Editorial

PERK Director Responds

Dr. Neumann's remarks were originally delivered during a CLAO “pro-con” symposium at the American Academy of Ophthalmology in 1985. Dr. Neumann had the “con” point of view, so most of his remarks are critical. Dr. Neumann compared the PERK study to the material reported by himself, Osher, and Fenzel, which made an important contribution by reflecting early experience in the development of radial keratotomy in the United States.1

Purpose of PERK
We designed the PERK study to test a single well-defined technique of radial keratotomy as done by ten surgeons on at least one eye of each patient and to study the outcome for 5 years. It was not the goal of the study to develop improved surgical techniques or to prove that the PERK technique was better than others.

Design and Protocol
Dr. Neumann states that “The principle limitation of the PERK study is the rigidity of the surgical protocol.” On the contrary, this is PERK’s greatest strength.2 The PERK study was designed according to the principles of modern clinical trials,3,4 the cornerstone of which is a clearly defined protocol, written in advance and adhered to throughout the study.

By defining the exact surgical technique and by using it on all patients, the PERK study details exactly how the results are obtained and allows other investigators to replicate the surgery and the study—a basic tenet of the scientific method. Dr. Neumann's study, on the other hand, utilizes a hodgepodge of evolving surgical techniques that included seven different patterns of incisions done with three different metal knife blades. No criteria were spelled out in his article for the assignment of the diameter of the optical zone or for the selection of the number of incisions. The location of the preoperative paracentral pachymetry reading used to set the blade length was not specified. No mention was made of how preoperative variables such as the amount of myopia or patient age were used in selecting in the surgical plan. Therefore, one does not know exactly how the results were achieved and it would be impossible to replicate his study as published.

Dr. Neumann seems to criticize the PERK study for not using the results of the first eye as the basis for operating on the second. In fact, the protocol required patients to wait 1 year between surgery on their first and second eyes to allow the refraction to stabilize more than it would by 3 to 6 months. The protocol used the result on the first eye at 1 year as the basis for designing the surgical technique for the second eye. We reported the results at 1 year in only the first eye of each patient because we adhered to a basic premise of prospective clinical trials in ophthalmology: that only one eye of each patient should be included in a specific study group to avoid a “double dose” from a single patient, especially under-responders or over-responders. Dr. Neumann included two eyes of 48% of his patients.

Consistency of clinical examination is important in any clinical trial. For example, the PERK study used cycloplegic refractions, but Dr. Neumann reported a mixture of manifest and cycloplegic refractions.

Dr. Neumann criticizes the PERK study for including the learning curve of all but one surgeon. In fact, three of the surgeons had extensive experience with radial keratometry before commencement of the study; seven had completed corneal fellowships. All surgeons excluded their first ten cases so that the learning curve would be a minimal part of the PERK results; Dr. Neumann included his. Dr. Neumann's own data showed that his learning curve flattened somewhere during the first 20 cases; that flattening could easily have occurred at the end of the first ten. There were no statistically significant dif-
ferences in the results among the nine PERK centers, suggesting that the surgeons were able to follow the protocol with similar skill.

**Surgical Technique**

Dr. Neumann cites "limitations in (the PERK) surgical technique." Far from being limited, the PERK surgical technique utilized the three basic components most commonly used by surgeons presently doing radial keratotomy in the United States: intraoperative ultrasonic pachymetry, a diamond-bladed micrometer knife, and eight centrifugal incisions. By contrast, many of the techniques in Dr. Neumann's study have either fallen into disuse or are employed by a minority of surgeons: retrobulbar anesthesia, metal-bladed knives, optical pachymetry, centripetal incisions, and elliptical trepanes or parallel incisions for astigmatism.

In terms of safety, the PERK study reported no scars within the central clear zone, contrasted to 13% in Neumann's study, and perforations in less than 2% of eyes, contrasted to 26% in Neumann's study. With comparisons like these, the PERK technique can hardly be considered "limited."

Dr. Neumann criticizes the diameter of the optical clear zones used in the PERK study, stating that 0.25-mm increments were not used—but he did so in only 10% of cases—and that the clear zone markers did not extend outside the range of 3.0 to 4.0 mm—but his did so in only 4% of cases.

**Results**

Dr. Neumann labels the PERK study "deficient" because it limited the range of preoperative myopia to between 2.00 diopters and 8.00 diopters (D) and because the surgical technique was less effective than his in correcting higher myopes. Clearly, defining a study population is not a deficiency. We did not think the PERK technique would be effective for higher myopes, so we excluded them.

He is correct in pointing out that the PERK technique was inadequate for many of the patients with myopia of -4.50 to -8.00 D. However, these less-than-desirable results do not detract from either the quality or the meaningfulness of the PERK study. In fact, they allow modification of the specific technique to improve the results for such patients in the future, such as making deeper incisions, considering the age of the patient, and varying the number of incisions. In contrast, Dr. Neumann's study did not indicate the surgical technique used on the patients with a poor result, and therefore, there is no way for the reader to identify the techniques that were inadequate or to suggest improvements.

To learn from our mistakes, we must know what they are.

Another way to compare studies of radial keratotomy is to compare the results predicted by regression analysis with those actually obtained. The PERK study shows a similar degree of predictability when compared to the studies of Arrowsmith and Marks and of Deitz and Sanders. The percentage of patients with less than 1.00 D difference between predicted and actual change in refraction was 69% in PERK (Lynn et al, unpublished data, 1986) and 65% in Arrowsmith and Marks and for 1.50 D the difference was 86% in PERK and 94% in Deitz and Sanders (3-month follow-up).

This striking similarity demonstrates that the PERK study is not "deficient" when compared to other major studies. Dr. Neumann's published data are inadequate to compare predicted and achieved results.

**Factors Affecting Outcome**

Dr. Neumann criticizes the PERK study for not considering the effect of "corneal elasticity, corneal curvature . . . age, sex, and intraocular pressure . . . factors that are now recognized to affect the surgical outcome." He is correct that none of these variables was used in the preoperative PERK protocol. Indeed, none of these variables was described as a preoperative variable in Dr. Neumann's study. Contrary to his statement, Dr. Neumann's own analysis indicated that corneal curvature and preoperative intraocular pressure did not affect his surgical results.

Our unpublished data (Lynn et al, 1986) and subsequent studies of preoperative factors have shown only patient age as a major determinant of the outcome 1 year after surgery, with older patients achieving greater effect—an observation also made retrospectively by both Dr. Neumann and the PERK study. Of course, extreme values of other factors may affect outcome.

**Follow-up and Statistical Analysis**

The strength of—and greatest challenge for—any long-term study is to maintain the patient population for the duration of the follow-up. Of the 435 eyes in the PERK study, 99.5% were followed for the first year. By contrast, Dr. Neumann followed only 80.5% of the patients. What was the outcome in the other 20%? We don't know. One out of five was missing!

Dr. Neumann criticizes the PERK study for combining the 6-month data on reoperated eyes with the 1-year data on the other eyes. Since the goal of the PERK study was to test the effect of only a single operation, using 6-month data was preferable to excluding these cases (which were the ones with the worst outcome) or—as Dr. Neumann did—including the results after the second operation. Dr. Neumann did not specify in his report which cases had two operations.

The statistical methods used in the PERK study are those commonly applied in clinical trials. The PERK refraction results are presented in 0.50-D steps for each central clear zone group, so that the outcome of each technique is
very clear. In contrast, Dr. Neumann's major results are presented as unorthodox arithmetic neologisms, including an "efficiency quotient" and a "total excursion." It is difficult to determine the outcome of the surgery; for example, his report does not give the percentage of eyes that had a final refraction within 1 D of emmetropia. Dr. Neumann also offers some unusual definitions, such as that for "undercorrection," which he defines as less than 50% correction of the original myopia. Therefore, an 8.00 D myope who has a residual refractive error of −3.00 D would not be considered undercorrected.

Dr. Neumann contends that the visual acuity is the true measure of the outcome of radial keratotomy. I disagree, because the visual acuity alone can be misleading. For example, in the PERK study, patients with an uncorrected visual acuity of 20/20 at 1 year after surgery had refractive errors that ranged from approximately −1.50 D to +3.00 D. Although the visual acuity outcome in this group was satisfactory, the refractive outcome often was not. In fact, 25% of the patients that saw 20/20 were overcorrected by 0.62 D to 3.00 D.6

I agree fully with Dr. Neumann that there is not a direct correlation between the change in refraction, keratometry, and visual acuity, as documented in both his study1 and the PERK study.5 I also agree that the patient's subjective response should be evaluated, as was done in the PERK study by a formally-prepared, field-tested psychometric examination.9

Cost of Research

Dr. Neumann observes that the PERK study was expensive. In scientific investigation, as in life in general, one gets what one pays for. Informal trials done with inadequate preoperative planning, inadequate clinical and biostatistical personnel, and inadequate follow-up are likely to produce inadequate results. The fact that such studies are cheaper is no advantage; in fact, they may be a waste.

All multicenter prospective clinical trials are extremely expensive;6 the PERK study is no exception. The quality of the results from the PERK study easily justifies its expense, particularly when one considers that some 11 million myopes in the United States are potential candidates for radial keratotomy—a cost of $2.30 each, according to Dr. Neumann's figures. An individual deciding whether or not to have radial keratotomy would surely consider the information in the PERK study worth the price of a Big Mac, fries, and a coke.

Consider the relative cost of the PERK study compared with the money spent by patients for the procedure. Approximately 150,000 patients (two eyes each) have had radial keratotomy procedures done in the United States at a cost of $1,500 per eye; a total of $450 million has been spent by patients and received by ophthalmologists. The $4,783,000 cost of the PERK study cited by Dr. Neumann is 10.6% of this amount. Surely, this is a reasonable ratio spent on the scientific study of a relatively new procedure.

To keep expenses down, none of the physicians in the PERK study charged either the patients or the government for their services. In an era when volunteerism on behalf of the public good is in vogue, these physicians stand as sterling examples. Similarly, recognizing the need for more information about radial keratotomy, a number of other ophthalmologists have invested their personal time, resources, and money in the study of this procedure.

Conclusion

The truth about radial keratotomy comes from many quarters—individual experience, informal studies, and formal trials—as continued on page 205

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demonstrated over the past century. In modern times, we are most likely to discover the truth if we adhere to the highest principles of scientific clinical experimentation and investigation, and if we overcome the myriad frustrating obstacles that the real world throws in the way of applying these principles, as has the PERK study.

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References

Prednisolone acetate in a combination. Poly-Pred® (prednisolone acetate, neomycin sulfate, polymyxin B sulfate)
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INDICATIONS AND USAGE: A steroid/anti-inflammatory combination is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical radiation, thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-inflammatory component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

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CONTRAINDICATIONS: Epithelial herpes simplex keratitis (identicid keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of the ocular structures. Hypersensitivity to a component of the medication. (Hypersensitivity to the antibiotic component occurs at a higher rate than for other components.)

The use of these combinations is always contraindicated after uncomplicated removal of a corneal foreign body.

WARNINGS: Prolonged use may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If these products are used for 10 days or longer intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients. Employment of a steroid medication in the treatment of herpes simplex requires great caution.

There exists a potential for neomycin sulfate to cause cutaneous sensitization. The exact incidence of this reaction is unknown.

PRECAUTIONS: The initial prescription and renewal of the medication order beyond 20 milliliters should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and where appropriate fluorescein staining. The possibility of persistent fungal infections of the cornea should be considered after prolonged steroid dosing.

ADVERSE REACTIONS: Adverse reactions have occurred with steroid/anti-inflammatory combination drugs which can be attributed to the steroid component, the anti-inflammatory component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available.

Reactions occurring most often from the presence of the anti-inflammatory ingredients are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage: posterior subcapsular cataract formation and delayed wound healing.

Secondary infection: The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly susceptible to develop coincidently with long-term applications of steroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

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