the statistical analysis of the data was performed as follows: Since the data were longitudinal in nature, in order to determine which variables were significant in the development and severity of PEK, a cumulative logit model was fitted to the data, considering PEK to be the dependent variable. The generalized estimating equation (GEE) method under the GENMOD procedure in SAS PC version 8.0 was used for this model.<sup>10-12</sup> To see the significance of each independent variable, a simple regression model was fitted with each independent variable. These included the preoperative and postoperative factors as already detailed (eg, patient's age and postoperative medications). Variables that were significant ( $P \leq .05$ )

in the isolated simple regression analysis were further included in a multiple regression model to determine their statistical influence on the resulting PEK. Odds ratios were reported on the basis of the final multiple regression model in which the effect of each independent variable on the dependent variable was adjusted by other factors with a  $P$  value < .05.

For macro-epithelial defects, rim defects, and hurricane keratopathy, a binary model was used to perform statistical analysis. At each visit, the abnormality was either present or absent. Univariate regression analysis was performed to select significant independent variables. Again, odds ratios were provided only for those variables that remained significant after the influence of other variables were taken into account as dictated by the final multiple regression model.

For filamentary keratopathy, three possible outcomes were recorded. The abnormality was either present or absent; if present, it was either related to or not related to the sutures. Univariate analysis was performed in a similar fashion to select independent variables, and an odds ratio was reported on the basis of the final multiple regression model.

## RESULTS

### 1. ANALYSIS OF RISK FACTORS IN THE DEVELOPMENT OF PEK

The results of the statistical analysis of the factors affecting PEK and its severity are summarized in Tables I through V. The values featured in these tables represent the postoperative data for the 67 patients described who manifested PEK as the only epithelial abnormality. Thirty-four males and 33 females fell into this cohort, totaling 269 visits. In 63% of visits, grade 1 or higher PEK was noted. Ninety-nine visits had grade 0 PEK, 44 had grade 1 PEK, 46 had grade 2, 46 had grade 3, and 34 visits had grade 4 PEK. The variable factors are divided into donor, recipient preoperative, and recipient postoperative.

As shown in Tables I and II, the age of the donor, death-to-preservation time, preservation-to-surgery time, total time, and the epithelial status of the donor all had insignificant impact on development of PEK. The only preoperative factor with a statistical significance in the development of PEK, according to the single variable regression analysis, was the recipient's age, with a  $P$  value of .0137 (Table III).

As shown in Table IV, the use of any topical antibiotics with the exception of trimethoprim sulfate had a  $P$  value of less than 0.05, indicating a statistically significant effect on PEK using single variable regression. The use of topical

TABLE I: DONOR VARIABLES AND THEIR EFFECT ON PEK

DONOR	MINIMUM	MAXIMUM	MEAN	SD	P VALUE
Age (yr)	9	81	57.88	15.06	.9461
Death-to- preservation time (hr)	1	13.25	7.61	3.11	.7125
Preservation-to-surgery time (hr)	5.23	170.83	96.59	45.17	.8439
Total time (hr)	13.38	178	103.22	45.33	.9383

PEK, punctate epithelial keratopathy.

TABLE II: SIGNIFICANCE OF DONOR EPITHELIAL STATUS ON PEK

DONOR	GOOD	MILD	MODERATE	SEVERE	P VALUE
Epithelium°	8	41	17	1	.1813

PEK, punctate epithelial keratopathy.

°As detailed in "Methods" section.

TABLE III: SIGNIFICANCE OF RECIPIENT PREOPERATIVE VARIABLE FOR DEVELOPMENT OF PEK

VARIABLE	MINIMUM		MEAN		MAXIMUM		SD	P VALUE	
Patient age (yr)	13		62.55		86		17.86	.0137	
Patient sex	M 34				F 33			.2045	
Preoperative diagnosis	ABK/PBK 11		Fuchs' 21		HSV 6	KCN 7	Other 22		.1476
Corneal sensation	0/6 1	1/6 7	2/6 8	3/6 8	4/6 10	5/6 10	6/6 22	Missing 1	.2392
Schirmer test	Normal 46				Abnormal 21				.9856
Anterior blepharitis	True 17				False 50				.9291
Postblepharitis	True 42				False 15				.1307

ABK, aphakic bullous keratopathy; HSV, herpes simplex virus; KCN, keratoconus; PBK, pseudophakic bullous keratopathy; PEK, punctate epithelial keratopathy.

TABLE IV: POSTOPERATIVE MEDICATIONS AND SIGNIFICANCE ON PEK

TOPICAL MEDICATION	USED	NOT USED	P VALUE
Pred-Forte	94	175	.0633
Inflamase	163	108	.1598
Dexamethasone	7	262	.8602
Antibiotic (any)	102	167	
Oceflox	70	199	<.0001
Erythromycin	19	250	.0036
Polytrim	11	258	.1466
Other antibiotics	16	253	.0054
Lubricant (any)	50	219	.2046
Artificial tears	4	265	.1211
Celluvisc	21	248	.8065
Refresh Plus	16	253	.5318
Other lubricants	3	266	.2449
Other medicine	1	268	.3154

PEK, punctate epithelial keratopathy.

TABLE V: SIGNIFICANCE OF TIME ELAPSED AFTER SURGERY ON PEK

TIME	MINIMUM	MAXIMUM	MEAN	SD	P VALUE
Days	4	139	46.89	35.81	<.0001

PEK, punctate epithelial keratopathy.

corticosteroids and lubricants did not have a statistically significant effect on PEK.

Time elapsed after penetrating keratoplasty was found to be significant, with a *P* value <.001, as shown in Table V.

*Odds Ratio for Factors Significant in the Development of PEK*

All variables affecting PEK status with *P* values less than or equal to 0.05 were not finally significant in the development of PEK when adjusted to account for the effect of the other variables. The variables found to have no significant effect on PEK in the combined model were the use of erythromycin ointment and use of “other antibiotics,” and the odds ratios for the remaining significant variables are provided in Table VI.

The odds ratios reported in Table VI indicate the relative chance of developing PEK in respect to a given variable. All odds ratios are evaluated relative to 1.000, such that an odds ratio of 1.000 indicates no negative or positive influence on PEK. For example, the odds of having a greater degree of PEK is 0.9806 times less likely at a visit 1 day later (eg, on the 100th postoperative day than on the 99th postoperative day) when all other variables hold the same value. Similarly, the odds of having more PEK and using antibiotics is 6.9028 times that when not using any antibiotics. When individual antibiotics were analyzed, use of Ocuflax was found to show an odds ratio of less than 1.000, indicating lower chance of PEK while using Ocuflax.

**2. ANALYSIS OF RISK FACTORS FOR HURRICANE KERATOPATHY**

Hurricane keratopathy is a binary variable and was therefore analyzed using all 80 patients with all 332 visits. Hurricane keratopathy was present in 50 visits. Univariate

regression analysis of donor, preoperative, and postoperative risk factors yielded the results presented in Tables VII through IX.

Further analysis of the variables with *P* values < .05 in the final model determined that preoperative corneal sensation, anterior blepharitis, and total time elapsed from death of the donor to surgery had an impact on hurricane keratopathy. The odds ratio is shown in Table X.

These numbers indicate that a patient with diminished preoperative corneal sensation is 8.83 times more likely to develop hurricane keratitis than a patient with normal corneal sensation. The other factors can be interpreted the same way.

**3. ANALYSIS OF RISK FACTORS FOR MACRO-EPITHELIAL DEFECTS**

Presence of a macro-epithelial defect is a binary variable and was analyzed using all 80 patients at all 332 visits. A macro-epithelial defect was detected in 27 of those visits, with 305 visits free of macro-epithelial defects. Univariate regression analysis of donor and of preoperative and postoperative risk factors yielded the results in Tables XI through XIII.

Significant variables in this univariate analysis were the use of prednisolone acetate (Pred-Forte), antibiotics (any), trimethoprim sulfate, and lubricant (any). In the final combined model, only the use of antibiotics (any), trimethoprim sulfate, and lubricant (any) were associated with the development of a macro-epithelial defect. The odds ratios for these variables are provided in Table XIV.

On average, the odds of having macro-epithelial defects and using any antibiotic is 2.7585 times the odds of having macro-epithelial defects and not using any antibiotic, when adjusted for other risk factors in the final

TABLE VI: ODDS RATIO FOR SIGNIFICANT FACTORS AFFECTING PEK

VARIABLE	ODDS RATIO	SE	95% CI	
			MINIMUM	MAXIMUM
Recipient's age	1.0276	0.0084	1.0113	1.0442
Days after surgery	0.9806	0.0036	0.9736	0.9876
Antibiotic (any)	6.9028	2.7624	3.1506	15.1239
Ocuflax	0.3662	0.1447	0.1688	0.7943

PEK, punctate epithelial keratopathy.

**TABLE VII: SIGNIFICANCE OF DONOR RISK CHARACTERISTICS FOR THE PRESENCE OF HURRICANE KERATOPATHY**

DONOR	P VALUE
Age (yr)	.5144
Death to preservation time (hr)	.2642
Preservation to surgery time (hr)	.0404
Total time (hr)	.0389
Epithelial status <sup>o</sup>	.7827

<sup>o</sup>As described in "Methods" section.

**TABLE VIII: SIGNIFICANCE OF RECIPIENT PREOPERATIVE VARIABLES ON HURRICANE KERATOPATHY**

RECIPIENT PREOPERATIVE	P VALUE
Patient age	.1093
Patient sex	.7710
Preoperative diagnosis	.0573
Corneal sensation	.0373
Schirmer test	.9600
Anterior blepharitis	.0318
Posterior blepharitis	.0170

multiple regression analysis. The odds of having macro-epithelial defects and using trimethoprim sulfate is 2.3585 times the odds of having macro-epithelial defect and not using trimethoprim sulfate. The odds of having macro-epithelial defects and using a lubricant is 3.9942 times the odds of having macro-epithelial defects and not using any lubricant.

**4. ANALYSIS OF RISK FACTORS FOR FILAMENTARY KERATOPATHY**

In this study, filamentary keratopathy had 3 possible recordings: none, suture-related, and non-suture-related. We used all 332 visits from 80 patients. Filamentary keratopathy was absent in 285 visits and present in 47 visits. Of these, 9 were felt to be suture-related.

The significance of donor, preoperative, and postoperative risk factors in the development of filamentary keratopathy as determined by a univariate regression analysis is shown in Table XV. No independent variables were found to have statistical significance in relation to the development of filamentary keratopathy after penetrating keratoplasty.

**TABLE IX: SIGNIFICANCE OF RECIPIENT POSTOPERATIVE VARIABLES ON HURRICANE KERATOPATHY**

RECIPIENT POSTOPERATIVE	P VALUE
Time elapsed (days)	.5572
Prednisolone acetate	.3859
Prednisolone sodium phosphate	.1598
Dexamethasone	.3393
Antibiotics (any)	.9118
Ofloxacin	.3015
Erythromycin	.1885
Trimethoprim sulfate	.4180
Other antibiotics	.7713
Lubricants	.3726

**5. ANALYSIS OF RISK FACTORS FOR RIM DEFECTS**

The presence of rim defect was a binary variable, and all 332 visits by the 80 patients in the study were utilized in this analysis. Patients were found to have no rim defect on 317 visits and rim defect in 15 visits. Table XVI shows the results of the univariate regression analysis of the correlation between the dependent variables studied and the presence of a rim defect.

Although time elapsed since surgery, use of an antibiotic and use of erythromycin were found to be significantly correlated to the presence of a rim defect in the univariate model; only the time elapsed since surgery and the use of erythromycin were correlated with the presence of a rim defect in the final combined model. The odds ratio for the correlation between the presence of a rim defect and these 2 variables is provided in Table XVII.

These results suggest that a longer time elapsed since surgery was associated with a lower prevalence of rim defect. The use of erythromycin was associated with higher prevalence of rim defect.

**DISCUSSION**

Our study demonstrated that the majority of patients in the first 3 months after penetrating keratoplasty had some degree of punctate keratitis. In 63% of the visits, patients were noted to have grade 1 or higher PEK. Older patient age and use of topical antibiotics were significantly associated with higher probability of PEK. On the other hand, when antibiotics were individually analyzed, use of

**TABLE X: ODDS RATIO FOR SIGNIFICANT FACTORS AFFECTING PEK**

FACTOR	ODDS RATIO	SE	95% CI	
			MINIMUM	MAXIMUM
Corneal sensation 0/6 vs 6/6	8.8265	5.8955	2.3837	32.6835
Anterior blepharitis	3.2815	1.0634	1.7388	6.1931
Total time (hr)	1.0136	0.0043	1.0053	1.0220

TABLE XI: SIGNIFICANCE OF DONOR CHARACTERISTICS ON MACRO-EPITHELIAL DEFECT

DONOR	P VALUE
Age (yr)	.1589
Death to preservation time (hr)	.6384
Preservation to surgery time (hr)	.1685
Total time (hr)	.1646
Epithelial status <sup>o</sup>	.5660

<sup>o</sup>As defined in "Methods" section.

TABLE XII: SIGNIFICANCE OF PATIENT'S PREOPERATIVE CHARACTERISTICS ON MACRO-EPITHELIAL DEFECT

RECIPIENT PREOPERATIVE	P VALUE
Patient age (yr)	.8581
Patient sex	.5871
Preoperative diagnosis	.7413
Corneal sensation	<sup>o</sup>
Schirmer test	.1718
Anterior blepharitis	.1481
Posterior blepharitis	.2415

<sup>o</sup>Not available with the statistical analysis software used.

ofloxacin was associated with a lower probability of PEK. The reason for this is unclear. Our data also indicated that patients tended to have less PEK as time after surgery elapsed. Donor age, time elapsed after harvest, tear function, original diagnosis, and the use of topical corticosteroids did not appear to have a significant effect on PEK. These results correlate well with our previous analysis of PEK after penetrating keratoplasty, in which PEK was the most common surface abnormality postoperatively and was correlated primarily with older recipient age.<sup>13</sup>

The high prevalence of punctate staining after keratoplasty reflects an abnormal epithelial barrier function.<sup>14</sup> Barrier function and stromal fluorescein uptake of the corneal epithelium after keratoplasty have been investigated by other groups.<sup>15,16</sup> Shimazaki and associates<sup>15</sup> studied the barrier function of 69 eyes after keratoplasty by using fluorophotometry. Their study indicated that the barrier function of the epithelial cells was significantly decreased, and stromal fluorescein uptake was increased by a magnitude of tenfold after PKP compared to native corneas. The investigators also noted a direct relationship

TABLE XIII: SIGNIFICANCE OF POSTOPERATIVE VARIABLES ON MACRO-EPITHELIAL DEFECT

RECIPIENT POSTOPERATIVE	P VALUE
Days after surgery	.1228
Prednisolone acetate	.0122
Prednisolone sodium phosphate	.1818
Dexamethasone	<sup>o</sup>
Antibiotic (any)	.0029
Ocuflox	.6433
Erythromycin	.1567
Polytrim	.0352
Other antibiotics	.2805
Lubricant	0.0105

<sup>o</sup>Not available with the statistical analysis software used.

between recipient age and abnormality in the barrier function of the epithelium. These findings correlate with our observation of increased PEK in older patients. However, these investigators found no relationship between the length of time postoperatively and the barrier function of the epithelium, while we noted that PEK decreased with time after surgery, as might be expected. One explanation for this discrepancy is that in the study by Shimazaki and associates, barrier function was measured with a fluorophotometer and not a slit lamp. Fluorophotometry may be more sensitive in picking up small degrees of dye uptake than slit-lamp examination.

There have been contradictory reports regarding the epithelial barrier after keratoplasty. Boot and colleagues<sup>17</sup> studied epithelial permeability in 27 eyes that had penetrating keratoplasty and found no significant difference between these and normal eyes. In their study, most of the patients (21 of 27 eyes) had keratoconus. Since keratoconus patients tend to be younger, the findings may be attributed to age.

Patients had a higher probability of PEK while receiving any topical antibiotics. Surprisingly, when antibiotics were individually analyzed, patients had a lower probability of developing PEK when taking ofloxacin. Topical antibiotics, especially the aminoglycosides, are known to cause corneal toxicity.<sup>18</sup> To our knowledge, there have been no studies on the effect of ofloxacin on corneal epithelial wound healing. These findings may suggest that ofloxacin is a less toxic antibiotic after keratoplasty. Patel and associates<sup>19</sup> compared the rate of epithelial healing after PRK

TABLE XIV: ODDS RATIO AND CONFIDENCE INTERVALS FOR SIGNIFICANT VARIABLES IN THE PRESENCE OF A MACRO-EPITHELIAL DEFECT

FACTOR	ODDS RATIO	SE	95% CI	
			MINIMUM	MAXIMUM
Antibiotic (any)	2.7585	0.7312	1.6408	4.6376
Polytrim	2.3585	0.5280	1.5209	3.6576
Lubricant (any)	3.9942	1.1651	2.2549	7.0749

**TABLE XV: SIGNIFICANCE OF DONOR, PREOPERATIVE, AND POSTOPERATIVE RISK FACTORS IN THE PRESENCE OF FILAMENTARY KERATOPATHY**

DONOR	P VALUE
Age	.4573
Death-to-preservation time (hr)	.6264
Preservation-to-surgery time (hr)	.4534
Total time (hr)	.3647
Epithelial status <sup>o</sup>	.7109
<b>Recipient preoperative</b>	
Patient age (yr)	.5852
Patient sex	.1833
Preoperative diagnosis	.3029
Corneal sensation	.8065
Schirmer test	.5391
Anterior blepharitis	.0858
Posterior blepharitis	.6724
<b>Recipient postoperative</b>	
Time elapsed since surgery (days)	.1337
Prednisolone acetate	.4866
Prednisolone sodium phosphate	.7423
Dexamethasone	.4474
Antibiotic (any)	.4060
Ofloxacin	.3673
Erythromycin	.2380
Trimethoprim sulfate	.1340
Other antibiotics	.6811
Lubricant (in general)	.3516
Other medicine	.5162

<sup>o</sup>As described in “Methods” section.

**TABLE XVI: SIGNIFICANCE OF DONOR, PREOPERATIVE, AND POSTOPERATIVE RISK FACTORS IN THE PRESENCE OF A RIM DEFECT**

DONOR	P VALUE
Age (yr)	.4342
Death-to-preservation time (hr)	.8496
Preservation-to-surgery time (hr)	.1916
Total time (hr)	.2399
Epithelial status <sup>o</sup>	†
<b>Recipient preoperative</b>	
Patient age (yr)	.9647
Patient sex	.8475
Preoperative diagnosis	†
Corneal sensation	†
Schirmer test	.8702
Anterior blepharitis	.7368
Postblepharitis	.3638
<b>Recipient postoperative</b>	
Time elapsed since surgery (days)	.0206
Prednisolone acetate	.8153
Prednisolone sodium phosphate	.8640
Dexamethasone	†
Antibiotic (in general)	.0069
Ofloxacin	.9586
Erythromycin	.0290
Trimethoprim sulfate	.3294
Other antibiotics	.8488
Lubricant	†
Other medicine	†

<sup>o</sup>As described in “Methods” section.

†Not available with statistical analysis software used.

when either ciprofloxacin or ofloxacin was used. The investigators noted that patients who were treated with ofloxacin had a statistically significant shorter time to complete re-epithelialization. Whether these observations are applicable to post-PKP corneas is not known.

The prevalence of hurricane keratopathy was 15% of all visits. Decreased preoperative corneal sensation, anterior blepharitis, and total elapsed time from death of the donor to surgical implantation of the cornea were found to be associated with a higher probability of hurricane keratopathy. Our prevalence was lower than that observed by other investigators. Mathers and Lemp<sup>8</sup> noted the prevalence to be as high as 70% after keratoplasty. The follow-up time in their study was longer than ours (up to 18 months), and they also used epithelial specular microscopy to study the configuration of the surface cells,

a technique that, again, may be more sensitive than slit-lamp examination. The same researchers indicated that when slit lamp was used, only 30% of patients had a vortex pattern. The application of topical medications may contribute to the development of hurricane keratopathy. Dua and coworkers<sup>20</sup> reported 6 cases of hurricane keratopathy that developed in eyes with no previous ocular surgeries. In 5 cases, long-term topical steroid use was a factor. Mackman and associates<sup>9</sup> also reported 15 cases of hurricane keratopathy after PKP in patients who were using Maxitrol<sup>TM</sup>. We found no association between topical medications and the development of hurricane keratopathy. This may be due to the difference in our post-operative regimens compared to those of other studies. Mathers and Lemp<sup>8</sup> also observed that after suture removal, the vortex pattern resolved.

**TABLE XVII: ODDS RATIOS FOR SIGNIFICANT VARIABLES IN THE PRESENCE OF RIM DEFECT**

FACTOR	ODDS RATIO	SE	95% CI	
			MINIMUM	MAXIMUM
Time elapsed since surgery (days)	0.9894	0.0035	0.9825	0.9963
Erythromycin	3.8076	1.5434	1.7204	8.4272

In 8% of the visits, a macro-epithelial defect was reported, and in 4.5% of the visits, a rim defect was recorded. We found the use of any antibiotics, trimethoprim sulfate specifically, and use of lubricants to be associated with higher probability of a macro-epithelial defect. This phenomenon may not, of course, be specific to these substances. Time elapsed from surgery was associated with lower probability of rim defect, and the use of erythromycin was associated with higher probability of rim defect. This probably represents a selection bias, since patients who were found to have large epithelial defects or rim defects were selectively treated with either aggressive lubrication or erythromycin ointment, and the analysis does not suggest a true causal relationship.

The prevalence of epithelial defects in the patients analyzed here is lower than that reported in literature. Previous studies showed that 76% of eyes after PKP for bullous keratopathy had epithelial defects after surgery.<sup>21</sup> Another study reported that 26% of patients after keratoplasty had epithelial defects greater than 2 mm on the first postoperative day.<sup>22</sup> The primary reason for the lower prevalence in our study is that observation of the epithelium in our study was initiated after the first postoperative week. The prevalence of macro-epithelial defects and rim defects was higher in the original cohort of 121 patients. However, if a patient had a nonhealing epithelial defect requiring a contact bandage lens or tarsorrhaphy, precluding the observation of epithelium, the patient was excluded from the study.

We did not find any association between the use of topical corticosteroids and epithelial defects. Corticosteroids have been shown in experimental animals to delay epithelial healing.<sup>23,24</sup> Work by other investigators, however, has not demonstrated a deleterious effect of steroid on the corneal epithelium. Sugar and associates<sup>25</sup> studied 39 eyes after PKP and found no delay in epithelial healing with the use of steroids.

The status of the donor epithelium had no significant effect on the status of the epithelium after surgery. Meyer and Bahn<sup>21</sup> studied the effect of donor epithelium on 66 eyes undergoing keratoplasty and found a direct relationship between the status of the donor epithelium and the length of time that was required for the graft epithelium to heal completely. In their study, the epithelium was checked daily after surgery, and the longest time for complete epithelial healing was 12 days. Our earliest recording was at 4 days postoperatively, and much more commonly it was at 7 days. Therefore, our data may have missed the period of time during which the donor epithelium has the greatest effect. In addition, the corneas in their study were stored in McCarey-Kaufman medium, while all the corneas used in the present study were stored in Optisol™.

Work by Chou and associates<sup>26</sup> and Kim and colleagues<sup>27</sup> demonstrated that longer storage time and longer death-to-harvest time were associated with epithelial defects after keratoplasty. Our data did not show any correlation between storage time and epithelial defect. We did, however, note an increase in the probability of hurricane keratopathy within an increased total time from death to transplantation. It should be noted that in both the studies mentioned, the epithelial defects were recorded 1 day after the transplant, while our observations started later in the postoperative course. It would be expected that most epithelial abnormalities on the first postoperative day would be related to the donor epithelium and not the host.

We noted filamentary keratitis in 14.2% of the visits. None of the variables analyzed in this study appeared to be significant in the development of filamentary keratitis. In a previous report by Rotkis and associates, 39% of patients with the preoperative diagnosis of keratoconus had postoperative filamentary keratopathy. However, when the investigators analyzed their data, no statistically significant relationship between the preoperative diagnosis and the development of filamentary keratitis was found.

We recognize that there may be concerns about methodology that must be considered before drawing firm conclusions from this data. First, at least 4 different surgeons participated in the surgery. Although our analysis did not suggest that surgeon differences were associated with the prevalence of postoperative surface changes, difference in surgical technique could potentially play a role in the type and prevalence of surface changes in the postoperative period. In this study, the 2 primary surgeons (M.J.M., I.R.S.) used similar surgical techniques and postoperative treatment regimens. All surgeries were under their direct supervision both intraoperatively and postoperatively. We felt that this controlled adequately for surgeon differences. In addition, the estimates of severity of postoperative surface changes were graded in a subjective fashion by different observers in the postoperative period. To control for subjective differences, the observers used "reference diagrams" that were included on each postoperative evaluation sheet, allowing the observer to "grade" by comparison to the reference drawing. This methodology was employed to standardize as much as possible the estimates of the severity of surface disease during postoperative assessments.

Most ophthalmologists who perform corneal transplantation or care for corneal transplant patients express concern about postoperative complications, including graft rejection and infection. These are, nonetheless, relatively rare, albeit serious complications. However, surface keratopathy is ubiquitous after keratoplasty. While it

may be transient, it can also produce significant adverse symptoms for the patient, may delay visual rehabilitation, and may place the eye at risk for more serious, vision-threatening complications. The purpose of this study was, therefore, to highlight the types and extent of this very commonly encountered postoperative problem. Our study demonstrates that older age, preoperative lid disease, and decreased preoperative corneal sensation appear to increase the probability of clinically significant epithelial surface abnormalities after keratoplasty. While these associations are not unexpected, recognition of these risk factors in advance of surgery will alert the surgeon to the need for appropriate management. This recognition will hasten the visual recovery of the patient and minimize the more serious risks engendered by an incompetent surface after corneal transplantation.

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## DISCUSSION

DR WOODFORD S. VANMETER. Mr. President, Mr. Secretary, members and guests: I appreciate the opportunity to discuss this paper. Many thanks to the authors for sending the manuscript to me promptly.

AJ Bron reported in 1973 whorl patterns in the post-graft corneal epithelium.<sup>1</sup> Vortex patterns of the corneal epithelium,<sup>2</sup> and hurricane keratopathy<sup>3</sup> have both been described following keratoplasty. All corneal transplant surgeons are familiar with post-keratoplasty epitheliopathy, which can range from complete absence of the corneal epithelium with basement membrane damage to a perfectly clear and healthy epithelium on day 1 following keratoplasty. Stulting and colleagues showed in 1987 that the absence of the corneal epithelium did not affect graft rejection, but Stulting noted that the overall failure rate in his series was higher in the group with the epithelium off than the group with the epithelium on, underscoring the importance of a healthy epithelium.<sup>4</sup>

Epithelial regeneration on a graft is more complicated than epithelial regeneration in a native cornea. Donor corneal epithelium itself has been stored for days in tissue culture medium, and may not be amenable to instant resurfacing even under ideal conditions. Relative denervation of the cornea, poor lubrication, installation of frequent and often toxic topical medications and an abnormal cornea and lid anatomical relationship all may impede restoration of normal surface.

The authors have set out to determine the type and

prevalence of epithelial abnormalities in the intermediate postoperative period and to define the donor and recipient variables that influence the status of the graft epithelium. Using slit lamp examination and fluorescein staining, the authors examined the donor epithelium and recipient variables such as dry eyes, blepharitis, corneal sensation and postoperative medications. Outcome measures examined were superficial punctate keratitis, epithelial defects, hurricane keratopathy, rim defects and filamentary keratitis measured by slit lamp examination and fluorescein staining. A detailed statistical analysis was provided using univariate and combined statistical models to determine the impact of each variable on postoperative epithelial pathology.

The authors found that 63% of patients had superficial punctate keratitis, which correlated with old age and topical antibiotics administered postoperatively. Fifty-one percent of patients developed hurricane keratopathy, which was associated with decreased corneal sensation, blepharitis and increased storage time.

With any detailed statistical model, clinically significant results depend on carefully controlled variables. I would like to ask the authors to comment on 3 additional features in this study which might help corneal surgeons utilize the conclusions noted. 1) Reliable information on the donor epithelium status is difficult to determine. Not all surgeons perform biomicroscopic evaluation of the donor cornea prior to keratoplasty. The use of lubricating ointment, antibiotics and ice on the cadaver prior to harvesting the cornea is difficult to determine in most circumstances. A wide variety of antibiotics, (including aminoglycosides, neomycin and povidone-iodine), are used in preparation of the donor cornea. Cost controls limit the options of many eye banks and cheaper substitutes to quality antibiotics are constant temptation. 2) The actual mechanism for preservation of the epithelium intraoperatively is not mentioned in this paper, although many surgeons now use viscolastic to help the corneal epithelium. Use of topical Healon instead of balanced salt solution to maintain the corneal epithelium has been advocated.<sup>5</sup> In addition to intraoperative care of the epithelium, surgical time, which would obviously be increased with additional procedures or with residents or fellows involved in the surgery, is important. 3) Finally, the status of the epithelium on day 1 is not noted. The authors used 1 week as the time of the first observation. Corneal epithelial status on day 1 can vary from a complete epithelial defect to a normal epithelium, and this author (WSVM) anecdotally notes that those patients with a completely normal epithelium on day 1 have fewer surface problems than those with large epithelial defects on day 1. Measures which promote a healthier epithelium during and immediately after surgery reduce the likeli-

hood of epitheliopathy in the intermediate post-operative period.

Dr. Mannis and co-workers have previously linked recipient age to the development of surface disease,<sup>6</sup> a variable that can hardly be obviated by the operating surgeon. In that paper, postoperative surface keratopathy was not associated with donor epithelial status, suggesting that intraoperative or postoperative variables are mainly responsible for the changes noted in the postoperative period. However, because preoperative donor assessment is performed by multiple observers, many of whom do not have medical backgrounds, the possibility remains that some preoperative donor epithelial features go unnoticed, due to the imperfection of undisciplined senses.

The authors should be commended for their thoughtful attention to post-keratoplasty epitheliopathy and for their detailed statistical analysis of possible contributing factors. The relative risk of elderly patients with lid disease, keratoconjunctivitis sicca, or glaucoma medications should be recognized in the preoperative evaluation of the keratoplasty patient. Early recognition and treatment of surface disease, whether by observation, lubrication or tarsorrhaphy, may help reduce the extent and severity of post-keratoplasty epitheliopathy. The authors effectively demonstrate that avoiding postoperative mechanical and chemical trauma to the graft and nurturing the corneal surface can improve graft longevity and reduce the incidence of post-keratoplasty complications.

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[Editor's note] DR LINSEY FERRIS commented that supportive measures such as artificial tears, punctal occlusion, and Healon could produce both beneficial and deleterious effects. He asked about the use of soft contact lenses after keratoplasties; what is the best lens and when should it be used. DR DAN B. JONES asked about the role of postoperative topical drugs such as steroids, antibiotics (which ones, for how long and why?), other topical medicines (especially glaucoma drugs), and artificial tears (were they

routinely used and were they preservative free?), DR KENNETH R. KENYON noted that over 25% of keratoplasties fail because of ocular surface problems. He emphasized the importance of evaluating the status of the corneal epithelium, particularly at the limbus, before surgery to determine if additional preventative measures such as punctal occlusion, tarsorrhaphy, amniotic membrane grafts, or limbal autographs should be used. DR THOMAS O. WOOD mentioned that he had almost eliminated postoperative problems from ocular surface disease by doing a simple tarsorrhaphy with a nylon suture in almost all of his cases and thermal punctal occlusion in many.

DR MARK J. MANNIS. I would like to thank Dr VanMeter for his thoughtful comments on our paper. The attempt to correlate the types and degree of surface disorders with the many variables that factor into the dramatically rearranged corneal surface after keratoplasty is a daunting task. We agree that one must take into account a multiplicity of potential influential factors including pre-operative donor status, the length of surgery and the specific surgical techniques employed, and, of course, the many factors that come into play post-operatively. In the analysis of our results, some of the findings were as we had anticipated. Others were counter-intuitive. The challenge has been to determine which of these factors are true clinical phenomena and which are purely statistical entities.

In answer to the specific areas of concern articulated by Dr VanMeter, we would comment as follows:

First, with regard to the statement that the eye bank evaluation of the donor epithelium is not standard across the board, we agree. The American eye banking system has made tremendous strides in standardizing the tissue evaluation process. Nonetheless, it is just beginning to develop standards of evaluation and description that utilize similar terminology and that are translatable from city to city and from eye bank to eye bank. In the present study, virtually all tissue was funneled to the surgeons through a single eye bank, upon which we could rely for uniform assessment. It is accurate to say, however, that most corneal surgeons do not personally evaluate donor epithelium prior to the use of the tissue and that they rely on the assessment of the eye bank personnel. Perhaps our results should suggest that in higher risk cases, special effort should be made to ensure that the donor epithelium is healthy and intact and is personally evaluated by the surgeon prior to keratoplasty.

The second issue—that of attempts to preserve the epithelium during the procedure—is also very important.

We did not control for these factors in this study. Indeed, in some cases we applied viscoelastic to the surface of the graft during surgery while in others, only standard lubrication with balanced salt solution was employed. These techniques were neither recorded nor isolated as variables in the study. We agree, nonetheless, that the post-operative status of the epithelium may vary significantly depending on factors, including the length of surgery, the degree of hydration, and conscious attempts by the surgeon to avoid epithelial trauma.

Finally, we agree that this study does not specifically address the immediate post-operative status of the graft epithelium. The corneal epithelium on the first post-operative day, as Dr VanMeter has correctly described, may range from being totally intact to being completely absent. While our treatment of the surface may differ clinically based on the findings on post-operative day one, it is not clear that the first post-operative day is truly predictive of the subsequent course long-term. We believe that the status of the recipient's surface is far more important to efficient re-epithelialization of the graft than is the status of the donor epithelium on day one. An intact epithelium provides a "jump start" for surface maintenance, but it does not determine the subsequent course. The long-term status of the epithelium is largely recipient dependent. We plan to return to our database to evaluate this issue in the near future.

Dr Dan Jones has aptly commented on the nature of the medications used in this series, specifically with regard to the use of the solutions versus suspensions. Contrary to our expectations, we did not correlate increased or more severe surface keratopathy with suspensions.

We would also concur with Drs Linsey Farris and Thomas Wood that the surgeon can vastly improve the surface rehabilitation of the patient by employing adjunct measures including temporary or permanent punctal occlusion, temporary tarsorrhaphy, as well as the judicious use of therapeutic contact lenses.

In summary, we have attempted to identify those individuals who would be at significant risk for surface problems after keratoplasty. The complexity of the issues makes this a difficult task. Nonetheless, in the elderly patient or the patient with dry eye, blepharitis, or mechanical lid problems that can be identified in advance of surgery, special measures to nurture health of the surface can be undertaken before, during and after the procedure. We thank Dr VanMeter again for his comments, and we appreciate the opportunity to present these data before the American Ophthalmological Society.

# THE NEGATIVE ERG IS NOT SYNONYMOUS WITH NIGHTBLINDNESS\*

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BY *Gerhard W. Cibis, MD*<sup>1</sup> AND *Kathleen M. Fitzgerald, PhD*<sup>2</sup> (BY INVITATION)

## ABSTRACT

**Purpose:** To provide electroretinographic differentiation between 4 genetically distinct conditions associated with a negative, Schubert-Bornschein type electroretinogram (ERG): Complete congenital stationary night blindness (cCSNB), incomplete CSNB (incCSNB), Duchenne muscular dystrophy, and a family with an autosomal dominantly inherited negative ERG.

**Methods:** ERGs were recorded in all subjects according to the ISCEV standards. Additionally, a long-duration flash was used under photopic testing conditions to separate depolarizing (ON) and hyperpolarizing (OFF) bipolar cell contributions. Dark adaptometry was obtained in cooperative adult subjects.

**Results:** We were unable to differentiate between these 4 genetically distinct conditions using the scotopic ERG response to the bright white flash only. The photopic, cone-derived ERG to both short- and long-duration flashes was more informative in making distinctions between these 4 disorders and understanding the possible mechanisms behind the abnormal ERG.

**Conclusion:** None of these disorders are progressive or a result of abnormal photoreceptor phototransduction. We suggest that they each represent a signal transmission error at the photoreceptor to depolarizing bipolar cell synapse that affects both rod and cone output. We propose that vision is spared in the latter 2 conditions because of timing errors in transmission as opposed to a complete signaling block, as seen in cCSNB.

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## INTRODUCTION

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At the onset of light, photoreceptors hyperpolarize and glutamate is reduced at the synapse where photoreceptors, bipolar cells, and horizontal cells make their contact.<sup>1</sup> This subsequent glutamate uptake causes bipolar cells to either depolarize or hyperpolarize depending on their specific receptor subtypes.<sup>2</sup> The electroretinogram (ERG) records this activity: hyperpolarization of photoreceptors results in the negative-going a wave, and the subsequent activity of the postsynaptic second-order neurons, primarily depolarizing, on ON bipolar cells results in the ERG b wave.<sup>3-7</sup>

The negative ERG described by Schubert and Bornschein<sup>8</sup> refers to the response recorded to a bright white stimulus under scotopic testing conditions in the dark-adapted subject. The resulting waveform is made up of a large, photoreceptor-derived a wave followed by a subnormal, postsynaptic b wave. The investigators assigned the description to the ERG seen in complete congenital stationary night blindness (cCSNB), and the

Schubert-Bornschein eponym became synonymous for both the negative ERG phenotype and cCSNB.

In time, a number of conditions other than cCSNB were identified that were also associated with a negative ERG (Table I). The mechanisms behind these disorders are varied. Some conditions are stationary, while others are associated with progressive vision loss. Thus, the Schubert-Bornschein eponym became lost for disease categorization but not for the negative ERG, which retained its association with night blindness.

In this article, we describe 4 genetically distinct disorders all indistinguishable on the basis of their negative ERG alone. All 4 are stationary disorders, and 2 are not associated with clinically measurable visual deficits. Expanding our ERG protocol to include long-duration photopic stimuli allowed us to understand the phenotypic differences in the ERG between these 4 disorders.

## METHODS

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### SUBJECTS

Clinical patients were identified through the department of ophthalmology at The Children's Mercy Hospital, Kansas City, Missouri, and referred to the Vision Science Laboratory for an ERG. Subjects included 11 boys with cCSNB, 6 boys with incomplete CSNB (incCSNB), 51 boys with Duchenne muscular dystrophy (DMD), and 3 girls and

\*From the Sections of Ophthalmology and Rehabilitative Medicine,<sup>1</sup> The Children's Mercy Hospital Vision Science Laboratory,<sup>2</sup> University of Missouri, Kansas City, School of Medicine,<sup>1,2</sup> and the Department of Ophthalmology, Kansas University School of Medicine.<sup>1,2</sup> Supported by the Katharine B. Richardson Associates, Inc.

**TABLE 1: OCULAR DISORDERS ASSOCIATED WITH A NEGATIVE ELECTRORETINOGRAM**

<b>Genetic</b>
Complete and incomplete CSNB
X-linked retinoschisis
Early retinitis pigmentosa
Oguchi disease
Duchenne muscular dystrophy
<b>Vascular</b>
Ischemic central vein occlusion
Central retinal artery occlusion
<b>Drug toxicity</b>
Quinine <sup>23</sup>
Vincristine
<b>Systemic</b>
Cancer-associated retinopathy
Melanoma-associated retinopathy
<b>Degenerative myopia</b>

CSNB, congenital stationary night blindness.

1 boy with an autosomal dominant negative ERG (ADNE). Some subjects were part of a clinical investigation and were recruited for participation in the study following the tenets of the Declaration of Helsinki after obtaining Internal Review Board approval and informed consent. Children who could not cooperate with the ERG were sedated with oral chloral hydrate syrup, 50 mg/kg. The ERGs were compared to the data of age-matched pooled normal subjects. The ERG data are contained in a normative database compiled and updated continuously for 17 years.

#### ERG

The methods for recording clinical ERGs and long-duration photopic ERGs have been described in previous publications. Under scotopic testing conditions, a dim blue flash ( $-1.00 \log \text{cd-sec/m}^2$ ) and bright white flash ( $2.0 \log \text{cd-sec/m}^2$ ) were delivered. Under photopic testing conditions, the following stimuli were used: a brief white flash on a steady Ganzfeld background ( $2.0 \log \text{cd-sec/m}^2$  flash with a  $1.5 \log \text{cd/m}^2$  background), 30-Hz flicker ( $0.5 \log \text{cd-sec/m}^2$  with  $0.5 \log \text{cd/m}^2$  background), and a long-duration photopic stimulus ( $3.0 \log \text{cd-sec/m}^2$  with  $2.0 \log \text{cd/m}^2$  background). The long-duration stimulus remained on for 200 msec and off for 100 msec and was recorded in a 300 msec window.

#### DARK ADAPTOMETRY

The pupils were dilated with 1.0% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride drops. Following 5 minutes of adaptation to a  $2.8 \log \text{cd/m}^2$  full-field stimulus, absolute threshold was tested for 40 minutes using the Goldmann-Weekers dark adaptometer. The test light was 11 degrees in diameter and centered at 10 degrees from foveal fixation, and the intensity ranged

from  $-8.5$  to  $-1.5 \log \text{cd/m}^2$ . Results were compared to age- and sex-matched control subjects.

## RESULTS

### COMPLETE CONGENITAL STATIONARY NIGHT BLINDNESS (CCSNB, CSNB1, MIM310500)

X-linked cCSNB is associated with moderate to high myopia, nystagmus, and elevated cone threshold during dark-adaptometry testing with no rod contribution to the response (Fig 1). Under scotopic testing conditions, the ERG shows an absence of rod-derived b waves, a negative response to a bright white stimulus, and an abnormal cone-derived response with a square a wave followed by a positive peak (Fig 2). Use of a long-duration flash under scotopic testing conditions shows that the photopic ON response is blocked and the response consists only of a cone photoreceptor-derived a wave, a hyperpolarizing trough (probably generated by the hyperpolarization of horizontal and hyperpolarizing bipolar cells at the onset of light), followed by a positive-going response at the offset of light, the d wave (Fig 2). Therefore, the positive peak seen in the response to the short photopic flash is not the b wave but is the OFF response, or the d wave. The gene for cCSNB, designated NYX, encodes a leucine-rich repeat protein of 481 amino acids and is found in the inner segments of photoreceptors, outer and inner nuclear layers, and the ganglion cell layer of human retinal sections.<sup>9</sup>

### INCOMPLETE CONGENITAL STATIONARY NIGHT BLINDNESS (INCCSNB, CSNB2, MIM300071)

IncCSNB is an X-linked nonprogressive disorder associated with elevated rod threshold of 1.0 to 1.5 log units (Fig 1), reduced visual acuity, and moderate hyperopia or myopia.<sup>10</sup> The ERG differs from the complete form (Fig 2). The rod-derived b waves are diminished but recordable, the response to the bright flash is negative, and cone-derived responses are nearly abolished. Use of the long-duration photopic flash highlights the differences between the 2 stationary disorders. In incCSNB, the ON response is reduced but not absent. There are prolonged oscillations with a small depolarization lasting approximately 50 msec imbedded in the hyperpolarizing trough. The OFF response is present but also prolonged. It is lacking the steep, rapid depolarization seen in both normal and cCSNB subjects. Therefore, cone signaling to both depolarizing and hyperpolarizing bipolar cells is altered. Mutations in the calcium-channel  $\alpha 1$ -subunit gene, CACNA1F, are responsible for incCSNB.<sup>11</sup>

### DUCHENNE MUSCULAR DYSTROPHY (DMD, MIM310200)

DMD affects 1 in 3,500 live male births, resulting in a

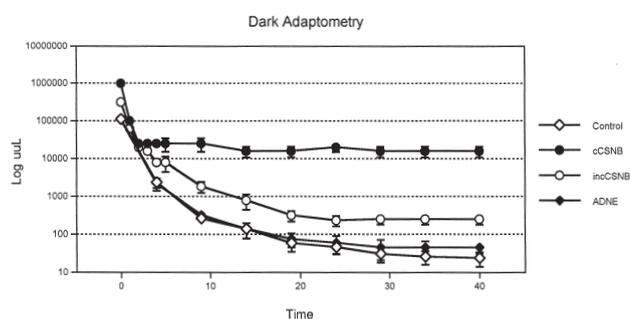


FIGURE 1

Goldmann-Weekers dark adaptometry in 3 groups of subjects with negative electroretinograms (ERGs): complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), and autosomal dominant negative ERG (ADNE). Subjects were age-matched with control subjects. Subjects with cCSNB show elevated cone threshold and no rod function. Subjects with incCSNB show elevated rod threshold of approximately 1 log unit. Subjects with ADNE do not differ from control subjects.

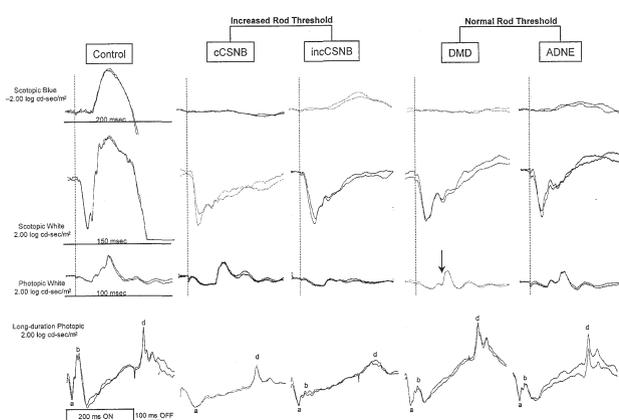


FIGURE 2

Representative electroretinograms (ERGs) of controls and subjects with complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), Duchenne muscular dystrophy (DMD), and autosomal dominant negative ERG (ADNE). Details of the ERGs are described in detail in the text. Dashed vertical line represents stimulus onset to a brief-duration flash. Long-duration flash is illustrated on bottom left as a square wave stimulus with a duration of 200 msec ON and 100 msec OFF. Waves a, b, and d are labeled in the long-duration photopic condition. Arrow in DMD panel points to missing photopic second oscillatory potential (O2).

wasting muscle disease and death in the second decade of life. Mutations in the gene for dystrophin, a cytoskeletal protein, result in the disease. A negative ERG is associated with DMD when the mutation disrupts the translation of the smaller dystrophin isoform, Dp260 (260kDa)<sup>12-15</sup> (Fig 3). Mutations involving exon 30 and higher of the dystrophin gene result in the negative ERG phenotype, while upstream mutations result in a near normal ERG.<sup>16</sup> Despite the abnormal ERG, there is no visual abnormality associated with DMD, and rod threshold is normal.<sup>17</sup> The DMD ERG shows severely reduced amplitude to the dim blue stimulus (Fig 2). The b wave is barely recognizable.

The response to a bright white flash is negative. The cone-derived response to a short flash shows a nearly normal response with the exception of the absence of the second oscillatory potential, O2. In normal subjects, there are 2 small oscillations that ride the ascending limb of the b wave. The long-duration flash shows a normal cone-generated wave followed by a subnormal ON response.<sup>18</sup> The ON response retains the oscillatory potentials but also shows a low amplitude and rapid depolarization followed by the hyperpolarizing trough. The OFF response is normal.

#### AUTOSOMAL DOMINANT NEGATIVE ERG (ADNE)

We have identified a family with a negative ERG phenotype with no muscle or eye disease.<sup>19</sup> Visual acuity, visual fields, and rod threshold are normal. No genetic mutation has yet been identified in this family. We investigated the possibility of a mutation in the gene for mGluR6, the metabotropic glutamate receptor subtype 6 specific to depolarizing bipolar cells. When mGluR6 is knocked out in gene-targeted mice, they exhibit a negative ERG. No mutation was found in this family. The ERG shows a recordable but diminished b wave to the dim blue flash under scotopic testing conditions. The response to the bright white stimulus is negative (Fig 2). The photopic response to the brief flash is normal; however, when the flash duration is extended, it is apparent that the ON response is attenuated. Like incCSNB and DMD, the oscillatory potentials are retained. Like cCSNB and DMD, the OFF response is preserved.

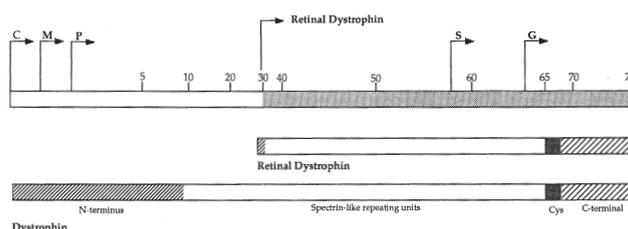


FIGURE 3

Schematic drawing of dystrophin gene, retinal dystrophin (Dp260), and full-length dystrophin (Dp427). The gene comprises 79 exons. Promoters for full-length isoforms found in cortex, muscle, and brain (C, M, and B) are at the 5' region. Smaller isoforms found in Schwann (S) cells (Dp116) and glia (G) (Dp71) have promoters in downstream 3' region. Location of first exon used in retinal dystrophin is indicated. Boys with mutations involving exons 30 through 79 have an abnormal electroretinogram.

#### DISCUSSION

We have described the negative ERG phenotypes in 4 genetically distinct disorders. In 2 of these disorders (DMD and ADNE), there is no visual abnormality associated with the abnormal ERG. Unlike cCSNB or incCSNB, rod threshold is normal. Rod threshold in

incCSNB is elevated but not to the extent of cCSNB, where there is no measurable rod threshold.

In these 4 distinctly different groups, the scotopic ERG to the bright white flash fits the Schubert-Bornschein eponym (Fig 4). From these 4 waveforms, it is impossible distinguish one disorder from the other despite their very different clinical phenotypes. Since rods

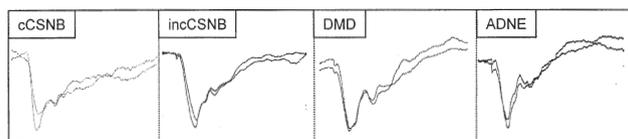


FIGURE 4

Schubert-Bornschein type electroretinograms in all 4 conditions: complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), Duchenne muscular dystrophy (DMD), and autosomal dominant negative ERG (ADNE). All responses were recorded under scotopic testing conditions in dark-adapted subjects. Stimulus was a bright white (2.00 log cd-sec/m<sup>2</sup>) flash designed to elicit responses from both rods and cones.

communicate only with a single rod bipolar cell and the intensity of the bright white flash is high enough to also generate cone activity, the response to a bright flash under scotopic testing conditions is a mixture of rod-to-rod depolarizing bipolar cell signals, cone-to-cone depolarizing and hyperpolarizing bipolar cell signals, as well as responses from horizontal and amacrine cells. Under standard clinical testing conditions, it is difficult to separate these multiple postsynaptic responses from each other. At best, we can attribute the leading edge of the a wave to photoreceptor hyperpolarization. More informative is the response to long-duration photopic stimuli. These responses make the distinctions between the 4 groups and may explain the difference in visual outcome.

While the response to the long-duration stimulus under photopic testing conditions is also a response of multiple cell types, there is still a sense of how each cell type is contributing to the response. There should be no rod contribution to the response, since the subject is light-adapted and there is a bleaching background light. Therefore, the leading edge of the a wave is a cone response. The ON response is a mixture of rapid depolarization of the sign-inverting depolarizing bipolar cells and slower hyperpolarization of the sign-conserving hyperpolarizing bipolar cells and horizontal cells, resulting in a long hyperpolarizing trough prior to the OFF response. The rapid oscillations are most likely generated by amacrine cells in the more proximal retina. The OFF response is also a combination of events, including the hyperpolarization of depolarizing bipolar cells and depolarization of hyperpolarizing bipolar cells and horizontal cells at the offset of light.

In cCSNB, there is a complete block at the

photoreceptor to depolarizing bipolar cell synapse. There remains a hyperpolarizing trough, presumably initiated by the horizontal cells and hyperpolarizing bipolar cells, and there is normal depolarization of the sign-conserving cells at the offset of light. As suggested by others, it appears that both rod and cone ON pathways are blocked, which results in the more significant vision loss and no measurable rod threshold.<sup>20</sup>

In incCSNB, there remains a slow, subnormal depolarizing bipolar cell response with rapid oscillations. This would indicate that some signal is still reaching the depolarizing bipolar cell and more proximal areas of the retina, as indicated by the oscillatory potentials. The hyperpolarizing bipolar cell signal is also attenuated, low in amplitude, and prolonged in time. This would indicate that both ON and OFF pathways are affected, but enough transmission of signal occurs to allow for measurable rod threshold and better visual outcome than cCSNB.

The long-duration photopic ERG in DMD retains more of the ON response than either of the 2 preceding conditions. The OFF response is well preserved, presumably normal. There are no clinically measurable visual abnormalities in this population, which would indicate that despite the abnormal ERG, the signals are reaching the proximal retina and brain. When the ON response is isolated by pharmacologically blocking the hyperpolarizing bipolar cells, it was shown to be a large-amplitude response with a rapid time course.<sup>21</sup> Sieving<sup>22</sup> created a model in which he introduced a series of timing delays in the ON response to demonstrate the effect of the delay on the ON response amplitude. With a 5 msec delay, the model is nearly identical to the response seen in DMD. Therefore, we believe the ON response is present in DMD, but the time course is altered, allowing for clinically normal vision but resulting in alterations in the ERG. Dystrophin is found at the outer plexiform layer in retina, most likely in photoreceptor cells. In DMD, only the rod and cone depolarizing bipolar signals are altered; therefore, we propose that the role of Dp260 is to stabilize the photoreceptor/depolarizing bipolar cell/horizontal cell invaginating synapse and that instability of this connection allows for an alteration in signal time course and the ERG phenotype without loss of vision.

The etiology of the abnormal ERG in ADNE remains unknown. While the ERG phenotype is most similar to that seen in DMD, there is no muscle disease in this family and the inheritance pattern is autosomal dominant, ruling out a role for dystrophin. Furthermore, there were no mutations in the gene for the mGluR6 receptor. It is possible in this family, as in DMD, that the signals from photoreceptors to second-order neurons are delayed, not blocked, which results in an abnormal ERG phenotype with no clinically measurable loss of vision or abnormal

fundus findings.

All of these cases show a Schubert-Bornschein ERG phenotype to a single bright flash under scotopic testing conditions in the dark-adapted patient, yet there are significantly different clinical outcomes. None of these disorders are progressive or are a result of abnormal photoreceptor phototransduction. Use of the long-duration photopic ERG was instrumental in demonstrating the differences in retinal signals of the cone pathway. We suggest that each of these disorders represents a signal transmission error at the photoreceptor to depolarizing bipolar cell synapse that affects both rod and cone output. We propose that vision is spared in DMD and ADNE because of timing errors in the transmission of signals between first- and second order-retinal neurons.

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## DISCUSSION

DR BARRETT KATZ. John Dowling claimed the B wave, as conventionally elicited, emanated from the Mueller cell; Herman Burian recognized the extensive subtleties this analysis overlooked. As Dr Cibis reminded the AOS before, Burian taught that such a simplification was like going to the elevator shaft of a tall building, placing one's ear against that elevator shaft, and then claiming that all the noises coming from each and every floor of that tall building (transmitted up the elevator shaft) were somehow generated by that elevator shaft. Dr Cibis leads the charge that cries, there is more going on in generating the B wave than just the Mueller cell.

In this paper, Dr Cibis convincingly demonstrates that there are neuronal junction defects as well as blocking defects that may arise between the photoreceptors and the depolarizing bipolar cells. Both defects alter the physiology within proximal retina, leading to an ERG that looks to most of the rest of us, for all intents and purposes, like that expected in CSNB, yet when analyzed with long duration photopic ERG methodology, yields singular defects that allow for finer discrimination of retinal anomaly. And each defect has its characteristic ERG markers.

Most of us knew the ERG allows one to make inferences about retinal function not possible upon clinical or histopathological observations alone. Yet Dr Cibis has demonstrated that the conventional ERG misses many of the subtleties of visual physiology. Specifically, cone visual signals within the retina are processed through 2 separate pathways, one an ON-center bipolar cell path, the

other, an OFF-center bipolar cell pathway. While we are just learning about what different psychophysical parameters these pathways subserve, we are more and more convinced that each can suffer preferential insults declared phenotypically as different retinal processes. Dr Cibis brings us just such an analysis here. He persuasively demonstrates that when the ERG is elicited with the technique of long duration light flashes, we can sort out ON versus OFF pathway changes within the visual system.

The clinical import of this modality is apparent. By analyzing the depolarizing [ON] and hyperpolarizing [OFF] pathways of cone vision post-synaptically to photoreceptors, one can differentiate at least 4 sub-types of "negative ERGs" that are genetically distinct, and clinically disparate. These entities are complete CSNB, incomplete CSNB, Duchenne's Muscular Dystrophy, and Autosomal Dominantly inherited Negative ERG. Each is non-progressive. Each seems to be caused by synaptic irregularity, rather than a result of abnormal photoreceptor phototransduction. Two are not associated with recognizable defects of the visual system.

What does all this imply?

1. In the retina, as in life, timing is everything; if vision is spared, as in Duchenne MD, and AD Negative ERG, then visual information is reaching appropriate areas of both retina and brain; complete signal blockage is expected to affect vision, timing errors do not;
2. By expanding one's ERG protocol, the use of the long duration photopic ERG to separate ON- and OFF-bipolar cell contributions to the photopic ERG allows a finer understanding of the functional implications of retinal disorders;
3. Altered retinal physiology may be a manifestation of disease localized at the level of the synapse, analogous to the synaptic anomaly most commonly seen in ophthalmology and neurology - myasthenia gravis.
4. The ERG can provide a laudable clinical addition to the understanding and classification of such retinal disorders, and the new and improved ERG may be the ancillary test to bring the neurologist and the ophthalmologist together again.

I ask Dr Cibis to speculate:

- Why doesn't the alteration of timing postulated in Duchenne's MD and Autosomal Dominantly inherited

Negative ERG degrade vision? When demyelination of the optic nerve occurs, and causes dispersion problems of the visual signal, as in garden variety optic neuritis, vision is degraded.

- What candidates do you have for us, as unifying etiologies of these anomalies of retina and nervous system?
- What are the sites of the effects of these shared selfish genes in MD, and cCSNB?

I commend Dr Cibis for the work, the paper, and the creativity of thought and reason that they demonstrate.

DR GERHARD W. CIBIS. Thank you very much, Dr Katz. Dr Lichter says that this organization represents if nothing else, history. Also, I thank you very much for the mention of my mentor Dr Burian.

I can answer the first question about why doesn't timing degrade vision. Dr Paul Sieving speculates that a 5 ms delay in the transmission can create the negative ERG. So that is a very subtle timing which can only be found in very subtle ways. In collaboration directed by Dr Vance Zemon of Yeshiva University we reported at the last ARVO meeting that in some Visual Evoked Response testing on patients with Duchenne's muscular dystrophy where they presented a center stimulus with an isoluminant surround, they were able to tease out a VER abnormality between the parvocellular and magnocellular system. If you know this is a timing defect and you now structure your vision tests not on a 20/20 Snellen chart or a Goldman Visual Field machine but a very sophisticated VER analysis you can find defects in the vision that you would expect to have.

Can you give us some speculation about the underlying unity of these anomalies that cause such disparate clinical declarations?

We believe that the proteins play a structural role somewhere in the anatomy of the synapse that I showed you. The dystrophin protein specifically, we think, somehow stabilizes the glutamate release mechanism and if that structure is not anchored properly the neurotransmitter would not be released in a timely fashion. Similarly we don't know where the calcium channels are in this system. We do know what sort of a role they play but not if they are either positioned inappropriately or the mechanism is timed inappropriately.

# THE ADVANCED GLAUCOMA INTERVENTION STUDY (AGIS): 10. VARIABILITY AMONG ACADEMIC GLAUCOMA SUBSPECIALISTS IN ASSESSING OPTIC DISC NOTCHING\*

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BY Douglas E. Gaasterland, MD, Beth Blackwell, ScD (BY INVITATION), Leonard G. Dally, MSc (BY INVITATION), Joseph Caprioli, MD, L. Jay Katz, MD (BY INVITATION), Fred Ederer, MA, FACE (BY INVITATION) AND The AGIS Investigators (SOME BY INVITATION)

## ABSTRACT

*Purpose:* An analysis of data from the Advanced Glaucoma Intervention Study (AGIS) has found eyes reported to have partial optic disc rim notching (not to the edge) at baseline to have less risk of subsequent visual field loss than eyes with no notching. Because this is counterintuitive and because classification of notching had not been defined in the AGIS protocol, we have assessed AGIS ophthalmologists interobserver and intraobserver agreement on notching.

*Methods:* Fourteen glaucoma subspecialists classified notching in 26 pairs of stereoscopic disc photographs of eyes with mild to severe glaucomatous optic neuropathy. They classified images as showing either no notching, notching not to the edge, or notching to the edge. Several hours later, 10 of them classified the same images a second time.

*Results:* In an analysis of interobserver agreement, of 26 stereoscopic images, a plurality of ophthalmologists classified notching as absent in 9 (35%), as present but not to the edge in 7 (27%), and as present and to the edge in 10 (38%). All 14 ophthalmologists (100%) agreed on the classification of 7 (27%) of the images, and 13 of the 14 ophthalmologists (93%) agreed on the classification of 4 additional images (15%). Of these 11 images with at least 93% agreement, notching was reported as absent in 3 (27%) and to the edge in 8 (73%). In the remaining 15 images, there was substantial disagreement about whether notching was present and, if so, whether it was to the edge. In an analysis of intraobserver agreement, none of the 10 ophthalmologists who completed the viewing a second time classified all eyes exactly the same as the first time, though 5 ophthalmologists made 4 or fewer reclassifications. Overall, 80% of the original classifications were reproduced on second reading. Of the initial classifications that were not reproduced, slightly more than half were first classified as having notching not to the edge.

*Conclusion:* Without definitions or examples of optic disc rim notching, the glaucoma subspecialists had relatively high intraobserver agreement but were likely to disagree with each other in characterizing the degree of disc rim notching. We recommend development of a standard photographic classification of disc rim notching. The classification should be tested for inter- and intra-observer agreement.

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## INTRODUCTION

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When protocol development and planning for the Advanced Glaucoma Intervention Study (AGIS) started in 1986, the investigators recognized the importance of optic

disc analysis in glaucoma diagnosis and monitoring. In order to reduce study cost and complexity, however, they accepted a recommendation to eliminate stereoscopic optic disc photography and an optic disc photograph reading center from the study plan. Instead, the investigators decided to use clinical stereoscopic slit-lamp biomicroscopic examinations to evaluate optic disc rim characteristics, including a determination as to whether there was notching of the neural rim of the optic disc and, if so, whether it extended only partially or completely to the edge of the disc.

In an ongoing data analysis to determine which baseline characteristics are predictive of subsequent deterioration of visual function, we find that eyes in one, but not the other, randomly assigned surgical treatment sequence and reported to have partial disc rim notching (not to the

\*From the Department of Ophthalmology, Georgetown University School of Medicine, Washington, DC (Dr Gaasterland); the EMMES Corporation, Potomac, Maryland (Dr Blackwell, Mr Dally, and Mr Ederer); Jules Stein Eye Institute, University of California, Los Angeles (Dr Caprioli); and Wills Eye Hospital, Philadelphia, Pennsylvania (Dr Katz). A complete list of the AGIS investigators and their participating institutions appears at the end of this manuscript. Supported by grants 2 U10 EY06824 through 2 U10 EY06827, 2 U10 EY06830 through 2 U10 EY06835, 2 U10 EY07057, and 7 U10 EY09640 from the National Eye Institute and the Office of Research on Minority Health, National Institutes of Health, US Department of Health and Human Services, Bethesda, Maryland.

edge) at baseline have a significantly lower rate of subsequent visual field loss than eyes reported to have no notching. This counterintuitive result has prompted us to question the consistency of and agreement among AGIS glaucoma subspecialists in classifying this optic disc characteristic.

There have been several interesting studies of the reproducibility of determining optic disc cupping.<sup>1-6</sup> We have found no reports of studies of reproducibility of determining optic disc rim notching.

## METHODS

### OVERALL AGIS METHODS

The AGIS protocol and the baseline characteristics of the 591 subjects enrolled in AGIS from 11 (later 12) participating clinical centers are described in detail elsewhere.<sup>7</sup> We briefly summarize the AGIS methods here. Appropriate institutional review boards approved the AGIS protocol, and all enrolled patients provided informed consent.

To be eligible for AGIS, patients had to be between 35 and 80 years old and have open-angle glaucoma that could no longer be controlled by medications alone. Additionally, the eye, while on maximum tolerated and effective medical treatment, had to meet one of several combinations of intraocular pressure (IOP) and visual field defect score criteria. One of the combinations that established eligibility of an eye was a glaucomatous visual field defect and consistently elevated IOP of 18 mm Hg or greater and deterioration of the optic disc neural rim. Disc rim deterioration was defined as occurrence of one or more of the following: development of disc rim hemorrhage, decrease in rim width of at least 50% in any one location, development of a notch to the edge of the disc, or increase of horizontal or vertical cup-disc ratio of 0.2 or greater. At the baseline slit-lamp biomicroscopic fundus examination, the AGIS ophthalmologist determined horizontal and vertical cup-disc ratio (from the neural rim widths in the horizontal and vertical meridians), location of the thinnest rim, hemorrhage(s) on rim tissue, and notching. If there was notching, the examiner reported whether it was to the edge of the disc or not. No definitions or guidelines for the three-category classification of notching were provided.

### METHODS OF THE PRESENT STUDY

Expert academic glaucoma subspecialist ophthalmologists at 2 centers provided high-quality stereoscopic photographs of optic discs of glaucoma patients. One set of images, from the Jules Stein Eye Institute, Los Angeles, California, consisted of 13 pairs of sequential 35 mm full-frame transparencies; the other set, from the Wills Eye Hospital, Philadelphia, Pennsylvania, consisted of 13 pairs

of simultaneous 35 mm split-frame photographs. The photographs were of eyes judged by the providers to have mild to severe glaucomatous optic neuropathy and no notching, notching to the edge of the disc, or notching not to the edge. Based on the providers' appraisal of notching, one of us (D.E.G.) arrayed the photographs in each set in a disarranged order of notching.

During a 1-day meeting of the full group of AGIS investigators in September 2000, 14 academic glaucoma subspecialists each viewed and classified the 26 stereoscopic pairs of photographs. In the morning, without provision of notching definitions or discussion of definitions, each ophthalmologist viewed the 26 paired stereoscopic disc images in the disarranged order of notching and recorded his or her assessment of each optic disc as having no notching, notching not to the edge, or notching to the edge. In the afternoon of the same day, 10 of the observers, masked as to their previous responses, viewed the 26 paired images in the same order and recorded their assessments a second time.

## RESULTS

### INTEROBSERVER AGREEMENT

Agreement among all 14 ophthalmologists occurred for only 7 of the 26 paired stereoscopic disc images (27%) (Table I); all agreed that 3 images showed no notching (an example is shown in Fig 1) and that 4 showed notching to the edge (an example is shown in Fig 2). Agreement among 13 or 14 observers (93% to 100% concordance)

TABLE I: INTEROBSERVER AGREEMENT: ASSESSMENTS FROM 14 GLAUCOMA SUBSPECIALIST OPHTHALMOLOGISTS OF OPTIC DISC NOTCHING IN STEREOSCOPIC DISC PHOTOGRAPHIC IMAGES OF 26 GLAUCOMATOUS EYES

	NO. OF DISC IMAGES	DEGREE OF NOTCHING REPORTED		
		NONE	NOT TO EDGE	TO EDGE
	3	14	0	0
	1	12	2	0
	1	10	4	0
	1	10	3	1
	2	9	5	0
	1	9	3	2
	1	4	8	2
	1	3	8	3
	1	3	7	4
	1	3	3	8
	1	2	10	2
	1	1	3	10
	1	1	0	13
	2	0	9	5
	1	0	8	6
	3	0	1	13
	4	0	0	14
Total	26	118	90	156

occurred for 11 images, with the observers agreeing that 3 images showed no notching and 8 showed notching to the edge of the disc.

In their classifications of the 26 stereoscopic images, a majority of the ophthalmologists agreed for 25 images. The size of the majority was less than two thirds for 9 of the images. The majority reported no notching in 9 images, notching not to the edge in 6, and notching to the edge of the disc in 10 (Table I). For 1 image, half the observers reported that notching was not to the edge, 3 observers reported no notching, and 4 reported notching to the edge (Fig 3).

Substantial numbers of dissimilar responses occurred both in images that the majority classified as having no notching and in images the majority classified as having notching to varying extent. In fact, for 4 of the images, the size of the majority was only 57% (8/14) of the ophthalmologists. For example, for 1 image, 8 observers reported notching not to the edge while 3 reported no notching and 3 reported notching to the edge (Fig 4).

#### **INTRAOBSERVER AGREEMENT**

Although none of the 10 ophthalmologists who completed a second evaluation of the 26 stereoscopic images demonstrated perfect agreement with his or her first classification, 5 classified at least 22 (85%) of the 26 images the same each time. Of the 5, 1 ophthalmologist classified only 1 image differently at the second viewing and 4 classified 2 to 4 images differently.

Table II shows the results of the first classifications for each of the 10 ophthalmologists and the changes in classification on the second reading. Out of 260 chances (10 ophthalmologists and 26 images) for intraobserver agreement, there is agreement in 209 (80%). Of the 51 paired observations that differed, 27 (53%) were in the images classified at first assessment as having notching not to the edge, while the remainder were divided almost equally between those classified during first assessment as having no notching and those as having notching to the edge. There was 87% (72/83) intraobserver agreement on images classified as having no notching on first assessment, 56% (34/61) agreement on having notching not to the edge on first assessment, and 89% (103/116) agreement on having notching to the edge on first assessment (Table II).

#### **DISCUSSION**

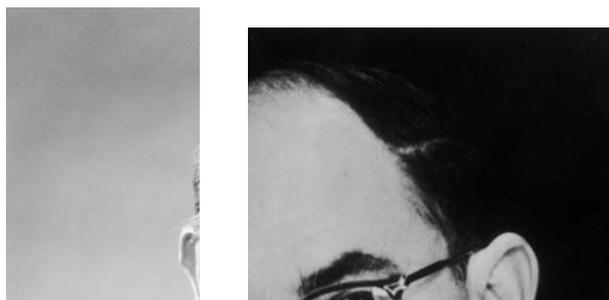
In this study of agreement among AGIS glaucoma subspecialist ophthalmologists in identifying optic disc rim notching in stereoscopic photographic images of optic discs, we find that for 11 of the 26 images presented there is substantial agreement between observers about the degree of notching (Table I). For 12 images, the ophthal-

mologists widely disagreed as to whether there was no notching, notching not to the edge, or notching to the edge. By contrast, when the observers classified the images a second time, a large majority (80%) of the second classifications were in agreement with the first classification (Table II). This indicates that the ophthalmologists participating in this study generally have consistent personal definitions of the 3 degrees of optic disc rim notching, but that they often differ between one another about the definitions.

Agreement among ophthalmologists in a study like this depends not only on the choice of photographs but also on the clarity and detail of instructions provided to the readers prior to assessment. Interestingly, in 1 study of optic disc cupping, even when efforts were made to provide clear definitions and instructions, along with photographic examples, a high level of disagreement continued.<sup>1</sup> Because the AGIS protocol did not provide definitions or guidelines on how to classify optic disc rim notching during clinical stereoscopic slit-lamp biomicroscopic fundus examination, we implemented the present study of stereoscopic photographs without instruction or guidelines on how to classify notching into the three-category response requested on AGIS data forms.<sup>8</sup>

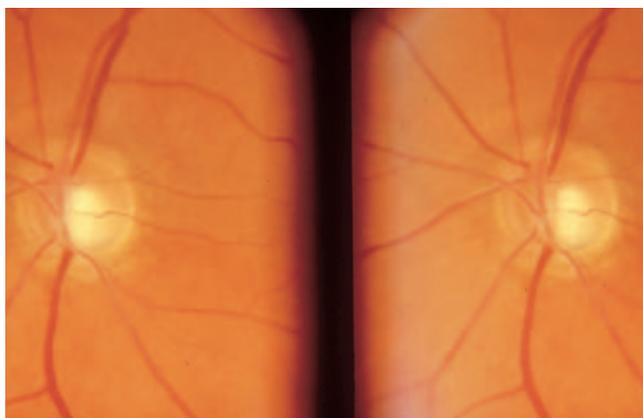
Several aspects of the current study design may have caused an artefact in the intraobserver reproducibility. First, one participating ophthalmologist (D.E.G.) had earlier disarranged the images in the 2 sets based on the classification provided by the source ophthalmologists. Repeating the analysis after removing the assessments of this ophthalmologist (D.E.G.) had little effect on the results (data not shown). Second, with the interval between the first and second classifications only a few hours and with no rearrangement of the order of the images in the sets, it is possible that some readers remembered some of their first assessments.

For years, most ophthalmologists have recognized disc rim notching (focal rim thinning) as a sign of glaucoma damage. For example, in a seminal study, Hitchings and Spaeth<sup>9</sup> included focal notching of the neuroretinal rim as 1 of 5 morphologic types of change found in glaucomatous optic discs. Yet, of 4 current glaucoma textbooks,<sup>10-13</sup> notching is listed in the index of only 1,<sup>10</sup> and a description of disc rim notching is provided in only 2.<sup>10,11</sup> In planning AGIS, the investigators assumed that all participating ophthalmologists shared a clear ability to recognize and characterize this sign of glaucomatous optic neuropathy. According to their examinations, at study baseline 196 of 770 enrolled eyes (25%) had optic disc rim notching to the edge and another 79 eyes (11%) had notching not extending to the edge of the disc. On the basis of the results of the present study, we question the reliability of the classifications, particularly for the 79 eyes reported as having notching not to



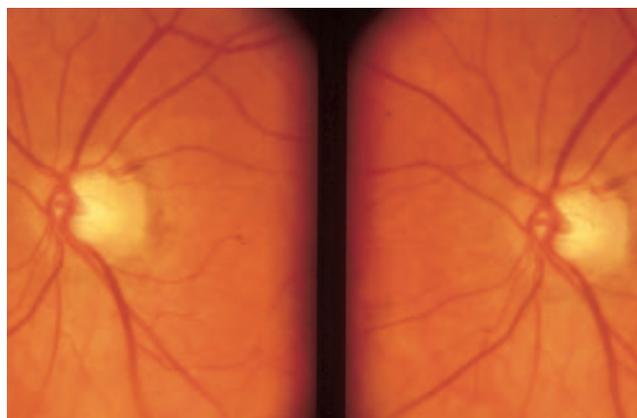
**FIGURE 1A AND 1B**

Stereoscopic pair of sequential full-frame photographs showing an optic disc characterized by all of 14 expert observers as having no notching of neural rim.



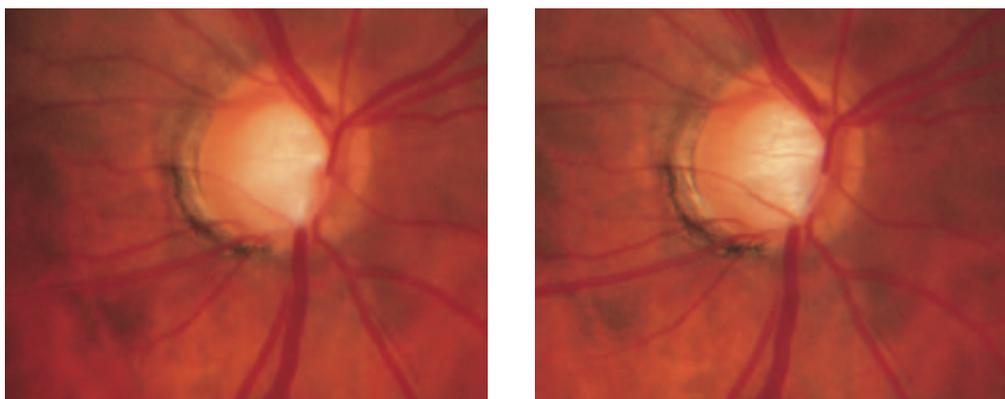
**FIGURE 2**

Stereoscopic pair of simultaneous split-frame photographs showing an optic disc characterized by all of 14 expert observers as having notching of neural rim to edge of disc.



**FIGURE 3**

Stereoscopic pair of simultaneous split-frame photographs showing an optic disc characterized by 7 of 14 expert observers as having notching not extending to edge of disc, by 3 others as having no notching, and by another 4 as having notching to edge of disc. There is a disc rim hemorrhage at the 1:30-o'clock meridian.



**FIGURE 4A AND 4B**

Stereoscopic pair of sequential full-frame photographs showing an optic disc characterized by 8 of 14 expert observers as having notching not extending to edge of disc, by 3 others as having no notching, and by another 3 as having notching of neural rim to edge of disc. A wisp of vitreous condensation extends off nasal rim in this eye. The first classifications by 10 expert observers of notching in this image often differed from the second.

TABLE II: INTRA-OBSERVER AGREEMENT: CLASSIFICATIONS OF OPTIC DISC NOTCHING AND CHANGES IN CLASSIFICATIONS DURING SECOND ASSESSMENT OF STEREOSCOPIC DISC PHOTOGRAPHS OF 26 GLAUCOMATOUS EYES BY 10 GLAUCOMA SUBSPECIALIST OPHTHALMOLOGISTS\*

FIRST ASSESSMENT OF NOTCHING										
		NONE	NOT TO EDGE	TO EDGE		NONE	NOT TO EDGE	TO EDGE		
SECOND ASSESSMENT OF NOTCHING										
OBSERVER	NO. OF CHANGES	NONE	NOT TO EDGE	TO EDGE	NONE	NOT TO EDGE	TO EDGE	NONE	NOT TO EDGE	TO EDGE
1	1	7	1			5				13
2	2	11	1			5			1	8
3	3	10				2	1		2	11
4	4	11	1	1		2		2		9
5	4	4	1		1	6	2			12
6	5	8	2			3	3			10
7	7	8	2		1	4	2	1	1	7
8	7	5	1		1	4	4		1	10
9	7	4			4	3	1		2	12
10	11	4		1	5		2	3		11
Changes:	51		9	2	12		15	6	7	
No changes:		72				34				103

\*Several hours after their first assessment, ophthalmologists, masked as to first responses, again viewed and classified same image sets with images in same order as during first assessment.

Note: Shaded columns have no change in second assessment compared with first assessment.

the edge of the disc. The 7 images with the largest number of interobserver and intraobserver disagreements in the present study are the 7 classified by at least half of the ophthalmologists as having notching not to the edge.

We recognize that in this study some agreement could have occurred by chance. The kappa statistic, which has been used to assess the degree of concordance in multi-observer studies, measures the amount of agreement beyond what is expected to occur by chance. We calculated kappa ( $\kappa$ ) for the present study, finding  $\kappa = 0.51$  ( $P < .001$ ) for inter-observer agreement among the 14 ophthalmologists who classified the 26 images. For intraobserver agreement, we found  $\kappa$  to range from 0.36 to 0.94 (mean, 0.69). In recognition that the amount of agreement in the present study may be affected by the composition of the photographic sets, and because, as Siegel and coauthors stated,<sup>14</sup> "...by itself, kappa is not informative enough to evaluate the appropriateness of a grading scheme for comparative studies," we decided not to emphasize the kappa statistic in this report.

Similar to the previous findings on optic disc cupping by Kahn and associates,<sup>1</sup> Lichter,<sup>2</sup> and other investigators,<sup>3,6</sup> we have found substantial variation among expert observers in classifying notching of the neural rim of the optic disc. It is reassuring that individual ophthalmologists in this study tended to be consistent in classifying the images.

This leads to some recommendations for future

research in optic disc rim notching. A critical step is to develop a photographic classification of notching along the lines of the Airlie House Classification of diabetic retinopathy<sup>15</sup> or the LOCS II classification of cataract.<sup>16</sup> The classification, to be based on standard photographs that illustrate or set limits on various degrees of notching, should be tested for intraobserver and interobserver agreement and then modified as needed. The standard photographs should be stereoscopic, taken by either the sequential full-frame or simultaneous split-frame technique. If good reproducibility is achieved, the classification can be applied in single center or multicenter studies in which notching of individual optic discs is assessed either at a disc photograph reading center or by ophthalmologists sitting at slit-lamp biomicroscopes. A good classification could become widely adopted and might provide a basis for comparisons with results from retinal nerve fiber layer analyzers.

## APPENDIX

### AGIS CENTERS AND INVESTIGATORS: PARTICIPATING INSTITUTIONS, CURRENT INVESTIGATORS, AND FORMER INVESTIGATORS WHO PARTICIPATED FOR 2 OR MORE YEARS

#### STUDY CO-CHAIRMEN

Douglas E. Gaasterland, MD; Fred Ederer, MA, FACE

**CLINICAL CENTERS**

Abbreviations: CD, Clinic Director; CI, Co-Investigator; CC, Clinic Coordinator; CM, Clinic Monitor; SD, Satellite Director; SC, Satellite Coordinator; T, Technician.

*Emory University, Atlanta:* Allen Beck, MD (CD); Anastasios Costarides, MD (CI); Donna Leef, MMSc, CO, COMT (CC)(CM); John Closek, COT (T); Juanita Banks (T); Sheena Jackson (T); Kathy Moore (T). Past participating personnel: Angela Vela, MD (CD); Reay H. Brown, MD (CD); Mary Lynch, MD (CI); Johnny Gunsby, COT; Kathy Lober, COA; Twyla Marsh, COA; Candace Stepka

*Georgetown University, Washington, DC:* Douglas E. Gaasterland, MD (CD); Robin Montgomery, COA (CC)(CM); Donna Clagett, COA (T). Satellite facility: Frank Ashburn, MD (SD); Karen Schacht, COT (SC). Past participating personnel: Ellen Coyle, COMT (CC); Melissa Kellogg Garland, COA (CC); Susan Lauber, MA (CC); Karl Michelitsch, COMT (CC) (deceased); Suzanne Plavnieks, COT (CC); Lynn Vayer, COT (SC); Elizabeth Burt, COT; Mary Hundley, COT; Anne Rae, COT

*Medical College of Virginia, Richmond:* Robert C. Allen, MD (CD); Eydie Miller, MD (CI); Amy Sporn, OD (CC)(CM). Past participating personnel: C. Kay Fendley, COT (CC); L. Sharon Hoyle, COMT

*Ohio State University, Columbus:* Paul A. Weber, MD (CD); Kathryne McKinney, COMT (CC)(CM); Diane Moore, COA (T). Satellite facility: N. Douglas Baker, MD (SD); Fred Kapetansky, MD (CI); David Lehmann, MD (CI); Tammy Lauderbaugh (T). Past participating personnel: Robert Derick, MD (CI); Becky Gloeckner, COT (SC); Lori Black, COA (SC); Kris Coleman, COT; Mary Cassady, COA; Lisa J. Sharf, COA; Billi Romans; Yvonne Satterwhite; Lori Simmons

*Piedmont Hospital, Atlanta:* M. Angela Vela, MD (CD); Thomas S. Harbin Jr., MD (CI); Laura Brannon, COMT (CC)(CM); June LaSalle, COA (T); Gail Degenhardt (T); Stephanie Ann Bridgman (T). Past participating personnel: Randall R. Ozment, MD (CI); Johnny Gunsby, COT (T); Montana Hooper, COT (CC); Julie Wright, COT (T); Stacy Goldstein, COMT (SC); Linda Butler, COT; Marianne Perry, COT; Anne Eckel, COA; Anja Martin, COA; Celeste Session, COA; Dana Nummerdor; Lisa Wille

*Oakland University/Detroit, Southfield, Michigan:* Marshall N. Cyrilin, MD (CD); Holly Dubay (CC)(CM). Past participating personnel: Roselyn Fazio, BS, COT (CC); Patricia S. Corbin (CC)

*University of Illinois, Chicago:* Jacob T. Wilensky, MD (CD); Kim Lindenmuth, MD (CI); David Hillman, MD (CI); Catherine A. Carroll, COMT (CC)(CM); Jennifer Hatton, COT (T). Satellite facility: Sriram Sonty, MD (SD); Catherine A. Carroll, COMT (SC). Past participating personnel: Eve J. Higginbotham, MD (CD); Gary Scholes, MD (CI); Rosanna Uva, COT (CC); Julie Fiene, COT; Diane Frohlichstein, COT; Valeria Gates, COT; Loreen Pappas, COT; Donna Rathbone, COT; Marlem Tadelman, COT; Gloria Hopkins, LPN

*University of Michigan, Ann Arbor:* Paul R. Lichter, MD (CD); Terry J. Bergstrom, MD (CI); Sayoko E. Moroi, MD, PhD (CI); Carol J. Pollack-Rundle, COMT (Co-CC)(T); Carol Standardi, RN, CRNO (Co-CC)(CM); Lynette Abt, COT (T); Terri Van Heck, COT (T). Past participating personnel: Gregory L. Skuta, MD (CD); Eve J. Higginbotham, MD (CD); Robert M. Schertzer, MD (CI); Donna Wicker, OD; Barbara Michael, COT; Desiree Aaron, COA; Judith Birk, COA; Rebecca S. Brown, COA; Joyce Dederian, COA; Linda Kruscke, COA; Jennifer Ziehm-Scott, COA; Renee Papierniak-Dubiel

*University of Virginia, Charlottesville:* Bruce E. Prum Jr, MD (CD); Steven A. Newman, MD (CI); Lee Powell, COT (CC)(CM); Christine Evans, COMT (T); Nancy Barbour, COA (T); Lil Shoffstall-Tyler, COA (T); Terri Voight, COA (T). Past participating personnel: John R. Nordlund, MD, PhD (CD); Louis J. Schott, MD (CI); Robert Fornili, OD (CC); James Chisholm, COA; Carolyn Harrell, COA; Christi Harris, COA; Ellen Murphy, COA

*Washington Hospital Center, Chevy Chase, Maryland:* Arthur L. Schwartz, MD (CD); Howard Weiss, MD (CI); Anne Boeckl, MS (CC)(CM); Christine Tillman, (T). Satellite facility: Anne Boeckl, MS (SC); Lois Maloney, COT (T). Past participating personnel: Maria Cirone, MD (CI); John Gurley, MD (CI); Mark Morris, MD (CI); Maureen O'Dea, MD (CI); Stephen Pappas, MD (CI); Scott Wehrly, MD (CI); Cathy Reed, COMT (CC); Cindy V. Witol, CO (CC); Janet Browning, COT; Karen Carmody, COT; Teresa Driskell; Elaine Harris; Patrick Lopez, COT; Richard Mercer; Victoria Monks, COA; Kathy Vawter, COA; Jing Zhao (T)

*Wills Eye Hospital, Philadelphia:* L. Jay Katz, MD (CD); George L. Spaeth, MD (CI); Richard P. Wilson, MD (CI); Jonathan Myers, MD (CI); Fillis Samuel, COT (CC)(CM); Alaine Meli (T). Past participating personnel: Sue Kao, MD (CI); Annette Terebuh, MD (CI); Coleen C. Beckershoff

*Yale University, New Haven:* M. Bruce Shields, MD (CD); George Shafranov, MD (CI); Ann Leone, COT (CC)(CM); Gail Grottole, COA (T). Past participating personnel: Eydie Miller, MD (CD); Joseph Caprioli, MD (CD); Charles Tressler, MD (CI); Maureen Roche-Manna, COMT (CC)

#### **COORDINATING CENTER**

*The EMMES Corporation, Rockville, Maryland:* Paul C. VanVeldhuisen, MS (Director, Coordinating Center); Fred Ederer, MA, FACE (Epidemiologist); Len G. Dally, MSc (Statistician); Beth Blackwell, ScD (Statistician); Pam Inman (Data Manager); Susan Raitt, MA (Administrative Coordinator). Past participating personnel: Anne S. Lindblad, PhD (Deputy Director); James D. Knoke, PhD (Deputy Director), E. Kenneth Sullivan, PhD, (Director); Lie-Ling Wu, MS (Statistician); Gary Entler, COT (Protocol Monitor); Pamela Phillips, MHS (Protocol Monitor); Carol Smith, MPH (Protocol Monitor), Marline Bradford (Data Manager), Marsha Denekas, MLT (Data Coordinator); Elizabeth L. Wagner, MPH (Data Coordinator); Elaine Stine (Alternate Interviewer); Katherine L. Tomlin, MA (Administrative Coordinator); Tamara Voss, BA (Administrative Coordinator)

#### **SPONSOR**

National Eye Institute and The Office of Research on Minority Health, National Institutes of Health, Bethesda, Maryland: Mary Frances Cotch, PhD (NEI Representative); Lois J. Eggers (Grants Management Specialist). Past participating personnel: Richard L. Mowery, PhD (NEI Representative); Frances Goff (Grants Management Specialist); Carolyn Grimes (Grants Management Specialist); Gaye Lynch (Grants Management Specialist)

#### **STUDY GROUPS**

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*Operations Committee:* Fred Ederer, MA, FACE; Douglas E. Gaasterland, MD; Paul C. VanVeldhuisen, MS; Arthur L. Schwartz, MD (consultant). Past participating personnel: Anne S. Lindblad, PhD; James D. Knoke, PhD; E. Kenneth Sullivan, PhD

*Steering Committee:* Permanent members: Fred Ederer, MA, FACE; Douglas E. Gaasterland, MD; Arthur L. Schwartz, MD; Aaron Kassoff, MD (consultant); Mary Frances Cotch, PhD. Elected investigator members: Marshall N. Cyrlin, MD (1988-1990); M. Angela Vela, MD (1988-1989); Joseph Caprioli, MD (1988-1990); Eve J. Higginbotham, MD (1989-1991); Gregory L. Skuta, MD (1990-1992); L. Jay Katz, MD (1991-1993); Paul A. Weber, MD (1992-1994); Robert C. Allen, MD (1993-1995); Jacob T. Wilensky, MD (1994-1996); Eydie Miller, MD (1995-1997); Reay Brown, MD (1996-1998); Bruce Prum, MD (1997-1999); Marshall Cyrlin (1998-2000); Allen Beck (1999-2001); Paul Lichter, MD (2000-2002). Elected Clinic Coordinator members: Donna Leef, MMSc, COMT (1988); Kathryn McKinney, COMT (1989); Cathy Reed, COMT (1990); Rosanna Uva, COT (1991); Fillis Samuel, COT (1992); Maureen Roche-Manna, COMT (1993); Carol Standardi, RN, CRNO (1994); Ellen Coyle, COMT (1995); Anne Boeckl, MS (1996); Carol J. Pollack-Rundle, COT (1997); Catherine A. Carroll, COMT (SC) (1998); Amy Sporn (1999); Ann Leone (2000). Past participating member: Richard L. Mowery, PhD

*Training and Certification Faculty:* Fred Ederer, MA, FACE; Douglas E. Gaasterland, MD; Aaron Kassoff, MD (Consultant); L. Jay Katz, MD; Donna Leef, MMSc, COMT; Gregory L. Skuta, MD; Carol Standardi, RN CRNO; Fillis Samuel, COT. Past participating personnel: Anne S. Lindblad, PhD; Cathy Reed, COMT; Coleen C. Beckershoff; Gary Entler, COT; Elizabeth L. Wagner, MPH

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## DISCUSSION

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DR MICHAEL A. KASS. Gaasterland and co-workers reviewed intraobserver and interobserver agreement in judging the presence of notching of the optic disc rim in glaucomatous optic nerves. They developed a set of 26 pairs of stereoscopic optic disc photographs, which were reviewed by 14 glaucoma subspecialists who participated in the AGIS trial. The authors found relatively good intraobserver but only fair interobserver reliability in judging notching.

To some extent, the higher intraobserver reliability may be overstated. The glaucoma subspecialists reviewing the photographs were aware that this was a study that included a large number of optic discs with notched rims. The classification system had only 3 possible outcomes (no notching, partial notching, and notching to the rim), thereby reducing the number of choices available to the readers. The readers looked at the photographs in the morning and then again later in the day; thus, the 2 reading sessions were separated by hours rather than by days, months, or years, as would be more typical. It appears from my reading of the manuscript that 2 of the 14 glaucoma subspecialists in this study supplied the photographs and thus may have been more aware of the status of the optic discs.

Other authors have also found a lack of agreement between glaucoma specialists in judging optic disc photographs. In 1976, Paul Lichter reported to this meeting that significant variability existed between glaucoma specialists in evaluating the cup/disc ratio from stereoscopic photographs.<sup>1</sup> The question is whether optic disc photographs can be assessed with a higher degree of interobserver and intraobserver agreement. It is my belief that this is possible, but requires a far more detailed protocol and the use of a reading center. I propose that high degrees of reproducibility can be obtained if the following steps are taken.

1. Develop a standardized protocol for taking, labeling, and shipping photographs.
2. Institute a standardized protocol for training and certifying photographers.
3. Develop a standardized protocol for training readers.
4. Institute a protocol for dealing with conflicting results, ie, reaching consensus.
5. Monitor protocol adherence in an ongoing fashion, including retraining of photographers and readers.
6. Develop a set of standard photographs for training and retesting readers and classifying discs.

In the Ocular Hypertension Treatment Study (OHTS), we have had the opportunity to utilize an optic disc reading center with all of the aforementioned features. We have looked at baseline cup/disc ratio and then re-read the same photographs 1 year, 2 years, and 3 years later. The technicians who read these photographs were not aware that they were re-reading the same set. The percent of regradings at Years 1, 2, and 3 that differed by  $\geq 0.2$  disc diameters from the estimate of horizontal cup/disc ratio made at entry, was 4 %, 6 %, and 7 %, respectively.<sup>2</sup> The OHTS did not specifically address the question of notching; however, I believe that the use of standardized protocols, standardized training, and ongoing monitoring of protocol adherence can produce highly reproducible measurements.

I thank Dr Gaasterland and the other authors for the opportunity to review this paper.

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[Editor's note] DR RICHARD P. MILLS pointed out that clinicians cannot agree on the disc notching and other measurements of glaucoma damage, and even on the definition of glaucoma. When confronted with objective measurements of disc morphology, nerve fiber layer measurements, and quality of life, why do we insist upon agreement and reproducibility levels that are higher than we expect of our own clinical assessment? DR JAKOB WILENSKY reiterated the importance of standardization and training of the examiners to achieve reproducible results. DR FREDRICK L. FERRIS emphasized that evaluations by clinicians yield the poorest results in terms of reproducibility because they used preconceived ideas and experience rather than defined rules. DR ALBERT W. BIGLAN pointed out the problems of seeing the projected slides with true binocular vision. DR BARRETT KATZ asked

how this information about discordance among observers influenced the author's method for the evaluation of optic discs.

DR DOUGLAS E. GAASTERLAND. Dr Michael Kass commented on the short interval between readings in our study and that this may have affected reproducibility. Further, he stated, the observers expected to find notching frequently in the images. Indeed, there are alternative study designs. For example, our study might have been better done with a larger number of images and by including duplicate photographs in a single reading set to be examined by the observers during one reading session. In another design, we could have had a long interval between 2 or more reading sessions. The desirability of rigorous training of observers that he emphasized is obvious, and we emphasized it in our paper.

The investigator who supplied the photographs from one center did not participate in the reading exercise. The investigator from the other photograph source center was not the person who picked the images for the set. It is possible he had seen some of the patients or their photographs in the past. He did not participate in the repeat analysis of the images. I doubt his historical proximity to the images has influenced results of our study.

Dr Kass observed that Dr Lichter, as his thesis for the American Ophthalmological Society in 1976, presented one of the earliest studies of glaucoma subspecialist accuracy and reproducibility in interpreting photographic records of optic disc cupping. That is why I was pleased to be able to present this paper on interpretation of optic disc notching at the present American Ophthalmological Society meeting.

There is accuracy possible in optic disc photographic analysis should we follow the procedures Dr Kass outlined. These are a part of the Ocular Hypertension Treatment Study (OHTS) protocol. I think these procedures are important in clinical trials, and it is a false economy to omit them. Further, clinical trials need to keep long-term documentation of accurately attained measurements. In my mind, photographs are the best current approach for optic disc analysis and record preservation.

Dr Richard Mills commented that disagreements between experienced observers about supposedly obvious clinical details are a fact of life. Here is an example. Recently, I had my eyes read by one of the new disc

analyzers operated by a person with limited experience. The analysis said I have left eye glaucoma. I said, let's repeat that. An hour later we repeated it, and I was cured. So a high degree of accuracy is possible, but it is true that in this technological age we must attain proficiency in using both old and new tools. It takes training.

Dr Jabob Wilensky seconded the need for standardization and training. He gave an example from experience with Ran Zeimer's flicker comparator for disc photographs. In one study, trained resident physician observers were more accurate with this device than untrained community glaucoma subspecialist clinicians. My friend and teacher, Dr Elmer Ballintine, regularly used the flicker comparator to analyze serial monocular disk photographs from ocular hypertension patients. He voiced great enthusiasm for the method.

I agree theoretically with Dr Rick Ferris, who emphasized a need for highly trained non-clinicians to staff reading centers—clinicians bring a host of personal experience to the assessment, and this may interfere with reproducible reading of photographic records.

Dr Albert Biglan pointed out that for binocularity we need peripheral vision for fusion. This requires picture slides without words on them, and it requires that we observe 2 projected pictures forming a stereoscopic pair by slightly crossing, not diverging, our eyes. My slides violated both principles. For this presentation, I briefly tried to reverse the images—the observer's right eye image on the left side and vice versa. However, 2 of the 4 stereoscopic pairs I showed are in simultaneous split frame format, and I couldn't easily switch the right and left images. So I too, if sitting at the back of the room, would see a peak coming toward me, instead of a cup in the disc, as I looked at the images by crossing my eyes slightly. Next time I do this I'll put the paired images in a crossed configuration on a single slide without writing on it.

Finally, in response to Dr Barrett Katz who, after emphasizing the discordance among the observers in our study, asked whether this has changed my clinical behavior when looking at optic discs. The answer is simple. I have confidence in my clinical ability to recognize glaucomatous optic neuropathy. I believe my interpretations and those of other glaucoma subspecialists are reproducible; yet, this study indicates that discussion, training, and using photographic examples might bring our optic disc analyses into better agreement.



# CHANGE ON THE HORIZONTAL AND VERTICAL MERIDIANS OF THE CORNEA AFTER CATARACT SURGERY\*

BY John C. Merriam, MD, Lei Zheng, MD (BY INVITATION), Joanna Urbanowicz, MD, PhD (BY INVITATION), AND Marco Zaider, PhD (BY INVITATION)

## ABSTRACT

**Purpose:** To compare the course and magnitude of change on the horizontal and vertical meridians of the cornea after 5 different incisions for cataract: extracapsular cataract extraction (ECCE), 6 mm superior scleral tunnel (6Sup), 3 mm superior scleral tunnel (3Sup), 3 mm temporal scleral tunnel (3Temp), and 3 mm temporal corneal incision (3Cor).

**Methods:** Retrospective chart review of 665 cases of preoperative regular astigmatism. The preoperative keratometry (K) reading was subtracted from the postoperative K reading to determine mean net change on each meridian at 1 day, 1 week, 2 weeks, 1 month, 1.5 months, 2 months, 4 months, 6 months, and 12 months and at 6-month intervals thereafter. After the superior incisions, the temporal changes on each meridian are well described by an analytic model with an initial and final plateau. The changes after the temporal incisions are described by a linear equation.

**Results:** After each superior incision, the steepness and length of the transition from the initial to final plateau for each meridian depend on incision length. Considering the uncertainty of measuring K, the corneal meridians stabilized 4.5 months after ECCE, 1.2 months after 6Sup, and 0.3 months after 3Sup. No significant change was detected on the horizontal and vertical meridians after 3Temp and 3Cor.

**Conclusion:** The magnitude and the duration of changes on the horizontal and vertical meridians of the cornea after cataract surgery depend on both incision length and location. Small temporal incisions induce less change than superior incisions.

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## INTRODUCTION

In 1864, Donders noted that "To the very ordinary causes of altered, and consequently irregular arching of the cornea, belongs the *extraction of cataract*."<sup>1</sup> With the introduction of the keratometer in 1881, surgeons could measure corneal astigmatism reliably;<sup>2</sup> yet without techniques to control surgically induced astigmatism, clinicians showed little interest in the keratometer. At the 103rd meeting of the American Ophthalmological Society in 1967, Harold Beasley reported the keratometric changes after intracapsular cataract extraction (ICCE). One of the reasons for his study was to determine if changes in the procedure might "reduce the total astigmatism."<sup>3</sup> Soon after this report, advances in ophthalmic surgery—the operating microscope, fine sutures and, later, the intraocular lens and phacoemulsification—stimulated interest in the effect of various incisions on postoperative astigmatism. This study compares the change in the horizontal and vertical meridians of the cornea after 5

different incisions for cataract: extracapsular cataract extraction (ECCE), 6 mm superior scleral tunnel for phacoemulsification (6Sup), 3 mm superior scleral tunnel (3Sup), 3 mm temporal scleral tunnel (3Temp), and 3 mm temporal corneal incision (3Cor).

## METHODS

This study is a retrospective review of 665 cases from a single surgeon's practice (Table I). Some patients in the ECCE and 6Sup groups have been followed for more than 10 years after surgery, but the review of these groups is limited to the first 5 years after operation because the number of patients decreases with time. Review of the smaller incisions is limited to 4 years after 3Sup and 3Temp and 3 years after 3Cor.

## SURGICAL TECHNIQUES

### ECCE

A fornix-based conjunctival flap and a partial-thickness, posterior limbus incision were made superiorly from approximately the 10-o'clock to the 2-o'clock positions. The length of the incision was not measured routinely; incisions were assumed to have an average arc length of 12 mm. A double-armed 8-0 black silk suture was passed

\*From the Edward S. Harkness Eye Institute, College of Physicians and Surgeons, Columbia University, New York, New York (Dr Merriam, Dr Zheng, Dr Urbanowicz), and the Division of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York (Dr Zaider).

TABLE I: PATIENT DATA

INCISION	PATIENTS				EYES		
	FEMALE	MALE	MEAN AGE (YR)	AGE RANGE (YR)	NO.	OD	OS
ECCE	80	48	74	40 - 93	163	94	69
6Sup	44	35	74	46 - 92	91	43	48
3Sup	66	50	73	38 - 92	141	72	69
3Temp	45	28	79	44 - 96	87	52	35
3Cor	85	56	74	43 - 97	183	97	86

across the wound nasally and temporally prior to completing the section with superblade and corneoscleral scissors. After delivery of the lens, cortical cleanup, and placement of the intraocular lens (IOL), the preplaced silk sutures were tied, and the wound was closed with additional interrupted sutures of 10-0 nylon. The silk sutures were removed when they became loose or exposed (generally about 6 weeks after surgery); few nylon sutures were removed unless they were loose and exposed.

#### Phacoemulsification

The sclerocorneal tunnels began approximately 1.5 mm posterior to the limbus. The clear corneal incision (3Cor) was initiated temporally with a 2.6 mm keratome. After capsulorrhexis and phacoemulsification, the incision was enlarged to accommodate a 6 mm polymethyl methacrylate (PMMA) IOL (6Sup) or a foldable IOL (3Sup, 3Temp, 3Cor). The incisions were not measured after IOL insertion and are assumed to be approximately 6 mm for the PMMA IOLs and 3 mm for the foldable IOLs. The 6.0 mm sclerocorneal tunnel was closed with 2 interrupted sutures of 10-0 nylon. The superior and temporal 3.0 mm sclerocorneal tunnels were not sutured or were closed with a single radial 10-0 nylon suture. No sutures were removed unless they became loose and exposed. The clear corneal incisions usually were hydrated. In rare cases, the corneal incision was closed with a single 10-0 nylon suture that was removed in a week.

#### DATA ANALYSIS

The series includes only eyes with regular preoperative astigmatism (major axis within 15° of 90° or 180°) and at least 3 reliable postoperative keratometry (K) measurements. Eyes with preoperative oblique astigmatism were excluded because of an insufficient number of patients for long-term analysis. Eyes that developed an inadvertent filtering bleb after surgery also were excluded. The cornea generally was too irregular for reliable keratometry immediately after ECCE; data for this group begin 2 weeks after surgery. K values were recorded on the first day after phacoemulsification. The ECCE, 6Sup, and 3Cor groups included eyes with both “with the rule” and “against the rule” astigmatism. Nearly all eyes in the

3Sup group had “with the rule” astigmatism preoperatively, and nearly all eyes in the 3Temp group had “against the rule” astigmatism preoperatively. The preoperative and postoperative keratometry readings from the clinical records were sorted (FileMaker Pro 4.1, FileMaker, Inc, Santa Clara, California) to the following postoperative times: 1 day, 1 week, 2 weeks, 1 month, 1.5 months, 2 months, 4 months, 6 months, and 12 months, and to 6-month intervals thereafter. Because patients do not return at precise intervals after surgery, these are average times. All patients returned on the first postoperative day. The 1- and 2-week times are within 3 days of the specified times, and succeeding times are the center of a gradually increasing interval. After 12 months, the time represents the center of a 6-month interval.

The preoperative horizontal K reading was automatically subtracted from the postoperative horizontal K reading, as was the preoperative vertical K reading from the postoperative vertical K reading. For this study, the horizontal axis ranges from 0° to 44° and from 135° to 180°, and the vertical axis from 45° to 134°. A positive result indicates that the meridian is steeper, and a negative result that the meridian is flatter. Mean changes at each time interval were exported into Excel 2000 (Microsoft, Redmond, Washington), Origin 6.0 (Microcal Software, Inc, Northampton, Massachusetts), and SPSS 9.0.0 (SPSS, Inc, Chicago, Illinois) for analysis and graphing.

The change in the horizontal and vertical K values after the 3 superior incisions is consistent with a transition from an initial plateau to a final plateau.<sup>4,5</sup> The analytical expression that follows was proposed originally to describe the change in surgically induced astigmatism after ECCE:

$$D(t) = D_i - (D_i - D_f)e^{(-\alpha/t^\beta)} \quad (1)$$

In this expression,  $D(t)$  is the diopters of change in the horizontal or vertical K value at time  $t$  after surgery, and  $D_i$  and  $D_f$  are the initial and final values of  $D(t)$ . The parameters  $\alpha$  and  $\beta$  determine the slope and extent of the ascending ( $D_i < D_f$ ) or descending ( $D_i > D_f$ ) portion of  $D(t)$ . Best-fit parameters were calculated for the observed changes in horizontal and vertical K values after ECCE, 6Sup, and 3Sup.

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The data for 3Temp and 3Cor are described by a linear equation:

$$D(t) = a + bt. \tag{2}$$

$\chi^2$  analysis showed that the fits were very good for all incisions. 95% confidence intervals were calculated for all curves.<sup>6</sup>

**RESULTS**

**SUPERIOR INCISIONS**

The data are given in Tables II through IV, and the resulting fitting parameters in Table VII. After each incision, the vertical and horizontal meridians return to their preoperative levels ( $D = 0$ ) at similar times (Figs 1 through 6). The mean time for the horizontal and vertical meridians to return to their preoperative levels decreased with incision size: 3.2 months after ECCE, 1.2 months after 6Sup, and 1.0 month after 3Sup.

The horizontal and vertical meridians continue to change after returning to their preoperative levels. The compound error of 2 independent observations is  $\sqrt{(Error_1)^2 + (Error_2)^2}$ . If the variability of each K measurement is 0.25D, the compound error is about 0.35D.<sup>7</sup> When the remaining change in K is less than this compound error, the cornea is assumed to have stabilized. Within the limits of measurement error, at 4.5 months

after ECCE, 1.3 months after 6Sup, and 0.3 months after 3Sup, no further change can be detected.

The differences between  $D_i$  of the vertical and horizontal meridians and between  $D_f$  of these meridians are estimates of the initial and final net change in corneal astigmatism (Table VII, Fig 7). Incision length has more impact on the initial change in corneal astigmatism than on the final change. Each 3 mm increase in incision length adds almost 1.0D to the initial net change in corneal astigmatism but only about 0.15D to the final net change in corneal astigmatism (Fig 7).

**TEMPORAL INCISIONS**

Change on the horizontal and vertical meridians is described well by a linear fit (Tables V and VI). At the 95% confidence level, the slopes are consistent with zero (Figs 8 through 11, Table VIII).

**DISCUSSION**

When Donders<sup>1</sup> observed that cataract surgery contributes to corneal astigmatism, sutures were not used. One hundred years later, when John McLean discussed Harold Beasley's paper at the American Ophthalmological Society, he noted that even one suture "markedly reduced the astigmatism..."<sup>3</sup> He also thought that 2 sutures were better than 1 and that 3 were better than 2, but there was little improvement in final postoperative astigmatism with

TABLE II: CHANGE IN KERATOMETRY VALUES AFTER ECCE

VERTICAL DATA		HORIZONTAL DATA			
MONTHS AFTER ECCE	MEAN D°	SD†	MEAN D°	SD†	N‡
0.5	1.9	1.07	-1.72	0.73	30
1	1.62	1.28	-1.4	1.1	102
1.5	1.27	1.29	-0.83	1.2	71
2	0.56	1.03	-0.29	1	108
4	0.03	0.94	0.17	0.86	62
6	-0.35	0.91	0.32	0.79	71
12	-0.34	0.85	0.38	0.83	82
18	-0.26	0.95	0.56	0.66	65
24	-0.37	0.76	0.64	0.76	54
30	-0.54	0.91	0.52	0.69	56
36	-0.41	0.94	0.6	0.73	51
42	-0.7	0.97	0.5	0.78	43
48	-0.54	0.86	0.68	0.75	53
54	-0.58	0.86	0.58	0.67	44
60	-0.67	0.78	0.62	0.71	68

**Total**

**960**

°Mean diopters of change.

†Standard deviation.

‡Number of data points.

TABLE III: CHANGE IN KERATOMETRY VALUES AFTER 6SUP

VERTICAL DATA			HORIZONTAL DATA		
MONTHS AFTER 6SUP	MEAN D <sup>°</sup>	SD <sup>†</sup>	MEAN D <sup>°</sup>	SD <sup>†</sup>	N <sup>‡</sup>
0.03	0.64	0.9	-0.72	0.73	45
0.25	0.45	0.82	-0.52	0.7	67
0.5	0.24	0.73	-0.03	0.63	25
1	0.16	0.67	-0.02	0.55	68
1.5	0.03	0.64	0.26	0.45	35
2	-0.13	0.6	0.18	0.5	53
4	-0.19	0.6	0.19	0.45	45
6	-0.32	0.45	0.2	0.39	56
12	-0.38	0.49	0.15	0.37	54
18	-0.41	0.48	0.19	0.5	52
24	-0.48	0.45	0.22	0.4	50
30	-0.42	0.45	0.26	0.42	51
36	-0.52	0.52	0.23	0.48	39
42	-0.45	0.43	0.34	0.39	41
48	-0.46	0.47	0.35	0.48	38
54	-0.41	0.55	0.31	0.44	32
60	-0.34	0.47	0.45	0.43	26
<b>Total</b>					<b>777</b>

°Mean diopters of change.

†Standard deviation.

‡Number of data points.

TABLE IV: CHANGE IN KERATOMETRY VALUES AFTER 3SUP

VERTICAL DATA			HORIZONTAL DATA		
MONTHS AFTER 3SUP	MEAN D <sup>°</sup>	SD <sup>†</sup>	MEAN D <sup>°</sup>	SD <sup>†</sup>	N <sup>‡</sup>
0.03	0.21	0.69	-0.72	0.73	126
0.25	0.18	0.63	-0.52	0.7	49
0.5	0.1	0.56	-0.03	0.63	77
1	0.05	0.51	-0.02	0.55	83
1.5	-0.07	0.41	0.26	0.45	47
2	-0.01	0.56	0.18	0.5	72
4	-0.09	0.45	0.19	0.45	67
6	-0.08	0.49	0.2	0.39	91
12	-0.12	0.5	0.15	0.37	85
18	-0.19	0.45	0.19	0.5	87
24	-0.13	0.5	0.22	0.4	66
30	-0.2	0.52	0.26	0.42	48
36	-0.15	0.58	0.23	0.48	48
42	-0.12	0.58	0.34	0.39	48
48	-0.12	0.54	0.35	0.48	36
<b>Total</b>					<b>1,030</b>

°Mean diopters of change.

†Standard deviation.

‡Number of data points.

more than 3 sutures.

Beasley used 3 preplaced and 2 postplaced 6-0 silk sutures for ICCE. Immediately after surgery, the majority of his patients had an increase in “with the rule” astigmatism,

but by the last day of his study, day 46, the majority of the patients had “against the rule” astigmatism.<sup>3</sup> The development of finer sutures and the operating microscope gave surgeons more precise control of wound appo-

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TABLE V: CHANGE IN KERATOMETRY VALUES AFTER 3TEMP

TABLE V: CHANGE IN KERATOMETRY VALUES AFTER 3TEMP					
VERTICAL DATA			HORIZONTAL DATA		
MONTHS AFTER 3TEMP	MEAN D°	SD†	MEAN D°	SD†	N‡
0.03	0.02	0.63	0.04	0.46	78
0.25	-0.09	0.62	0.05	0.51	30
0.5	0.03	0.47	0.05	0.36	48
1	0.08	0.57	0.07	0.51	68
1.5	0.23	0.48	0.1	0.69	32
2	0.17	0.54	0.48	0.38	53
4	0.12	0.5	0.15	0.36	45
6	0.08	0.52	0.15	0.45	48
12	0.04	0.43	0.08	0.36	50
18	0.12	0.42	0.11	0.42	52
24	-0.01	0.41	0.09	0.52	38
30	-0.01	0.5	0.17	0.54	36
36	0.17	0.53	0.21	0.54	33
42	0.03	0.41	0.22	0.51	28
48	0.11	0.46	0.21	0.65	23
<b>Total</b>					<b>662</b>

\*Mean diopters of change.  
†Standard deviation.  
‡Number of data points

TABLE VI: CHANGE IN KERATOMETRY VALUES AFTER 3COR

TABLE VI: CHANGE IN KERATOMETRY VALUES AFTER 3COR					
VERTICAL DATA			HORIZONTAL DATA		
MONTHS AFTER 3COR	MEAN D°	SD†	MEAN D°	SD†	N‡
0.03	0.12	0.59	-0.22	0.47	172
0.25	0.09	0.43	-0.14	0.41	95
0.5	0.1	0.51	-0.18	0.33	90
1	0.24	0.59	-0.07	0.44	126
1.5	0.11	0.49	-0.13	0.4	64
2	0.11	0.39	-0.09	0.4	87
4	0.1	0.41	-0.09	0.43	81
6	0.21	0.56	-0.01	0.43	83
12	0.12	0.42	0.1	0.36	84
18	0.19	0.74	-0.04	0.62	83
24	0.04	0.46	-0.06	0.34	88
30	0.08	0.39	-0.01	0.33	61
36	0.12	0.59	-0.09	0.47	34
<b>Total</b>					<b>1,148</b>

\*Mean diopters of change.  
†Standard deviation.  
‡Number of data points.

sition.<sup>8</sup> However, these technical developments did not solve the problem of surgically induced change in corneal astigmatism. A careful prospective study of ICCE performed with a microscope and 8-0 silk sutures also showed that “with the rule” astigmatism increased immediately after ICCE but that “against the rule” astigmatism predominated in time.<sup>8</sup>

Sutures may not be the only factor leading to an increase in “with the rule” astigmatism immediately after an incision on the superior meridian.<sup>3,8-11</sup> Kondrot<sup>12</sup> showed that even after a small unsutured scleral incision on the superior meridian, “with the rule” astigmatism may rise initially, perhaps on account of tissue shrinkage from cautery, but by 1 year, “against the rule” astigmatism predominated.

TABLE VII: PARAMETERS FOR NONLINEAR FIT OF 3 SUPERIOR INCISIONS

	ECCE				6SUP				3SUP			
	VERTICAL		HORIZONTAL		VERTICAL		HORIZONTAL		VERTICAL		HORIZONTAL	
	VALUE	CI°	VALUE	CI°	VALUE	CI°	VALUE	CI°	VALUE	CI°	VALUE	CI°
<b>D<sub>i</sub></b>	1.91	0.32	-1.75	0.19	0.63	0.12	-0.71	0.18	0.21	0.07	-0.45	0.65
<b>D<sub>f</sub></b>	-0.53	0.13	0.58	0.07	-0.51	0.10	0.28	0.06	-0.16	0.05	0.49	0.43
<b>α</b>	2.22	1.0	1.77	0.51	0.75	0.19	0.32	0.19	0.7	0.34	0.63	0.39
<b>β</b>	1.63	0.61	1.67	0.39	0.69	0.24	1.31	0.63	0.83	0.51	0.34	0.49

\*95% confidence interval.

TABLE VIII: PARAMETERS FOR LINEAR FIT OF 2 TEMPORAL INCISIONS

	3TEMP				3COR			
	VERTICAL		HORIZONTAL		VERTICAL		HORIZONTAL	
	VALUE	CI°	VALUE	CI°	VALUE	CI°	VALUE	CI°
<b>a</b>	0.07	0.07	0.07	0.03	0.14	0.05	-0.11	0.06
<b>b</b>	4E-05	0.003	0.003	0.001	-0.001	0.003	0.003	0.004

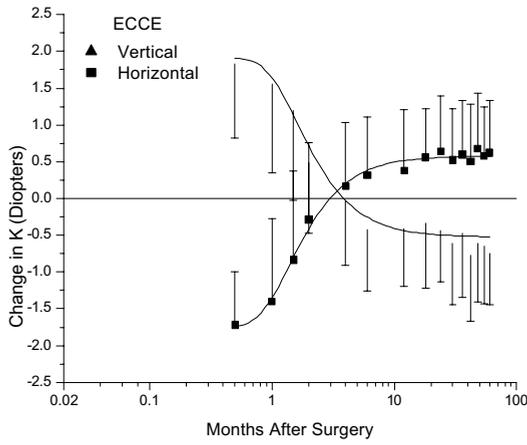
\*95% confidence interval

The effect of an astigmatic keratotomy is based on the premise that change in curvature in one meridian is balanced by an equal and opposite change in the orthogonal meridian.<sup>13,14</sup> The “mean” behavior represented by the curves may be used to test the concept of a coupling ratio. At the 95% confidence level, the ratio of the absolute value of  $D_i$  of the vertical and horizontal meridians cannot be distinguished from 1 for ECCE, 6Sup, and 3Sup. Similarly, the ratio of the absolute value of  $D_f$  of the 2 meridians cannot be distinguished from one for ECCE and 3Sup, but at the 95% confidence level the absolute value of  $D_f$  for the vertical meridian is greater than that for the horizontal meridian for 6Sup (Table VII). However, the absolute value of mean change on each meridian is within one standard deviation at all time intervals after surgery (Tables II through IV). Although these data appear to be consistent with a coupling ratio of 1, the mean is not representative of individual behavior. The range of change on each meridian after each incision is sufficiently great that the concept of the coupling ratio has limited clinical use. The mean change after the superior incisions decreases with incision size, making the long-term refractive effect of the smaller superior incisions more predictable, but also less useful for eliminating pre-operative “with the rule” corneal astigmatism. After both temporal incisions, the mean change is so close to zero that the surgeon cannot know if the incision will increase or decrease astigmatism on either meridian, however slightly.

In 1951 Floyd<sup>9</sup> noted that the greatest increase in corneal astigmatism after ICCE occurred during the first month and that a sharp drop generally took place during the second month. Cridland<sup>15</sup> showed that the postoperative change in refractive astigmatism may be approximated by an exponential decay. The keratometric data presented here for ECCE, 6Sup, and 3Sup confirm that the decay from  $D_i$  to  $D_f$  is exponential. As the size of the incision on the vertical meridian decreases, so does the absolute amount of change in corneal astigmatism and the time for the cornea to stabilize after surgery.

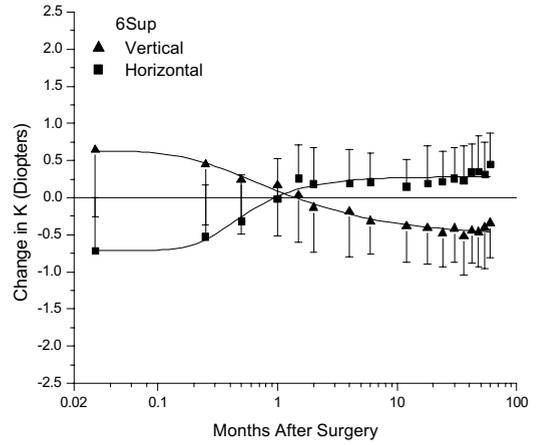
Why a 3 mm superior incision affects corneal curvature more than a similar temporal incision has not been explained. Viewed from the front, the typical human cornea is about 1 mm wider than tall.<sup>16</sup> Thus, superior incisions may be slightly closer to the corneal apex than temporal incisions. Moving a 3 mm incision further from the central cornea might be sufficient to reduce the change in corneal curvature to a level that is not detectable with keratometry. However, a larger incision would surely overwhelm the small astigmatic benefit of a 1 mm shift in position, and clinical studies of larger temporal incisions for ECCE and phacoemulsification indicate that they cause significantly less change in corneal curvature than comparable superior incisions.<sup>17,18</sup> Cravy<sup>17</sup> attributed the change after superior incisions to the distractive force of blinking. This and gravity may account for the difference in superior and temporal wounds, but it is also possible that the biology of the superior and temporal

*Change On The Horizontal And Vertical Meridians Of The Cornea After Cataract Surgery*



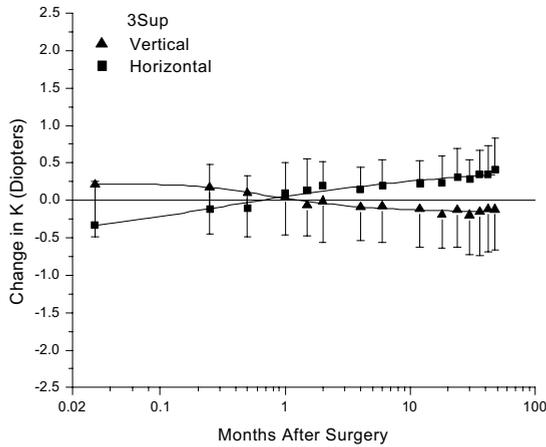
**FIGURE 1**

Semilogarithmic plot of mean and standard deviation of change on vertical and horizontal meridians after extracapsular cataract extraction (ECCE), with curves fit to the data.



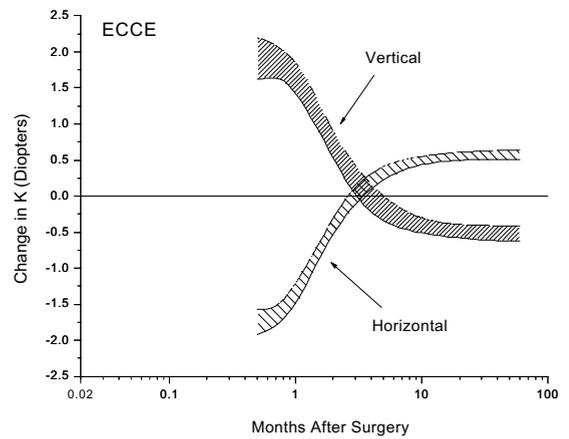
**FIGURE 2**

Semilogarithmic plot of mean and standard deviation of change on vertical and horizontal meridians after 6 mm superior scleral tunnel for phacoemulsification (6Sup), with curves fit to data.



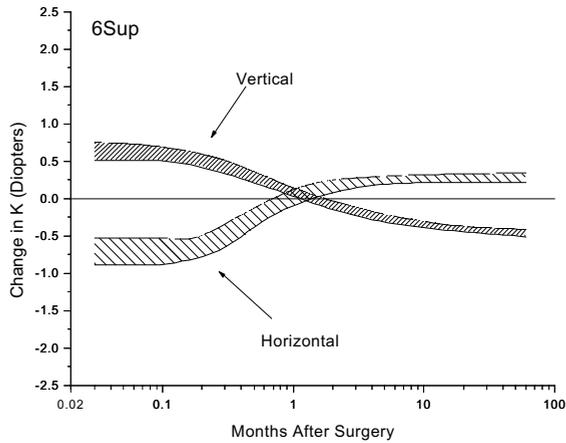
**FIGURE 3**

Semilogarithmic plot of mean and standard deviation of change on vertical and horizontal meridians after 3 mm superior scleral tunnel (3Sup), with curves fit to data.



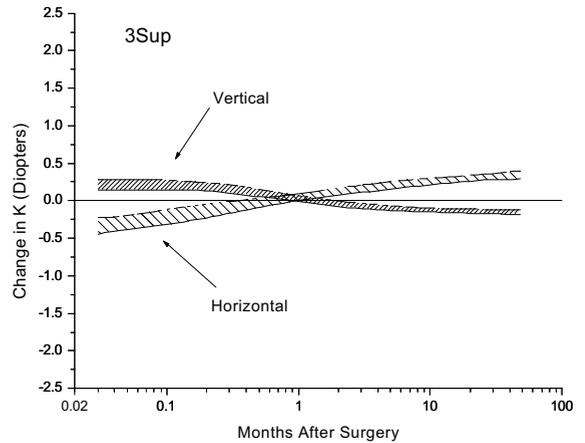
**FIGURE 4**

Semilogarithmic plot of 95% confidence intervals of the fits for change on vertical and horizontal meridians of cornea after extracapsular cataract extraction (ECCE).



**FIGURE 5**

Semilogarithmic plot of 95% confidence intervals of the fits for change on vertical and horizontal meridians of cornea after 6 mm superior scleral tunnel (6Sup).



**FIGURE 6**

Semilogarithmic plot of 95% confidence intervals of the fits for change on vertical and horizontal meridians of cornea after 3 mm superior scleral tunnel (3Sup).

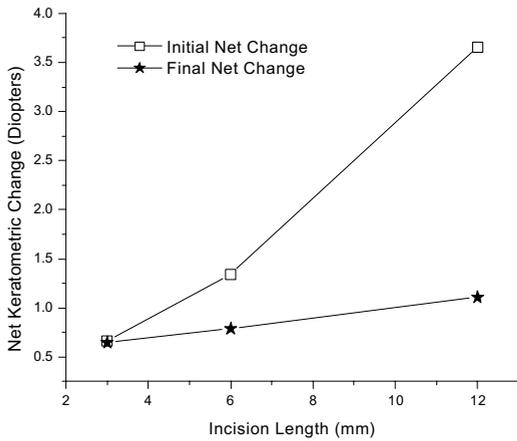


FIGURE 7

Relation of initial and final net change in corneal astigmatism and length of three superior incisions.

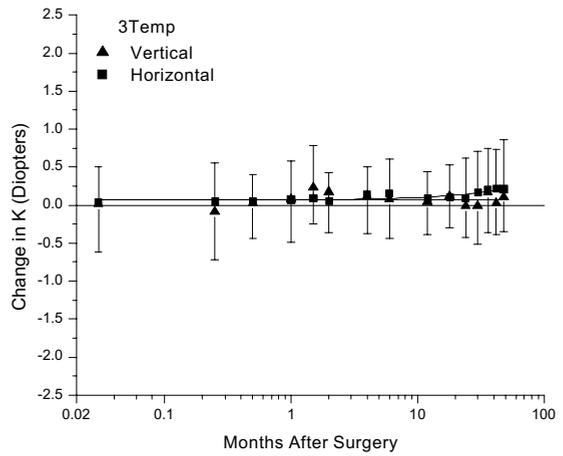


FIGURE 8

Semilogarithmic plot of mean and standard deviation of change on vertical and horizontal meridians after 3 mm temporal scleral tunnel (3Temp), with linear fits to data.

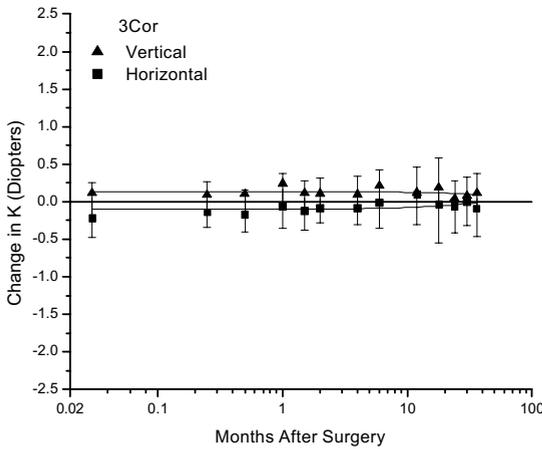


FIGURE 9

Semilogarithmic plot of mean and standard deviation of change on vertical and horizontal meridians after 3 mm temporal corneal incision (3Cor), with linear fits to data.

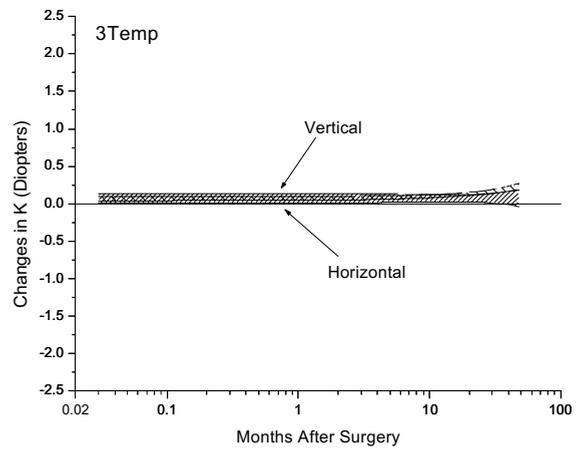


FIGURE 10

Semilogarithmic plot of 95% confidence intervals of the fits for change on vertical and horizontal meridians of cornea after 3 mm temporal scleral tunnel (3Temp).

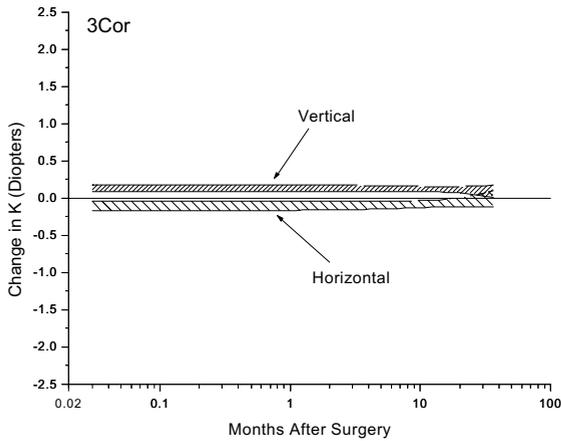


FIGURE 11

Semilogarithmic plot of 95% confidence intervals of the fits for change on vertical and horizontal meridians of cornea after 3 mm temporal corneal incision (3Cor).

cornea and limbus differs. It has long been known that the fine structure of the peripheral cornea differs from the central cornea, but it is not known if wound healing of the temporal cornea differs from that of the superior cornea.<sup>19</sup>

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## DISCUSSION

DR DOUGLAS D. KOCH. Thank you for the opportunity to discuss this interesting work. Dr Merriam and colleagues have in effect attempted to provide an astigmatic history of cataract surgery over the past 20 years. Their study confirms what cataract surgeons today accept as dogma: that small temporal incisions induce the smallest amount of surgically induced astigmatism and maximize astigmatic stability.

The most remarkable aspect of this study is the diversity of incisions and duration of follow-up for the patients included in their report. In the ophthalmic literature there are no studies that match or even approach the authors' accomplishments in these 2 areas. This study is also the first to mathematically describe the rate of astigmatic change for various incision types.

As a retrospective study, this report has several drawbacks. The authors report on 665 patients, but the total pool of patients from which these are drawn is not provided. If a large number of patients were lost to

follow-up, this could bias their results. This problem could be ameliorated somewhat if the authors provided an analysis of the same cohort of patients preoperatively and at each key postoperative interval.

There are some uncertainties regarding data acquisition. This study is based on keratometry readings that were presumably obtained only once per visit by a variety of technicians; this certainly could introduce variability in their data. In addition, the surgical techniques were obviously not strictly controlled. For example, some of the superior 3 mm incisions were sutured, whereas others were left unsutured. Another potential variable is that incision size was not actually measured. The authors indicate that the smallest superior and temporal incisions were 3 mm in size, but the technology for achieving incisions this small has generally not been available until recently. I therefore suspect that these incisions were 3.5 mm and perhaps even 4 mm in length. This might be a minor quibble, but it has relevance as we try to understand the impact of reducing small incisions by small amounts, such as 0.3 to 0.5 mm.

A major concern with this study is their basic methodology for data analysis. The authors use an unorthodox and scientifically imprecise method for recording and analyzing keratometric astigmatism. They included only patients whose initial astigmatic meridian was within 15° of 90° or 180°, thus presumably excluding a large number of patients. More importantly, postoperative keratometry values were recorded as either superior or horizontal, depending upon their orientation relative to the 45°-135° meridians. The magnitude of error introduced by this methodology could be large. For example, a patient with astigmatism of 42 x 44 at 90 would be recorded identically to a patient with astigmatism 42 x 44 at 136°, which generates approximately a one-diopter error at both the horizontal and vertical meridians.

There are now scientifically validated methodologies for analyzing astigmatic data. In the January issue of the *Journal of Cataract & Refractive Surgery*, we published 8 papers that describe state-of-the-art techniques in this area.<sup>1-8</sup> Two fundamental aspects of these analytical approaches are particularly relevant to Dr Merriam's work.

First, with vector analysis one can calculate astigmatic changes with-the-wound and against-the-wound.<sup>9</sup> For this type of analysis, the authors could graph the data as they have done in their study, substituting for the existing data the scientifically accurate with-the-wound and against-the-wound changes. This would permit the inclusion of all patients preoperatively and would ensure accurate analysis of all postoperative astigmatic changes, regardless of the location of the steep and flat meridians.

Secondly, aggregate analysis of the surgically induced

changes in astigmatism over time can be calculated.<sup>10</sup> This type of vector analysis would enable the authors to demonstrate the mean magnitude and direction of the astigmatic changes for each incision type at each postoperative interval. With bivariate analysis<sup>3-5</sup> of these data, the authors could statistically compare incision types and determine when stability was achieved for each.

I believe that Dr Merriam's study can provide important new information regarding the astigmatic effects of various cataract incisions, despite the problems inherent in the retrospective nature of this study. I encourage him to re-analyze the data using the more scientific rigorous methodology that is now available. I congratulate Dr Merriam for this interesting and valuable study.

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[Editor's note] DR JAMES C. BOBROW felt that vector analysis would be a more accurate way to look at the data. He asked if one really wanted to achieve the same astigmatism as existed prior to surgery rather than to place the incision to minimize or eliminate pre-existing astigmatism. He also wondered about long term results, having noted in his own patients a tendency to develop increasing astigmatism in the horizontal meridian with time.

DR JOHN C. MERRIAM. I would like to thank Dr Koch and Dr Bobrow for their thoughtful comments. Doug and I had a conversation by email before the meeting, and I anticipated some of his comments today. This is indeed a retrospective study. Although we have a large database, I am not sure if we have sufficient numbers of patients in each group to do a long-term "cohort" study, as he

suggested. Unless the cohort was large, one would still wonder if it was representative of the general patient population. Dr Koch asked if there were several technicians: I performed all of the keratometry readings for this study. He also noted that the phaco groups include some wounds that were sutured and that we did not actually measure each incision. The 6 mm phaco incisions routinely had 2 simple vertical 10-0 nylon sutures, and the 3 mm wounds were closed with a single suture only when there was concern about a wound leak. We have looked at the effect of a single suture on these small wounds and found that the long-term development of astigmatism is the same. All the incisions for a 6 mm IOL and some 3 mm incisions were measured with a caliper. With experience, I stopped measuring the incision routinely for foldable lenses. The actual size of the incisions in each group surely did vary a little, but we do not think that this is a significant factor. The sclera and cornea are elastic, and any intraoperative measurement of internal wound length is subject to error. The final induced changes from the superior 3 and 6 mm incisions are so close that we do not think we can measure the effect of slight variability in the length of these incisions. Whatever the range of incision length, we demonstrated no significant change from the temporal incisions.

Dr Koch has suggested some alternative ways to analyze our data. We already have looked at our data in a number of ways, including vector analysis and some axis-based techniques of assessing surgically induced astigmatism. These results will be the subject of a future report. He expressed concern that this study included only patients with regular pre-operative astigmatism. We excluded patients with pre-operative oblique astigmatism because we suspect that these eyes may behave differently after incisions on the horizontal and vertical meridians and the number of such patients in each group was not large enough for long-term analysis. His main concern was that the potential for error is great when the axis is close to 45° or 135°. To our knowledge, this is the first study to consider the variability of the K reading as experimental error. I generally measure K's once before other routine office procedures, but I often measured the K's 2 or more times during a single office visit. Both the value of the K reading and its axis may vary, sometimes surprisingly. It seems misleading to us to worry about the effect of a 1° or 2° shift in axis when one cannot measure the axis with such precision in routine clinical practice. However, if the number of data points close to 45° or 135° were large, Dr Koch is correct that the potential for error in the curve fittings might be significant. Fortunately there are relatively few patients, even with the larger incisions, who have such oblique astigmatism after surgery. Of the 4577 data points in this study, only 18 have an axis between 40° and 50° or between 130° and 140°. Twelve of these points

are from the ECCE group, 4 from 6Sup, and 1 each from 3Sup and 3Temp. The potential for error from these patients is nil. The results of curve fittings are indistinguishable whether they are all excluded, all included with the vertical group, or all included with the horizontal group. After Dr Beasley's paper in 1967, Dr Sloane from Boston, whose book on optics I used as a resident, commented on how quickly the cornea became regular after intracapsular extraction. Certainly there is less induced oblique astigmatism after today's smaller incisions than after ICCE.

Dr Bobrow wondered whether we could use these incisions to change pre-operative corneal astigmatism. We have looked at that question with our data set, and we

don't find that the astigmatic effects of the superior incisions are reliable enough to be truly predictive. He also mentioned that he thinks that corneal astigmatism may continue to change for 10 or more years after surgery. Some of the patients who had ECCE have been followed for more than 15 years, although the data presented here were limited to 5 years. To compare all of the incisions will require years of data accumulation. However, after 5 years we think that it is important to consider the effect of age because the cornea does change with age. To distinguish the effect of the incision from the effect of age requires large numbers of patients and controls and is not a simple matter.



# THE REPRODUCIBILITY OF OPHTHALMIC UTILITY VALUES\*

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BY Gary C. Brown, MD, MBA, Melissa M. Brown, MD, MN, MBA (BY INVITATION), Sanjay Sharma, MD, MSc, MBA (BY INVITATION), George Beauchamp, MD, AND Hussein Hollands, MSc (BY INVITATION)

## ABSTRACT

*Purpose:* Utility values have been used in the ophthalmic literature to measure the quality of life associated with a health state. By convention, a utility value of 1.0 is associated with perfect health, and a value of 0.0 is associated with death. Construct validity of utility values has been demonstrated, particularly in regard to decreasing utility values as the vision decreases in the better seeing eye, but long-term test-retest reliability has not been demonstrated. The purpose of this study was to demonstrate the test-retest reliability of ophthalmic utility values.

*Methods:* One hundred fifteen patients with ophthalmic diseases and stable visual acuity underwent time trade-off utility analysis with retesting at various intervals ranging from 1 month to 2 years. The results were analyzed using the Wilcoxon signed rank test. The study was designed to have an 80% power, using a two-sided alpha of 5%, to be able to detect a 10% difference between the test and retest groups.

*Results:* The mean time from testing to retesting was 0.87 years, with a median time of 1.0 year and range of 1 month to 2 years. The mean utility value in the test group was 0.766 (SD = .21; 95% CI, 0.730 - 0.802), while the mean utility value in the retest group was 0.763 (SD = .22; 95% CI, 0.724 - 0.802). The difference between the means of the test-retest groups was not significant ( $P=.99$ ). The intraclass correlation between the initial and follow-up utility scores was .5246 ( $P<.00005$ ).

*Conclusions:* Ophthalmic utility values appear to have good test-retest reliability over prolonged periods of time. This information is important because it gives researchers increased confidence in the validity of basic tools for ophthalmic cost-effective (cost-utility) analyses.

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## INTRODUCTION

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Utility values are measures that quantify the quality of life associated with a health state.<sup>1,5</sup> By convention, utility values range from 1.0, associated with perfect health, to 0.0, associated with death. The closer the value to 1.0, the better the quality of life associated with a health state, while the closer to 0.0, the poorer the quality of life. For example, mild angina has been associated with a utility value of 0.90, while severe angina has been associated with a value of 0.50.<sup>2</sup>

Utility value analysis has also been undertaken in patients with ophthalmic disease.<sup>9-17</sup> It has been demonstrated that

utility values in patients with ophthalmic disease most closely correlate with the visual acuity in the better-seeing eye. For example, a patient with bilateral ocular disease and a visual acuity of 20/20 in the better-seeing eye has been shown to have a utility value of 0.92, while a person with the same underlying ocular disease and acuity of 20/200 in the better-seeing eye has been shown to have a utility value of 0.66.<sup>11</sup>

Construct validity has been demonstrated for ocular utility values,<sup>18</sup> as has test-retest reliability on a short-term (28-day) basis.<sup>19</sup> To our knowledge, however, test-retest reliability has not been demonstrated on a longer-term basis. For this reason, we undertook a study to evaluate the test-retest reliability of ocular utility values in a patient population with known ocular disease.

## PARTICIPANTS AND METHODS

Over a 2-year period, from December 1998 through November 2000, we collected time trade-off utility data on over 1,000 adult patients with various ocular diseases gathered from vitreoretinal (G.C.B.) and comprehensive ophthalmology (M.M.B.) practices. Data for the present

\*From the Center for Evidence-Based Health Care Economics, Flourtown, Pennsylvania (Dr Gary Brown, Dr Melissa Brown, Dr Hollands, Dr Sharma); the Retina Vascular Unit (Dr Gary Brown) and the Cataract and Primary Eye Care Service (Dr Melissa Brown), Wills Eye Hospital, Jefferson Medical College, Philadelphia; the Center for Ocular Cost-Effective Health Policy (Dr Hollands, Dr Sharma), Queens Medical College, Kingston, Ontario, Canada; and the Department of Ophthalmology, Southwestern Texas Medical Center, Dallas (Dr Beauchamp). Supported in part by the Retina Research and Development Fund, Philadelphia; the Principle's Research Initiative Fund, Kingston; and the Premier's Excellence Award, Toronto, Ontario, Canada.

study were gathered from the group of these patients that was seen in follow-up examination. An attempt was made to consecutively include follow-up data on all patients who had initially undergone utility value evaluation. The utility study was approved by the Institutional Review Board of Wills Eye Hospital, Philadelphia.

Each person underwent a complete ophthalmologic examination, including best-corrected Snellen visual acuity, slit-lamp biomicroscopy, and dilated fundus examination. Snellen visual acuity was selected for measurement, since it is the most commonly used system in clinical practice, and an objective of the study was to most closely simulate real-life practice. In those instances in which the visual acuity could be improved with pinhole above the best-corrected visual acuity, the pinhole vision was selected as the best vision. Since people often squint to improve vision, this again was thought to more accurately represent the actual visual potential in a real-life setting. The length of time of visual loss from the initial loss to the initial examination was recorded, as was the time from the initial examination to the follow-up examination.

Exclusion criteria included the absence of any ocular disease, unwillingness to answer the questions posed in the study, and obvious Alzheimer's disease or some other form of dementia. A change in visual acuity between the initial and follow-up visits of 1 or more lines in the better seeing eye or 2 or more lines in the poorer seeing eyes was also an exclusion criterion.

#### UTILITY VALUE ASSESSMENT

The standardized and validated methodology of utility value assessment has been previously described.<sup>9-14,17</sup> In essence, each patient was asked how many additional years of life he or she expected to live. The patient was then presented with the following theoretical scenario: "If the vision in each of your eyes could be returned to (or maintained as) normal (20/20) on a permanent basis by a treatment that always works, what is the maximum number of your theoretical remaining years—if any—that you would be willing to trade in order to have the treatment?" The time trade-off utility value was then calculated by subtracting the proportion of the remaining years traded from 1.0. For example, if a patient who expected to live another 20 years was willing to trade 5 of those years in return for guaranteed normal vision, the resultant utility value would be 0.75, calculated as follows:  $1.0 - (5/20) = 0.75$ .

At follow-up examination, the same time trade-off questions were asked in a double-blind fashion, with neither the patient nor the interviewer having access to previous utility values. The interviewers, however, did compare initial visual acuity with the acuity on follow-up examination at the time of data analysis, since those patients in

whom there was a change in visual acuity (either worsening or improvement) between visits were ineligible for the study. Patients were not routinely asked to come in for follow-up for utility evaluation but were examined at their follow-up visits related to their ocular abnormalities.

It should be noted that in previous studies, about 5% to 10% of patients who initially agreed to participate in utility value assessments were unable to answer the questions once they were posed.<sup>9,10,12-14</sup> In the present analysis, however, none of the patients who initially answered the ocular utility value questions were unwilling or unable to do so at the follow-up examination.

#### STATISTICAL METHODS

Means, medians, standard deviations, and 95% confidence intervals were calculated for the initial and follow-up groups using an Excel 97 statistical package (Microsoft, Tacoma, Wash). SPSS 10.1 software (SPSS, Inc, Chicago, Ill) was employed to perform the Kolmogorov Smirnov evaluation for normalcy, the Wilcoxon signed rank test for nonparametric data, the Spearman's rho correlation coefficient, and the intraclass correlation.

A power calculation using Epi-Stat (Centers for Disease Control, Atlanta, Ga) revealed that for a two-sided alpha of 5%, 115 patients in each of the initial and follow-up groups were required for a power of 80% to detect a 10% difference between the groups. Variances were obtained from a previous large utility value study on ophthalmic patients.<sup>12</sup>

#### RESULTS

Repeat utility values were obtained on 175 patients, among whom 125 demonstrated stable visual acuity conforming with study entrance criteria during the follow-up period. Included among the 125 subjects in the study were 45 men and 80 women. The mean age was 65.1 years (SD = 12.1; 95% CI, 62.9 - 67.3). The median age was 68 years, and ages ranged from 37 to 82 years. There were 121 white and 4 black subjects. The mean number of years of education was 13.0 (SD = 2.7; 95% CI, 12.5 - 13.5), with a median of 12 years and a range of 4 to 20 years. A summary of the clinical characteristics of the sample is shown in Table I.

The predominant ocular diseases in the 125 subjects were as follows: diabetic retinopathy (54), macular degeneration (33), cataract (12), retinal detachment (9), retinal arterial or venous obstruction (6), amblyopia (3), glaucoma (2), corneal opacity (2), uveitis (2), macular hole (1), and macular pucker (1). These are shown in Table II.

The mean Snellen visual acuity in the better eye in the sample at initial entrance into the study was 20/40,

TABLE I: CLINICAL CHARACTERISTICS OF THE OPHTHALMIC SUBJECT COHORT (N=125)

**Sex**  
 Male: 45 (36%)  
 Female: 80 (64%)

**Age at initial examination**  
 Mean: 65.6 yr  
 Median: 68 yr  
 Range: 37 - 82 yr

**Race**  
 White: 121 (97%)  
 Black: 4 (3%)

**Education (years postkindergarten)**  
 Mean: 13.0  
 Median: 12.0  
 Range: 4 - 20

TABLE II. PREDOMINANT OCULAR DISEASES IN THE COHORT OF 125 SUBJECTS

DISEASE	NO.	(%)
Macular degeneration	54	(43)
Diabetic retinopathy	33	(26)
Cataract	12	(10)
Retinal detachment	9	(7)
Retinal arterial or venous obstruction	6	(5)
Amblyopia	3	(2.5)
Glaucoma	2	(1.5)
Corneal opacity	2	(1.5)
Uveitis	2	(1.5)
Macular hole	1	(1)
Macular pucker	1	(1)

with a range of 20/20 to light perception. The median visual acuity in the better seeing eye was also 20/40. The respective mean visual acuity in the poorer seeing eye was 20/100, with a range of 20/25 to no light perception. The median visual acuity in the poorer seeing eye was 20/300. Three subjects had 20/20 vision in each eye.

The mean time of visual loss to the level at the time of entrance into the study was 4.4 years, with a range of 1 month to 63 years and a median time of 2 years of visual loss. When the 3 subjects with visual loss occurring predominantly secondary to amblyopia were excluded, the mean time of visual loss was 3.1 years. As stated in the "Participants and Methods" section, only subjects in whom the vision remained the same in the better seeing eye and changed no more than 1 Snellen gradation better or worse in the poorer seeing eye were included in the study.

The mean utility value for the group at the time of initial examination was 0.766 (SD = .20; 95% CI, 0.728 - 0.802). The median value was 0.80. Utility values in the initial groups ranged from 0.20 to 1.0. At the time of follow-up, the mean utility value for the group was 0.763

(SD = .22; 95% CI, 0.724 - 0.802), with a median value of 0.80. Utility values in the follow-up group ranged from 0.17 to 1.0. The mean time of follow-up between the measurements was 0.87 year, with a median time of 1.0 year and a range of 1 month to 2 years.

The one-sample Kolmogorov Smirnov evaluation for normalcy of distribution revealed a Z value of 2.196 for the initial utility values ( $P < .001$ ) and a Z value of 2.214 ( $P < .001$ ) for the follow-up utility values, indicating that neither of the utility value distributions was normal. Bar graphs of the utility value distributions at initial examination and follow-up examination are shown in Figs 1 and 2,

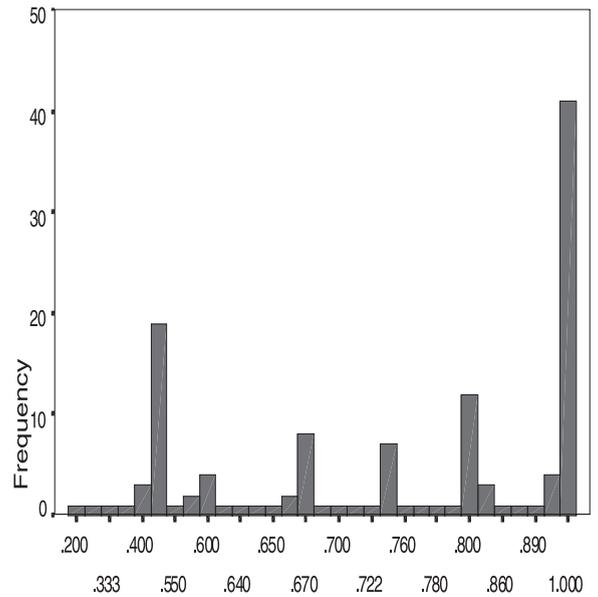


FIGURE 1

Distribution of initial utility values (INITUTIL) in the 125-subject cohort.

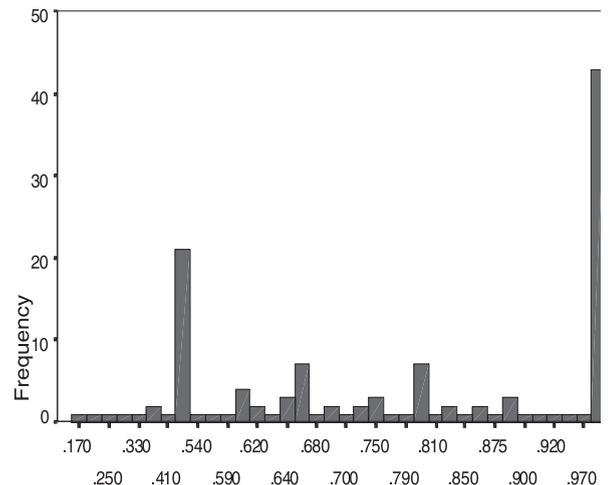


FIGURE 2

Distribution of retest (follow-up) utility values (FUUTIL) in the 125-subject cohort.

respectively. Because of the nonparametric characteristics of the utility values, the Wilcoxon signed rank test, the nonparametric variant of Student's *t* test, was used to statistically assess utility values and the utility calculation parameters of years to live and time of life traded.

The mean initial utility value for the cohort was .766 (SD = .21; 95% CI, 0.730 - 0.802), while the mean utility value in the retest group was 0.763 (SD = .22; 95% CI, 0.724 - 0.802). The difference between the means of the test and retest groups was not significant ( $P = .99$ ).

When the mean amount of time each subject expected to live was examined, it was noted that the average number of remaining years at initial evaluation was 16.6 (SD = 9.8; 95% CI, 14.9 - 18.3), with a range of 5 to 40 years. At follow-up examination, the mean number of years remaining was 16.8 (SD = 10.5; 95% CI, 14.0 - 18.6), with a range of 2 to 45 years. The difference between the means of the initial and follow-up groups was not significant ( $P = .777$ ).

The mean number of years traded at initial examination was 3.4 (SD = 3.7; 95% CI, 2.7 - 4.1), with a range of 0 to 20 years, while the mean number of years traded at follow-up was 3.9 (SD = 4.3; 95% CI, 3.1 - 4.7), with a range of 0 to 20 years. The difference between the means of the initial and follow-up groups was not significant ( $P = .474$ ). A summary of these study results is shown in Table III.

An intraclass correlation was also performed between the initial and follow-up utility scores. The correlation was .5246 (95% CI, 0.3850 - 0.6408). This was highly significant ( $P < .00005$ ).

Correlations were also performed between visual acuity and utility values using Spearman's rho correlation coefficient. The correlation between initial utility values and vision in the better seeing eyes was .524 ( $P < .001$ ), while that between initial utility values and vision in the poorer seeing eye was .365 ( $P < .001$ ).

## DISCUSSION

Utility value analysis is a tool that allows the measure of the quality of life associated with a health state. According

to Guyatt and associates,<sup>20,21</sup> it is imperative for a good quality-of-life measurement tool to have construct validity, reliability, ease of administration, and the capacity to be readily interpretable. Overall construct validity was not addressed in the present analysis but requires comparing a parameter (in this case, utility values) with other patient characteristics and examining logical relationships that should exist. Construct validity has been previously shown for ophthalmic utility values, particularly in relation to the visual acuity in the better seeing eye.<sup>18</sup> Data from the analysis presented here also indicate a substantially higher correlation between utility values and visual acuity in the better seeing eye than between utility values and visual acuity in the poorer seeing eye.

Our data suggest that ophthalmic utility values appear to be highly reproducible, even over prolonged periods. This information is critical to confirm the reliability of ocular utility values, an important aspect of construct validity. It has previously been demonstrated that ophthalmic test-retest utility values are reliable on a short-term (4-week) basis,<sup>19</sup> with an intraclass correlation between initial and follow-up utility values of 0.7634. This indicates an excellent reliability for subsequent time trade-off utility responses, according to Rosner.<sup>22</sup> In the present study, we found an intraclass correlation of .5246, considered to be good reproducibility.<sup>22</sup> This gives us even greater confidence in the time trade-off methodology for ophthalmic utility value assessment, since the mean time between the initial and follow-up utility values in the present study was 0.87 years, with a range as high as 2 years between test and retest data.

The mean time of visual loss in subjects in this series was 3 years. Thus, it is uncertain whether this reproducibility found in subjects with longer-term visual loss holds for cases of acute visual loss (<1 month). It has been demonstrated in both patients with diabetic retinopathy<sup>10</sup> and patients with visual loss occurring secondary to multiple causes<sup>12</sup> that ophthalmic utility values are similar whether the visual loss has occurred for 1 year or less or for more than 1 year. In subjects with visual loss occurring secondary to age-related macular degeneration,<sup>13</sup> however, the time trade-off utility value has been shown to be significantly lower in those who have had visual loss for 1 year or less than in those who have had visual loss for more than 1 year. Thus, at least for visual loss associated with age-related macular degeneration, there may be a compensatory mechanism that allows for some improvement of the quality of life over time.

In addition to reliability within the same population, it has been shown that ophthalmic utility values are comparable across international borders.<sup>23</sup> They also appear to transcend differences in age, sex, race, and level of formal education.<sup>12</sup> Other tools, including the VF-14,<sup>24</sup> the

TABLE III: CLINICAL DATA ON THE OPHTHALMIC SUBJECT COHORT AT INITIAL AND FOLLOW-UP EXAMINATIONS (N=125)

CATEGORY	INITIAL EXAM	FOLLOW-UP EXAM	P VALUE*
Mean vision in better seeing eye	20/40	20/40	NA
Mean utility value	0.765	0.761	.991
Mean years of life expectancy	16.6	16.8	.777
Mean years traded	3.4	3.8	.474

NA, not applicable.

\*Using the Wilcoxon signed rank test.

51-item National Eye Institute Visual Function Questionnaire,<sup>25</sup> and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),<sup>26</sup> have also been used to measure quality of life in ophthalmic patients. These instruments measure primarily the functional ability associated with a health state and can provide valuable information. Utility values, however, are believed to be more all-encompassing quality-of-life measures,<sup>6,8</sup> since they also take into account factors such as socioeconomic status, support systems, anxiety, psychologic overlay, and other entities that may not be addressed or emphasized by the previously mentioned instruments. Utility analysis furthermore allows a comparison of widely disparate medical specialties, an endeavor that can be difficult with certain of the other quality-of-life measures.

Perhaps the most important aspect of utility value analysis, compared with other quality-of-life tools, is that it is a critical component of cost-effective (cost-utility) analysis.<sup>27-31</sup> With cost-utility analysis, the patient-perceived value conferred by a medical intervention can be amalgamated with the cost and compared across virtually all interventions in health care. Knowing that ophthalmic utility values are reproducible and reliable on a test-retest basis over a prolonged period of time, as found in the present study, gives researchers greater confidence in the validity of cost-effective analyses in the arena of ophthalmic interventions.

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## DISCUSSION

DR MALCOLM L. MAZOW. I appreciate the authors sending the paper in ample time for me to be able to review it and have a colleague assist with the statistics. There are a few issues that I would like to discuss.

Why did you choose to compute the confidence

interval instead of the predictive interval? By using the Bland Altman to look at the predictive interval, one could look at the individuals rather than groups. This would allow a better look at 1, 2 and 3 standard deviations. Test/retest should be for individuals and not groups as one would like to know how many fall out of the 68% range of 1 standard deviation. I am unclear about the comparison of good eye to bad eye, as visual perception occurs with (requires) use of both eyes.

This study looked at a very homogeneous group. I would like to see a more heterogeneous group tested and stratification of the various categories so that the individuals could be more accurately assessed. Ethnicity, age, occupation and diagnosis seem important. What about gender? Expected years to live and the number of years one is willing to give up is most certainly related to the patients' age at the time of diagnosis. A youngster of 17 might be much more willing to give up several years at the end of their life, which is way down the road in their mind, than an adult of 70. Also, one's education, vocation, and avocation, should impact the number of years they would be willing to give up for better vision. Another consideration might be the subjects overall health, and the condition of their other senses.

Perhaps, the practices involved did not lend themselves to such variations, but I think this should be looked at in future investigations.

As we are all aware, the name of the game in medical care is cost analysis. Therefore, it is incumbent on all of us to explore issues that can have an effect on the acceptance of various treatments that affect the quality of life of our patients, as this paper does.

I know you are all as concerned as I am about this issue and only hope that as we continue to prove how important quality of life can be for patients, we can impact the treatment available. In this regard, I've looked at the importance of the treatment of amblyopia in children, and now we are embarking on a study of adult strabismus and how improvement of this condition positively affects patients' lives.

[Editor's note] DR IVAN R. SCHWAB asked how differing sociological values were factored into the equation, pointing out as an example that some individuals were willing to pay a significant amount for refractive surgery while others were happy that their vision was correctable with glasses or contact lenses. DR ALBERT W. BIGLAN asked if and how adverse results from surgery were considered.

DR GARY C. BROWN. In answer to Dr Mazow's excellent questions, visual utility values tend to be nonparametric at levels of 20/60 or better, but parametric, or normally distributed when the vision drops to 20/70 or worse. In the

latter situation, confidence intervals can be employed.

In regard to the quality of life, it turns out that it is the good eye that is the most important and correlates with utility values. When we looked at variants of combining vision in both eyes, the vision in the better seeing eye correlates just as well as using a combination of 75% good eye, 25% bad eye and 50% good eye, 50% bad eye. The poorer seeing eye plays a secondary role; it is the better seeing eye that is more critical.

The vision in the second eye, however, is also valuable because people with 1 good eye constantly worry about their good eye. They worry about what is going to happen to that good eye, and they worry so much that it decreases their quality of life.

Concerning age and utility values, between the ages of 25 and 85 years the values for the same health state appear to be similar in younger and older groups. Utility values also transcend levels of society, since people with an 8th grade education have the same utility values as those with college education for the same health state. The values seem innate to human nature.

The comorbidity question is a good one. What about people with systemic comorbidities? For example, does someone who has diabetes derive less value from cataract surgery than somebody who doesn't have diabetes? We thought this was a very important question. It turns out that when we do a multiple regression analysis, ocular utility values are not affected by systemic comorbidities. So, somebody who has heart disease or a bad hip receives just as much improvement in quality of life from cataract surgery as someone who otherwise has perfect health. This strongly suggests that we should not discriminate against the disabled when therapeutic interventions are being considered.

Dr Schwab talked about the willingness to pay method of utility value measurement. There are a number of ways to measure utility values and willingness to pay is one methodology. We have avoided it since we believe people with more money are willing to pay more for a therapeutic intervention, thus confounding quality of life issue. That's why we elect to stay with the time trade-off methodology of utility value measurement.

The last question – Dr Biglin's question. With decision analysis an integral part of cost utility analysis, one can take into account the adverse effects, or the disutilities, associated with any type of health state. Cost utility analysis incorporates utility values with decision analysis and takes into account improvement in length of life and quality of life, as well as adverse effects; it correlates the value obtained from an intervention with the associated costs. We believe cost-utility analysis will play a dominant role in how health care is delivered within a decade.

# CORNEAL MELTS ASSOCIATED WITH TOPICALLY APPLIED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS\*

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BY *Allan J. Flach, MD*

## ABSTRACT

*Purpose:* Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to prevent miosis during cataract surgery, to treat ocular allergies, to prevent excessive postoperative inflammation following cataract surgery, and to treat cystoid macular edema following cataract surgery. They have also been used to control pain and photophobia following radial keratotomy and excimer laser photorefractive keratectomy. During August of 1999, severe complications following topical NSAID use, including corneal melting, were reported by members of the American Society of Cataract and Refractive Surgery (ASCRS) responding to a survey distributed in letters from ASCRS to its members. The purpose of this report is to review 11 cases of corneal melting in patients treated with topical NSAIDs, with special attention to the observed toxicity and its relationship to dose and duration of treatment, coexistent disease and therapies, and the indication for treatment. The goal of this study is to identify factors useful in minimizing the occurrence of corneal toxicity.

*Methods:* The medical records and/or histories of 11 patients with corneal melting associated with the use of topical NSAIDs are reviewed, with special attention to the indication for treatment, the dose and duration of treatment, and coexistent diseases and medical treatments. In addition, the relationship between NSAID treatment and surgery and between NSAID treatment and onset and extent of corneal toxicity are described.

*Results:* Each of the 11 patients appeared to suffer severe corneal toxicity following the topical use of 0.5% diclofenac ophthalmic solution. Generic diclofenac (Falcon) (Alcon Laboratories, Inc, Fort Worth, Texas) was associated with 7 and Voltaren (Ciba Vision, Atlanta, Georgia) with 4 of these cases. Duration of treatment prior to corneal melting varied from 6 days to 17 months. Associated ocular and systemic diseases and their respective treatments complicate the analysis of these cases. In addition, the indication for treatment with topical NSAIDs was frequently unclear.

*Conclusions:* The inconsistent and variable dose-toxicity relationships suggest that coexistent factors other than a simple drug toxicity are implicated, if not causative, in NSAID-associated corneal melting. These cases demonstrate the importance of making a clinical diagnosis before treatment and of following the clinical course of patients carefully during treatment.

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## INTRODUCTION

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Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to prevent miosis during cataract surgery, to treat ocular allergies, to prevent excessive postoperative inflammation, and to treat cystoid macular edema following cataract surgery. These agents have also been used to control pain and photophobia following radial keratotomy and excimer laser photorefractive keratectomy.<sup>1,2</sup> During August of 1999, severe complications following topical NSAID use, including corneal melting,

were reported by members of the American Society of Cataract and Refractive Surgery (ASCRS) responding to a survey distributed in letters from ASCRS to its members.<sup>3,4</sup> This led to a recall of Falcon, a generic form of diclofenac ophthalmic solution (Alcon Laboratories, Inc, Fort Worth, Texas).<sup>5</sup> Some have concluded that the availability of generic diclofenac was the sole reason that corneal toxicity was observed.<sup>6</sup> However, the potential importance of completing a careful review of all of these reported cases before concluding that an isolated drug toxicity explains the appearance of these severe corneal toxicities has been recently emphasized.<sup>7</sup> The purpose of this report is not to substitute itself for a complete analysis of the cases of corneal melting, but only to provide an interim review of 11 cases of corneal melting in patients treated with topical NSAIDs, with special attention to the observed corneal toxicity and its relationship to dose and duration of treatment, coexistent diseases and therapies,

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and indication for treatment. The goal of this report is to help identify factors potentially useful in minimizing the occurrence of corneal toxicity while we await a more thorough examination of the factors associated with these toxicities.

**METHODS**

The medical records and histories of 11 patients with corneal melting associated with the use of topical NSAIDs were reviewed, with special attention to the indication for treatment, the dose and duration of treatment, and coexistent diseases and medical therapies. These 11 cases consist of 5 published cases,<sup>8</sup> 3 cases reported as a poster presentation,<sup>9</sup> and 3 cases from the author's referral practice. Seven cases mentioned at the 104th Annual Meeting of the American Academy of Ophthalmology (AAO) are also included.<sup>6</sup>

**RESULTS**

Each of the 11 patients presented with severe corneal toxicity and a history of treatment with 0.5% diclofenac ophthalmic solution. Generic diclofenac (Falcon) was associated with 7 and Voltaren (Ciba Vision Corporation, Atlanta, Georgia) was associated with 4 of these cases. A summary of the 11 cases is provided in Table I. A brief description of each case follows:

**CASE 1**

A 76-year-old woman with a history of dry eye (Schirmer test results, 2 mm and 5 mm) developed a red, painful eye

3 months following cataract surgery. She was treated with Falcon for 10 days, and after a corneal infiltrate with 80% tissue loss was observed, she eventually perforated. Culture revealed group *B streptococcus*.

**CASE 2**

A 66-year-old woman with a history of dry eyes was treated with Voltaren and apraclonidine hydrochloride (Iopidine) (Alcon Laboratories, Inc) following cataract surgery. After 4 days of treatment, she complained of a foreign body sensation in the eye. The eye was red and photophobic, and she stated that the Voltaren burned more upon instillation. She was told to refrigerate the Voltaren to reduce the burning sensation and to continue treatment. She presented 29 days after surgery with 50% tissue loss. She had reduced values on the Schirmer test.

**CASE 3**

A 77-year-old man was treated with Voltaren and tobramycin-dexamethasone drops (TobraDex) (Alcon Laboratories, Inc) following cataract surgery. Although he had normal examination results 1 week after surgery, he presented with corneal perforation in the area of surgery 18 days after surgery. He had reduced values on Schirmer tests (12 mm and 8 mm) and diminished corneal sensation.

**CASE 4**

A 71-year-old diabetic man with systemic hypertension was treated with Falcon and 1% prednisolone given 6 times daily following cataract surgery. He experienced discomfort and hyperemia on postoperative day 7, and he noted decreased vision on postoperative day 9. Perforation occurred on postoperative day 11.

TABLE I. SUMMARY OF CASES

CASE(AGE/SEX)	TREATMENT DURATION	CORNEAL PERFORATION	NSAID (REGIMEN)	OTHER MEDICATIONS	INDICATION FOR TREATMENT (CULTURED ORGANISM)
1. 76 F	10 days	Yes	Falcon (QID)	Tears	Unknown (streptococci)
2. 66 F	29 days	No (keratitis)	Voltaren (QID)	Glaucoma medications, tears	Unknown (NP)
3. 77 M	18 days	Yes	Voltaren (QID)	Dexamethasone, tobramycin, tears	Postsurgery Inflammation (NP)
4. 71 M	11 days	Yes	(Falcon) (QID)	Prednisolone	Unknown (no growth)
5. 79 M	17 days	Yes	Falcon (QID)	Glaucoma medications, prednisolone	Unknown (NP)
6. 27 M	5 days (6 hr)	Yes	Falcon (QID)	Rimexolone, Ciloxan	Unknown (NP)
7. 47 F	4 days	No (descemetocele)	Falcon (QID)	Corticosteroid	Unknown (NP)
8. 80 M	10 mo	No (descemetocele)	Voltaren (QID)	None	Unknown (NP)
	7 mo	No (descemetocele)	Falcon (QID)	None	Unknown (NP)
9. 65 F	5 mo	No (keratitis)	Voltaren (QID)	Flarex, Alcaine	Corneal abrasion? (NP)
10. 71 F	5 days	No (keratitis)	Voltaren (TID)	Econopred, Ciloxan	Dellen? (NP)
11. 77 F	14 days	Yes	Falcon (6/day)	Polymixin B sulfate, neomycin, dexamethasone	Unknown (NP)

NSAID, nonsteroidal anti-inflammatory drug; NP, not performed.

**CASE 5**

A 79-year-old man underwent argon laser trabeculoplasty and was treated with 1% prednisolone with good results. His eye became painful and developed an anterior chamber reaction 3 weeks following surgery. Falcon was added to a regimen of brimonidine tartrate ophthalmic solution (Alphagan) (Allergan, Inc, Irvine, California), dorzolamide (Trusopt) (Merck & Co, West Point, Pennsylvania), timolol maleate (Timoptic) (Merck & Co), and latanoprost (Xalatan) (Pharmacia Corp, Kalamazoo, Michigan). Increased pain, photophobia, and hyperemia developed over 2 weeks, and he presented with 99% tissue loss and a descemetocele 17 days after initiation of treatment with Falcon.

**CASE 6**

A 27-year-old man presented 5 days following excimer laser surgery complaining of pain. No corneal thinning was observed on examination. He was using rimexolone (Vexol) (Alcon Laboratories, Inc), ciprofloxacin (Ciloxan) (Alcon Laboratories, Inc), and Falcon ophthalmic medications. Falcon was discontinued, but he continued to use rimexolone and ciprofloxacin. He returned in 6 hours with a corneal perforation.

**CASE 7**

A 47-year-old woman with a history of radial keratotomy 20 years previously returned for excimer laser surgery. She received postoperative treatment with Falcon, fluorometholone acetate (Flarex) (Alcon Laboratories, Inc), and ciprofloxacin. She returned on postoperative day 4 complaining of pain. Her medical regimen was discontinued, and cephazolin and tobramycin eye drops were prescribed. The cornea continued to melt, and a topical corticosteroid was added to the regimen. She required a penetrating keratoplasty 5 months later.

**CASE 8**

An 80-year-old man developed cystoid macular edema 5 months after cataract surgery. He was treated with Voltaren for 10 months without toxic effects. Falcon was substituted, and after 7 months he presented with pain. Corneal thinning was observed, and a descemetocele was noted after 48 hours.

**CASE 9**

A 65-year-old woman with trichiasis and a history of cataract surgery 3 years previously underwent a YAG capsulotomy during which she suffered a corneal abrasion. After treatment with Voltaren without patching, she developed a recurrent corneal erosion. She was treated with intermittent patching, Voltaren, proparacaine hydrochloride (Alcaine) (Alcon Laboratories, Inc),

fluorometholone, and a bandage contact lens for 2 weeks. Voltaren was discontinued, after which she developed bullous keratopathy. Despite intermittent debridement, epilation, and treatment with Voltaren and Flarex, her cornea continued to exhibit a superficial punctate keratitis. She eventually underwent a penetrating keratoplasty with good results.

**CASE 10**

A 71-year-old woman was treated with Voltaren, prednisolone acetate (Econopred) (Alcon Laboratories, Inc), and ciprofloxacin following cataract surgery. She presented on postoperative day 5 with ocular pain, and a dellen was observed during examination. Voltaren was discontinued, and goniosol hydroxypropyl methylcellulose (Ciba Vision) was added to the Econopred treatment. Following a poor response to patching, she underwent conjunctival grafting with good results.

**CASE 11**

A 77-year-old woman with an eye that had been irritated for many months following a complicated cataract surgery presented with increased pain and redness in that eye and an associated "injection of the upper tarsus" of unknown origin. She was treated with Voltaren every 4 hours. She returned in 2 weeks using Falcon and a steroid-antibiotic eye drop. She eventually suffered corneal melt with central perforation.

**OTHER CASES**

In addition to these 11 cases, corneal melting in 7 "healthy, asymptomatic eyes" following refractive or cataract surgery in patients treated with Falcon were reported at the 104th Annual Meeting of the AAO.<sup>6</sup> Although detailed clinical descriptions were not provided for these cases, at least 2 of the patients were said to have a history of punctal plug insertion, which suggested clinically significant dry eyes. In addition, it was noted that all 7 cases had occurred in one practice, while the nation's "top 15 prescribers of Voltaren" have yet to report a severe case of corneal toxicity with use of topical NSAIDs. The speaker concluded that use of Falcon was the cause of all of the cases of corneal melting observed.

**DISCUSSION**

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Corneal complications related to topical NSAID use are uncommon. Superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported following the use of these anti-inflammatory agents.<sup>10-13</sup> These findings are not surprising, because most topically applied medications, particularly those with preservatives, are associated with potential corneal toxicity.<sup>14,15</sup> However, the

reports of corneal melting associated with topical NSAID treatment are surprising and of great interest. Because both infectious and noninfectious corneal melting disorders have many different causes, careful examination of patients is important before a drug toxicity is identified as the cause in all of these cases.<sup>16</sup>

Generic diclofenac (Falcon) may be the sole reason that corneal melting occurred in 2000. Unfortunately, this conclusion is supported only by anecdotal presentations that include a minimum of data with limited analysis and little or no discussion or consideration of complicating factors and alternative explanations.<sup>6</sup> The 7 cases of corneal melts in Falcon-treated patients that were presented at the AAO annual meeting<sup>6</sup> are difficult to discuss because the associated environmental factors and clinical descriptions were not provided. Furthermore, it appears that potentially important coexistent ocular disease was largely ignored during the review of these cases. For example, 2 patients requiring punctal plugs were included as “healthy, asymptomatic patients,” ignoring the fact that patients with Sjögren’s syndrome can develop sterile corneal ulcerations and perforations without any medical treatment or surgical procedure.<sup>17</sup> In addition, patients with mild and clinically insignificant keratitis sicca have developed severe penetrating and perforating ulcers following cataract surgery without any associated medical treatments.<sup>18</sup> Finally, it is impressive that there appears to be an unbalanced geographic distribution of these cases of corneal melting. An asymmetric distribution of an observed drug toxicity can reflect production or manufacturing problems in a specific lot of drug.<sup>19</sup> Therefore, it is of paramount importance to complete a careful review of all of the reported cases of corneal toxicity before concluding that an isolated drug toxicity explains the appearance of these severe corneal toxicities.<sup>7</sup>

This review of 11 cases of corneal toxicity observed in patients using topically applied diclofenac does not provide compelling evidence of an isolated drug toxicity. The potential causes of acute corneal melting suggest that many cases are unrelated to medical treatment, as summarized in Table II.<sup>20</sup> There is little evidence that these potential causes were carefully excluded from these 11 cases. A clinical diagnosis and therefore an indication for anti-inflammatory treatment were lacking in 8 of 11 cases. It is particularly impressive how seldom an infectious cause was ruled out despite the presence of an uncomfortable red eye of uncertain origin (9 of 11 patients). Three patients (cases 1, 2, and 3) had dry eyes. A deficient tear film has been associated with corneal melting<sup>11,17,18</sup> In addition, abnormal tear production may contribute to enhanced corneal toxicity from topical therapy, particularly if preservatives are present. Therefore, coexistent diseases may have contributed to any or all of the observed

corneal melting in this small series of 11 cases.

Coexistent local and systemic medical treatments complicate the analysis of these cases of corneal toxicity. For more than 2 decades, corticosteroids have been recognized as a cause of corneal toxicity. In fact, 25 cases of corneal perforation reminiscent of these cases of corneal melting have been reported by a single observer.<sup>21</sup> Therefore, the use of corticosteroids by 8 of 11 of these patients may be important. In further support of this possibility, it is of note that in case 7, a descemetocoele formed despite discontinuation of Falcon and during use of only a corticosteroid. In addition, patient 5, who eventually perforated, was using not only a corticosteroid but also multiple medications, some of which predispose to dry eye (hydrochlorothiazide and timolol) and others that have significant potential for inducing corneal toxicity (dorzolamide, timolol, brimonidine, and latanoprost).

A touchstone for the determination of pharmacologic toxic disease has been proposed.<sup>22</sup> I advocate use of the following Koch-type postulates for a toxic etiology:

- The clinical signs of toxicity must be reproducible in experimental animals.
- The toxic dose-response may show normal scatter of random distribution, but no patient must get toxic effects from doses differing by several orders of magnitude.
- Cessation of dosage should be followed by a decrease in toxicity.

The corneal toxicity reported in these 11 cases does not fulfill these criteria.

Corneal melting has not been reproduced in experimental animals with use of topically applied, commercially available, brand-name NSAIDs. To the contrary, well-designed laboratory studies suggest that these topically administered NSAIDs may be beneficial in protecting animals from corneal melting.<sup>20</sup> In addition, carefully

TABLE II: POTENTIAL CAUSES OF ACUTE CORNEAL MELTING

Herpes simplex keratitis
Mooren’s ulcer
Rheumatoid arthritis
Bacterial keratitis
Keratoconjunctivitis sicca
Erythema multiforme
Alkali burn
Anterior-segment dysgenesis
Herpes zoster
Neuroparalytic keratitis
Wound melt/keratoplasty
Pemphigoid
Rosacea keratitis
Thermal burn
Vernal keratoconjunctivitis

Information from Kenyon.<sup>20</sup>

controlled, prospective, double-masked, randomized clinical studies in hundreds of patients indicate that topically applied brand-name NSAIDs appear safe for use in patients.<sup>1,2</sup> Therefore, it is unlikely that there is something distinctive about the diclofenac molecule that predisposes to severe corneal toxicity. It remains to be seen how carefully the generic NSAID Falcon has been tested for the potential of inducing a corneal melt in experimental animals.

An incredibly inconsistent dose-toxicity relationship exists within the group of 11 cases described here. In case 8, for example, the patient was treated with Voltaren for 10 months and Falcon for 7 months for cystoid macular edema following cataract surgery without apparent toxicity. Then, for unexplained reasons, the patient developed corneal thinning with descemetocoele formation over 48 hours while using Falcon. This history of prolonged exposure without corneal toxicity followed by an acute corneal melt is not typical of an isolated drug toxicity.

Patient 9 was referred to the author as a possible case of NSAID-induced corneal melt. This case clearly demonstrates how resistant a cornea can be to the potential corneal toxicity of Voltaren. The patient was treated for various indications, including corneal abrasion, recurrent corneal erosion, and bullous keratopathy with Voltaren therapy. Despite concurrent treatment with Flarex and Alcaine, with and without patching, bandage contact lens application, and intermittent debridement, no significant thinning of the cornea was noted during 5 months of treatment. This is remarkable. The coexistent corneal treatments could have in and of themselves caused considerable corneal damage, but little was observed.

Finally, in case 6, the patient had a normal corneal examination 5 days after excimer surgery only to have perforation 6 hours later while using Falcon. It is difficult to find any drug or chemical toxicity reported within the literature with such a rapid course. Therefore, a comparison of cases 6, 8, and 9 makes clear an unusual inconsistency of observed corneal toxicity with topically administered diclofenac. This is unlike an isolated drug toxicity.

Case 10 demonstrates the importance of careful post-operative examinations. This patient was referred to the author because she was unhappy despite a good visual outcome. She believed that she had suffered an "eye melting" due to Voltaren use. Five days following cataract surgery, she had a painful eye and was treated with Voltaren and Econopred. She was carefully examined, and a dellen was recognized and appropriately treated. Fortunately, the patient was not simply treated aggressively for a resistant postoperative inflammatory response without benefit of an examination. It is likely that the careful follow-up care that she received helped her to avoid severe corneal damage related to an improperly treated dellen. It is ironic that the patient ignored the extensive diagnostic and

therapeutic efforts of her surgeon and the resultant excellent visual outcome, but instead gravitated toward a potential toxicologic explanation that was at the time popularized in the tabloids and debated on the Internet.

Overall, this review of 11 cases of corneal toxicity observed in patients using topically applied diclofenac reveals an inconsistent and variable dose-toxicity relationship. Furthermore, all of the cases are complicated by coexistent diseases and medical therapies. This makes it difficult to establish a definitive diagnosis for the observed corneal melting. These cases underscore the importance of making a clinical diagnosis before initiating nonspecific anti-inflammatory treatment and the need for careful follow-up of patients after surgical procedures.

While we await a definitive analysis of all the reported cases of corneal melting associated with topical NSAID use, it seems prudent to keep in mind an admonishment from Sir William Osler concerning the potential toxicity of medications, quoted by Dr Fred Wilson II in his American Ophthalmological Society thesis:<sup>23</sup>

In the fight which we have to wage incessantly against ignorance and quackery among the masses and follies of all sorts among the classes, diagnosis, not drugging, is our chief weapon of offence. Lack of systematic personal training in the methods of the recognition of disease leads to the misapplication of remedies, to long courses of treatment when treatment is useless, and so directly to that lack of confidence in our methods which is apt to place us in the eyes of the public on a level with empirics and quacks.

## CONCLUSIONS

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The inconsistent and variable dose-toxicity relationships reflected in these 11 cases of corneal melting in patients using topical diclofenac suggest that coexistent factors other than a simple drug toxicity are implicated, if not causative, in these toxicities. Concurrent ocular and systemic disease in many of these patients, as well as their use of medications including corticosteroids, complicates this analysis. The occurrence of corneal melting can be minimized by attempting to make a definitive diagnosis before initiating anti-inflammatory treatment and by careful follow-up examinations of patients after surgery.

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## DISCUSSION

DR MICHAEL A. LEMP. Dr Flach has called our attention, by way of a retrospective series of 11 patients, to the contemporary vexing problem of keratolysis associated with the use of non-steroidal anti-inflammatory topical medications. He points out the compounding variables in these cases and suggests that co-existing factors rather than a simple drug toxicity are implicated.

Indeed, the conditions associated with these, and other previously recorded cases include cataract surgery, dry eye in a significant number of these patients,

autoimmune disease and co-existent bacterial ulcers in some of these patients. Both the brand (Voltaren) diclofenac and the generic brand have been implicated, about 60% of the cases having been treated with the generic brand.<sup>1</sup>

Corneal melting or keratolysis in the absence of treatment with NSAIDs, occurs in the association with autoimmune disease, keratoconjunctivitis sicca, diabetes and steroid use (which occurred in a number of these patients). Recently analysis of tissue removed from a patient suffering a corneal melt associated with NSAID use suggests that this keratolysis was mediated by matrix metalloproteinases (MMPs). MMP is a family of degradative enzymes. They degrade collagen I, II, III, V, VII, in addition to basement membrane, laminin, and proteoglycans. In a case report by O'Brien et al, MMP8 was identified.<sup>2</sup> The source of this is thought to be neutrophils and epithelium; this enzyme degrades collagens I, II and III. In addition, MMP2 and MMP9 have been identified after refractive surgery and in patients with keratoconjunctivitis sicca.<sup>3</sup>

It seems likely that possible triggers of MMPs include: keratoconjunctivitis sicca, ocular surface disease, bacterial infections, NSAIDs, preservatives in topical medications, and surgery. In a predisposed ocular surface, the use of NSAIDs may substantially increase the risk of a clinically significant episode of keratolysis.

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[Editor's note] DR OLIVER SHINE discussed the paper he co-authored that analyzed 140 patients with corneal toxicity associated with the use of NSAID's, and the problem of multiple events and underlying diseases which could affect the cornea in these patients. DR TAYLOR ASBURY mentioned that Dr Philips Thygeson was one of the first physicians to describe corneal melting associated with the use of topical medicines (corticosteroids).

DR ALLAN J. FLACH. First I want to thank Dr Michael Lemp for agreeing to discuss my paper and also Drs Tuck Asbury and Oliver Shine for their interest and comments. Dr Asbury reminds us that it was Dr Philips Thygeson who first emphasized the dangers of corneal melts associated with corticosteroids and that he was elected to the

AOS in 1936. I would like to add that Dr Thygeson, while not physically as active as he would like to be, is still intellectually active at 97 years of age. Although he must lift himself from his bed with block and tackle, he continues to have many interests including the history of American Indians of the southwestern United States. In fact, I recently sent him an article concerning Geronimo as reflected in the writings of Edgar Rice Burroughs.

One of my greatest fears is to prepare to present a paper and submit a copy of the manuscript, only to have a similar paper appear in print just prior to my presentation. Today my greatest fear has been fully realized. Not only 1 but 3 papers have been recently published on corneal melts associated with topical NSAIDs.<sup>1,2,3</sup> Dr Lemp has mentioned one of them and Dr Shine is a co-author on another.<sup>1,2</sup> Fortunately, my paper is reasonably consistent with all 3 of them in terms of its observations and conclusions. Dr Lemp has summarized the results of O'Brien et al's case study of 1 case in which the matrix metalloproteinases (MMPs) may have been implicated in the observed corneal melting reported in a patient using topical NSAIDs.<sup>1</sup> This report compliments a poster presentation provided by Apte et al at the 104th Annual Meeting of the American Academy of Ophthalmology on this same subject as is mentioned within the text of my presentation.<sup>4</sup> While both paper and poster share the common suggestion that the observed corneal melts are consistent with enhanced MMP activity, both presentations agree that clear evidence for a definitive etiologic relationship between NSAIDs and corneal melts is lacking and more study is indicated to clarify the role of MMPs and possibility of NSAID associated corneal melts.

Dr Shine has mentioned an analysis of 140 patients demonstrating corneal toxicity associated with the use of topically applied nonsteroidal anti-inflammatory agents (NSAIDs) that he has recently co-authored.<sup>2</sup> He has appropriately underscored the difficult issues complicating the review of these cases including the presence of multiple compounding events, multiple chronic diseases and questions about the actual identity of the NSAID in question. However, even within these limitations some distinct patterns found within the analysis speak to causality in association with the generic diclofenac, which is no longer on the market, and severe keratitis. Corneal toxicity may have been occasionally associated with brand name diclofenac (Voltaren, Novartis) or ketorolac (Acular, Allergan), when used for long periods of time in patients with underlying pre-existing eye disease but it is not possible to know for certain these were actually the drugs dispensed by the pharmacist.

Since its publication I have had the opportunity to review this study and, unfortunately, its design has several significant shortcomings.<sup>2</sup> The analysis does not include

the geographical distribution and specific origin of the 34 cases of severe corneal toxicity. As mentioned in my presentation this afternoon, we know at least 7 of these cases of severe corneal melting are reported from a single surgeon's practice.<sup>5</sup> In addition, less than 2% of the entire membership (over 5000 ophthalmologists) of the American Society of Cataract and Refractive Surgery reported corneal problems with NSAIDs.<sup>2</sup> This unequal distribution of cases of corneal melts may reflect a difference between individual batches or lots of a given drug or other important localized differences in technique or practice. This deserves further study to help understand the origin and pathogenesis of the observed corneal melts.

It does not seem appropriate to analyze cases of uncomplicated keratitis and corneal melts with equal attention and emphasis as was done in this study because keratitis is such a common finding during any eyedrop treatment as mentioned within my paper. Of greatest importance and interest are the 34 cases of severe corneal toxicity. Therefore, the report of this study would benefit greatly from a more careful description and discussion of each of the 34 severe cases of corneal toxicity with special attention to the working diagnosis and indication for treatment with a topical NSAID in each case, to the presence of coexistent ocular and systemic disease and coexistent medical treatments, in particular the use of corticosteroids. This data is largely omitted from the publication of this study.<sup>2</sup>

The study has unexpected outcomes that must be explained or at least discussed. More specifically, the study fails to find an association of corneal melts, or even keratitis, with dry eye. This is not consistent with past experience and our existing literature both of which clearly identify dry eyes, even asymptomatic dry eyes, as predisposed to corneal melts with or without coexistent surgery or medical therapy.<sup>6,7</sup> It is also of concern that this study states within its discussion that postoperative sterile corneal ulcers are most often associated with Mooren's ulcer or collagen vascular disease with no mention of the potential association with dry eyes with this complication. The report concludes that there was no association of increased toxicity with off-label use of NSAIDs. This conclusion seems inconsistent with the study's finding that the more severe cases of corneal toxicity were more likely to have other than cataract surgery and that nonsurgical cases tended to have much greater doses of NSAIDs than surgical cases. Both these statements suggest off-label use. These inconsistencies deserve discussion.

Although it is clear that the authors of this report of 140 patients devoted a great deal of time and effort to the study the final publication provides less information and discussion of this important issue than it deserves.

The third paper recently published reports 16 cases

of keratitis, ulceration and perforation associated with topical NSAIDs.<sup>3</sup> Some of these cases may be the same cases included in previously discussed studies. However, all of the 16 cases had extenuating circumstances including dry eye, coexistent steroid treatment, rosacea and often an unclear indication for the treatment with an anti-inflammatory agent. Therefore, the observations and results from this study are consistent with the presentation and conclusions that I have provided this afternoon.

Unfortunately, at present, no controlled study exists that permits us to make any conclusions about the risks associated with topical NSAID use and severe corneal toxicity. Although it seems clear that there is a small but definite incidence of corneal melting following cataract surgery associated with dry eye and other predisposing diseases, the question remains whether any specific drug treatment or changes in our current surgical techniques or regimens increase the likelihood of these corneal melts following contemporary anterior segment surgery.

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# COMPARISON OF CONTRAST SENSITIVITY, VISUAL ACUITY, AND HUMPHREY VISUAL FIELD TESTING IN PATIENTS WITH GLAUCOMA\*

BY *Jacob T. Wilensky, MD*, AND (BY INVITATION) *Anjali Hawkins, MD, PhD*

## ABSTRACT

*Purpose:* To investigate the relationship between large-letter contrast sensitivity, high-contrast visual acuity, and visual field defects in patients with glaucoma.

*Methods:* Patients with a diagnosis of glaucoma, glaucoma suspect, or ocular hypertension whose visual acuity was 20/40 (logMAR = 0.3) or better were included in the study. Visual acuity was measured using the Lighthouse visual acuity charts. Contrast sensitivity was measured using the Pelli-Robson (PR) chart. The mean depression (MD) score from the most recent Humphrey visual field was used to quantify the visual field defect.

*Results:* A total of 120 eyes were studied. The PR contrast sensitivity score correlated more strongly with the MD of the visual field ( $r = .589, P < .001$ ) than did the logMAR visual acuity ( $r = .193, P = .035$ ). When just the eyes with open-angle glaucoma were considered ( $N=54$ ), the correlation was even greater for the PR score ( $r = .638$ ). In ocular hypertensive eyes ( $N=25$ ), the correlations to PR and logMAR were not that different ( $r = .394$  for PR,  $r = .303$  for logMAR). Pseudophakic eyes did not show as strong a correlation ( $r = .335$ ) as did phakic eyes ( $r = .591$ ).

*Conclusion:* For glaucomatous eyes with visual acuity of 20/40 or better, a decrease in the contrast sensitivity correlates with increased visual field loss. We speculate that this decrease in contrast sensitivity in glaucoma patients may account for their complaints of poor vision despite normal or near normal visual acuity.

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## INTRODUCTION

It has been well demonstrated that contrast sensitivity in visual function is affected in glaucoma.<sup>1-3</sup> Numerous reports have indicated that contrast sensitivity does seem to be selectively affected by the glaucoma process to a greater extent than is Snellen (high contrast) visual acuity. However, most of these studies have concentrated on investigations as to whether it would be possible to detect glaucoma in patients with various contrast sensitivity tests prior to visual field damage.<sup>4</sup> We have been impressed that some of the functional complaints of some of our glaucoma patients might represent manifestations of their loss of contrast sensitivity, and we wanted to try to quantify this loss related to their glaucoma damage. To this end, we began a preliminary study in which we obtained contrast sensitivity measurements by use of the Pelli-Robson chart<sup>5</sup> and related these findings to visual field performance on the Humphrey visual field analyzer.

## METHODS

Patients with the diagnosis of glaucoma, suspected glau-

coma, or ocular hypertension were studied. Patients were diagnosed as having glaucoma if they had characteristic visual field loss and optic nerve head changes; as suspected of having glaucoma if they had suspicious optic nerve head changes, but not characteristic visual field loss; and as having ocular hypertension if they had intraocular pressure (IOP) greater than 21 mm Hg but no definite visual field loss or optic nerve head changes. Only patients whose best corrected Snellen visual acuity on a projected office chart was 20/40 or better were included.

Best corrected visual acuity of the patients was remeasured using a back-illuminated Lighthouse visual acuity chart at 4 m (Fig 1). Acuity measured was reported using the logMAR scale. The contrast sensitivity was measured using the Pelli-Robson chart in a front-illuminated box so that the illumination of the chart was standardized. The Pelli-Robson chart consists of opto types 20/60 in size, whose size remained constant throughout but whose contrast decreased both across and down the chart (Fig 2). The visual fields of the patients were plotted using the 24-2 program on the Humphrey visual field analyzer.

Regression analysis programs were used to compare the logMAR visual acuity scores with the Pelli-Robson scores, and each of these scores with the mean deviation score from the Humphrey visual fields. These analyses were performed for all patients. We arbitrarily decided to analyze left eyes only because of the problems with using

\*From the Department of Ophthalmology, University of Illinois College of Medicine at Chicago. Supported in part by the Carson Gabriel Fund and a departmental grant from Research to Prevent Blindness, Inc, New York, New York.

both eyes of the same patient. Multivariate analysis was also performed with consideration of factors such as age, race, and lens status. In addition, the results of the visual acuity and the contrast sensitivity tests were compared with those of a group of age-matched normal patients who had had these tests performed on the same equipment as part of a separate study. However, visual field tests were not performed for these patients.

## RESULTS

A total of 120 patients were analyzed: 54 had open-angle glaucoma, 14 had suspected glaucoma, and 25 had ocular hypertension; the remainder had other forms of glaucoma. The mean age was  $61.72 \pm 12.67$  years. The male-female ratio was almost equal. Sixty-seven patients were white, 41 were black, and 12 were Asian or Hispanic. There was a significant correlation between the mean deviation on the Humphrey perimeter and the contrast sensitivity score on the Pelli-Robson charts (Fig 3). For the left eyes of all the patients in the study, this correlation was 0.589 with a  $P$  value of less than .001. In contrast, the correlation between the mean deviation on the Humphrey visual field and the logMAR visual acuity was 0.193 (Fig 4). In patients with chronic open-angle glaucoma, the correlation between the visual field deviation and the Pelli-Robson score was 0.638 with a  $P$  value of less than .001 (Fig 5). For the logMAR visual acuity, the correlation was 0.266 and  $P$  value was 0.054 (Fig 6). In contrast, the correlation of ocular hypertensive patients was 0.394 for the Pelli-Robson score (Fig 7) and 0.303 for the logMAR visual acuity (Fig 8). Correlations were calculated for phakic and aphakic eyes. In phakic eyes, the correlation was 0.591 ( $n=105$ ) (Fig 9), while in pseudophakic eyes, it was 0.335 ( $n=15$ ) (Fig 10).

## DISCUSSION

*Contrast* describes the difference in the average luminance between 2 visible areas. *Contrast sensitivity* is the measure of the ability to detect a difference in the luminance between 2 areas. If the 2 areas are adjacent to each other, the ability to detect a difference in luminance is called *spatial contrast sensitivity*. If the areas occur sequentially in time, the ability to detect a difference in luminance is called *temporal contrast sensitivity*.

The effects of glaucoma on both types of contrast sensitivity have been studied with use of a large number of different tests.<sup>14</sup> The Pelli-Robson chart represents a low-tech, reasonably available method of measuring spatial contrast sensitivity that is compatible with clinical practice. It has been shown to yield reliable, reproducible results.<sup>6</sup> Accordingly, we chose to use this fairly quick and inexpensive test to study our glaucoma patients to see what we could learn about the association of contrast sensitivity

measurement and visual field loss. To minimize other variables such as cataracts and possible intercurrent ocular conditions (eg, diabetic retinopathy, age-related maculopathy), we chose to limit our test population to individuals with visual acuity of 20/40 or better as measured in the office. The patients were then retested using the Lighthouse visual acuity charts and the Pelli-Robson charts in a standardized fashion with controlled illumination.

We were uncertain which visual field measurement should be studied. We assumed that diffuse ganglion cell damage should affect contrast sensitivity more than focal damage, so we chose to use the mean deviation as the indication of visual field damage rather than number or location of depressed test spots.

As we expected, there was a correlation between increasing visual field deficit and decreased contrast sensitivity. This was much greater than the correlation between logMAR visual acuity level and field loss. These findings, however, were somewhat limited by the fact that there were relatively few patients with even moderately advanced visual field deficits. As we test more patients with more advanced field defects but still good visual acuity, we feel that this correlation will show up even better.

We find it interesting that the correlation in the ocular hypertensive group was much less strong than in the open-angle glaucoma population. There are several possible explanations. First, the number of patients is relatively small. Second, it may be that some of these ocular hypertensive patients are just that and do not have any glaucoma damage. It would be interesting to try to identify patients who do seem to show a decreased Pelli-Robson score and to observe them prospectively to determine whether they are more likely over time to develop visual field loss than are ocular hypertensive individuals who have normal scores.

One somewhat unexpected finding is the difference between the phakic and pseudophakic individuals. It may be that some haze on the posterior capsule or some optical elements of the intraocular lens itself may negatively affect contrast sensitivity. In one study of the effects of cataracts on Pelli-Robson scores,<sup>7</sup> posterior subcapsular cataracts had the greatest impact. We did not assess the status of the posterior capsule in our pseudophakic patients. If it is the intraocular lens itself that is responsible for this finding, then this will have to be factored in when we study pseudophakic individuals in the future. On the other hand, the number of pseudophakic patients is small. We need to study more pseudophakic eyes to see if this difference persists.

We have been impressed clinically that many patients with more advanced glaucoma frequently complain of hazy or misty vision even though they are able to read 20/30 or 20/40 on the Snellen chart in the office. We

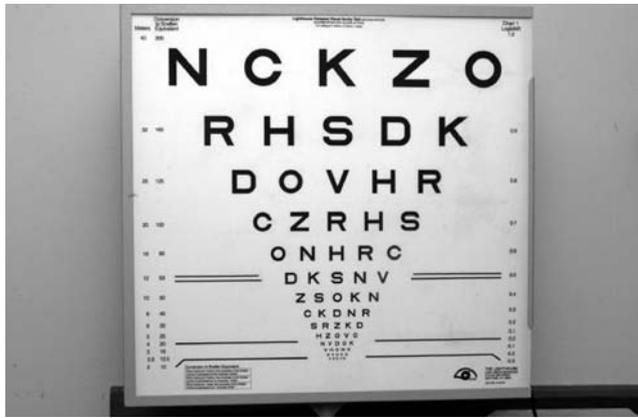


FIGURE 1

Back-illuminated Lighthouse visual acuity chart.



FIGURE 2

Pelli-Robson chart.

Humphrey Mean Deviation vs. Large Letter Contrast Sensitivity  
All Patients - Left Eye

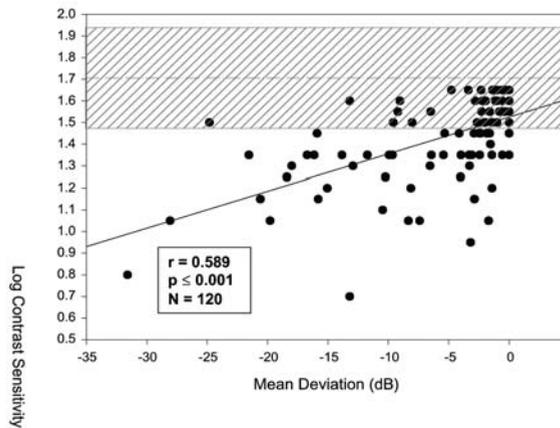


FIGURE 3

Correlation between mean deviation on Humphrey perimeter and contrast sensitivity score on Pelli-Robson chart in all patients.

Humphrey Mean Deviation vs. High Contrast Visual Acuity  
All Patients - Left Eye

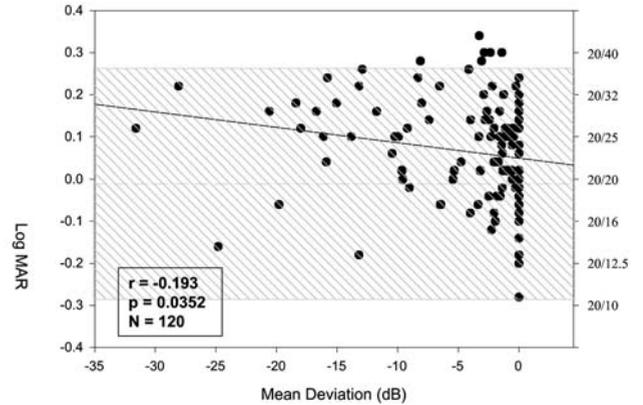


FIGURE 4

Correlation between mean deviation on Humphrey visual field and logMAR visual acuity in all patients.

Humphrey Mean Deviation vs. Large Letter Contrast Sensitivity  
Chronic Open Angle Glaucoma Patients - Left Eye

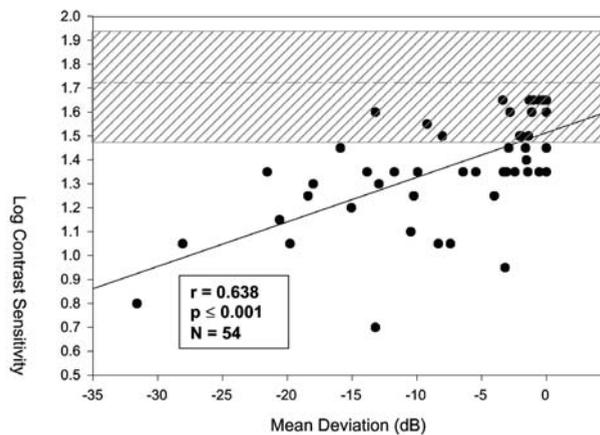


FIGURE 5

Correlation between mean deviation on Humphrey visual field and contrast sensitivity score.

Humphrey Mean Deviation vs. High Contrast Visual Acuity  
Chronic Open Angle Glaucoma Patients - Left Eye

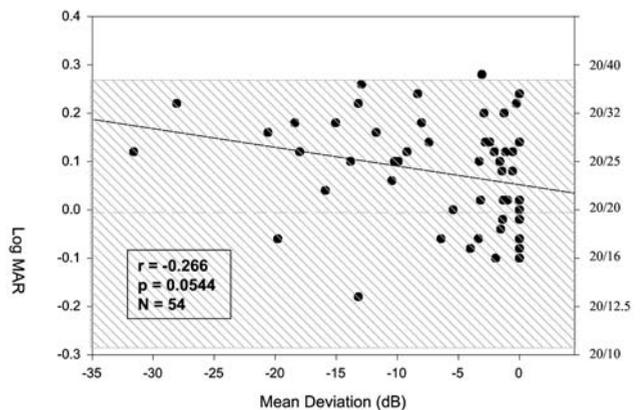
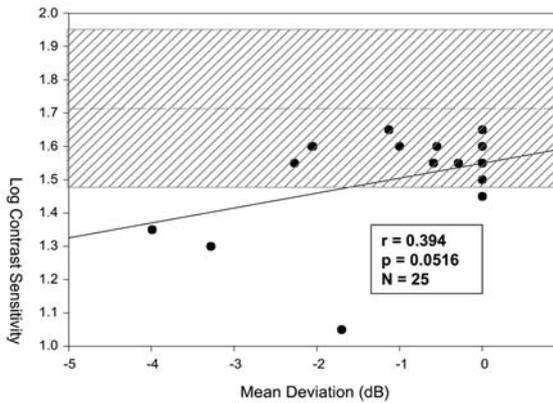


FIGURE 6

Correlation between mean deviation on logMAR visual acuity and on Humphrey visual fields in patients with chronic open-angle glaucoma.

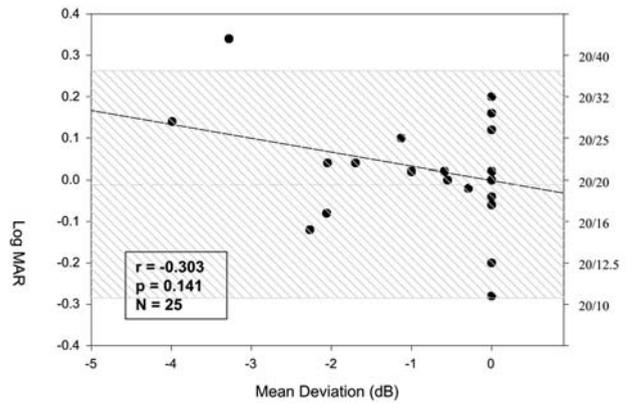
**Humphrey Mean Deviation vs. Large Letter Contrast Sensitivity  
Ocular Hypertension Patients - Left Eye**



**FIGURE 7**

Correlation between mean deviation on Humphrey visual field and contrast sensitivity in patients with ocular hypertension.

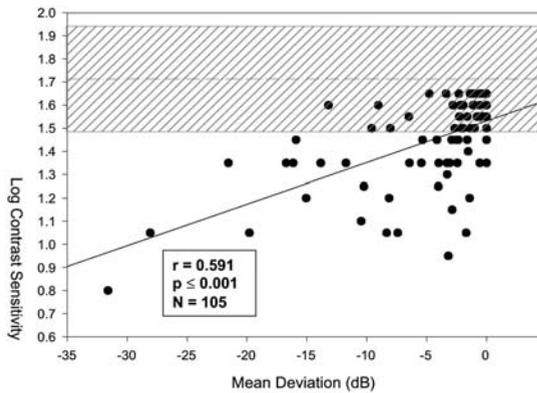
**Humphrey Mean Deviation vs. High Contrast Visual Acuity  
Ocular Hypertension Patients - Left Eye**



**FIGURE 8**

Correlation between mean deviation on Humphrey visual field and contrast sensitivity in patients with ocular hypertension.

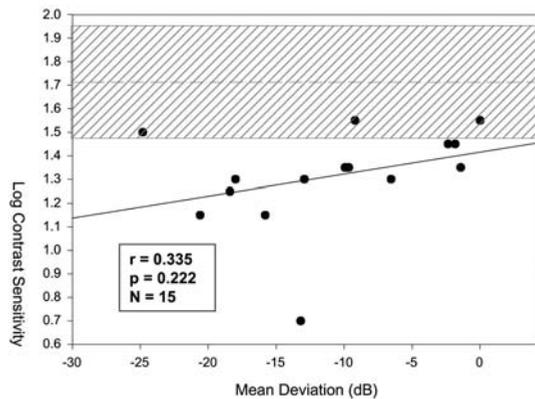
**Humphrey Mean Deviation vs. Large Letter Contrast Sensitivity  
Phakic Patients - Left Eye**



**FIGURE 9**

Correlation between mean deviation on Humphrey visual field and contrast sensitivity in phakic patients.

**Humphrey Mean Deviation vs. Large Letter Contrast Sensitivity  
Pseudophakic Patients - Left Eye**



**FIGURE 10**

Correlation between mean deviation on Humphrey visual field and contrast sensitivity in aphakic patients.

believe that this may be a manifestation of their loss of contrast sensitivity and that the world around them is a gray mist because of this lack of contrast sensitivity. With the type of testing we describe here, we should be able to document and quantify such loss of contrast sensitivity in such patients. Potentially, changes in contrast sensitivity over time might be a more sensitive indicator of progression of glaucoma damage than some of the other tests that we are using now. Obviously, much more extensive testing and prospective studies will be required before we can find out whether this supposition has any validity.

**SUMMARY**

We have demonstrated that in patients with good visual acuity and early glaucomatous visual field damage, there is a positive correlation between decrease in contrast sensi-

tivity as measured by the Pelli-Robson chart and the amount of visual field loss as indicated by the mean deviation. We feel that this correlation may help explain some of the symptoms that our patients exhibit and may serve to develop improved testing to monitor the status of our glaucoma patients prospectively.

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**DISCUSSION**

DR RICHARD P. MILLS. My thanks to the program committee for selecting me to discuss this fine paper. I have chosen to focus on 2 facets of this work: first, the correlation between contrast sensitivity and visual fields, and second, the speculation that contrast sensitivity might be a better predictor of glaucoma patient complaints than our traditional measures.

First of all, if I may be permitted a global summary of the literature on spatial contrast sensitivity and visual fields in glaucoma, it is as follows:

1. contrast sensitivity is moderately well correlated with loss of differential light sensitivity over the entire visual field, especially centrally, and
2. there is good evidence that contrast sensitivity abnormalities often precede glaucomatous visual field loss in early glaucoma, but
3. contrast sensitivity is an insufficiently sensitive predictor of visual field loss either at onset of disease or as it progresses to be used in place of traditional measures.

Table I shows the correlations between spatial contrast sensitivity and mean defect in the visual field found by Dr Wilensky and others<sup>1,2</sup> in mixed groups of glaucoma and ocular hypertensive patients. All Pearson “r” coefficients are in the moderate range, somewhat lower for Mutlukan and Skarf perhaps because some of their patients had neuro-ophthalmic diagnoses and because they were using a contrast sensitivity test of their own design. Note the higher correlations for the central visual field points; perhaps Dr Wilensky could comment about central field data in his patients.

This paper finds modest correlation of contrast sensitivity and mean defect at  $r = 0.4$  in the ocular hypertensive subset of patients, possibly because some of them had early glaucoma without definite glaucomatous field loss, similar to what others have found. The fact that pseudophakes had weaker correlations than phakic patients comes as no great surprise, and could relate to posterior capsular haze or IOL type.<sup>3</sup>

Enthusiastic as we may become about contrast sensitivity measurement, there is insufficient sensitivity to warrant displacing our tried and true clinical measures. Wood and Lovie-Kitchin<sup>4</sup> found a low sensitivity at acceptable specificity levels for all contrast sensitivity tests they studied, including Pelli-Robson, in detection of glaucoma. Mizokami and Asai<sup>5</sup> showed that contrast sensitivity testing at 2.5 and 3.5 cycles/degree, where the Pelli-Robson test operates, does not discriminate well between stages of visual field loss from early to late.

Can contrast sensitivity better predict the troubles about which our patients complain than our current clinical measures? Pelli-Robson scores and visual field extent were better predictors of mobility performance in patients with macular degeneration<sup>6</sup> and retinitis pigmentosa<sup>7</sup> than visual acuity, motion sensitivity, scanning ability, and figure-ground discrimination in dim light. From a group of tests used by Ross et al, perceived visual disability among glaucoma patients was best predicted by near visual acuity, visual field mean defect, and contrast sensitivity measures.<sup>8</sup> We are fortunate that Pelli-Robson testing has been added to the testing in the Collaborative Initial Glaucoma Treatment Study (CIGTS), with its robust quality of life measurement and large sample size, so we should be able to answer the question of the use of contrast sensitivity tests in predicting patient-perceived disability within the next several years.

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TABLE I: CORRELATIONS BETWEEN CONTRAST SENSITIVITY AND GLOBAL VISUAL FIELD SENSITIVITY (GLAUCOMA AND OCULAR HYPERTENSIVE PATIENTS)

	WILENSKY AND HAWKINS N = 120	ZULAUF AND FLAMMER <sup>1</sup> N = 60	MUTLUKAN AND SKARF <sup>2</sup> N = 143
	HUMPHREY MD V. PELLI-ROBSON (3CY/DEG)	OCTOPUS MS V. HAAG STREIT VISOMETER	HUMPHREY MD V. CUSTOM CS TEST (5 CY/DEG)
Total VF	0.59	0.63	0.42
Central VF	-	0.76	0.53

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# INTRAVITREAL INJECTION OF TISSUE PLASMINOGEN ACTIVATOR FOR CENTRAL RETINAL VEIN OCCLUSION\*

BY Michael J. Elman, MD, Robert Z. Raden, MD (BY INVITATION), AND Anita Carrigan (BY INVITATION)

## ABSTRACT

*Purpose:* This pilot study evaluated the feasibility of intravitreal injections of tissue plasminogen activator (tPA) in eyes with central retinal vein occlusion (CRVO).

*Methods:* Between August 1997 and October 2000, 9 eyes with CRVO were treated with intravitreal injection of tPA, 100  $\mu$ g (50  $\mu$ g/0.1mL), and paracentesis. After the injection, each patient was placed at strict bed rest in the supine position for 6 hours. Each patient was administered one baby aspirin daily. Best corrected visual acuity with Light House charts was obtained at each visit. A change of 3 or more lines of vision from pretreatment levels at 6 months' follow-up or a change in one level (ie, counting fingers to hand motions) was deemed significant.

*Results:* All patients were followed up for at least 6 months. Four of 9 eyes (44%) showed 3 or more lines improvement at 6 months. In this group, the average improvement was 7 lines. Two eyes showed 6 or more lines loss of vision at 6 months. Four eyes showed dramatic improvement in visual acuity within 1 month of injection. There were no adverse effects related to treatment. Three eyes subsequently developed retinal or anterior-segment neovascularization requiring panretinal photocoagulation; all were graded as ischemic CRVO on fluorescein angiography at baseline.

*Conclusion:* Intravitreal tPA can be injected safely and easily. Local injection of tPA should spare the patient the serious systemic risks of intravenous tPA administration, such as stroke. Given the morbidity of CRVO, further investigation with this therapy to establish both efficacy and safety seems warranted.

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## INTRODUCTION

Central retinal vein occlusion (CRVO) is a common retinal vascular problem that frequently can devastate vision.<sup>1-3</sup> Histopathologic studies implicate thrombosis at the central retinal vein at the level of the lamina cribrosa retrolaminar optic nerve as the cause of CRVO.<sup>4-7</sup> Intravascular pressure is thought to increase from resistance to blood flow from the thrombus, leading to breakdown of the blood retinal barrier and extravasation of blood and fluid throughout the retina, with the typical "blood and thunder" appearance of CRVO. Continued extravasation can lead to a self-perpetuating spiral of increased edema and capillary closure. Should sufficient damage to the capillary bed ensue, retinal ischemia may liberate vasoproliferative factors, which stimulate the development of anterior- or posterior-segment neovascularization.

Several investigators have reported on systemic treatment with thrombolytic agents in CRVO.<sup>8-12</sup> Because of systemic risks, this approach has not been widely adopted or definitively studied. To limit the systemic side effects, investigators have used other approaches to deliver the

thrombolytic agent locally, such as intravitreal injection and intravenous retinal cannulization.<sup>13-15</sup> Lahey and associates<sup>14</sup> and Glacet-Bernard and colleagues<sup>15</sup> first reported on the intravitreal injection of tissue plasminogen activator (tPA) for CRVO. This pilot study was designed to evaluate the effects of intravitreal injection of tPA in eyes with acute CRVO.

## PATIENTS AND METHODS

We reviewed the records of all patients treated with intravitreal injections of tPA for CRVO. All patients were treated within 1 month of the onset of symptoms, or within 1 month of a documented worsening of visual acuity and fundus presentation of the CRVO. All patients were treated between August 1997 and October 2000 and were followed for a minimum of 6 months. Patients were examined 1 day, 1 week, and 1 month after tPA administration and then monthly thereafter until 6 months postinjection. Examinations at each visit included ocular and medical history, visual acuity measurement on a Lighthouse (ETDRS) chart, slit-lamp biomicroscopy, tonometry, dilated biomicroscopic fundus examination, fluorescein angiography, and fundus photography. For analysis, the denominators of the visual acuities were converted to their logarithm

\*From the Elman Retina Group, Baltimore, Maryland.

using the logMAR method.<sup>16</sup> Counting fingers vision was deemed to be equivalent to 20/800, hand motions to 20/1600, and light perception to 20/3200. Thus, a change in level of vision from hand motions to counting fingers was deemed to be equivalent to doubling of the visual angle, or equal to 0.3 log units.

Intravitreal tPA was administered in each patient in the minor operating room of an adjacent community hospital. The tPA was prepared by the hospital pharmacy and diluted to a dose of 50 µg in 0.1 mL volume in a sterile tuberculin syringe. The patients were placed in the supine position and the affected eye anesthetized with a retrobulbar injection of 2% lidocaine. Topical ciprofloxin drops were administered before and immediately after the procedure. After the periorbital skin was cleansed with povidone-iodine (Betadine) solution, a sterile drape was placed over the involved eye. With a 30-gauge needle on an open barrel syringe, a paracentesis was performed to remove 0.2 mL of aqueous. With a caliper, a distance 3.5 mm posterior to the limbus was marked on the inferior temporal conjunctiva. At the marked spot, the conjunctiva and sclera were perforated, aiming for the center of the vitreous, with a 30-gauge needle on the tuberculin syringe containing the tPA. A total of 0.2 mL (100 µg) of tPA was injected into the vitreous with the bevel up. As the needle was withdrawn from the eye, a cotton-tipped applicator was placed on the injection site for 1 minute to provide tamponade against subconjunctival bleeding. The injection site and the fundus were inspected for complications using indirect ophthalmoscopy with scleral depression. Thereafter, 5% homatropine drops and ciprofloxin drops were instilled on the cornea and an eye patch was placed. Each patient remained at strict bed rest in the supine position for the next 6 hours in the recovery room to facilitate pooling of the tPA over the posterior pole. Prior to discharge, the patch was removed and the patient examined with a near vision acuity card, tonometry, and indirect ophthalmoscopy. At discharge, each patient was started on a regimen of 1 enteric-coated baby aspirin daily.

## RESULTS

Nine eyes in 9 patients were treated with intravitreal tPA injections. The pertinent data are summarized in Table I. The mean patient age was 65.5 years and the median age was 66 years.

None of the eyes sustained any complications related to the injection, such as vitreous hemorrhage, choroidal hemorrhage, retinal detachment, or endophthalmitis. Three eyes (cases 7, 8, and 9), all ischemic, subsequently developed ocular neovascularization, which regressed in all eyes in response to panretinal photocoagulation.

Table I shows the pretreatment and 6-month post-

treatment visual acuities, with the change in lines of visual acuity 6 months after treatment. Four of 9 eyes (44%) showed 3 or more lines improvement at 6 months. In this group, the average improvement was 7 lines. Two eyes showed 6 or more lines loss of vision at 6 months. Four eyes showed dramatic improvement in visual acuity within 1 month of injection (cases 3, 4, 5, and 6). In each, the injection was administered within 2 weeks of the onset of symptoms. Each of these eyes was also judged to be perfused on the pretreatment fluorescein angiogram. In contrast, none of the ischemic eyes improved beyond 20/400, although 2 of 4 eyes (cases 7 and 8) showed significant improvement of 3 or more lines from pretreatment vision. Two eyes (cases 2 and 8) received tPA in response to marked worsening of clinical appearance and visual acuity. In case 2, initial visual acuity was 20/80, the angiogram showed a perfused CRVO, and there was no afferent papillary defect. One month later, the vision dropped to counting fingers, the angiogram showed conversion to the ischemic variant, and an afferent papillary defect was detected. Despite the tPA injection, the vision did not improve beyond counting fingers. In case 8, initial vision measured 20/40 and remained stable for 3 months. At that point, the vision suddenly dropped to counting fingers, the fluorescein angiogram converted from perfused to ischemic, and the fundus appearance dramatically worsened. The tPA was injected within 1 month of the worsening of symptoms, and the vision improved from counting fingers to 20/400. Of note, this patient was diabetic and developed ocular neovascularization.

## DISCUSSION

Although tPA is presumed to cross the venous vessel wall to reach the retrolaminar clot, this has not been established. Lack of a suitable animal model and the inability to image the small clot in the retrolaminar central vein, let alone see it dissolve in response to any treatment, hinders our ability to evaluate thrombolytic therapy irrespective of the mode of delivery. However, the histopathologic evidence for the development of CRVO and the successful reports of tPA use for submacular hemorrhage provide the rationale for the use of intravitreal tPA in CRVO.

Lahey and associates<sup>14</sup> were the first to report on intravitreal tPA injection for CRVO. They treated 23 CRVO eyes and showed doubling of the visual angle in 4 eyes. Although 1 eye developed a small vitreous hemorrhage, there were no major complications related to the treatment.

Glacet-Bernhard and colleagues<sup>15</sup> treated 15 CRVO eyes with intravitreal tPA. None of the eyes sustained serious complications related to the intravitreal tPA injection. At the end of follow-up, visual acuity "was improved

TABLE 1: STUDY RESULTS

CASE	AGE	SEX	PRETREATMENT VISION	VISION AT 6 MO	VISION CHANGE AT 6 MO	BASELINE MEDICAL CONDITIONS	BASELINE ANGIOGRAM
1	66	M	20/63	Counts fingers	-11	Hypertension	Perfused
2	59	F	Counts fingers	Counts fingers	0	Hypertension, Coumadin	Ischemic
3	72	M	20/125	20/32	6	Plavix	Perfused
4	61	F	20/32	20/20	2	Hypertension, glaucoma	Perfused
5	77	F	20/125	20/80	2	Hypertension, diabetes	Perfused
6	68	F	Counts fingers	20/50	12	Hypertension	Perfused
7	79	M	Hand motions	20/320	7	Hypertension	Ischemic
8	51	M	Counts fingers	20/400	3	Diabetes	Ischemic
9	57	F	Counts fingers	Light perception	-6	None	Ischemic

in 5 eyes (36%), unchanged in 5 eyes (36%), and worsened in 4 eyes (28%).” The investigators did not report change in lines of acuity, particularly at a set point in time after treatment. As in our series, none of the ischemic eyes showed improvement of visual acuity beyond 20/200; all of the eyes with dramatic improvement following tPA were nonischemic.

Although our series is small, the percentage of eyes gaining 3 or more lines vision at 6 months post-treatment (44%) parallels the improvement (42%) we saw with intravenous tPA. However, the nature of this report (small sample size, absence of randomized controls) precludes comparison between the efficacy of intravenous tPA and intravitreal tPA. Indeed, definitive recommendations regarding efficacy can be made only through a randomized controlled study. However, we were able to demonstrate the feasibility and relative safety of this approach. Together with the cases reported by Lahey and associates<sup>14</sup> and Glacet-Bernhard and colleagues,<sup>15</sup> a total of 47 eyes with CRVO have been reported to have undergone intravitreal tPA injection without any major complication. Although Hrach and coworkers<sup>20</sup> reported fundus pigmentary alterations in cats at a concentration of 50 µg/mL, we did not observe retinal pigment changes at this dose. The poor natural history of CRVO, the lack of a safe and effective treatment, the scientific rationale underlying thrombolytic treatment in CRVO, and the apparent relative safety and feasibility of intravitreal tPA injections strongly support further, more definitive investigations of its efficacy and safety in CRVO.

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## DISCUSSION

DR ANDREW K. VINE. Despite extensive research concerning the risk factors for central retinal vein occlusion, we have no effective therapy for this condition which results in significant visual morbidity. In assessing possible innovative therapies, Dr Elman and colleagues have retrospectively reviewed 9 patients with central retinal vein occlusion who were treated with an intravitreal injection of tissue plasminogen activator (t-PA) 100 micrograms, followed by aspirin therapy. There is no mention whether the protocol was approved by an IRB. The authors state that 4 of the 9 patients showed an improvement in visual acuity of 3 or more lines by 6 months.

These results, however, are partially based on the authors assumptions that hand motions visual acuity is equivalent to 20/1600, and that counting fingers visual acuity is equivalent to 20/800. With these assumptions, the authors state that an improvement from hand motions to 20/320 is an improvement in 7 lines of visual acuity. Hand motions and count fingers visual acuities are poor measurements of visual acuity. The authors used EDTRS charts<sup>1</sup> which are designed to be used at 4 meters. If the patient is unable to read the largest letters, the patient can be moved to 2 meters or 1 meter from the chart. A visual acuity of 5/200 is a reproducible measurement of visual acuity, whereas hand motions or count fingers are not.

This study is the third uncontrolled pilot study<sup>2,3</sup> of intravitreally injected t-PA in eyes with recent onset central retinal vein occlusion. The similarities and differences of these 3 studies are listed in Table I. Follow-up visual acuities of the treated eyes are summarized in Table II. An improvement in visual acuity of 3 lines or more ranged from 28% to 44% in these 3 studies, but without a control group it is not possible to state whether the treatment was actually efficacious. In a small series<sup>4</sup> evaluating the natural course of central retinal vein occlusion, 40% of eyes with a non-ischemic central retinal vein occlusion had a visual improvement of 3 lines or more.

Previous studies with the rabbit model<sup>5-7</sup> have shown

that topical t-PA results in reasonable levels in the aqueous, and that subconjunctival t-PA results in significant vitreous levels; but intravitreal t-PA did not diffuse through the intact neural retina in this model. If intravitreal t-PA can reach the central retinal vein and cause lysis of the presumed intraluminal thrombus, one would expect some rapid improvement in retinal circulation time post injection. In our series<sup>3</sup> from France, however, none of the eyes showed an improvement in retinal circulation time on the first day post injection. Fifty percent of eyes actually showed a decrease in retinal circulation time and 50% showed no change. Only at the end of follow-up was an improvement in retinal circulation time seen in 38% of eyes.

This study combined with the 2 previous investigations<sup>2,3</sup> support the conclusion that intravitreal t-PA is safe. Whether a controlled study to show the efficacy of this therapy should be undertaken is questionable. In our series<sup>3</sup> of 15 patients, only 1 patient with an underlying thrombotic disorder, showed a dramatic improvement in visual acuity the first day post injection. More aggressive fibrinolytic therapy suggests that intravitreal t-PA for central retinal vein occlusion will not be effective. Paques and co-investigators<sup>8</sup> have used selective cannulation of the ophthalmic artery to infuse Urokinase directly into the ophthalmic artery in patients with central retinal vein occlusion. Despite this aggressive approach, only 1 of 14 patients with classical central retinal vein occlusion showed a temporary improvement in visual acuity. If injection of fibrinolytic agents directly into the ophthalmic artery of eyes with central retinal vein occlusion is ineffective, then it is very unlikely that intravitreal t-PA will be an effective therapy.

The timing of t-PA therapy for central retinal vein occlusion may be critical. In our series,<sup>3</sup> the only patient who showed an immediate improvement in visual acuity was treated on the same day his symptoms developed. In Dr Elman's series, patients were treated within 1 month of the onset of symptoms. A previous case report<sup>9</sup> documented a recanalized thrombus in a central retinal vein which had developed 11 days after first symptoms appeared. With a recanalized thrombus, both intravitreal and intra-arterial t-PA would be ineffective. It is possible that the thrombus or occlusion is extensively developed when the patient has initial symptoms.

Many features of central retinal vein occlusion

TABLE I: INTRAVITREAL T-PA FOR CENTRAL RETINAL VEIN OCCLUSIONS

STUDY	LAHEY	GLACET-BERNARD	ELMAN
Number of eyes with CRVO <sup>o</sup>	23	15	9
t-PA mg	65-110	75-100	100
Additional treatment	ASA† or LMWH‡	LMWH‡	ASA

<sup>o</sup>central retinal vein occlusion

†aspirin

‡low molecular weight heparin

TABLE II: IMPROVEMENT IN VISUAL ACUITY BY 3 LINES POST INJECTION OF T-PA

STUDY	LAHEY	GLACET-BERNARD	ELMAN
VA ↑ 3 Lines	10 (43%)	4 (28%)	4 (44%)
VA ↓ 3 Lines	3 (13%)	4 (28%)	2 (22%)
Same VA	10 (43%)	6 (43%)	3 (33%)

remain unknown. Although development of an intraluminal thrombus<sup>10</sup> is assumed to be the final or precipitating event, there are many aspects of central retinal vein occlusion which would not be amenable to fibrinolytic therapy. These features include vascular compression from the adjacent sclerotic artery which shares a common adventitia with the central retinal vein, and increasing phlebosclerosis with age.

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[Editor's note] DR. RICHARD P. MILLS asked why some of the successful examples of TPA treatment showed collateral vessels at the disc? He pointed out that if the clot in the central retinal vein were lysed by the treatment, there would be no continued stimulus for the development of collaterals.

DR MICHAEL J. ELMAN. I would like to thank Dr Vine for a very thought provoking discussion. Let me start by trying to answer Dr Mills' question and the answer is I don't know. First, we don't know definitively if the treatment even works. With respect to the issues that Dr Vine raised, equating a change in vision between hand motions and counting fingers to doubling of the visual angle was not my innovation. This approach was used in the Ischemic Optic Neuropathy Decompression Trial. The IONDT was a randomized controlled clinical trial evaluating optic nerve sheath decompression for the treatment of ischemic optic neuropathy. This trial underwent peer

review by the NIH. As Vice Chairman of the IONDT, I can tell you that this aspect of the study design was never questioned. Considering a change in level of vision is comparable to doubling of the visual angle is an assumption. I agree that it would be preferable if we could measure all the visions on a visual acuity chart. If one were to design a trial, perhaps one would want to stratify the pre-enrollment population based on those who have visions on the chart versus those who don't. In fact I believe that was done in the analysis of the IONDT.

The natural history of CRVO is variable. In the CVOS only 6% of patients with 20/50 to 20/200 visual acuity at the start of the trial improved 3 or more lines without treatment.

Reproducible retinal circulation times have always been a very difficult thing for us to measure. We tried timed transits in the TICVO pilot study and were not successful. When we started giving t-PA intravenously we shared your feelings. We thought that t-PA was going to be Drano for the eye and that we would have to give a beeper to every photographer so that as soon as we administered this drug we would be able beep them to run and photograph the eye as the blood was going "whoosh" through the freshly opened central retinal vein. That isn't the way it works. And if you think of it there might be a good reason. When one does surgery on the eye, or any other part of the body, to correct an abnormality, function on the operated part doesn't go back to normal overnight, although our patients think it should. For example, if a patient undergoes orthopedic surgery on his knee he is not going to go back to running the next day. Healing takes time. Even if t-PA does work in CRVO, there is fluid accumulation in the macula, which takes time to improve. So I don't necessarily think that a change in visual acuity the next day or perhaps a change in circulation time would necessarily be critical but again it is an area of concern and needs to be investigated further. These methods are indirect measures of clot dissolution. Ideally we want to directly image the clot before and after treatment. In contrast to our cardiology colleagues, this remains impossible for CRVO.

With respect to other papers on thrombolytic therapy, I can only offer the data in our intravenous t-PA paper, published as my AOS thesis, which do not support this conclusion. Finally, timing of the infusion is important. There is information in the literature suggesting there is still substrate for the t-PA to act on at 2 weeks. Unfortunately to my knowledge, there are no reports in the literature of histopathology in CRVO at 1 month's duration. So if one were to design a trial I think I would do pre-randomized stratification for treatment divided between patients with symptoms less than 2 weeks duration and those between 2 and 4 weeks.

Thank you again for your attention.



# MONITORING OF CONTROLLED ACCOMMODATIVE ESOTROPIA\*

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BY Edward L. Raab, MD

## ABSTRACT

*Purpose:* To ascertain an examination interval that will not increase the risk of untimely detection of decompensation of accommodative esotropia whether or not initial nonoperative treatment must be supplemented.

*Methods:* The records of 63 patients with controlled accommodative esotropia examined at 3- to 6-month intervals were reviewed for age at first control, the occurrence of decompensation, initial refraction and subsequent changes, and the need for increased correction of hyperopia or the addition of bifocals.

*Results:* Decompensation occurred in 11 patients, not associated with substantial refractive changes toward or away from emmetropia. No instance of decompensation occurred in the first 12 months of observation, and only 11.5% occurred within 2 years. Although 7 of these decompensated patients were among the 18 (28.6%) requiring supplemental nonoperative treatment, their mean initial hyperopia and annual refractive change did not differ significantly from the 11 patients who did not decompensate. Eight (18.6%) of 43 patients who were first controlled earlier than age 48 months later decompensated; 3 (15.0%) of 20 patients with later onset reached this outcome.

*Conclusions:* Monitoring controlled accommodative esotropia at intervals of 9 to 12 months is adequate for most patients, at least over the first 2 years, other than those requiring treatment for associated conditions such as amblyopia. Refractive error changes and the need for supplemental treatment after initial control are not prominently associated with decompensation. Age at onset of accommodative esotropia earlier or later than 48 months did not influence rapidity of decompensation.

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## INTRODUCTION

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According to conventional teaching, patients with accommodative esotropia require close follow-up, especially prior to age 6 years.<sup>1</sup> In addition to monitoring for the development of amblyopia, such follow-up is thought to ensure detection of (1) decompensation to a nonaccommodative deviation, a sequel affecting 11% to 48% of these patients,<sup>2,5</sup> and (2) the need for increased treatment measures to continue adequate control<sup>6</sup> or opportunities to incrementally reduce treatment to encourage the expansion of fusional divergence.<sup>7</sup>

In the author's experience, once satisfactory alignment has been obtained, visits at the 3- to 6-month intervals usually recommended often uncover none of these "events." Fewer visits that still accomplish the goals of treatment can simplify the management of such cases, an important advantage in the managed care setting.

This report examines whether lengthening the interval between examinations of patients with accommodative esotropia still allows timely discovery of features determining changes in their treatment.

\*From the Department of Ophthalmology, Mount Sinai School of Medicine of New York University, New York, New York. Supported by an unrestricted grant from Research to Prevent Blindness, Inc.

## SUBJECTS AND METHODS

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This retrospective study included 63 patients observed for at least 6 months after initial treatment of accommodative esotropia reduced the deviation to no more than 10 prism diopters (PD), as determined by prism and alternate cover testing, approximately 6 weeks after prescription of the appropriate cycloplegic correction, with a bifocal addition if indicated. Exclusion criteria were major neurologic conditions, prominent nystagmus, extraocular muscle palsy, restricted rotations, and Duane syndrome. Coexisting vertical deviations, oblique dysfunctions, prior surgery for infantile esotropia, and amblyopia were not reasons for exclusion, as the behavior of accommodative esotropia in these settings is similar to that in cases without these additional attributes.<sup>3,8</sup>

Decompensation was defined as a primary position distant esodeviation, originally but no longer reduced to 10 PD or fewer by control of accommodation. No patient entered the study already showing decompensation (ie, all entered as cases of accommodative esotropia responsive to treatment). Thirty-three patients were initially evaluated while under successful treatment that had been instituted elsewhere. This precluded reliably establishing a date of onset of the deviation. Duration from the author's verification of control to either decompensation or the

need for more intense treatment was determined for each subject.

The author performed all examinations. Retinoscopy was accomplished 45 to 60 minutes after 2 instillations of 1% cyclopentolate hydrochloride. Measurements of refractive error refer to the eye preferred for fixation. Refractive error determinations usually were made at approximately annual intervals. Changes in hyperopia were annualized by extrapolation over the longest interval from initial examination up to age 8 years (the typical peak for any increases<sup>9</sup>) for which a subsequent measurement was available.

Initial treatment consisted of prescription of the full, or within 0.50 D of the full, cycloplegic retinoscopic findings. When a high near-to-distance alignment comparison was present,<sup>3,4</sup> a bifocal addition of +2.50 D sphere to both eyes was employed. Some patients subsequently required a stronger refractive correction or inclusion of a bifocal for residual uncompensated esotropia.

Means, standard deviations, and significance determinations were calculated using the 2-tailed *t* test for unpaired data. Although results at further intervals are included, emphasis is on outcomes within the first 2 years of observation.

**RESULTS**

Decompensation was observed in 11 patients, at a mean interval from first observation of 45.1 months (range, 13 to 169 months). Of 60 patients followed up for at least 1 year, none showed decompensation within that period. Two (18.1%) of the 11 patients decompensating did so within 18 months, and 6 (54.5%) within 2 years (Table I). This represents 3.7% and 11.5%, respectively, of the patients observed at these intervals.

As in most retrospective studies, follow-up was not uniform. A modified life table approach was used to further define decompensation rates. The pooled decompensation rate of 21.4% determined in prior studies<sup>1,3,4</sup> suggests that no more than 1 of the 3 patients (1.5% of the entire series) not examined up to 1 year after establishment of control should be assumed to have decompensated in that interval. Use of this method of correcting for later follow-up loss leads to the estimate of 15 patients decompensating, with only 3 (20%) occurring within 18 months and 8 (53.3%) within 24 months (Table I).

Eighteen of the 63 patients whose refractive correction initially had been sufficient later required increased treatment to maintain control, as a first event. Eleven patients received this assistance in the first year after initial observation. They accounted for only 3 (27.3%) of those who eventually decompensated. Six patients (3 in the second year) needing stronger treatment after the first

TABLE I: INTERVAL TO DECOMPENSATION

INTERVAL FROM FIRST OBSERVATION (MO.)	PATIENTS OBSERVED	PATIENTS DECOMPENSATING	
		OBSERVED*	ASSUMED*
0-6	63	0	0
7-9	61	0	0
10-12	60	0	1
13-15	58	1	2
16-18	54	2	3
19-21	54	4	5
22-24	52	6	8
25-27	50	6	8
28-30	44	6	9
31-33	42	7	10
34-36	36	8	12
37+	33	11	15

\*Cumulative.

year later furnished 3 to the group later decompensating (Table II).

There were 40 patients in this series whose first event had been weakening of the refractive correction with maintenance of satisfactory alignment. Only 2 (5.0%) of these patients eventually decompensated, at 19 and 54 months, respectively. Moreover, of 9 patients in this group who required a reinstatement of stronger accommodation control as a second event after this first reduction, only 1 decompensated, 62 months after this measure (not tabulated).

Initially determined hyperopia was distributed normally in the series. For the decompensated patients and for patients remaining controlled, mean initial hyperopia, standard deviation, and range were clinically and statistically the same (Table III). This result is consistent with a

TABLE II: DECOMPENSATION AFTER STRONGER TREATMENT

INTERVAL FROM FIRST OBSERVATION (MO)	PATIENTS REQUIRING* INCREASED Rx*	PATIENTS LATER DECOMPENSATING*
0-6	6	2
7-9	9	3
10-12	11	3
13-15	15	5
16-18	16	5
19-21	17	6
22-24	17	6
25-27	17	6
28-30	17	6
31-33	17	6
34-36	17	6
37+	18	7

\*Cumulative.

prior study.<sup>3</sup>

The mean annual change in hyperopia for the decompensating patients was clinically similar to the results of

TABLE III: INITIAL HYPEROPIA

PATIENTS	MEAN (D)	SD (D)	RANGE (D)
Decompensated (N = 11)	3.77	1.56	2.00 to 7.00
Controlled (N = 52)	4.00	1.82	1.25 to 8.00
$P = 0.35$			

D, diopters.

other studies of decompensation<sup>3</sup> and of unselected, principally nonstrabismic patients.<sup>9</sup> The same determination for patients remaining controlled is clinically comparable, and statistically the differences are not significant (Table IV).

Initial hyperopia for the subgroup of patients whose first event was stronger treatment and who later decompensated was similar for those whom stronger treatment

TABLE IV: ANNUAL CHANGES IN HYPEROPIA

PATIENTS	MEAN (D PER YR)	SD (D)	RANGE (D PER YR)
Decompensated (N = 11)	+0.07	0.58	-1.00 to +0.88
Controlled (N = 50*)	-0.05	0.51	-1.44 to +1.37
$P = 0.53$			

D, diopters.  
\*Information unavailable for 2 patients.

re-stabilized (Table V). Likewise, both segments of this group showed only very modest, statistically and clinically similar annual increases in hyperopia (Table VI).

Because the tendency to decompensate presumably is aggravated by the more precise requirement for sustained accommodative (despite optical compensation) and convergence effort in older children as their intellectual maturity increases, the possible influence of age at initial

TABLE V: INITIAL HYPEROPIA AND STRONGER TREATMENT

PATIENTS	MEAN (D)	SD (D)	RANGE (D)
Decompensated (N =7)	3.82	1.68	2.00 to 7.00
Controlled (N = 11)	5.05	2.04	2.25 to 8.00
$P = 0.20$			

D, diopters.

TABLE VI: ANNUAL REFRACTIVE CHANGES AND STRONGER TREATMENT

PATIENTS	MEAN (D)	SD (D)	RANGE (D)
Decompensated (N = 7)	+0.17	0.61	-1.00 to +0.88
Controlled (N = 11)	+0.12	0.36	-0.38 to +0.82
$P = 0.89$			

D, diopters.

control on the subsequent appearance of decompensation was examined. Forty-eight months was selected as the reference age. Of 43 patients first controlled earlier than this age, 8 (18.6%) decompensated. Three (15.0%) of 20 patients first controlled at later than 48 months of age reached this outcome. The difference in these rates is not significant. For both age-groups, the interval from control to decompensation also was not significantly different (Table VII). A similar analysis based on age 30 months, the reported mean age at onset of accommodative esotropia,<sup>1(p99)</sup> gave comparable results (not tabulated).

TABLE VII: AGE AND DECOMPENSATION

AGE (MO)	NO. OF PATIENTS	NO. (%) DECOMPENSATING	INTERVAL (MO) FROM CONTROL (MEAN, SD)
≤48	43	8 (18.6)	47.4 ± 53.5
>48	20	3 (15.0)	39.0 ± 20.2
$P = 0.81$			

## DISCUSSION

Management of these patients had been carried out according to usually advocated principles.<sup>1,6</sup> The study questions were prompted by the retrospective observation that very often 1 or more periodic examinations had been superfluous, resulting only in continuation of treatment without change.

Extension of the time between examinations is desirable if it does not compromise care. These results indicate that decompensation is unlikely to occur in less than 12 months after control of accommodative esotropia is initially established. Moreover, the need for supplemental treatment, even if arising in the first year of monitoring, usually is not a warning that closer follow-up is necessary. Not answered by this study is whether, if follow-up intervals are extended from 6 to even 12 months, a relatively short delay in detecting decompensation adversely affects the final sensory and motor outcome.

This does not support the classic notion that progressive, substantially increasing hyperopia requiring

continued exertion of accommodation and its associated convergence is among the prominent causes of decompensation. Further, the refractive change findings seen here suggest again that emmetropization, considered by some to be a universal tendency, is not typically found in accommodative esotropia patients younger than 8 years of age.<sup>3</sup>

## CONCLUSIONS

Omitting examination for 1 year after verifying control of the accommodative esotropia would not have delayed the detection of any patient's decompensation. Deferral of follow-up even to 18 months would not have prevented detection for the majority of these patients.

While less than optimal control of accommodative esotropia may logically be thought to invite decompensation, patients with unstable alignment due to the need for stronger treatment were not more susceptible to decompensation in the first year after initial treatment compared to later intervals.

Observation at an interval of less than 18 months following reduction of initial treatment, whether or not remaining entirely adequate to maintain control, would not have identified decompensation, a result consistent with that of a prior study.

Initially determined hyperopia was not predictive of decompensation.

Since decompensation after control of accommodative esotropia usually is not due to large, rapid increases in hyperopia, closer follow-up for the purpose of repeated refraction would not have improved the identification of future decompensation.

Age at onset of accommodative esotropia was not determined to be a risk factor for early decompensation.

Unless there are coexisting problems, such as amblyopia, inferior oblique overaction, or DVD, follow-up for controlled accommodative esotropia, at least over the first 2 years following the attainment of satisfactory control, can be extended to 9 to 12 months.

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## DISCUSSION

DR PAUL R. MITCHELL. Dr Raab has presented a new concept in the monitoring of accommodative esotropia, at intervals of 9 to 12 months, over the first 2 years after control has been established, unless there are associated conditions such as amblyopia, inferior oblique overaction, and dissociated vertical deviations. The records of 63 patients with accommodative esotropia examined at 3 to 6 month intervals were reviewed in a retrospective study, for the occurrence of decompensation, changes in refractive error, and the need for increased hyperopic correction or the addition of bifocals. The 63 patient group included 33 patients who were initially evaluated while under successful treatment which had been instituted elsewhere, which precluded the opportunity of establishing accurately a date for the onset of the eye deviation.

Dr Raab excluded those patients with major neurologic conditions, prominent nystagmus, extraocular muscle palsy, restricted rotations, and Duane syndrome. But, he did not exclude coexisting vertical deviations, oblique dysfunctions, prior surgery for infantile esotropia, and amblyopia.

In Table I, Dr Raab describes decompensation in 11 patients, 17.5% of the group of 63 patients. Twenty-one patients were lost to follow-up, and by the end of the period of study of 37+ months, a total of 33 patients had been observed. The exact number of decompensations of the 21 patients lost to follow-up can only be hypothesized. If all 21 decompensated, then the rate of decompensation could be 11+21/63 (51%). If none of the 21 decompensated, then the rate would be 17.5%. The true percentage is somewhere between these 2 numbers. In evaluating the number of decompensations per time interval, the percentage increases with time, as fewer were observed and as more patients were lost. At the 12 months interval, 0% decompensation, at 18 months, 2/54 (3.7%), at 24 months, 6/52 (11.5%), at 30 months, 6/44 (13.6%), at 36 months, 8/36 (22.2%) and at 37+ months 11/33 (33%) decompensation.

In Table II, 18 patients of the 63 required increased hyperopic correction, a bifocal, or supplementary anticholinesterase medication. With each time interval, the percentage of decompensation increased. At 12 months, 3/11 (27.3%), at 18 months, 5/16 (31.3%), at 24, 30, and

*Monitoring of Controlled Accommodative Esotropia*

TABLE I: INTERVAL TO DECOMPENSATION

INTERVAL FROM FIRST OBSERVATION (MONTHS)	PERCENTAGE	PATIENTS OBSERVED	PATIENTS DECOMPENSATING	PATIENTS LOST
0-6		63	0	0
7-9		61	0	2
10-12		60	0	1
13-15		58	1	2
16-18	2/54=3.7%	54	1	3
19-21		54	2	0
22-24	6/52=11.5%	52	2	3
25-27		50	0	3
28-30	6/44=13.6%	44	0	0
31-33		42	1	6
34-36	8/36=22.2%	36	1	0
37+	11/33=33%	33	$\frac{3}{11}$	$\frac{1}{21}$

TABLE II: DECOMPENSATION AFTER STRONGER TREATMENT

INTERVAL FROM FIRST OBSERVATION (MONTHS)	PERCENTAGES	PATIENTS REQUIRING	PATIENTS LATER DECOMPENSATING
0-6		6	2
7-9		3	1
10-12	3/11=27.3%	2	0
13-15		4	2
16-18	5/16=31.3%	1	0
19-21		1	1
22-24	6/17=35.3%	0	0
25-27		0	0
28-30	6/17=35.3%	0	0
31-33		0	0
34-36	6/17=35.3%	0	0
37+	7/18=38.9%	$\frac{1}{18}$	$\frac{1}{7}$

36 months, 6/17 (35.3%), and at 37+ months, 7/18 (38.9%). These were 7 of the 11 patients who decompensated in Table I.

There are a number of areas of concern with this paper, not only with the way the data was collected and presented, but also with the conclusion. The paper is not a summary of pure accommodative esotropia and the conclusions should be tempered. Were the patients selected at random, in sequence, or selectively chosen? Were they excluded if their deviation with eyeglass correction was more than 10 diopters? What diagnosis did each patient have, besides accommodative esotropia? Of the 33

patients treated elsewhere and acquired by Dr Raab, more information would be of value. Which patients were they, of the 63 total, and when did they decompensate, relative to patients treated initially by Dr Raab? Was there any difference in the rate of decompensation? If Dr Raab's initial patients did not decompensate for a year, then why did those patients ... "evaluated while under successful treatment that had been instituted elsewhere" not show a tendency to decompensate sooner? Or did they decompensate at the same rate? Dr Raab stated that the date of onset of the deviation was not reliable. Should these 33 patients have been included if the date of onset

of the deviation was not reliable? Should they have been tabulated separately?

Pure accommodative esotropia presents intermittently between 7 months of age and 7 or 8 years of age, with an average of 2 1/2 years, typically with binocular vision already established prior to the onset of the deviation. Accommodative esotropia developing after early surgery for congenital esotropia has successfully aligned the eyes, reveals a different sensory and motor presentation, including oblique muscle dysfunction, and the dissociated strabismus complex. The major differences in complexity are not discussed in this paper, by grouping these patients together, and there is no indication in the outcome tables as to which patients have which condition. The manuscript briefly mentions that amblyopia should be treated, and sensory data is not detailed except for a comment in the discussion: "if...a relatively short delay in detecting decompensation adversely affects the final sensory and motor outcome."

Dr Raab's definition of decompensation is "distant esodeviation, originally but no longer reduced to 10 prism diopters or fewer by control of accommodation." In fact, deterioration is a far more serious matter, than just alignment status measured in prism diopters. Deterioration is the replacement of intermittent esotropia with constant esotropia, which has the potential to create a lifelong problem. The loss of bifixation and absence of alternation results in amblyopia. With decompensation of accommodative esotropia and 3 months of constant esotropia, bifixation is lost forever. The monofixation syndrome is the result.

Pratt-Johnson admonished all ophthalmologists to develop a special routine in treatment of accommodative esotropia. One should consider that any child with the onset of intermittent esotropia, which after workup appears to have accommodative esodeviation, deserves treatment as soon as possible after onset, to prevent losing bifixation and having to resort to monofixation. For this reason, the only logical treatment is for the children to be examined as soon as possible after the onset of the intermittent esodeviation, and followed closely to detect a trend toward decompensating to comitant esotropia after originally being compensated by anti-accommodative therapy.

Perhaps the data presented in the manuscript suggests that because decompensation did not occur in the first year of treatment, that the frequency of examinations should then be increased in subsequent years, when decompensation is more likely to occur. The lack of compliance in wearing eyeglasses certainly rates as one of the leading causes of decompensation. Children's eyeglasses are prone to damage or loss, often resulting in the absence of wearing them for lengthy periods of time. Repeated

parental instruction about the importance of constant eye-glass wear is part of the responsibility assumed by the ophthalmologist caring for these vulnerable young patients. Increasing the intervals between visits, as Dr Raab's conclusion in this paper seems to advocate, must be weighed against the potential problems this policy could cause.

Thank you for the opportunity to discuss this paper, and I thank Dr Raab for providing the manuscript and tables in a timely fashion.

[Editor's note] DR MALCOLM R. ING asked about the role of compliance in the incidence of decompensation. DR DAVID L. GUYTON asked about the effect of residual accommodation and whether an adequate cycloplegic refraction was obtained. DR JOHN F. O'NEIL asked if the difference in time of onset of the esotropia influenced the rate of decompensation. DR ALLAN J. FLACH asked about the duration of follow-up and the problems presented by patients who do not keep their follow-up appointments.

DR EDWARD L. RAAB. I am pleased that the Program Committee included this presentation in our meeting, and that it has led to a substantial amount of thoughtful comment.

Dr Mitchell mentioned the imprecision in establishing a date of onset for the many patients that were already under care successfully when I became their ophthalmologist. He is correct, but if it influences the results at all, it actually extends the time they remained under initial control and I think strengthens my observations.

Dr Mitchell also discussed follow-up loss. The manuscript will reflect that I handled follow-up loss by deriving an average decompensation rate of 21.4% from prior reported studies, so that if 3 patients were not observed over the entire first year, and rounding up to the nearest whole patient, I assumed that one of those would have decompensated. Therefore, only one of 63 patients would have been missed if not reexamined for an entire year. Employing the same analysis at later intervals leads to the same conclusion.

As I stated, my particular interest was in the first 2 years. Beyond that, or once there are signs of impending decompensation, whether or not it is advisable to maintain an extended follow-up interval is undetermined. I agree with Dr Mitchell that this question is examined best in a randomized, controlled trial comparing outcomes with shorter and longer intervals, but I cannot offer that information based on this work. The series was obtained from a section of my files and were identified by a color code. I have enough material for a much larger series, but it would be no less retrospective.

Dr Ing asked whether compliance was an issue here. Rather than how many patients decompensated or why

they decompensated, I was looking at *when* they decompensated. That was the practical question I was addressing, so I can't really give an answer on the compliance factor.

Dr Guyton queried about adequacy of cycloplegia. I was taught that the definition of adequate cycloplegia is not based on the drug that was used, but on the residual accommodation in the particular patient with whatever agent was given. If there is no more than about a diopter of residual accommodation on dynamic retinoscopy, i.e., with distant fixation and then with near fixation, this would be considered clinically adequate cycloplegia. None of these patients had atropine. All had cyclopentolate 1%, and none were examined before 45 minutes after the first instillation. Although I did not investigate this in every patient in this study, my habit in the ordinary course of practice is to "spot check" periodically, and of those that I did check, I thought there was adequate cycloplegia.

I did not examine the emmetropization question, so I cannot answer Dr Guyton's question about whether "pushing plus" retards this phenomenon. My concern was the downside risk of decompensation, and I would be

looking to push rather than cut back when I thought this was about to occur.

Dr O'Neill asked about early v. late onset and more difficult management of patients presenting very early. Yes, in general that has been my experience, although not overwhelmingly. I did not analyze it for the purposes of this study.

Dr Flach suggests that a longer follow-up interval could imply an attitude on the practitioner's part that returning is not important. I have not noticed this since adopting my conclusion, but it is a possibility. As to his other question, I have not been contacting accommodative esotropia patients about follow-up unless they are under treatment for amblyopia or threatening to decompensate. I certainly do this for such conditions as congenital glaucoma, aniridia or Sturge-Weber syndrome where glaucoma is a prominent possibility, and acquired extraocular muscle palsies, and I agree that insuring adequate follow-up of whatever we are treating is a worthwhile goal.

Thank you again for your interest.



# NORTH CAROLINA MACULAR DYSTROPHY: CLINICOPATHOLOGIC CORRELATION\*

BY Kent W. Small, MD, AND (BY INVITATION) Irene Voo, MD, John Flannery, PhD, Nitin Udar, PhD, AND Ben J. Glasgow, MD

## ABSTRACT

**Purpose:** To describe the clinical and histopathologic findings in a 72-year-old woman with North Carolina macular dystrophy.

**Methods:** Clinical examination was performed by slit-lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, and focal electroretinography. Histopathologic examination of the enucleated left eye consisted of light microscopy.

**Results:** Light microscopy demonstrated a discrete macular lesion characterized by focal absence of photoreceptor cells and retinal pigment epithelium. Bruch's membrane was attenuated in the center of the lesion and associated with marked atrophy of the choriocapillaris. Adjacent to the central lesion, some lipofuscin was identified in the retinal pigment epithelium.

**Conclusions:** North Carolina macular dystrophy has both clinical and microscopic appearances of a well-demarcated retinal and pigment epithelial lesion confined to the macula. This is consistent with the clinical impression that it is a focal macular dystrophy.

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## INTRODUCTION

North Carolina macular dystrophy was the first macular dystrophy to be reliably mapped on the human genome (MCDR1).<sup>1</sup> This autosomal dominant macular dystrophy was first described in families living in the mountains of North Carolina. Subsequently, it has been reported in many unrelated families from the United States, United Kingdom, France, Germany, and Belize.<sup>1-3</sup> There is great phenotypic variability, with fundus appearances ranging from a few yellow drusen-like lesions less than 50  $\mu$ m in the central macula (grade 1) to larger confluent lesions (grade 2) and macular staphyloma (grade 3).<sup>1</sup> The disease is generally stable, except in those who develop choroidal neovascular membranes. We report the first clinicopathologic correlation of a subject (No. 1001) from a Caucasian family (No. 1292) with MCDR1.<sup>1</sup> This family had no known genealogical relationship to the original North Carolina family (No. 765); however, they share the same affected haplotype on chromosome 6q16 and

therefore are part of the original North Carolina macular dystrophy family.<sup>1</sup>

## CASE REPORT

At the initial examination in her home performed by K.W.S. in 1988, the 62-year-old patient was found to have bilateral macular scars with a best-corrected visual acuity of 20/40 in the right eye and 20/20 in the left eye. Institutional review board-approved consent forms were signed before the examinations. She stated that she had had decreased visual acuity since the age of 21 years and in about 1980 had "a bleed" in both eyes. Visual function spontaneously recovered in the left eye, but the right eye had residual metamorphopsia.

In 1990, she was examined again by K.W.S. at her residence. Best-corrected visual acuity at near had decreased to 20/100 in the right eye and 20/40 in the left eye. Color vision testing with Ishihara plates (Kanehara & Co, Ltd, Tokyo, Japan) was grossly abnormal with the patient missing 7 of 14 in the right eye and 5 of 14 in the left eye. Color fundus photographs taken with a handheld KOWA camera documented the disease as grade 2 bilaterally (Fig 1). There was a small area of apparent atrophy with some scarring at the central macula and drusen in the periphery. Focal electroretinograms (ERGs) were performed with the Doran maculoscope (Worham, Mass). Results were

\*From the Department of Ophthalmology, UCLA School of Medicine, Jules Stein Eye Institute (Dr Small, Dr Voo, and Dr Udar); the Department of Pathology, UCLA School of Medicine, Jules Stein Eye Institute (Dr Glasgow); and the School of Optometry and Helen Wills Neuroscience Institute, University of California, Berkeley (Dr Flannery). Supported in part by grant RO110239 from the National Institutes of Health/National Eye Institute (Dr Small).

within normal range (0.182  $\mu\text{V}$  amplitude, 37.4 msec implicit time foveal ERG right eye; 0.209  $\mu\text{V}$  amplitude, 35.8 msec implicit time parafoveal ERG right eye; 0.172  $\mu\text{V}$ /36.5 msec foveal ERG left eye; 0.108  $\mu\text{V}$ /34.9 msec parafoveal ERG left eye).

At a subsequent examination in the subject's home in 1995, visual acuity in the right eye had improved to 20/70; acuity in the left eye was stable at 20/30 with the patient using a near vision card and wearing bifocals. At this visit, the macular lesions were unchanged at grade 2 severity. The subject died of a malignant astrocytoma in 2000.

## MATERIALS AND METHODS

The patient's eyes were enucleated 2 hours after death. The left eye was fixed in a buffered formaldehyde and glutaraldehyde solution, and the right eye was frozen in liquid nitrogen for future studies shortly after enucleation. The left eye was opened in a horizontal plane above the optic nerve. A large segment containing the optic nerve head and macular lesion was processed in routine fashion for light microscopy. Four hundred serial sections were prepared and stained with hematoxylin and eosin and periodic acid–Schiff stains.

## RESULTS

### GROSS PATHOLOGY

No gross abnormalities in size, structure of the anterior segment, or optic nerve were noted. The fundus appearance correlated with the previously taken photographs: a small area of apparent atrophy with some scarring at the central macula bilaterally and drusen in the periphery (Fig 2).

### LIGHT MICROSCOPY

Examination with light microscopy showed a discrete lesion in the fovea characterized by the abrupt transition from relatively normal macula to complete absence of photoreceptor cells and the underlying retinal pigment epithelium (RPE) (Figs 3A, 3B, 4). We did not document any evidence of choroidal neovascularization. Adjacent to the foveal lesion there was intercapillary pillar thickening of the choriocapillaris (Fig 5). Some accumulation of lipofuscin was identified within the RPE immediately bordering the lesion but not in the periphery (Fig 5). Occasional glial cells and pigmented macrophages were interposed between Bruch's membrane and the outer plexiform layer. Rare plasma cells and eosinophils were present. Central in the lesion, Bruch's membrane was severely attenuated and focally absent. The choriocapillaris was atrophic (Fig 6). Drusen were present throughout the eye but

particularly abundant closest to the optic nerve and in the macula (Figs 7 and 8). Examination of the remainder of the posterior pole and periphery revealed only occasional drusen.

## DISCUSSION

To date, the only macular dystrophies with histopathologic findings available for comparison to North Carolina macular dystrophy are Best's macular dystrophy,<sup>4,6</sup> fundus flavimaculatus with atrophic macular degeneration,<sup>7,10</sup> and adult-onset foveomacular pigment epithelial dystrophy (AOFPED).<sup>12,13</sup> The previous studies all included examination by light and electron microscopy. A common feature found in these diseases was prominent lipofuscin accumulation in the retinal pigment epithelium. Some studies also documented accumulation within the photoreceptors<sup>5,10</sup> and choroid.<sup>4</sup> This accumulation distended the RPE cells and caused great variability in size, up to 125  $\mu\text{m}$  in diameter, with desquamation<sup>7,8,10</sup> or eventual rupture of contents into the subretinal space and apparent phagocytosis by pigment-laden macrophages and photoreceptors.<sup>5-8,10</sup> Similarly, we noted PAS-positive material consistent with lipofuscin in the macula of the patient described in the case report. The photoreceptor involvement in the studies varied from shortened outer segments<sup>4,6,10</sup> to complete degeneration, as was evident in our case.<sup>5-7,10</sup> Another notable finding in the macular dystrophies was choroidal neovascular membranes in Best's disease, which was absent on our case.<sup>4,6</sup> Curiously, we did find an anomalous retinal vessel in the outer nuclear layer in our case (Fig 8). Basal laminar and linear deposits were prominent in AOFPED.<sup>12,13</sup> Macular drusen and a discontinuous Bruch's membrane were observed in Best's disease as well as in our case.<sup>4</sup> Decreased ganglion cells were found in fundus flavimaculatus but not in our case.<sup>10</sup>

In our case as well as in the case of fundus flavimaculatus with atrophic macular degeneration reported by Eagle and associates,<sup>7,11</sup> there was replacement of the photoreceptors by presumed glial cells and choriocapillaris atrophy. However, unlike in our case, Bruch's membrane was normal in the case of fundus flavimaculatus. Lopez and colleagues<sup>8</sup> also found, in a case of autosomal dominant fundus flavimaculatus, an area of complete RPE and photoreceptor loss in the macula, similar to our case. The photoreceptor autolysis and RPE atrophy noted by Dubovy and associates<sup>13</sup> in a case of AOFPED, was surrounded by adjacent RPE cells distended by lipofuscin. Our findings show granular PAS-positive material consistent with lipofuscin surrounding the focal lesion but not distended. In the center of the lesion where the photoreceptors were absent, the retinal pigment epithelium was also absent and Bruch's membrane was irregular and discontinuous.



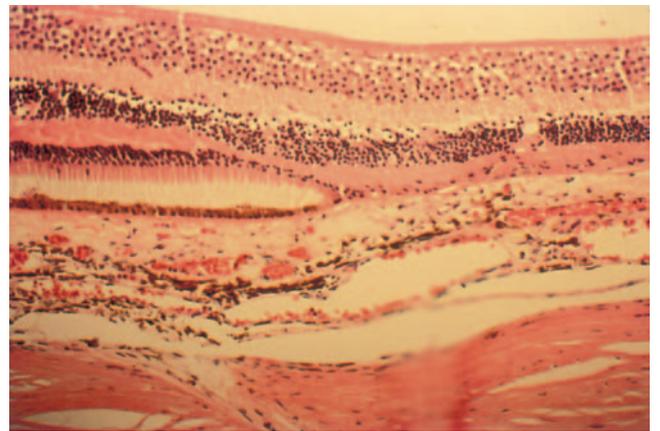
**FIGURE 1**

Fundus photographs of right (left) and left (right) eyes of subject described in case report, taken with a Kowa handheld camera in 1990



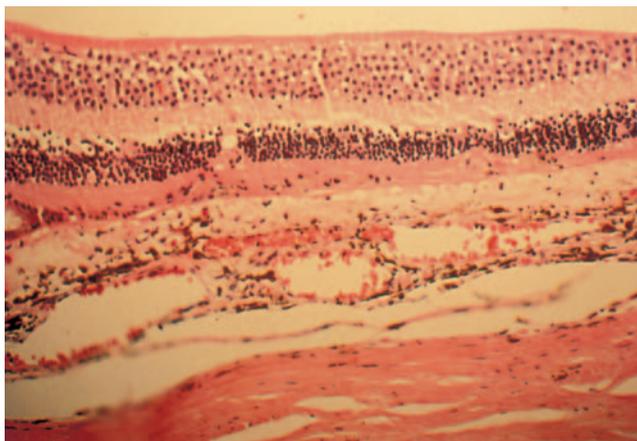
**FIGURE 2**

Gross photographs of left eye of subject described in case report, showing a focal macular lesion.



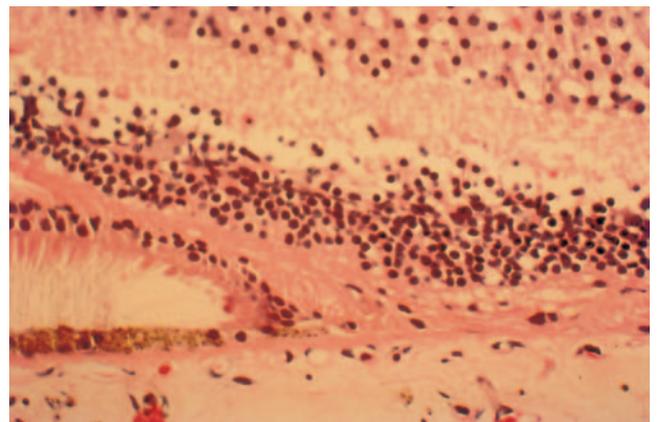
**FIGURE 3A**

Light microscopy showing abrupt transition from relatively normal macula to loss of photoreceptors and retinal pigment epithelium (hematoxylin and eosin, x 30).



**FIGURE 3B**

Light microscopy showing foveal region and loss of photoreceptors (hematoxylin and eosin, x 30).



**FIGURE 4**

Light microscopy at higher magnification than in Fig 3, showing abrupt transition from relatively normal macula to loss of photoreceptors and retinal pigment epithelium (hematoxylin and eosin, x 125).

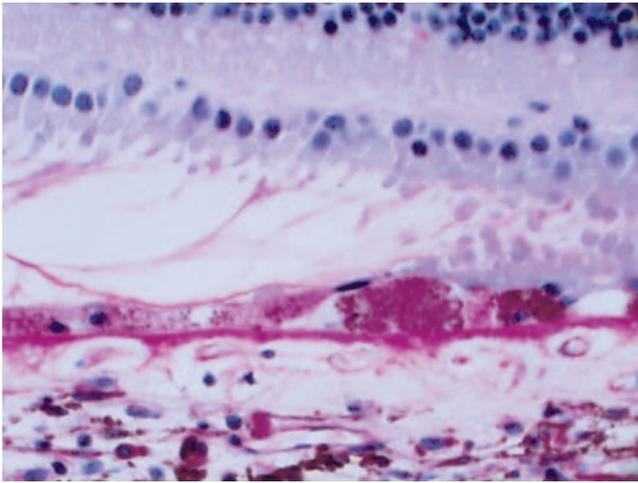


FIGURE 5

Retina adjacent to that shown in Fig 3. Note granular material positive for periodic acid-Schiff within retinal pigment epithelium and focal thickening of Bruch's membrane (periodic acid-Schiff, x 500).

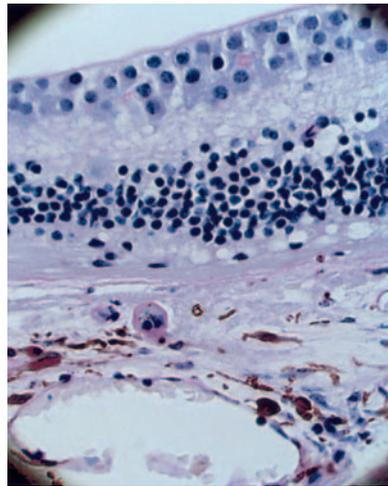


FIGURE 6

Photomicrograph showing marked thinning and apparent focal absence of Bruch's membrane. Choriocapillaris is atrophic (periodic acid-Schiff, x 500).

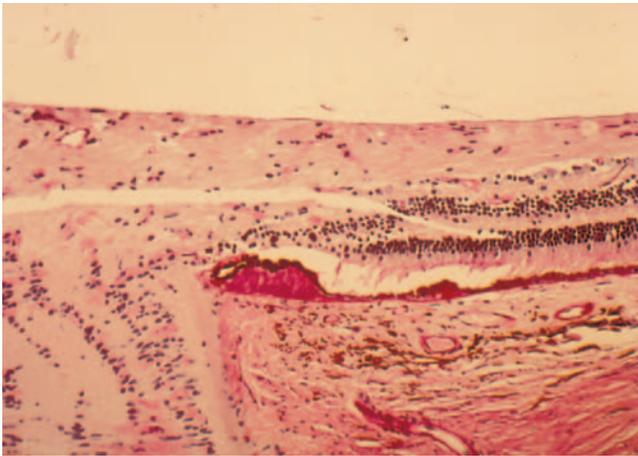


FIGURE 7

Photomicrograph showing large drusen and material positive for periodic acid-Schiff between Bruch's membrane and retinal pigment epithelium adjacent to optic nerve (periodic acid-Schiff, x 215).

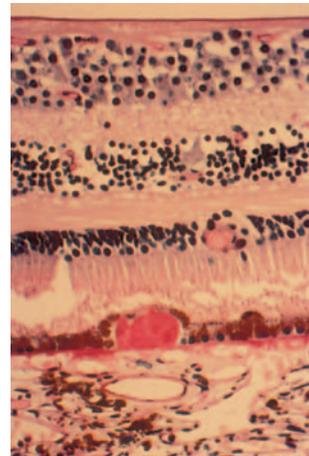


FIGURE 8

Photomicrograph showing large lobulated drusen in macula. Material positive for periodic acid-Schiff is interspersed between Bruch's membrane and vessels on choriocapillaris (periodic acid-Schiff, x 215).

The case of North Carolina macular dystrophy reported here most resembles that of AOFPED in that a discrete lesion involves only the central macula. The accumulation of lipofuscin within the retinal pigment epithelium adjacent to the lesion is characteristic of all cases of fundus flavimaculatus and Best's macular dystrophy and at least some cases of AOFPED. Drusen, as well as atrophy and fibrosis of the choriocapillaris, were present in the cases of AOFPED.

The case of North Carolina macular dystrophy presented here represents only one manifestation of a disease with highly variable expressivity. Therefore, additional histopathologic correlations will be needed to more fully understand this disease, and extrapolations from the findings of this single case should be made cautiously. Some

of the cases of AOFPED have been related to a mutation in the peripherin gene. Further genetic studies are needed to identify the genetic abnormalities and pathogenesis of North Carolina macular dystrophy.

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## DISCUSSION

DR W. RICHARD GREEN. Dr Small and coworkers have provided a light microscopic evaluation of an eye of a person with the North Carolina macular dystrophy. Unfortunately, the authors found no clues to the understanding of the pathogenesis of the disorder. Whether or not there is an accumulation of lipofuscin in the RPE is insufficiently documented. Checking for autofluorescence and electron microscopy of the RPE adjacent to the area of atrophy would provide more documentation.

The partial atrophy of the photoreceptor cells at the margin of the area of atrophy where the RPE is relatively intact suggests that the primary defect may be in the photoreceptor cells rather than the RPE.

There is no question that variable scarring has been observed clinically in some cases of North Carolina Macular Dystrophy. In the study presented here, the authors describe the ophthalmoscopic appearance of "macular scars" and the gross appearance of "some scarring" in the central macula. The use of the term scar seems inappropriate in this case as no scarring is evident in the fundus photographs and none was observed histopathologically.

I would like to ask the authors if they attach any pathogenetic significance to the changes in the choriocapillaris that they described.

I would also like to ask Dr Small if he still believes that the North Carolina Macular Dystrophy and Central Areolar Pigment Epithelial Dystrophy are the same as he

noted in the Archives of Ophthalmology, April, 1992. If that dystrophy is the same as central areolar choroidal sclerosis, then there have been numerous previous histopathologic studies - by Ferry, Eagle, Maumenee and Green. Carr observed a progressive intensity of disease in three generations. Ferry observed similar features as noted by Dr Small - loss of RPE and the photoreceptor cell layer and partial atrophy of the photoreceptor cell layer over intact RPE at the margin. Eagle documented the accumulation of lipofuscin by autofluorescence and we did the same by electron microscopy.

The authors do not indicate whether the subject of this study was a member of the pedigree(s) of North Carolina Dystrophy in which Dr Small reported genetic linkage analysis in his AOS thesis in 1998.

And finally, is the North Carolina Macular Dystrophy the same dystrophy reported in a North Carolina pedigree by Lefler, Wadsworth and Sidbury? Those authors, as well as Banks Anderson, observed an associated aminoaciduria. I ask Dr Small to clarify these points.

[Editor's note] DR RALPH C. EAGLE JR. commented that molecular biologic techniques will be required to understand North Carolina Macular Dystrophy. The histopathologic abnormalities in this case are non-specific, end-stage manifestations of macular degeneration.

DR KENT W. SMALL. I would like to thank Dr Green for his insights and for making his thoughts available to me prior to this meeting. This is a sign of a true gentleman and I appreciate his efforts. I will try to address his latter and simpler questions first, followed by attempting to address the more complicated issues.

First, how does this individual and family 1292, that we reported in this histopathologic case, relate genealogically to other published families with similar diseases? This family, 1292, is for all practical purposes a genealogic branch of the main large North Carolina Macular Dystrophy Family #765. Family 1292 had a branch that is from Western North Carolina and did descend from this area. Additionally, the disease associated haplotype on chromosome 6 is identical for families 1292 and 765, meaning North Carolina Macular Dystrophy Family for one in many centiMorgans around the locus. The probability of observing this by chance is smaller than 1 in a billion. Therefore, this individual reported today in this family is part of the same family described by Lefler, Wadsworth and Sidbury and Frank called hereditary macular degeneration and aminoaciduria. The aminoaciduria was subsequently determined to be a red herring and was published by Frank et al as dominant progressive foveal dystrophy. I have been able to document the relationship between these 2 families at the genealogical as well as the

molecular level. I also have extensive data, as shown in my AOS thesis, that the families of central areolar pigment epithelial dystrophy, described by Fetkenhour et al and Leveille et al, are indeed also the same phenotype as North Carolina Macular Dystrophy. From my experiences with North Carolina Macular Dystrophy, I feel strongly that “lumping” of phenotypes is far more appropriate than “splitting.” I would like to emphasize the need to study large numbers of affected individuals and large numbers of families in order to appreciate the full phenotypic variability of a disease. None of these family members, nor any subjects with central areolar pigment epithelial dystrophy, have been previously published histopathologically. The disease that Dr Green mentioned described by Carr, which has a middle age onset and is progressive, is actually described as central areolar choroidal dystrophy by Don Gass. This is a separate disease entity. Therefore, the case presented herein is indeed the very first histopathologic correlation of North Carolina Macular Dystrophy.

Now for the more complex issues, such as the pathogenesis and the significance of the changes in the choriocapillaris. I do not believe it is possible from histopathologic studies to determine if the focal absence of the choriocapillaris, as observed in our case, is the primary cause or a secondary effect from the absence of the retinal pigment epithelium. In my opinion, to attach pathogenic significance to this finding would be speculative at best.

I also agree with Dr Green and Dr Eagle that the term “scar” to describe the lesion in this subject is perhaps not as precise as we would like. There does appear to be “glial replacement” of the photoreceptors in a focal and discrete fashion, and this has been a finding that has been described as a “scar” by others in the past. This lesion in this patient does not appear to represent “confluent drusen” as I once believed, however.

I agree with Dr Green that the significance of the lipofuscin accumulation in the retinal pigment epithelium

outside the macular lesion is unclear. We did demonstrate PAS positive material consistent with lipofuscin. Since graciously receiving Dr Green’s comments, we have performed autofluorescent studies. Dr Glasgow feels that there is more autofluorescence in the posterior pole in our case compared to an age-matched control. The significance of this finding, however, still remains unclear. The retinal pigment epithelium normally autofluoresces and lipofuscin is a pigment found in the normal aging process. Even if there is a pathologic amount of lipofuscin, we still would not understand the pathogenesis of North Carolina Macular Dystrophy. Dr Flannery, one of my coauthors, did not feel that electron microscopy was important because the retinal pigment epithelium appeared normal to him outside the lesion.

For the really difficult issue: the pathogenesis of North Carolina Macular Dystrophy, also called MCDR1. I agree totally with Dr Green that our histopathologic study did not reveal any new clues to MCDR1, but I would not have expected a histopathologic study to reveal the pathogenesis of a genetic disease. We still do not know if MCDR1 is a disease primarily of photoreceptors, retinal pigment epithelium or choriocapillaris. Indeed, histopathologic studies of Stargardt’s disease, fundus flavimaculatus, Best’s disease and adult onset foveal macular pigment epithelial dystrophy were also incapable of precisely identifying which tissue was the site of primary disease and which tissue was secondarily affected. All of these diseases were previously thought to be primarily a retinal pigment epithelial disease until molecular genetic studies demonstrated that some are actually due to mutated proteins in the photoreceptors. Therefore, I maintain that clues to the pathogenesis of MCDR1 will only be discovered once the genetic defect is found. I predict that the gene is involved in the development of the macula since these lesions are congenital and fairly stationary throughout the life of the affected individual.

Again, I would like to thank the Society for this opportunity.

THESES



# THE EFFECT OF TRABECULECTOMY ON OCULAR HEMODYNAMICS\*

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BY Louis B. Cantor, MD

## ABSTRACT

*Purpose:* To evaluate the effects of chronic reduction of intraocular pressure (IOP) on ocular hemodynamics.

*Methods:* Multisite, prospective evaluation of patients requiring trabeculectomy for treatment of glaucoma. Patients were recruited from the glaucoma service of 2 university hospitals. Patients were evaluated prior to surgery and at 3, 6, and 12 months after trabeculectomy. Color Doppler imaging was used to measure blood flow in the ophthalmic artery, central retinal artery, and short posterior ciliary arteries. Heidelberg retinal flowmetry was used to evaluate perfusion in the peripapillary and optic disc capillary beds. IOP was measured at baseline and at each study visit.

*Results:* There were highly significant reductions in IOP from presurgical baseline measures. At 3 months, mean IOP reduction was 17.1 mm Hg (62.3%;  $P < .001$ ). At the 6- and 12-month evaluations, the mean IOP reductions were 15.7 mm Hg (57.3%) and 15.5 mm Hg (56.5%), respectively,  $P < .001$ . Despite the significant reduction in IOP, there were no significant differences in any ocular blood flow parameters before and after trabeculectomy.

*Conclusions:* The findings of this study suggest that chronic reduction of IOP does not alter ocular blood flow and that IOP may be an independent risk factor for progression of glaucoma. These findings also suggest that the eye has the ability to autoregulate to chronically increased IOP over time and that additional studies evaluating the long-term effects of IOP changes are needed to further define this relationship.

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## PURPOSE

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For more than a century, elevated intraocular pressure (IOP) has been associated with increased visual field loss in patients with open angle glaucoma, and current treatment strategies place primary importance on lowering IOP to decrease the rate of optic nerve damage. The etiology of the optic neuropathy has been proposed to involve, at least in part, inadequate blood flow to the optic nerve head.<sup>1-4</sup> However, the relationship between IOP and ocular blood flow has yet to be fully defined. Previous studies examining this relationship have used patients with artificially elevated pressure and have found that acutely increasing IOP results in a significant decrease in ocular blood flow.<sup>5,6,6A</sup> Few data are available as to whether decreasing naturally elevated IOP improves ocular hemodynamics. Furthermore, studies evaluating blood flow parameters before and after filtration surgery have usually included patients receiving topical glaucoma medications at the time of the preoperative assessment, confounding comparisons with postoperative hemodynamic measurements. This investigation evaluates the ocular hemodynamics of naturally elevated IOP in patients with primary open angle glaucoma, as well as the effects of glaucoma filtration surgery, and the lowering of IOP, on ocular hemodynamics.

## HYPOTHESIS

Glaucoma filtration surgery that effectively lowers IOP has no significant long-term effect on ocular hemodynamic parameters; there is no significant difference in ocular hemodynamic parameters measured before and after trabeculectomy.

## INTRODUCTION

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Several risk factors have been associated with the development of glaucomatous optic neuropathy, including elevated IOP,<sup>7,8</sup> advancing age,<sup>9</sup> diabetes mellitus,<sup>10,11</sup> African heritage,<sup>12,13</sup> vascular disease,<sup>9</sup> genetic predisposition, and many others.<sup>14-16</sup> The causes of glaucoma are still largely unknown, and the contribution of vascular factors to the progression of glaucomatous damage has become an active area of investigation in the last decade. Research identifying higher prevalence of compromised autoregulation,<sup>17-19</sup> circulatory disorders,<sup>20-25</sup> and vascular risk factors<sup>20,26-29</sup> in glaucoma patients has suggested that impaired ocular blood flow might cause glaucomatous damage, yet damage to the optic nerve head by increased IOP alone has been documented.<sup>30-32</sup> The role of vascular factors, with or without elevated IOP, is still not clearly understood.

The application of ultrasound technology to the study of vascular tissue in the eye has resulted in a greater understanding of ocular hemodynamics, and color

\*From Indiana University School of Medicine, Indianapolis.

Doppler imaging (CDI) has become an important tool. CDI is an ultrasonic imaging modality that provides a display of blood flow velocity imposed over a conventional gray-scale B-mode ultrasound image.<sup>33</sup> The principle of Doppler ultrasound is well known.<sup>34-37</sup> Determination of the blood flow velocity is derived from the ultrasound frequency shift when it is reflected from moving blood cells. The measured velocities are assumed to correlate with blood flow. In ophthalmology, CDI can be used to measure the blood velocity in the ophthalmic artery, the central retinal artery, and posterior ciliary arteries. However, the instrument provides inadequate resolution to allow for the measurement of the diameter of the orbital vessels, and hence a direct extrapolation from blood velocities to blood flow is not possible.<sup>33</sup>

The reliability and reproducibility of CDI were evaluated by Quaranta and associates.<sup>38</sup> In this study the investigators evaluated the intra-observer reliability of CDI for the measurement of ophthalmic artery blood flow in 35 patients. The results suggest that CDI is a reliable tool for the quantitative assessment of blood flow in the ophthalmic artery with a measurement variance of 5.6% for peak systolic velocity, 11.4% for the end diastolic velocity, and 6.2% for the mean envelope velocity. The test/retest reproducibility of CDI for the other orbital vessels were assessed by Harris and associates.<sup>33b</sup> Coefficients of reliability were 12%, 25%, and 19% for peak systolic velocity, 6%, 11% and 25% for end diastolic velocity and 4%, 11%, and 38% for the resistive index for the ophthalmic artery, central retinal artery, and short posterior ciliary artery respectively. The CDI measures were highly reproducible for the ophthalmic artery, reasonably reproducible for the central retinal artery, and most variable for the short posterior ciliary artery.

Laser Doppler velocimetry is based on the fact that the frequency of laser light scattered by a moving object, such as an erythrocyte, is shifted by an amount proportional to the velocity of the object.<sup>33,37</sup> This technique has been further modified to use multiple scattering angles<sup>39,40</sup> to obtain hemodynamic measurements in the capillary bed of the optic nerve head.<sup>41</sup> This technique, called confocal scanning laser Doppler flowmetry, generates a localized perfusion map of the imaged area with a high resolution. The Heidelberg retina flowmeter (HRF) is an instrument combining the principles of both laser flowmetry and confocal scanning laser Doppler techniques.<sup>33</sup> With use of a scanning laser beam, this method enables high-definition topography of perfused vessels of the optic nerve and retina with simultaneous evaluation of blood flow parameters.<sup>42-44</sup>

Joos and coworkers<sup>45</sup> evaluated the reproducibility of this technology measuring the velocity, blood volume, and blood flow in the optic nerve head during multiple sessions with a non-confocal system. After 3 months of operator experience, the standard deviation of the intrasession variation was 18% of the velocity mean value

and 24% of the flow mean value. The findings suggest that laser Doppler flowmetry, after sufficient operator training, is sufficiently precise to measure human optic nerve head microvascular hemodynamics.

Another study specifically evaluating factors affecting HRF measurements of the retinal and optic nerve head blood flow was conducted by Kagemann and colleagues.<sup>46</sup> In this study the angle of incidence between laser beam and fundus and the camera distance from the eye were evaluated for their possible effect on the measurement of blood velocity, volume, and flow. Both intersession and intrasession variability ratings were calculated, and the images were examined using a pixel-by-pixel histogram of blood flow. Although the ocular hemodynamic measures were unaffected by the angle of incidence between the fundus and the laser beam, the flow measurements showed increasing variability as the camera distance from the eye increased. The coefficient of variation for intersession measures was 7%, but the 4-week intrasession coefficient of variance averaged 30%. In contrast, intersession variability was decreased by using flow histograms of the image with an average value of 16% for total flow and 17% for flow in the pixel of median flow.

Although CDI and HRF are optimally used to measure different ocular hemodynamic parameters, there is a high degree of correlation between the outcome measures. Bohdanecka and associates<sup>33</sup> used both CDI and HRF technology to determine the relationship between blood flow velocities in retrobulbar vessels and blood flow at the optic nerve in glaucoma patients. Correlations between HRF recordings in the optic nerve head and CDI measurements in the ophthalmic artery, the central retinal artery, and the posterior ciliary arteries in the same patients were evaluated. All 3 HRF parameters correlated with CDI measurements obtained from the retrobulbar vessels, with the most significant correlations being between the HRF volume and the end diastolic velocity (EDV) in the ophthalmic and the medial posterior ciliary arteries, and the peak systolic velocity (PSV) in the lateral ciliary artery. The investigators also concluded that glaucoma patients with altered blood flow in retrobulbar vessels are likely to show an alteration in optic nerve blood flow as measured with the HRF.

Doppler ultrasound was utilized in a separate study conducted by Rojanapongpun and associates<sup>32</sup> that evaluated the velocity of ophthalmic artery blood flow in patients with chronic open-angle glaucoma and normal-tension glaucoma (NTG), compared with normal controls. The researchers reported that peak flow velocity, mean velocity, and diastolic velocity were all reduced in the patients with either NTG or chronic primary open-angle glaucoma (POAG), compared with the normal controls. The patients with NTG also had significantly slower mean flow velocities than those with chronic open-angle glaucoma.

A similar study by Rankin and associates<sup>47</sup> also found

that both POAG and NTG patients had significantly reduced blood flow velocities compared with normal controls. In this study patients with chronic open-angle glaucoma showed a statistically significant decrease in mean diastolic velocity and an increase in the mean resistance index (RI) in the central retinal artery and the short posterior ciliary arteries. The resistance index was calculated as  $(RI = [PSV - EDV] / PSV)$ . Patients with NTG showed similar changes, most notably in the central retinal arteries, compared with normal subjects. However, unlike in the previous study,<sup>32</sup> there were no statistically significant differences in any measure of ocular blood flow between the patients with chronic open-angle glaucoma and those with NTG. Harris and associates<sup>32B</sup> found similar results, and that vasodilator therapy, by increasing  $P_{CO_2}$ , reversed the increased vascular resistance.

A study by Duijm and associates<sup>48</sup> evaluated the retinal and choroidal hemodynamics in normal control subjects and patients with ocular hypertension, POAG, and NTG. Contrary to the reports of Rojanapongpun<sup>32</sup> and Rankin,<sup>47</sup> the retinal arteriovenous velocity was significantly slower in patients with POAG, but not in patients with NTG, compared with normal controls. The researchers concluded that the choroidal and retinal vascular systems behave differently in POAG and NTG and that these differences may be important in the management of glaucoma. However, the conflicting findings in these studies illustrate the complexity of the relationship between IOP and ocular hemodynamics.

#### **OCULAR BLOOD FLOW IN UNTREATED GLAUCOMA**

Because most studies of ocular hemodynamics involve glaucoma patients using ocular hypotensive agents, it is difficult to determine if these agents have a confounding effect on the blood flow parameters measured. Several studies in recent years have used color Doppler imaging to study blood flow in untreated patients. One such study<sup>49</sup> evaluated untreated patients with POAG or NTG, compared with a group of normal controls, and found that the EDV in the central retinal artery was significantly lower in patients with POAG than in normal subjects. Patients with POAG had significantly greater ophthalmic artery PSVs than patients with NTG or normal subjects. The resistance indices of both the ophthalmic and central retinal arteries were significantly greater in patients with POAG than in normal subjects, and the central retinal artery RI was significantly greater in NTG patients than normal subjects. The investigators concluded that there was an increased resistance to blood flow in the central retinal artery of untreated POAG and NTG patients and also in the ophthalmic artery of patients with POAG. In addition, the ophthalmic artery peak systolic velocity was elevated in untreated POAG patients.

A later study<sup>50</sup> supported the conclusion that there is a definite pattern of altered ocular circulation in patients

with glaucoma. There was a significant reduction in choroidal and short posterior ciliary artery circulation in untreated POAG patients compared with ocular hypertensive patients. Moreover, these patients were matched for age and IOP, thus removing 2 demonstrated confounding factors<sup>51-54</sup> in an attempt to identify any IOP-independent changes in blood flow in POAG patients. Interestingly, even after controlling for factors known to affect perfusion pressure, the investigators found evidence of reduced ocular blood flow in POAG compared with ocular hypertension. Laser Doppler flowmetry results showed a significant reduction in blood velocity, volume, and flow at the lamina cribrosa and the temporal neuroretinal rim in POAG compared with ocular hypertension. The ocular pulse amplitude, pulsatile ocular blood flow, and pulse volume were significantly lower in the POAG group compared with the ocular hypertension group.

#### **THE ROLE OF VASOSPASM AND AUTOREGULATION IN THE PATHOPHYSIOLOGY OF THE GLAUCOMAS**

The hypothesis that vasospasm is involved in the pathogenesis of glaucoma is supported by many recent studies. O'Brien and Butt<sup>24</sup> reported that patients with NTG had significantly reduced finger blood flow after immersion in cold water, compared with patients with untreated POAG and normal controls, as well as significantly longer recovery time to pre-immersion flow. Moreover, the POAG patients also had a significantly prolonged recovery time, relative to normal controls. Other studies have reported an increased incidence of migraine in patients with NTG<sup>29,55</sup> and an association between NTG and an increased incidence of vasospasm,<sup>56</sup> significantly reduced blood flow in the fingers,<sup>57</sup> and a pathologic blood cell velocity.<sup>58</sup>

Faulty autoregulation of blood flow may also be characteristic of circulatory irregularity in patients with glaucoma. Evans and associates<sup>19</sup> compared measures of retrobulbar hemodynamics in patients during postural change. When changing from the upright to the supine position, both glaucomatous patients and normal controls demonstrated significant increases in ophthalmic artery EDV and significant decreases in ophthalmic artery RI. Normal subjects also showed a significant decrease in central retinal artery RI, but glaucoma patients did not. The investigators concluded that these findings indicate that posture change exposes a vascular autoregulatory deficit in glaucoma patients, with the most prominent deficit in the vessels distal to the central retinal artery.

The possibility of an autoregulatory deficit in glaucoma patients is also supported by a large community-based screening of 5,308 individuals over the age of 40.9. In this survey, POAG was defined by demonstrable ocular nerve damage, without consideration of IOP. In this study, systolic and diastolic blood pressures were positively related to

POAG, and this relationship was modified by age, with a stronger association found among older subjects. Lower perfusion pressure was also strongly associated with an increased prevalence of POAG. The investigators concluded that these findings suggest that POAG is associated with a breakdown of autoregulation and alterations in factors related to ocular blood flow.

#### **INTRAOCULAR PRESSURE AND OCULAR HEMODYNAMICS**

Abnormally elevated IOP has long been associated with the progression of glaucomatous damage. However, the relationship between IOP and blood flow velocities in the ocular vessels has yet to be clearly defined. Michelson and Harazny<sup>50</sup> attempted to quantify the relationship between ocular pulse pressures and retinal vessel velocities using pulsed Doppler sonography. The relationship between the pulse-curves of the blood velocity in the ophthalmic artery, the central retinal vein and artery, and the IOP in 23 eyes of healthy subjects was evaluated. In all eyes, the researchers found a significant linear relationship between the blood velocity in the central retinal vein and IOP.

The effect of moderate changes in IOP on ocular hemodynamics was further evaluated by Findl and colleagues.<sup>5</sup> In this study, elevations in IOP of 10 mm Hg and 20 mm Hg were induced by a suction cup in 10 healthy patients. Blood flow velocities in the central retinal artery and in the ophthalmic artery were measured by Doppler sonography, while ocular fundus pulsations in the macula and the optic disc were measured by laser interferometry. The investigators reported that as IOP was artificially increased, blood flow velocity in the central retinal artery was reduced with both 10 mm Hg and 20 mm Hg elevations in IOP. The RI in the central retinal artery was significantly increased at both 10 mm Hg and 20 mm Hg. An increase in IOP was also found to correlate with significant reductions in fundus pulsations, which were more pronounced in the macula. In contrast, increasing IOP did not affect blood flow parameters in the ophthalmic artery.

A later study evaluated the autoregulatory capacity of the ciliary arteries in response to acutely elevated IOP.<sup>6</sup> In this study, color Doppler imaging was performed on the short posterior ciliary arteries of 10 normal subjects at baseline and at incrementally increasing IOP. With use of a scleral suction cup, IOP was elevated to 25, 30, 40, and 50 mm Hg. Systolic and diastolic flow velocities were measured and resistivity indexes were calculated. The investigators reported that both systolic and diastolic flow velocities significantly decreased linearly with each incremental increase in IOP, while the RI increased linearly with each incremental increase in IOP. On the basis of these results, they concluded that the normal healthy eye is unable to autoregulate blood flow velocities in response to sharp elevations in IOP.

Although the previously mentioned studies clearly demonstrate a linear relationship between IOP and changes in ocular blood flow, the subjects were all normal. This selection of normal subjects may limit the applicability of their findings to patients with glaucoma. One of the few studies to use patients with glaucoma in an evaluation of the effects of acute IOP elevations was conducted by Quaranta and colleagues in 1994.<sup>7</sup> This study, using patients with NTG and normal controls, found that although there were significant decreases in pulsatile ocular blood flow in both groups with IOP elevations of either 5 or 10 mm Hg, the decrease was significantly greater in the patients with NTG. The researchers concluded that these findings indicate an altered response of the vascular system with NTG, perhaps due to faulty myogenic autoregulation in reply to increased perfusion pressure.

Although the previous studies all describe the effect of elevated IOP on ocular hemodynamics, it is important to note that numerous studies report altered ocular blood flow in patients with low-tension glaucoma and NTG.<sup>32, 48-49</sup> Moreover, glaucomatous optic nerve damage and visual field loss can occur at any level of IOP.<sup>8, 60</sup>

#### **THE EFFECT OF OCULAR HYPOTENSIVE AGENTS ON OCULAR HEMODYNAMICS**

In recent years, numerous studies have illustrated the effects of a wide range of ocular hypotensive agents on ocular blood flow. Turacli and coworkers<sup>61</sup> investigated the effect of betaxolol, a beta-1-selective adrenoceptor antagonist, on ocular blood flow and visual function in patients with NTG (n = 36 eyes). After 1 year of treatment with 0.5% betaxolol hydrochloride, the resistivity of the ophthalmic artery was significantly reduced and visual fields were significantly improved. The RIs in the central retinal artery and posterior ciliary artery were also improved but not to a statistically significant extent. These findings seem to indicate that ocular hemodynamics and visual function may be improved by long-term use of betaxolol in patients with NTG.

However, these findings were contradicted by a later study by Harris and colleagues.<sup>62</sup> This study examined whether or not dosages of betaxolol and dorzolamide sufficient to lower IOP significantly in NTG patients (n = 9) had a comparable or a dissimilar impact on the retinal and retrobulbar circulation. In this open-label, 4-week, crossover study, both betaxolol and dorzolamide significantly lowered IOP, but only dorzolamide significantly accelerated arteriovenous passage of fluorescein dye in the inferior temporal quadrant of the retina, as measured by scanning laser ophthalmoscopy. Neither drug affected arteriovenous passage in the superotemporal retina or the central retinal or ophthalmic artery flow velocity (as measured by CDI) in this short-term study, suggesting

that any effects of betaxolol on ocular blood flow are seen only after long-term use in patients with NTG.

These findings would seem to conflict with those of Arend and associates,<sup>63</sup> who evaluated the effect of topical beta-adrenoreceptor blocking agents on circulation in the retina and optic nerve head. In this study, betaxolol, levobunolol, and timolol were each given to 12 subjects on separate occasions at least 2 weeks apart. Macular capillary blood velocity, epipapillary blood velocities, arteriovenous passage times, and arterial and venous diameters were measured by digital image analysis of scanning laser fluorescein angiograms before the drugs were instilled and 2 hours later. All 3 drugs, despite their differing beta-adrenergic properties, increased blood velocities in the epipapillary and retinal capillaries, while decreasing arteriovenous passage time by approximately 25%. There were no changes in arterial and venous diameters as measured by digital image analysis scanning laser fluorescein angiograms. The investigators concluded that the increased blood velocities in retinal and epipapillary capillaries, in concert with decreased retinal arteriovenous passage time, with constant retinal arterial and venous diameters, may indicate improved retinal perfusion after drug treatment. It is important to note that healthy, nonglaucomatous patients were used in this study, whereas the evaluation by Harris and colleagues, reporting that short-term use of betaxolol did not affect retinal hemodynamics, used patients with NTG. This disparity of results may highlight the confounding nature of extrapolating findings in normal controls to patients with glaucoma.

The impact of dorzolamide on ocular pulse amplitude in POAG patients was evaluated by Schmidt and coworkers,<sup>64</sup> who reported that there were significant reductions in both IOP and ocular pulse amplitude after treatment with dorzolamide for 2 days compared with baseline measures.

Interestingly, prescription medications are not the only substances found to alter ocular blood flow. A recent Phase I clinical trial<sup>65</sup> reported that ginkgo biloba extract, 40 mg taken orally 3 times daily for 2 days, significantly increased end diastolic velocity in the ophthalmic artery when compared with placebo-treated baseline in 11 healthy volunteers. No side effects were reported, and IOP was not altered.

Although numerous ocular hypotensive agents have been found to affect ocular hemodynamics in both healthy persons and glaucoma patients, a causal relationship between decreased IOP and improved ocular blood flow has not been proved. In fact, ocular blood flow appears to be unaffected by brimonidine tartrate, which is comparable to timolol in ocular hypotensive efficacy.<sup>66,67</sup> Lachkar and associates<sup>68</sup> found that hemodynamics in the posterior segment of the eye, as measured by color Doppler ultrasound, were not altered by short-term brimonidine therapy.

Although IOP was significantly reduced by a mean 17.7%, velocities and resistivity indices in the ophthalmic artery, central retinal artery, nasal artery, and temporal ciliary arteries showed no statistically significant differences between brimonidine 0.2% and placebo, nor were there any significant changes from baseline. These findings were supported by a later study,<sup>69</sup> which also found no significant changes in retinal capillary blood flow in ocular hypertensive subjects treated with brimonidine, despite a 16.2% to 17.9% reduction in IOP.

#### **TRABECULECTOMY AND OCULAR HEMODYNAMICS**

Trabeculectomy is commonly performed in patients with chronic open-angle glaucoma, since it appears to be the best surgical method for preservation of the visual field.<sup>70</sup> The effect of trabeculectomy, with its corresponding decrease in IOP, on ocular hemodynamics has only begun to be studied. One of the few studies evaluating this relationship used CDI in a prospective population of 20 patients about to undergo trabeculectomy.<sup>71</sup> Patients were evaluated before surgery and then at 2-, 5-, and 14-week intervals after surgery. At nearly all postoperative evaluations, there were statistically significant increases in the mean and end diastolic velocity and a significant reduction in the vascular resistance of the central retinal artery and both short posterior ciliary arteries. Although the velocity increased in the ophthalmic artery at all time points, only one of 3 postoperative intervals for mean velocity and 2 of the 3 intervals for EDV were statistically significant. There were no significant changes in resistance. The investigators concluded that these findings were consistent with increased blood flow through the central retinal artery and short posterior ciliary arteries with the reduction in IOP after trabeculectomy.

In contrast, James<sup>72</sup> reported finding no significant change in pulsatile ocular blood flow, as measured in patients in a reclined position, despite a significant reduction in IOP following surgery. However, when ocular blood flow was evaluated with patients in a standing position, there were significant increases in pulsatile ocular blood flow at 3 and 6 months after trabeculectomy. James hypothesized that these findings may reflect a return to more normal autoregulatory ability in patients who have undergone a dramatic reduction in IOP. It is important to note that the patients in this study, as well as in the previous report, were using a variety of topical ocular hypotensive medications at the time of surgery. As previously summarized, certain antiglaucoma medications may influence ocular hemodynamics and thus may have a confounding effect on the postsurgical evaluation.

The purpose of the present investigation is to evaluate the ocular hemodynamics of naturally elevated IOP in patients with primary open-angle glaucoma as well as the

effects of glaucoma filtration surgery and the lowering of IOP on ocular hemodynamics.

## METHODS

### PATIENTS

Seventeen patients (19 eyes) with POAG who were assessed to have IOP too high for their degree of optic nerve cupping and visual field loss were recruited from the glaucoma services of 2 hospitals for trabeculectomy surgery. Included patients had POAG, NTG, or pigmentary or pseudoexfoliative glaucoma with IOPs of 32 mm Hg or less with their current medical therapy. Patients using topical or oral antiglaucoma medications were washed out using the following schedule: topical beta blockers and latanoprost, 4 weeks; brimonidine or other alpha adrenergics, 2 weeks; topical miotics, 2 weeks; oral or topical carbonic anhydrase inhibitors, 1 week. Patients were excluded if they had either primary or secondary angle-closure glaucoma, a cup-to-disc ratio greater than 0.9, split fixation on recent visual fields, a visual field defect approaching the central 5 degrees of fixation, previous intraocular surgery on the study eye, or a history of orbital or ocular trauma, or if any alterations in ongoing systemic vasoactive medication regimens were anticipated.

All patients signed an informed consent statement outlining the risks of washout from antiglaucoma medication and blood flow measurement that had been reviewed and approved by the University Institutional Review Board.

### PROCEDURES

Prior to surgery, all patients underwent a comprehensive examination. A thorough ocular examination was conducted that included visual acuity, biomicroscopy, and funduscopy. IOP, using Goldmann applanation tonometry, was also measured. Blood pressure was measured with a standard sphygmomanometer, and heart rate was measured by taking the pulse at the radial artery with patients in a seated position.

Hemodynamics in the ophthalmic artery, short posterior ciliary arteries, and central retinal artery were evaluated by using color Doppler imaging. Each patient was seated in a reclined position and asked to relax. A sterile, ophthalmic methylcellulose gel was then applied to the closed eyelid to act as a coupling agent for the ultrasound transducer. Ultrasound waves of known frequency were then sent out from the transducer (Quantum 2000, 7.5-MHz linear array transducer). The returning reflected waves were analyzed for frequency shifts, and these frequency shifts were then extrapolated into a range of colors and shades on a video screen. These colors and shades correspond to direction and velocity, respectively. From these data, 3 measurements were obtained: the peak systolic

velocity, the end diastolic velocity, and the resistance index.

The Heidelberg retina flowmeter (Heidelberg Engineering, Heidelberg, Germany), based on scanning Doppler flowmetry, was used to measure perfusion within peripapillary and optic disc capillary beds. The HRF utilized a low-intensity infrared laser beam to scan the fundus. Moving red blood cells striking the beam caused a portion of the light to be Doppler shifted. Shifts within the reflected light were analyzed to determine the blood velocities present within the scanned tissue. Using the amplitude of the Doppler shifts, the volume of moving blood was determined. The data regarding velocity and volume were then combined to compute total blood flow, and a physical map of flow volumes contained in the retina was created. Interpretation of these flow maps was done using an original, previously described HRF measurement method by Kagemann, Harris, and coworkers.<sup>46</sup> All measurement points of sufficient image quality were displayed by histogram, and cumulative percentage landmarks were used to describe the shape of the flow distribution within the retina. This technique also allows for discrimination of perfused and avascular tissue, producing measurements of the degree of vascularity of the fundus.

Each patient then underwent a trabeculectomy utilizing current trabeculectomy techniques. For all procedures, a limbus-based conjunctival and Tenon's flap was dissected superiorly. In most cases, mitomycin-C was given at a concentration of 0.2 mg/cc for 2 minutes beneath the conjunctival and Tenon's flaps. When mitomycin-C was used, the surgical site was subsequently irrigated generously with balanced salt solution. An approximately 3 x 3 mm rectangular scleral trabeculectomy flap was fashioned and dissected anteriorly into clear cornea. Hemostasis was achieved with wet-field cautery. A paracentesis was performed through clear cornea. The trabeculectomy block was excised utilizing a combination of a blade and scissors. A peripheral iridectomy was performed. The scleral flap was sutured into position with 2 10-0 nylon sutures posteriorly, with placement of additional sutures as necessary to control the egress of aqueous. The conjunctival and Tenon's flaps were closed in a two-layered fashion with running Vicryl suture on a vascular needle. The anterior chamber was re-formed with a combination of balanced salt solution and viscoelastic as needed. If the anterior chamber remained formed with no visible leaking from the bleb, the procedure was concluded, and a combination antibiotic-steroid ointment and patch were applied to the eye. Postoperative medications dispensed included a topical corticosteroid, antibiotics, and cycloplegics as indicated.

In addition to having routine postoperative evaluations, each patient returned for a comprehensive examination at month 1 and months 3, 6, and 12. All procedures

followed at the preoperative examination and described above were repeated for each of these evaluations. Eyes were excluded from follow-up if any subsequent ocular surgery, such as cataract surgery, was required.

**STATISTICAL ANALYSIS**

Student's *t* tests were used to evaluate all IOP, heart rate, blood pressure, color Doppler imaging, and Heidelberg flowmetry data. Bonferroni's correction was applied for multiple *t* tests from the same data set. The target sample size of 15 eyes would provide 90% power to detect a difference of 10%. The a priori alpha level was .05 for all tests.

**RESULTS**

Of the enrolled patients, 58.8% (10/17) were female, 88.2% (15/17) were white, and 76.5% (13/17) had a diagnosis of POAG. The mean age of the study population was 62.1 years (+ SD, 13.4; range, 41-85). The most commonly used systemic medications were Glucophage (3/17; 17.6%), Glucotrol (2/17; 11.8%), Synthroid (2/17; 11.8%), estrogens (2/17, 11.8%), and albuterol (2/17; 11.8%; Table I). During the study, 94.1% of patients (16/17) either had

TABLE I: PATIENT DEMOGRAPHICS

	N	%
<b>Sex</b>		
Male	7	41.2
Female	10	58.8
<b>Race</b>		
White	15	88.2
African American	2	11.8
<b>Diagnosis</b>		
POAG	13	76.5
NTG	1	5.9
Narrow angle	1	5.9
Fuch's eye	1	5.9
Pseudoexfoliative	1	5.9
<b>Comorbid conditions</b>		
Hypertension	9	52.9
Diabetes	5	29.4
Asthma	2	11.8
Migraine	2	11.8
Hypothyroidism	2	11.8
Congestive heart failure	1	5.9
Atrial fibrillation	1	5.9
Arrhythmia	1	5.9
<b>Systemic medications</b>		
Glucophage	3	17.6
Glucotrol	2	11.8
Synthroid	2	11.8
Albuterol	2	11.8
Estrogen	2	11.8
Cardura	1	5.9
Coumadin	1	5.9
Procardia	1	5.9
Verapamil	1	5.9

no alterations in their ongoing vasoactive medication regimens or did not use vasoactive medications. One patient underwent cardiac bypass surgery 5 months after trabeculectomy and discontinued vasoactive medication.

As expected, there were highly significant reductions in IOP from presurgical baseline measures in the surgical eyes. At 3 months, there was a mean IOP reduction of 17.1 mm Hg (62.3%;  $P < .001$ ). At the 6- and 12-month evaluations, the mean IOP reductions were 15.7 mm Hg (57.3%) and 15.5 mm Hg (56.5%), respectively ( $P < .001$ ). Interestingly, there were also small reductions in IOP in the fellow eyes, but these reductions were not statistically significant ( $P \geq .139$ ; Fig 1). There were no significant changes in heart rate or blood pressure from baseline measures at any study visit.

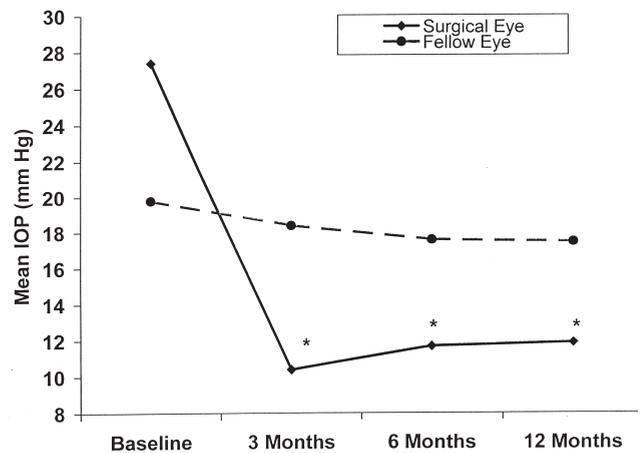


FIGURE I

Mean reduction in IOP from baseline in surgical and fellow eyes following trabeculectomy. Mean IOP reductions in surgical eyes were significant at each study visit ( $P < .001$ ) (indicated by asterisks). Mean IOP reductions from baseline in fellow eyes were not statistically significant at any follow-up visit ( $P > .139$ ).

Despite the significant decrease in IOP following trabeculectomy, there were no significant changes in the peak systolic velocity, end diastolic velocity, or resistive index in the ophthalmic artery (Table II). The PSV, EDV, and RI in the central retinal artery also remained unchanged from pretrabeculectomy measures at all study visits (Table III). There were no significant changes in any parameters in the fellow eyes at any follow-up visit.

There were also no significant changes in hemodynamic measures in the nasal and temporal posterior ciliary arteries following trabeculectomy (Tables IV and V, respectively). There were no statistically significant changes in PSV, EDV, or RI in either vessel in either the surgical or fellow eyes.

There were also no significant changes in blood flow in the peripapillary or optic disc capillary beds, as measured by HRF (Table VI).

**TABLE II: BLOOD FLOW IN THE OPHTHALMIC ARTERY AT PRESURGERY BASELINE AND AT EACH STUDY VISIT WITH *P* VALUES FOR CHANGE FROM BASELINE**

	PEAK SYSTOLIC VELOCITY			END DIASTOLIC VELOCITY			RESISTIVE INDEX		
	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>
Baseline	30.74 (13.04)	19		7.82 (3.12)	19		.73 (0.06)	19	
Month 3	31.13 (10.22)	15	.924	8.17 (2.48)	15	.724	.73 (0.04)	15	.980
Month 6	28.22 (10.05)	15	.541	7.44 (2.94)	15	.725	.73 (0.07)	15	.831
Month 12	27.72 (7.0)	11	.485	6.96 (2.15)	11	.429	.75 (0.06)	11	.642

**TABLE III: BLOOD FLOW IN THE CENTRAL RETINAL ARTERY AT PRESURGERY BASELINE AND EACH STUDY VISIT WITH *P* VALUES FOR CHANGE FROM BASELINE**

	PEAK SYSTOLIC VELOCITY			END DIASTOLIC VELOCITY			RESISTIVE INDEX		
	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>
Baseline	6.50 (2.12)	19		1.41 (0.49)	19		.76 (0.10)	19	
Month 3	7.21 (2.21)	15	.35	1.66 (0.63)	15	.212	.77 (0.05)	15	.841
Month 6	7.05 (1.58)	15	.411	1.87 (0.74)	15	.098	.74 (0.07)	15	.403
Month 12	7.10 (1.47)	11	.418	1.74 (0.38)	11	.152	.75 (0.03)	11	.830

**TABLE IV: BLOOD FLOW IN THE NASAL POSTERIOR CILIARY ARTERIES AT PRESURGERY BASELINE AT EACH STUDY VISIT WITH *P* VALUES FOR CHANGE FROM BASELINE**

	PEAK SYSTOLIC VELOCITY			END DIASTOLIC VELOCITY			RESISTIVE INDEX		
	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>
Baseline	6.91 (2.16)	16		1.59 (0.36)	16		.75 (0.10)	16	
Month 3	7.72 (5.10)	14	.568	2.32 (1.69)	14	.133	.70 (0.08)	14	.109
Month 6	5.82 (1.83)	13	.158	1.93 (1.03)	13	.319	.64 (0.22)	13	.088
Month 12	6.45 (1.68)	8	.607	1.59 (0.26)	8	.991	.74 (0.80)	8	.763

**TABLE V: BLOOD FLOW IN THE CENTRAL RETINAL ARTERIES AT PRESURGERY BASELINE AND EACH STUDY VISIT WITH *P* VALUES FOR CHANGES FROM BASELINE**

	PEAK SYSTOLIC VELOCITY			END DIASTOLIC VELOCITY			RESISTIVE INDEX		
	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>	MEAN (SD)	N	<i>P</i>
Baseline	6.64 (2.26)	16		2.08 (1.45)	16		.686 (0.16)	16	
Month 3	6.56 (2.26)	8	.940	2.13 (.80)	8	.919	.62 (0.27)	8	.200
Month 6	6.82 (2.13)	10	.834	2.23 (1.36)	10	.787	.70 (0.09)	10	.995
Month 12	5.52 (1.58)	7	.250	1.71 (.40)	7	.522	.63 (0.28)	7	.256

**TABLE VI: HEIDELBERG RETINAL FLOWMETRY DATA WITH *P* VALUES FOR CHANGES FROM BASELINE**

	COUNT	10%		25%		50%		75%		90%	
		MEAN	<i>P</i>	MEAN	<i>P</i>	MEAN	<i>P</i>	MEAN	<i>P</i>	MEAN	<i>P</i>
Baseline	45	95.39		224.47		440.96		709.95		1012.65	
Month 3	34	100.60	.589	238.22	.520	461.70	.613	742.63	.618	1049.27	.671
Month 6	26	100.88	.580	235.63	.62	458.85	.669	760.47	.461	1077.31	.491
Month 12	18	107.28	.472	226.04	.96	428.24	.821	673.59	.658	946.72	.525

## DISCUSSION

For more than a century, elevated IOP has been considered to be the primary cause of visual loss in patients with open-angle glaucoma. Current treatments focus overwhelmingly on lowering IOP in glaucomatous patients, preferably below 20 mm Hg.<sup>73</sup> While a reduction in IOP is clearly beneficial for the preservation of the visual field, the progression of visual field loss and glaucomatous optic nerve damage has been well documented in the absence of abnormally elevated IOP.<sup>8,59,74</sup> Vascular factors have long been considered in the etiology of glaucoma, with the central thesis being that faulty autoregulation or inappropriate vasospasm or vasoconstriction causes inadequate perfusion of the optic nerve head and or retina, resulting in tissue death and visual field loss.<sup>75-77</sup>

The findings of the present study illustrate that although ocular hemodynamics may be influenced by elevated IOP, dramatic chronic decreases in IOP produced by trabeculectomy in untreated eyes do not lead to improved ocular blood flow as measured by the techniques utilized in this study. This result contrasts sharply with those of several recent studies that reported a direct relationship between changes in IOP and altered ocular hemodynamics. By using a suction cup, Findl and Strenn<sup>5</sup> increased IOP by 10 and 20 mm Hg in normal subjects. In that study, a 20 mm Hg increase in IOP caused a significant reduction in the mean flow velocity in the central retinal artery. Moreover, the RI in the central retinal artery increased significantly, with IOP elevation of just 10 mm Hg. In the present study, there were mean reductions in IOP of 15.5 to 17.1 mm Hg, with no significant change in ocular blood flow in the central retinal artery. Hemodynamics in the ophthalmic artery remained unchanged in both studies, despite significant reductions in IOP.

Acute changes in IOP have also been found to alter ocular blood flow in the posterior ciliary arteries. Joos and associates<sup>6</sup> reported that artificially elevating IOP to 25, 30, 40, and 50 mm Hg reduced blood flow, clearly demonstrating that there is an inverse linear relationship between IOP and blood flow in these vessels. In contrast, the results of the present study suggest that the movement of blood in the posterior ciliary arteries is not dependent on chronic reductions of IOP.

There are several possible explanations for the findings in the present study, compared with previously published works. First, the previously cited studies using scleral suction cups to induce artificially acute IOP elevations were all in normal subjects, with normal baseline IOPs. For instance, in the study by Joos and associates,<sup>6</sup> the mean baseline IOP was 15 (+5) mm Hg. In contrast, the mean baseline IOP of subjects in the current study was

27.4 (+6.5) mm Hg. Additionally, the single study that used patients with glaucoma to evaluate the effect of acute pressure change on ocular blood flow enrolled only patients with NTG, thus limiting the applicability of the findings to patients with NTG or POAG.<sup>7</sup> The extrapolation of findings in a small number of normal subjects to a larger population of patients with glaucoma may be limited by the exclusion in each of these studies of normals with comorbid conditions prevalent in glaucoma patients, such as diabetes and hypertension.

Interestingly, there was also a significant mean reduction in IOP in the fellow eye of patients following trabeculectomy. Though not statistically significant, this reduction may be due to an increase in compliance to previously prescribed treatment regimens of ocular hypotensive agents in the nonsurgical eye following surgery.

The findings of the present study are contrary to those reported by Tribble and colleagues,<sup>71</sup> who found that trabeculectomy resulted in significant improvements in blood velocity in the central retinal artery and short posterior ciliary arteries, but are similar to the findings of James,<sup>72</sup> who reported that trabeculectomy failed to produce significant improvements in pulsatile ocular blood flow when evaluated in a reclined position. It may be important to note that patients in the previous studies were using ocular hypotensive medications at the time of surgery, and thus the effect on ocular blood flow of these medications may have acted as a confounding influence. In contrast, the present study had only patients who were not using ocular hypotensive medications at the time of surgery owing to the inability to tolerate the medications, lack of efficacy, or completion of an appropriate washout period prior to surgery.

Numerous studies have documented that reducing IOP does not necessarily halt the progression of visual field loss in glaucoma patients, although greater IOP reductions have been associated with a reduced risk of visual field deterioration. The extent to which IOP must be lowered to reduce the risk of visual field loss is unclear. Recent research that evaluated the correlation between interocular difference in the progression of glaucomatous damage and interocular differences in the retrobulbar blood flow found that interocular differences in the progression of visual field damage were not related to IOP.<sup>78</sup> Moreover, eyes with more marked damage had lower mean blood flow velocities in the ophthalmic artery, higher RIs in the central retinal artery, and higher PSV in the ophthalmic artery. However, it may be important to note that these patients were also taking a variety of ocular hypotensive medications and that the possible effect of these medications on the preservation of the visual field was not taken into consideration. In addition, it has been reported that glaucoma patients with progressive visual

field loss show altered hemodynamics in the short posterior ciliary arteries and the central retinal artery, especially in the absence of increased ocular pressure,<sup>79</sup> and that patients with low-tension glaucoma exhibit significantly lower pulsatile ocular blood flow than normal controls.

Although numerous studies have evaluated the effect of acute IOP changes on ocular hemodynamics, the effects of chronically elevated pressures are still unclear. The results of the present study, in which IOP was reduced chronically without any significant changes in ocular hemodynamics, suggest either that chronically elevated IOP has no effect on reducing blood flow or that any pressure-induced changes are irreversible when the IOP is reduced. Although the latter hypothesis is not currently supported by published reports, there is some evidence that the eye may autoregulate in response to changes in IOP within a certain range. Pillunat and associates<sup>80</sup> in normal eyes measured the average velocity, the number of moving erythrocytes, and the volume of flow in the capillary bed of the optic disc at spontaneous levels of IOP and at pressures artificially elevated to 25, 35, 45, and 55 mm Hg. Of the 10 patients evaluated, 7 maintained their baseline blood flow across the lower range of IOP but showed a reduction in flow at both 45 and 55 mm Hg. In contrast, 2 subjects exhibited a linear decline in blood flow with even slight elevation in IOP. These 2 subjects were reevaluated on 6 additional occasions and consistently exhibited the same lack of autoregulation. However, autoregulation was evident at other locations on the discs of these individuals. The investigators concluded that their findings supported the theory that in most individuals, the optic nerve head is able to maintain a constant blood flow over a range of elevated IOP.

The elimination of the possible confounding effects of ocular hypotensive agents in this study may have influenced the observed lack of significant change in ocular blood flow parameters following chronic reduction of IOP. Although numerous studies have found that ocular hypotensive medications alter ocular hemodynamics, it is not possible to determine if the changes in ocular blood flow are due to a vascular effect of the drug or to the acute reduction in IOP. Moreover, if the eye autoregulates over a period of time, it is possible that even the drug effects on ocular blood flow that are often seen with chronic therapy are true vascular effects of the drug and not necessarily related to decreases in IOP.

## SUMMARY

The findings of this study suggest that chronically decreasing IOP alone may not improve ocular hemodynamics in glaucoma patients, suggesting that IOP is a risk factor for optic nerve head damage independent of the effects of

elevated IOP on ocular blood flow. Moreover, although the evaluation of the effect of acute changes in IOP on ocular hemodynamics may provide some insight into the mechanisms of the pathology, it is possible that the eye may have the ability to manifest changes chronically that may not be evident from short-term studies. As glaucoma is a long-term disease, the contribution of IOP, ocular hemodynamics, or other variables that contribute to either visual field stability or progression of glaucoma may best be understood by considering their chronic influence throughout the course of the disease.

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# DEVELOPMENT OF A QUANTITATIVE METHOD TO MEASURE VISION IN CHILDREN WITH CHRONIC CORTICAL VISUAL IMPAIRMENT\*

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BY William V. Good, MD

## ABSTRACT

*Purpose:* Cortical visual impairment (CVI) is the most common cause of bilateral vision impairment in children in Western countries. Better quantitative tools for measuring vision are needed to assess these children, to allow measurement of their visual deficit, and to monitor their response to treatment and rehabilitation. The author performed a series of experiments to assess the use of the sweep visual evoked potential (VEP) as a quantitative tool for measuring vision in CVI.

*Methods:* The first experiment was a reliability measure (test/retest) of VEP grating acuity thresholds of 23 children with CVI. To validate the VEP procedure, VEP grating acuity was compared to a clinical measure of vision, the Huo scale, and to a psychophysical measure of vision, the Teller Acuity Card procedure. Finally, the sweep VEP was tested as a tool for defining optimal luminance conditions for grating acuity in 13 children with CVI, by measuring grating thresholds under 2 different luminance conditions: 50 and 100 candela per square meter ( $\text{cd/m}^2$ ).

*Results:* Retest thresholds were similar to original thresholds ( $r^2 = 0.662$ ;  $P = .003$ , 1-tailed  $t$  test). Grating VEP measures correlate significantly with the clinical index ( $r^2 = 0.63$ ;  $P = .00004$ ). Teller acuity measurements are also similar to VEP measures in children ( $r^2 = 0.64$ ;  $P = .0005$ ) but show lower acuities compared to the VEP for children with particularly low vision. Finally, 3 of 13 children tested under 2 background luminance conditions showed paradoxical improvement in grating threshold with dimmer luminance.

*Conclusions:* The sweep VEP tool is a reliable and valid means for measuring grating acuity in children with CVI. The tool also shows promise as a means of determining the optimal visual environment for children with CVI.

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## INTRODUCTION

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The leading cause of bilateral vision impairment in children in Western countries is cortical visual impairment (CVI).<sup>1,2</sup> This surprising finding, which reflects a change in the epidemiology of childhood vision impairment, stems from better outcomes in the management of some pediatric eye diseases (eg, congenital cataracts) as well as higher survival rates of children with perinatal hypoxia and ischemia (ie, preterm infants with damage to the central nervous system). CVI is caused by bilateral cerebral damage, either to the optic radiations or visual cortex, resulting in deficits in bilateral central visual acuity. This disorder typically occurs perinatally and is often of long duration, hence the need for better quantitative methods to assess vision in this population of preverbal children. Such methods, which are currently not available, could be used to determine the level of visual disability and the severity of the injury as well as to monitor rehabilitation in

children with CVI. *The goal of this study is to establish a quantitative method for measuring vision in children with CVI, based on the hypothesis that the sweep visual evoked potential (VEP) is a reliable and valid method in this approach.*

The sweep VEP was chosen as a possible tool for quantitative measurements of vision in children with CVI because it offers certain advantages. First, no verbal response from the patient is required to make the measurement. Second, a motor response in the form of head movement or eye movement to view the visual stimulus is also not necessary.

The sweep VEP is an untested method of studying children with CVI. To test the author's hypothesis, the *reliability* of the sweep VEP was first determined by using a grating stimulus in a repeat examination of a group of children with CVI. Second, the *validity* of the sweep VEP was tested by correlating the results of grating acuity measures in this patient population with (1) a clinical index and (2) Teller grating acuity measures (a behavioral test). Finally, this study also investigates the potential value of the sweep VEP in delineating a visual rehabilitation program for children with CVI. Specifically, grating acuity was measured under different lighting conditions

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(luminance) to determine whether a specific lighting condition(s) might improve visual function in some children. The hypothesis of this particular experiment is that certain children may be better managed (literally, may see better) in an environment with favorable lighting conditions.

Included in the following section is a clear definition of CVI, a discussion of the clinical findings related to this condition, evidence supporting CVI as an important cause of bilateral visual impairment in children, and a description of the underlying causes of CVI. Because the prognosis for visual development or recovery in CVI is variable, it becomes essential to establish an effective rehabilitation program. This section will serve as a preamble to the study, in which different background luminances were used to measure vision in children with CVI. The methods and results of this work will be presented after reviewing earlier neuroimaging, VEP, and behavioral measures of vision for CVI. The present study shows that the sweep VEP is a reliable and valid method of studying vision deficits in children with brain damage. Furthermore, the sweep VEP may be useful in defining a rehabilitation strategy for children with vision loss caused by central nervous system injury.

## **CORTICAL VISUAL IMPAIRMENT: BACKGROUND INFORMATION**

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### **DEFINITION AND TERMINOLOGY**

Cortical visual impairment is a neurologic impairment defined as bilateral loss of central vision (visual acuity) caused by damage to the central nervous system. In other words, visual acuity is reduced as a result of nonocular disease.<sup>3,4</sup> CVI occasionally coexists with other eye abnormalities, for example, in certain neurodegenerative disorders that affect the retina and central nervous system (eg, adrenoleukodystrophy). Strictly speaking, CVI manifests as impaired visual acuity with normal pupillary reaction bilaterally and a normal outcome on ophthalmologic examination.

In some cases, CVI is an acute reaction to a reversible disease process, such as transient CVI associated with head trauma. These cases rarely come to the attention of the ophthalmologist because symptoms and signs recede after a few hours or days. The research presented in this study concerns the condition known as *chronic CVI*.

Certain terms are sometimes used synonymously with CVI. *Cortical blindness* is the term initially coined by Marquis in 1933 to describe patients with visual loss but normal pupillary reactions.<sup>5</sup> While this diagnostic term is still used for adults with loss of vision due to central nervous system injury, its use for children is not recommended because the term *blindness* implies total loss of vision.

One of the remarkable aspects of CVI is the near universal retention of residual vision, a phenomenon that explains many of the diagnostic features of CVI, discussed below. In fact, children with CVI are rarely ever completely blind. The term *cerebral blindness or impairment* is preferred by some investigators, because the term encompasses a wide range of etiologies that may affect gray matter and white matter.<sup>6-10</sup> *Nonocular visual impairment* also is used by some,<sup>11</sup> but this term is confusing because ocular impairment may occur simultaneously with cortical impairment, particularly in children.

In summary, the term *cerebral visual impairment* is arguably more accurate in defining children with visual impairment caused by neurologic injury, but *cortical visual impairment* is so entrenched in the literature that it is preferred. In fact, vision impairment due to white matter disease (eg, periventricular leukomalacia) will invariably also affect the visual cortex directly or indirectly, lending accuracy to the term CVI.

The possibility that a broader range of visual impairments could be added to the general CVI category has also been addressed in recent years.<sup>9</sup> In CVI, visual acuity is decreased because areas subserving macular function have been damaged. The macula is subserved by as much as two thirds of the visual cortex,<sup>12,13</sup> so loss of visual acuity is very likely to accompany any injury to this part of the brain. Yet there are many other types of visual function that may be damaged without affecting visual acuity. Prosopagnosia, the inability to recognize faces, occasionally occurs in children in the absence of loss of visual acuity.<sup>14</sup> Simultagnosia occurs after bilateral superior occipital lobe injuries, resulting in the inability to focus on more than 1 visual object at a time.<sup>15</sup> In cerebral akinetopsia, afflicted individuals cannot perceive moving objects.<sup>15</sup> In all these cases, visual acuity may be normal, despite the presence of a vision abnormality. Dutton<sup>15</sup> recently proposed that these visual disturbances be termed *cortical visual dysfunction* (CVD). Certain children with CVI may show signs of CVD, but typical cases of CVD (those without acuity loss) should not be grouped with CVI. The term *cortical visual impairment* in this context will therefore be reserved for visual impairment in children with associated reduced visual acuity.

A spectrum of other related disorders is also arguably due to associated visual cortex damage. Learning disabilities including dyslexia are sometimes attributed to cortical visual damage. Again, in this paper we will adhere to the strict definition of CVI, which must include loss of visual acuity associated with neurologic damage.

### **PHYSICAL FINDINGS**

The clinical examination is usually sufficient to establish the diagnosis of CVI. Children affected by CVI, who have

no anterior visual pathway abnormality, will have a normal eye examination but show poor visual behavior. For example, they will fail to regard a face or to pay visual attention to their surroundings. The ophthalmoscopic examination in typical cases of CVI is normal. Some children will have both anterior visual pathway disease *and* CVI. In these cases, clinical judgment is used to determine whether a component of vision impairment is caused by CVI. Additional physical findings may help to clarify the diagnosis and must be taken into account in determining the overall management of the child with CVI.

Children with CVI may experience head and eye movement difficulties.<sup>16</sup> Abnormalities such as apraxia of eye movement and gaze palsies are common and pose potential problems in diagnosis of CVI. Pursuit eye movement problems are very common in CVI and can also be problematic for affected children. In these ocular motor disturbances, it may be difficult to distinguish the true loss of visual acuity from a disorder of eye movement that may mimic vision impairment. In fact, one benefit of developing a quantitative tool to measure vision in CVI would be the ability to distinguish true acuity loss from eye movement disorders mimicking vision loss in nonverbal children.

Visual field defects are also common in CVI.<sup>10,17</sup> Measurement of visual field defects is difficult, even in normal children.<sup>18,19</sup> A type of confrontation device has been used effectively to measure visual fields by so-called confrontational examination, which relies on the child's eye or head movement to indicate that a target has been observed. With severe cases of CVI, where motor control is poor, measurement of visual field may be particularly difficult.

The blink response to threat is not useful in the diagnosis of visual disability. The response to threat is a learned behavior, not present until the age of 3 months. Children with CVI develop this response at an even later age, which complicates any interpretation of the response.

#### *Behavioral Findings in Cortical Visual Impairment*

A constellation of complex behavioral changes is known to occur in CVI, and these are particularly noteworthy because they probably are adaptations to an underlying visual impairment problem.<sup>20</sup> The first of these is slow, inefficient, and highly variable visual performance. CVI patients characteristically have a short visual attention span.<sup>5,16,21,22</sup> They typically see better in familiar surroundings<sup>5,23</sup> and when they are relaxed and well rested. This variable visual efficiency, with better visual behavior noted at some times, could challenge the accurate and meaningful measurement of vision. If reliable, quantitative visual acuity measures could be obtained, then other aspects of behavior associated with vision could account for this variation in visual behavior (eg, poor motor control mimicking

vision impairment or "subclinical seizures" interfering with visual behavior).

Color vision and perception of movement are often preserved in patients with CVI, a finding which sometimes leads to the construction of visual stimuli (eg, optotypes) in color, rather than in black and white, to enhance the vision of children with CVI.<sup>23-26</sup> Red and yellow are frequently cited as preferred colors for CVI patients.<sup>16,24</sup> In the experiments reported here, children with CVI were asked to view black and white stimuli, but future studies using color stimuli could also help to guide rehabilitation efforts for CVI.

Often, CVI patients use peripheral vision to search for objects. They may turn their heads before reaching for an object (retinal reach),<sup>3,5</sup> with the head turned away from the side affected by vision loss. It has been hypothesized that this behavior is due to a desire to use peripheral vision,<sup>5,27</sup> or perhaps to allow time to assimilate and process visual information. People with visual impairment often bring objects closer to their eyes to increase linear magnification of the object of visual interest. CVI patients also display this behavior, although they may do so to simplify their field of view by excluding extraneous visual information and reducing the "crowding" effect.<sup>16,21</sup> This effect occurs when flanking visual targets inhibit a person's ability to see the foveal target (ie, the visual target of interest).

Gazing at lights is a common feature in patients with CVI<sup>28</sup> and provides the basis for one aspect of this study. Some patients with CVI flick their fingers in front of the light source, or blink excessively, or gaze at flickering fires, or stare at spinning fans.<sup>25</sup> Paradoxically, a third of CVI patients exhibit photophobia<sup>26</sup> but still gaze at lights from time to time. Children tend to outgrow their photophobic behavior. If a test were devised to determine the specific lighting condition that would permit enhanced vision in different subgroups of children with CVI, it could provide important information on the optimal visual environment for a visual rehabilitation program. For example, the child who fares better in reduced lighting conditions might see better and learn faster in an environment with reduced background luminance.

#### **EPIDEMIOLOGY OF VISUAL IMPAIRMENT IN CHILDREN**

In the past, conditions such as congenital cataracts and retinopathy of prematurity were usually responsible for bilateral low vision in children. These conditions are now more easily treated with advanced microsurgical instruments in the case of cataracts and with cryotherapy or laser therapy for retinopathy of prematurity. Hence, CVI has emerged as a major cause of visual impairment in children,<sup>21,24</sup> particularly in developed countries,<sup>3</sup> where new treatment options have extended to these other eye diseases. (Not included in this section is a discussion of

unilateral vision impairment commonly observed in amblyopia, for example.)

The incidence of CVI is increasing.<sup>23</sup> In a study of 5 Nordic countries, Rosenberg and colleagues<sup>29</sup> noted that brain damage accounts for a growing number of cases of childhood visual impairment. The investigators implicated improved medical care since critically ill children are now more likely to survive with increasingly severe medical problems. CVI per se is not life-threatening, although the neurologic abnormalities associated with CVI may have been fatal in the past. In Chile, 2.1% of blind children or those with severe visual impairment, who are enrolled in schools for the blind, can attribute their visual difficulties to CVI.<sup>30</sup> This finding is an underestimate, however, because students with higher functioning skills are generally enrolled in schools for the blind; also, many children were too young for formal education at the time of the study. Rogers<sup>31</sup> investigated visual impairment in Liverpool. CVI was the most common diagnosis (49% of the study population) among children with both visual impairment and additional neurologic disability. The Oxford Register of Early Childhood Impairments<sup>2</sup> reports the overall incidence of bilateral vision impairment at 0.5%, with 29.5% of the cases due to CVI. The second leading cause of vision impairment in this register is nystagmus, at 14.1%. In Northern California, CVI is the leading cause of visual impairment in children under the age of 5 years.<sup>1</sup>

The overall incidence of bilateral vision impairment in children in Western countries is probably 0.5%.<sup>2</sup> If a third of these cases are due to CVI, then this disorder will affect more than 1 in 1,000 children, making CVI an important cause of vision impairment in this population. CVI usually occurs in conjunction with other serious neurologic abnormalities, such as seizures and motor deficits.<sup>32</sup> There is no known treatment. In fact, no satisfactory method exists for quantifying visual deficit in these children. To establish a successful treatment or rehabilitation regimen, it is important to establish a method to evaluate the effectiveness of the treatment modality.

#### ETIOLOGY OF CORTICAL VISUAL IMPAIRMENT

Disorders of the human visual system can be divided into at least 2 categories: those that affect the anterior visual pathways and those that affect retrogeniculate or posterior pathways (optic radiations and visual cortex). A third potential category encompasses the large array of conditions where the child's visual perception is altered (eg, CVD). This classification scheme is useful because diseases that affect bilateral anterior, as opposed to retrogeniculate, visual pathways produce different clinical findings. In this section, we review diseases and etiologies that affect the visual cortex and associative cortical areas. For

a child to suffer impaired visual acuity from a central nervous system injury, the injury must be bilateral. Unilateral injury affecting the optic radiations or visual cortex will cause a hemianopia without loss of visual acuity.

#### *Hypoxia/Ischemia*

The most common cause of CVI is a hypoxic/ischemic injury,<sup>3,21,24,33-35</sup> usually in the perinatal period. Events such as placental insufficiency, dystopia, and asphyxia from many causes are usually responsible for insufficient oxygenation in the infant's brain. At least 60% of children with neonatal hypoxic/ischemic encephalopathy have cerebral visual impairment.<sup>9</sup> In one study of children who sustained perinatal hypoxia, *all* subjects had some form of visual impairment.<sup>17</sup> The pattern of neurologic damage varies depending on whether the injury occurs in a preterm infant or in a term (or postterm) infant. A third pattern of injury is seen in full-term infants with profound asphyxia, as discussed below.

Hypoxia (lack of oxygen) or ischemia (tissue death due to loss of blood flow and, thus, oxygen deprivation) in the preterm baby leads to a characteristic injury of the brain, namely periventricular leukomalacia (PVL).<sup>25,36</sup> The mechanism and distribution of injury in the preterm infant are predicated on the location of the watershed zone, which is in the germinal matrix, adjacent to the ventricles and in close proximity to the optic radiations. PVL can be detected by a number of methods, including magnetic resonance imaging (MRI), in which the affected tissue around the ventricles of the brain appears white owing to loss of fluid and increased density of tissue. In serious cases of PVL, cysts may form in the affected tissue.<sup>8</sup> Such cystic change, particularly in the posterior part of the brain (as opposed to periventricularly located cysts), is associated with a poor neurologic and visual prognosis.<sup>8,11,25</sup>

In term or near-term infants, hypoxia/ischemia causes injury to the brain, in the distribution of the cerebral arteries and in their watershed zones. Germinal matrix vessels have regressed by 32 weeks' gestation, so that periventricular white matter is usually spared. The prognosis for recovery of vision is probably better when the injury involves the striate cortex, not the optic radiations;<sup>37</sup> term infants usually experience direct damage to the striate from hypoxia/ischemia.

In cases of severe asphyxia in term infants (eg, caused by prolonged cardiac arrest; severe abruptio; severe, prolonged hypotension), damage occurs chiefly in the basal ganglia and hippocampus. Involvement of basal ganglia on neuroimaging indicates a particularly poor developmental and visual prognosis.<sup>38</sup> Basal ganglia disorders are almost invariably accompanied by generalized involuntary movements involving the head, neck, and eyes, which interfere with motor functions and vision.<sup>39</sup>

Focal infarction (stroke) is also a possible effect of perinatal hypoxia and ischemia. Mercuri and colleagues<sup>40</sup> report that the left hemisphere, particularly in the area of the middle cerebral artery, is susceptible to focal infarction in the perinatal period, although a bilateral insult is required for the development of CVI.

#### *Shunt Failure*

Transtentorial herniation can lead to compression of the posterior cerebral arteries against the tentorial edge.<sup>33</sup> This can lead to ischemia and occipital lobe infarction. The neurologic damage is more severe if there is a rapid onset, as more gradual compression allows the vascular system to compensate.<sup>33</sup>

#### *Epilepsy*

Wong<sup>22</sup> reported a poor prognosis when the cause of “cortical blindness” was status epilepticus. Fortunately, status epilepticus is now rare. Chen and associates<sup>41</sup> also suggest that epilepsy is associated with a poorer prognosis. CVI is very common in infants with infantile spasms, especially when the electroencephalogram (EEG) is hypsarrhythmic. The abnormal visual function can result from loss of visual acuity and impaired perception. While the etiology of infantile spasms is often unclear, the cause of the profound visual inattentiveness is the same brain disturbance that results in seizures and in abnormal EEG patterns.

#### *Infections*

Bacterial meningitis,<sup>24</sup> encephalitis,<sup>5</sup> and meningitis/encephalitis<sup>21</sup> may cause CVI. Bacterial meningitis is associated with a poorer prognosis than other causes of CVI.<sup>41</sup> Congenital toxoplasmosis can also cause CVI, as may neonatal herpes simplex.<sup>33</sup>

#### *Drugs or Poisons*

Antenatal use of cocaine and amphetamines will occasionally cause CVI.<sup>32</sup> The presumed mechanism of injury is damage to developing or already developed central nervous system vessels caused by vasoactive substances, resulting in infarction of key neurologic structures.

#### *Metabolic Disease*

Most of the neurodegenerative disorders have the potential to disrupt cortical vision. It is unlikely that children will present with the isolated finding of CVI. One exception is the case of adrenoleukodystrophy, which may show prominent visual manifestations early in its course.<sup>42,43</sup>

#### *Complications of Cardiac Treatment*

CVI has been reported in children after cardiac arrest and open heart surgery.<sup>24,44</sup> Wong<sup>22</sup> reported a poor prognosis when the cause of “cortical blindness” was cardiac arrest.

#### *Trauma*

Head injury is a major cause of CVI,<sup>21</sup> with half of the trauma cases the result of battering (ie, child abuse). Trauma-induced CVI is frequently described as transient and is often accompanied by headaches, confusion, and vomiting.<sup>45</sup> Children may be especially prone to such injury because of flexible skulls, relatively less cerebral-spinal fluid volume, and a relatively reduced distance between cortex and cranium, compared with adults. Cranial injury may induce transient ischemia or edema.<sup>44,45</sup> Vasospasm is more likely to occur in children than in adults and may cause hypoxia in the occipital cortex owing to its location between the 3 major cerebral arteries. There may be some link between transient posttraumatic CVI and migraine headaches. Posttraumatic visual problems may lead to complete blindness.<sup>44</sup>

#### *Twin Pregnancy*

There have been reports in the literature implicating twin pregnancy as a cause of CVI.<sup>24,46</sup> Monochorionic twins are particularly vulnerable, presumably due to twin-to-twin transfusions. Ironically, the larger twin is usually more adversely affected because of its expanded blood volume and resulting vascular stress. Clinicians should investigate the possibility of a twin pregnancy when faced with a child with neurologic damage or CVI.

#### *Central Nervous System Developmental Defects*

Central nervous system developmental defects may be associated with CVI.<sup>41</sup> Examples include lissencephaly, holoprosencephaly, and schizencephaly. At least some of these disorders may also be associated with optic nerve hypoplasia, occasionally making the distinction between CVI and anterior visual pathway visual deficits difficult.

#### **ASSOCIATED NEUROLOGIC AND OPHTHALMOLOGIC DEFICITS**

Neurologic disorders are frequently seen in association with CVI. Whiting and associates<sup>5</sup> reported that all subjects in their study had associated neurologic deficits: abnormal mental development, cerebral palsy, seizures, microcephaly, hydrocephalus, sensorineural hearing loss, myelomeningocele, and progressive CNS degeneration. In fact, chronic CVI is virtually always associated with other serious neurologic abnormalities.<sup>21,22,31,32,47</sup>

Chronic CVI is also associated with ophthalmologic abnormalities, including various types of nystagmus, strabismus, and refractive error.<sup>21,48</sup> Optic nerve atrophy, which itself causes vision impairment, has been seen in patients with CVI<sup>39</sup> and will cause the diagnosis of CVI to be uncertain in some cases. Clinical judgment is used to distinguish anterior pathway disease from CVI in these cases, because there is no precise test to determine the

relative contribution of optic atrophy or CVI to the overall vision impairment of a given child. While strabismus, nystagmus, and refractive errors are not diagnostic of CVI, they are also often present in patients with CVI<sup>32</sup> and should be corrected (eg, with glasses) to maximize residual vision.<sup>21</sup> Since hypoxic/ischemic insults are often the cause of CVI, other visual deficits also could be caused by the same initial insult. Visual field development may be delayed in premature children who suffer perinatal hypoxia/ischemia. Strabismus with a cerebral origin may also occur in these children.<sup>8</sup>

#### **PROGNOSIS**

Most patients with CVI do not regain normal vision.<sup>17</sup> However, improvement is usually seen.<sup>3,17,21,32</sup> Visual improvement may be sudden, particularly in cases of traumatic injury; more typically, visual recovery is gradual. Very little is known about specific prognostic findings in CVI. However, many researchers state that children with CVI have a poor prognosis when they display extensive motor involvement, severe seizures, and low intellectual functioning.<sup>23,32,37</sup> In other words, children with CVI and extensive neurologic damage have the least favorable prognosis for recovery of vision. The finding of periventricular leukomalacia confers a particularly poor prognosis,<sup>37</sup> compared to damage to the visual cortex per se.

#### **TOOLS FOR MEASURING THE VISUAL DEFICIT IN CORTICAL VISUAL IMPAIRMENT**

Quantitative information about a patient's condition can be clinically useful and comforting to patients and their families. A variety of techniques can be used to assess the extent of injury to the posterior visual pathways, but while a particular technique may be a good predictor of prognosis in experimental cohorts, in the case of individuals, such predictions are less useful.<sup>10,25</sup> Clinical assessment must be performed in conjunction with brain imaging studies.

#### **FORCED CHOICE PREFERENTIAL LOOKING**

In forced choice preferential looking (FPL), an observer located behind a screen presents a series of cards with different grating lines to the child. A grating card is displayed on one side of the child's visual field, while a luminance-matched blank field is displayed on the other side. When children see the grating card, they usually will look at it. The observer notes the child's eye movements without knowing on which side the grating card appeared, and acuity is determined by noting the finest grating to which the child reliably orients his or her gaze (Teller Acuity Procedure). Inattention or inability to direct gaze could prevent a child from following a stimulus above chance

levels.<sup>45</sup> Moreover, FPL measures may be difficult to interpret in children with head and eye movement difficulties. Thus, failure to reliably direct gaze toward a grating card may be partly determined by motor coordination problems in the child with CVI. On the other hand, FPL testing may reveal specific defects in gaze control in conjunction with other tests.

#### **ELECTROENCEPHALOGRAM**

The VEP provides general information about geniculocortical dysfunction and occipital responses to photic stimuli.<sup>24</sup> The EEG can be interpreted in association with VEPs. The presence of normal alpha rhythm, superimposed on a normal background, rules out cortical visual impairment and homonymous hemianopia due to cortical lesions.<sup>27</sup> Reactive alpha rhythm is a good prognostic finding in CVI.<sup>27</sup> Recently, alpha reactivity has been successfully applied to the study of patients who have misrouting of visual pathways, such as occurs in albinism.<sup>49</sup> The study of alpha rhythm may therefore have application to visual disturbances that cause hemispheric visual system asymmetries.

#### **NEUROIMAGING**

Neuroimaging of the brain can be used to confirm the clinical diagnosis of CVI.<sup>23</sup> Magnetic resonance imaging is often used to detect PVL in the first days of life, although the child's visual outcome cannot be accurately predicted on the basis of neuroimaging findings.<sup>8</sup> MRI is also used to assess asphyxia in neonates<sup>50</sup> and may be a better predictor of outcome in the first week following injury. A normal MRI scan correlates with normal vision, although an abnormal MRI finding does not necessarily indicate loss of visual acuity.<sup>51</sup> MRI scans can be used to detect delayed myelination, which can be caused by perinatal hypoxia,<sup>51</sup> and are more reliable in the detection of damage to the optic radiations than to the visual cortex.<sup>10</sup> Finally, the MRI scan may show selective damage to periventricular white matter, with a less favorable prognosis for visual recovery.<sup>38,51</sup>

#### **SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY**

The single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are used to investigate changes in cerebral blood flow.<sup>52</sup> These tools may be better at predicting outcome than MRI scans but have not been widely used, mainly because PET requires delivery of a small amount of a radioactive isotope.

#### **ULTRASOUND**

Ultrasound, which is portable and noninvasive, is often used to detect PVL in the first days of life and may be

more sensitive than MRI during this period. In most cases, ultrasonography is performed transfrontally.<sup>53</sup> Eken and colleagues<sup>7</sup> found that ultrasound could be used to correlate structural abnormalities with visual outcome.

#### **FUNCTIONAL MAGNETIC RESONANCE IMAGING**

Functional magnetic resonance imaging (fMRI) shows promise as a diagnostic tool. The fMRI demonstrates areas of the brain that are metabolically active. However, fMRI requires an alert, immobile, cooperative patient and, therefore, has limited use in children.

#### **VISUAL EVOKED POTENTIALS**

Research on VEPs has focused mainly on this method's usefulness in confirming CVI or on its prognostic value for visual outcome.<sup>54</sup> Several types of VEPs can be performed, including the transient, nonpatterned flash VEP and the transient pattern reversal VEP, each of which yields information about the temporal waveform of responses to single presentations of a visual stimulus. Clarke and colleagues<sup>11</sup> found that CVI patients with normal flash VEPs had a good prognosis for improvement. Flash VEP may not accurately assess higher levels of visual processing, however, pattern VEPs are more useful for monitoring visual development and rehabilitation in children.<sup>35</sup>

Multichannel VEPs have been used to diagnose CVI. Ratios of activities between multiple recording electrodes in children with CVI can be calculated and compared mathematically to normal, control subjects. Children with CVI show low occipital to parietal activity, helping to confirm the diagnosis.<sup>55</sup>

In the steady-state sweep VEP, a patterned stimulus is periodically temporally modulated (eg, at 2.5 Hz or above) while the pattern elements gradually change size. An evoked response is time-locked to the stimulus modulation, and the amplitude of the response varies with stimulus visibility, allowing visual thresholds to be quantitatively estimated.

Steady-state VEPs show promising potential for quantification of visual loss in CVI and offer the advantage of testing several types of visual function (eg, contrast sensitivity, grating acuity, vernier acuity).<sup>56,57</sup> This is the type of VEP stimulus chosen for the set of experiments described in this thesis.

## **METHODS**

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### **SUBJECTS**

The institutional review board approved this research project, which also conforms to the Helsinki criteria for human research. Written informed consent was obtained from the parents after the procedure had been carefully

explained to them. The subjects were a group of children recruited from the practice of the author or from the practice of other pediatric ophthalmologists in the region. In some cases, the Blind Babies Foundation of Northern California helped with further recruitment. The author reviewed the medical records of the patients.

The ages of the subjects at the time of enrollment in the study ranged from 6 months to 16 years, although most were younger than 3 years. All subjects had a clinical history consistent with an injury to the central nervous system, mostly due to perinatal hypoxia/ischemia. In most children, injury was sustained in a natal or perinatal event. A few children had developed encephalitis in the first year of life. CVI was diagnosed on the basis of poor visual attention or behavior associated with a normal ophthalmologic examination and normal pupillary responses. In almost all cases, the degree of vision impairment was considered clinically profound. Information on etiology, age at onset of CVI, age at test, and type of data (reliability) obtained is presented in Table I. Table II shows diagnosis, age at onset of CVI, and age at testing of different luminance conditions. When no threshold could be determined, this was recorded as "no" measurable threshold, and the data was included.

VEP grating acuity was measured in 23 subjects and then retested in the reliability phase of the experiment. Grating visual acuity was measured at least once with sweep VEP techniques in 41 children, while 21 consecutive children were assessed using the Teller Acuity Card procedure (see below). A clinical assessment (Huo scale rating) was determined for 29 of the children, and luminance comparisons for 13 children. Every effort was made to measure Huo criteria, Teller acuity, repeat thresholds, and luminance comparison thresholds in consecutive children. In some cases, however, children could not return because of intercurrent illness or other conflict.

### **STIMULI**

Vertical sine-wave luminance gratings were created on the face of a 24 x 18-cm video monitor at a space average luminance of 100 cd/m<sup>2</sup> and a Michelson contrast of 80%. The gratings were generated by a raster graphics board (NuVistat) at a resolution of 1,536 x 480 pixels. Subjects were tested at a distance of 70 to 100 cm from the video monitor screen in a darkened examination room. They were given a fixation toy, consisting of a small piece of jewelry or animal model, but most were unable to attend to it. The proximity of the monitor screen to the subject's face helped to ensure fixation. The subject's visual attention was carefully assessed by direct observation.

#### *Sweep VEP Stimulus and Measurements*

For the VEP grating acuity measurements, a pattern onset-offset stimulus was displayed that modulated at a

TABLE 1: CLINICAL CHARACTERISTICS OF CHILDREN WITH CVI AND TYPE OF TESTS PERFORMED

PATIENT	AGE AT TEST	AGE AT CVI ONSET*	ETIOLOGY	RELIABILITY	TELLER	HUO
1	71 wk	Preterm (0)	HIE	X	X	X
2	2.7 yr	Perinatal (0)	HIE	X	X	
3	11 yr	Perinatal (0)	HIE	X	X	X
4	45 wk	Perinatal (0)	HIE	X	X	X
5	28 wk	Perinatal (0)	HIE	X		X
6	2.2 yr	Perinatal (0)	HIE	X	X	X
7	2.4 yr	Perinatal (0)	HIE	X		X
8	6.9 yr	Perinatal (0)	HIE	X		X
9	91 wk	Perinatal (0)	HIE	X		X
10	2.8 yr	Perinatal (0)	HIE	X	X	
11	5.9 yr	6 mo	Encephalitis	X	X	
12	70.9 wk	Perinatal (0)	HIE: Twin	X		
13	47 wk	Perinatal (0)	HIE: Twin	X		
14	2.2 yr	Perinatal (0)	HIE	X		X
15	100 wk	Perinatal (0)	HIE	X	X	
16	27.7 wk	Prenatal (0)	HIE	X	X	X
17	1.5 yr	Perinatal (0)	HIE	X		
18	2.5 yr	Perinatal (0)	HIE	X		X
19	46 wk	Perinatal (0)	HIE	X		
20	63 wk	Preterm (0)	HIE	X		
21	2.9 yr	4 mo	Trauma/auto accident	X	X	X
22	10 mo	Preterm (0)	HIE (ROP)	X		X
23	18 mo	Premature (0)	HIE	X		X
24	5.0 yr	Perinatal (0)	HIE		X	
25	4.0 yr	Perinatal (0)	Mitochondrial disease		X	X
26	15.6 wk	Perinatal (0)	Perinatal		X	X
27	4.5 yr	Perinatal (0)	HIE		X	X
28	2.8 yr	2 yr	HIE,cardiac arrest		X	X
29	4.7 yr	15 mo	Encephalitis		X	X
30	3.3 yr	5 mo	CVA		X	X
31	71.6 wk	Perinatal (0)	HIE		X	
32	4.8 yr	Perinatal (0)	Trisomy 13/encephalocele		X	X
33	9.0 yr	Perinatal (0)	HIE		X	X
34	3 mo	Perinatal (0)	HIE		X	
35	9.9 yr	Perinatal (0)	HIE			X
36	15.9 wk	Perinatal (0)	HIE			X
37	97 wk	Preterm (0)	HIE (shaken)			X
38	4.0 yr	5 mo	Meningitis			X
39	60.1 wk	4 mo	Near SIDS			X
40	3.0 yr	Perinatal (0)	HIE			X
41	5.0 yr	Perinatal (0)	HIE			X

CVA, cerebrovascular accident; CVI, cortical visual impairment; HIE, hypoxic/ischemic encephalopathy; ROP, retinopathy of prematurity; SIDS, sudden infant death syndrome; reliability, test-retest.

\*Zero indicates age at onset to be birth.

frequency of 5 Hz. This temporal frequency was chosen on the basis of preliminary pilot data in children with CVI<sup>57</sup> and to avoid frequencies that might induce seizure activity in susceptible children. Subjects were tested in a consistently dimly lit room, usually sitting on a parent's lap or in a wheelchair, with head and torso immobilized.

Each threshold was measured using the swept parameter technique. The grating stimulus was presented over 10 equally spaced, linear steps from above threshold to below threshold. Threshold was determined for each trial by extrapolating the VEP response to zero. Threshold

measures from multiple (at least 10) 10-second trials were averaged for each testing condition. The grating was set at 1 to 3 cycles/degree (cpd), depending on the subject (ie, those with better visual fixation were started at higher acuities) and then swept to a spatial frequency of 10 to 20 cpd, again depending on the subject. For example, those children with higher grating acuities were tested from 3 to 20 cpd. When threshold measures could not be determined, "no measurable grating threshold" was recorded in the data, and the trial was repeated in the retesting phase of the experiment (Fig 1).

TABLE II: CLINICAL CHARACTERISTICS AND ADDITIONAL TESTING OF CHILDREN WITH CVI UNDERGOING VEP GRATING ACUITY ANALYSIS UNDER 2 LUMINANCE CONDITIONS

PATIENT*	AGE AT TEST	AGE AT CVI ONSET†	DIAGNOSIS
1 (4)	45 wk	Perinatal (0)	HIE
2 (5)	28 wk	Perinatal (0)	HIE
3 (11)	5.9 yr	6 mo	Encephalitis
4 (36)	15.9 wk	Perinatal (0)	HIE
5 (28)	2.8 yr	2 yr	HIE, cardiac arrest
6 (new)	6.0 yr	4 mo	Meningitis
7 (12)	70.9 wk	Perinatal (0)	HIE: Twin
8 (13)	47.0 wk	Perinatal (0)	HIE: Twin
9 (31)	71.6 wk	Perinatal (0)	HIE
10 (15)	100 wk	Perinatal (0)	HIE
11 (23)	18 mo	Premature	HIE
12 (33)	9.0 yr	Perinatal (0)	HIE
13 (new)	18 mo	Perinatal (0)	HIE

CVI, cortical visual impairment; HIE, hypoxic/ischemic encephalopathy; VEP, visual evoked potential.

\*Number in parenthesis indicates patient number when tested under Table I.

†Zero indicates age at onset to be birth.

Children with neurologic disease could have reduced VEP responses on account of seizures, anticonvulsants, poor accommodation, nystagmus, and roving eye movements. Careful monitoring of visual fixation helped to obviate some of these issues, as did signal averaging across many trials. We had no means to monitor accommodation in these experiments.

An EEG was also performed during the experiment to check for intercurrent seizure activity and to monitor background noise. A few of the children experienced an underlying seizure disorder during testing, and the experiment was interrupted for a few minutes and then resumed. No child suffered a grand mal convulsion during the study, nor were there any other clinical complications. For the retest phase of the experiment, subjects returned

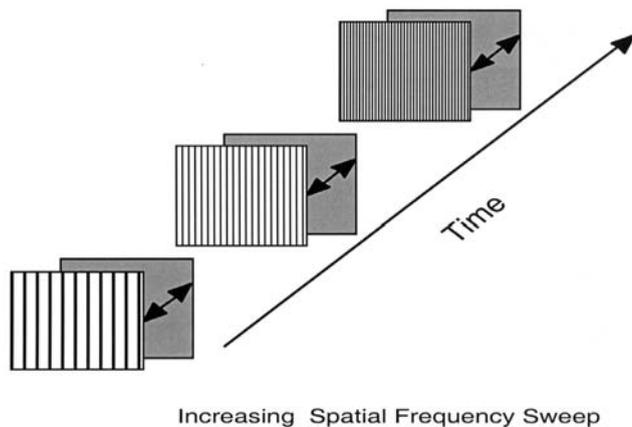


FIGURE 1

The sweep visual evoked potential grating stimulus.

on a different day for a second testing session under similar experimental conditions, usually 1 to 3 months after the first session. In a few cases, retesting was delayed because the child had been ill and/or hospitalized.

Two different experimental conditions were chosen for the luminance-effect experiment, based on earlier work by Allen and colleagues,<sup>55</sup> which indicated that VEP grating thresholds peak above approximately 1 cd/m<sup>2</sup>. The background luminance was therefore set at either 50 or 100 cd/m<sup>2</sup> (Fig 2), each of which should yield comparable grating thresholds. Grating thresholds were determined as already described and were evaluated by statistical analysis (see below).

High Mean Luminance                      Low Mean Luminance

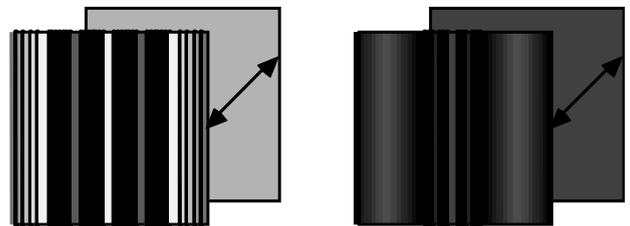


FIGURE 2

Comparison of luminance conditions in 13 subjects. Left, high luminance (100 cd/m<sup>2</sup>); right, low luminance (50 cd/m<sup>2</sup>).

### Behavioral Procedure

Twenty-one children were also tested using the Teller Acuity Card procedure, which measures grating acuity according to behavioral responses to a visual stimulus.<sup>59</sup> A masked and well-trained observer administered the test at a distance of 1 m from the subject. The testing stimulus was presented in a room with no visual distractions. The subject's response to the stimulus was assessed by the observer and recorded as the highest spatial frequency that the subject responded to reliably. In some cases, the subject's head and neck were stabilized to promote best performance. Because many of the children experienced motor problems, a white stage was not used as background in this part of the study.

### COMPARISON TO HUO CRITERIA OF CLINICAL VISUAL BEHAVIOR

Twenty-nine children in the study were assigned a clinical score based on criteria established by Huo and colleagues<sup>60</sup> for clinical visual behavior. The score for each subject is derived from clinical observations recorded either in the author's practice or at the onset of the VEP experiment. Clinical scores were assigned without prior knowledge of the VEP threshold measure.

Huo's criteria are ranked from 1 to 6 according to the

following scale that we modified for this study: (1) light perception only; (2) fixation on a face; (3) reliable fixation on small objects in the environment; (4) visual acuity 20/200 to 20/800, either actual or estimated; (5) visual acuity 20/50 to 20/200, either actual or estimated; and (6) normal visual acuity. The Huo score was then compared to the VEP threshold data. Estimations of measurable visual acuity (eg, 20/200) seldom had to be based on clinical judgement, which is potentially very unreliable. Most children in whom a Snellen acuity could be recorded were neurologically higher functioning and verbal.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using the Matlab software application. A 1-tailed *t* test of paired comparisons was run in 3 data sets, each containing acuity measurements taken under 2 different conditions: test versus retest, VEP versus Teller acuity data, and 50 cd/m<sup>2</sup> versus 100 cd/m<sup>2</sup>. This test returns a significance level (*P*) indicating the probability that the mean difference between test acuity and retest acuity is zero.

The test-retest reliability measure was computed by using a type 2 regression analysis to determine if there is a significant level of correlation (ie, reliability) between the 2 conditions. Linear regression of these data resulted in a correlation coefficient whose significance is measured as a *P* value. This *P* value indicates the probability of obtaining this correlation coefficient from 2 totally uncorrelated sets of measurements.

Linear analysis was also run for the Teller-VEP data and the Huo-VEP data to determine whether a correlation exists between these measures of vision. The analysis was run on linear and logarithmically derived data sets to determine whether statistical significance could be derived from both types of data.

A type 2 regression analysis was also used to compare grating acuity to Huo criteria.

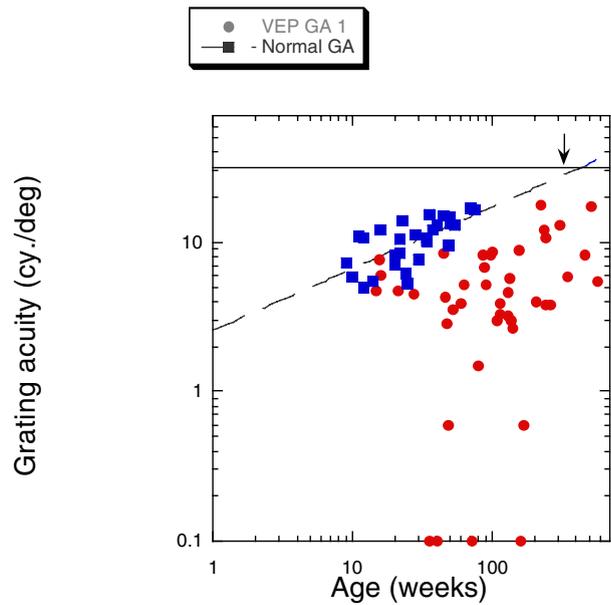
**RESULTS**

**VEP GRATING ACUITY RESULTS**

Figure 3 shows the range of VEP grating thresholds obtained for 41 children with CVI compared to results of normal control children. The figure shows that older children tend to demonstrate higher grating acuities, suggesting an improving developmental trend, since nearly all children had perinatal disease (ie, concurrent with onset of CVI: see discussion below). A wide range of acuities can be seen, although most children with CVI achieved VEP grating acuity measures below 10 cpd.

**RELIABILITY TESTS OF VEP GRATING ACUITY**

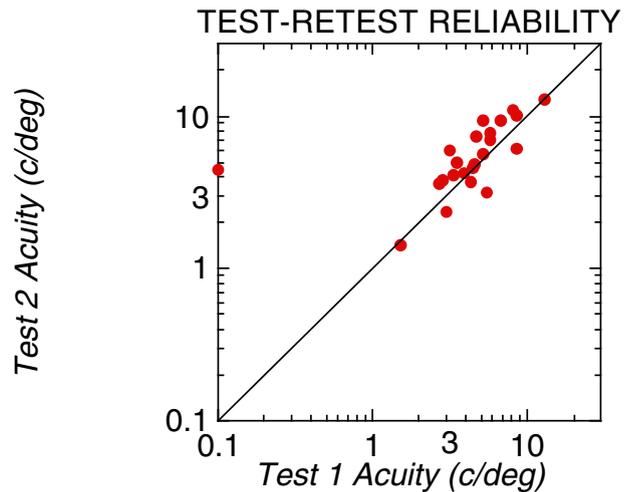
Test-retest reliability scores are shown graphically in



**FIGURE 3**

VEP grating acuity measures in all children tested. Results are compared to normative data from Skoczenski and Norcia.<sup>56</sup> Arrow points to line indicating normal, mature grating acuity. VEP grating acuity is presented on log scale. GA, grating acuity.

Fig 4. Twenty-three subjects were available for retesting, and the results in the second examination confirmed the reliability of the method; that is, the results of the second test were similar to those of the first, with one exception. The repeat examination was performed within 3 months of the initial examination, with few exceptions (illness pre-



**FIGURE 4**

Test-retest results of 23 subjects. X axis represents first test, and Y axis shows results of retest. Linear regression model for these data yields the equation  $y = 0.87x + 1.67$ ;  $r^2 = 0.662$  ( $P = .0003$ ). Standard errors (SE) on slope and intercept were 0.27 and 0.35, respectively. Note that most data points are above the line. This suggests improvement between first and second tests. A 1-tailed *t* test of paired comparisons is significant at the .048 level when calculated for log acuities and at the .006 level when calculated for linear acuities.

cluded prompt follow-up).

Linear regression analysis of these data yielded  $r^2 = 0.662$ , which is significant at  $P = .0003$  (1-tailed  $t$  test). The  $P$  value indicates the probability of obtaining this correlation coefficient from 2 totally uncorrelated measurements (ie, the test and the retest from each subject). Results of this test point to the likelihood that the test is highly reliable.

Most data points are above the exact reliability line, suggesting that some improvement in VEP grating acuity or in the ability to measure it occurs in a short time in children with CVI. A less likely explanation would be that children showed test improvement with practice. This is less likely because so many of the children were substantially intellectually impaired. When grating acuities are plotted logarithmically, a 1-tailed  $t$  test of paired comparisons yields a test-retest significance level at  $P = .048$  (significant difference). Excluding left and right outliers,  $P = .018$ . Note that one data point on the graph is far from the cluster. Even including this point, as noted previously,  $P$  is significant at the .048 level.

When the same data points are compared on a linear scale, the 1-tailed  $t$  test yields  $P = .006$ . Excluding the 2 outliers,  $P = .001$ .

**COMPARISON OF THE SWEEP VEP WITH PSYCHOPHYSICAL MEASUREMENT OF GRATING ACUITY**

Figure 5 shows the results of a comparison study between VEP grating acuity and a psychophysical measure of grating acuity, the Teller Acuity procedure. In general, children showed lower acuities on the behavioral measure, compared to the electrophysiological (VEP) measure. In the high acuity range, a better approximation of the 2 types of tests was noted. Regression analysis of the data

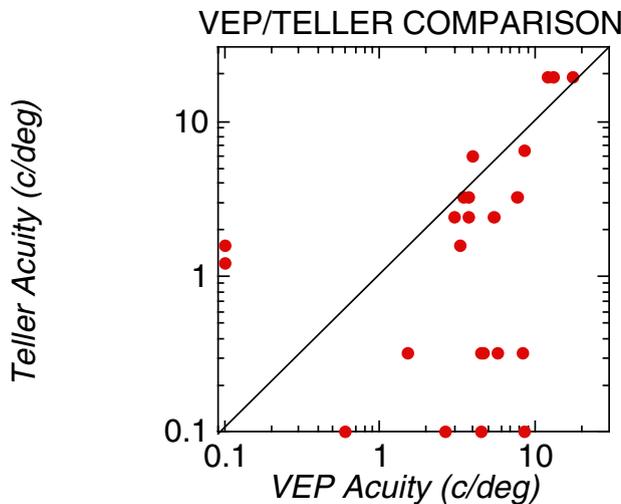


FIGURE 5

Results of Teller acuity compared to VEP grating acuity in the same subjects. Note better apparent correlation at higher acuities. The linear regression equation for these data is  $y = 1.15x + 2.31$ ;  $r^2 = 0.64$ ;  $P = .0005$ .

yields the linear equation  $y = 1.15x + 2.31$ ;  $r^2 = 0.64$ ;  $P = .0005$ , indicating a strong correlation between the 2 data sets. A 1-tailed  $t$  test of paired comparisons yields  $P = .008$  for log acuities and  $P = .035$  for linear acuities. This  $P$  value is the probability that the difference between the Teller acuity data and VEP data is 0 and demonstrates the likelihood that the data sets, while correlated with each other, are also different.

**COMPARISON OF SWEEP VEP GRATING ACUITY AND A CLINICAL INDEX OF VISION (HUO CRITERIA)**

A correlation was found between VEP thresholds for grating acuity and clinical findings (Fig 6). Most children had low (poor) clinical scores, and these correlated with low thresholds on the VEP tests. Regression analysis of these data yields the equation  $y = 2.60x - 0.72$ , with a correlation

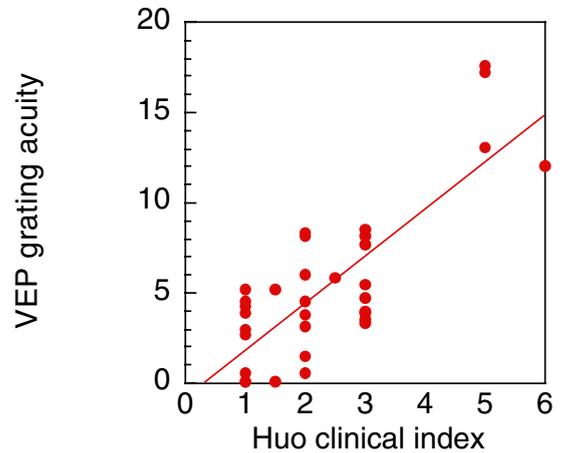


FIGURE 6

Huo clinical measurement compared to VEP acuity measurement. VEP grating acuity is validated by the clinical measurement (linear regression equation is  $y = 2.60x - 0.72$ ;  $r^2 = 0.63$ ;  $P = .00004$ ).

coefficient of 0.63, which is significant at  $P = .00004$ . Regression of log VEP acuity versus Huo index generated a correlation coefficient of 0.33 with  $P = .03$ .

**RESULTS OF LUMINANCE VARIATION**

Figure 7 shows VEP grating thresholds for 13 subjects, taken at 50 and 100  $cd/m^2$ . Note that some subjects show unexpected improvement in dimmer luminance conditions (50  $cd/m^2$ ), while others show a decline in acuity in dimmer luminance. As would be expected, a number of children showed no effect.

**DISCUSSION**

The clinical measurement and assessment of vision in children with CVI is difficult and often inaccurate, for many reasons. The first of these is that children with CVI are usually preverbal because the neurologic injury has

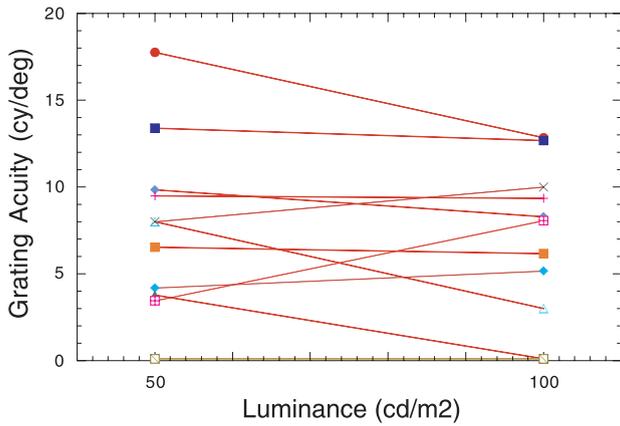


FIGURE 7

Results of testing of 13 children under 2 luminance conditions: 50 and 100  $\text{cd}/\text{m}^2$ . X axis shows the 2 conditions, and Y axis indicates linear grating acuity thresholds. Note that some children have lower, while others have higher, thresholds at 100  $\text{cd}/\text{m}^2$ , an unexpected finding. Three children had low grating acuities, and these did not vary between luminance conditions; thresholds for these children is not plotted. Children with normal vision would not be expected to show a difference between these conditions.

occurred in the perinatal period, or nonverbal because the injury has also caused widespread neurologic damage. Therefore, the clinician cannot expect reliable, verbal feedback from the patient affected by CVI. Furthermore, many children with CVI also have motor complications, including disturbances of ocular motor function. Some children with CVI are unable to make an appropriate eye, head, or neck movement to look at an object of visual interest in their environment, even though they may be able to “see” the object. This difficulty in motor control may complicate the interpretation of behavioral signs of vision in children with CVI (eg, psychophysical measurements of vision). Given the increasing incidence of CVI, there is a great need to establish quantitative measures to assess vision in this population of children.

In this study, the author tested the reliability of the sweep VEP for measuring grating acuity in children with CVI. Several strategies were employed to examine whether the measurements obtained with the sweep VEP actually reflect the underlying visual status of the child with cortical visual impairment. These tests, devised to validate the experimental procedure, suggest that the technique reliably reflects the underlying visual status of the child. The results obtained in this study show promise for the future implementation of this technique in the clinical setting. Finally, different lighting conditions were used in an attempt to determine the usefulness of the VEP technique in predicting a rational rehabilitation strategy. To this effect, grating acuity was measured under different luminance conditions to determine if children affected by CVI show their best visual performance in relatively dim or brightly lit surroundings.

The choice of grating acuity as a VEP stimulus was based on the potential for comparison with a well-known behavioral measure of grating acuity, the Teller acuity procedure, and on the large amount of data from other studies examining Teller acuity in children. Grating acuity as measured using the Teller acuity procedure has been used to monitor and assess vision in other landmark studies of conditions that cause bilateral vision impairment (eg, retinopathy of prematurity).<sup>61-63</sup>

Grating acuity has limitations. Grating acuity only roughly approximates optotype acuity and is probably subserved by different cortical mechanisms than those used for recognition acuity. In the future, other stimuli may offer a better reflection of optotype (Snellen) acuity. Vernier acuity threshold measurements show promise in this regard.<sup>64,65</sup> Grating acuity thresholds were chosen for these experiments because there is more scientific experience measuring grating acuity in young and nonverbal children, particularly using preferential looking techniques.

The VEP technique in this study differs from techniques used in previous investigations of children with CVI. In this series of experiments, we used a swept stimulus pattern technique to measure a threshold for grating acuity. Other investigators have tested flash or pattern reversal VEP.<sup>11,35</sup> The sweep VEP requires multiple trials but records a threshold and provides additional data on signal-to-noise ratios. The VEP stimulus can be varied to adjust to the individual patient tested and can measure thresholds under a number of different stimulus conditions. In this set of experiments, we measured grating thresholds, but vernier acuity, contrast, and luminance thresholds can also be recorded.

The VEP was chosen as an experimental tool for several reasons. Children with CVI have a predilection to look at light, and so it was hoped that a luminescent stimulus source (the monitor) might attract the child's attention.<sup>26,27</sup> CVI is usually accompanied by significant motor deficits. These deficits may preclude a motor movement to regard an object or stimulus of visual interest. Although studies of forced preferential looking can be performed on this group of children, they may be hampered by this motor deficit. With the VEP stimulus, a child can be positioned directly in front of the monitor, so that the stimulus subtends a wide angle of the subject's visual field. The child's head and neck can be stabilized whenever necessary to prevent inadvertent motor movements away from the stimulus. Other advantages and disadvantages of the VEP will now be discussed vis-à-vis the results of the various experiments.

#### MEASUREMENT OF GRATING ACUITY IN A LARGE COHORT OF CHILDREN WITH CVI

In all, 41 subjects with CVI had at least 1 session during

which a VEP grating threshold was determined (Fig 3). Results are compared to a well-established historical control group,<sup>56</sup> also measured on the same stimulus and equipment. Grating thresholds are lower in children with CVI than in normal controls. The results also suggest a trend toward improvement with increasing age, although caution is indicated in interpreting developmental trends in these cross-sectional data. The data could also simply demonstrate a spectrum of static vision impairment in a heterogeneous population of children. Favoring the view that developmental improvement in grating thresholds occurs in this cohort is the finding that second tests of acuity in the reliability experiment were usually better, and to a statistically significant degree, than first tests.

The ability to obtain these data in a large cohort adds further evidence that the sweep VEP tool may be a useful technique for measuring children with CVI. One criticism of the VEP technique is difficulty applying it to children in the age range from 18 months to 4 years. In this cohort, we were successful in obtaining data across a broad age spectrum.

Another criticism of the technique is difficulty measuring sweep VEP thresholds in children with neurologic disease (see below). Such children may have brain malformations, roving eye movements, seizure activity, or depressed cortical activity caused by anticonvulsants. In these experiments, we coped with these problems by averaging the VEP signal across many trials and by carefully monitoring visual fixation. Nevertheless, our threshold results could have been uniformly depressed as a result of these problems. The reliability of our results offers some reassurance that this was not usually the case.

#### **RELIABILITY OF VEP GRATING THRESHOLD MEASUREMENTS IN CHILDREN WITH CVI**

Can a VEP grating threshold measure be reproduced reliably in the same child with CVI? Common arguments against the use of the VEP for clinical measurement stem from the concern that at any given time, the VEP threshold measurement could be variable (reliability), or that the VEP measure is not a reflection of the underlying disease or disease severity (validity). This cohort of patients with severe neurologic disability and a wide spectrum of vision impairment, ranging from light perception only vision to visual acuity of 20/50, is arguably the most difficult in which to assess vision. Problems encountered in measuring vision in these children included convulsive episodes during the test procedure; variable concentration caused by convulsions, anticonvulsants, or underlying severe central nervous system damage; motor impairment making it necessary to immobilize the child's head and/or torso so as to be able to direct the child's gaze to the stimulus; poor attention, particularly in the higher-functioning

children; and unpredictable illness in members of the cohort, making appointments problematic at times.

Signal averaging across many trials helped to obviate some of these problems. The VEP apparatus allows the tester to stop the trial and restart the same trial when fixation on the screen is lost, or when seizure activity or motion interferes with the test. Nevertheless, testing in some of the children was difficult, and it is possible that the VEP underestimated or poorly estimated acuity at least in some of the cohort. Structural brain abnormalities also could interfere with signal measurements and could cause the sweep VEP to measure acuity incorrectly.

Other investigators have encountered problems using the sweep VEP to measure acuity thresholds in children. In normal children, pooled data from subjects tested and retested show good reliability, but there is variability for each subject.<sup>66</sup> The sweep VEP may be useful for neurologically or developmentally impaired children, but inconsistent scores still occur.<sup>67</sup> Infants tested in different behavioral states may show variation in performance when tested with the VEP.<sup>68</sup> There is also evidence that certain anticonvulsants can interfere with VEP measurements.<sup>69</sup> For these reasons, results from these experiments should be viewed as preliminary.

The sweep VEP has been shown to be a reliable test in application to a normal cohort.<sup>70</sup> In this experiment, the author has demonstrated that it is usually reliable in a population with cortical visual loss, despite the potential problems noted above. Only one subject could not reliably repeat the test, because he was significantly neurologically obtunded at the second examination. Factors that may enhance the reliability of the sweep VEP include signal averaging across multiple, 10-second trials, the use of a luminescent stimulus source, and the fact that the test does not always require motor/behavioral responses as a prerequisite to measuring vision.

#### **COMPARISON OF SWEEP VEP RESULTS TO A CLINICAL MEASURE OF VISION**

Most of the subjects in this cohort had not attained any language milestones. In normal, preverbal children, (normal) visual acuity is inferred on the basis of normal pupillary responses, good visual fixation, normal anatomy, and the absence of nystagmus, strabismus, or refractive errors. All these factors were also normal in the cohort with CVI, except visual fixation. A clinical system was therefore devised that takes into account fixation and behavior.<sup>60</sup> In previous work,<sup>60</sup> these Huo criteria were used to monitor improvement in a large population of children with CVI. However, the criteria are very difficult to apply and, admittedly, an approximation of vision in children with CVI. The approximate nature of clinical assessment is the very problem necessitating a better, quantitative measure

of vision in children with CVI.

Nevertheless, as one means of validating the VEP grating acuity data, it seemed prudent to compare the VEP thresholds to a clinical measure. The VEP measures would be suspect if they bore no relationship to the clinical status of the child. A strong correlation between clinical signs and electrophysiologic measures was found when thresholds were compared from children in whom a masked clinical assessment was obtained.

#### COMPARISON OF VEP GRATING THRESHOLD MEASURES TO FORCED CHOICE PREFERENTIAL LOOKING MEASURES

Another clinical measure of vision is forced choice preferential looking. In this test, a child is confronted with a blank card on one side and a grating card on the other. A threshold can be measured by testing the subject with increasingly difficult-to-see stimuli, until the child cannot see the grating card and thereby fails to make an eye movement to notice the card. The Teller acuity procedure has become a widely accepted means of measuring grating acuity in preverbal children. The test has been shown to be reliable and can be validated against clinical findings, both in normal subjects and in children with a variety of diseases.

However, FPL, of which Teller acuity is an example, could have limitations in the study of CVI. Its application to children with poor motor control is potentially problematic, because a motor movement is required to demonstrate visual perception. Despite the fact that FPL correlates with visual outcome in studies of another important cause of blindness in children, retinopathy of prematurity,<sup>61-63</sup> the FPL measures are sometimes not as sensitive as desired; that is, a normal or near-normal FPL result in an infant may only approximate Snellen visual acuity.

The Teller acuity card procedure offers a well-standardized means for comparison of VEP data. Figure 5 shows this comparison of 21 children with CVI. The graph shows that the VEP acuities were consistently higher, particularly in children with poorer vision. In children with better vision, a better correlation can be seen between Teller grating acuity and VEP grating acuity.

Results of this comparison should be interpreted cautiously. It is possible that fatigue in performance could be a greater factor when the Teller procedure is performed after the VEP, since FPL requires a motor response to a visual stimulus. Even so, the 2 measures, Teller acuity and VEP acuity, can be shown to correlate with each other, further validating the VEP as a potentially useful clinical and research tool.

One interpretation of the data is that behavioral testing underestimates vision in children with poor motor control. In support of this is the observation that

higher-functioning children showed FPL results more consistent with VEP results. Higher-functioning children are much more likely to be ambulatory and to have better neck, torso, and eye movement control. In the author's view, it is unlikely that the VEP overestimates vision in lower-functioning children, although this is also another interpretation. It is likely that the VEP measures grating acuity in children who cannot demonstrate the motor behavior linked to vision.

#### EFFECT OF LUMINANCE ON VEP GRATING ACUITY

Important clinical observations could be tested using the VEP system. Children with CVI show behaviors that have not been fully explained or confirmed quantitatively. One seemingly paradoxical behavior was measured: light attraction seen in some children with CVI and photophobia seen in others. The author tested the hypothesis that variations in illuminance of a grating stimulus will alter the grating threshold in some children with CVI.

Normal infants and adults have been studied at varying retinal illuminations. Dobson and colleagues<sup>71</sup> used a behavioral technique (FPL) to measure grating acuity in 2-month-old infants and adults at a wide range of luminances. They found that adults and infants reach a peak threshold at the same luminance, which in their study was approximately 44 TD, corresponding to approximately 10 cd/m<sup>2</sup>. Brown and colleagues<sup>72</sup> arrived at similar conclusions in a study performed in 1987. In a similar study using the VEP, Allen and associates<sup>58</sup> found that grating acuity thresholds peaked above about one cd/m<sup>2</sup>. Below the luminance level of approximately one cd/m<sup>2</sup>, there is a decremental increase (worsening) in grating threshold as luminance decreases.

Given the results of these past experiments, 2 conditions were chosen for this study: 50 and 100 cd/m<sup>2</sup>. If children with CVI behaved comparably to normal subjects reported by these other groups, there should be no significant difference in grating thresholds at the 2 different luminance levels. Taken as individuals, some children see better, some see worse, and others show no change with brighter illumination. The number of subjects makes statistical analysis of the data problematic. Furthermore, it is likely, on the basis of clinical histories, that these subjects are a heterogeneous group, some with better visual function and some with worse in dim luminance conditions.

One possibility to explain the variation in acuities seen is that the subject's accommodation or pupil size is affected by the different stimulus conditions, as it is well known that accommodation is erratic in infants.<sup>73,74</sup> However, the change in pupil size would not alter the luminance effect enough to affect grating thresholds. Even so, the result should be that brighter illuminance would increase (worsen) grating thresholds. There is

nothing about varying luminance per se that should affect accommodative response. Another issue could be that these particular subjects are simply unreliable, showing varying threshold responses at different times. This also is unlikely (see above discussion of reliability).

Spatial resolution, particularly at high spatial frequencies, is mediated by a number of factors, including photoreceptor spacing<sup>75</sup> and optics of the visual system under investigation.<sup>76,77</sup> In children with brain damage and poor vision, any mechanistic explanation of variations in grating acuity with luminance must evoke postphotoreceptor, central nervous system processes. In this regard, central photophobia has been described in adults as a result of thalamic stroke, the so-called thalamic glare syndrome.<sup>78</sup> The thalamus plays an important role in modulating afferent central nervous system input. Damage to the thalamus is known to occur in severe cases of perinatal hypoxia/ischemia. A thalamic injury mechanism still may not explain improved acuity seen in some children under conditions of diminished illuminance, unless the effect of luminance variation is exaggerated considerably at the postreceptor, higher-order neuron level.

Perhaps some other mechanism can explain the reason children with CVI are often drawn to look at brightly illuminated objects. This illuminance study seems to confirm this clinical finding: some of the children studied showed improved grating thresholds under brighter illumination. This finding is also unexpected, given previous studies' findings on the stability of grating acuity across a wide range of luminance conditions. It is also important to note the observation that some children showed the expected finding, no change in acuity as luminance varies. This additional observation points to the potential value of quantitatively analyzing the child's response to a different luminance condition.

Although a plausible mechanistic explanation for improvement under bright or dim luminance is lacking, this finding still has potential clinical significance. Predicting the child's optimal visual environment may go a long way toward maximizing a rehabilitation program tailored to the individual. If a child sees better at reduced luminance, for example, his or her teachers would be well advised to consider this as they present the child with visual learning tasks.

These series of experiments have shown that the sweep VEP is a reliable and valid tool for measuring vision in children with CVI. Furthermore, the tool may be used to help define a rehabilitation program for individual children. The VEP tool still has its limitations. It is complicated and requires 2 people to run effectively. VEP measurements are time-consuming as well. It is hard to imagine the sweep VEP as an office procedure in the near future.

On the other hand, time spent with children and their

families was invaluable. And, since most children showed some quantifiable grating acuity, confirming parents' perceptions and often contradicting reports from schools or family physicians, the impact on the families was usually very positive.

Future investigations in this laboratory will focus on expanding the use of the sweep VEP to measure vernier acuity in children with CVI and on endeavoring to develop VEP measures of cognition, since it is often not known whether children with CVI understand what they see.

## CONCLUSIONS

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1. Children with CVI show a spectrum of grating acuity impairment that can be measured using the sweep VEP technique.
2. The sweep VEP measures grating acuity in a reliable fashion.
3. When compared to a clinical measure of vision, the Huo scale, the VEP threshold measurement is valid and approximates clinical findings.
4. Compared to the Teller acuity procedure, the VEP appears to also be a sensitive index of vision. Teller acuity may underestimate grating acuity in CVI in some children. An alternative hypothesis is that VEP grating acuity overestimates grating acuity in some children. The VEP technique correlates significantly with the Teller acuity procedure, further validating the VEP technique.
5. The VEP tool may be useful for defining a rehabilitation program for visually impaired children. When children were tested under different luminance conditions, they showed an unexpected range of grating acuities, depending on the individual child.

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# INTRAOCULAR RETINAL PROSTHESIS

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BY Mark S. Humayun, MD, PhD

## ABSTRACT

*Purpose:* An electronic implant that can bypass the damaged photoreceptors and electrically stimulate the remaining retinal neurons to restore useful vision has been proposed. A number of key questions remain to make this approach feasible. The goal of this thesis is to address the following 2 specific null hypotheses: (1) Stimulus parameters make no difference in the electrically elicited retinal responses. (2) Just as we have millions of photoreceptors, so it will take a device that can generate millions of pixels/light points to create useful vision.

*Methods:* For electrophysiologic experiments, 2 different setups were used. In the first setup, charge-balanced pulses were delivered to the retinal surface via electrodes inserted through an open sky approach in normal or blind retinal degenerate (rd) mice. In the second setup, the rabbit retina was removed under red light conditions from an enucleated eye and then maintained in a chamber while being superfused with oxygenated, heated Ames media. In both setups, stimulating electrodes and recording electrodes were positioned on the retinal surface to evaluate the effect of varying stimulation parameters on the orthodromic retinal responses (ie, recording electrode placed between stimulating electrodes and optic nerve head).

For psychophysical experiments, visual images were divided into pixels of light that could be projected in a pattern on the retina in up to 8 sighted volunteers. Subjects were asked to perform various tasks ranging from reading and face recognition to various activities of daily living.

*Results:* Electrophysiologic experiments: In a normal mouse, a single cycle of a 1-kHz sine wave was significantly more efficient than a 1-kHz square wave ( $P < .05$ ), but no such difference was noted in either of the 8- or 16-week-old rd mouse groups (8-week-old,  $P = .426$ ; 16-week-old,  $P = .078$ ). Charge threshold was significantly higher in 16-week-old rd mouse versus both 8-week-old rd and normal mouse for every stimulus duration ( $P < .05$ ). In all groups, short duration pulses (40, 80, and 120  $\mu$ s) were more efficient in terms of total charge (the product of pulse amplitude and pulse duration) than longer (500 and 1,000  $\mu$ s) pulses ( $P < .05$ ). In all groups, applying a pulse train did not lead to more efficient charge usage ( $P < .05$ ).

Psychophysical experiments: In high-contrast tests, facial recognition rates of over 75% were achieved for all subjects with dot sizes of up to 31.5 minutes of arc when using a 25 x 25 grid with 4.5 arc minute gaps, a 30% dropout rate, and 6 gray levels. Even with a 4 x 4 array of pixels, some subjects were able to accurately describe 2 of the objects. Subjects who were able to read the 4-pixel letter height sentences (on the 6 x 10 and 16 x 16 array) seemed to have a good scanning technique. Scanning at the proper velocity tends to bring out more contrast in the lettering. The reading speed for the 72-point font is a bit slower than for the next smaller font. This may be due to the limited number of letters (3) visible in the window with this large font.

*Conclusions:* Specific parameters needed to stimulate the retina were identified. Delineating the optimum parameters will decrease the current requirements. Psychophysical tests show that with limited pixels and image processing, useful vision is possible. Both these findings should greatly simplify the engineering of an electronic retinal prosthesis.

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## INTRODUCTION

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### I. HISTORICAL OVERVIEW AND CURRENT APPROACHES

Blindness afflicts more than 1 million Americans, and approximately 10% have no light perception.<sup>1</sup> A number of

approaches, including gene and drug therapies, are currently being pursued in the hope of preventing blindness.<sup>2,3</sup> Nevertheless, once vision is totally lost, only 2 of the existing approaches show promise for reversing the ailment: retinal transplantation<sup>3,4</sup> and bioelectronic visual prosthesis.

During the 18th century, scientists understood that electricity could elicit a response in biological tissues.<sup>5,6</sup> The era of electronic implants was ushered in by both cardiac pacemakers and cochlear implants.<sup>7,8</sup> Since then, along with the development of a visual prosthesis, electrical stimulation has been proposed to restore limb function

\*From the Retina Institute, Doheny Eye Institute, Keck School of Medicine of USC, Los Angeles, California. Supported by grant EY 11888 from the National Eye Institute, BES 9810914 from the National Science Foundation, and EY 12893 from the National Institutes of Health.

in paraplegics and quadriplegics<sup>9-11</sup> as well as to suppress intractable pain<sup>12</sup> and Parkinsonian tremor.<sup>13</sup>

### 1.1 Cortical Prosthesis

Work toward a visual prosthesis started with electrical stimulation of the visual cortex. Direct electrical stimulation of the cortical surface under local anesthesia of a sighted human subject resulted in seeing a spot of light (phosphene). The position of the light in space corresponded correctly to the stimulated anatomical region.<sup>14</sup> Subsequently, similar results were obtained in blind patients.<sup>15-17</sup> In another experiment, electrodes were implanted over a period of 3 to 10 weeks on the occipital cortex of 3 blind patients. Two of these patients were able to locate a light source by scanning the visual field with a photocell, the output of which electrically stimulated the cortex via a wire passing through the scalp and skull.<sup>18</sup>

A key experiment in this field was performed when 80 electrodes were implanted on the visual cortical surface of a 52-year-old nurse blind from bilateral severe glaucoma and retinal detachment in the left eye. Wires through a burr hole connected each electrode to a radio receiver screwed to the outer bony surface. An oscillator coil was placed above a given receiver in order to activate the receiver via radio frequency and stimulate the cortex. With this system, the patient was able to see light points in 40 different positions of the visual field, demonstrating that half of the implanted electrodes were functional. This experiment showed that a chronically activated electrical stimulation device could be safe.<sup>19</sup> A second implantation by the same group was performed in a blind 64-year-old patient with retinitis pigmentosa (RP). He was able to read random letters at 8.5 characters per minute.<sup>20</sup>

In spite of the ability to induce phosphenes, there were many difficulties to overcome. These included phosphene flickering during surface stimulation;<sup>19,21,23,24</sup> the need for high currents and large electrodes to induce phosphenes;<sup>24</sup> and interactions between phosphenes when electrodes were placed less than 2.4 mm apart. The same stimulating electrode inducing multiple phosphenes and those produced were inconsistent. Occasionally, pain was induced owing to meningeal stimulation. Other drawbacks included limited two-point discrimination, local heating and electrolysis,<sup>25</sup> and phosphene persistence following cessation of electrical stimulation.<sup>26</sup>

In spite of all the shortcomings, efforts continued and other 64-channel platinum disc electrode arrays were implanted on the occipital cortical surface of blind patients.<sup>21,27-29</sup> The prosthesis allowed blind patients to read "phosphene Braille" 2 to 3 times faster than tactile Braille and to recognize 6-inch characters at 5 feet (approximately 20/1200 visual acuity).<sup>30</sup> It was also found that phosphene brightness was a logarithmic function of stim-

ulating current amplitude.<sup>27</sup>

However, the need for smaller electrodes and more localized phosphenes forced the development of intracortical electrodes.<sup>26,31-36</sup> During a planned neurosurgical procedure to excise epileptic foci of the brain under local anesthesia, 1 group inserted 37.5 mm-diameter iridium microelectrodes into the occipital cortex of these patients. Stimulation was performed with both surface and intracortical electrodes. Both methods elicited phosphenes, but the stimulus current threshold for intracortical microstimulation was 10 to 100 times lower than that for stimulation using surface electrodes.<sup>26</sup> Based on intracortical electrodes, a new cortical prosthesis with 38 microelectrodes was implanted in an area 40.8 x 19.2 mm in the visual cortex of a 42-year-old patient totally blind for 22 years due to glaucoma. The electrodes were implanted for a period of 4 months, and this experiment showed that despite being blind for many years, the subject was able to perceive phosphenes at a predictable and reproducible location in the visual space.<sup>32</sup> It was also demonstrated that simple patterned perceptions could be evoked by electrical stimulation via small groups of these microelectrodes. Electrodes spaced as close as 500  $\mu$ m apart generated separate phosphenes, and at levels near threshold, the phosphenes usually had colors.

Undoubtedly, the lower current threshold of the intracortical microstimulation, the predictable forms of generated phosphenes, the absence of flicker phenomenon, reduction of phosphene interactions, the opportunity to increase the number of electrodes, the power requirement improvement, and the current per microelectrode reduction are the main advantages of the intracortical microstimulation approach.<sup>26,32</sup> Because of these advantages, all major efforts investigating the development of a visual cortical prosthesis have abandoned the use of surface electrodes and are developing intracortical microstimulating electrodes.

There are advantages and disadvantages that are associated with the cortical stimulation approach in general. The skull will protect both the electronics and the electrode array, and a cortical prosthesis will bypass all diseased neurons distal to the primary visual cortex. By doing so, it has the potential to restore vision to the largest number of blind patients. However, spatial organization is more complex at the cortical level and 2 adjacent cortical loci do not necessarily map out to 2 adjacent areas in space, so that patterned electrical stimulation may not produce the desired patterned perception. In addition, the convoluted cortical surface makes it difficult for implantation, and surgical complications can have devastating results, including death.

### 1.2 Retinal Prostheses

During the early 1970s, it became clear that blind humans

can also perceive electrically elicited phosphenes in response to ocular stimulation, with a contact lens as a stimulating electrode.<sup>37-39</sup> When obtainable, these electrically elicited responses indicated the presence of at least some functioning inner retinal cells. Since a number of blinding retinal diseases are due predominantly to degeneration of outer retina or photoreceptors,<sup>40-42</sup> the idea of stimulating the remaining inner retina has been proposed (Figs 1 and 2).

Progress in the field of neural prostheses has converged with advances in retinal surgery to enable the development of an implantable retinal prosthesis. At present, this implant is aimed at patients blinded primarily by photoreceptor loss such as RP and some forms of age-related macular degeneration (AMD). These 2



FIGURE 1

Intraocular retinal prosthesis. Both power and data are delivered via an inductive link. Camera (not shown) and transmitter coil are in glass frame, and receiver coil is placed in sulcus. Microelectronics are positioned in vitreous so as to reduce risk of harming retina through either mechanical or electrical damage. Only a delicate electrode array is affixed to retina to transmit electrical pulses. Primary (arrow) and secondary (arrowhead) coils. Asterisk denotes a rectifier and regulator, a retinal stimulator with a telemetry protocol decoder, and stimulus signal generator. Plus symbol denotes an electrode array.

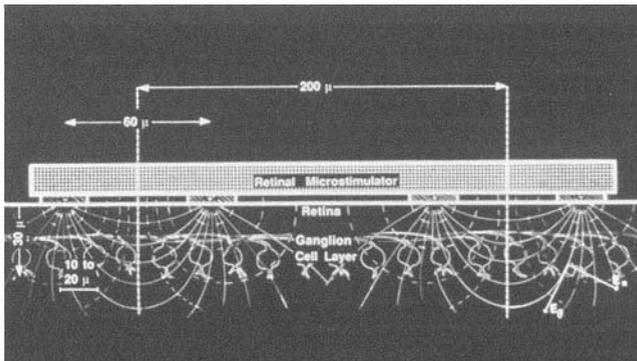


FIGURE 2

Schematic of epiretinal electrode array part of intraocular retinal prosthesis. By passing electrical current between electrodes, electronic implant will excite remaining underlying retinal neurons.

degenerations are common and account for a significant percent of the blind population. The incidence of RP is 1 per 4,000 live births, and there are approximately 1.5 million people affected worldwide, making RP the leading cause of inherited blindness.<sup>2</sup> AMD is the main cause of visual loss among adults older than 65 years of age in Western countries. Annually, there are approximately 700,000 new patients in the United States who lose vision on account of this illness, and 10% of these become legally blind each year.<sup>43</sup>

Postmortem morphometric analysis of the retina of patients with RP has shown that many more inner nuclear layer cells (bipolar cells and others, 78.4%) are retained compared to outer nuclear layer (photoreceptors, 4.9%) and ganglion cell layer (29.7%).<sup>40-42</sup> Similar results have been found in patients with AMD.<sup>44</sup> Given that there is limited transsynaptic neuronal degeneration, it does seem feasible to stimulate the remaining retinal neurons.

Currently, several groups have been developing retinal and optic nerve prostheses.<sup>45-53</sup> These groups can be classified according to the location of their device: on the retinal surface (epiretinal), in the subretinal space, or around the optic nerve (Fig 3).

To examine if these remaining retinal neurons could be electrically excited in a manner that might restore useful vision, intraocular retinal stimulation studies were performed. Prior to the surgical procedure, patients had to pass a screening test, which grossly tested the inner retinal function. In this screening test, in an outpatient clinic setting, they had to perceive light in response to electrical stimulus delivered by a contact lens connected to a computer (electrical evoked response). Following this initial screening, the surgery involved a three-port pars plana vitreoretinal procedure with subconjunctival anesthesia placed only over the sclerotomies in order to avoid

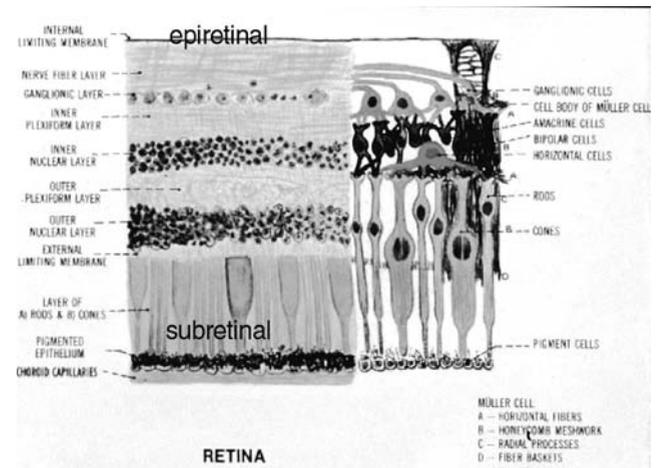


FIGURE 3

Retinal cytoarchitecture. Text shows placement of epiretinal and subretinal devices.

disrupting the optic nerve function. Different types of hand-held stimulating electrodes were positioned on the retinal surface (ie, almost touching the internal limiting lamina). Computer-generated current pulses were then delivered through these electrodes, and the patients were then asked to tell the surgeons about their visual perceptions.

Focal electrical stimulation elicited “phosphenes” in all the patients, and 4 or 5 patients were able to describe spatial and temporal aspects of the stimuli. The resolution was estimated to be 4.5 per 200, consistent with crude ambulatory vision.<sup>54</sup>

Recently, epiretinal electric stimulation was further tested in nine other patients with RP or AMD.<sup>47</sup> Two patients were tested with an electrode array consisting of 3 x 3, 5 x 5, or 3 x 7 electrodes. Seven other subjects were tested with simple devices consisting of 3 platinum electrodes packaged as a surgical instrument in a handpiece. The study showed that in the patients with RP, the electrical stimulation threshold was dependent on the electrode’s location (ie, the macular region required higher threshold currents than the peripheral retina to elicit visual perceptions). Also, patients with less advanced RP or AMD required lower threshold currents than those with more advanced disease. These findings are important because lower thresholds would allow for smaller and therefore higher density of electrodes and hence greater resolution. Lower threshold values in healthier retinas were later confirmed by other experiments.<sup>55-58</sup>

Perhaps the most important result of these human studies was the patients’ ability to use the pattern electrical stimulation to recognize shapes and forms. Patients were able to identify crude forms such as a single letter or a box shape during the short period of electrical stimulation testing. When the electrical stimulation ended, there was no persistence of the image. Later, another group also confirmed some of these results in healthy retina of a sighted volunteer.<sup>58</sup> Other important psychophysical perceptions in this study included flicker fusion (at a frequency of 40 to 50 Hz) and different color perceptions.<sup>47</sup>

Thus far, the results mentioned have all been from the epiretinal electrical stimulation. By having a significant portion of the electronics wearable at the eyeglass frame rather than implanted, the epiretinal implantation minimizes the risk of failure and optimizes the ease of replacement or upgrading the electronics. Additionally, a majority of the implanted intraocular electronics could be placed in the vitreous cavity, a naturally existing fluid-filled space, which greatly helps in dissipating heat generated by the electronics.<sup>50,59,60</sup> However, an epiretinal prosthesis will be exposed to ocular rotational movements, making the need for a nontraumatic yet sturdy attachment method paramount. Also, by physically being closer to the retinal ganglion cells (RGCs), it may be more difficult to

stimulate bipolar cells, and therefore one may lose the visual processing that takes place in this layer.

The subretinal approach has equally made great strides. Recently, a phase I clinical trial of subretinal visual prosthesis implantation in 3 human subjects was announced. Measuring 2 mm in diameter and 0.25 mm thick, this retinal prosthesis contains 3,500 solar cells that generate power from light that enters the eye.<sup>61</sup> The subretinal positioning of the retinal prosthesis has the advantage of placing the stimulating electrodes closer to the bipolar cells, which may also permit lower stimulus thresholds.<sup>48,49,62-65</sup> However, the placement of any object between the choroid and the retina can be more disruptive to the nutritional supply of the retina derived from the choroid.<sup>48</sup> Another drawback of this method is the limited amount of light that can reach the array coupled with the inefficiency of modern-day photovoltaic or solar cells. This translates into using a very bright and nonfeasible image intensifier (10 suns) in order for the stimulator chip to generate the level of currents that have resulted in visual perceptions in the blind. Regardless of whether the implant is positioned on the epiretinal or subretinal surface, there are distinct advantages and inherent disadvantages associated with these intraocular retinal stimulation approaches. The advantages include the ability to use existing physiologic optics and retinotopic organization of the eye in addition to the natural processing ability along the proximal visual pathways. Furthermore, the vitreous cavity fluid can be utilized as a heat sink, and the prosthesis could be visualized by dilating the pupil in an outpatient setting. Less surgical morbidity and mortality are expected in comparison to any of the cortical prostheses implantation methods. The disadvantages of the retinal stimulation approach include the following; possible disruption of retinotopic organization due to nonselective stimulation of ganglion cells’ axons; possible difficulties in chronic attachment of a device to the retina; inability to properly encode many properties of the visible light (eg, color, intensity) that the retina naturally does so well; and the fact that this approach is limited to outer retinal pathologies.

### 1.3 Optic Nerve Prosthesis

Investigators have also stimulated the optic nerve.<sup>66,67</sup> In spite of the relative ease of reaching the optic nerve during surgery, the high density of the axons (1.2 million within an approximately 2 mm-diameter cylindrical structure) could make it difficult to achieve focal stimulation and detailed perceptions. In addition, any surgical approach to the optic nerve requires dissection of the dura and can have harmful side effects. Similar to the retinal prosthesis approach, optic nerve stimulation requires intact RGCs and is limited to outer retinal pathologies.

Recently, 1 of the groups chronically implanted a self-sizing spiral cuff electrode with 4 contacts around the optic nerve of a 59-year-old blind patient with RP. Electrical stimuli applied to the optic nerve produced localized, often colored phosphenes that were broadly distributed throughout the visual field and were reliably reinduced 118 days after surgery. Changing the pulse duration (PD) or pulse frequency could vary phosphene brightness.<sup>52</sup>

Yet another approach, a hybrid retinal implant, proposes to develop an integrated circuit, which would include both electronic and cellular components. The electronics will perform image recognition, and the neurons on the device will extend their axons to synapse with the lateral geniculate body and thus create the device-CNS interface and restore vision.<sup>53,68</sup> The advantage of this approach is to be able to reconstruct an eye with total or inner retinal degeneration. Disadvantages include difficulties in precisely directing axons to the lateral geniculate body, developing the interface between the electronics and neurons, and an environment to enable survival of the cellular components while being housed in microelectronics.

#### *1.4 Sensory Substitution Devices*

As an alternative to direct stimulation of the visual system neurons, several other approaches have attempted to convert visual information into vibrotactile or auditory signals (ie, sensory substitution devices<sup>69,70</sup>). The distinct advantage of these approaches is that the device is wearable and not implantable. However, these devices have never reached widespread acceptance because they do not restore the sensation of vision, have low resolution, occupy another sensory modality, can evoke pain, and can have a prolonged learning period.

## **2. BIOCOMPATIBILITY**

Biocompatibility issues are of paramount concern with any implantable device. The implant has to be constructed and implanted in a manner so as not to damage the tissue but also so the implant will function reliably over many decades. In the case of an electronic retinal prosthesis, there are both mechanical and electrical concerns.

### *2.1 Mechanical Biocompatibility*

**2.1.1 Infection and inflammation.** Despite the fact that the CNS and the eye have been described as immunologically or partially immunologically privileged sites,<sup>71,72</sup> the course of inflammation is identical to that occurring elsewhere in the body once an incitement of inflammation has occurred.<sup>73</sup> Mere surgical manipulation, as well as infection, biodegradation, or the release of toxic substances from the implant, can provoke the inflammatory response.

Bacterial infections are often delayed and appear to be due in part to the host's inability to respond properly to infections. Their origin is frequently distant infected sites in the body or skin flora.<sup>74</sup> Less often, the origin is infected implants and surgical and nursing staff.

**2.1.1.1 Cortical implantation.** The biocompatibility of various chronic intracortical stimulating arrays was examined. Preliminary experiments of chronic implantation of stimulating devices over the cortex revealed a fibrous membrane covering the surface of every implant that was examined 6 weeks or more after insertion. These membranes had little effect on threshold for stimulation.<sup>19</sup> There was only 1 report on the need to remove a chronic device from the cortical surface of a patient because of a blood-borne infection.<sup>30</sup>

**2.1.1.2 Retinal prosthesis.** The field of retinal prostheses is relatively new, and few reports on chronic implantation and adverse reaction are available. In the few experiments done, some used only sham devices with no electrical stimulation in order to examine mechanical biocompatibility. In 1 such study, performed in 4 dogs, no retinal detachment occurred and only retinal pigment epithelium (RPE) changes were noted near the retinal tacks, which were used for fixation of the epiretinal implant.<sup>59</sup> In another study, it was reported that 9 of 10 rabbits were implanted without serious complications. The implant was stable at its original fixation area, and no change in retinal architecture underneath the implant was found by light microscopy. In 3 cases, mild cataract formation was observed, and in 1 case, a total retinal detachment was found after 6 months of follow-up.<sup>75</sup> In another study, 3 rabbits were implanted with an electrode array in the subretinal space. No side effects were reported.<sup>63</sup>

In a single case of implantation of optic nerve stimulating electrodes in a human, no acute or chronic side effects were noted.<sup>52</sup> No acute damage has been noted after electrical stimulation of the sciatic nerve of cats with similar cuff electrodes.<sup>76</sup>

**2.1.2 Attachment.** Any implanted electronic device will be exposed to movements and should be attached in a stable manner to its intended anatomical location. In particular, the epiretinal prosthesis will be exposed to countercurrent movements in response to ocular rotational movements that can reach a speed of 700 degrees visual angle per second.

The attachment methods differ according to different approaches and different locations along the visual pathways. The preferable fixation site of the intracortical microstimulation arrays is probably the cortex itself, and not the skull, because of the constant movement of the brain in relation to the skull. These arrays are currently inserted either by manual insertion of individual or groups of 2 to 3 electrodes normal to the cortical surface to a

depth of 2 mm<sup>32</sup> or by a pneumatic system that inserts 100-electrode arrays into the cortex in about 200 ms.<sup>77</sup>

The subretinal approach takes advantage of the adherence forces between the sensory retina and the retinal pigment epithelium to keep the array in place. On some occasions, though, the array can be displaced after implantation.<sup>64</sup> The surgical procedure is performed extraocularly through the sclera (ab-externo) or intraocularly through a retinotomy site after a vitrectomy procedure. One of the groups used a custom-made implantation tool to insert the device into the subretinal space.<sup>45</sup>

Bioadhesives, retinal tacks, and magnets have been some of the methods examined for epiretinal attachment. In 1 study, the retinal tacks and the electrode array remained firmly affixed to the retina for up to 1 year of follow-up with no significant clinical or histologic side effects.<sup>59</sup> Similar results were shown in rabbits.<sup>75</sup>

In another study, 9 commercially available compounds were examined for their suitability as intraocular adhesives in rabbits. One type of adhesive (SS-PEG hydrogel, Shearwater Polymers Inc) proved to be strongly adherent and nontoxic to the retina.<sup>78</sup> Others have conducted similar experiments.<sup>79</sup>

**2.1.3 Coating the electronics (hermetic seal).** All visual prostheses will consist of various electronic components. Implanted electronic elements such as data and power receivers and the stimulation processor must be hermetically sealed from the corrosive biological fluid.<sup>10</sup> This protective coating should last for several decades. The requirement of hermetically sealing a circuit in the case of neural stimulating devices is complicated by the demand that multiple conductors (feed-throughs) must penetrate the hermetic package so that the stimulation circuit can be electrically connected to each electrode site in the electrode array. These connections are the most vulnerable leakage points of the system.

The pacemaker industry has developed effective encapsulation using a hermetically sealed titanium case. Glass and ceramic packages have proved to be good hermetic cases as well. Integrated circuit electrodes and sensors require less bulky encapsulation. In the last few years, much attention has been focused on the development of miniature hermetic packages for microelectrode protection, though few provide a high number of reliable feed-throughs in a small volume.<sup>80</sup> Many types of welding or sealants tend to leak over time, are not biocompatible, and are expensive. The most encouraging results of hermetic packaging come from medical implant companies, such as Advanced Bionics (Sylmar, Calif), that involve novel use of organic polymers in combination with either ceramic or titanium cases.<sup>81</sup>

Yet another hermetic packaging technique is based on electrostatic (anodic) bonding of glass to silicon. The

process generates a high electric field at the glass-silicon interface and causes a permanent and irreversible fusion bond between silicon and glass.<sup>10,82,83</sup> Using a silicon substrate allows many micron scale feed-throughs to be micromachined into the hermetic package. Recently, a new technique of aluminum/silicon-to-glass solder bonding was developed. This technique provides more than 10 megapascals of bonding strength and a good hermeticity.<sup>84</sup>

In summary, techniques for coating the electronics are a fundamental step to the future feasibility of any visual prosthesis, which has the daunting hurdle of hermetically sealing a small electronic package with a high number of feed-throughs.

## 2.2 Electrical Stimulation Biocompatibility

**2.2.1 How much current can be used before impairing the physiological function of the cells?** When applying electrical stimulation, neural damage limits need to be considered. Among the early studies that have had a significant impact on this field are the histopathologic studies of long-term stimulation of neural tissue<sup>85-87</sup> and the electrochemical studies of the electrode-electrolyte interface.<sup>88</sup> The relative safety of biphasic charge balanced waveforms compared to monophasic waveforms was demonstrated.<sup>89</sup>

Any net direct current (DC) can lead over time to irreversible electrolyte reactions. A biphasic current waveform consisting of 2 consecutive pulses of equal charge but opposite polarity has no DC component. A simple monophasic waveform is unacceptable for neural stimulation because it delivers DC and creates irreversible faradic processes. Faradic reactions involve electron transfer across electrode-tissue interface and oxidation/reduction of chemicals. It is also necessary to know the chemical reversibility of electrode materials and stimulation protocols. Chemical reversibility requires that all processes occurring at an electrode subjected to an electrical pulse, including H<sub>2</sub> and O<sub>2</sub> evolution, will be chemically reversed by a pulse of opposite polarity. Chemical reversibility can be examined by cyclic voltammetric analysis<sup>90</sup> and other methods such as direct observation of gas bubbles, UV spectroscopy, or atomic absorption spectrometry of in vitro pulse solutions. Corrosion effects on electrode surfaces can be examined by scanning electron microscopy.

It was shown that electrical stimulation-induced neural injury is dependent on current amplitude and pulse frequency, but more important, on charge density and charge per phase.<sup>91-93</sup> The charge per phase is defined as the integral of the stimulus current over half (1 phase) of 1 cycle of the PD. Charge density is defined as charge per phase divided by the electrochemically active surface area of the electrodes. From these definitions, it can be understood that very small electrodes can produce very low

current thresholds, yet may produce unacceptably high charge densities. Since total charge density is responsible for the damage of tissue and electrodes, there is a theoretical limit as to how small the electrodes can be.<sup>94,95</sup> Total charge delivered to the tissue cannot be ignored, even though it is within safe limits of the size of the electrodes being used. Put another way, the threshold for neural damage is related not only to the charge density, but also to the total charge.<sup>92,96</sup>

Using simple waveforms, conservative charge density/charge limits for chronic stimulation with platinum are 100  $\mu\text{C}/\text{cm}^2$  and 1  $\mu\text{C}/\text{phase}$ . For activated iridium oxide (IrOx) electrodes, the limit is 1  $\text{mC}/\text{cm}^2$  and 16  $\text{nC}/\text{phase}$ . Nevertheless, chronic stimulation can reduce the maximum charge density that is safely injectable.<sup>97</sup> Many of the studies that were done to determine these limits were performed in cortical tissue<sup>91,92</sup> or obtained from studies on electrical stimulation of the auditory nerve.<sup>98</sup>

In spite of all the limitations and difficulties, it was found that neural stimulation with electrical pulses can be safe and have stable, effective long-term results.<sup>93,99,100</sup> It was also shown that transient changes in neural response properties, such as stimulation-induced depression of neuronal excitability, are caused by electrical stimulation, but these have not been correlated to histologically detectable tissue damage.<sup>93,96,101</sup> In other studies, it was shown that repeated stimulation did not change the threshold amplitudes over time since implantation.<sup>19,28,52</sup>

Despite established safe limits for neural stimulation, long-term in vivo retinal stimulation must be performed before any conclusions regarding threshold stimulation parameters of the retina are made. The reason is that the threshold at which damage occurs cannot be freely extrapolated from 1 neural tissue to another.<sup>102</sup>

**2.2.2 How much heat can the device produce?**  
Different components of the visual prostheses can produce excessive heat and cause damage if not kept below a certain limit. Many of the studies regarding thermal exposure damage studied the effects of microwave and other electromagnetic field exposures. The safe limit is usually considered to be 1.6 (0.06°C) or 8 W/kg (0.3°C) (uncontrolled or controlled exposure to microwave radiation, respectively), above which any heating would be undesirable.<sup>103</sup> The retina's ability to dissipate and tolerate heat generated by an intraocular electronic heater was studied in 16 dogs. It was shown that no more than 50 mW of power over a 1.4  $\text{mm}^2$  area can be applied directly onto the retina for more than 1 second. However, using the same heater, a power of 500 mW in the midvitreous for 2 hours did not cause any histologic damage. It was concluded that heat-producing components of the device (coils for radio frequency telemetry and electronic chips) should be placed far away from the retina, probably right

behind the iris and/or in the midvitreous. Placing the electronics directly in contact with the retina, either epiretinally or subretinally, has a high risk of causing heat injury. Thus, only the electrode array, which produces a relatively small amount of heat, should be put in direct contact with the retina.

**2.2.3 Powering the implant.** Supplying adequate electrical power is a concern for any implantable electronic device. Some electrical stimulators for chronic pain treatment use a battery and rely on repeated surgery to replace it. Alternatively, it is possible to power implants without a physical connection (wirelessly) through an inductive link. Inductive links are commonly created between 2 coils of metallic wire, with a primary coil (the coil that has a signal directly applied by a circuit) and a secondary coil (the coil in which a current is induced).<sup>104</sup> Pacemakers and cochlear implants are inductively powered. There are several parameters that can be adjusted when designing an inductive link. These parameters include the diameter and turns of the primary and secondary coils and the relative position of the 2 coils. Large primary and secondary coils may be undesirable for aesthetic reasons and anatomical constraints, respectively. Power transfer is maximized if the coils are coplanar.<sup>105</sup> This is not practical for most implants, and the coil planes are slightly offset, decreasing efficiency for what is already an inefficient method of transferring power. Typical power transfer rates are approximately 2%. The primary reason for this inefficiency is the fact that the magnetic field spreads indiscriminately from the transmitter. Nevertheless, the average power supply to drive both the inductive link and the stimulator chip (for 100 electrodes) is around 5 mW.<sup>106</sup> Mathematical estimates of millimeter-sized coils have estimated that up to 50 mW of power can be recovered using a 9 cm-diameter primary coil and a 1.5 mm secondary coil.<sup>106</sup> These calculations show that enough energy can be delivered into the eye by this method. Alternatives have been proposed for delivering power to ocular implants, taking advantage of the transparent optical pathway. One conceptual device included a laser that would excite implanted photodiodes to produce electric current. While this link would be more efficient than the inductive link, since the laser could be targeted, it raises safety concerns owing to the known deleterious effects of laser light on the retina.<sup>60</sup>

One subretinal device that does not have any external connections is powered solely by incident light with wavelengths of 500 to 1,100nm.<sup>64</sup> This same principal is used by another group.<sup>48,107</sup> One of the disadvantages of this method is the amount of light that must reach the array. The light intensity needed to activate the photosensors is in the range of 600 to 1,800  $\text{W}/\text{m}^2$ .<sup>108</sup> This range is far beyond the sunlight intensity on earth (fluorescent light 10  $\text{W}/\text{m}^2$ , sunlight

100 W/m<sup>2</sup>). To overcome this problem, additional energy in the near infrared light was added to the spectrum of solar cells of the microphotodiode.<sup>109</sup> The infrared light is tolerated by the retina up to intensities of 200 mW/cm<sup>2</sup>, in contrary to the visible light (100 mW/cm<sup>2</sup>). However, additional microelectronic circuitry to process and direct this power is necessary, and the concomitant heat dissipated by such a device may lead to retinal damage.

**2.2.4 Electrodes.** The electrode array is in direct contact with biologic tissue. Thus, it has the potential to damage the tissue mechanically, chemically, and physically, and vice versa.<sup>110</sup> The electrodes' charge transfer efficiency will affect every subsystem of the prosthesis by influencing the power requirements and the electrode density.

Different materials were tested for the fabrication of electrode arrays. Even the "noble" metals (platinum, iridium, rhodium, gold, and palladium) corrode under conditions of electrical stimulation.<sup>111,112</sup> Platinum and platinum-iridium alloys are the most widely used for neural stimulating electrodes because of its resistance to corrosion and considerable charge-carrying capacity. The unavoidable dissolution of platinum under electrical stimulation decreases when a protein is included in the solution and with continuous stimulation.<sup>112</sup>

Iridium oxide electrodes belong to a new category termed "valence change oxides." IrOx has been used in research for nearly 20 years, but a commercial microstimulator with a single IrOx electrode (BION, Advanced Bionics) has only recently been approved for human use. IrOx is exceptionally resistant to corrosion. The charge density limit for chronic stimulation is 1 mC/cm<sup>2</sup>, and it has a safe stimulation limit of 3 mC/cm<sup>2</sup> *in vitro*.<sup>113</sup> IrOx electrodes have been proved to withstand more than 2 billion 10-mA current pulses without degradation.<sup>10</sup>

Recently, a titanium nitride (TiN) thin-film electrode has demonstrated charge injection limits of 23 mC/cm<sup>2</sup>, higher than both platinum and IrOx.<sup>114</sup> Though TiN electrodes have better mechanical properties than IrOx electrodes, they seemed to have adverse effects on retinal cells' survival when in direct contact. However, it was clear that no soluble factor is responsible for decreased cell survival, and they are still used for fabricating electrode arrays.<sup>48</sup>

When trying to figure out the accepted dimensions of electrodes, one should refer to safe charge density measurements. For example, as was discussed earlier, the charge injection limits for platinum and IrOx electrodes are 100  $\mu$ C/cm<sup>2</sup> and 1mmC/cm<sup>2</sup> respectively. Thus, the maximum sizes based on a 1- $\mu$ C charge requirement for threshold intraocular stimulation of patients with RP would be 0.01 cm<sup>2</sup> and 0.001 cm<sup>2</sup> for platinum and IrOx, respectively. For disc electrodes, these values correspond to minimum disc radii of 0.56 mm for platinum and 0.18 mm for IrOx. In addition, experiments with frog retinas

demonstrated that a 3-dB rise in threshold occurs in about 0.25 mm. So, edge-to-edge separation between neighboring disc electrodes should be no less than 0.25 mm.<sup>115</sup>

Another possibility is to use capacitor electrodes. These electrodes operate without any faradic reactions. A thin surface layer of dielectric material insulates the metal from the solution and prevents electrochemical reactions. The most practical material is anodized tantalum because of the small amount of DC leakage. However, these electrodes have lower safe injectable charge density and charge storage ability when compared to platinum, IrOx, and TiN electrodes.<sup>116</sup>

The charge density limits are measured for uniform current distribution. However, because of certain geometric considerations, neural prosthetic electrodes are likely to have nonuniform current distributions, which can exceed the chemically reversible limits.<sup>117</sup> For example, it has been shown that disc electrodes create uneven current density, with the highest densities or "hot spots" being near the edges of the disk. If the disks are recessed even to a small depth, the current density is more evenly distributed.<sup>118</sup>

Some of the methods used for the visual prosthesis deserve special considerations. The subretinal device is composed of subunits measuring 20 x 20  $\mu$ m. Every subunit is a combination of a silicon microphotodiode and a stimulating electrode. The density of the subunits is 1,100 subunits/mm<sup>2</sup>. This device can theoretically create a barrier between the retina and the choroid, which provides nourishment to the outer layers of the retina. To prevent the barrier effect, 1 of the groups incorporated porous electrode array structures to facilitate nutritional exchange between the retina and the underlying choroid. The size requirements will limit the power of the subretinal implant.<sup>64</sup> In addition, the electronic device creates heat, which may affect the delicate sensory retina above it. Patches of fibrosis and RPE changes were observed after chronic subretinal implantation, and histologic examination of the retina showed declining inner nuclear and ganglion cell layer densities<sup>64</sup> but no inflammatory response. Another report showed that there was irregular glial proliferation above the electrode array.<sup>48</sup>

The principal difference between the cortical and retinal prostheses is the design of the electrode array. As was discussed earlier, the cortical electrode array should probably consist of penetrating microelectrodes. One group, developing a cortical implant, has focused on the use of doped silicone for their penetrating electrode array for cortical stimulation.<sup>33</sup> The tips of the 1.5/1.0 mm long electrodes are covered with platinum. The array typically looks like a nail bed and consists of 100 penetrating electrodes. The diameter of each electrode at its base is 80 to 100  $\mu$ m and 2 to 3  $\mu$ m at the tip. Chronic implantation of this electrode array varied from no reaction at all to a

thin capsule around each electrode track, to extensive gliosis with buildup of fibrotic tissue between the array and the meninges, resulting in array displacement and bleeding.<sup>33</sup> Thin capsules around electrode tracks and tissue accumulation on pulsed CNS electrodes were also reported by others.<sup>93-97</sup> Nevertheless, tissue encapsulation does not always preclude effective stimulation.<sup>97,119</sup>

Another electrode technology uses silicon micromachining to fabricate multichannel arrays for neural prostheses applications. Microfabricated silicon electrodes were initially conceived in the early 1970s.<sup>120</sup> In the subsequent years, the dimensions of these electrodes have been decreased, utilizing the concurrent advances in the microelectronics industry. Today, micromachined silicon electrodes with conducting lines of 2  $\mu\text{m}$  are standard.<sup>121-124</sup> These fabrication processes have been advanced by the microelectronics industry and therefore allow the integration of microelectronics and the electrode array into a monolithic device. The primary reason for the inclusion of on-chip electronics in such a device is to minimize the number of external leads required between the electrode sites and the outside world. Recording/stimulating sites are located along the silicone probe substrate. These probes are capable of extracellular recording/stimulating of many cells in neural tissue simultaneously on a spatially distributed basis.<sup>82,125-129</sup> Chronic implantation and in vitro testing have demonstrated the ability of silicon devices to maintain electrical characteristics during long-term implantation.<sup>97</sup>

Some general conclusions can be drawn from the preceding discussion. A stimulating electrode array must meet several requirements. These include a high number of densely packed electrodes to provide a high acuity image and individual electrodes that can safely inject a large amount of charge. Current electrode technology that is employed in neural prostheses uses handmade electrode arrays with a small electrode count (up to 32), most likely an insufficient number for a visual prosthesis. Micromachining technology has been used to fabricate electrodes for neural stimulation, but these devices have not been optimized for use in the eye.

The global shape of the array, the shape of each electrode, the way to insert and attach it, and other factors depend on the anatomical location of stimulation. If either IrOx or TiN electrodes can be successfully incorporated into a visual stimulating array, then the potential advantages include more input channels, higher image quality, and reduced power consumption.

### 3. SCOPE OF THIS THESIS

Because of the enormous number of scientific disciplines involved in constructing and showing the feasibility of an

electronic retinal implant, it is easy to lose focus and get overwhelmed. However, the 2 most critical pieces of the development effort that remain not completely solved are that of optimizing electrical stimulation parameters for the retina and defining the number of electrical contacts needed with the retina to enable useful vision. Delineating these parameters is at the crux of the engineering of the electronic implant, as it has direct consequences on power requirements, heat dissipation, image processing, and the safety of the retinal and other ocular tissue. In this thesis, we address these issues through different experiments. The first set of experiments uses 2 different electrophysiological setups to optimize the stimulating parameters. The second set of experiments uses psychophysics to determine the number of inputs and image processing that would be needed to provide useful vision.

## METHODS

### 1. ELECTROPHYSIOLOGIC EXPERIMENT

All animal protocols used in this study were in accord with the Association for Research in Vision and Ophthalmology guidelines for animal care and use as well as approved by the Johns Hopkins Animal Care and Use Committee.

#### 1.1 *In Vivo* Mouse Experimental Setup

1.1.1 *Animal model and preparation of the retina.* Three different groups of mice were used in this study: 8-week-old normal-sighted male mice C57BJ/6J (Jackson Labs, Bar Harbor, Me), 8-week-old retinal degenerate (rd) male mice C3H (Charles River, Wilmington, Mass), and 16-week-old rd male mice. The mice were anesthetized with an intraperitoneal injection of ketamine (80 mg/kg, Ketaject, Phoenix Pharmaceutical, St Joseph, Mo) and xylazine (10 mg/kg, Xyla-ject, Phoenix Pharmaceutical). The mouse was given subsequent doses every half hour to maintain it at the initial plane of anesthesia. The body temperature of the mouse was maintained at 35°C with a heating pad (Frederick Haer, Inc, Bowdoinham, Me). At the conclusion of the experiment, the mouse was sacrificed by a lethal dose of pentobarbital injected intraperitoneally (120 mg/kg).

For the surgical procedure, the mouse was placed in a custom-built stereotactic head holder to maintain the head in a fixed position and to allow access to the eye. The holder was placed under a light microscope on a vibration-isolated table. A 30-gauge needle was used to make a small incision in the cornea. Next, the central corneal button was removed using scissors. Sodium hyaluronate (Healon GV, Pharmacia, Columbus, Ohio) was injected behind the lens to deliver the intact lens out of the eye and to prevent the eye from collapsing. Finally,

the recording and stimulating electrodes were positioned on the retinal surface optic (Fig 4).

**1.1.2 Retinal recording.** Two tungsten-recording microelectrodes (5 Mohm, A-M Systems, Everett, Wash) were positioned on the retinal surface with a micromanipulator (MX-100, Newport, Irvine, Calif). A ground electrode was placed in the mouth. A differential amplifier (Dagan Corporation, Minneapolis, Minn) was used to condition the signal (20 K gain, 0.3 to 3 kHz). Data acquisition and stimulus output were accomplished via a commercial electrophysiology system (ACDaq, Seattle, Wash).

**1.1.3 Light stimulation.** Light responses were obtained by full-field illumination from a 1,000-lumen Xenon light source (model 201, ILC Technology, Sunnyvale, Calif) coupled to a fiber optic light probe. Light was delivered to the surface of the retina via the fiber optic light pipe. Retinal recordings were synchronized to the light stimulus through the use of a computer-controlled light shutter (Uniblitz T132, Vincent Associates, Rochester, NY).

**1.1.4 Electrical stimulation.** A 125  $\mu\text{m}$ -diameter platinum wire was used to stimulate in a monopolar configuration (ie, the current return electrode was placed at a distance on the tail of the animal). The stimulus output waveform was converted to constant current by a stimulus isolator. Electrical stimulation was performed in dark condi-

tions. Several stimulus waveforms were used. The first half-pulse was cathodic and the second half-pulse was anodic. There was no delay between the cathodic and anodic phases. All trials were performed using charge-balanced waveforms. Response threshold as a function of stimulus strength was determined for several waveforms. A single biphasic pulse was investigated at 5 pulse durations (40, 80, 120, 500, and 1,000  $\mu\text{s}$ ). A single cycle of a 1-kHz sine wave was also used. Finally, pulse trains were investigated (5 x 40  $\mu\text{s}$ , 10 x 40  $\mu\text{s}$ , 5 x 80  $\mu\text{s}$ , 10 x 80  $\mu\text{s}$ , 5 x 120  $\mu\text{s}$ , and 10 x 120  $\mu\text{s}$ ) to compare with single pulse. Stimulus threshold was defined as the stimulus that would elicit an action potential in 2 of 3 trials. Action potential threshold was set to 3x peak noise (noise was typically  $\pm 10 \mu\text{V}$ ).

The threshold charge was statistically analyzed using a Student *t* test for comparison of 2 sets of data and ANOVA for comparison of multiple data sets. A  $P < .05$  was considered statistically significant.

## 1.2 In Vitro Retinal Isolate Experiments

**1.2.1 Retinal harvesting and maintenance.** Thirty-eight adult ( $\sim 2$  kg) Dutch belted rabbit eyes were anesthetized with 2 cc of a mixture of 60% ketamine (80 mg/kg, Ketaject, Phoenix Pharmaceutical) and 40% xylazine (10 mg/kg, Xylaject) through intramuscular injection. The eye was

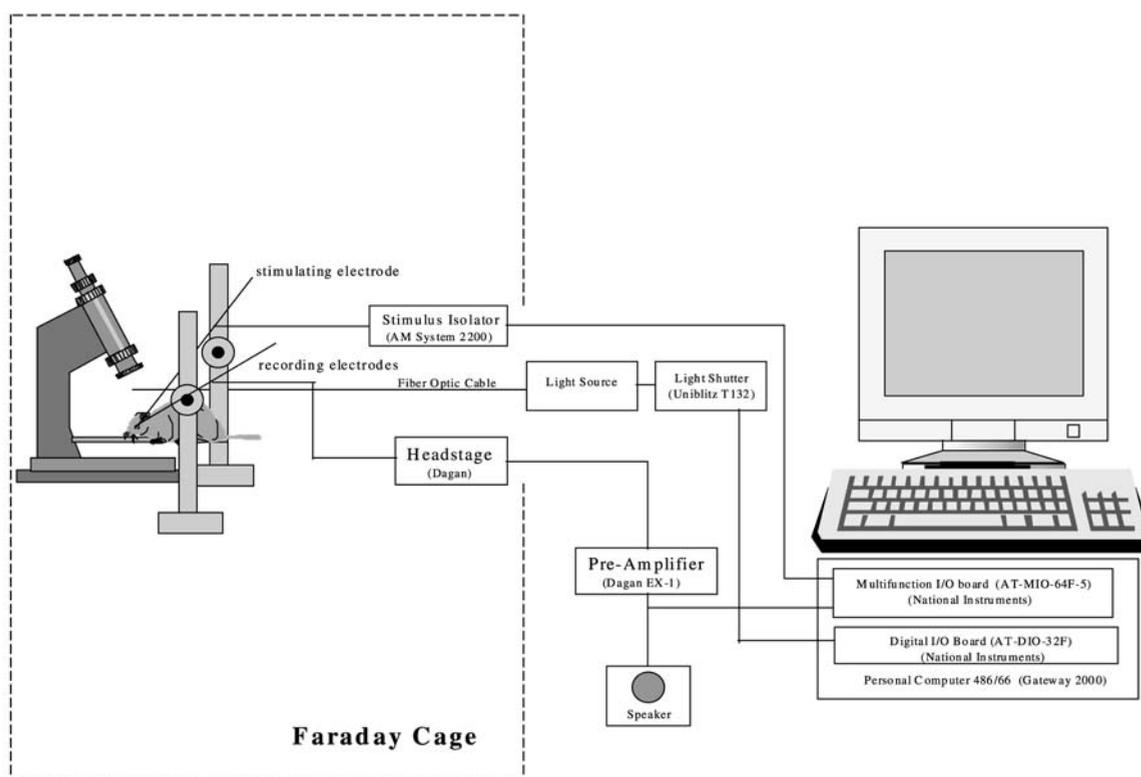


FIGURE 4

Setup for in vivo mice retinal recordings, which is inside a Faraday cage. Under computer control, either a light or an electrical stimulus can be delivered and a retinal ganglion cell response simultaneously recorded.

enucleated, and the retina was dissected out of the eyeball, and then transferred to Ames' medium (Sigma Chemical Co) bubbled with 95% oxygen and 5% carbon oxide and heated to 37°C. A heated chamber (ORC-1, Center for Network Neuroscience, University of North Texas, Denton) was used to hold the retina and allow a flow of solution through the chamber (Figs 5 and 6)

1.2.2 *Stimulus and recording electrodes.* Two types of stimulation electrodes were used: platinum macroelectrode (125  $\mu\text{m}$  and 25  $\mu\text{m}$  diameter, Frederick Haer, Inc) and a photolithographically defined microelectrode array (MMEP4, Center for Network Neuroscience). The MMEP4 has an 8 x 8 grid of 22  $\mu\text{m}$ -diameter gold electrodes patterned on a glass plate. Two identical electrodes were used in dipole configuration, 1 as the current source and the other as the current sink. MMEP electrodes were at a fixed distance of 100  $\mu\text{m}$ . The macroelectrodes were positioned individually, but the edge-to-edge distance was estimated to be 300 to 400  $\mu\text{m}$  based on the known diameter of the outer cannula. Electrical stimulation was performed with the stimulating electrodes on either the ganglion cell surface or the photoreceptor surface. Two pen-

etrating tungsten electrodes (A-M Systems) were used for differential recording and set between optic disc and the stimulation electrodes. The retinal location of the recording electrodes was verified by recording spontaneous and light-driven action potentials. The distance between stimulation and recording electrodes was approximately 2 mm. Six test conditions were studied: 3 electrodes (MMEP, 125  $\mu\text{m}$ , and 25  $\mu\text{m}$ ) each in 2 positions (PR-stimulating electrodes on photoreceptor surface and GL-stimulating electrode on ganglion cell surface).

1.2.3 *Stimulus and recording parameters.* Stimulus generation and data acquisition were controlled by a computer-based system (ACDaq, AC Instrumentation, Seattle, Wash). A battery-powered preamplifier (P15, Grass Instruments, Quincy, Mass) was used for initial filtering and amplification (10x gain, and a bandwidth of 3 to 300 Hz). A second filter (Dagan Corporation) was used to condition the signal. The combination of the 2 filters yielded a 20-K gain and a bandwidth of 0.3 to 3 kHz. Light responses were obtained in response to a light stimulus from a 1,000-lumen Xenon light source (model 201, ILC Technology) coupled to a fiber optic light probe. Retinal recordings were synchronized to the light stimulus through the use of a computer-controlled light shutter (Uniblitz T132, Vincent Associates). Current pulses were generated by a custom-built voltage-to-current converter under computer control.

1.2.4 *Stimulus waveforms.* In each of the 6 electrode configurations, biphasic stimulus pulses were applied. All pulses were cathodic first with a 4-ms delay between the first and second phase. The pulses were varied in phase duration (0.1 ms, 0.5 ms, and 1 ms). The initial stimulus amplitude was set to 3.2  $\mu\text{A}$  and increased in steps of 1.6  $\mu\text{A}$  until a response was elicited. The threshold of the response was defined with the response rate over 3 quarters. We also double-checked the responses with other waveforms. The latency was defined as the time from the end of the stimulus to the beginning of the response at the threshold stimulus. For statistical analysis, the natural logarithm of each value was used to do ANOVA and *t* tests.

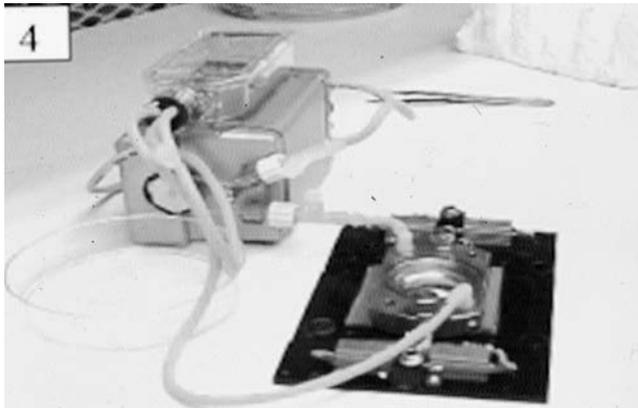


FIGURE 5

Isolated retinal setup, which is housed inside a Faraday cage. Metallic ring overlies an electrode array, forming a watertight chamber for retinal tissue. Chamber is connected to oxygenated, heated Ames media via rubber hoses.

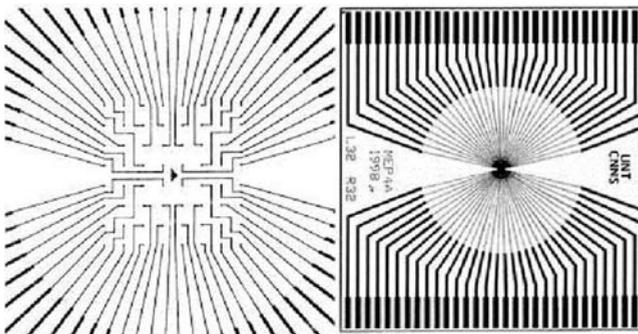


FIGURE 6

Photomicrograph of Indium-tin-oxide electrode array (MMEP array). Wires terminate in small electrodes that are used to stimulate overlying retinal tissue.

## 2. PSYCHOPHYSICAL TESTING

### 2.1 Facial Recognition

Subjects were 4 college graduates aged 25 to 32 years of age. The subjects were volunteers with a best corrected visual acuity of 20/20. Prior to their participation in the study, written informed consent was obtained from all participants and each participant was given a copy of the signed consent form.

The facial images for the study were composed of a database of 60 patients and hospital employees. The group was composed of equal numbers of men and

women and black and white individuals. In each of these 4 groups were equal numbers of “old,” “middle aged,” and “young” individuals. Using a digital camera with a resolution of 640 x 480 pixels with 256 gray levels, 1 straight-on image and 4 averted images of each individual were captured for use in the study. Facial images displayed occupied a visual field of 13° horizontally when measured from ear to ear.

With use of Microsoft Visual Basic, software was developed to perform the facial recognition task using a 400-mHz Pentium II personal computer, a Diamond Stealth video card with 2 megabytes of memory, with video output to a modified Low Vision Enhancement System (LVES) display. The LVES display has a vertical visual field of 36° and a horizontal visual field of 48°. The display has 480 vertical pixels and 640 horizontal pixels. Thus, each pixel represents 4.5 minutes of arc. The LVES is capable of displaying 256 gray levels.

The LVES head-mounted display was fitted to each subject. A test screen was then utilized for subjects to focus the image to correct for refractive errors in their right eye. In the monocular trials, subjects viewed a test set of 4 facial images displayed using the full resolution of the display. The 4 faces in each trial were matched for sex and race (Fig 7).

After these images were reviewed, subjects depressed the space bar to view the test image, start the viewing timer, and clear the screen. The test image was an averted facial image of 1 of the individuals seen in the test set. Subjects viewed the test image by scanning a grid of dots, simulating pixelized prosthetic vision over the averted facial image using a mouse-pointing device (Fig 8).

Upon determining the identity of the test image, subjects again depressed the space bar. This stopped the viewing timer and returned the display to the original test set of 4 facial images. Using the mouse-pointing device, subjects matched the face in the test image with 1 of the 4 faces from the test set. Subjects performed 204 trials with the test images viewed under high-contrast conditions with a background level of 0. During the trials, the dot size, dot spacing, grid size, number or gray levels, and dropout percentage were varied. A second trial was then conducted in which the test images were viewed under low-contrast conditions with a background gray level set at 30% for all 3 primary colors (red, green, and blue).

### 2.1 Letter/Symbol Recognition and Activities of Daily Living

Hospital employees and undergraduate students were recruited as volunteers. All 8 volunteers had 20/30 vision or better either without correction or with contact lens correction.

A PC video camera captured images that were

converted into pixels by real-time software. The pixelized image was displayed on the PC monitor as well as on a head-mounted display (HMD) worn by test subjects. The camera used was Logitech QuickCam Pro, which has the following specifications: manual focus lens type 6 mm,  $f=2.0$ , field of view 46° and a CCD resolution of 640 x 480 pixels (VGA specification). The pixelizing software filter was provided by Second Sight, LLC, Valencia, Calif. It converts the entire video image into an array of discrete squares (“pixels”). Each pixel is a solid gray-scale figure representing a mean luminance across its aperture in the image captured by the camera. For example, if the target area for 1 pixel were centered on a black object larger than the pixel’s aperture, the pixel would be black. However, if the camera was redirected so that the pixel’s target area was half on the black object and half on a white



FIGURE 7

Representative set of four faces used in face discrimination protocol.

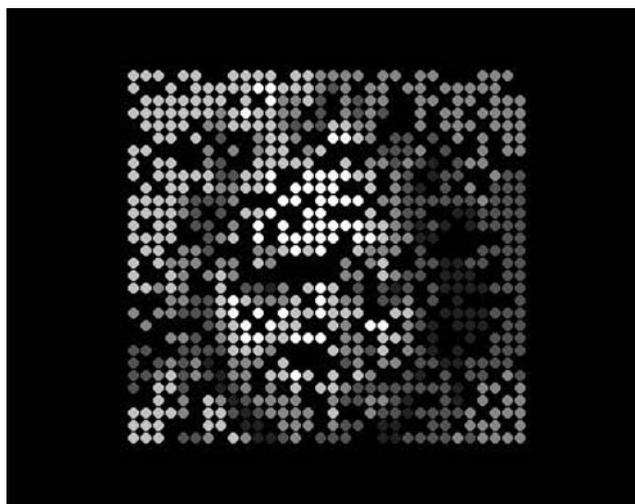


FIGURE 8

Appearance of a face after it has been pixelized using the modified Low Vision Enhancement System (LVES).

background, the entire pixel would be medium gray. Adjustable property settings of the filter include number of rows, columns, gray scale levels and the height and width of percentages of each pixel (with the remaining portion being a gray gap between adjacent pixels). To provide a realistic rendition of dynamic range and resolution expected from a retinal prosthesis, maximum contrast (100%) and number of simultaneous, gray-scale levels (6) were held constant. All other properties were adjusted for the individual arrays (see below). A Belkin Expand View video output splitter enabled us to display identical images on the HMD by test subjects and our PC monitor for observer viewing. The HMD, a PLM-100 Personal Video Headset by Sony, resembles a large visor and contains 2 0.7-inch LCDs projecting 1 to each eye. This monitor has a “see-through” feature, which normally allows the wearer to see the real world while simultaneously viewing a transparent image of the monitor. To eliminate outside visual input, subjects wore a black felt blindfold over the HMD. Making no other adjustments, we utilized all standard display parameters.

According to the parameters described above, the actual 4 x 4 array will cover 7.3° of retina in both the x axis and the y axis. (1.3° for each of the 4 electrodes and 0.7° for each of the 3 spaces). The 16 electrode pixelized simulation was sized such that the angle subtended by the image composed 7.3° of the subjects’ visual field. We assumed the same electrode diameter and spacing for the 6 x 10 electrode array as the 4 x 4. This translates to 11.3° in the y axis and 19.3° in the x axis. The physical sizing of the simulated array was done as described for the 4 x 4 array. The dimensions of our 16 x 16 electrode array were restricted to fit within a 3.5 mm scleral incision. The y axis of the 6 x 10 array would do just that, so we use the same arc length here in both axes (11.3°). This simulation assumes the eventual capacity to manufacture small electrodes with safe charge densities. Again, a template was made for sizing of this electrode as in the previous 2. Last, the size of the entire array established, the height and width percentage of the pixels were altered such that spaces between pixels were approximately one-half the size each pixel.

2.1.1.1 *First set of tasks.* The first set of tasks involved obtaining visual data at a distance ranging from 10 to 70 cm. The camera was placed in a modified adjustable head strap in a midline position above the eyes. This allowed subjects to control the camera with head movements. All 4 tasks in this first set were completed with the 4 x 4 array then repeated with the 6 x 10 array and finally with the 16 x 16. The expected visual acuities are 20/2400 for the 4 x 4 and 6 x 10 arrays and 20/865 for the 16 x 16 array.

2.1.1.1.1 *Tumbling E.* With the test subject seated, a standard 20/200 E (8.8 cm tall; size of each branch was

20% of the height) was placed in front of them on a large white background. They were asked to identify which direction the E was facing (ie, up, down, left, or right). They began at a distance of 70 cm. If they could not identify the direction, the distance was decreased to 50 cm, then 30 cm, and finally 10 cm. The distance at which they first recognized the orientation of the E was recorded for each array. It was assumed that subjects could correctly identify the orientation at closer intervals once they have done so for a given distance.

2.1.1.2 *Object recognition.* A plate, cup, spoon, and pen were placed on a black table sequentially in front of the subject for a maximum of 3 minutes each. The only information about the objects given was that they were all common items that most people use on a daily basis. Subjects were instructed to describe the object’s shape, size, and overall appearance. If they thought they could identify the object, they were asked to say “My guess is...” They were allowed only 1 guess per object. An accurate description but incorrect guess was awarded 1 point. A correct guess was awarded 2 points. No points were given for inaccurate descriptions.

2.1.1.3 *Candy pour.* Two white cups were placed 5 to 10 cm apart on a black table. The cup in front of the subject’s dominant hand contained 10 pieces of hard candy, and the other cup was empty. The subject’s task was to pick up the full cup with the dominant hand and pour the candies into the empty cup touching it neither with the hand nor with the full cup. The number of candies successfully poured into the empty cup was counted.

2.1.1.4 *Cutting.* A hollow black rectangle printed on a standard sheet of white 8.5 x 11-inch paper was handed to the subject. The task was to cut around the outside of the black rectangle on all 4 sides. Total cutting time was noted. Accuracy was judged by measuring the distance between the cut and the actual target. If the cut was 1 cm or less from the target, this was judged to be correct. The cumulative length of the correct cut was measured and recorded as a percentage of the length of all 4 sides of the rectangle (59.2 cm).

2.1.2 *Second set of tasks.* The second set of tasks required that the camera be quite steady and very close to the object. To accomplish this, the video camera was mounted on a platform such that the lens was 4.5 cm from the target. There were also 2 straight edges on the table that helped maintain the camera and the viewing material in the proper orientation for reading during scanning.

2.1.2.1 *Symbol recognition.* With the 4 x 4 array, subjects scanned over 3 symbols on a Light House Key Card. Correct responses (“house,” “circle,” “square”) were awarded 2 points, close responses were awarded 1 point, and inaccurate responses were awarded no points.

2.1.2.2 *Reading.* The Minnesota (MN) Read Acuity

Chart (A) was used for reading material. This chart consists of sentences of 10 to 12 words. Each is printed in a progressively smaller Courier bold font. With the 6 x 10 array, subjects were asked to read the first sentence (72-point font). With the 16 x 16 array, they were asked to read the first 5 sentences. Time required to complete each sentence, as well as the number of words read correctly, was recorded.

## RESULTS

### 1. ELECTROPHYSIOLOGIC RESULTS

#### 1.1 In Vivo Mice Experiments

A light-driven response was easily obtained from normal mouse but could not be obtained from either 8-week-old or 16-week-old RD mouse, despite multiple placements of the recording electrodes (Figs 9 and 10).

Single-unit spontaneous activity was obtained from all 3 mouse groups. The spontaneous activity was used to determine when the recording electrode was in the proximity of the ganglion cells. Electrical elicited responses were obtained from each group: 8-week-old normal mouse (n=14), 8-week-old rd mouse (n=15), and 16-week-old rd mouse (n=10). The charge threshold was compared across all 3 groups and for different waveforms within the same group.

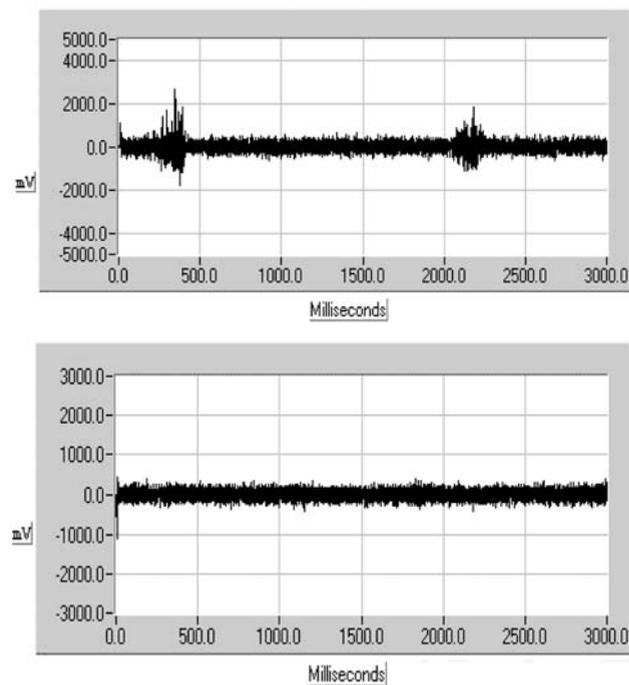


FIGURE 9

Top, Light-driven retinal ganglion cell response from normal mouse. Two distinct bursting neuronal activities were recorded at onset and offset of light stimulus (ie, On and Off responses, respectively). Bottom, Absence of such light-driven retinal ganglion cell responses in rd mouse.

In normal mouse, a single cycle of a 1-kHz sine wave was significantly more efficient than a 1-kHz square wave ( $P < .05$ ) (Fig 11), but no such difference was noted in either of the rd mouse groups (8-week-old,  $P = .426$ ; 16-week-old,  $P = .0783$ ) (Fig 12).

Charge threshold was significantly higher in 16-week-old rd mouse versus both 8-week-old rd and normal mouse for every stimulus duration ( $P < .05$ ). In all groups, short-duration pulses (40, 80, and 120  $\mu$ s) were more efficient in terms of total charge (the product of pulse amplitude and pulse duration) than longer (500 and 1,000  $\mu$ s) pulses ( $P < .05$ ). However, much more total current was required to elicit a response with short pulses. In all groups, applying a pulse train did not lead to more efficient charge usage ( $P < .05$ ).

#### 1.2 In Vitro Retinal Isolate Experiments

For photoreceptor-side stimulation, macroelectrode stimulus threshold current was significantly lower than threshold current delivered with the MMEP ( $P < .05$ ) (Fig 13). When using the MMEP for stimulation, ganglion cell surface stimulus threshold was significantly lower than photoreceptor-side stimulus threshold ( $P < .05$ ). No difference between ganglion cell stimulation and photoreceptor-side stimulation existed using the macroelectrodes. For all groups, the stimulus current thresholds of 1-ms pulse-width groups were significantly lower than those of 0.1-ms

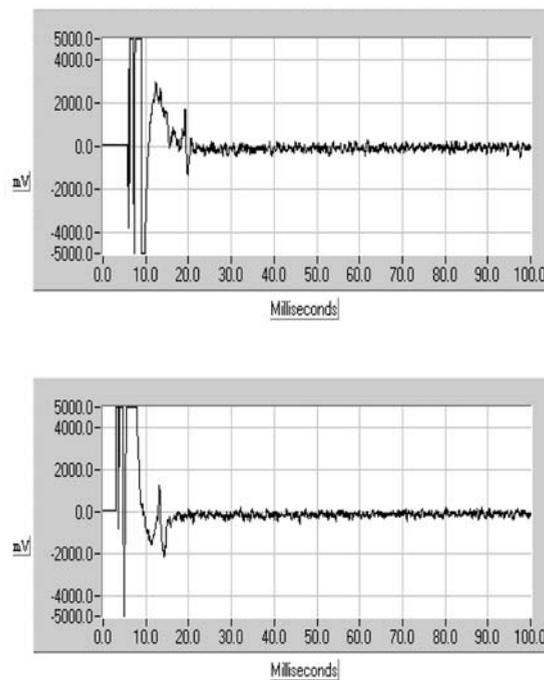


FIGURE 10

Electrically elicited retinal ganglion cell (RGC) response. First tracing above baseline is stimulus artifact. RGC response can be seen at 20 and 15 ms in top (normal mouse) and bottom (rd mouse) pictures, respectively.

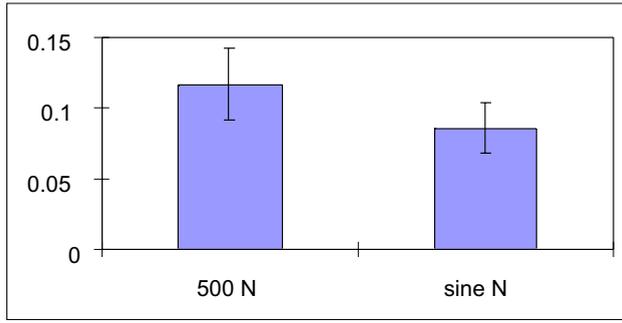


FIGURE 11

Thresholds charge to elicit a retinal ganglion cell response in normal mouse with either a 500-micropulse-wide square wave (500 N) or a 1-kHz sine wave (sine N). The y axis units are microcoulombs. Bars denote standard deviations.

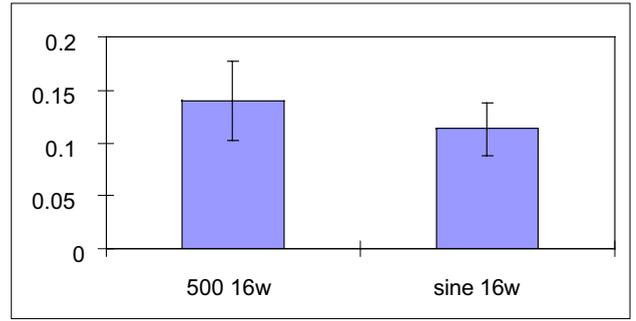


FIGURE 12

Thresholds charge to elicit a retinal ganglion cell response in a 16-week-old mouse with either a 500-micropulse-wide square wave (500 N) or a 1-kHz sine wave (sine N). The y axis units are microcoulombs. Bars denote standard deviations.

pulse-width groups. Response latency was studied with 1 ms pulses for both electrodes and stimulus sites (Fig 14). All groups demonstrated similar latency except the MMEP/PR group.

2. PSYCHOPHYSICAL TEST RESULTS

2.1 Face Recognition

In high-contrast tests, facial recognition rates of over 75% were achieved for all subjects with dot sizes of up to 31.5 minutes of arc when using a 25 x 25 grid with 4.5 arc minute gaps, a 30% dropout rate, and 6 gray levels (Fig 15).

This corresponds to sampling with at least 11 cycles per face horizontally, ear to ear. The results deteriorated when

sampling lower rates, 7 cycles per face or less (Fig 16).

All subjects were able to correctly identify at least 75% of the facial images with dot gaps of up to 31.5 minutes of arc when using a 25 x 25 grid with 13.5 minute dots a 30% dropout rate, and 6 gray levels (Fig 17).

In testing increases in gap size, facial recognition rates dropped when the sampling interval dropped from 9 cycles per face to 7 cycles per face. Using a 25 x 25 grid spanning a field of 7.5° or a 32 x 32 grid with a field of 10°, subjects achieved facial identification rates over 80%. All subjects achieved facial recognition rates of over 80% in resolution testing with 6 gray levels and dropout rates of less than 30% (Fig 18).

High-contrast facial recognition rates exceeded low-contrast facial recognition rates. During low-contrast testing, facial recognition rate of over 80% for all subjects was achieved only with a 25 x 25 grid, with 13.5 arc minute dots, 4.5 arc minute gaps, a 30% dropout rate, and 6 gray levels.

The average correct response time provides a

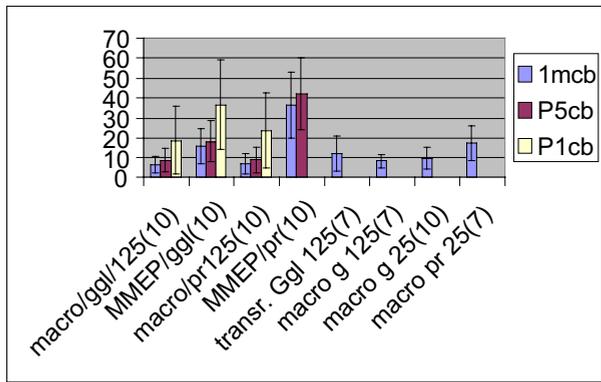


FIGURE 13

Threshold in microamps (y axis) with respect to electrode size and positioning on retina (x axis). Threshold currents are shown for 3 different pulse widths: 1 mcb = 1 ms cathodic first biphasic; P5cb = 0.5 ms cathodic first biphasic; P1cb = 0.1 ms cathodic first biphasic. Macro/ggl/125 = 125µ diameter. macroelectrode positioned on ganglion cell side; MMEP/ggl = MMEP electrode (20µ diameter) positioned on ganglion cell side; macro/pr125, 125µ diameter macroelectrode positioned on photoreceptor side; MMEP/pr = MMEP electrode (20µ diameter) positioned on photoreceptor side; transr Ggl 125 = transretinal electrode configuration with 125µ diameter electrodes; macro g 125, macro g 25, macro pr 25 = 125µ diameter electrode positioned on ganglion cell side, 25µ diameter electrode positioned on ganglion cell side, 25µ diameter electrode positioned on photoreceptor side, respectively. Numbers with each abbreviation on x axis are number of animals from which recordings were made.

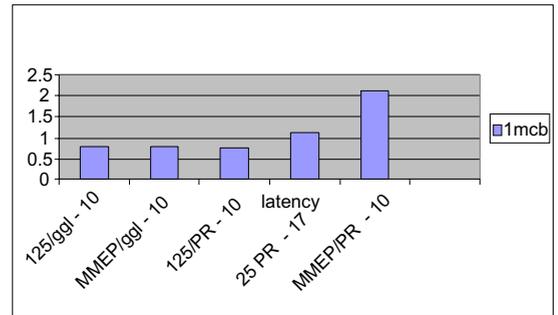


FIGURE 14

Latency in ms (y axis) using a pulse of 1 ms cathodic first biphasic pulse (1 mcb). 125/ggl = 125µ diameter electrode positioned on ganglion cell side; MMEP/ggl = MMEP (20µ diameter) electrodes placed on ganglion cell side; 125/PR = 125µ diameter electrode positioned on photoreceptor side; 25 PR = 25µ diameter electrode positioned on photoreceptor side; MMEP/PR = MMEP (20µ diameter) electrode positioned on photoreceptor side. Numbers with each abbreviation on x axis are number of animals from which recordings were made.

High Contrast, 25x25 Grid, 4.5 Arc Minute Gaps, 30% Drop-out, 6 Gray Levels

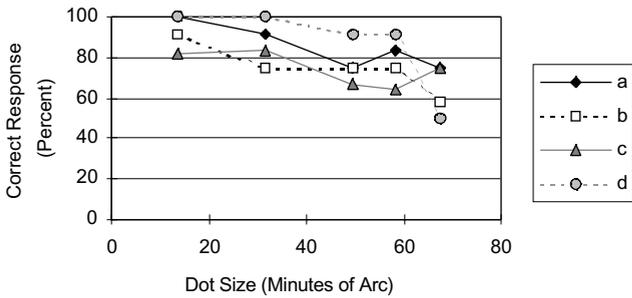


FIGURE 15

Decline in correct facial recognition as dot size increases. Data are from 4 subjects labeled a, b, c, and d.

High Contrast, 25x25 Grid, 4.5 Arc Minute Gaps, 30% Drop-out, 6 Gray Levels

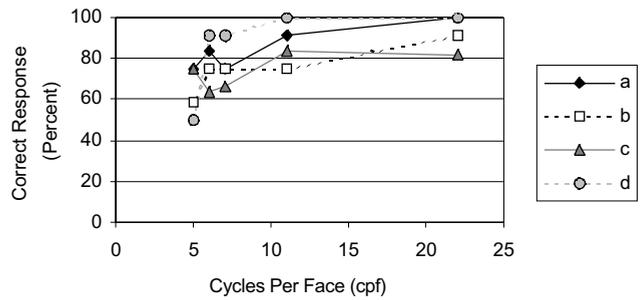


FIGURE 16

Decrease in facial recognition as a function of cycles per face. Data are from 4 subjects labeled a, b, c, and d.

High Contrast, 25x25 Grid, 13.5 Arc Minute Dots, 30% Dropout, 6 Gray Levels

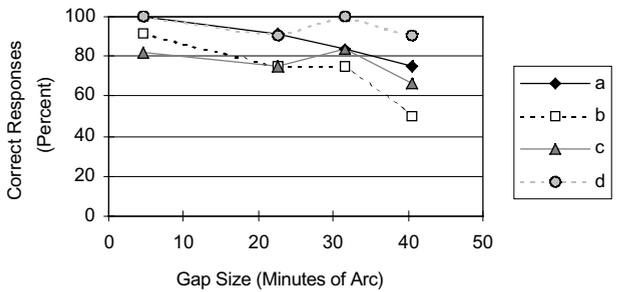


FIGURE 17

Effect of dot spacing on facial recognition. Data are from 4 different subjects labeled a, b, c, and d.

High Contrast, 13.5 Arc Minute Dots, 4.5 Arc Minute Gaps, 30% Dropout, 6 Gray Levels

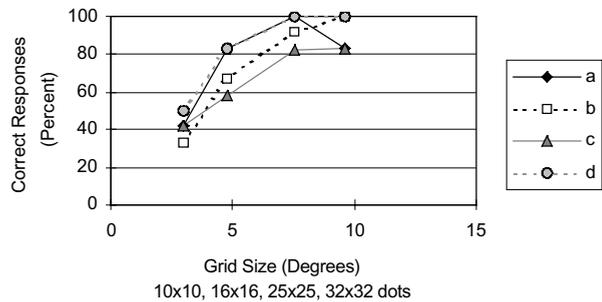


FIGURE 18

Effect of 6 levels of gray scaling on facial recognition. Data are from 4 subjects labeled a, b, c, and d.

measure of the analysis necessary to identify the face under evaluation (Fig 19).

An identification index was created as a measure of the speed and accuracy of the subject's responses under various testing conditions. The score is calculated by first squaring the percentage of correct responses and then subtracting the square of the number 50 from this value. The result is then divided by the average number of seconds required for a correct response. Thus, a positive score results when the subject identifies over half of the images correctly. Rapid responses also result in higher scores when the subject is able to identify the faces over 50% of the time. Recognition rates of less than 50% result in negative scores. To exceed an identification index of 1,000, a subject correctly identifying 80% of the faces correctly would need to do so with an average correct response time of less than 4 seconds.

Only 6 testing conditions yielded an average identification index score greater than 1,000. In all cases with an average identification index greater than 1,000, the gap size was 3.5 arc minutes and the resolution was 6 gray levels. In the high-contrast tests, grid sizes were at least 25 x 25 and the dropout rate was 30% or less with dot sizes of

13.5 arc minutes or 31.5 arc minutes. In the low-contrast cases in which the average identification index was greater than 1,000, the dot size did not exceed 13.5 arc minutes and the grid size was 32 x 32 with a 30% dropout rate, or 25 x 25 with a 10% dropout rate.

## 2.2 Letter/Symbol Recognition and Activities of Daily Living

The Tumbling E Test showed that when using a 4 x 4 array, 87% of subjects could determine orientation of E at 10 cm (Fig 20). This corresponds with a Snellen acuity of 20/1810 (see Appendix for calculation of acuity). Using a 6 x 10 array, 87% of subjects could determine orientation of E at 30 cm, which corresponds with a Snellen acuity of 20/1330. Using a 16 x 16 array, 75% determined orientation at 70 cm. This is equivalent to a Snellen acuity of 20/420.

Results of the object recognition task are shown in Fig 21.

With the candy pouring task, many subjects touched 1 cup to the other just before pouring the candy, despite taking measures to avoid contact. Therefore, the data reflect both visual and tactile information (Table I).

Results for 7 of 8 subjects performing the cutting task

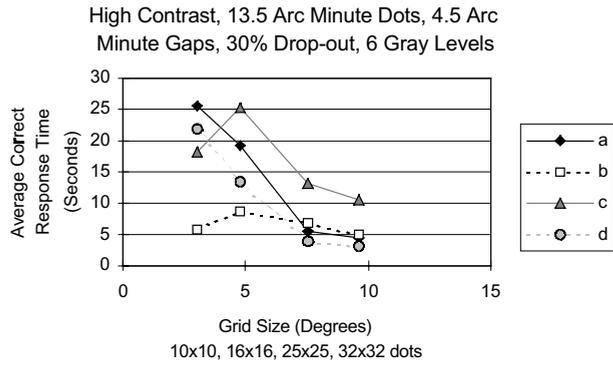


FIGURE 19

Average correct response time to identify a face. Data are from 4 subjects labeled a, b, c, and d.

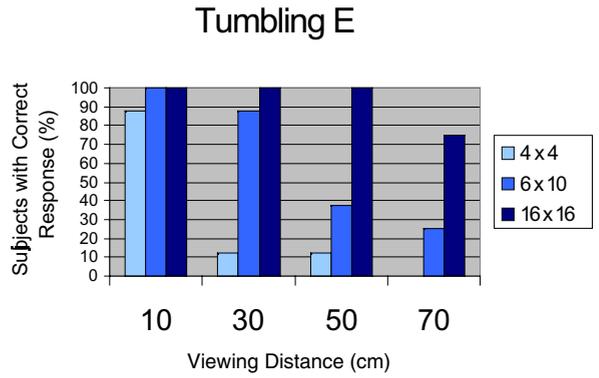


FIGURE 20

Correct percentage of responses during a Tumbling E Test using different sized pixel arrays as a function of viewing distance.

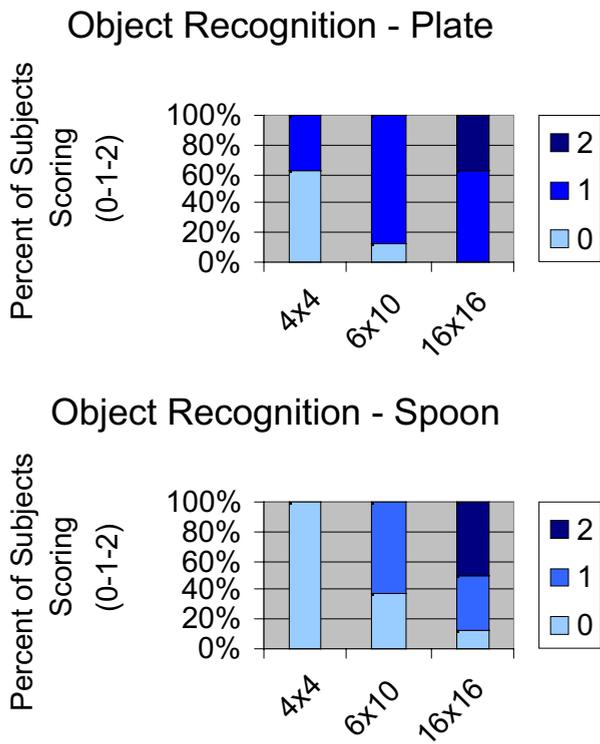


FIGURE 21

Object recognition using different number of pixel arrays. A score of zero was given for incorrect answer, a score of 1 for correct description but not exactly identifying the object, and a score of 2 for exact object recognition.

are shown in Fig 22. These 7 subjects used only visual information to cut the target object. The subject who was omitted from the results folded the paper to create a tactile target for cutting. His accuracy and cutting time were much higher than those of the other subjects.

Results of the symbol recognition task are shown in Fig 23.

In the reading test, only 3 of the 8 subjects using a 6 x 10 array could read the first sentence on the Minnesota Reading Card, which has a 72-point font (Fig 24). They correctly identified all 10 words with an average reading

speed of 1.06 words per minute. Using a 16 x 16 array, all subjects were able to read all 10 to 12 words of both the first line of the Minnesota Reading Card (smallest font size, 72) as well as the first 5 sentences (smallest font size, 57). Using the same 16 x 16 array, all subjects read all 10 words of a 45-point font except 1 who read only 6 words. All subjects using the same array could read all 10 words of 36-point font except 1 who read only 8 words). When the point font was further reduced to 27, only 2 subjects read all 11 words, 1 subject read 5 words, and 1 subject read 4 words, 2 subjects read 3 words, 1 subject read 2 words, and 1 subject

TABLE I: NUMBER OF CANDIES SUCCESSFULLY POURED INTO A CUP IN 10 TRIALS

SUBJECT NO.	NO. OF CANDIES POURED		
	PIXEL NUMBER ARRAY		
	4x4	6x10	16x16
1	10	10	8
2	0	10	10
3	10	7	10
4	0	0	10
5	10	10	10
6	10	9	10
7	7	6	10
8	1	10	10

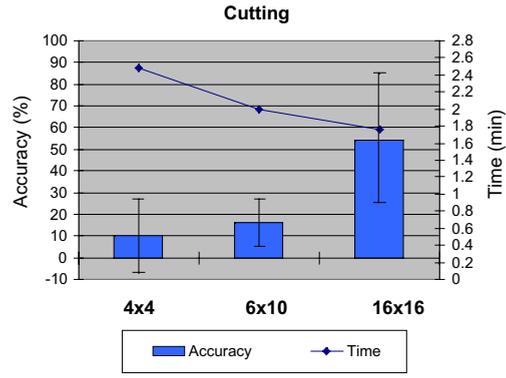


FIGURE 22

Percent accuracy and time to do cutting are represented as a function of different number of pixel arrays. Error bars represent standard deviation.

### Symbol Recognition

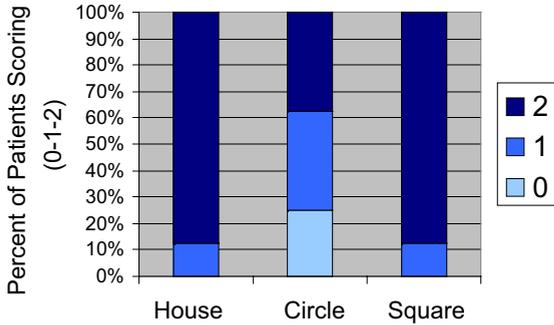


FIGURE 23

With a 4 x 4 pixel array, subjects scanned over three symbols on a Light House Key Card. Correct responses (“house,” “circle,” “square”) were awarded 2 points, close responses were awarded 1 point, and inaccurate responses were awarded no points.

read 0 words. One subject complained of motion sickness while viewing the scanning letters. This was the same subject who read 6 words on the 45-point font, 8 words on the 36-point font, and 0 words on the 27-point font.

Most subjects (87%) were able to read the 36-point font. The capital letter had a height of 0.8 cm. Reading this at a distance of 4.5 cm corresponds to a visual acuity of 20/600 with the 16 x 16 array.

## DISCUSSION

### I. ELECTRICAL STIMULATION OF NEURONS

#### 1.1 Physiology of Neuron Excitation

In 1939, it was found that during the propagation of an action potential in the giant axon of a squid, the conductance of the membrane to ions increased dramatically.<sup>129</sup> Subsequently, during the early 1950s, the first complete description of the ionic mechanisms underlying the action potential was proposed.<sup>130,131</sup> Electrical stimulation elicits a

### Reading Speed

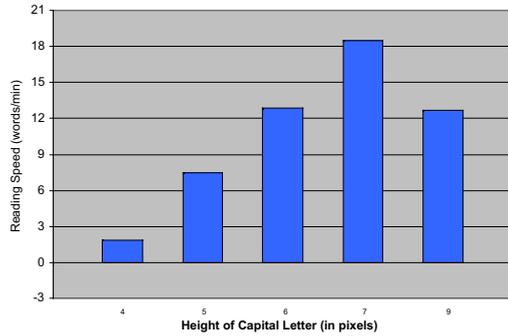


FIGURE 24

Reading speeds as a function of letter height.

neural response by opening the voltage-sensitive ion channels, bypassing the chemically gated channels in the stimulated cell. Neuronal excitation threshold is the minimum electrical stimulus amplitude and duration required for initiating an action potential. Once the membrane reaches a certain potential, a trigger mechanism is released and an action potential results (all-or-none mechanism). Many of the studies designed to explore safe and effective parameters of electrical stimulation were based on extracellular recording of such action potentials.

Similarly, early experiments showed that secondary slow-wave retinal potentials have been induced by transretinal electrical stimulation of an amphibian eyecup preparation.<sup>132,133</sup> However, it should be noted that in the retina (photoreceptor, bipolar and horizontal cells) and probably in other parts of the central nervous system, there are neurons that, when excited, do not generate action potentials but only graded potentials.<sup>133</sup> In these neurons, electrical stimulation can evoke a graded potential that can be very difficult to document with extracellular recordings.

A number of factors can influence the efficacy of electrical stimulation. First, the threshold depends on the electrical properties and anatomy of the target neural elements, and what portion of the cell (dendrite, cell body, and axon) is stimulated. For example, because RGC axons are unmyelinated and of a small diameter, they are difficult to excite. Consequently, one computational model of extracellular field stimulation of the RGC has shown that even though the axon is closer to the epiretinal stimulating electrode, the extracellular stimulation threshold of the RGC soma is 58% to 73% lower than its axon.<sup>134</sup>

Second, the threshold is obviously affected by the distance from the electrodes to the target cell. However, there can be an inhibitory effect from the stimulation. For example, for myelinated axons, it has been shown that those axons very close (<500  $\mu\text{m}$ ) to the electrode may not be stimulated because of current flow considerations.<sup>135</sup> Third, the threshold is also affected by inter-electrode separation as well as the PD.<sup>134,136</sup> Fourth, threshold can vary significantly owing to the impedance of tissues, and errors can be associated with the assumption that tissue electrical properties are the same in every stimulated compartment (isotropic tissue properties), especially with bipolar electrical stimulation.<sup>137</sup>

Fifth, there is a well-defined relationship between the threshold current/charge and stimulus PD required for neuronal activation.<sup>138-140</sup> As the PD decreases, the threshold current increases. This relationship begins to break down at the extremes (ie, a very short current pulse cannot activate a nerve regardless of the amplitude). Similarly, as the PD increases, the threshold current approaches a minimum value called the rheobase, below which an action potential cannot be elicited regardless of PD. A chronaxie is the pulse width for which the threshold current is twice the rheobase current.<sup>135</sup> Charge, which accounts for both the pulse amplitude and PD, is probably the most meaningful parameter for the electronic prosthesis. This is because electrode metals can withstand only certain charge density before irreversible toxic reactions occur at the electrode tissue interface.

Sixth, in addition to current amplitude, charge, and PD, investigators found that threshold is affected by the frequency of stimuli.<sup>32,52</sup> In one of the experiments, the threshold was constant at frequencies of 150 to 200 Hz and increased 50% at 75Hz.<sup>32</sup> Furthermore, it was found that only those pulses delivered in the first 100 ms would determine the sensory response for trains of stimulus pulses at any specified set of parametric values.<sup>29</sup>

Seventh, the polarity of electrical stimulation is also an important factor. Neurons can be activated by cathodic threshold activation, anodic pulses, and biphasic pulses.<sup>141-144</sup> In many neural systems, higher currents were required to reach threshold with anodic stimulation compared to

cathodic stimulation, so cathodic stimulation is considered the preferred polarity for most of the visual prostheses.<sup>135</sup> Biphasic waveform can have either a cathodic or anodic wave first. However, for most applications, cathodic first biphasic pulses have resulted in the lowest thresholds.<sup>56,88,145</sup> The 2 phases of the biphasic pulse are used for charge balancing and thus avoiding irreversible reactions at the tissue electrode interface, which in its extensive form can result in electrolysis and significant pH changes as well as electrode metal deposition into tissue. The 2 phases can have equal amplitudes and PD but can also be asymmetric, with 1 of the phases having a lower amplitude but large duration in order to result in charge balance. Asymmetric charge-balanced biphasic waveforms were discovered to increase the reversible charge injection limits.<sup>142</sup> However, to date, in a series of patients that underwent retinal electrical stimulation, there was no difference between monopolar versus bipolar stimulation and cathodic versus anodic first stimulation.<sup>47</sup>

Eighth, another variable for threshold stimulation is the waveform. There are 2 basic waveforms for neural stimulation: sinusoidal and pulsatile (square) waveforms. There are many variants of these basic waveforms that can be used for different purposes. Experiments that were performed to examine the question of the optimal stimulation waveform showed that a pulsatile (square) waveform has the lowest threshold. The different threshold values found for electrical stimulation of several points along the visual pathways are presented in Tables II and III.

It should be noted that these studies were performed in different species, at different electrophysiological sites, using different electrode sizes, and with different stimulus parameters (eg, pulse frequency, PD, waveforms, pulse trains). The threshold measured is either physiological (recording evoked potentials or single neuron responses from RGC or primary visual cortex neurons) or by measuring psychophysical responses (phosphene perception or behavioral reaction in monkeys<sup>144</sup>). Thus, these results can give only an estimate of electrical stimulation threshold values of various locations along the visual system, and only a few conclusions can be drawn as to the methods to be used during electrical stimulation. It is clear that the psychophysical threshold for intracortical microstimulation<sup>26,32,33</sup> is lower than the threshold of surface cortical stimulation. In addition, the *in vitro* electrophysiologic threshold is lower than the *in vivo* electrophysiologic and psychophysical thresholds.<sup>47,54,58,143,144,146</sup> This discrepancy is maybe due to the fact that the visual system cannot recognize a single RGC action potential. If this is the case, the exact number of stimulated RGCs for *in vivo* psychophysical thresholds should be determined.

Typical charge density threshold values (0.16 to 70  $\text{mC}/\text{cm}^2$ ) for retinal stimulation of patients with RP were

TABLE II: THRESHOLD PARAMETERS FOR DIFFERENT TYPES OF VISUAL PROSTHESES

CORTICAL SURFACE STIMULATION	INTRACORTICAL MICROSTIMULATION	EPIRETINAL STIMULATION	SUBRETINAL STIMULATION	OPTIC NERVE STIMULATION
Blind glaucoma patient, 4 mA, 200 $\mu$ sec, 100 Hz, electrode diameter 0.8 mm, charge density 159 $\mu$ C/cm <sup>2</sup> /pulse <sup>19</sup>	Macaques, current threshold 1-5 $\mu$ A, electrode surface area 0.3 <sup>-1.6</sup> $\times 10^{-3}$ mm <sup>2</sup> , charge density threshold 100-1,800 $\mu$ C/cm <sup>2</sup> <sup>144</sup>	Rabbits, extradural recording, threshold current 105-720 $\mu$ A, PD 100 $\mu$ sec, electrode diameter 40 $\mu$ m, charge density threshold 0.8-5.7 mC/cm <sup>2</sup> <sup>60</sup>	Normal rabbits (cortical recordings), electrode surface area 0.36 cm <sup>2</sup> , charge density threshold 2.8-100 nC/cm <sup>2</sup> <sup>63</sup>	RP patient, threshold current 30 $\mu$ A, PD 400 $\mu$ sec, electrode area 0.2 mm <sup>2</sup> , frequency 160 Hz, charge density threshold 24 $\mu$ C/cm <sup>2</sup> /pulse <sup>52</sup>
Blind human-optic atrophy, 620 $\mu$ A, 0.1 msec 120 Hz 1 mm electrodes, charge density 7.9 $\mu$ C/cm <sup>2</sup> /pulse <sup>15</sup>	Epileptic patients, current threshold 20-200 $\mu$ A, electrode surface area 200 $\mu$ m <sup>2</sup> , PD 0.4 msec, frequency 100 Hz, train length 0.1-1 sec, charge density 3.9-39 mC/cm <sup>2</sup> <sup>25</sup>	RP and AMD patients, threshold current 500 $\mu$ A, PD 2 msec PD, charge density threshold 0.16-70 mC/cm <sup>2</sup> , (1 $\mu$ C/phase) <sup>47</sup>		
Normal sighted patients, 0.25-1 mm diameter Pt electrodes, 0.5 msec PD, 60-120 Hz, 1 mA <sup>21</sup> , charge density 63-1,000 $\mu$ C/cm <sup>2</sup> .	Blind glaucoma patient, threshold current 1.9-25 $\mu$ A, PD 200 $\mu$ sec, electrodes surface area 200 $\mu$ m <sup>2</sup> , charge density 0.2-2.4 mC/cm <sup>2</sup> <sup>32</sup>	Laser treated human retinas, threshold current 100-600 $\mu$ A, 0.1-0.6 $\mu$ C, 0.8-4.8 mC/cm <sup>2</sup> <sup>153</sup>		
Cats, PD 0.5 sec, frequency 60/120 Hz, trains up to 4 sec, current threshold 1-3 mA, electrode surface area 0.5-2 $\times 10^{-3}$ , charge density threshold 25-4,000 $\mu$ C/cm <sup>2</sup> <sup>21</sup>	Cats, auditory behavioral task, charge threshold - 8.9 nC/phase, charge density threshold ~18 mC/cm <sup>2</sup> <sup>33</sup>	Normal mice, 0.055 $\mu$ C, 455 $\mu$ C/cm <sup>2</sup> , 16-week-old rd mice - 0.075 $\mu$ C, 621 $\mu$ C/cm <sup>2</sup> electrode diameter 125 $\mu$ m, PD 0.08 msec <sup>55</sup>		
Human subjects. Current threshold 0.79-3.50 mA (average 1.76 mA), train 0.5 sec, PD 0.25 msec, electrodes surface area 1-2mm <sup>2</sup> , charge density threshold 22-44 $\mu$ C/cm <sup>2</sup> /pulse <sup>28</sup>		Normal mice, threshold current 240 $\mu$ A, threshold charge density 1.9 $\mu$ C/cm <sup>2</sup> , rd mice 592 $\mu$ A, charge density 4.8 $\mu$ C/cm <sup>2</sup> , electrode diameter 125 $\mu$ m, PD 1 msec <sup>56</sup>		
Human subject, frequency 30 Hz, 1-50 pulses, PD 0.5 msec, voltage threshold 10-20 volts, no impedance reported <sup>30</sup>		Normal human subject, 19 $\mu$ C/cm <sup>2</sup> (12 $\mu$ A, PD 2 msec, electrode diameter 400 $\mu$ m). RP patient, 0.3 mC/cm <sup>2</sup> , (1.5 mA, PD 0.25 msec, electrode diameter 400 $\mu$ m) <sup>58</sup>		

AMD, age-related macular degeneration; PD, pulse duration; Pt, platinum; RP, retinitis pigmentosa.

well above the safe threshold for platinum electrodes chronic stimulation.<sup>54</sup> Other investigators reported comparable threshold values recently (0.3 mC/cm<sup>2</sup> in a patient with RP).<sup>55</sup> These values are affected by the fact that many times the stimulating electrodes were as far as 0.5 mm from the retinal surface. Nevertheless, one cannot exclude the fact that the degenerated retina may require higher charge. If the charge requirements are higher

because of the relative degeneration of the retina, then for these patients with more degenerated retinas, the electrodes sizes will have to be larger in order to reduce the charge density and keep it within safe limits for long-term stimulation.

### 1.2 In Vitro Retinal Experiments

A limited number of in vitro experiments to define threshold

TABLE III: THRESHOLD PARAMETERS FOR EPIRETINAL VERSUS SUBRETINAL PROSTHESES

EPIRETINAL STIMULATION	SUBRETINAL STIMULATION
Pt electrodes. 2.98 $\mu\text{C}/\text{cm}^2$ (bullfrog). 8.92 $\mu\text{C}/\text{cm}^2$ (normal rabbit). 11.9 $\mu\text{C}/\text{cm}^2$ (chemically RD rabbit). <sup>46</sup>	Chick isolated retina. 35 $\mu\text{A}$ PD 0.4 msec, electrode surface area 0.01 $\text{mm}^2$ , charge threshold 14 nC/phase, charge density threshold 178 $\mu\text{C}/\text{cm}^2$ . <sup>146</sup>
Human isolated retina. Electrode diameter 10 $\mu\text{m}$ , PD 400 $\mu\text{sec}$ , threshold current, 0.18 $\mu\text{A}$ - 0.52 $\mu\text{A}$ , threshold charge density 91-264 $\mu\text{C}/\text{cm}^2$ . <sup>149</sup>	Retinal degenerate rats (RCS) isolated retina. Threshold charge density 500 $\mu\text{C}/\text{cm}^2$ . <sup>149</sup>
Rabbit isolated retina, 51.85 $\mu\text{C}/\text{cm}^2$ (ganglion side stimulation) vs. 55.35 $\mu\text{C}/\text{cm}^2$ (photo receptor side), PD 1 msec. <sup>143</sup>	

currents for retinal electrical stimulation have been performed in different preparations. One study of normal retinal stimulation was performed in bullfrog eyecups and reported a charge threshold of 3.75 nC with biphasic square current pulses of 75 msec/half phase.<sup>147</sup> Another study was performed with normal human isolated retinas. These retinas came from normal subjects submitted to enucleation on account of orbital cancer. Charge density threshold values were between 91  $\mu\text{C}/\text{cm}^2$  and 264  $\mu\text{C}/\text{cm}^2$ . These results were similar to findings in isolated rabbit retinas, concluding that rabbits are a good model to study retinal electrical stimulation.<sup>143,145,148</sup>

Reported in this thesis are our electrical stimulation results from rabbit retinal isolate. Threshold parameters during various in vitro electrical stimulation experiments, including from this thesis, are shown in Table III. Among the parameters tested were the electrode position (ganglion or photoreceptor cell side) and the stimulating electrode size (10, 25, 125  $\mu\text{m}$  diameter). It was shown that the charge density threshold for stimulation from the ganglion side is lower (51.85  $\mu\text{C}/\text{cm}^2$ ) than from the photoreceptor side (55.35  $\mu\text{C}/\text{cm}^2$ ), especially when using 125  $\mu\text{m}$  diameter electrodes. Other investigators have obtained even lower thresholds (0.4 nC) when stimulating from the photoreceptor side.<sup>146</sup>

One study that was performed on isolated retinas from retinal degenerate rats<sup>150</sup> reported a threshold charge density of 500  $\mu\text{C}/\text{cm}^2$ . Again, we can see that a much higher-charge density threshold is required to stimulate diseased retinas, similar to in vivo experiments. Given that stimulation thresholds change depending on the health of the retina, future experiments need to study and compare stimulation thresholds between normal and retinal degenerate retinas.

### 1.3 In Vivo Experiments

Since many of the experiments prior to a safe and effective implantation in humans have been and will be performed in animals, methods of recording the function of

the central visual system have been developed. Threshold parameters during various in vivo electrical stimulation experiments are shown in Table II.

Several experiments using scalp and subdermal electrodes positioned over the visual cortex were performed to conclude that electrical evoked responses (EER) can be recorded after external electrical stimulation of the eye.<sup>37-39,45,63,116,151,152</sup> In one of the studies, it was discovered that the EER stimulation threshold was significantly increased for advanced retinal degenerate dogs (RCD1) versus normal dogs (4 mA versus 1.1 mA,  $P < .05$ ).<sup>57</sup>

Penetrating electrodes within the cortical tissue have the potential to record single neuron activity in addition to multiunit activity recorded by epidural electrodes.<sup>35,152</sup> One of the studies involved normal and retinal degenerate (rd) mice. Single cortical neuron response to retinal electrical stimulation showed dose-dependant effect, and similar to other studies, the current amplitude threshold was significantly lower for normal mice (240  $\mu\text{A}$ ) versus rd mice (592  $\mu\text{A}$ ,  $P = .001$ ).<sup>56</sup>

Other invasive methods for recording visual evoked potentials have also been studied. In vivo retinal stimulation with an epiretinal microfilm electrode array was performed in normal cats with recording of the responses from the visual cortex being performed with epidural recording electrodes. The charge balanced threshold value was 178  $\mu\text{C}/\text{cm}$ .<sup>21,46</sup> Subdural electrodes were also used recently to record visual and electrical evoked potentials and proved to have lower thresholds than subdermal electrodes.<sup>152</sup>

In the experiments reported in this thesis, responses for electrical stimulation of the eye were recorded from ganglion cells in the same stimulated eye. Normal mice were compared to rd mice of different ages in regard to electrical stimulation threshold. A 1-kHz sinusoidal waveform was more efficient than a biphasic current pulse of 500  $\mu\text{s}/\text{phase}$  in normal mice, but in the 2 rd-mice groups, threshold charge was not dependent on waveform shape. RD mouse retina is almost completely absent of

photoreceptors, but the inner retina (bipolar cells and retinal ganglion cells) is less affected. This suggests that the sinusoidal waveform is more suitable to stimulate the photoreceptor cells, but there is no difference between sinusoidal waveform and square waveform when stimulating the inner retina. Pulse trains were tested to determine if a series of pulses would “appear continuous” to the retinal cells and thereby use less charge to elicit a response. The opposite was found to be the case. A train of 5 x 40- $\mu$ s/phase pulses (where the pulse train lasted for 0.6 ms) required 2 to 3 times as much current as a continuous 0.5-ms pulse, meaning the cells did not respond to the train of short pulses as if it was a single long pulse. In fact, the current threshold for the pulse train was only slightly lower than a single 40- $\mu$ s pulse.

The excitation threshold was significantly higher for 16-week-old rd mice versus normal mice (0.075 versus 0.055  $\mu$ C for 0.08-ms square pulse,  $P < .05$ ). This is most likely due to the more degenerated inner retina requiring more current to excite it. The number of intact inner retinal cells in an 8-week-old mouse retina is more than that of a 16-week-old mouse retina. This result correlates well with data obtained from short-term electrical stimulation tests in humans, in which it was demonstrated that areas of more severe retinal damage, either from RP or laser damage, had a higher electrical stimulus threshold.<sup>153</sup>

In all mice groups, short-duration pulses (40, 80, and 120  $\mu$ s) were more efficient in terms of total charge than longer pulses (500 and 1000  $\mu$ s). However, because the current pulses are so short, a relatively large current is required to reach threshold. Electronics capable of delivering high current, even for a short time, may be difficult to implement in a design that is efficient in terms of size and power consumption. Moreover, longer pulses may also preferentially target the bipolar cell layer and therefore possibly make use of more of the inner retinal neuronal function.<sup>115</sup> The pulse threshold data can also be used to design a retinal stimulating array. Each individual stimulating electrode within the array must be designed such that it can safely supply the appropriate level of stimulating current to the retina. The design considerations are electrode material and electrode size. Assuming a planar, platinum disc electrode, the diameter of this electrode would have to be 170  $\mu$ m to support 0.07  $\mu$ C (the threshold charge in 8-week rd mouse with a 0.5 ms pulse). This assumes a safe chronic stimulation limit of 0.1 mC/cm<sup>2</sup> for platinum. As the precise technology to be used for the retinal prosthesis becomes clear, neural response data like that reported here will be essential to the development of the final device.

#### 1.4 Future Studies in Electrophysiology

Future studies are needed to identify the target cell for

retinal electrical stimulation. The thickness of the nerve fiber and the ganglion cell layers is at least 20 to 200 and 20 to 40  $\mu$ m, respectively. Thus, an epiretinal implant places the stimulating electrodes at quite a distance from the desired target of signal initiation (ie, the ganglion or the bipolar cell layers). Since there is a 3-dB rise in threshold for every 250  $\mu$ m,<sup>115</sup> more current will be necessary for electrical stimulation. Stimulating the bipolar cells could allow for more of the natural retinal processing to take place. Stimulating the ganglion cells, which are closer to the epiretinal electrode array, may require less current but could require more image processing and complex stimulation patterns to account for the lost retinal processing.

The cell bodies (somas) of these ganglion cells are mapped over the surface of the retina in a manner that approximates the projection of the visual world onto the surface of the retina. However, at any particular location on the surface of the retina, axons from peripheral sites course over the individual ganglion cell bodies. If these superficial passing axons were preferentially stimulated, groups of ganglion cells from large areas of the retina would be excited. One might expect the visual perception of such a stimulus to appear as a wedge or arc because of the characteristic course of the ganglion cell axons in the nerve fiber layer. On the other hand, if the ganglion cell bodies or deeper retinal cells were stimulated, one would expect the visual perceptions to be focal spots.

Early experiments showed that inner retinal layers can be electrically stimulated and elicit an EER.<sup>132,154</sup> It has also been shown that phosphenes elicited by electrical stimulation over a krypton laser scar (causing outer retinal damage) best simulated the visual perceptions previously reported due to electric stimulation in blind RP and AMD patients, suggesting that the site of electric stimulation in those patients is the inner retina.<sup>153</sup> These results, although suggestive, have not determined the exact target cell for retinal electrical stimulation.

Another line of evidence came from electrical stimulation of the retinas of patients with RP or AMD. When stimulated with platinum disc electrodes 50 to 200  $\mu$ m in diameter, the patients reported spots of light and not wedges.<sup>47,54,58</sup> This would implicate that the electrodes did not preferentially stimulate the RGC axons.

Additionally, circumstantial evidence suggesting that retinal bipolar cells may be the target for retinal electrical stimulation comes from postmortem morphometric analysis of the retinas of both RP and AMD patients. This analysis has shown that there were many more bipolar cells left compared to RGCs in the retinas of these patients.

Recently, latency experiments that were conducted in isolated frog retinas showed that higher currents stimulate RGCs directly, while lower currents activate other cells

(photoreceptors, bipolar cells).<sup>115</sup> Another finding was that the target cells of shorter PD (<0.5 ms) were RGC cells/axons, whereas a deeper cellular element was the target for longer PD (>0.5 ms). This is consistent with the finding that deeper retinal cells have unusually long chronaxies compared to RGCs.<sup>115</sup>

In conclusion, there are several lines of evidence to suggest that epiretinal electrical stimulation of the retina can result in well defined retinotopic visual percepts. To get such phosphenes one should avoid RGC axonal stimulation and probably activate bipolar cells by varying stimulation parameters.

## **2. PSYCHOPHYSICAL EXPERIMENTS**

In an effort to define the minimum acceptable resolution for useful vision, several psychophysical experiments were performed. As early as 1965, it was suggested that 600 channels, or points of stimulation, would be sufficient for reading ordinary print.<sup>155</sup> Others suggested that 80 to 120 points (pixels) are sufficient for large-print reading, while 200 points may allow recognition of simple obstacles.<sup>156</sup>

More recent studies of simulated pixelized vision showed that 625 points of stimulation is a better estimate for useful vision.<sup>157-159</sup> These studies were conducted with a portable “phosphene” simulator, which consisted of a small head-mounted video camera and monitor worn by a normally sighted human subject. To simulate a discrete phosphene field, an opaque perforated film masked the monitor. The visual angle subtended by images from the masked monitor was 1.7° or less, depending on the mask, and fell within the fovea of the subject. It was concluded that 625 electrodes implanted in a 1-cm<sup>2</sup> area near the foveal representation of the visual cortex could produce a phosphene image with a visual acuity of approximately 20/30. Such acuity could provide useful restoration of functional vision for the profoundly blind.<sup>159</sup>

In another experiment, in which the same methods were used, the reading speed was measured in subjects viewing pixelized text. The results indicated that a 25 x 25 pixel array representing 4 letters of text is sufficient to provide reading rates near 170 words per minute with scrolled text, and near 100 words per minute with fixed text.<sup>158</sup>

The feasibility of achieving visually guided mobility was investigated with a similar device. Normally sighted human subjects were required to walk through a maze that included a series of obstacles. The results indicated again that 625 pixels provided useful visually guided mobility. Walking speed increased fivefold during 3 weeks of training.<sup>157</sup>

To make a cortical electrode array of 600 or more channels, several methods were proposed. Considering the visual cortex mean extent of 9.7 cm<sup>2</sup>, the number of

penetrating electrodes that can be inserted, using current technologies, can reach 10,000 or more.<sup>128</sup>

Although these studies began to delineate the number of electrodes needed, the fact that all the pixels were projected on a very small area of the retina made it impractical to translate to the design of the retinal prosthesis, in which the electrodes would be spread over the entire macular region. The results from experimentation presented in this thesis address this shortcoming by projecting the pixels over the entire macular region. With our setup face recognition, reading speeds as well as certain activities of daily living were tested.

### *2.1 Face Recognition and Reading Speed*

This simulation indicates that rapid and accurate facial recognition can be achieved by using pixelized dot images. The performance was maximized when the pixelized grid was at least 25 x 25 dots in size with 6 levels of gray-scale resolution. Excellent speed and accuracy were achieved with dot sizes of 13.5 arc minutes, gap sizes of 4.5 arc minutes, and dropout rates of 30% or less. High-contrast images resulted in improved facial recognition rates. High facial recognition rates required sampling the facial images at eight or more cycles per face. An increased concentration of dots per character resulted in increased reading speed. As the frequency of dots approaches the Nyquist limit, reading speed decreased dramatically. A larger grid area also improved reading speed. A grid size of 7° is acceptable, but marked improvement was noted with a grid size of 10°.

This simulation of pixelized prosthetic vision suggests that prosthetic visual devices designed to the specifications above may be capable of providing individuals with visual perceptions that would enable a high facial recognition rate and adequate large-print reading speeds. Specifically, a fair level of visual function can be achieved with pixelized vision using a 16 x 16 grid encompassing a 10° field, high-contrast imaging, and 4 or more gray levels. Simulation studies such as this will help to further establish design criteria to maximize the performance of such implants.

### *2.2 Letter/Symbol Recognition and Activities of Daily Living*

One of the most important findings of these experiments was the impact of being able to scan. Even with a very rudimentary electrode array of 4 x 4, 87% of the subjects could correctly identify a tumbling E. Certainly, with 16 x 16 electrodes, most of the subjects could even perform complex tasks such as object recognition and cutting. The impressive ability to perform with such a limited number of pixels in lieu of the fact that we have 100 million, if not more, photoreceptors bodes well for the development of

a retinal prosthesis. If the electronic implant had to stimulate the retina in millions of points, this would be impossible owing to the extreme amounts of power requirements and heat dissipation that would irreversibly damage the retina. However, electrode technology and stimulation parameters more than likely could result in a retinal prosthesis with 16 x 16 electrodes placed over the macular region.

The small number of pixels needed to perform complex tasks should not be a total surprise. Albeit, a different sensory system, clinical experience with the cochlear implant has demonstrated that electrical stimulation with as few as 4 to 8 input channels allows patients to talk over the phone. Perhaps a similar phenomenon (redundancy in visual information) and the plasticity of the visual cortex will permit fewer retinal stimulating electrodes to give blind patients some useful vision.

However, the result from these psychophysical tests does need to be taken in its context. The electrical stimulation to produce phosphenes at the retinal level is undoubtedly going to stimulate groups of neurons in a manner very different than how light pixels stimulate the normal retina. Thus, the definitive answer to the number of electrodes or pixels needed to be generated by an electronic device still will be determined when blind patients are fitted with these implants and allowed to use them in their activities of daily living.

### 2.3 Future Studies

Future studies may investigate the parameters necessary for pixelized vision to provide the sufficient visual information for individuals to independently perform activities of daily living (ADLs). Such survival tasks may include eating, self-care (health care and personal hygiene), communicating with others, and independent mobility. Another method of assessing visual function includes the ability to perform more complex visually guided tasks, known as instrumental activities of daily living ([I]ADLs) such as managing personal finances, shopping, and house-keeping.

Future simulation studies may also evaluate the impact of frame rates less than 30 Hz and flicker. Additionally, the effect of image enhancement may also be investigated. Such studies may examine the effects of edge detection, high pass filtering, black-white image reversal, and magnification.

## 3. SUMMARY

The 3 levels of hierarchy in the sensory systems (namely, receptor organ, sensory pathways, and perception) suggest a similar architecture for artificial sensory systems. Accordingly, artificial systems should include a transducer

corresponding to the receptor organ, an encoder corresponding to the sensory processing system, and finally an interpreter corresponding to perceptual functions. In other words, the visual environment is captured and processed by a photosensing device such as a digital camera, and the pixelized information is transmitted to a stimulating electronic chip. This chip, in turn, activates a penetrating electrode array with a pixelized pattern that allows the patient to correctly see the image.

The epiretinal implant is designed to have 2 units, 1 extraocular and 1 intraocular. Previously, a visual intraocular prosthetic chip including a photosensor, processor, and a stimulus-driving chip was developed.<sup>160</sup> However, it became apparent that an improvement could be achieved in having photosensing<sup>161</sup> or video capture performed extraocularly. This modification would allow for enhanced videoprocessing, more custom control over the video signal, and less hardware to be implanted into the eye. The 2 units are connected by either a modulated laser<sup>51</sup> or an inductive link,<sup>106</sup> allowing the intraocular unit to derive both power and data signals from the extraocular unit. The extraocular unit includes a video camera and a video processing board, a telemetry/laser protocol encoder chip, a radio frequency amplifier, and a primary coil (or laser source). The intraocular unit consists of a secondary coil, a rectifier and regulator, a retinal stimulator with a telemetry protocol decoder, a stimulus signal generator, and an electrode array.

The subretinal approach uses direct visible and infrared light. The stimulation power is then locally enabled by an amorphous silicon photoconductor, according to the image projected onto the device by the optical system of the eye. The photodiodes, in turn, activate adjacent electrodes, which stimulate the bipolar/ganglion cells above them.<sup>48,49</sup>

Many of the electronic components of the cortical prosthesis system should be similar to those of the retinal prosthesis. However, the cortical prosthesis will also need a complex real-time algorithm to map the visual information correctly onto the cortex via microelectrodes. One of the cortical prosthesis groups still uses a connecting "pedestal" that perforates the scalp and links the processing computer with the electrode array. This pedestal allows the passage of wires through the skin.<sup>23,26</sup> With current technologies, it might be possible to miniaturize the electronics and use wireless connections between the sensor and the stimulator to decrease the bulkiness of the device.

Attempts at implanting electronic devices at various parts along the visual pathways were discussed. Both major achievements and obstacles remaining were summarized. Given that intact neurons along the visual pathways can be found in almost all blind patients, it is only

our lack of understanding that prevents us from stimulating them in a safe and effective manner. We believe that as our knowledge increases about how to stimulate neurons with microelectronics and as microelectronics and material sciences continue to evolve, we should one day be able to restore vision to the blind. Given the advances that have been made in this field, we can only hope that the day such devices are widely used is in the near future and not decades away.

## APPENDIX

### I. METHODS

#### *Pixelized Vision Simulator*

Several video camera adjustments were made to maximize contrast. Brightness was set at 131, contrast 255, cyan 0, yellow 0, saturation 74, video quality 0, and exposure time 128; light sensitivity was varied between 255 and 68.

#### *Sizing of Arrays*

This was done by first determining the percentage of visual field occupied by the active monitor displayed in the headset. Utilizing the “see-through” feature, the length of the active window image was measured in space at a fixed distance from the eye. Using simple trigonometry, the angle was found to be 28°. This number was correlated to the size of the active window on the PC monitor. It was found that a 7.6-cm image on the computer monitor created a 7.3° image displayed on the retinal surface. A template was made to use as a guide for manually resizing the display window on the computer monitor.

#### *Setup for First Set of Tasks*

The camera was focused appropriately for a 10- to 70-cm range. Video camera light sensitivity was set at 68 for these tasks in order to minimize a washout effect seen under the lights when the camera is mounted on the subject’s head.

#### *Calculation of Expected Visual Acuity*

For a completely unambiguous identification of an E, each branch of the E must lie at the center of 2 noncontiguous pixels (2 center-to-center distances). A person with 20/20 vision can differentiate the images of 2 lines at 2 arc minutes apart on the retina. This can be expressed in the following equation:

$$\frac{X}{20} = \frac{2 \text{ center-to-center distances in the array}}{2 \text{ arc minutes}}$$

X is the new denominator in the Snellen acuity. Two center-to-center distances are 4° (240 arc minutes) for the 4 x

4 and 6 x 10 arrays and 1.6° (96 arc minutes) for the 16 x 16 array. This gives the expected visual acuities of 20/2400 for the 4 x 4 and 6 x 10 arrays and 20/865 for the 16 x 16 array.

#### *Tumbling E*

At each distance, subjects were encouraged to scan vertically and horizontally with the camera. Subjects were discouraged from guessing, and if they incorrectly identified the direction, the letter was rotated before the next attempt so that they still had all 4 options.

#### *Object Recognition*

For this task, the subjects were allowed to move the camera as close to the object as they desired. They were encouraged to look at it from a seated position as well as standing and looking directly down on it. They were also permitted to place their hand on the table without touching the object for the purpose of size comparison. Object 1 was a white plate 22.5 cm in diameter. Descriptions judged as accurate included circular, round, flat, and disk-like. Descriptions judged as inaccurate included rectangular, plus-sign, and triangular. Object 2 was a white cup, 9 cm tall, 5 cm in diameter at its base, and 8 cm in diameter at its rim. Descriptions judged as accurate included wider top, thinner bottom, straight edges while seated, circular while standing over object. Descriptions judged as inaccurate included: square, rectangular, crosslike, and star-shaped. Object 3 was a white spoon, 14.5 cm long, with a 1.1-cm-wide handle and 4.1-cm-diameter head. Accurate descriptions were stop-sign shaped, straight line that is fuller on top, lollipop-like. Felt to be inaccurate were sticklike, rectangular, and crosslike. Object 4 was a white ink pen, 14 cm long and 0.7 cm thick. Accurate descriptions were long, thin, and sticklike. Judged as inaccurate were circular and an ill-defined shape.

#### *Candy Pour*

The cups were white, 9 cm tall, 5 cm in diameter at the base, and 8 cm in diameter at the rim. The candies were disc-shaped, 2.5 cm in diameter, and 0.8 cm thick. Subjects were asked to visually locate the 2 cups and encouraged to view them from different angles, including standing and looking directly down on them. The observer stabilized the cup as the subject began their pour.

#### *Cutting*

The sides of the rectangle were 2.6 cm thick, 15 cm long, and 14.6 cm wide. Subjects were given a pair of blunt-ended safety scissors in their dominant hand. A black cloth was held behind the sheet of paper to add more contrast. Subjects were encouraged to locate their hand and scissors before starting to cut.

### Setup for Second Set of Tasks

The camera was refocused for this new distance. The light intensity setting was also increased to 255, which optimized the contrast at this distance. Subjects were briefly instructed on how to use the apparatus and were allowed to practice manually scanning the platform-mounted camera across sample reading material.

### Symbol Recognition

Each symbol was a hollow black object with 0.6 cm thick lines. The first symbol tested represented a house and was 4.4 cm wide and 4.5 cm tall at the center. The second symbol was a circle with a 4.4 cm diameter. The last was a square measuring 4.4 cm per side. A close response for the house was "arrow." Close response for the circle was "oval," and that for the square was "rectangle." Inaccurate response for the circle was "square" or "hexagon."

## 2. RESULTS

### Calculation of Actual Visual Acuity

First we multiply the angle the letter would subtend on the retina (if it were viewed by the naked eye) by the magnification factor inherent in our system.

$$(2 \text{ arc tan } 0.5h/d) \times y/46^\circ = Z^\circ$$

where:

h= height of the letter

d= distance of camera lens from the letter

y= amount of retinal surface exposed to visual input

7.3° for 4 x 4 array

15.3° for 6 x 10 array

11.3° for 16 x 16 array

46°=visual field captured by the camera

Z= height of letter on retinal surface

Since we know the height of a 20/20 letter E subtends 5 arc minutes on the retina, it is possible to calculate visual acuity with our setup.

$$\frac{X}{20} = \frac{Z \times 60}{5 \text{ arc minutes}}$$

where:

X= the denominator in Snellen acuity

### Reading

With a 6 x 10 array reading 72-point font, the height of the capital letter was 4 pixels. With a 16 x 16 array, the height of the capital letter in the 72-font sentence was 9 pixels. It was 7 pixels in the 57-point font, 6 in the 45-point font, 5 in the 36-point font, and 4 in the 27-point font. Subjects were encouraged to use the context of the sentence to help identify more difficult words.

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# GLAUCOMA PATIENTS' ASSESSMENT OF THEIR VISUAL FUNCTION AND QUALITY OF LIFE\*

BY Henry D. Jampel, MD, MHS

## ABSTRACT

*Purpose:* To determine how glaucoma patients with various degrees of vision loss rate their vision, and to determine if the Esterman binocular visual field test and other visual function tests correlate with those ratings.

*Methods:* Two hundred thirty-seven glaucoma patients evaluated their vision using 2 utility tests, the linear rating scale and the time trade-off test, and 2 quality-of-life instruments, the National Eye Institute Visual Function Questionnaire (VFQ) and the Short Form 36 (SF-36). Their results were compared to clinical tests of their vision and to persons with normal vision (n=12) and blind persons (n=12).

*Results:* On a scale of 0 (blind) to 100 (ideal), subjects with normal vision rated their vision higher ( $90 \pm 8.0$ ) than did glaucoma subjects and suspects ( $75.7 \pm 17.6$ ) and "blind" subjects ( $15.6 \pm 15.3$ ),  $P = .001$ . Mean scores for the Esterman test were  $89.7 \pm 13.4$  for the glaucoma group. The Esterman test correlated moderately with the overall VFQ score (partial correlation coefficient [PCC] = 0.32,  $P = .001$ ), but only weakly with the linear rating scale (PCC = 0.17,  $P = .02$ ) and the time trade-off test (PCC = -0.16,  $P = .06$ ). Correlation between the linear rating scale and the overall VFQ score was good (PCC = 0.56,  $P = .0001$ ) and was moderate with several domains of the SF-36 (eg, social function PCC = 0.32,  $P = .0001$ ).

*Conclusions:* Utility values that glaucoma patients assign to their vision do not correlate well with Esterman test results. A challenge for the future will be designing clinical tests that better correlate with patient perceptions.

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## INTRODUCTION AND LITERATURE REVIEW

The glaucomas are a heterogeneous group of diseases that have in common a characteristic form of damage to the optic nerve. The damage generally results in typical changes in optic disc morphology and visual field. The primary focus in the care of glaucoma patients has been the prevention of ongoing damage to the optic nerve and consequent visual field loss.

Visual field defects in glaucoma tend to affect the midperipheral visual field first and only later in the disease involve central vision and then fixation. This pattern of visual field loss in glaucoma has led to the impression that the glaucoma patient is asymptomatic until late in the disease. Only when visual field loss impinges upon or involves central vision does the patient become aware of a functional defect.

Objective end points in the management of patients with glaucoma are important and include the level of intraocular pressure, appearance of the optic nerve, and status of the visual field. In addition, over the past several years an increased awareness of the effect of glaucoma

on the patient's quality of life (QOL) has developed. This parallels an increased interest throughout ophthalmology in the impact of disease and therapy on QOL. The impact of cataract,<sup>1,4</sup> macular degeneration,<sup>5,9</sup> diabetic retinopathy,<sup>10,11</sup> refractive error,<sup>12-14</sup> corneal disease,<sup>15</sup> and choroidal melanoma<sup>16,17</sup> on QOL have all been evaluated.

QOL in patients with ocular disease can be measured by using either vision-directed instruments or generic instruments designed for examining overall health. Other investigators have described the characteristics and the strengths and weaknesses of these instruments,<sup>8,18,19</sup> and so they will not be described at length herein. Vision-directed instruments described in this thesis include the National Eye Institute Visual Function Questionnaire (VFQ),<sup>20,21</sup> the VF-14,<sup>22-24</sup> the Activities of Daily Vision Scale (ADVS),<sup>25,26</sup> and the Glaucoma Symptom Scale;<sup>27</sup> the generic instruments mentioned are all versions of the Medical Outcomes Study Short Form (eg, SF-36).<sup>28-30</sup>

Several investigators have examined QOL in glaucoma patients. Sherwood and coinvestigators<sup>31</sup> examined QOL in glaucoma patients by using a generic instrument. They found that patients with glaucoma had lower scores on all domains of the SF-20 than control subjects, but they did not adjust for general medical comorbidity, which could have influenced results. Similarly, Wilson and colleagues<sup>32</sup> administered the SF-36 instrument to glaucoma

\*From the Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland. Supported by the Glaucoma Research Foundation, San Francisco, California.

patients, people suspected of having glaucoma (glaucoma suspects), and controls (no glaucoma) and found that the scores were lowest for the glaucoma patients, intermediate for the glaucoma suspects, and highest for the controls. However, they did not report the severity of damage among the glaucoma patients, again limiting the conclusions that they could reach.

Other investigators have looked at vision-specific measures of QOL in glaucoma patients. Parrish and coworkers<sup>33</sup> found that there was a moderate correlation between binocular visual field impairment and scores on the VFQ and the VF-14. Mills<sup>19</sup> has reported only weak correlations between QOL and the ocular characteristics at enrollment of subjects in the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Finally, Gutierrez and associates<sup>34</sup> found that greater visual field defects in the better eye of glaucoma patients were associated with poorer scores on the VFQ and VF-14 QOL instruments. Of particular note was the suggestion that there was a linear relationship between visual field loss and QOL responses and that changes in QOL were present even with small amounts of visual field loss. These findings are particularly provocative because they suggest that even early visual field loss may affect patients' QOL and that visual field loss need not threaten fixation nor involve an entire hemifield before affecting the functional well-being of patients. These findings call into question the clinical aphorism that glaucoma is a "sneak thief" of vision and that it has no effect until damage is profound.

Preliminary attempts have been made to design QOL instruments that are specific to the symptoms of glaucoma<sup>27</sup> and the effect of glaucoma therapy on QOL.<sup>35</sup> QOL assessment in glaucoma is becoming increasingly important, as attested to by the incorporation of QOL instruments into the study design of both the Ocular Hypertension Treatment Study (OHTS)<sup>36</sup> and the CIGTS clinical trials.<sup>19</sup>

The QOL instruments that are in common use suffer from an important limitation. While they identify declines in visual function among patients, they fail to elicit from patients how their visual function influences their lives. Two patients with the same score on a QOL instrument may differ substantially in how dissatisfied or distressed they feel about their QOL. For instance, 2 patients may give the same response to a question concerning how difficult it is to perceive colors, and hence their score on this question would be the same. However, for the patient who is a painter, the importance of having a color vision problem may be much greater than for other patients.

To address this aspect of the QOL effects of a disease, it is necessary to measure the preference values that

patients assign to their health status,<sup>37</sup> where preference values are defined as "the levels of subjective satisfaction, distress, or desirability that people associate with a particular health state."<sup>38</sup> Several tools, generally referred to as utility tests, have been developed to measure the preference values that patients assign to their health status.<sup>39</sup> This utility approach has several strengths for assessing health-related QOL, including producing a single score on a 0-to-1 scale; incorporating information on risk attitudes, time preference, and trade-offs among different situations; and being able to be combined with pecuniary measure of costs and benefits.<sup>40</sup> On the other hand, there are drawbacks to the utility approach, including lack of precision, the need for labor-intensive interviews, and the requirement of native language ability in the language in which the materials are presented.<sup>40</sup>

Some of the most widely used tools are the standard gamble,<sup>7,41</sup> the time trade-off,<sup>7</sup> and the linear rating scale.<sup>38</sup> The *standard gamble* is the classic method of measuring preferences. The subject is asked what risk he or she would take in order to reach a certain health state. For example, a completely paralyzed patient would be offered a theoretical treatment, which would either cure the paralysis or immediately kill the patient. The subject would determine how much of a risk of death he or she would tolerate for the chance of a cure. The amount of chance taken is used as a measure of how undesirable the patient perceives the present disease state: the greater the risk tolerated, the worse the disease state. The *time trade-off* technique is an alternative to the standard gamble that is simpler to administer.<sup>42</sup> Subjects are asked how many years of their remaining life in their current state of health they would be willing to give up in order to have perfect health for the rest of their life. The *linear rating scale* originated in psychometrics.<sup>39</sup> Subjects are shown a line on a page where 0 at one end represents an undesirable state (death or blindness) and 100 at the other end represents perfect health (or vision). The subject then places his or her assessment of health at the appropriate point along the line. The linear rating scale is the most efficient of the 3 methods to administer but has the disadvantage of not providing direct cardinal utility measures.<sup>43</sup>

The use of utility measures to determine patient preferences in ophthalmology is relatively new, but several interesting studies have been reported. Torrance<sup>44</sup> refers to the state of "being blind, deaf, or dumb" as being given a utility value of 0.39 on a scale where 0 represents death and 1.00 represents perfect health. Bass and colleagues<sup>45</sup> used a linear rating scale to determine how patients awaiting cataract surgery felt about their vision. They found that the patients' preference values for their vision were related to problems in specific aspects of daily life (such as feelings of depression and problems interacting with

people) but generally not to traditional clinical measures of visual acuity. Although the cataract patients' preference values regarding their vision were significantly correlated with a visual function index, the correlation coefficient was only about 0.5, indicating that the assessment of visual functioning used did not fully predict how a patient felt about his or her visual impairment.

Brown, Brown, and colleagues have assessed utility problems in patients with age-related macular degeneration<sup>7</sup> and diabetic retinopathy.<sup>11</sup> In patients with age-related macular degeneration, they demonstrated that patients with visual acuity in the better eye of 20/20 to 20/25 would be willing on average to trade 11% of their remaining life to obtain perfect vision in both eyes, whereas those with visual acuity of counting fingers or light perception in their better eye would be willing to give up 60% of their remaining life. Similarly, for diabetic retinopathy the investigators used both time trade-off and standard gamble techniques to demonstrate that vision loss is associated with a decrease in patients' ratings of their vision.<sup>11</sup> In his American Ophthalmological Society thesis, Brown<sup>8</sup> reported the relationship between visual acuity and utility instruments in a large group of his patients with predominantly retinal disease. In a study to determine whether there are differences in QOL between patients with choroidal melanoma treated with enucleation or radiation therapy, Cruickshanks and associates<sup>17</sup> used the time trade-off measure and found that there was no difference between the 2 treatment groups.

To my knowledge, there have been no studies of glaucoma patient preference values for the visual states associated with glaucoma damage. Given physicians' impression that vision loss in glaucoma patients has little impact early in the disease, and the finding by Gutierrez and associates<sup>34</sup> that patient responses to QOL instruments may become abnormal early in the course of the disease, further investigation into patient perception of the disease process seemed warranted. For this reason, I undertook an investigation into glaucoma patients' perception of the impact of glaucoma on their vision and life.

## **SUBJECTS AND METHODS**

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### **SUBJECTS**

Subjects were recruited from 3 glaucoma practices during the period of October 1998 to August 1999. One practice was university-based (site A); one was a university-affiliated, community hospital-based, practice (site B); and the third was a suburban private practice (site C).

Before the beginning of each clinical session, records of all patients who had undergone automated static perimetry and were being followed up for glaucoma or suspicion of glaucoma were reviewed. The eligibility

criteria were visual acuity of at least 20/40 or better in 1 eye, age of 21 years or older, and the presence in the medical record of a reliable automated visual field in at least 1 eye within the past 9 months (patients with poor vision in 1 eye or with a perfectly normal fellow eye may not have undergone visual field testing in both eyes). Patients were excluded from consideration if they had diabetic retinopathy, macular detachment, or a history of retinal reattachment surgery, intraocular surgery, or laser treatment within the previous 2 months; were scheduled for intraocular surgery; or were thought to have an optic neuropathy other than glaucoma. Patients whose pupils were pharmacologically dilated were not considered for participation on that day because of the unknown effect of pupil size on the Esterman binocular visual field test. Likewise, patients who were scheduled to undergo automated visual field testing were also not considered that day owing to concerns of fatigue from taking multiple visual field tests in one session. Patients not fluent in English or judged not mentally able to complete the study were excluded.

The charts of all potential patients were flagged. Many potential patients were not approached about participation in the study for logistical reasons, which included lateness of the hour, inability of the patient to stay for participation, lack of availability of the interviewer, and lack of availability of a perimeter. The remaining patients were approached about participation in the study by either the study coordinator or the patient's physician. The study protocol, which had been reviewed and approved by the Institution Review Board governing each center, was explained to each patient. The age, race, sex, and visual acuity of patients who declined participation in the study were recorded. Each participant gave informed written consent.

In addition to those subjects who were glaucoma patients or patients followed up for suspicion of glaucoma, we enrolled 2 additional groups of subjects. The *blind* subjects were patients followed up by the physicians participating in the study. They all had visual acuity recorded as no better than counting fingers in their better eye, and none were able to walk without help because of their visual impairment. All had a history of glaucoma; many had other ocular diseases. The *normal* subjects were patients who came to site A annually for an eye checkup, had no known ocular disease except for refractive error, and had normal acuity and a normal eye examination, including a normal optic disc examination. The *blind* and *normal* subjects were recruited to obtain an estimate of the floor and ceiling for answers to the linear rating scale and time trade-off tests. Therefore, no effort was made to match them with the glaucoma patients and glaucoma suspects in terms of age, race, sex, or any other demographic characteristic. With the exception of 1

“blind” subject, the 12 “blind” subjects and the 12 “normal” subjects were recruited at site A.

**INTERVIEW PROCESS**

All interview materials were administered face-to-face by the same experienced interviewer. Periodically, with the patient’s permission, the interviews were audiotaped and reviewed by the principal investigator for quality assurance.

All subjects (glaucoma, blind, and normal) were given the following questionnaires, which were administered in random order:

- A *comorbidity, medication, and demographics questionnaire* in which subjects were asked about whether or not they had diabetes, hypertension, heart disease, breathing difficulties, or arthritis, and what medications they were taking for their general health. Subjects were also asked about the highest level of education obtained, family history of glaucoma or blindness, and current job status (employed, unemployed, or retired).
- The 25-question version of the *National Eye Institute VFQ*. This questionnaire was chosen as an instrument to assess how subjects fare with their day-to-day visual tasks. The psychometric properties of the VFQ have been well defined,<sup>21</sup> and its utility as a vision-targeted, health-related QOL survey has been demonstrated.<sup>20</sup> A longer (51-item) version of the VFQ has been used previously in published studies of the effect of glaucoma on QOL.<sup>33,34</sup> The 25-question version has been shown to correlate well with the longer version.<sup>46</sup>
- The *Short Form 36 (SF-36)* of the Medical Outcomes Study. This is a survey that was designed as a generic measure of health status. Multiple studies in many disciplines of medicine have used the SF-36.<sup>15</sup> We chose it so that the scores of our subjects might potentially be compared to those of patients with other diseases.

We initially had planned to use the visual ophthalmic symptoms (FUNC-4) portion of the Glaucoma Symptom Scale designed by Lee and associates<sup>27</sup> as well. However, we decided not to use it because of the substantial number of patients that we studied who had little vision in 1 eye. When piloted, these patients answered “no” to such questions as, “Do you see halos around lights?” with their “non-seeing” eye. Therefore, both patients with perfect vision and those with no vision would have provided the same answer to this question.

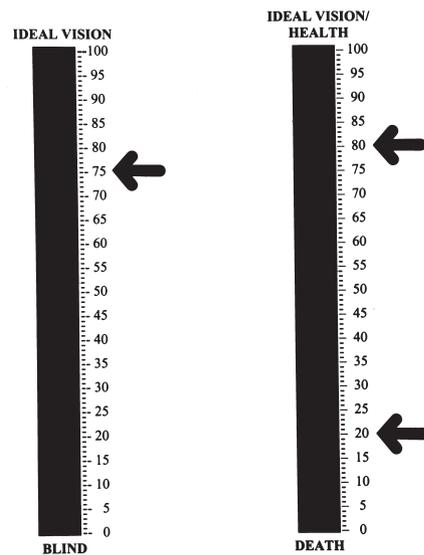
After completion of these questionnaires, patients were administered 2 utility tests. Visual props using large print, such as a “feeling thermometer” for the rating scale, were used to present the tasks to decrease the “cognitive

burden” placed upon subjects.<sup>43</sup>

- The *linear rating scale* was presented in the form of 2 “feeling thermometers,” which were large cardboard props with a “0” at the bottom and “100” at the top (Fig 1). The first thermometer was labeled “ideal vision” at the top and “blind” at the bottom. Subjects were asked the question “On a scale of 0 to 100, where 0 represents blindness and 100 represents ideal vision, how would you rate your current vision?” Subjects then placed a marker on the thermometer corresponding to their assessment of vision (in this example, 75). If the subjects asked, they were instructed to rate the vision while wearing glasses. This number is referred to in the “Results” section as the *linear rating*.

Subjects were then asked to turn their attention to the second “feeling thermometer.” The interviewer told the subjects that a score of 100 on this thermometer represents perfect health and vision and a score of 0 represents death. The interviewer asked the subject 2 questions: (1) “On a scale where 0 now represents death and 100 represents ideal health and ideal vision, where would you rate your ‘overall health,’ assuming you had ideal vision?” (2) “On a scale where 0 now represents death and 100 represents ideal health and ideal vision, where would you rate being completely blind, assuming you had your same current health?”

The answers to the first and second questions on the second thermometer (80 and 20, respectively, in this example) are equivalent to the 100 and the 0 on the first



**FIGURE 1**

Two “feeling thermometer” props used in administration of linear rating scale. On thermometer at left, the subject has rated his vision as 75; on thermometer at right, the subject rated his general health as 80 and blindness as 20.

thermometer. Therefore the rating of vision determined in the first thermometer on a blind to perfect vision scale can be expressed on the second thermometer on a life-and-death scale. This number is referred to in the "Results" section as the *adjusted linear rating*. In the example illustrated in Fig 1, the adjusted linear rating is 75% of the distance between 20 and 80, yielding a score of 65.

- In the *time trade-off test*, the interviewer first calculated from mortality tables the life expectancy of the individual subject on the basis of age, sex, and race. The subject was then presented with a choice of 2 lives. In the first life, the subject would live for the time equivalent to his or her life expectancy, with his or her current vision. In the second life, the subject would be given ideal vision, but the remaining life would be shorter (Fig 2). Through a series of bracketed questions, the percentage of remaining life that the subject would sacrifice in order to have ideal vision during remaining life was determined.<sup>43</sup> In this example, a patient with a life expectancy of 40 years (life B) would be willing to give up 16 years of remaining life for ideal vision (life A).

One to 6 months later, 13 patients completed the linear rating scale, and 14 patients the time trade-off, a second time, to determine the reproducibility of the tests.

**BINOCULAR VISUAL FIELD TESTING**

After completion of the interview, we tested each glaucoma patient and glaucoma suspect with the binocular Esterman visual field testing on the Humphrey Field Analyzer II perimeter. The Esterman binocular visual field test was originally developed for manual perimeters, and like its monocular predecessor, it gives more weight to the functionally more important parts of the visual field (ie, central and inferior).<sup>47</sup> The testing strategy plots the visual field exactly as the patient uses his or her eyes, as a whole binocular unit, without occlusion.<sup>48</sup>

The Esterman binocular visual field test has been adapted to automated perimeters.<sup>48,50</sup> On the Humphrey

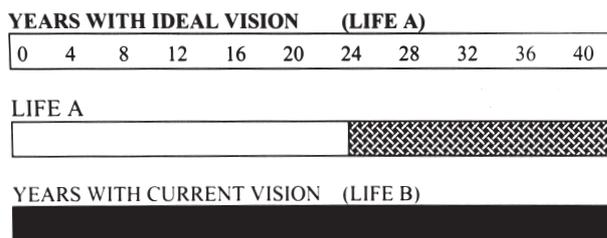


FIGURE 2

Prop used to administer the time trade-off test. In this example, a patient with a life expectancy of 40 years (life B) would be willing to give up 16 years of his remaining life for ideal vision (life A).

Field Analyzer II, the test uses a grid of 120 test points to examine more than 130 degrees of visual field (Fig 3). Each location is tested once with a size III white stimulus with an intensity of 10 dB. Missed points are retested, and 2 negative responses are recorded as a defect. Stability of fixation is monitored indirectly by observation.<sup>50</sup>

Patients were asked to wear their current refractive correction for distance, if they had their glasses with them.

**CLINICAL RECORD REVIEW**

The clinical records of all glaucoma patients and glaucoma suspects were reviewed and their ocular medications, ocular comorbidity (eg, cataract, posterior capsular opacification, diabetic retinopathy), and past ocular surgery were recorded. The Advanced Glaucoma Intervention Study (AGIS) visual field score for each eye was calculated from the subject's most recent automated threshold visual field tests.<sup>51</sup>

**DATA ANALYSIS**

Visual acuities were transformed from Snellen acuities to logMAR scale. Acuities of counting fingers, hand motions, light perception, and no light perception were assigned logMAR values of 1.5, 2.0, 2.5, and 3, respectively.

Mean deviation and corrected pattern standard deviation (CPSD) were obtained from the hard-copy printout of the visual fields. The AGIS scores were calculated by entering the values for the deviation from age-matched normal at each point into software designed to calculate the AGIS score. The determination of which eye was the "better" eye was based on its mean deviation. The Esterman score was calculated by dividing the number of correct responses by the total number of stimuli (120) and

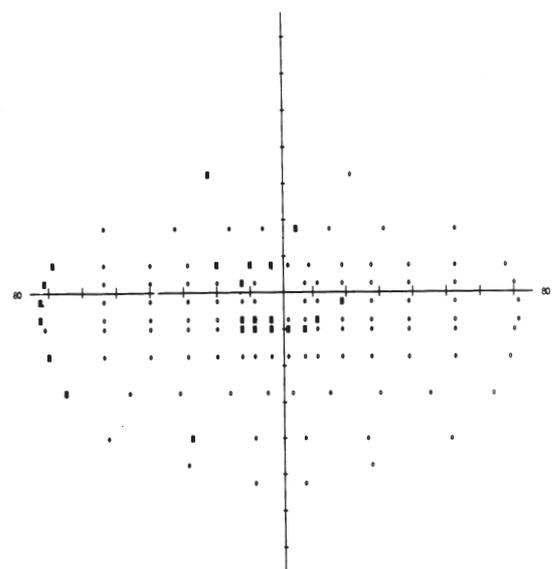


FIGURE 3

Printout of test points of automated Esterman binocular visual field test.

multiplying by 100.

Subscale scores were calculated for the SF-36 and VFQ. The time trade-off score was calculated by dividing the number of years given up by the patient by the life expectancy and multiplying by 100.

All data were entered into Microsoft Access and then uploaded into the statistical packages SAS and STATA for statistical analyses. Descriptive data were tabulated for the study patients as well as the groups of “blind” and “normal” subjects. Analysis of variance (ANOVA) procedures were used to test for differences between continuous variables measured for the study patients across the 3 centers. When assumptions for the ANOVA were violated, the Kruskal-Wallis procedure was used, as in the case of the utility tests and VFQ and SF-36 scores.<sup>52</sup> Chi-square tests were used to test for associations between categorical measures for the study patients across the 3 centers. Similar testing procedures were used to compare the participating and nonparticipating study patients and to compare the 3 groups of subjects, namely, the glaucoma patients and glaucoma suspects, the “blind” subjects, and the normal patients.

To determine the strengths of linear associations between continuous variables for the study patients, partial correlation coefficients (PCCs) were calculated on the basis of multiple linear regression models. Regressions were adjusted for age, race, sex, and the logMAR acuities for both the better and worse eyes, when visual acuity was not a primary variable. When visual acuity was the primary variable, regressions were adjusted only for age, race, and sex. Data quality checks were made using adjusted variable plots generated from the multiple linear regressions. Bootstrap methods were used to test the PCCs when the normality assumption was violated.

To consider the possibility that some associations might not be linear but instead demonstrate a threshold effect, we examined scatterplots of clinical function tests (visual acuity and monocular and binocular visual field scores) plotted against the QOL and utility scores.

Four of the domain scores of the VFQ (general health, general vision, color vision, and peripheral vision) were derived from the answer to only one question, so that the only possible scores were 0, 25, 50, 75, and 100. Therefore, these domains were treated as ordinal variables and a multiple PCC was calculated when determining the strength of the linear association between these domains and other continuous variables.

In interpreting the values of correlation, it must be appreciated that for some of the visual function tests and utility tests, higher scores signify better vision, and for others, higher scores signify worse vision. Table I lists which variables are positively correlated with better function and which with worse function. This is important

in determining whether a correlation is truly positive or negative. For instance, the higher the Esterman binocular visual field score, the better the function, and the lower the time trade-off score, the better the patient's assessment of function. Therefore, the Esterman binocular visual field test and the time trade-off score are correlated when the PCC is negative.

Correlations were considered good if the PCC was between 0.4 and 0.6, fair if between 0.2 and 0.39, and poor if less than 0.2.

## RESULTS

### DEMOGRAPHICS

Two hundred and thirty-seven patients followed up for glaucoma or suspicion of glaucoma who met eligibility criteria and agreed to participate were enrolled in the study. One hundred and three subjects were seen at the site A, 49 were seen at site B, and 85 were seen at site C.

The mean age of the glaucoma patients and glaucoma suspects was 71 years, 21% were African American, and there was a slight preponderance of women (Table II). One third had a positive family history of glaucoma. Most had at least a high school education and were now retired. Many of them had chronic health conditions, such as arthritis and hypertension. The “normal” subjects were a younger and healthier group, and the “blind” subjects were intermediate in age, had a stronger family history of glaucoma, and had had more glaucoma surgery than the study subjects (glaucoma patients and glaucoma suspects).

The subjects in the 3 centers did not differ in terms of age, race, sex, or use of glaucoma medications, but the subjects from site C were more likely to have undergone surgery for glaucoma (Table III).

Forty-five patients (16%) were invited to participate in the study but declined. The age, race, and sex did not differ between the study participants and the decliners (Table IV). The rate of participation did not differ among the 3 study centers. The visual acuity in the better eye was worse in the nonparticipants than in the participants.

### CLINICAL CHARACTERISTICS

The mean logMAR visual acuity was  $0.09 \pm 0.10$  (Snellen equivalent of 20/25) in the study subjects' better eye and  $0.48 \pm 0.65$  (Snellen equivalent of 20/60) in the worse eye (Table V). The mean intraocular pressures were  $16.5 \pm 4.9$  in the right eye and  $17.4 + 7.1$  mm Hg in the left eye. Not surprisingly, these values were intermediate between the “normal” and the “blind” subjects. The visual field scores in the better eye of  $-5.3$ ,  $4.0$ , and  $4.2$ , for mean deviation, AGIS score, and CPSD represent on average mild visual field loss; the corresponding scores in the worse eye of  $-10.6$ ,  $7.8$ , and  $6.4$  represent on average moderate visual

**TABLE I. DIRECTION OF CORRELATIONS\***

VARIABLE	LINEAR RATING + SCALES	TIME TRADE-OFF -	VFQ SCORES+	SF-36 SCORES +
Esterman binocular visual field scores +	+	-	+	+
LogMAR scores -	-	+	-	-
Mean deviation +	+	-	+	+
AGIS scores -	-	+	-	-
CPSD -	-	+	-	-
Linear rating scales +			+	+
Time trade-off -			-	-

AGIS, Advanced Glaucoma Intervention Study; CPSD, corrected pattern standard deviation; SF, Short Form; VFQ, Visual Function Questionnaire.

\*If a test has a + by its name, then the more positive the test result, the better the visual function or assessment of the visual function. If a test has a - its name, then the more positive the test result, the worse the visual function or assessment of the visual function.

The symbols within the grid are the sign expected when there is a positive correlation between the variable listed down the left side and the variable across the top. For instance, a positive relationship between a logMAR score and the time trade-off test would have a plus sign in front of it, whereas a positive relationship between an AGIS score and a VFQ score would have a negative sign in front of it.

**TABLE II. DEMOGRAPHICS**

	STUDY SUBJECTS (GLAUCOMA AND SUSPECT) N = 237	"NORMAL" N = 12	"BLIND" (≤ CF ACUITY OU) N = 12
Age	70.6 ± 11.8 [22-92] <sup>°</sup>	49.7 ± 8.5 [31-63]	63.3 ± 19.5 [30-92]
Caucasian	187 (79%)	12 (100%)	3 (25%)
Male	101 (43%)	10 (83%)	5 (42%)
No. of glaucoma medications	1.3 ± 1.2 [0-4]	0.0	1.3 ± 1.5 [0-4]
No. of glaucoma surgeries	0.8 ± 1.5 [0-10]	0.0	1.9 ± 3.1 [0-10]
Family history of glaucoma	81 (34%)	3 (25%)	7 (58%)
Family history of blindness	30 (13%)	1 (8%)	4 (30%)
Family history of blindness from glaucoma	17 (7%)	0 (0%)	2 (17%)
No. with ≥ high school education	211 (89%)	12 (100%)	8 (67%)
Full-time employed	39 (16%)	8 (67%)	1 (8%)
Hypertension	98 (41%)	2 (17%)	6 (50%)
Diabetes	28 (12%)	0 (0%)	4 (33%)
Heart problems	53 (22%)	0 (0%)	4 (33%)
Breathing problems	43 (18%)	1 (8%)	3 (25%)
Arthritis	136 (57%)	1 (8%)	5 (42%)

CF, counts fingers.

<sup>°</sup>Mean ± standard deviation [range].

**TABLE III. CHARACTERISTICS OF STUDY CENTERS**

	SITE A	SITE B	SITE C
No. of Patients	125	49	63
Age	69.0 ± 13.2 <sup>°</sup>	72.7 ± 9.5 <sup>°</sup>	72.2 ± 10.1 <sup>°</sup>
Caucasian	100 (80%)	34 (69%)	53 (84%)
Male	58 (46%)	17 (35%)	26 (41%)
Patients taking glaucoma medication	78 (62%)	33 (67%)	44 (70%)
Patients with previous glaucoma surgery <sup>†</sup>	33 (26%)	17 (35%)	32 (51%)

<sup>°</sup> Mean ± standard deviation.

<sup>†</sup>  $P < .001$  for previous glaucoma surgery;  $P > .05$  for all other comparisons.

field loss. The mean Esterman binocular visual field score (maximum of 100) was 89.7 (range, 15.8-100).

**AGGREGATE PERFORMANCE ON QUALITY OF LIFE AND UTILITY INSTRUMENTS**

On the linear rating scale, on which subjects rated their

vision on a scale of 0 (blind) to 100 (ideal), the glaucoma patients had scores between the "normal" and the "blind" subjects with means of  $90 \pm 8.0$ ,  $75.7 \pm 17.6$ , and  $15.6 \pm 15.3$  for the "normal", glaucoma, and "blind" subjects, respectively (Table VI). The differences were statistically significant ( $P = .0001$ ). When the same preference was

TABLE IV: COMPARISON OF PARTICIPANTS AND NONPARTICIPANTS

	PARTICIPANTS N = 237	NONPARTICIPANTS N = 45
Age	70.6	71.8
Race		
White	187 (78.9%)	20 (71.4%) <sup>°</sup>
Black	47 (19.8%)	8 (17.8%)
Hispanic	1 (0.4%)	0
Other	2(0.8%)	0
Sex		
Male	101(42.6%)	18 (40%)
Female	136 (57.4%)	27 (60%)
Site		
A	125 (52.7%)	19 (42.2%)
B	49 (20.7%)	12 (26.7%)
C	63 (26.6%)	14 (31.1%)
Visual acuity		
logMAR better eye†	0.09	0.17
logMAR worse eye	0.48	0.54

<sup>°</sup> Of 28 known (17 with missing data).  
<sup>†</sup> P = .009 for logMAR better eye; P > .05 for all other comparisons.

transferred to a death (0) to ideal vision (100) scale (adjusted linear rating), the same statistically significant relationship held, with means of 89.6 ± 8.2, 71.4 ± 19.3, and 53.7 ± 24.2, respectively (P = .0003). The ratings of their general health and of the theoretical state of total blindness were lower in the glaucoma subjects than in the other 2 groups, but the difference was not statistically significant (P = .06 and .11, respectively).

On the time trade-off test, none of the 12 “normals” was willing to trade life for improved vision, whereas 6 of 12 “blind” patients were willing to trade some time for ideal vision. On average, the “blind” patients would give up one third of their remaining life for ideal vision. Glaucoma patients were closer to “normals” than to “blind” in this regard, with only 45 of 228 (20%) willing to trade any life for ideal vision.

The scores of all 3 groups were similar on the SF-36 general health perception subset (P = .62, ANOVA), although the glaucoma subjects were again intermediate. The summary scores on the VFQ differed among the 3 groups (P = .0001, ANOVA). As anticipated, they were highest in the “normals” at 92.8 ± 6.4, intermediate for the

TABLE V: CLINICAL CHARACTERISTICS

	STUDY SUBJECTS (GLAUCOMA AND SUSPECT) N = 237 <sup>°</sup>	NORMAL N = 12 <sup>°</sup>	BLIND N = 12 <sup>°</sup>	NO. OF SUBJECTS
logMAR better eye	.09 ± .10† [-0.12-0.4]	.01 ± .05 [-0.12-0.1]	1.7 ± 0.5 [0.7-2]	
logMAR worse eye	.48 ± .65 [0-3]	.05 ± .09 [0.00-0.3]	2.5 ± 0.6 [1.5-3]	
IOP OD (mm Hg)	16.5 ± 4.9 [4-40]	15.5 ± 3.5 [10-21]	28.0 ± 11.1 [12-44]	
IOP OS (mm Hg)	17.4 ± 7.1 [3-70]	15.2 ± 2.9 [12-21]	23.3 ± 17.7 [4-58]	
MD, better eye	-5.3 ± 6.4 [-27.9, 3.78]			207
MD, worse eye	-10.6 ± 8.3 [-32.1, 0.73]			197
AGIS score, better eye	4.0 ± 4.9 [0, 20]			211
AGIS score, worse	7.8 ± 6.1 [0, 20]			213
CPSD, better	4.2 ± 3.5 [0, 12.8]			207
CPSD, worse	6.4 ± 4.3 [0, 16.3]			197
Esterman binocular visual field	89.7 ± 13.4 [15.8, 100]			200

AGIS, Advanced Glaucoma Intervention Study; CPSD, corrected pattern standard deviation; IOP, intraocular pressure; MD, median deviation.

<sup>°</sup>Mean ± standard deviation [range].

†Applies to first 4 rows only.

TABLE VI: AGGREGATE PERFORMANCE ON QUALITY OF LIFE AND UTILITY INSTRUMENTS

	NORMAL N = 12	STUDY SUBJECTS (GLAUCOMA AND SUSPECT)	BLIND N = 12	P VALUE
Linear rating of vision	90 ± 8.0	75.7 ± 17.6 (n=234)	15.6 ± 15.3	.0001
Rating of general health	93.3 ± 5.0	81.7 ± 16.8 (n=233)	89.0 ± 13.5	.062
Rating of total blindness	54.6 ± 37.6	37.6 ± 27.7 (n=225)	43.8 ± 28.5	.11
Adjusted linear rating	89.6 ± 8.2	71.4 ± 19.3 (n=223)	53.7 ± 24.2	.0003
Time trade-off (% life remaining)	0.0 ± 0.0	6.1 ± 16.7 (n=228)	33.1 ± 39.2	.048
SF-36 general health perception	69.8 ± 11.9	65.9 ± 19.5 (n=237)	62.2 ± 16.7	.59
Overall score VFQ	92.8 ± 6.4	78.3 ± 14.9 (n=237)	36.6 ± 12.9	.0001

<sup>°</sup>Mean + standard deviation.

glaucoma patients at  $78.3 \pm 14.9$ , and lowest for the "blind" patients, at  $36.6 \pm 12.9$ .

**REPRODUCIBILITY OF THE LINEAR RATING SCALE AND TIME TRADE-OFF TESTS**

The intraclass correlation for the responses to the linear rating scale question "How do you rate your vision?" was 0.88 (95% confidence interval, 0.77-1.00) (Fig 4), whereas

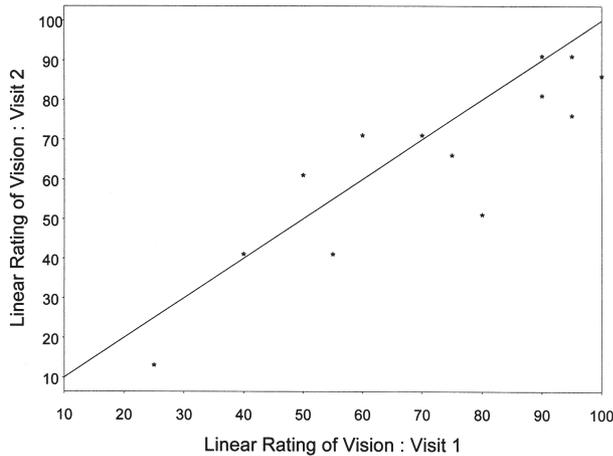


FIGURE 4

Reproducibility of linear rating scale. Thirteen patients performed linear rating scale twice 1 to 6 months apart. Intraclass correlation was 0.88 (95% CI, 0.77-1.00).

the intraclass correlation for the adjusted linear rating score, in which answers are transposed to a death to perfect health and vision scale was 0.78 (95% confidence interval, 0.56-0.99) (data not shown). Therefore, the linear rating scale demonstrated good reproducibility in this small sample.

On the time trade-off test, 9 of 14 subjects were unwilling to trade any time at either visit. Of the other 5

subjects, 3 were willing to give up 10% to 30% of their remaining life on the first visit, but none on the second, whereas one subject gave up 10% on the first visit and 90% on the second visit. Because so many of the answers were 0%, the data concerning reproducibility of the time trade-off test are difficult to interpret.

**RELATIONSHIP OF CLINICAL TESTS OF VISUAL FUNCTION TO QOL AND UTILITY TESTS**

An important hypothesis tested in this study was that the patient's binocular visual field, as assessed using the Esterman binocular visual field test, would be correlated with patient responses on the utility tests (linear rating and time trade-off). However, the correlation of the Esterman binocular visual field test with the linear rating scale (PCC, 0.17), the adjusted linear rating scale (PCC, 0.17), and the time trade-off test (PCC, -0.14) was poor (Table VII). The correlation of the Esterman binocular visual field test with all domains of the SF-36 was poor (best PCC of 0.18 for the physical function domain), whereas its correlation with the overall score on the VFQ-25 was fair (PCC, 0.32). Correlation was highest (PCC, 0.38) with the vision social function domain of the VFQ-25. Figure 5 contains scatterplots of the Esterman score versus the linear rating score and VFQ-25 summary score and demonstrates clustering of the Esterman scores in the range of 80 to 100.

We next examined whether the other clinical vision measures correlated better with the linear rating and time trade-off tests than did the Esterman. The measure that correlated best with the linear rating scale was the logMAR visual acuity in the worse eye (PCC, -0.30), and the measures correlating best with the time trade-off were the CPSD in the better eye (PCC = 0.24) and logMAR acuity in the worse eye (PCC = 0.22).

TABLE VII: RELATIONSHIP OF QUALITY OF LIFE AND UTILITY TESTS TO CLINICAL TESTS OF VISUAL FUNCTION

	LINEAR RATING	LINEAR RATING (ADJUSTED)	TIME TRADE-OFF	VFQ OVERALL	VFQ (MOST CORRELATED DOMAIN)	SF-36 (MOST CORRELATED DOMAIN)
Esterman binocular	0.17 (.07)*	0.17 (.13)	-0.14 (.31)	0.32 (.001)	0.38 (0.003) VSF	0.18 (.04) PF
LogMAR better eye	-0.15 (.03)	-0.10 (.16)	0.01 (.87)	-0.18 (.004)	-0.27 (.001) DRIVE	-0.11 (.11) VITAL
MD better eye	0.20 (.008)	0.08 (.34)	-0.17 (.02)	0.32 (.001)	0.44 (.001) VSF	0.20 (.007) SF
AGIS score better eye	-0.15 (.03)	-0.07 (.46)	0.10 (.18)	-0.22 (.008)	-0.36 (.001) VSF	-0.17 (.02) SF
CPSD better eye	-0.21 (.003)	-0.05 (.51)	0.24 (.005)	-0.12 (.13)	-0.27 (.001) PV	-0.10 (.20) SF
LogMAR worse eye	-0.30 (.001)	-0.12 (.13)	0.22 (.04)	-0.32 (.001)	-0.32 (.001) VD	-0.10 (.14) GH
MD worse eye	0.13 (.07)	0.14 (.08)	-0.16 (.013)	0.21 (.003)	0.38 (.001) PV	0.04 (.54) SF
AGIS score worse eye	-0.10 (.15)	-0.08 (.30)	0.06 (.36)	-0.22 (.001)	-0.41 (.001) PV	-0.11 (.10) SF
CPSD worse eye	-0.15 (.04)	-0.11 (.15)	0.13 (.01)	-0.03 (.63)	-0.18 (.006) PV	0.16 (.03) PHY

AGIS, Advanced Glaucoma Intervention Study; CPSD, corrected pattern standard deviation; DA, distance activity; DRIVE, driving; GH, general health; MD, mean deviation; PF, physical function; PHY, role physical; PV, peripheral vision; SF, social function; VD, dependence; VITAL, vitality; VSF, vision social function.

\*Partial correlation coefficient, with P value in parentheses.

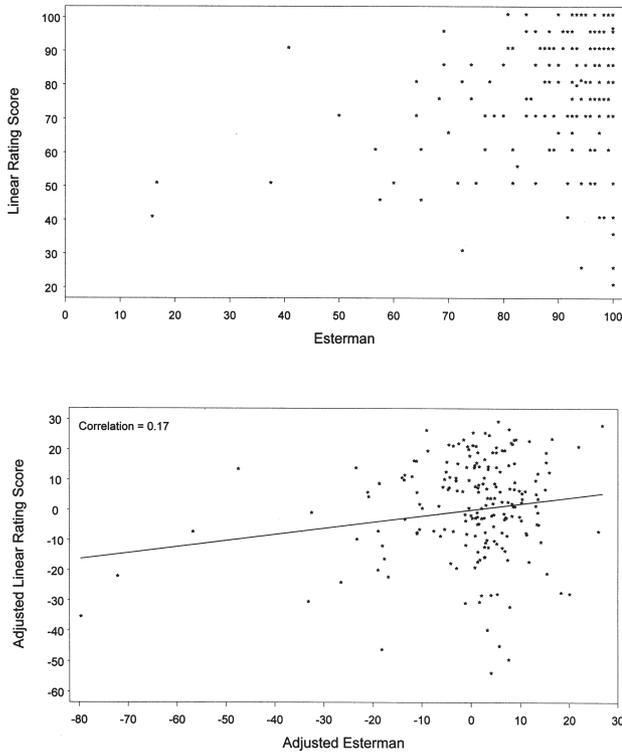


FIGURE 5A

Correlation of Esterman score with scores on linear rating test and VFQ-25 summary score. Top, Scatterplot of Esterman score versus score on linear rating test. Note clustering of Esterman scores between 80 and 100. Bottom, Adjusted variable plot of Esterman score versus linear rating score.

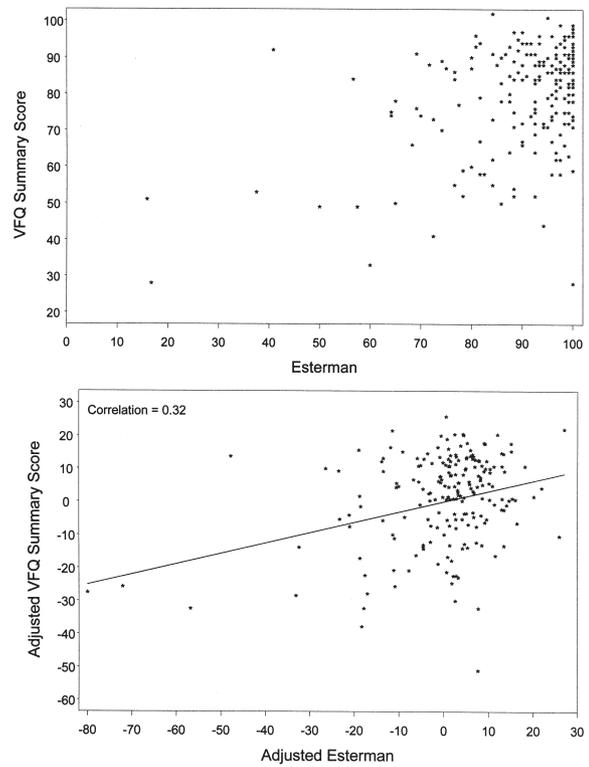


FIGURE 5B

Correlation of Esterman score with scores on linear rating test and VFQ summary score. Top, Scatterplot of Esterman score versus VFQ summary score. Bottom, Adjusted variable plot of Esterman score versus VFQ summary score.

Of all the utility and QOL instruments, the overall VFQ score appeared to have the best overall correlation with the clinical parameters of visual function (Esterman test, visual acuity, and visual field scores). Although not formally statistically analyzed, the ranking of these tests in terms of correlation with the clinical parameters is VFQ overall > linear rating > time trade-off > best SF-36 domain > linear rating adjusted. It should be re-emphasized that none of the correlations were very strong. Within the VFQ, the social function and peripheral vision domains had the strongest correlations with the clinical parameters. The PCC for the social function domain was 0.38 with the Esterman and 0.46 with the mean deviation in the better eye. It generally had a stronger correlation than the overall VFQ score (Fig 6). The single-question peripheral vision domain question also correlated fairly well with several clinical parameters.

The vision tests that appeared to correlate best with the battery of utility and QOL tests were the logMAR in the worse eye (low of -0.12 to high of -0.32), followed by the Esterman binocular visual field test (low of -0.14 to high of 0.38), and the mean deviation in the better eye (low of 0.08 to high of 0.44). The linear rating and VFQ overall scores correlated as highly with the logMAR in the worse

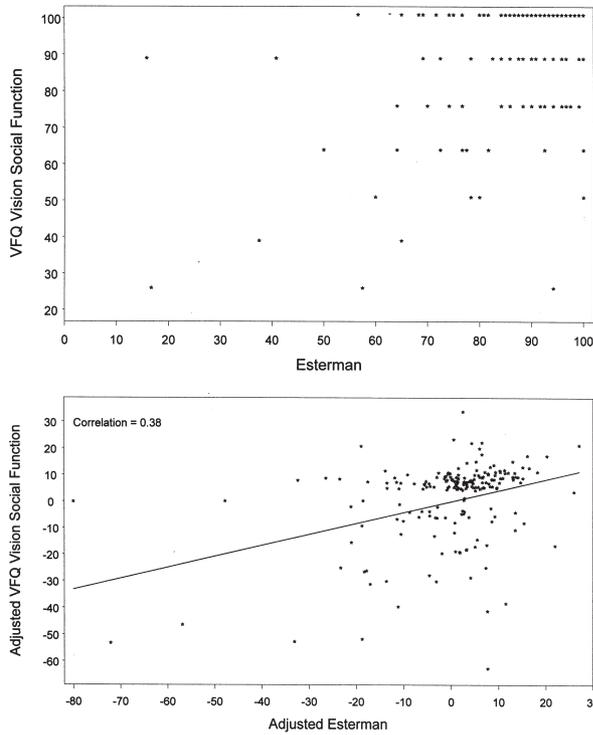
eye as with any other measure of visual function. Overall, the clinical tests of the better eye and of the worse eye correlated about equally with the QOL and utility tests.

**CORRELATION OF UTILITY TESTS AND THE VFQ-25**

The correlation of the linear rating score, (PCC, 0.56) and the adjusted linear rating score (PCC, 0.43) to the overall score on the VFQ was good (Fig 7 and Table VIII). The PCCs of the linear rating scale with the various domains of the VFQ with more than one question (continuous scores) were similar, ranging from 0.42 to 0.47, except for driving (0.30) and ocular pain (0.15). For the domains with only one question (Table IX), the linear rating scale correlated best with the general vision (multiple PCC [MPCC] of 0.55) and peripheral vision (MPCC, 0.43) and poorly with color vision (MPCC, 0.19).

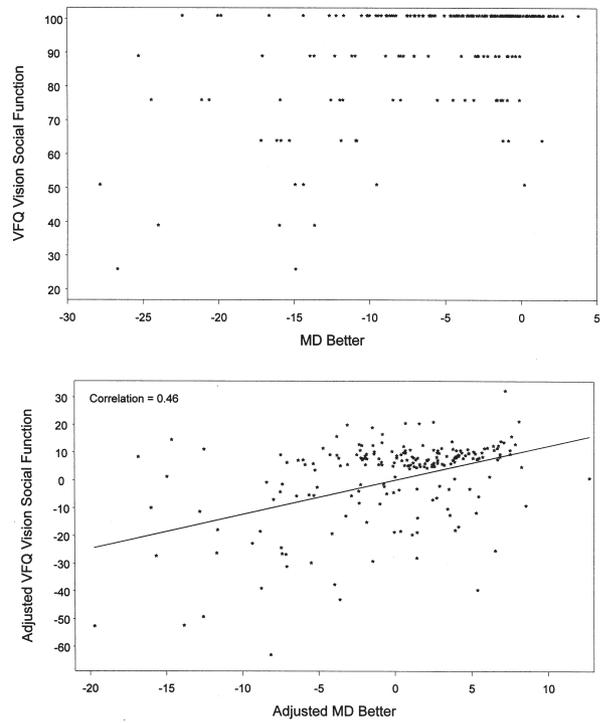
The adjusted linear rating scale had uniformly lower correlation with the VFQ and its domains, with a PCC of 0.43 with the overall VFQ score, and PCCs ranging from 0.26 to 0.36 for the other domains of the VFQ with more than one question, except for ocular pain (0.16). It also had a pattern of correlation similar to the linear rating scale for the domains with only one question, except for general health, which had an MPCC of 0.54.

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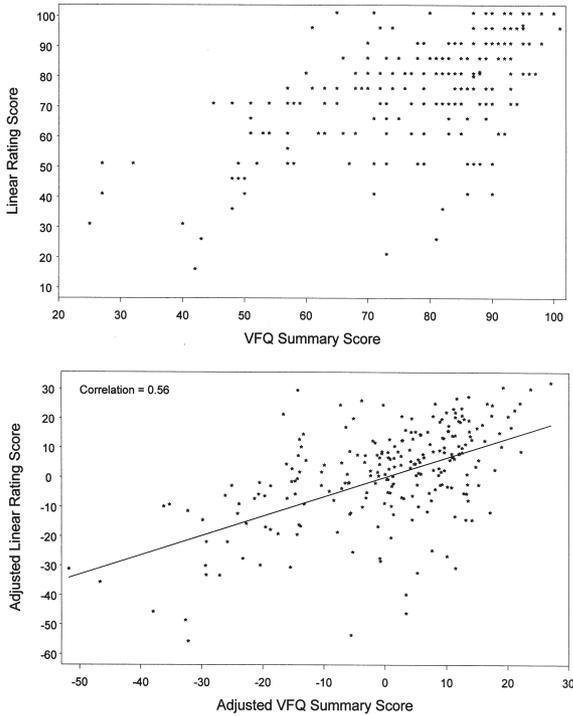
**FIGURE 6A**

Correlation of Esterman score and mean deviation in better eye with vision social function domain of VFQ. Top, Scatterplot of Esterman score versus score on vision social function domain. Bottom, Adjusted variable plot of Esterman score on vision social function domain.



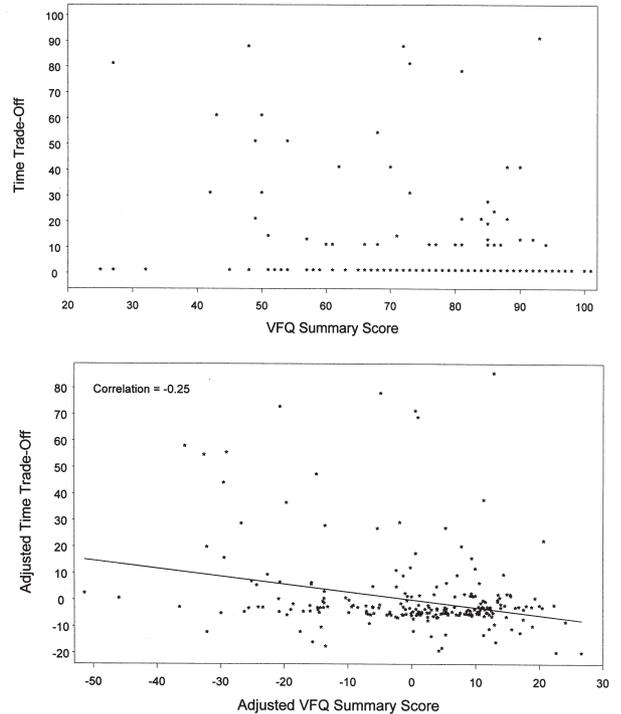
**FIGURE 6B**

Correlation of Esterman score and mean deviation in better eye with vision social function domain of VFQ. Top, Scatterplot of mean deviation in better eye versus vision social function domain score. Bottom, Adjusted variable plot of mean deviation in better eye versus vision social function domain score.



**FIGURE 7**

Correlation of VFQ summary score with linear rating score. Top, Scatterplot of VFQ summary score versus linear rating score. Bottom, Adjusted variable plot of VFQ summary score versus linear rating score.



**FIGURE 8**

Correlation of VFQ summary score with time trade-off score. Top, Scatterplot of VFQ summary score versus time trade-off score. Bottom, Adjusted variable plot of VFQ summary score versus time trade-off score.

TABLE VIII: RELATIONSHIP OF LINEAR RATING SCORES AND TIME TRADE-OFF TO VFQ (DOMAINS WITH CONTINUOUS SCORES)

	LINEAR RATING	RATING OF ONE'S OWN GENERAL HEALTH	RATING OF BLINDNESS	ADJUSTED LINEAR RATING	TIME TRADE OFF
Overall VFQ score	0.56 (.0001)*	0.32 (.0001)	0.14 (.05)	0.43 (.0001)	-0.25 (.001)
VFQ subscales					
Ocular pain	0.15 (.048)	0.14 (.018)	0.04 (.54)	0.16 (.022)	-0.04 (.75)
Near vision	0.47 (.0001)	0.24 (.0002)	0.08 (.35)	0.33 (.0001)	-0.14 (.06)
Distance vision	0.43 (.001)	0.29 (.001)	0.11 (.10)	0.36 (.001)	-0.21 (.001)
Social function	0.46 (.0001)	0.21 (.04)	0.03 (.63)	0.28 (.0002)	-0.26 (.01)
Vision specific mental health	0.45(.0001)	0.16 (.016)	0.16 (.028)	0.30 (.0001)	-0.15 (.006)
Vision specific role difficulties	0.42 (.001)	0.19 (.02)	0.11 (.16)	0.27 (.0001)	-0.21 (.004)
Vision specific dependency	0.46(.0001)	0.19(.02)	0.06 (.39)	0.29(.0001)	-0.24 (.003)
Driving	0.30(.0001)	0.17 (.02)	0.06 (.29)	0.26 (.0001)	-0.25 (.0001)

\*Partial correlation coefficient, with *P* value in parentheses

TABLE IX: RELATIONSHIP OF LINEAR RATING SCORES AND TIME TRADE-OFF TO VFQ (DOMAINS WITH ORDINAL SCORES)

	LINEAR RATING	RATING OF ONE'S OWN GENERAL HEALTH	RATING OF BLINDNESS	ADJUSTED LINEAR RATING	TIME TRADE-OFF
General health	0.35 (.0001)*	0.67 (.0001)	0.19 (.002)	0.54 (.0001)	0.25 (.003)
General vision	0.55 (.0001)	0.33 (.0001)	0.16 (.003)	0.43 (.0001)	0.32 (.0001)
Color vision	0.19 (.004)	0.16 (.01)	0.17 (.003)	0.14 (.02)	0.12 (.11)
Peripheral vision	0.43 (.0001)	0.28 (.0001)	0.09 (.06)	0.31 (.0001)	0.29 (.0005)

\*Multiple partial correlation coefficient, with *P* value in parentheses.

The correlation of the time trade-off test with the overall VFQ score was fair (-0.25) (Fig 8 and Tables VIII and IX), and correlations with the domains were also lower than for the linear rating scales. Similar to the linear rating scales, correlation was lowest with the ocular pain and color vision domains.

The correlation between the subjects' assessment of their general health on the linear rating scale (second column from the left in Tables VIII and IX) and the overall VFQ score was fair (PCC, 0.32) but correlated highly with the general health question of the VFQ (MPCC, 0.67). The general health question reads, "In general, would you say your overall health is excellent, very good, good, fair, or poor?" The subject's assessment of what a state of total blindness would be like (third column from the left in Tables VIII and IX) was poorly correlated with the overall VFQ score and with the domain scores.

**CORRELATION OF UTILITY TESTS AND THE SF-36**

The correlation of the linear rating scale with the domains of the SF-36 ranged from poor (mental function, PCC of 0.11) to fair (social function, PCC of 0.32) (Table X). Contrary to the findings with the VFQ, the adjusted linear rating scale had higher correlations with the domains of

the SF-36 than did the linear rating scale. In particular, the correlations were good with general health (PCC, 0.53), physical function (PCC, 0.50), and vital function (PCC, 0.46). The time trade-off was poorly correlated with the domains of the SF-36, except for the social function domain, which had a PCC of -0.25.

The subjects' assessment of their general health on the linear rating scale (second column from the left) showed a good correlation with the general health (PCC, 0.61), physical function (PCC, 0.56), and vital function (PCC, 0.53) domains and poor correlation with the mental function (PCC, 0.16) domain.

The subjects' assessment of what a state of total blindness would be like (third column from the left) was poorly correlated with all domains.

**NONLINEAR ASSOCIATIONS**

To determine if there might be a nonlinear relationship (eg, a threshold visual field loss at which patient assessment of vision markedly decreased), we examined scatterplots of visual acuity and visual field scores as independent variables and QOL and utility scores as dependent variables. No threshold or nonlinear relationships were detected.

TABLE X: RELATIONSHIP OF LINEAR RATING SCORES AND TIME TRADE-OFF TO SF-36

	LINEAR RATING	RATING OF ONE'S OWN GENERAL HEALTH	RATING OF BLINDNESS	ADJUSTED LINEAR RATING	TIME TRADE OFF
General health	0.29 (.0001)*	0.61(.0001)	0.16 (.03)	0.53(.0001)	-0.08 (.21)
Role-physical	0.24 (.002)	0.32 (.0001)	0.07 (.35)	0.29 (.0001)	-0.15 (.17)
Physical function	0.28 (.0001)	0.56 (.0001)	0.14 (.04)	0.50 (.0001)	-0.10 (.27)
Role-emotional	0.17 (.04)	0.21 (.001)	0.01 (.83)	0.20 (.004)	-0.15 (.17)
Social function	0.32 (.0001)	0.44 (.0001)	0.08 (.32)	0.37 (.0001)	-0.25 (.005)
Pain	0.15 (.01)	0.39 (.0001)	0.11 (.06)	0.30 (.0001)	-0.06 (.26)
Mental function	0.11 (.04)	0.16 (.004)	0.05 (.38)	0.14 (.03)	0.02 (.94)
Vital function	0.28 (.0001)	0.53 (.0001)	0.15 (.04)	0.46 (.0001)	-0.14 (.07)

\*Partial correlation coefficient, with *P* value in parentheses.

## DISCUSSION

This study confirms and adds to the growing literature on QOL in glaucoma patients. The unique aspect of this study is the addition of utility testing to patient evaluation. To the best of our knowledge, this has not previously been done in glaucoma subjects and suspects.

Two utility tests were studied: the linear rating scale and the time trade-off test. On the linear rating scale, we asked subjects to rate their vision on a blindness to ideal vision scale (a number we referred to as the linear rating score) as well as to rate their general health and the state of blindness on a death to ideal health scale (adjusted linear rating score). This “cascading” technique theoretically allows the transformation of the perception of vision loss to a death and perfect health scale, which then can be directly compared with utility values derived from other disease states, such as angina and arthritis. For instance, Torrance and Feeny<sup>53</sup> have reported utility values for mild angina as 0.90, home dialysis as 0.64, and blindness as 0.39. Bass and associates<sup>45</sup> reported a utility value of 0.68 for vision in a cohort of patients about to undergo cataract surgery. On the adjusted linear rating scale, we found that glaucoma subjects and suspects rated the utility of their vision as 0.71 and that the blind rated the utility of their visual state as 0.54. Given different patient populations, variation in technique, and the fact that our “blind” patients still had some residual vision, our results seem comparable to those of other investigators.<sup>45,53</sup> In fact, our glaucoma suspects and patients rated the state of blindness with a utility of 0.38, remarkably close to that reported by Torrance and Feeny<sup>53</sup> and to the value of 0.33 reported by Bass and associates.<sup>45</sup> The correlations of the “adjusted” linear rating scores with tests of visual function and QOL measures scores were similar to the “unadjusted” linear rating scores.

In contrast to the linear rating scale, the findings on the time trade-off test were less informative. Eighty-six per cent of glaucoma subjects or suspects in the current

study were unwilling to give up time for improved vision, calling into question the discriminative power of the time trade-off test in this population. This is in contrast to the findings of Brown and colleagues,<sup>8</sup> who reported that 43% of 81 patients with visual acuities of 20/20 or 20/25 were willing to give up at least some portion of their remaining life to achieve perfect vision on the time trade-off test and that, on average, patients with 20/20 acuity in the better eye were willing to give up 8% of their remaining life. Reasons why some of their subjects with good acuity were willing to trade time while our subjects would not include the following: the quality of vision in some of Brown's patients might have been poor because of distortion or decreased contrast sensitivity; the peripheral vision in those patients was poor; the worse eye function was of unrecognized importance; and the time trade-off questions were posed to the patients in different ways in that study and in the current study.

One of the major hypotheses tested in this study was that visual function as assessed on a binocular visual field test would correlate well with patients' evaluation of their vision on utility testing. This hypothesis was not borne out by the data. In fact, the correlation of the Esterman binocular visual field test with both the linear rating scale (PCC, 0.17), the adjusted linear rating scale (PCC, 0.17) and the time trade-off test (PCC, -0.14) was weak. Furthermore, the other clinical measures we examined fared little better. The visual function measures that correlated most highly with the utility tests (but still only with fair correlation) were the logMAR visual acuity in the worse eye (PCC of -0.30 for linear rating and 0.22 for time trade-off) and CPSD in the worse eye (PCC of -0.19 for linear rating and 0.26 for the time trade-off).

There are several possible reasons why I might have failed to find a strong correlation between either binocular visual field testing or monocular tests of vision and patients' assessment of their vision. First, the utility test might simply not have been able to distinguish persons with better vision from those with worse vision. This does

not seem likely for the linear rating scale because we also studied a small number of patients without ambulatory vision and a small number of patients with normal vision to determine the ceiling and floor effects of our utility instruments. The fact that the normals had higher scores on the utility instruments (eg, mean of  $90 \pm 8.0$  on the linear rating scale) and the blind much lower scores (mean of  $15.6 \pm 15.3$  on the linear rating scale) than our glaucoma suspects and patients (mean of  $75.7 \pm 17.6$  on the linear rating scale) provided encouragement that the tests had the potential of correlating with varying degrees of visual field loss. Furthermore, the reproducibility of the linear rating scale was good.

A second reason is that there may not be a close relationship between visual function and patient perception of that function. Perhaps, in contrast to the implications of the findings of Gutierrez and associates,<sup>34</sup> early visual field loss really does not affect patients' assessment of their vision and, in fact, is more of an all-or-none phenomenon, with patients only noticing marked visual field loss. However, we found no evidence for such a threshold effect.

Third, there might be a strong correlation between visual function and its perception, but the best tests for evaluating either function or the value of that function to the patient have not been developed. In terms of functional tests, we suspect that the reason that the correlation between the Esterman test and other parameters is only poor to fair is the lack of a broad range of values on the Esterman test in this study. Most of the scores on the Esterman binocular visual field test were clustered in the 80% and above range, which would make it extremely difficult to find a strong and meaningful correlation between the Esterman score and QOL and utility scores, even if one existed. This same clustering of scores toward 100 (perfect) on the Esterman test was also observed by Parrish and colleagues<sup>33</sup> and by Harris and Jacobs.<sup>54</sup> The latter investigators suggest that the stimulus intensity used in the Esterman test could be decreased to expand the useful range of scores. We are in the process of developing binocular visual field tests that will hopefully distribute the scores more widely and hence be more sensitive to varying degrees of impairment.

In terms of improving the utility tests, we are evaluating a modification of the time trade-off test that has shown preliminary promise.<sup>55</sup> In this variant, the patient is asked how many hours of wakefulness per day he or she would be willing to sacrifice in order to have an ideal state of vision for the rest of the day. This may be an easier concept for the patient, and hence more accurate, than giving up years of life to attain better vision.

In addition to correlating the results of clinical tests of visual function with the utility tests, we also correlated the clinical tests with the QOL instruments. Scores for the

VFQ, a vision-directed QOL instrument, were highest for the "normals," intermediate for glaucoma suspects and patients, and lowest for the blind subjects, but these groups did not differ on the scores for the SF-36, a generic QOL instrument. Although this study was not designed to determine if these QOL instruments could distinguish between persons with and without glaucoma and/or visual impairment, our findings in this regard are similar to those of Parrish and coworkers,<sup>33</sup> Gutierrez and associates,<sup>34</sup> and Sherwood and coinvestigators<sup>31</sup> for glaucoma and Cole and associates<sup>46</sup> for optic neuritis. The study of Wilson and colleagues<sup>32</sup> differed in that they found that glaucoma subjects scored worse than glaucoma suspects and controls on most domains of the SF-36, but the differences were small.

We also correlated the results of the Esterman binocular visual field test with VFQ and the SF-36. It is interesting to compare our results with the 2 other studies (Parrish and coworkers,<sup>33</sup> Mills<sup>19</sup>) that have evaluated binocular visual fields. Parrish and coworkers<sup>33</sup> used the same Esterman binocular visual field as we did. Our correlations between the Esterman and the VFQ were similar, if perhaps a little weaker, than theirs. Our correlation with the overall VFQ score was 0.32, whereas their correlations (their Table V), after correction for visual acuity, were in the same range for most subscales. Similar to Parrish and coworkers, we found that correlation of the binocular visual field test with the SF-36 subscales was universally poor, an anticipated finding, since the SF-36 does not target visual problems. Although Parrish and coworkers used the self-administered 51-item VFQ and we used the 25-item test given by an interviewer, it is unlikely that this difference accounts for the minor differences between our findings, because Cole and associates<sup>46</sup> have shown that the 51-item and 25-item VFQs give similar results.

Mills,<sup>19</sup> in his AOS thesis, also investigated the correlation between binocular field of vision and QOL instruments in newly diagnosed subjects with open angle glaucoma in the CIGTS. He combined the monocular visual field scores from each eye to arrive at a simulated binocular score, but this did not correlate well with either the vision-related QOL instrument (VAQ), or the generic QOL instrument (SIP) used in the CIGTS. Furthermore, when the Esterman test was integrated into the CIGTS protocol about 4 years into the study, he compared those Esterman scores with the subjects' responses to the QOL instruments upon entry into the study. Again the correlation was poor. Mills speculated that the lack of correlation between visual function and responses on the QOL instruments might have been due to the mild nature of the visual loss in the CIGTS patients at the beginning of the study. Since visual field loss was not a requirement for entrance into the study, 30% of subjects had no visual field loss at all. Subjects needed to

have 20/40 or better vision in both eyes to be eligible. If the visual function of the subjects were clustered toward the normal, it would be difficult to show a strong correlation between visual function and QOL.

Although the correlations between the clinical tests of visual function and the QOL and utility tests were not great, some clinical tests appeared more highly correlated overall than others. The vision test that appeared to correlate best overall with the utility tests and QOL instruments was the visual acuity in the worse eye (weakest correlation  $-0.10$ , strongest correlation  $-0.32$ ). The linear rating score and the overall VFQ-25 score correlated as highly with the visual acuity in the worse eye (PCCs of  $-0.30$  and  $-0.32$ , respectively), as with any other measure of visual function tested. This finding differs from those of Brown<sup>8</sup> and Steinberg and associates<sup>24</sup> in the cataract PORT study, who found that the relationship between acuity and QOL and utility instruments was stronger for the better eye than the worse eye. However, Bass and colleagues<sup>45</sup> reported that cataract patients' preference values for their preoperative vision correlated more strongly with the visual acuity in the worse eye than in the better eye. Furthermore, Turano and Rubin<sup>56</sup> studied the correlation between clinical measures of vision in glaucoma patients and their walking speed through an obstacle course and found that the mean deviation of the visual field in the worse eye had the strongest correlation. They could not explain their counterintuitive result. Analyzing the aggregate visual function and QOL/utility tests, correlations appeared to be about equal for the better and worse eyes. It should be emphasized that in none of these studies was the correlation with either better or worse eye particularly good.

Examining the opposite question of which QOL or utility instrument had the best correlation with the battery of clinical parameters of visual function that we tested, the overall VFQ score appeared to be best. Within the VFQ, the social function domain had the best correlation of all with the clinical parameters (0.38 with the Esterman and 0.46 with the mean deviation in the better eye) and was higher in general than the overall VFQ score. The social function domain comprises the following 2 questions:

- Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
- Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

This correlation supports the recent report of Klein and colleagues<sup>57</sup> that visual difficulties in common daily activities, such as reading a menu in dim light and finding a movie seat, were commonly reported by adults.

The final set of correlations examined was between the utility tests and the QOL instruments. As might be

expected, the correlation between the linear rating scale was particularly good with the overall VFQ score and with the subscale of general vision. Given the similarity of the question asked in the linear rating scale and that in the general vision subscale, it is somewhat surprising that the correlation is not even greater. Subscales of the VFQ that correlated much more weakly with the linear rating scale were ocular pain, driving, and color vision. This finding is expected, since pain in particular should have little to do with an assessment of vision and lends credence to the concept that the VFQ and linear rating scale are testing similar things.

Although the correlation of the linear rating scale with the domains of the SF-36 was not good, the adjusted linear rating scale had higher correlations in general, with good correlations with general health, physical function, and vital function. Furthermore, subjects' assessment of their general health on the linear rating scale showed good correlation with these same domains but poor correlation with the mental function domain, suggesting that subjects tended to give the same answer to similar questions asked in 2 different ways.

## **CONCLUSIONS AND RECOMMENDATIONS**

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The search goes on to understand better the significance to our patients of vision loss from glaucoma. The Esterman binocular visual field is a short test available for automated perimetry that is readily accepted by patients. I theorized that if the Esterman test correlated well with patients' assessment of their own visual function, it might be useful for determining the impact of glaucoma on our patients' lives. I tested this hypothesis but found that the correlation was generally weak.

One explanation that may in part explain the weak correlation is that the Esterman test, as currently configured for automated perimetry, is insensitive to early and moderate degrees of vision loss. This would make it difficult to correlate with any measure of glaucoma damage, whether functional or quality of life. To test the validity of this recommendation, my colleagues and I are in the process of testing several alternative binocular visual field tests that have been modified from the Esterman test. These tests employ stimuli that appear to be closer to the threshold values for normals at peripheral points than the 10-dB stimulus used in the Esterman. It is our hope that one of these tests, or a combination of these tests, will correlate strongly with patient responses on the utility and QOL instruments. This correlation could take the form of a linear relationship or one in which no change in response to these instruments is seen until there is a threshold amount of vision loss.

However, a lack of correlation between clinical tests

of visual function and QOL or utility tests does not necessarily mean that either the clinical tests or the QOL and utility tests are invalid. Each test may simply be testing different effects of a disease upon patients, and therefore, because they do not highly correlate, the tests are providing complementary information. It is unlikely that one test, be it visual function, assessment of QOL, or utility measurement, will yield the entire truth about the effect of glaucoma damage on our patients. Rather, it is more likely that any one test will yield only partial truths about the impact of this chronic disease upon patients. Clinical investigators should improve and refine existing tests and continue to develop newer tests to advance our understanding of the impact of glaucoma. Ultimately, however, it will be the ability of clinicians to integrate the results of multiple disparate tests with discussions with the patient that will determine how well they understand the effect of glaucoma on that patient. This understanding is critical in formulating a therapeutic strategy for each patient.

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# ENHANCEMENT OF SCLERAL MACROMOLECULAR PERMEABILITY WITH PROSTAGLANDINS\*

BY Robert N. Weinreb, MD

## ABSTRACT

*Purpose:* It is proposed that the sclera is a metabolically active and pharmacologically responsive tissue. These studies were undertaken to determine whether prostaglandin exposure can enhance scleral permeability to high-molecular-weight substances.

*Methods:* Topical prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) was administered to monkeys to determine if this altered the amount of scleral matrix metalloproteinases (MMPs). Experiments also were performed to determine whether the prostaglandin F (FP) receptor and gene transcripts are expressed in normal human sclera. Permeability of organ-cultured human sclera following prostaglandin exposure then was studied and the amount of MMP released into the medium measured. Finally, the permeability of human sclera to basic fibroblast growth factor (FGF-2) was determined following prostaglandin exposure.

*Results:* Topical prostaglandin administration that reduced scleral collagen also increased scleral MMP-1, MMP-2, and MMP-3 by  $63 \pm 35\%$ ,  $267 \pm 210\%$ , and  $729 \pm 500\%$ , respectively. FP receptor protein was localized in scleral fibroblasts, and FP receptor gene transcript was identified in sclera. Exposure to prostaglandin  $F_{2\alpha}$ , 17-phenyltrininor,  $PGF_{2\alpha}$ , or latanoprost acid increased scleral permeability by up to 124%, 183%, or 213%, respectively. In these cultures, MMP-1, MMP-2, and MMP-3 were increased by up to 37%, 267%, and 96%, respectively. Finally, transscleral absorption of FGF-2 was increased by up to 126% with scleral exposure to latanoprost.

*Conclusions:* These studies demonstrate that the sclera is metabolically active and pharmacologically responsive to prostaglandins. Further, they demonstrate the feasibility of cotreatment with prostaglandin to enhance transscleral delivery of peptides, such as growth factors and high-molecular-weight substances, to the posterior segment of the eye.

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## INTRODUCTION

Peptides, including growth factors and other high-molecular-weight substances, are potential therapeutic agents for delivery to the posterior segment in glaucoma, age-related macular degeneration, and other ocular disorders.<sup>1-4</sup> The potential benefit of such treatments is suggested by enhanced survival and differentiation of retinal neurons in cultures<sup>5-7</sup> and improved neuronal viability in experimental models<sup>8-11</sup> to which certain growth factors or neurotrophins have been added. However, targeted delivery of even low-molecular-weight drugs to the optic nerve, retina, and choroid has been problematic. Delivery of high-molecular-weight drugs is even more challenging. Methods for simple and safe drug delivery to the posterior segment clearly are needed if such neuroprotection strategies are to be effective.

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It is proposed here that enhancement of scleral macromolecular permeability with prostaglandins may be such a method. The hypothesis investigated in this thesis is that the sclera is metabolically active and that prostaglandin cotreatment activates enzymes that enhance scleral macromolecular permeability.

## CURRENT METHODS OF DRUG DELIVERY AND THEIR APPLICABILITY TO THE POSTERIOR SEGMENT

The applicability of current methods of drug delivery to the posterior segment is limited by poor drug absorption, particularly of high-molecular-weight substances.

### *Topical Application*

Topical application is the primary route of drug delivery to the anterior segment of the eye. This route of administration is noninvasive, simple for the patient to use, and relatively free of systemic side effects, particularly when applied with punctal occlusion or gentle lid closure to minimize systemic drug absorption. However, topical application requires rigorous patient compliance over an extended time to effectively treat chronic disease, and it is largely

ineffective for drug delivery to the posterior segment.

Many drugs are capable of penetrating intact corneal epithelium to achieve significant levels in the cornea, anterior chamber, iris, and ciliary body. Topically applied drugs also may enter the eye by crossing the conjunctiva and diffusing through the sclera, but do so only to a minor extent. Although the transcorneal penetration of drugs is essential to achieve therapeutic drug levels in anterior segment tissues, drugs applied to the cul-de-sac typically do not achieve pharmacologically active concentrations in posterior segment tissues following topical administration. An important factor that limits topical application as a means of drug delivery to the posterior segment is the loss of drug from the precorneal area. Induced lacrimation because of an instilled volume into the conjunctival sac, blinking, physiologic tear turnover, drug-protein binding, and enzymatic degradation of drug in tear fluid allow only a small amount of an applied dose to pass into the aqueous humor and surrounding tissues in the anterior chamber. Edelhauser and Maren found that lower corneal permeability in humans than rabbits may result, in part, from our fourfold greater blinking rate and twofold greater tear turnover.<sup>12</sup>

The corneal epithelium is another contributing factor that limits topical application, as it is a barrier to drug absorption, particularly for high-molecular-weight substances such as growth factors. As a result of these hurdles, the absorption of drugs applied topically to the eye is quite poor compared with the systemic route of administration. The extent of absorption, as measured by taking the ratio of the total amount of drug that has entered the eye divided by the instilled dose, ranges from 1% to 7% for ophthalmic drugs.<sup>13,14</sup> In contrast, the extent of absorption of systemic drugs is usually greater than 75%.

Within the anterior chamber, drug dilution and removal also reduce the amount of drug available for diffusion posteriorly to the optic nerve, retina, and choroid. Aqueous secretion within the anterior segment dilutes the aqueous humor drug concentration, and normal aqueous drainage removes drug that has penetrated the corneal tissues. Drug also may diffuse into blood vessels within the anterior segment and then be removed from ocular tissues.

A drug that is absorbed into the anterior chamber also must redistribute from the aqueous to the vitreous humor. However, a drug topically applied to the eye in general does not enter the vitreous in significant concentrations. Two main factors explain the relative lack of penetration in the vitreous cavity. One factor is that there is only a minute space between the ciliary processes and the lens, and drugs must diffuse against an aqueous humor flow gradient. Another factor is the relatively slow diffusion of drugs in the vitreous. Molecular charge and lipophilicity have little effect on the diffusion of drugs of ocular

interest.<sup>13-15</sup> Drug diffusion depends on molecular movement through an aqueous environment. Although it is not restricted by the presence of collagen in the vitreous, drug diffusion is too slow to allow significant drug accumulation within the vitreous. Finally, cell junction barriers, as discussed subsequently, can limit the diffusion of drugs within the vitreous into the optic nerve, retina, and choroid.<sup>15</sup>

#### *Systemic Administration*

Despite the excellent absorption of systemic drugs, systemic administration of biologically active agents is ineffective at achieving therapeutic levels in the posterior segment of the eye. In the intact eye, systemic routes, such as oral or parenteral, may not produce a high enough concentration of drug because of resistance to entry from blood-ocular barriers, metabolism of drug to an inactive species, or significant uptake into another organ or tissue. Drug absorption into the eye is increased during ocular inflammation, which is associated with a disruption of the blood-aqueous barrier, the blood-retinal barrier, or both. Even in this case, however, systemic drug administration at doses sufficient to be absorbed into the eye may cause unacceptable systemic side effects, since the drug actions are unlikely to be localized to the eye. As an example, neurotrophins, which are high-molecular-weight drug candidates for optic nerve and retinal neuroprotection, have many properties aside from their roles in neuronal survival and axonal growth associated with retrograde transport. Neurotrophins also are anterogradely transported and released from presynaptic to postsynaptic targets.<sup>16</sup> Further, they modulate membrane excitability, induce neuronal hypertrophy, and affect cell differentiation.<sup>2</sup> If cells throughout the body were exposed to exogenously administered neurotrophins, the systemic side effects would likely be ubiquitous and deleterious.

#### *Intravitreal Injection*

Intravitreal injection, most often via the pars plana, offers a direct route to the posterior segment and often can provide adequate tissue drug levels. For some infectious or inflammatory diseases of the posterior segment, intravitreal injections are an effective and essential component of treatment. Local delivery of drugs to the eye via intravitreal injection offers several advantages over other routes of administration. First, it avoids many of the side effects associated with systemic therapy. This is particularly of benefit in the case of medications that may be too toxic for systemic administration but are well tolerated by the eye. Second, it bypasses the blood-ocular barrier, allowing higher intraocular drug levels than might otherwise be achieved. This may be particularly advantageous for high-molecular-weight substances.

Even if a drug can be delivered intravitreally,

however, the barrier presented by the internal limiting membrane is an important factor that may preclude intravitreal delivery of many peptides, including growth factors and other high-molecular-weight substances, to the retina. In rabbits with experimental subretinal detachments, Takeuchi and associates<sup>17</sup> observed that fluorescein isothiocyanate albumin (67 kDa) injected intravitreally can diffuse, but only slowly, across the sensory retina into the subretinal space. Kamei and associates<sup>18</sup> injected tissue plasminogen activator (70 kDa) labeled with fluorescein isothiocyanate and rhodamine B isothiocyanate-labeled dextran (20 kDa) into the midvitreal cavity of normal rabbits and those with experimental subretinal hemorrhage. The smaller-molecular-weight dextran diffused slowly throughout the neural retina in each of the eyes. Intravitreal tissue plasminogen activator did not diffuse through the intact neural retina in any of them. Distribution of an intravitreal drug also may limit drug delivery to the retina. A drug with a rapid rate of clearance from the vitreous may require large boluses and frequent injections to ensure therapeutic levels over an extended period.

Intravitreal injections have the inherent potential side effects of retinal detachment, endophthalmitis, cataract formation, and vitreous hemorrhage. The benefits of treatment must supersede these risks. In chronic diseases, long-term intravitreal treatment also might need frequent injections. Repeated injections have incremental risks, and they generally would not be well tolerated by the patient. Therefore, sustained-release intravitreal drug delivery, which would require fewer injections, may be particularly advantageous for treatment of chronic eye diseases.<sup>19</sup>

The use of sustained-release drug delivery systems that are placed within the vitreous is being investigated for a number of eye diseases, including cytomegalovirus retinitis,<sup>20-23</sup> uveitis,<sup>24-26</sup> proliferative vitreoretinopathy,<sup>27-30</sup> and choroidal neovascularization. In addition to the advantages of intravitreal injection, sustained drug delivery offers the promise of relatively constant drug levels in the vitreous. On the other hand, drugs that may be safe to the eye when used for a short time may prove to be toxic with sustained intraocular levels. Further, once placed intraocularly, they would need to be surgically removed if there were untoward side effects. The devices, too, have risks and complications associated with their placement that may preclude their routine use in eyes with glaucoma or age-related macular degeneration. These limitations have delayed their introduction into clinical use, particularly for treatment of chronic diseases.

#### *Periocular Injection*

Directly introducing a drug into the tissues surrounding

the posterior segment by anterior or posterior sub-Tenon's, subconjunctival, or retrobulbar injection is another method of delivering drugs to the posterior segment of the eye. For many reasons, this is an attractive route for delivering drugs to the optic nerve, retina, or choroid. This route has a major advantage of bypassing the epithelial barriers of the cornea and conjunctiva, which limit drug absorption with topical application.

Despite the frequent clinical use of periocular injection for a plethora of ocular disorders, the mode of drug transfer from the periocular location into the ocular tissues is not clearly understood. The drug may leak from the conjunctival injection site and penetrate the cornea or may enter the eye in part via systemic absorption. Also, the drug may enter the eye through intrascleral vascular channels or through perivascular and perineural spaces surrounding penetrating blood vessels and nerves. Perhaps most significantly, the drug also may enter the eye after penetrating directly through the sclera.<sup>31,32</sup>

McCartney and associates<sup>33</sup> documented the direct penetration through underlying sclera of subconjunctival tritium-labeled hydrocortisone (molecular weight [MW], 362 Da), a low-molecular-weight drug, through the ocular tissues in the rabbit eye. In their study, the percentage of the total dose that penetrated into the eye appeared to be small (~1% to 2%). Studies in normal squirrel monkeys by Barza and associates<sup>34</sup> demonstrated that gentamicin (MW, 450 Da to 477 Da), a mixture of 3 similar low-molecular-weight compounds, also can penetrate directly through underlying sclera when administered by subconjunctival or retrobulbar injection. They also found the highest drug concentrations in the superior and inferior segments of the rabbit sclera, but no detectable drug in the nasal and temporal areas.<sup>35</sup> On the basis of these data, they hypothesized that the drug solution tends to remain localized and spreads over the superior segment nearest the injection site for a period long enough to be absorbed by the sclera. It then moves to the inferior segment, possibly as a result of gravity. Depending on the position of the subject, it is absorbed through the superior and inferior scleral surfaces rather than nasal and temporal areas. They observed significant levels in the retina and choroid, but not the vitreous.

Lim and associates<sup>36</sup> detected tissue plasminogen activator (MW, 70 kDa) in rabbit vitreous after subconjunctival injection, but the concentrations were very low. Subsequently, Lincoff and associates<sup>37</sup> observed that recombinant human interferon  $\alpha$ -2a (MW, 20 kDa) diffused into the rabbit choroid, but only in small amounts, after retrobulbar injection. The total choroidal concentration was only 3% of the amount injected in the retrobulbar space, and the serum concentration was less than 1% of the choroidal concentration. Weijtens and associates<sup>38,39</sup>

studied dexamethasone concentrations in subretinal fluid of patients with a rhegmatogenous retinal detachment undergoing a scleral buckling procedure with drainage. They found that a subconjunctival injection, preceded by topical cocaine to disrupt the corneal and conjunctival epithelial barrier, resulted in a higher maximal vitreous concentration of dexamethasone (MW, 393 Da) than a sub-Tenon's or retrobulbar injection. However, even the highest vitreous concentrations in their study were lower than those needed for a therapeutic effect based on in vitro testing of human retinal pigment epithelial cell proliferation.<sup>39</sup>

Although periocular injection can deliver some low-molecular-weight substances in clinically relevant concentrations to the posterior segment, the rate of delivery is not as effective with high-molecular-weight substances. Improvement in the extent of absorption can come from better retention at the site of absorption through the use of gels,<sup>40-42</sup> nanospheres,<sup>43</sup> liposomes,<sup>44-49</sup> or other biodegradable carriers. Improvement in the extent of absorption also can be achieved with improved penetrability. Methods to improve the penetrability of the sclera have been sparsely investigated.

## SCLERA

### Basics

The sclera is a densely collagenous, hypocellular and elastic tissue that is composed of a proteoglycan matrix and closely packed collagen fibrils.<sup>50-53</sup> It has been thought to be relatively inactive metabolically, having no intrinsic capillary bed and few fibroblasts. Duke-Elder<sup>54</sup> described the sclera as "inert and purely supportive in function." Watson and Hazleman<sup>55</sup> stated that it is "metabolically relatively inert."

The outer surface of the sclera is covered by the loosely organized episclera and its inner surface by the lamina fusca and suprachoroidal space. The sclera is perforated by the emissarial canals for arteries, veins, and nerves. Unlike corneal collagen, scleral collagen bundles do not lie in orderly, regular lamellae but are interlaced in an irregular fashion, which accounts for the lack of transparency. Collagen forms 75% of the dry weight of the sclera;<sup>56</sup> the remainder is made up of noncollagenous proteins and mucopolysaccharides.<sup>57,58</sup> Approximately 70% of the weight of intact sclera is water.

Spitznas<sup>59</sup> studied the ultrastructure of human scleral collagen posterior to the ora serrata and reported that the diameter of the fibrils in the outer layers is significantly larger than that of the inner layers. There is a ratio of 1:2 between the diameter of collagen fibrils in the innermost and outermost layers of human posterior sclera, respectively.<sup>59,60</sup> Shields and associates<sup>61</sup> observed that there is

significantly less difference in average collagen fibril diameter between the inner and outer portions of anterior compared with more posterior human sclera. According to them, Purnell and McPherson<sup>61</sup> suggested that the larger fibril diameter, which they extrapolated to looser fibril arrangement, might provide less resistance to aqueous flow through the intervening ground substance. Bundles of thinner fibers, possibly precollagen, are found near scleral fibroblasts. The length of the bundles is not known. The bundles have a slightly fusiform shape with tapering ends and dichotomous branches. The turnover rate of scleral collagen is also unknown. The flat and elongated cells, the scleral fibroblasts, are few in number and are separated by collagen. The long axis of the cell and nucleus is parallel to the surface. Long, thin cytoplasmic extensions from the cells are attenuated to a diameter one-third to one-half the size of the collagen bundles. Experimental studies in an avian model suggest that the sclera is derived from 2 sources, the ectodermal neural crest and mesoderm.<sup>62</sup>

The mean total scleral surface area is approximately  $17.0 \pm 1.5 \text{ cm}^2$ .<sup>63</sup> Mean scleral thickness  $\pm$  SD is  $0.53 \pm 0.14 \text{ mm}$  at the corneoscleral limbus, significantly decreasing to  $0.39 \pm 0.17 \text{ mm}$  near the equator and increasing to 0.9 to 1.0 mm near the optic nerve.<sup>64</sup> The sclera thins with age. The large surface area and thinness of the sclera are desirable features of a route for targeted drug delivery.

In a normal eye, blood vessels only traverse the sclera and do not supply it directly. Therefore, the stroma of the sclera derives its nutrition from a distance and not through intimate contact with the capillary bed. This implies that the sclera must be permeable to fluids and metabolites, as reported first by Bill.<sup>65</sup> The external movement of substances through the sclera results from a pressure difference between the suprachoroidal space, where the pressure is 1 to 2 mm Hg lower than intraocular pressure, and the episcleral tissue, where the pressure is near 0 mm Hg. Transscleral movement should theoretically be slowed by reducing intraocular pressure. Whether this flow forms part of the normal flow of fluid from the suprachoroidal space is uncertain.<sup>66</sup>

### Transscleral Fluid Movement

Drug penetration across the sclera is a route of entry into the eye for some ocular drugs, particularly those with low molecular weight. However, the details of transscleral fluid movement are poorly understood.

In addition to being the outer surface of the globe, the sclera is the distal component in the uveoscleral outflow pathway. Histologic analysis of sclera following injection of various tracers into the anterior chamber indicated the presence of transscleral fluid flux through the scleral

stroma, as well as possibly through narrow spaces around penetrating nerves and blood vessels.<sup>65,67-69</sup> However, there is little information regarding the character of this fluid movement. What factors influence scleral permeability? Does the sclera allow only unidirectional flow from within the eye to the outside? Or might the flow be bidirectional, and also from outside to within? Is it always passive, as might occur with porous diffusion through a fiber matrix? Or might it also be regulated by endogenous signals?

Assessment of drug diffusion through the sclera by *in vitro* permeability studies is a useful approach to estimate drug movement for *in vivo* conditions. Maurice and Polgar<sup>70</sup> examined diffusion across bovine sclera with a broad range of different molecular weight solutes and ions, including methylene blue (MW, 320 Da) and serum albumin (MW, 69 kDa). They showed first that the diffusion of the ions and solutes was inversely related to molecular weight. Shields and associates<sup>71</sup> performed an *in vitro* study with postmortem human eyes to assess the permeability of outer anterior sclera following trabeculectomy. They recognized the permeability of sclera to ferritin or india ink, and they speculated that the route of flow was through vessels in the flap or through the "collagen ground substance between individual fibrils." Ahmed and Patton<sup>72</sup> recognized that under certain conditions, even some topically applied drugs-timolol maleate (MW, 433 Da) and inulin (MW, 5 kDa)—can enter the eye via the transscleral route and bypass the anterior chamber. Edelhauser and Maren<sup>12</sup> reported that scleral permeability was greater than corneal permeability except for highly lipid soluble compounds, for which scleral and corneal permeability were the same.

Olsen and associates<sup>64</sup> examined the diffusion across human sclera by using a range of different molecular weight solutes as high as dextran (MW, 70 kDa). They confirmed in human sclera that the diffusion of the ions and solutes was inversely related to molecular weight. Moreover, they observed that the absorption of molecular weight substances greater than 5 kDa was poor. As they studied only tissue without macroscopically visible perforating channels or light and electron microscopic perforating vascular channels, their studies were most consistent with direct penetration through the sclera as an important vector for transscleral drug transfer into the eye. More recently, Ambati and associates<sup>73</sup> measured the permeability of rabbit sclera to a series of fluorescein-labeled hydrophilic compounds with a wide range of molecular weights as high as 150 kDa. Scleral permeability decreased with increasing molecular weight, a finding consistent with previous human and bovine data. They also suggested that molecular radius might be a better predictor of scleral permeability than molecular weight. These studies all are consistent with the sclera being

permeable, and the permeability being inversely related to the molecular weight of the permeating substance.

#### *Influencing Drug Penetration and Scleral Permeability*

The rate and extent of absorption are determined by both the physicochemical behavior of a substance and the permeability of the sclera. Absorption can be enhanced for a particular substance by increasing drug penetration or by increasing scleral permeability. Few methods have been tested to enhance either of these, particularly for molecular weight substances higher than 5 kDa.

Drug penetration into the eye may be increased with iontophoresis, the process of moving a charged molecule by an electric current across the cornea or sclera. Transcorneal iontophoresis has been shown to result in significantly higher drug levels than those found after multiple drop treatments.<sup>74</sup> However, it is questionable whether significant drug concentrations within the optic nerve, retina, or choroid can be achieved with it. Experimental studies by Lam and associates<sup>75</sup> have shown that toxic tissue-damaging effects might accompany drug delivery by transscleral iontophoresis. They observed local retinal and choroidal lesions following transscleral iontophoresis of various drugs. Current density and duration of application affected the size and severity of the lesions. This technique also is not practical.

Few studies have investigated the factors that contribute to scleral permeability. Olsen and associates<sup>64</sup> did not find any significant correlation between scleral permeability to inulin and age. They also observed that cryotherapy did not significantly affect scleral permeability to 5-fluorouracil (MW, 130), inulin, or dextran (MW, 40 kDa).<sup>64</sup> Further, scleral permeability to sucrose (MW, 342), inulin, and dextran (10 kDa) was unaffected by transscleral diode laser retinopexy.

Scleral permeability does appear to be related to scleral thickness. Shields and associates<sup>71</sup> found that increased outflow was inversely related to the scleral flap thickness in a small number (N=6) of postmortem human eyes that underwent experimental trabeculectomy. Scleral permeability to the low-molecular-weight substances dexamethasone and methotrexate (MW, 455) also was increased significantly with one half surgical thinning of the sclera.<sup>64</sup> Dan and Yaron<sup>76</sup> found increased transscleral flow of saline through bovine sclera with application of clostridial collagenase. Interestingly, they also observed that collagenase applied directly to rabbit sclera after a fornix-based peritomy resulted in scleral thinning and lower intraocular pressure.<sup>76</sup> Even with the use of a microapplicator, this response could not be precisely controlled. In contrast to increased permeability with scleral thinning, abnormal and thickened sclera may be associated with reduced permeability. Trelstad and associates<sup>77</sup>

found that sclera from 2 nanophthalmic eyes was thicker than normal and contained unusually disordered collagen fibrils. Yue and associates<sup>78</sup> found that collagen fibers were twisted and more closely packed in nanophthalmic eyes, changes consistent with reduced scleral permeability. Interestingly, Gass<sup>79</sup> first suggested posterior sclerotomy, which increases transscleral flow, as an effective treatment before entering the anterior segment to prevent choroidal effusion in these eyes. As recommended by Brockhurst,<sup>80</sup> vortex vein decompression also may be effective.

Scleral permeability also may be influenced by intraocular pressure. Rudnick and associates<sup>81</sup> recently evaluated the permeability of human sclera to 3 low-molecular-weight compounds (carboxyfluorescein, dexamethasone, and water) and found a small effect of intraocular pressure. They suggested that pressure-related compression of collagen and narrowing of intracollagen pathways within the sclera slow diffusion of small molecules, yet may completely block transport of macromolecules.<sup>81</sup>

By enhancing scleral permeability, one might be able to more effectively deliver drugs to the posterior segment. Enhanced scleral permeability also might lower uveoscleral outflow resistance and lower intraocular pressure.

#### *Can Transscleral Fluid Movement be Enhanced by Prostaglandins?*

The possibility that various prostaglandins (PGs) could modulate transscleral fluid movement and enhance scleral macromolecular permeability is suggested by several observations. First, topical treatment of monkey eyes with PGF<sub>2α</sub>-isopropyl ester (IE) for 5 days is known to enhance uveoscleral outflow and to reduce collagen type I and collagen type III immunoreactivity within sclera by 43% and 45%, respectively.<sup>82</sup> Second, scleral collagen is predominantly type I collagen and accounts for about one half of the total dry weight of sclera.<sup>56</sup> Finally, evidence that compaction of extracellular matrix affects transscleral permeability suggests that collagen density within sclera is an important determinant of permeability.<sup>83</sup> Hence, it is plausible that PG-mediated reduction of scleral collagens could significantly alter permeability. Increased local biosynthesis of matrix metalloproteinases (MMPs), a family of secreted neutral proteinases that can initiate specific degradation of key extracellular matrix components, may be regulating the reduction of scleral collagen following topical PG.<sup>84,85</sup>

PGs induced substantial remodeling of ciliary muscle extracellular matrix in situ that reflected MMP-mediated collagen reduction.<sup>82</sup> The sequence of cellular events underlying this response includes PG transduction at cell surface PG receptors, induction of MMP gene transcription, translation and secretion of proMMPs, activation of MMPs by proteolytic truncation, and MMP-mediated

initiation of collagen degradation in the ciliary muscle extracellular space.<sup>86</sup> There is immunohistochemical evidence that MMP-1, which can mediate normal turnover of fibrillar collagens, such as collagen type I and collagen type III, is present in normal human sclera.<sup>87</sup> Analysis with PG receptor agonists suggests that these PG responses are receptor-mediated.<sup>87</sup>

The biologic activity of a drug, whether it be therapeutic or toxic, is often proportional to the concentration of that drug at the receptor site. Moreover, the persistence of its effects is directly related to the residence time of the drug at the receptor. The PG receptor type that most specifically recognizes F family prostaglandins is the FP prostanoid receptor, a G-protein-coupled cell membrane receptor.<sup>88,89</sup> In situ hybridization and immunohistochemical studies have demonstrated FP receptor transcripts and protein in several anterior segment tissues of monkey eyes.<sup>90</sup> In the sclera, however, only FP receptor immunoreactivity has been observed,<sup>90</sup> and no evidence of FP receptor transcripts has been detected. It is possible that the sensitivity of the in situ hybridization technique used was insufficiently sensitive to detect small amounts of FP receptor mRNA. In view of the potential responsiveness of sclera to prostaglandins, direct assessment of FP receptor gene transcription and protein expression in human sclera clearly is needed.

If prostaglandin exposure does enhance scleral macromolecular permeability, the assertions that might be valid include the following:

- Topical prostaglandin administration reduces scleral collagen by increasing scleral metalloproteinase (MMP) activity.
- This effect is FP (prostaglandin F) receptor-mediated, and both gene transcription and protein expression are present in the sclera.
- Exposure of isolated sclera to specific FP receptor agonists increases scleral permeability in association with increased MMP expression.
- Transscleral absorption of a high-molecular-weight substance, basic fibroblast growth factor (FGF-2), increases with scleral exposure to prostaglandin.

## **METHODS**

### **1. MEASUREMENT OF SCLERAL MATRIX METALLOPROTEINASES AFTER TOPICAL PROSTAGLANDIN**

#### *PGF<sub>2α</sub>-IE-Treated Monkey Eye Tissue*

Young adult cynomolgus monkeys were evaluated by slit-lamp biomicroscopy on 2 occasions prior to initiation of treatment to confirm the absence of signs of ocular inflammation. In addition, integrity of the blood-aqueous barrier was confirmed by measuring the appearance and

disappearance of fluorescence in the anterior chamber (AC) following intravenous fluorescein administration. To qualify for further study, AC fluorescence levels and time course of appearance and decay in both eyes had to be similar and within the range of values obtained for control eyes in previous studies.<sup>91</sup> Monkeys meeting these conditions were presumed to have an intact blood-aqueous barrier.<sup>91</sup>

The following week each qualifying monkey received 2 µg PGF<sub>2α</sub>-IE (in 5 µL) twice daily (morning and afternoon, approximately 7 hours apart) in 1 eye and 5 µL of vehicle in the other eye for 5 days, as previously described. On the fifth day of treatment, slit-lamp biomicroscopy was performed. Eight eyes of 4 monkeys were evaluated. AC cells or flare was not observed during treatment of these monkeys.

The animals were sacrificed on day 5.<sup>92</sup> The vascular bed was perfused with lactated Ringer's solution to remove circulating MMPs from the ocular tissues. The anterior segments were dissected and immediately fixed in methacarn (60% methanol, 30% chloroform, 10% glacial acetic acid) for 3 hours. Increased sensitivity of immunohistochemical staining of various antibodies has been demonstrated for many antigens after methacarn fixation.<sup>92,93</sup> Fixed anterior segments were transferred to cold 100% ethanol. The tissues were embedded in paraffin and sections were collected from the midsagittal region of each eye on Vectabond coated slides (Vector Laboratories, Burlingame, Calif). For histopathologic analysis, 3 or 4 sections from each eye were stained with hematoxylin and eosin. All procedures were conducted in accordance with the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research. Tissue sections analyzed in the present study were cut from the same tissue blocks as sections analyzed in a previous study.<sup>92</sup>

#### *Immunohistochemistry*

Sclera was immunostained by a standardized protocol. Each step of the protocol was optimized as previously described.<sup>94</sup> The concentration of each solution containing antibodies or horseradish peroxidase-conjugated streptavidin was optimized to obtain submaximal (nonsaturating) staining intensity as determined by imaging densitometry (described in the next section). Finally, the incubation time with diaminobenzidine was optimized for each primary antibody to obtain the strongest signal (staining intensity) that still was increasing linearly with time. The elimination of saturating binding or development parameters from the protocol supports the position that the observed changes in staining intensity reflected differences in tissue content of target antigen.

Sections from the treated and control eyes were stained at the same time. Five sections, 10 µm thickness, from each eye were heated to 56°C for 20 minutes,

washed in 3 xylene changes to remove paraffin, and rehydrated through graded ethanols. The sections were treated with antigen retrieval solution (AR-10, Biogenex, San Ramon, Calif) at 95°C for 5 minutes. After cooling, the sections were exposed to 3% H<sub>2</sub>O<sub>2</sub> for 10 minutes to suppress endogenous peroxidase activity. To remove intrinsic melanin, sections were treated successively with aqueous potassium permanganate (2.5 g/L) for 10 minutes and oxalic acid (5 g/L) for 3 minutes.<sup>95-97</sup> After rinsing, the sections were blocked for 30 minutes with 0.1% bovine serum albumin (Sigma Chemical Co, St Louis, Mo) and incubated for 2 hours with affinity-purified polyclonal sheep anti-porcine MMP-1 (dilution 1:25, AB772, Chemicon, Temecula, Calif), polyclonal rabbit anti-human MMP-2 (dilution 1:100, AB809, Chemicon), or rabbit anti-human MMP-3 (dilution 1:1,000, AB810, Chemicon). These concentrations had been optimized in pilot studies for quantitative analysis. Specificity of these antibodies has been previously confirmed.<sup>97,98</sup> After rinsing, the sections treated with antibody to MMP-1 were exposed to biotinylated donkey anti-sheep IgG for 30 minutes (Biotin-SP-Conjugated Affinipure, Jackson ImmunoResearch Laboratories, Inc, West Grove, Pa, diluted 1:500). The sections exposed to antibodies to MMP-2 or MMP-3 were exposed to biotinylated goat anti-rabbit immunoglobulin (Biogenex) for 20 minutes. After rinsing, the sections were exposed to horseradish peroxidase-conjugated streptavidin for 20 minutes. Consecutively, each section was rinsed and incubated with 3,3-diaminobenzidine chromogen for 10 minutes (HRP-DAB Super Sensitive Immunodetection System, Biogenex). To facilitate comparability, sections from the control vehicle-treated and PG-treated eye of each monkey were immunostained at the same time.<sup>99,100</sup> To serve as controls for nonspecific staining, sections from each eye were simultaneously processed by the same protocol but without the primary antibody.

#### *Densitometric Analysis*

Immunohistochemical staining intensity was directly measured with a high-resolution imaging densitometer.<sup>94</sup> Measurements from multiple sections stained at the same time facilitated assessment of measurement precision and permitted statistical comparison of differences among control and experimental eyes. Immunostained sections were scanned by placing the slides directly on the platen of an imaging densitometer (model GS-700, Bio-Rad, Hercules, Calif). Resolution of the scans was set to 1,200 dpi (50 µm-wide pixels), and the scanning mode was set to transillumination. The optical density measurements of the immunostained sections all were less than 1.00 optical density units. Because the densitometer can accurately measure optical densities greater than 3.0 units (Bio-Rad

specifications), these measurements were well within the appropriate range for accurate determinations. The scanned digital data were displayed in a masked fashion and analyzed by using an image analysis program (Molecular Analyst : version 2.1, Bio-Rad). The optical density along 2 line segments positioned over the sclera was measured in each section by using two-dimensional imaging densitometry. A similar line segment was positioned perpendicular to the sclera adjacent to the ciliary body to assess background optical density.

Mean optical density scores were determined from the optical density volume scores (optical density x mm) and the corresponding line segments (mm).<sup>94</sup> For each eye, 10 scores were obtained from 5 midsagittal sections. Background optical density was defined as baseline and subtracted from the original optical density scores. The specific optical density scores along each line segment over the sclera were calculated by dividing the optical density area score (optical density (mm), provided by the densitometer) by the length of the line segment (mm) for that score. Mean specific optical density scores from the PG-treated eye of each monkey were compared to corresponding scores from the contralateral control eyes using the paired Student's *t* test. The unpaired Student's *t* test was used to compare the mean of mean optical density scores of all PG-treated and all control eyes. In each case, a *P* value less than 0.05 was considered significant.

## 2. FP RECEPTOR GENE TRANSCRIPTION AND PROTEIN EXPRESSION IN NORMAL HUMAN SCLERA

These experiments were undertaken to determine whether the FP receptor is expressed in normal human sclera.

### *Tissue Preparation*

Postmortem human eyes from a 76-year-old donor were obtained from within 24 hours of death. Eyes were placed in chilled Hepes-buffered saline solution (HBSS) and maintained on ice. Eyes were surgically cleaned of connective tissue, blood vessels, muscle, and conjunctiva and rinsed once in HBSS. The anterior chamber was removed by a circumferential incision approximately 4 to 5 mm behind the limbus and snap-frozen, as described below. A circumferential incision was made in front of the optic nerve head, and ocular contents, including retina and choroid, were removed. The sclera was cut into 10 mm-square pieces. Residual pigmented tissue was removed with a cotton-tipped applicator. Sclera tissue was further cut into 2 mm squares and placed in a sterile 50 mL conical tube on ice.

### *Isolation of Total RNA*

The scleral tissue squares were homogenized in 8 mL of

TRIzol reagent (Gibco, BRL, Life Technologies, Grand Island, NY) using a homogenizer (Polytron P-10; Brinkmann, NY). Homogenized sample was transferred to sterile 1.5-mL tubes in 1-mL aliquots and incubated for 5 minutes at 25°C. Chloroform (200 µL) was added to each tube and mixed by brief vortex and incubated for 3 minutes at 25°C. Samples were centrifuged (12,000 × 3) for 15 minutes at 4°C. The aqueous phase was transferred to fresh sterile 1.5 mL tubes. Isopropanol (500 µL/tube) was added and allowed to incubate for 10 minutes at 25°C. Samples were centrifuged (12,000 (× g) for 10 minutes at 4°C. Supernatant was removed, and the RNA pellet was washed with 75% ethanol/diethylpyrocarbonate water and air dried. RNA was resuspended in a total volume of 50 µL diethylpyrocarbonate water, and quality was checked by gel electrophoresis.

### *Reverse Transcription-Polymerase Chain Reaction (PCR)*

Primers were chosen to amplify 1,186-nucleotides of the human FP receptor. The sense primer (nucleotides 170 to 193) corresponds to a position 61 nucleotides upstream of the translation start site, and the antisense primer (nucleotides 1333 to 1356) corresponds to a position 39 nucleotides downstream of the stop codon in the human FP sequence. Both PCR primers were 100% homologous with the reported cloned sequence of the human FP receptor. The sense and antisense primers were used for reverse transcription (RT)-PCR as previously described with total RNA isolated from human sclera tissue.<sup>101</sup> The PCR (final volume, 50 µL) contained 5 µL of the RT reaction, 5 µL of 10X PCR buffer, 1 µL of 10 mM dNTP mixture, 1.5 µL of 50 mM MgCl<sub>2</sub>, 2.5 µL of the sense and antisense primers (20 µM), and 0.5 µL taq polymerase (all reagents from Gibco BRL, Grand Island, NY). The PCR program consisted of an initial step at 95°C for 3 minutes, followed by 30 cycles at 95°C for 1 minute, 55°C for 1 minute, 72°C for 1 minute, and a final step at 72°C for 7 minutes. Products were analyzed by electrophoresis in a 1% agarose gel.

### *FP Receptor Protein Localization in Sclera*

Antibodies to the human FP receptor were generated in rabbits by using a recombinant fusion protein consisting of glutathione-S-transferase and a portion of the carboxyl terminus of the receptor consisting of amino acids 317 to 362. Preparations of the fusion protein and antibody purification were done as described.<sup>102</sup> Initial characterization of the antibodies was done as previously described<sup>103</sup> using COS-7 (African green monkey kidney) cells transfected with plasmid DNA encoding the human FP receptor. For labeling of human tissues, pieces of sclera (8 to 10 mm square) were snap-frozen in embedding medium (OCT, Tissue-Tek, Miles Inc, Elkhart, Indiana), sectioned on a

cyrostat (8 to 10- $\mu$ m sections), mounted on glass coverslips, and postfixed in 4% paraformaldehyde. Tissue sections were washed twice with phosphate buffered saline (PBS) and then placed in 30 mM sodium chloride/300 mM sodium citrate for 20 minutes. Sections were then incubated in 100 mM glycine solution for 20 minutes to block nonspecific binding, and then washed twice in sodium citrate buffer for 10 minutes. Sections were permeabilized with 30 mM sodium chloride/300 mM sodium citrate containing 0.1% triton-X100 for 1 hour. After an overnight incubation at 4°C with the primary antibody (0.5 to 1.0  $\mu$ g/mL), the cells were washed with sodium citrate containing 0.05% triton-X100 and incubated for 1 hour at room temperature with secondary antibody (rhodamine red-goat-anti-rabbit, Molecular Probes, Eugene, Ore) at a dilution of 1:200. Coverslips were washed and mounted on glass slides for viewing.

### **3. MEASUREMENT OF HUMAN SCLERAL PERMEABILITY AND MMPs WITH PROSTAGLANDIN EXPOSURE**

If there is increased MMP-1, MMP-2, and MMP-3 immunoreactivity in the sclera of monkey eyes that have received topical PGF<sub>2 $\alpha$</sub> -IE treatment, it would be unclear whether it is a direct response, reflecting increased production within sclera, or an indirect consequence of increased MMP release into the suprachoroidal space of the uveoscleral outflow pathway by ciliary muscle cells. The following experiments were undertaken to investigate this question by determining whether exposure of organ cultures of human sclera to various PGs increases scleral permeability and whether this is associated with increased release of MMPs.

#### *Human Scleral Organ Cultures*

Twenty-three pairs of human eyes from donors 45 to 80 years old were obtained within 24 hours after death. Enucleation was completed within 6 hours postmortem, and the eyes were stored in a moist chamber at 4°C for less than 24 hours prior to generation of the organ cultures. Donors had no known history of glaucoma or other eye disease. The eyes were placed in Dulbecco's modified Eagle's medium and Ham's F12 nutrient mixture (DMEM-F12) medium containing 50 U/mL penicillin and 50  $\mu$ g/mL streptomycin for 15 minutes. This was repeated twice prior to dissection. Tenon's capsule and episclera were removed from the surface of the sclera using a sterile cotton-tip applicator. Curved scissors were used to excise circular pieces of sclera. The chosen areas were selected to avoid the perforating anterior ciliary vessels and the vortex veins. The uveal tissues and retina were gently removed from the vitreous side of the sclera with a cotton-tipped applicator. The circular pieces of scleral tissue were placed into 12-well culture plates containing DMEM-F12

supplemented with 1% fetal bovine serum and 1 ng/mL recombinant human FGF-2. As serum contains agents known to stimulate MMP biosynthesis,<sup>104</sup> low serum concentration was used to minimize nonspecific induction of MMPs. The cultures were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO<sub>2</sub>.

#### *Prostaglandin Treatments*

The culture medium was changed to fresh medium supplemented with PGF<sub>2 $\alpha$</sub> , 17-phenyltrior-PGF<sub>2 $\alpha$</sub> , PhXA85 (latanoprost acid) (Cayman Chemical Co, Grand Rapids, Mich), or vehicle control. 17-phenyltrior-PGF<sub>2 $\alpha$</sub>  and PhXA85 bind with greater specificity to the FP receptor (the endogenous PG-receptor that preferentially recognizes F-type prostaglandins) than PGF<sub>2 $\alpha$</sub> . Each PG was tested at concentrations of 100 nM, 200 nM, and 500 nM. PG concentrations were chosen on the basis of their receptor binding profiles as well as the observation that the peak concentration of PhXA85 observed in aqueous humor following topical application of a clinical dose of latanoprost to human eyes is approximately 100 nM.<sup>105,106</sup> Exposure durations of 24, 48, and 72 hours were chosen on the basis of previous experiments that found increased MMPs in ciliary smooth muscle cells exposed to PGs for 24 hours to 72 hours.<sup>107,108</sup> Experimental treatment was initiated by addition of the test PGs prepared from 10 mM stock solutions in ethanol and appropriately diluted with DMEM-12 nutrient mixture.

#### *Permeability Analysis*

Following 1- to 3-day incubation with test PG or vehicle control, the scleral tissue was clamped into the in vitro perfusion apparatus (Ussing apparatus, model CHM2; World Precision Instruments Inc, Sarasota, Fla). The 2 chambers, each with a 9 mm-diameter opening, sandwiched a 14 mm-diameter piece of scleral tissue. This assembly was held together with a clamp. Each unstirred chamber contained 0.75 mL and could be filled, drained, and purged through 3 ports. Three rhodamine-dextran polymers (Molecular Probes) (MW, 10,000, 40,000, and 70,000 kDa) were diluted in phenol red-free HBSS (250  $\mu$ g/mL). The "uveal-side" chamber was filled with phenol-free HBSS, and the "orbital-side" chamber was filled with rhodamine-dextran diluted in phenol red-free HBSS. Permeability was assessed in this direction because the orbital side was smoother than the uveal side, and thus the potential for measurement-altering small leaks around the edge of the tissue piece was less. Solutions were freshly prepared and warmed to 37°C prior to use. After assembly and filling, the system was placed in the 37°C incubator. The apparatus was checked after 30 minutes to verify that no leaks were present. Any leaks of the dextran solution were readily apparent owing to the dark red color

of the solution. Leaks of the phenol red-free Hanks from the uveal-side chamber were recognized by reduction of the level of the fluid visible through the clear walls of the chamber. Four hours later, a 750  $\mu$ L sample was removed through a valved port connected to the uveal-side chamber and stored at  $-80^{\circ}\text{C}$ . Samples were protected from light at all times before fluorescence measurement.

#### *Scleral Permeability Coefficient*

Diffusion from the "orbital" chamber to the "uveal" chamber was characterized by means of a permeability coefficient ( $P_c$ ), which is the ratio of steady-state flux (the mass of solute crossing a planar unit surface normal to the direction of transport per unit time) to the concentration gradient.<sup>64</sup> In this study, the concentration of "uveal-side" chamber,  $C_{U_t}$ , was less than 1% of the concentration in the "orbital" chamber,  $C_o$ , which did not change measurably over the course of the experiment. Hence, the permeability coefficient was calculated as follows:

$$P_c \text{ (cm/sec)} = (C_{U_t} - C_{U_{0.5}})V / AtC_o$$

where  $C_{U_{0.5}}$  and  $C_{U_t}$  are the concentration in the "uveal" chamber at 0.5 hour and at  $t$  hours, respectively.  $C_o$  is the initial drug concentration (0.25 mg/mL),  $A$  is the surface area of exposed sclera (0.65  $\text{cm}^2$ ),  $V$  is volume of the each chamber (0.75 ml), and  $t$  is duration of steady-state flux converted from hours to seconds. The term  $(C_{U_t} - C_{U_{0.5}}) / t$  is the permeation rate of dextran across each excised scleral piece ( $\mu\text{g/hr}$ ).

The fluorescence of rhodamine-dextran was measured with a spectrofluorimeter at room temperature. The excitation and emission wavelengths were 550 and 580 nm, respectively. Standard curves of fluorescence versus concentration were obtained by serial dilution of rhodamine-dextran dissolved in diffusion medium (phenol red-free Hank's buffered saline solution).

#### *Viability After Prolonged Exposure to Prostaglandins*

To assess viability in vitro, scleral organ cultures were incubated with 500 nM of each PG, the highest dose in this study, for 1, 2, or 3 days. Ethidium-homodimer was then added to the cultures to a final concentration of 1  $\mu\text{M}$  and the cultures were returned to the incubator for 30 minutes (Molecular Probes). As this dye cannot penetrate living cells, it is only bound to the DNA of dead cells in the cultures. The scleral cultures were rinsed with phosphate buffered saline without phenol red and then exposed to 2% paraformaldehyde in phosphate buffered saline for 10 minutes. The cultures were then permeabilized by passage through graded methanols (50%, 70%, 90%, 95%, and 100%), rehydrated, rinsed in phosphate buffered saline, and exposed to 5 mM Sytox green for 15

minutes. This stain cannot pass through the plasma membrane of living cells but readily stains DNA within dead cells. The cultures were rinsed twice with (PBS). The cultures were then homogenized in PBS using a homogenizer. The homogenates were centrifuged and the supernatants were collected.

Cell viability in these samples was determined by first measuring Sytox green fluorescence using a spectrofluorimeter (model SFM 25, Kontron, Zürich, Switzerland) with the excitation and emission wavelengths set at 500 and 525 nm, respectively. The amount of ethidium homodimer was then measured using a 550 nm excitation wavelength. This wavelength excited ethidium homodimer at 83% of maximal efficiency, but minimally excited Sytox green. The emission wavelength analyzed was 650 nm because it retained 71% of maximal efficiency for ethidium homodimer and eliminated greater than 99% of the cross-talk signal coming from Sytox green. The photomultiplier voltage was optimized to 480 V to obtain all readings on 1 setting. The signals from the ethidium homodimer were normalized with signals from the Sytox green by dividing the ethidium homodimer results by the Sytox green results. Positive (live) controls were fresh cultures not exposed to any treatment, and negative (dead) controls were cultures first treated with 2% paraformaldehyde for 10 minutes and permeabilized with graded methanols before evaluation. The viability of each sample was determined by interpolation from a standard curve that was generated by plotting positive and negative control values.

#### *Scleral Hydration Analysis*

Thirty scleral specimens were obtained from human eye bank eyes for the determination of scleral hydration. These studies were performed to ensure that maintaining sclera in the Ussing perfusion system did not hydrate the sclera, which may alter scleral permeability. Ten circular scleral pieces from 3-day-old preparations were incubated in DMEM/F-12 media only, or with media for 3 days followed by HBSS for an additional 4 hours. The preparations were then weighed by using an analytical balance (accuracy, 0.0001 g, Mettler, Geissen, Germany), dried to constant weight at  $100^{\circ}\text{C}$  for 24 hours, placed immediately in a tissue desiccator to cool for 30 minutes, and reweighed. Another 20 circular scleral pieces from fresh and 3-day-old moist chamber-stored globes perfused with HBSS and without perfusion were used to evaluate potential effects of storage. The level of hydration in each piece of sclera was calculated by the following equation:

$$\text{mg H}_2\text{O} / \text{mg tissue} = (\text{wet weight} - \text{dry weight}) / \text{dry weight.}$$

#### *MMP Immunosorbant Assays*

At the conclusion of the 1- to 3-day incubations with PGs

or vehicle, media samples were collected from the scleral cultures for enzyme-linked immunosorbant assay (ELISA) analysis. Measurements of MMP-1, -2, and -3 concentration were performed with commercially available ELISA kits (Biotrak, Amersham Pharmacia Biotech Inc, Piscataway, NJ). These assays are based on a two-site ELISA "sandwich" format, and detected both latent and active MMPs. For the MMP-1 assay, purified MMP standards and samples were incubated in microtiter wells pre-coated with anti-MMP-1 antibody. The wells were then washed, incubated with second polyclonal antibody to MMP-1, washed, incubated with anti-rabbit horseradish peroxidase, washed, and developed by tetramethyl benzidine. After development at room temperature, the absorbency was measured at 630 nm using a microtiter plate reader (SpectraMax 250, Molecular Devices, Sunnyvale, Calif.). The procedures for the MMP-2 and MMP-3 assays were the same except the antibodies were to MMP-2 and MMP-3, respectively.

#### *Statistical Evaluation*

Experimental differences between control culture results and a single treatment group were evaluated using the Student *t* test. When results from several treatment groups were compared to those of a single control, significance was evaluated using analysis of variance and the Student Newman Keuls test. A *P* value less than .05 was considered statistically significant.

#### **4. MEASUREMENT OF FIBROBLAST GROWTH FACTOR-2 PERMEATION THROUGH HUMAN SCLERA WITH PROSTAGLANDIN EXPOSURE**

These experiments were undertaken to determine whether exposure of scleral explants to the PG analogue latanoprost acid increases permeability to fibroblast growth factor-2 (FGF-2) (also known as basic fibroblast growth factor).

#### *Human Scleral Tissue Explant*

Eight pairs of human eyes from donors were obtained from the San Diego Eye Bank. Donors had no history of glaucoma or other ocular diseases. The mean age was  $70 \pm 6$  (mean  $\pm$  SD) years old. Each pair of eyes was enucleated within 5 hours after death and immediately preserved in a moist chamber at 4°C. Apparently intact eyes were selected and any eye showing scleral damage or thin sclera (posterior staphyloma) was not used. Within 24 hours after preservation, the sclera was dissected and placed into organ culture. Briefly, after incubation in HBSS medium containing 50 U/mL of penicillin and 50 U/mL of streptomycin for 30 minutes, residual extraocular muscles and orbital connective tissues were removed. Sclera was dissected into 4 pieces to exclude the long ciliary

nerve and artery, insertion of muscles, or vortex veins in each center area. Uveal tissue and retina were gently removed with a cotton-tipped applicator. Scleral pieces were placed into 12-well plates containing DMEM/F-12 supplemented with 1% fetal calf serum and 1 ng/mL human recombinant FGF-2. The low concentration of serum was used to minimize nonspecific increase of MMP because serum contains various stimulating factors of MMP synthesis. The explants were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO<sub>2</sub>.

#### *Latanoprost Acid Pretreatment*

To investigate the effect of latanoprost acid on the scleral permeability, the culture medium was changed to fresh medium supplemented with latanoprost acid (Cayman Chemical Co). Tested concentrations included 50, 100, and 200 nM, because the peak concentration in human aqueous humor following topical application of a clinical dose is ~100 nM.<sup>106</sup> After 3 days exposure, the permeability assay was performed.

#### *Scleral Permeability Analysis*

After 3 days' incubation, the scleral tissue was clamped into the in vitro Ussing perfusion apparatus. Each chamber contained 0.75 mL of fluid. The 2 chambers were facing an opening of 9 mm in diameter and were held together by a screw clamp. The scleral tissue was washed twice in phenol red-free HBSS to remove culture medium and carefully sandwiched to avoid vortex veins between both chambers. Both chambers were tightly clamped to avoid leakage of the medium. Each chamber had 3 ports to fill and drain samples. Tested molecules included human recombinant FGF-2 (16kD, R & D Systems, Minneapolis, Minn) and 10 kDa rhodamine-dextran polymer (Molecular Probes). This dextran was included in the analysis because it is stable in tissue, it has no physiologic activity, and its transscleral movement has been previously characterized in normal sclera.<sup>64</sup> Rhodamine-dextran or FGF-2 was diluted in phenol red-free HBSS and applied in the orbital side chamber. After checking that there were no leaks in the uveal side chamber, phenol red-free HBSS was filled in this side. After assembly of Ussing chambers, the system was incubated at 37°C in a humidified atmosphere of 95% air and 5% CO<sub>2</sub>. The assay of FGF-2 and dextran was dependently performed in the same scleral tissue. After the intended time, each sample was drained from the uveal side chamber and stored in a light-protected box.

#### *Measurement of Dextran*

Rhodamine-dextran concentration in the HBSS collected from the uveal side chambers was determined using a spectrofluorimeter. The excitation and emission

wavelengths were 550 and 580 nm, respectively. Standard curves of fluorescence versus concentrations were obtained by serial dilution of rhodamine-dextran dissolved in phenol red-free HBSS. Each sample was immediately measured 8 times, and the measurements were averaged.

#### Measurement of FGF-2 Concentration

FGF-2 concentration in the medium collected from the Ussing chamber was measured using a sandwich enzyme immunosorbent assay (R & D Systems). Optical density was measured at 450 nm and 540 nm using a microtiter plate reader (SpectraMax 250, Molecular Devices). To correct for nonspecific variation, the absorbance value at 540 nm was subtracted from that of 450 nm. Standard curves of absorbency versus concentrations were obtained by serial dilution of standard purified FGF-2.

#### Permeability Coefficient Determination

Diffusion from the orbital chamber to the uveal chamber was characterized by determination of a permeability coefficient ( $P_c$ ), which is the ratio of steady-state flux to the concentration gradient.<sup>64</sup> In this study, the concentration of agents in the uveal side chamber,  $C_{U_s}$ , was less than 1% of it in the orbital chamber,  $C_o$ , thus the change of  $C_o$  was assumed to be under the limit of detection. Hence, the permeability coefficient was calculated as follows:

$$P_c \text{ (cm/sec)} = (C_{U_t} - C_{U_0})V / C_o t S$$

where  $C_{U_0}$  and  $C_{U_t}$  are the concentration in the Ussing chamber at 0 hour and at  $t$  hours, respectively.  $C_o$  is the initial drug concentration in the orbital chamber.  $V$  is a volume of each chamber (0.75 mL), and  $t$  is a duration time of steady-state flux converted the unit from hour to second.  $S$  is the surface area of exposed sclera (0.65 cm<sup>2</sup>).

#### Statistical Evaluation

At least 7 experiments were performed on FGF-2 and dextran at each concentration of latanoprost acid. Each group was compared by using a Student's  $t$  test. A  $P$  value less than 0.05 was considered statistically significant. All data are presented as mean  $\pm$  SD.

## RESULTS

### I. MEASUREMENT OF SCLERAL METALLOPROTEINASES (MMPs) AFTER TOPICAL PROSTAGLANDIN

#### Immunohistochemistry

In the vehicle-treated monkey eyes, moderate immunoreactivity for MMP-1 was observed in the sclera (Fig 1). The distribution of MMP-2 immunoreactivity in the vehicle-treated eyes was similar with diffuse light staining

(Fig 1). Minimal MMP-3 immunoreactivity was present in the vehicle-treated eyes.

In the eyes treated with PGF<sub>2 $\alpha$</sub> -IE, there was increased MMP-1 and MMP-2 immunoreactivity in the sclera when compared with the corresponding vehicle-treated eye (Fig 1). Compared to the vehicle-treated eyes, moderate MMP-3 staining also was observed in sclera of the treated eyes.

#### Densitometric Analysis

The intensity of immunostaining was assessed along 2 lines placed over the image of the sclera observed with an imaging densitometer (Fig 2). Compared with the vehicle-treated eyes, there was increased MMP-1 immunoreactivity in all treated eyes (Table I). Table II shows the combined scores for MMP-1, MMP-2, and MMP-3. Overall, the optical density score for MMP-1 in the sclera in the treated eyes was increased by  $63 \pm 35\%$  (mean  $\pm$  SD). Similarly, the optical density score for MMP-2 was increased by  $267 \pm 210\%$ , and the MMP-3 optical density score in the treated eyes was increased by  $726 \pm 500\%$ . In

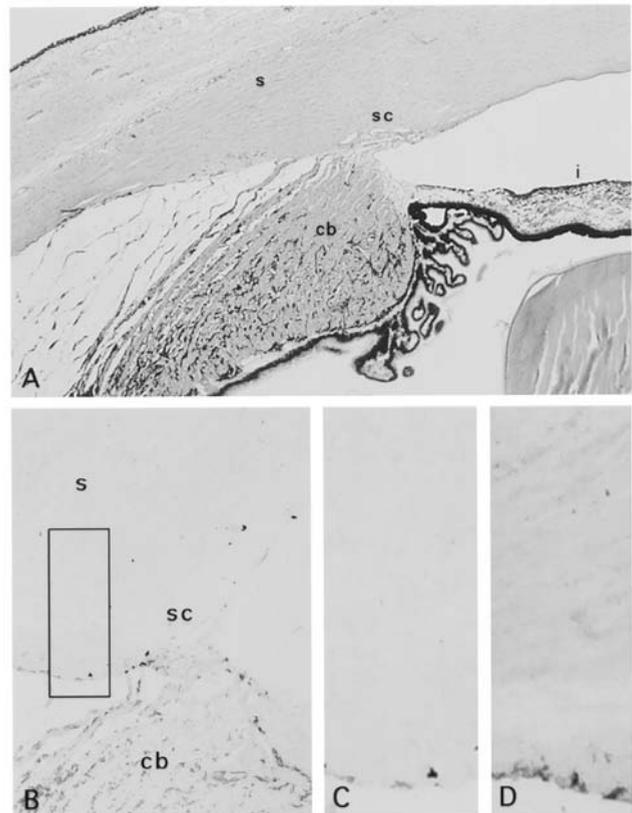


FIGURE 1

Anterior-segment tissues comparing hematoxylin and eosin staining (A) with MMP-1 immunoreactivity (B) containing sclera (s), ciliary body (cb), Schlemm's canal (sc), and iris (i). Dark areas in panel B indicate MMP-1 immunoreactivity. Box in panel B indicates scleral region shown at high magnification in panel C. D, Comparable area of sclera from eye that received topical PGF<sub>2 $\alpha$</sub> -IE shows increased MMP-1 immunoreactivity (magnification: A  $\times$  30; B  $\times$  39; C and D  $\times$  116).

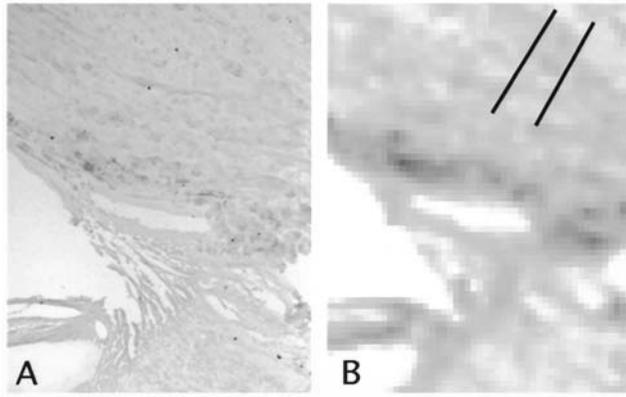


FIGURE 2

Comparison of bright field image of anterior segment (A) with densitometry image (B) showing placement of 2 measurement lines over sclera. Optical density along these lines was integrated and then mean optical density was determined by dividing the integrated score by the length of the measurement line (magnification  $\times 56$ ).

TABLE I: INCREASE OF MMP-1 IMMUNOREACTIVITY IN SCLERA OF 4 MONKEYS FOLLOWING 5 DAYS OF TOPICAL PGF<sub>2 $\alpha$</sub> -IE TREATMENT

MONKEY	CONTROL EYE <sup>o</sup>	TREATED EYE <sup>o</sup>	% INCREASE
1	0.0193	0.0240	24
2	0.0219	0.0458	109
3	0.0151	0.0230	51
4	0.0229	0.0386	68
Mean $\pm$ SD	0.0198 $\pm$ 0.0034	0.0328 $\pm$ 0.0112	63 $\pm$ 35

IE, isopropyl ester.

<sup>o</sup>Mean optical density.

TABLE II: MEAN INCREASE OF MMP IMMUNOREACTIVITY IN MONKEY SCLERA FOLLOWING 5 DAYS OF TOPICAL PGF<sub>2 $\alpha$</sub> -IE TREATMENT

MMP TYPE	ALTERNATE NAME	% INCREASE ( $\pm$ SD)	P VALUE <sup>o</sup>
MMP-1	Interstitial collagenase	63 $\pm$ 35	0.01
MMP-2	Gelatinase A	267 $\pm$ 210	0.005
MMP-3	Stromelysin-1	729 $\pm$ 500	0.02

IE, isopropyl ester.

<sup>o</sup> P value by Student's *t* test; N=4.

each case, the increases in the treated eyes were statistically significant when compared to the vehicle-treated eyes (Table II).

## 2. FP RECEPTOR GENE TRANSCRIPTION AND PROTEIN EXPRESSION IN HUMAN SCLERA

### FP Receptor Transcripts in Human Sclera

To confirm that human sclera tissue contained mRNA that encodes the prostanoid FP receptor, RT-PCR was performed with primers that were predicted to yield a

FP-specific product of 1,186 base pair (bp). Figure 3 shows an ethidium-stained agarose gel with the PCR products obtained from cDNA prepared using 3 different primer

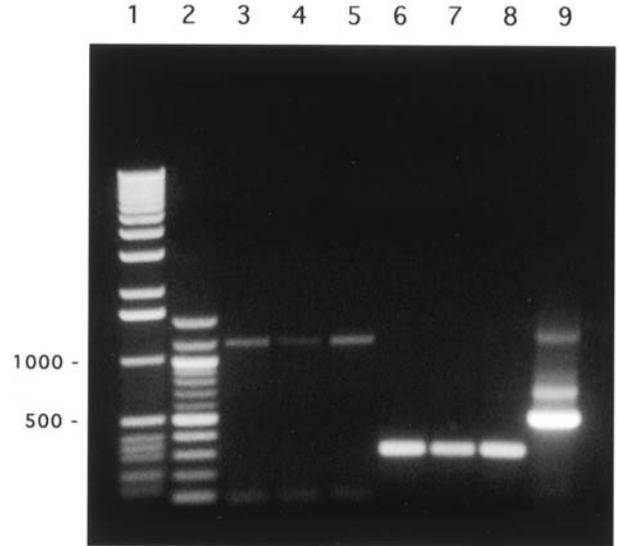


FIGURE 3

Reverse transcription-polymerase chain reaction (RT-PCR) of total RNA isolated from human sclera tissue and amplified with specific primers for human prostanoid FP receptor and for glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The products were separated by electrophoresis on a 1% DNA agarose gel. Standards (lanes 1 and 2) are 1 kilobase (kb) and 100 base pair (bp) DNA ladder (Gibco, BRL), respectively. Each reaction condition is represented. Lanes 3 (oligo DT alone), 4 (random primer alone), and 5 (oligo DT+random primer) yielded the predicted product (1,186 bp) after RT-PCR using total RNA isolated from donor sclera tissue, respectively. Lanes 6 (oligo DT alone), 7 (random primer alone), and 8 (oligo DT+random primer) represent the products obtained using specific primers for GAPDH from the identical RNA sample. The predicted product (299 bp) was obtained in each condition. The control (Gibco, BRL) for the cDNA synthesis reaction also yielded the predicted product size (500 bp, lane 9).

conditions from total RNA isolated from a single donor eye (lanes 1 through 3). Additionally, PCR products using primers specific for GAPDH that were predicted to yield a product of 299 bp were analyzed from the same cDNA samples used for amplification of the FP receptor transcript (lanes 4 through 6). The RT-PCR kit control was in vitro transcribed RNA from the chloramphenicol acetyltransferase (CAT) gene that was engineered to contain a 3' poly(A) tail. Gene-specific primers used were predicted to yield a CAT-specific product of 500 bp (lane 9). As shown, products of the expected sizes were obtained in all conditions with the RNA isolated from the donor sclera. Because the primers used for the amplification of the FP receptor mRNA were chosen to span an intron within the FP receptor gene, the PCR products did not result from the amplification of genomic DNA and are consistent with the presence of mRNA encoding a human prostanoid FP receptor.

### FP Receptor Protein in Human Sclera

Immunoreactivity for the FP receptor was observed within the cytoplasm of the scleral fibroblasts (Fig 4). The intensity of this granular staining was similar throughout the fibroblast processes that extended between the scleral collagen bundles. No staining of these collagen bundles was observed.

### 3. MEASUREMENT OF HUMAN SCLERAL PERMEABILITY AND MMPS WITH PROSTAGLANDIN EXPOSURE

#### Scleral Permeability

Scleral permeability was measured by assessing the flux of labeled dextrans across the scleral cultures in a Ussing chamber. Dextrans of different sizes were evaluated to model the potential differences among aqueous proteins of different sizes. As shown in Fig 5, flux across the scleral cultures incubated without PGs was  $1.5 \times 10^{-6}$  cm/second for 10 kDa dextran,  $0.7 \times 10^{-6}$  cm/second for 40 kDa dextran, and  $0.4 \times 10^{-6}$  cm/second for 70 kDa dextran. Moreover, these fluxes did not change among cultures incubated without PGs for 1, 2, or 3 days. In contrast, incubation with  $\text{PGF}_{2\alpha}$  significantly increased the flux of the 10 kDa tracer. These increases ranged from 21% to 124%, were dose-dependent, became larger as exposure time increased up to 3 days, and were significant for all concentration and tested time points ( $P < .05$ ). The flux of 40 kDa dextran also increased with increasing  $\text{PGF}_{2\alpha}$  and

exposure time; however, these increases ranged from 7% to 21%. These permeability increases were statistically significant only on day 3 in the case of 100 nM  $\text{PGF}_{2\alpha}$ , but were significant for 200 nM or 500 nM  $\text{PGF}_{2\alpha}$  on all 3 days. Similar to the 40 kDa dextran, the flux of 70 kDa dextran increased with  $\text{PGF}_{2\alpha}$  dose and exposure time by 5% to 28%. These increases were significant with longer treatments at 100 nM or 200 nM, and were significant with 500 nM  $\text{PGF}_{2\alpha}$  on all 3 days.

Incubation of scleral cultures with 17-phenyltrinor- $\text{PGF}_{2\alpha}$  also increased permeability of the scleral organ cultures to the labeled dextrans. Permeability to the 10 kDa tracer increased in a dose-dependent and time-dependent manner from 5% to 183% (Fig 6). These increases were significant for all conditions except 100 nM 17-phenyltrinor- $\text{PGF}_{2\alpha}$  exposure for 1 day. Permeability to the 40 kDa tracer increased in a dose- and time-dependent manner from 4% to 31%. These increases were significant at all concentrations tested on days 2 and 3. Permeability to the 70 kDa tracer increased from 9% to 24%. These increases were significant at all concentrations and times measured. Overall, the increases observed with 17-phenyltrinor- $\text{PGF}_{2\alpha}$  were similar to the increases observed with  $\text{PGF}_{2\alpha}$ . The exception to this was the larger permeability increase observed at 3 days with 100 nM 17-phenyltrinor- $\text{PGF}_{2\alpha}$  than with 100 nM  $\text{PGF}_{2\alpha}$ . PhXA85 generally induced moderately larger increases in scleral permeability than  $\text{PGF}_{2\alpha}$  or 17-phenyltrinor- $\text{PGF}_{2\alpha}$  (Fig 7). Flux of the 10 kDa tracer was increased by 45% to 213%. These increases were dose-dependent, became larger as exposure time increased up to 3 days, and were significant for all conditions. The flux of 40 kDa dextran also increased with increasing PhXA85 and exposure time; however, these increases ranged from 6% to 41%. These increases were significant for all conditions except 100 nM PhXA85 exposure for 1 day. Similar to 40 kDa dextran, the flux of 70 kDa dextran increased with PhXA85 dose and exposure time by 13% to 48%. Also, these increases were significant for all conditions except 100 nM PhXA85 exposure for 1 day.

#### Viability of Sclera

Survival of cells in the organ culture was assessed by measuring the exclusion of ethidium homodimer, a vital stain that binds to DNA. The standard for maximal viability was freshly obtained donor sclera, and the standard for complete loss of viability was donor sclera that had been exposed to 2% paraformaldehyde prior to ethidium homodimer exposure. As shown in Fig 8, viability for all cultures was about 83% on day 1, 81% on day 2, and 80% on day 3. Differences of viability among cultures exposed to 500 nM  $\text{PGF}_{2\alpha}$ , or 17-phenyltrinor- $\text{PGF}_{2\alpha}$  were less than 1% on all 3 days. This suggests that incubation with

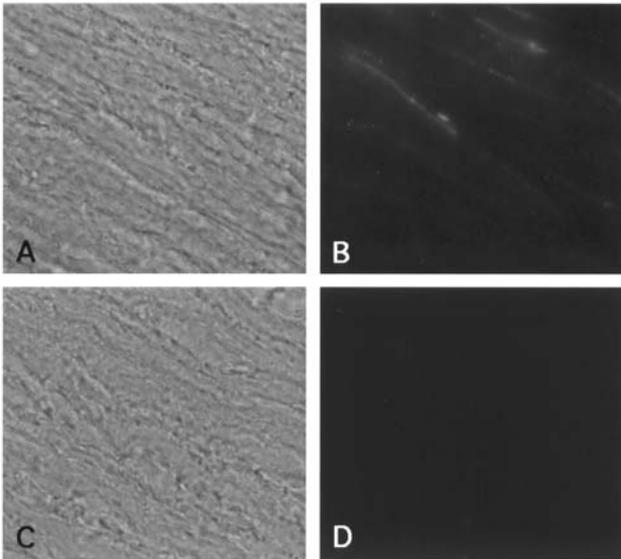


FIGURE 4

FP receptor immunoreactivity within human scleral fibroblasts (A, B) and staining control (C, D). For each specimen, the bright-field image (A, C) and the fluorescence image (B, D) are shown. Staining was similar throughout fibroblast processes that extended between the scleral collagen bundles. Control sections were processed without exposure to primary antibody (magnification,  $\times 280$ ).

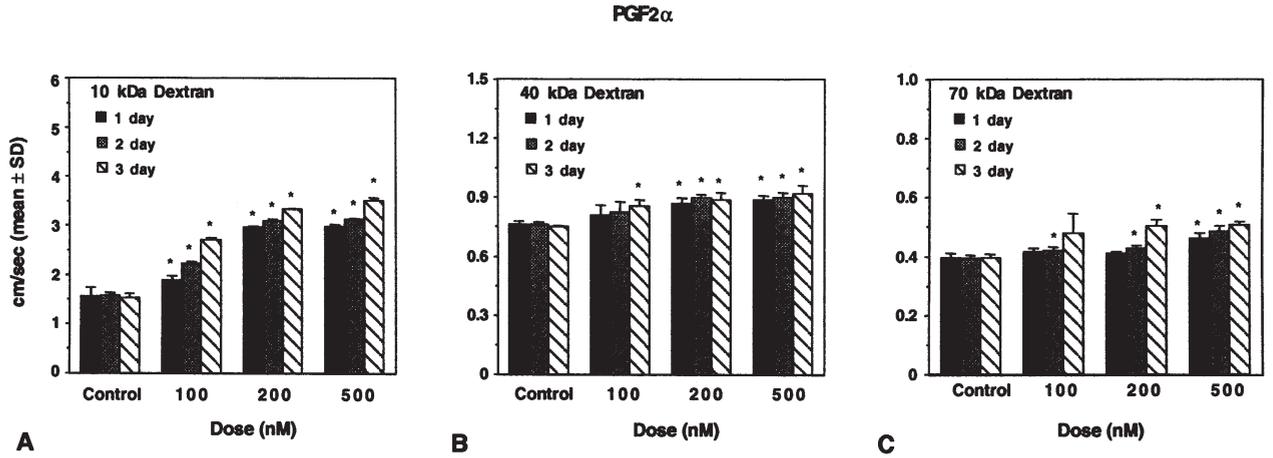


FIGURE 5

Scleral permeability after PGF<sub>2α</sub> exposure. Permeability determined by the transscleral movement of 10 kDa (A), 40 kDa (B), or 70 kDa (C) dextrans across treated sclera. Values represent mean (( 10-6 cm/sec) ± SD. Asterisk indicates *P*<.05 by the Student Newman Keuls test (N=4).

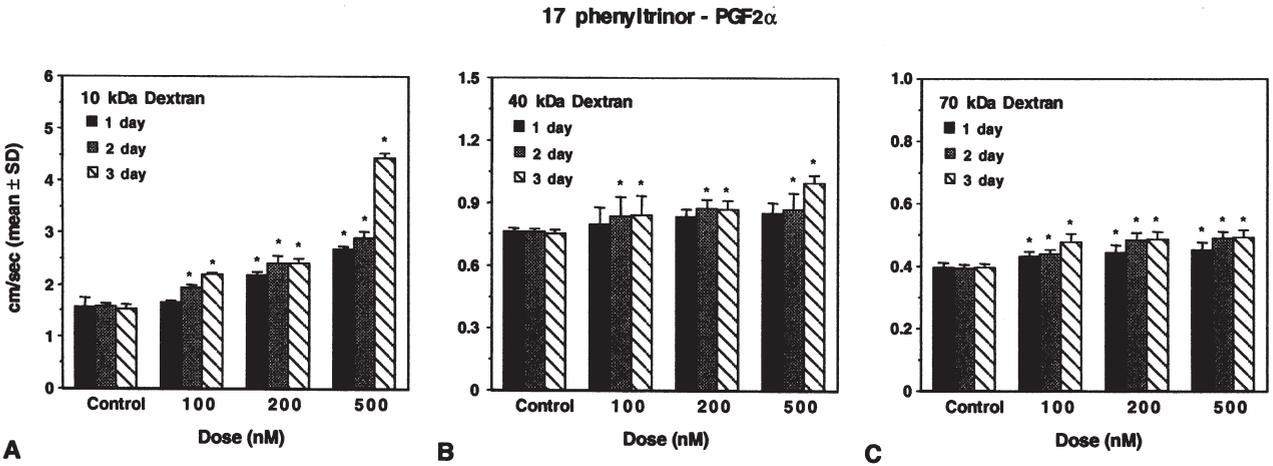


FIGURE 6

Scleral permeability after 17-phenyltrior-PGF<sub>2α</sub> exposure. Permeability determined by the transscleral movement of 10 kDa (A), 40 kDa (B), or 70 kDa (C) dextrans across treated sclera. Values represent mean (( 10-6 cm/sec) ± SD. Asterisk indicates *P*<.05 by the Student Newman Keuls test (N=4).

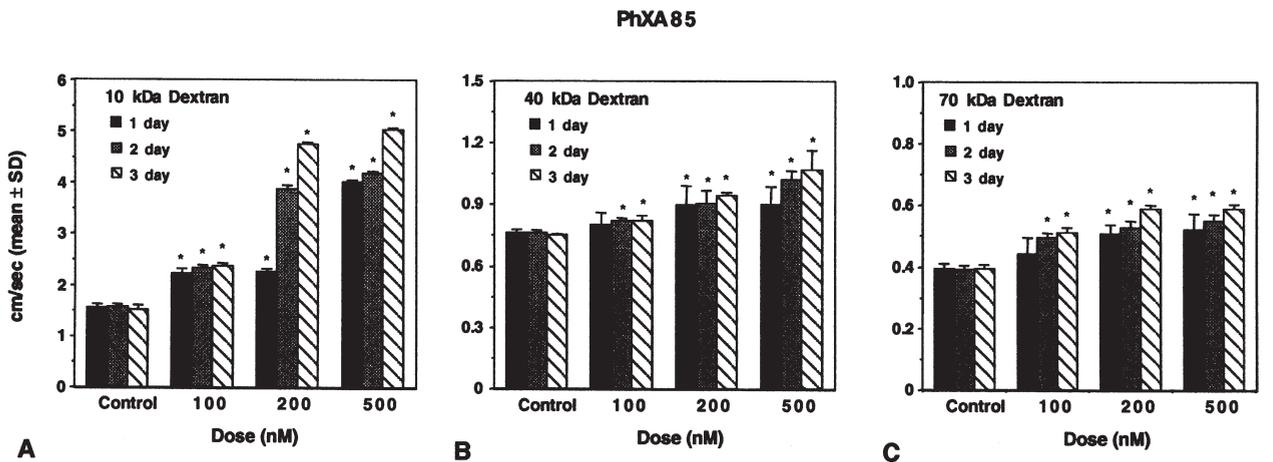


FIGURE 7

Scleral permeability after PhXA85 exposure. Permeability determined by transscleral movement of 10 kDa (A), 40 kDa (B), or 70 kDa (C) dextrans across treated sclera. Values represent mean (( 10-6 cm/sec) ± SD. Asterisk indicates *P*<.05 by the Student Newman Keuls test (N=4).

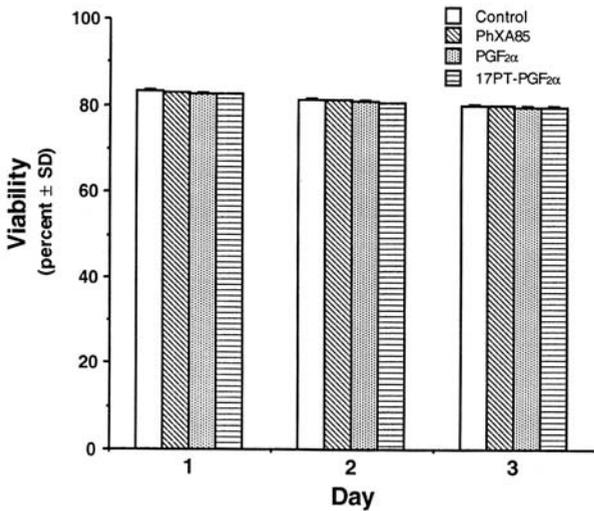


FIGURE 8

Cell viability within organ-cultured human sclera incubated for 3 days with vehicle, PGF<sub>2α</sub>, 17-phenyltrilor-PGF<sub>2α</sub>, or PhXA85. Concentration of each prostaglandin was 500 nM. Values represent mean ± SD (N=4).

these PGs for 3 days had minimal influence on cell survival in the scleral cultures.

#### Scleral Hydration

To evaluate whether changes in scleral hydration occur with the culture conditions, the water content in the scleral cultures was determined in scleral cultures exposed to HBSS for 4 hours at room temperature, to complete culture medium for 3 days at 37°C, or to complete culture medium for 3 days followed by 4 hours in HBSS. The mean water content, or scleral hydration, of fresh sclera was 3.05 ± 0.11 mg water/mg dry weight (N=5). As shown in Fig 9, scleral cultures incubated 4 hours in HBSS alone, in medium for 3 days, or in medium for 3 days followed by 4 hours in HBSS were insignificantly different from the fresh cultures ( $P < .05$ , Student Newman Keuls test). This indicated that these culture conditions did not alter hydration within the scleral cultures.

#### MMP Release Induced by Prostaglandin Treatments

One possible explanation for the observed increases in scleral permeability following exposure to the PGs is reduction in collagen content by MMPs. Hence, the media of scleral cultures incubated with PGF<sub>2α</sub>, 17-phenyltrilor-PGF<sub>2α</sub> or PhXA85 were assayed for changes in the concentration of MMP-1, MMP-2, and MMP-3. Among cultures incubated in control medium for 1, 2, or 3 days, there were no significant changes in the concentration of MMP-1, MMP-2, or MMP-3 (Figs 10 through 12).

Evaluation of MMP-1 in the media of the treated cultures showed moderate increases in cultures exposed to PGF<sub>2α</sub>, 17-phenyltrilor-PGF<sub>2α</sub> or PhXA85 (Fig 10). These increases ranged up to 37%, increased with time of

exposure, and were significant only for the higher concentrations and longer incubation times examined. Overall, there were slight increases of MMP-1 with increasing dose, and the effects of the different PGs tested were similar.

In contrast to MMP-1, increases in MMP-2 were much larger and ranged from 124% to 267% (Fig 11). These increases were significant in every condition examined and showed marked increases with increasing time of exposure. Overall, there were slight increases of MMP-2 with increasing PG concentration. The magnitude of the effects was least with 17-phenyltrilor-PGF<sub>2α</sub>, intermediate with PGF<sub>2α</sub>, and greatest with PhXA85.

MMP-3 concentration also increased in the media of cultures exposed to PGF<sub>2α</sub>, 17-phenyltrilor-PGF<sub>2α</sub> or PhXA85 (Fig 12). These increases ranged up to 96% and were larger than seen with MMP-1 but smaller than seen with MMP-2. These increases were clearly time-dependent, being generally insignificant on day 1 and significant on days 2 and 3. Dose dependence was clearly present with PhXA85 at every time point and less clear with PGF<sub>2α</sub> or 17-phenyltrilor-PGF<sub>2α</sub>.

#### 4. MEASUREMENT OF FIBROBLAST GROWTH FACTOR-2 PERMEATION THROUGH HUMAN SCLERA WITH PROSTAGLANDIN EXPOSURE

##### Time Course Analysis

The time course of FGF-2 penetration of sclera within the Ussing chamber was assessed by withdrawing a 40 μL sample from the test side at 30-minute intervals. As shown in Fig 13, the concentration increased linearly for the duration of the experiment.

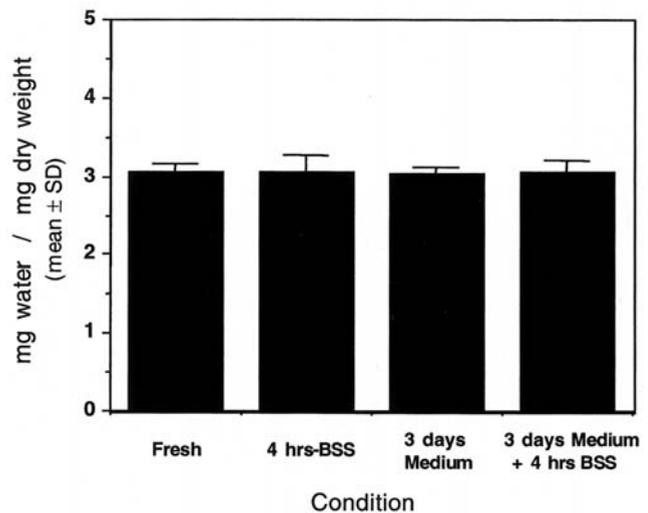


FIGURE 9

Evaluation of scleral hydration in fresh sclera, scleral organ cultures following incubation with Hank's balanced salt solution (BSS) for 4 hours (4hrs-BSS), tissue culture medium for 3 days (3days-Medium), or in culture incubated in medium for 3 days followed by 4 hours in Hank's balanced salt solution (3 days Medium + 4 hrs BSS). Values represent mean ± SD (N=5).

MMP-1

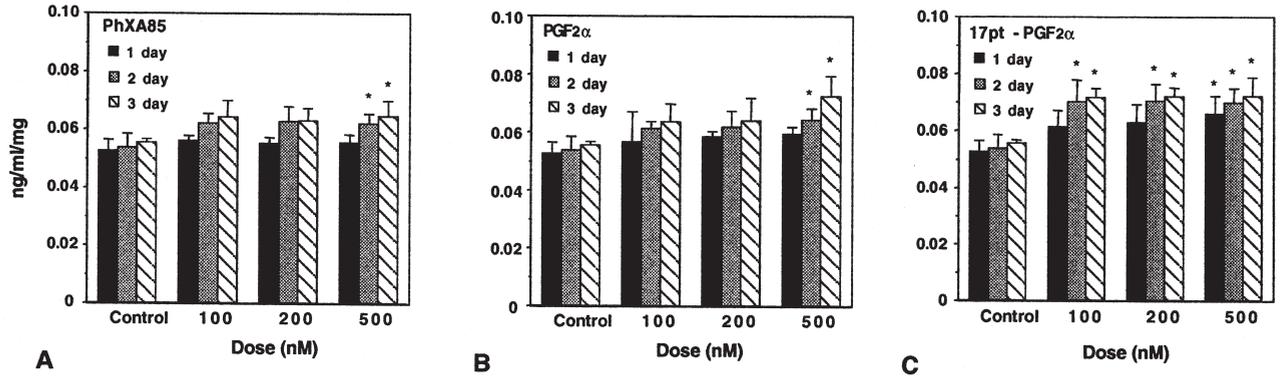


FIGURE 10

Concentration of MMP-1 in the medium of scleral organ culture exposed to PhXA85 (A), PGF<sub>2α</sub> (B), or 17-phenyltrininor- PGF<sub>2α</sub> (C) for 1 to 3 days as determined by ELISA. Cultures analyzed were from cultures generated from a 76-year-old male donor, a 66-year-old male donor, and a 45-year-old female donor (N=3). Values represent mean ± SD. Asterisk indicates P < .05 by the Student Newman Keuls test (N=4).

MMP-2

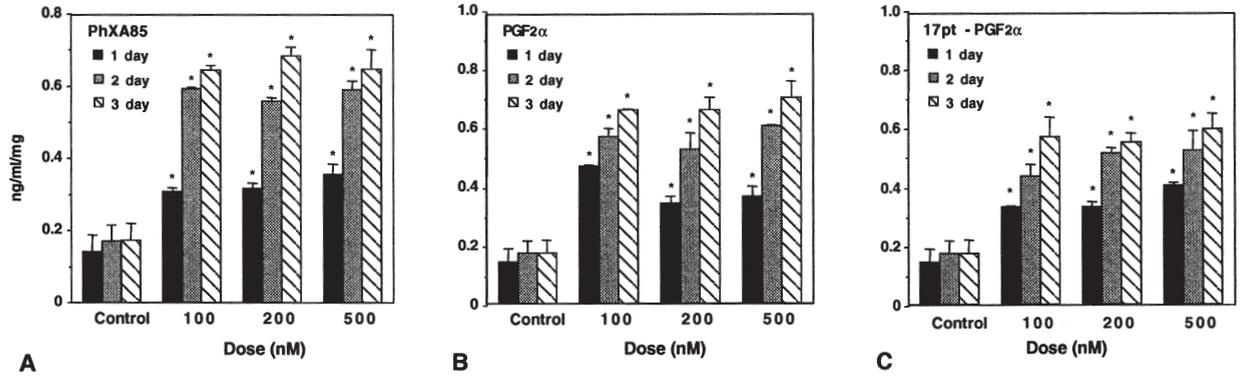


FIGURE 11

Concentration of MMP-2 in the medium of scleral organ culture exposed to PhXA85 (A), PGF<sub>2α</sub> (B), or 17-phenyltrininor-PGF<sub>2α</sub> (C) for 1 to 3 days as determined by ELISA. Cultures analyzed were from cultures generated from a 76-year-old male donor, an 80-year-old male donor, and a 66-year-old male donor. Values represent mean ± SD. Asterisk indicates P < .05 by the Student Newman Keuls test (N=3).

MMP-3

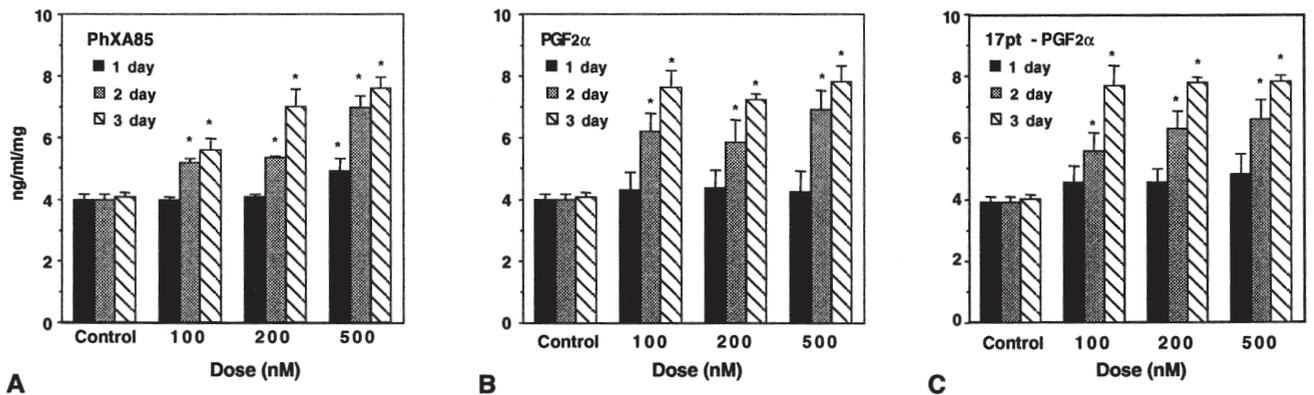


FIGURE 12

Concentration of MMP-3 in the medium of scleral organ culture exposed to PhXA85 (A), PGF<sub>2α</sub> (B), or 17-phenyltrininor- PGF<sub>2α</sub> (C) for 1 to 3 days as determined by ELISA. Cultures analyzed were from cultures generated from a 76-year-old male donor, a 66-year-old male donor, and a 45-year-old female donor. Values represent mean ± SD. Asterisk indicates P < .05 by the Student Newman Keuls test (N=3).

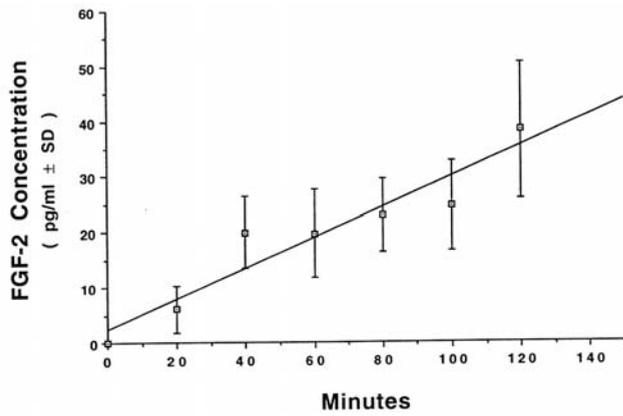


FIGURE 13

Time course of FGF-2 concentration in receiving Ussing chamber fitted with human sclera previously cultured for 3 days in control medium. Data presented as mean  $\pm$  SD ( $\times 10^{-8}$  cm/sec). Increase in concentration with time was linear ( $R^2=0.91$ ). Based on this, permeability was determined to be  $1.68 \times 10^{-8}$  cm/sec.  $N=4$  pairs of donor eyes. Mean age of donors was  $67.5 \pm 2.9$  (SD) years.

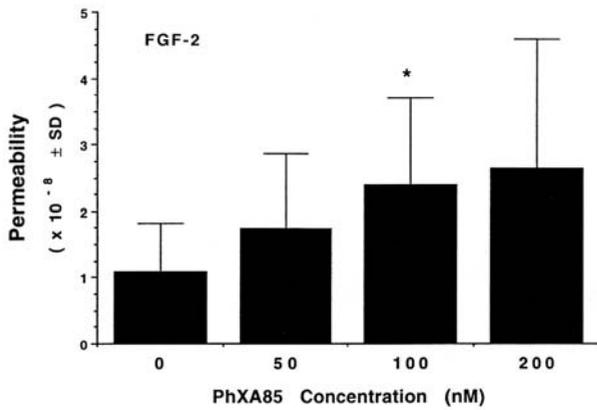


FIGURE 14

Scleral permeability to FGF-2 after exposure to various concentrations of PhXA85 for 3 days. Data presented as mean  $\pm$  SD ( $\times 10^{-8}$  cm/sec). Asterisk indicates  $P<.05$  by the Student Newman Keuls test.  $N=8$  pairs of donor eyes. Mean age of donors was  $71.8 \pm 6.9$  (SD) years.

#### Dose Response Analysis

Increasing the concentration of latanoprost acid in scleral explant cultures maintained for 3 days increased the permeability of both FGF-2 and 10 kDa dextran (Figs 14 and 15). FGF-2 permeability following 50 or 100 nM latanoprost acid was increased by an average of  $56 \pm 77\%$  and  $126 \pm 120\%$ , respectively (mean,  $\pm$  SD,  $N=8$ ). FGF-2 permeability in sclera incubated with 200 nM latanoprost acid was similar to sclera incubated with 100 nM latanoprost acid. In contrast, 10-kDa dextran permeability following 50, 100, or 200 nM latanoprost acid was increased by an average of  $50 \pm 24\%$ ,  $39 \pm 19\%$ , and  $48 \pm 24\%$ , respectively. The ratio of FGF-2 to 10 kDa dextran permeability ranged from 40-fold to 90-fold; however, there was no clear relationship between the magnitude of the ratio and the latanoprost acid dose.

## DISCUSSION

*The limits of the possible are enlarged.*

Ralph Waldo Emerson

In contrast to the sclera being "inert and purely supportive in function,"<sup>254</sup> these studies clearly demonstrate that it has the potential to be metabolically active, to be pharmacologically responsive, and to have other functions in addition to structural support. Moreover, PGs can directly induce sclera to undergo structural modifications that enhance transscleral permeability, a response that is likely mediated by FP receptors on scleral fibroblasts. These results may have important implications for the facilitation of macromolecule delivery to posterior segment tissues.

### I. TOPICAL PROSTAGLANDIN ADMINISTRATION REDUCES SCLERAL COLLAGEN BY INCREASING SCLERAL METALLO-PROTEINASES

The quantitative immunohistochemistry results show that topical treatment of monkey eyes with  $\text{PGF}_{2\alpha}$ -IE increased expression of MMP-1, MMP-2, and MMP-3 in the sclera adjacent to the ciliary muscle. Increased MMP biosynthesis could then reduce scleral collagens and other extracellular matrix molecules after treatment with topical  $\text{PGF}_{2\alpha}$ -IE. This reduction has been previously confirmed for collagen type I, collagen type III, and collagen type IV.<sup>82</sup> MMP-1 is known to hydrolyze a specific site found in collagen types I and III.<sup>109,110</sup> Likewise, MMP-2 is known to hydrolyze specific sites found in collagen type IV as well as in fibronectin. MMP-3 is known to hydrolyze specific sites found in collagen types III and IV, as well as

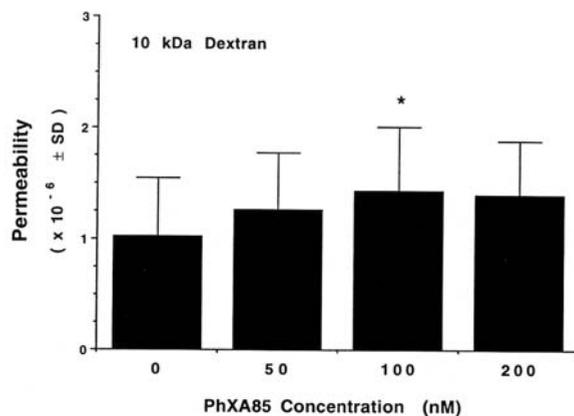


FIGURE 15

Scleral permeability to 10 kDa dextran after exposure to various concentrations of PhXA85 for 3 days. Data presented as mean  $\pm$  SD ( $\times 10^{-6}$  cm/sec). Asterisk indicates  $P<.05$  by the Student Newman Keuls test.  $N=8$  pairs of donor eyes. Mean age of donors was  $71.8 \pm 6.9$  (SD) years.

in fibronectin and laminin. Hence, the observed increases in MMPs-1, -2, and -3 suggest a concerted response leading to reduced scleral collagen. Other extracellular hydrolases also are likely to participate in the reduction of extracellular matrix. It should be noted that MMPs are secreted as inactive pro-enzymes that are subsequently activated by proteolytic truncation.<sup>111,112</sup> Also, MMP activity is regulated by the presence of tissue inhibitor of matrix metalloproteinases (TIMPs).<sup>113,114</sup> Each of the antibodies used can recognize both the proenzyme and the active enzyme. Thus, the magnitude of the increased MMP activity may be less than the magnitude of the increased immunoreactivity.

## **2. FP RECEPTOR GENE TRANSCRIPTS AND PROTEIN ARE PRESENT IN HUMAN SCLERA**

As the biologic activity of a drug is often mediated by a specific receptor, the observation of FP receptor transcripts and protein within human sclera suggests that FP receptor agonists can directly activate these receptors and initiate physiologic and pharmacologic responses. The predominant cell type in the sclera is the scleral fibroblast. Also present are vascular endothelial cells within the penetrating blood vessels. Scleral fibroblasts are interspersed among the collagen layers that make up the scleral stroma and biosynthesize scleral collagen. The immunohistochemical results in these studies confirm that FP receptor in sclera is present on the scleral fibroblasts. Cultured fibroblasts from other tissues are known to increase their production of MMPs following stimulation with certain peptides.<sup>115-117</sup> Hence, it is highly plausible that exposure of scleral fibroblasts to FP agonists may promote their biosynthesis of MMPs. The second cell type is the vascular endothelial cell of blood vessels penetrating the sclera. FP receptors have been detected in association with other ocular blood vessels.<sup>90</sup> However, previous studies indicate that specific FP receptor agonists have minimal effects on the permeability of intraocular blood vessels.<sup>118,119</sup>

## **3. PROSTAGLANDIN EXPOSURE INCREASES HUMAN SCLERAL PERMEABILITY AND MMPs**

Pharmacologic considerations of the permeability and MMP changes observed with the tested PGs further support involvement of FP receptor activation. The concentrations of PGF<sub>2 $\alpha$</sub>  and 17-phenyltrinor-PGF<sub>2 $\alpha$</sub>  tested were greater than the EC<sub>50</sub> for activation of the FP receptor.<sup>105</sup> It is possible that, if present, EP1 receptors also may have been activated by the PGF<sub>2 $\alpha$</sub>  or 17-phenyltrinor-PGF<sub>2 $\alpha$</sub>  treatments in this study as EC<sub>50</sub>'s for these agonists are 320 nM and 650 nM, respectively.<sup>105</sup> However, the response to PhXA85 is likely to reflect FP receptor activation, for

which the EC<sub>50</sub> is 100 nM, and not activation of EP1 or other PG receptors. The EC<sub>50</sub> concentrations for PhXA85 activation of PG receptors other than the FP receptor are at least tenfold higher than the highest PhXA85 concentration tested.<sup>105</sup> Hence, it is likely that the increased MMPs observed in the PG-treated scleral cultures were released by FP-receptor-mediated activation of scleral fibroblasts. These MMPs would be well positioned to initiate collagen remodeling within the scleral stroma that enlarged intrascleral supramolecular passages and thereby facilitated transscleral protein permeability. As the MMPs in the present experiments could accumulate in the closed culture system, whereas they might dissipate upon secretion in situ, the concentration of the MMPs measured may be greater than the concentrations that might occur in scleral interstitial fluid in situ.

The studies of dextran permeability indicate that PGs directly increase the permeability of human sclera in organ culture. This increase in permeability is accompanied by increased release of MMPs from scleral tissue. These changes are consistent with the reduced collagens observed in monkey sclera following topical PG treatment and suggest that remodeling of the scleral extracellular matrix may explain the increased permeability. Hydration analysis indicates that this response does not reflect any alteration of scleral hydration. Viability analysis indicates that this response is not associated with altered cell survival in the experimental system, nor is there any evidence of toxicity due to the PG treatments. These permeability changes are likely to be normal physiologic responses, as they are both dose- and time-dependent. That the PG treatments also increased release of MMP-1, MMP-2, and MMP-3 in these cultures suggests that the permeability changes may reflect a direct response of scleral tissue to PG exposure and that the mechanism of increased transscleral permeability likely reflects intrascleral collagen remodeling. This proposed model is well supported by the findings of Dan and Yaron,<sup>76</sup> who observed increased flow of saline across bovine sclera and thinning of rabbit sclera in response to focal application of clostridial collagenase, an MMP-1 analogue.

The permeability relationships of the various sizes of labeled dextran observed in the present control scleral cultures is similar to the permeability relationships<sup>64</sup> of these tracers previously observed in sclera freshly dissected from donor eyes. For example, the present study found that permeability of the 40 kDa dextran through the scleral organ cultures was 1.7-fold less than that of 10 kDa dextran. This is similar to the previous observation that 40 kDa dextran permeability is 1.4-fold to 3.8-fold less than 10 kDa dextran in freshly dissected sclera.<sup>64</sup> Likewise, the present observation that permeability of 70 kDa dextran in the scleral organ cultures was 3.7-fold less than

that of 10 kDa dextran is similar to the previous observation that 70 kDa dextran permeability was 2.6-fold to 4.2-fold less than 10 kDa dextran permeability in freshly dissected donor eye sclera.<sup>64</sup> These similarities suggest that hydrodynamic constraints to macromolecule movement through the scleral organ cultures were similar to freshly dissected donor sclera. Hence, the scleral cultures represent a reasonable model system in which to study modulation of transscleral macromolecule movement by PGs.

The greater increase in 10 kDa dextran permeability through PG-treated scleral cultures than was observed with 40 kDa or 70 kDa dextran suggests that PGs may alter the size of intrascleral supramolecular passages. Scleral collagen fibrils are organized into bundles that vary in their organization according to position near the outer or inner wall of the sclera.<sup>50-52</sup> Overall, the bundles vary in width and thickness, often give off branches, and intertwine with each other. At the outermost layers, there is substantial irregular intermingling of collagen fibrils in adjacent bundles. Like sclera, synthetic hydrogels contain substantial water content and long polymer units characterized by chemical cross-links and polymer entanglements.<sup>120,121</sup> Within pH-sensitive hydrogels, lower pH increases the size of pore channels through the matrix, while higher pH causes the gel network to swell with a resulting increase in the size of pore channels. Analysis of a pH-sensitive hydrogel confirmed that protein permeability is enhanced under conditions that increase the size of the pore channels.<sup>121</sup> Moreover, the magnitude of the permeability increase was greater with lower-molecular-weight proteins than with higher-molecular-weight proteins. This relationship among protein size, macromolecule permeability, and pore size also has been seen in hydrogels in which pore size was altered by changing the size of polymer subunits used to synthesize the hydrogel.<sup>121</sup> Hence, the greater permeability increases with the smaller dextran tracers that was observed in the PG-treated scleral cultures is consistent with enlargement of the intrascleral supramolecular passages.

The mechanism of increased permeability within the PG-treated scleral cultures is suggested by the increased amounts of MMP-1, MMP-2, and MMP-3 detected within the medium of the treated scleral cultures. Sclera contains collagen types I, III, VI, VIII, XII, possibly a small amount of collagen type V, as well as fibronectin.<sup>56,122-126</sup> Of these extracellular matrix components, MMP-1, MMP-2, and MMP-3 are known to cleave sites within collagen types I, III, V, and fibronectin.<sup>85,127</sup> Increased MMP-1, MMP-2, MMP-3, and MMP-9 has been found in cultures of human ciliary smooth muscle cells exposed to PGF<sub>2α</sub>, 17-phenyltrior-PGF<sub>2α</sub>, and PhXA85.<sup>107,108</sup> These treatments also induce reorganization of collagen type I, collagen type III, laminin, and collagen type IV within the

human ciliary muscle cultures.<sup>128,129</sup> Hence, increased MMPs within sclera are likely to mediate reduction of scleral collagens.

#### 4. TRANSSCLERAL PERMEATION OF FIBROBLAST GROWTH FACTOR-2 IS INCREASED WITH PROSTAGLANDIN EXPOSURE

The present results also indicate that exposure of human sclera to latanoprost acid, a prostaglandin analogue, increases FGF-2 permeability. This increase is dose dependent and increases with increasing exposure times. It is likely to reflect increased general permeability as it parallels increased permeability to 10 kDa rhodamine-labeled dextrans.

The greater permeability of 10 kDa dextran may be related to binding of FGF-2 to molecules within the sclera. These molecules include collagen types I, III, V, VI, and VIII and the glycosaminoglycans (GAGs) chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate, and hyaluronan.<sup>57,58</sup> Much of the chondroitin sulfate, dermatan sulfate, and keratan sulfate may be covalently linked to the proteoglycans decorin, biglycan, and aggrecan.<sup>58</sup> Immunoreactivity of each of these proteoglycans is distributed throughout the thickness of sclera.<sup>58</sup> It is well established that FGF-2 strongly binds to heparan sulfate (Kd=0.34 μM).<sup>130</sup> Recently, it has been shown that FGF-2 also can bind to dermatan sulfate (Kd=2.5 μM).<sup>131</sup> As each of these GAGs is present within sclera, it is possible that binding of FGF-2 to these extracellular matrix components could impede the movement of FGF-2 through the sclera.

Increased transscleral permeability to FGF-2 following PG treatments suggests that cotreatment with PGs could facilitate the use of FGF-2 to enhance survival of retinal neurons in glaucoma and other eye diseases. Previous studies have shown that FGF-2 can promote neuronal survival in vitro and in vivo.<sup>132,133</sup> Beneficial effects were observed with concentrations as low as 20 pg/mL. Moreover, intravitreal infusion of FGF-2 can promote neuronal survival following experimental axotomy, ischemia, neurotoxin treatment, or contusion of brain or spinal cord tissue.<sup>134-136</sup> However, infusion of FGF-2 can stimulate responses in many other tissues besides neural tissues that may be either beneficial or detrimental to the desired neural tissue response. There also may be specific requirements for additional factors in the case of retinal ganglion cells.<sup>137</sup> Further, systemic infusion of FGF-2 also can stimulate responses in many nonneural tissues that may be either beneficial or detrimental to the desired neural tissue response.<sup>138</sup> Hence, the ability to enhance scleral penetration of FGF-2 using PGs may allow a smaller concentration of FGF-2 to be delivered directly to the eye with consequent reduction of systemic absorption.

**SIGNIFICANCE OF INCREASED PERMEABILITY FOR INTRAOCULAR DRUG DELIVERY**

Assessment of drug diffusion in vitro permeability studies is a useful approach in the field of ocular pharmacokinetics to estimate drug movement for in vivo conditions. Intraocular absorption of a drug is directly related to the transport characteristics of absorptive tissues of the eye, such as the sclera. The increased scleral permeability following PG exposure may have implications for facilitating delivery of therapeutics to the posterior segment of the eye. For example, growth factors that may facilitate retinal neuron survival range from 10 kDa to 40 kDa (Table III).<sup>1,16,139</sup> Because of their size, these molecules cannot readily cross the cornea. Hence, a noncorneal absorption route through sclera may facilitate usefulness of such therapeutics.

It may not be sufficient only to increase scleral permeability to large molecules, as there also may be other limiting factors for drug absorption in the posterior seg-

**TABLE III: MOLECULAR WEIGHT AND SIZE OF SEVERAL NEUROTROPHIC PROTEINS**

MOLECULE	MOLECULAR WEIGHT (DA)	MOLECULAR RADIUS (NM) <sup>o</sup>
Fibroblast growth factor-2 (FGF-2)	18,000	2.1
Ciliary neurotrophic factor	22,800	2.3
Nerve growth factor-β	26,000	2.5
Brain-derived neurotrophic factor (dimer)	27,200	2.5
Neurotrophin-3 (dimer)	27,200	2.5
Neurotrophin-4 (dimer)	28,000	2.5

<sup>o</sup>Estimated.

ment. Orbital clearance, intraocular pressure, uveoscleral outflow, and choroidal blood flow might each limit drug access to the target tissues. Blood-ocular barriers, especially the blood-retinal barrier, also may be important.<sup>140-144</sup> However, the integrity of the blood-ocular barriers can be disrupted under certain conditions.<sup>17,145,146</sup> As an example, fluorescein (MW, 376) particles that are not bound to albumin can pass through the spaces between the endothelial cells of the capillaries of the choriocapillaris, but normally they cannot leak through the retinal pigment epithelium and zonula occludens between adjacent retinal pigment epithelial cells. Fluorescein in the choroid cannot enter the neurosensory retina unless there is a defect in the retinal pigment epithelium. Therefore, if the tight junctions of the blood-retinal barrier preclude retinal drug absorption of a transsclerally delivered drug, it may be possible to minimally damage retinal pigment epithe-

lial cells and transiently facilitate macromolecular movement from the suprachoroidal space to the retina.<sup>17,145</sup>

While the blood vessels in the optic nerve head, by virtue of tight junctions, have a blood-optic nerve barrier, it is significant that the optic nerve head itself is not thought to possess a blood-ocular barrier.<sup>147,148</sup> The border tissue of Elschnig (separating the peripapillary choroid and optic nerve head) allows choroidal interstitial tissue fluid to leak into the optic nerve head from the peripapillary choroid. Horseradish peroxidase (42 kDa) can enter the monkey optic nerve head from blood.<sup>148</sup> Glial cells at the edge of the optic disc form a barrier that prevents the spread of peroxidase into the retina.

Despite these possible limitations, the prospect of increased transscleral permeability by PG cotreatment may allow sufficient transscleral transport to provide delivery of therapeutics to posterior segment tissues in concentrations not otherwise possible. This may be particularly important for glaucomatous eyes, as elevated intraocular pressure may reduce scleral permeability, particularly for macromolecules.<sup>51</sup> Besides being important for macromolecule delivery to the posterior segment, transscleral fluid movement through scleral stroma may be important for uveoscleral outflow. Further study is needed to determine if PG-induced increases in transscleral permeability contribute to increased uveoscleral outflow facility and decreased intraocular pressure observed following topical PG treatments.

**CONCLUSION**

*Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.*

Winston Churchill

The sclera is not inert, but metabolically active. PG treatment can increase scleral MMPs and facilitate transscleral permeability. This can promote the transscleral movement of molecules as large as 70 kDa and may enhance transscleral delivery of a number of different ocular drugs.

Several findings reported here provide support for a series of cellular and molecular events that could explain the mechanism of this response. These findings include observation of a concomitant increase in the amount of MMPs within the sclera of PG-treated monkey eyes, the presence of FP receptor and protein within human sclera, increased MMPs within the medium of human scleral cultures incubated with PGs, and increases in the amount of FGF-2 permeation within human scleral cultures exposed to increasing concentrations of latanoprost acid. Decreased collagen type I and III has been observed previously in monkey sclera and ciliary muscle following repeated topical PG treatment.<sup>52</sup> Moreover, induction of

c-Fos, MMP synthesis, and collagen reduction in ciliary muscle cell cultures exposed to PGs also have been described.<sup>128,129,149</sup> Together, these observations suggest a cellular mechanism for the increased transscleral permeability occurring with PG exposure. As summarized in Fig 16, a PG diffuses into the scleral stroma following topical or periocular treatment. Within the sclera, it then binds to FP receptors on scleral fibroblasts. This triggers a cascade of molecular events that increase MMP gene tran-

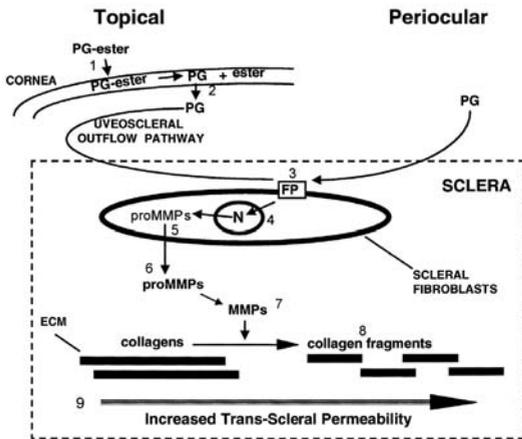


FIGURE 16

Model of FP receptor agonist action on sclera that results in increased transscleral permeability. FP receptor agonists (indicated by PG) can gain access to sclera either via topical drops (in which the PG is linked to an ester group to enhance transcorneal permeability), and then travel to sclera by uveoscleral outflow, or directly by periocular placement, as shown. Topical PG-ester is hydrolyzed as it passes through the cornea (1) into the anterior chamber (2). PG arriving at the sclera binds to FP receptors on scleral fibroblasts (3) and triggers signals that lead to increased MMP gene transcription (4) and proMMP biosynthesis (5) and secretion (6). Upon extracellular activation (7), the MMPs initiate collagen degradation (8) that results in increased transscleral permeability (9).

scription and lead to increased proMMP biosynthesis and secretion. Upon activation, the MMPs alter scleral collagen, which increases scleral permeability.<sup>69</sup> In this way, cotreatment with PGs may induce pharmacologic alterations of the sclera that promote transscleral delivery of peptide therapeutics. This could be useful for ameliorating some diseases of the posterior segment of the eye.

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