Letters to the Editor

"Fool's Gold, The Alchemist's Pot, Psychophysics and Glaucoma"

To the Editor:

Harry Quigley recently pointed out, to the chagrin of all psychophysicists, that before visual field changes are recorded in glaucoma, half of the optic nerve fibers already are dead.¹ Even if Quigley is off by a factor of 2 or 3, we should be ashamed of ourselves.

Why aren't we making more of a contribution to the early diagnosis of glaucoma? Something must be wrong with certain of our assumptions. In short, are we seeking the wrong answer to the right question or vice versa? Is it still another case of fool's gold, the alchemist's pot, or the Holy Grail?

At a meeting of the International Perimetric Society a few years ago, a number of us presented papers, all on the same theme.² We all agreed that early visual changes in glaucoma exhibited fluctuant behavior in different parts of the field; and that at least initially these functional changes are reversible. Thus, there are temporary remissions; and a good bit of the nerve fiber bundle layer or retina is involved.

Like everybody else, I have watched test after test, presented for consideration by the clinical cognoscenti, fall by the wayside. Glaucoma seems to affect everything to some degree, whether it be flicker, contrast sensitivity, interference acuity, color vision, as well as the more classical kinetic and static fields. We look for the Holy Grail of that special test that will reveal the early changes first. Yet, generally we conduct our tests clinically in an inordinately poor manner, and when assessing the same test location on multiple occasions. Thus, static perimetry has flourished in the ninteenth century. We come to realize that more detailed local analysis offers advantage in early diagnosis when dealing with the plateau region of the field, and when assessing the same test location on multiple occasions. Thus, static perimetry has flourished in the last generation; and because these techniques are easier to automate, this has become the dominant format in most new automatic perimetric devices.⁸

For reasons which are inexplicable, field testing has been remarkably resistant to change, even in the new automated versions. The basic psychophysics associated with visual testing in perimetry was worked out in the nineteenth century. We come to realize that more detailed local analysis offers advantage in early diagnosis when dealing with the plateau region of the field, and when assessing the same test location on multiple occasions. Thus, static perimetry has flourished in the last generation; and because these techniques are easier to automate, this has become the dominant format in most new automatic perimetric devices.⁸

Will our search for the magic test that will reveal the very first changes in glaucoma be successful? The answer is probably no. If, for example, clinicians will

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not calibrate or control lighting, we must forget subtle
tests of color.3 If standard lighting, visual correction,
and pupil size are not controlled or provided, contrast
sensitivity testing may not be practical.45

At recent symposia of the International Perimetric
Society (Sacramento, CA, 1982) and the Glaucoma
Society (San Francisco, CA, 1982), it became imme-
diately evident that the very first changes associated
with a nerve fiber bundle defect were rather local in
nature, and could be missed by “survey” approaches.
This point was made very nicely in papers by A. Heijl
and P. Airaksinen.9,10 If they knew exactly where to
look, using careful static procedures, they could find
early changes. Knowing where to look was based on
careful use of the Hoyt et al11 technique for finding
anomalous nerve fiber bundles by using red-free
ophthalmoscopy and retinal photography (also see
Ref. 12).

In a disease where there are fluctuant events, that
is, local changes that may exhibit exacerbations and
remissions (which reveal themselves at different points
and at different times during the early phases of the
disease), it is very hard to say that one test or another
showed the very first changes. To wait for permanent
field defects is to wait too long. What is called for is
great care in using established methods for central
screening, with concepts of false positives and negatives
fully understood by the practitioner when he performs
the test. The practitioner needs to ask how careful is
fixation monitored; he needs to determine if the patient
is focused in the cupola; he must question the numbers
and the locations of points that are screened across a
grid in the central 30°;13 and how close to static thresh-
holds should the individual be tested if suprathreshold
testing is used.18

Since the mid-sixties, I have taken another track in
my own work, which seems not to be fully appreciated
and which can be highly complimentary. Rather than
looking for the magic test, I have tried to develop
localizing tests, that is, tests that are biased in their
design such that they help define anomalies at specific
loci in the visual pathway. I honestly feel this is the
way to go. Localizing tests which help define changes
in specific layers are at least biased towards the affected
areas in most anomalies. Thus, in glaucoma, tests that
are biased towards changes in the inner plexiform layer
and the ganglion cell layer, offer particular advantage.14-17
In our armamentarium, this would include the sustained- and transient-like functions and the
flashing repeat static test (FRST).14-17 In other systems,
recent studies of patterned ERGs (suggesting ganglion
cell origin) seem to offer good opportunities for the
future.15,18 Drance and Heijl’s argument for long-term,
time-dependent changes in glaucoma in some indi-
viduals (based on a time-varying factor that is appar-
ently different than that which we have described for
other forms of optic nerve disease) may be useful,19
but practically, given the duration of their test, and
the fact that one must select a given point in the field
to perform it (and this may be a very local disease)
suggests that it will not be a practical clinical test in
terms of effective utilization of time.

Thus, rather than looking for the magic test, let us
look at established tests and the probabilities of de-
etection and accuracy with which these tests are applied
on the one hand, and on the other hand, let us look
at tests which bias towards affected local zones of
change where the disease process is most effective in
altering function. No one of us who performs these
tests is such an egotist that we feel that ours is the
only, or the best, or the unique test. Rather, these are
tests which have been shown to work. Let us use tests
that can be transferred readily to the clinic with relative
ease of calibration. Frankly, clinicians in the field will
not maintain Bureau of Standard or even laboratory
conditions, nor should we expect them to do so.

In short, we have been pursuing the wrong goals
with the wrong hopes. The path may be actually quite
a bit simpler, if only rational techniques are applied.

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The X, Y, Z Hypothesis of Corneal Epithelial Maintenance

To the Editor:

For the past few years, studies of corneal epithelial healing have focused on the changes that occur in the remaining epithelial cells and their substrate following acute epithelial removal. The processes of epithelial cell sliding, proliferation, and replication have been documented in the past, and more recent work has illuminated additional details of these responses to injury. These studies have produced useful generalizations that help in understanding the pathologic processes responsible for corneal epithelial defects in humans. However, we would suggest that a fresh look at the factors involved in corneal epithelial maintenance may serve to initiate new experiments and new observations which may further advance the therapy of corneal epithelial failure.

The mass of corneal epithelium probably does not change under normal circumstances. As shown in Figure 1, the corneal epithelial cell mass can be viewed as the resultant of three separate, independent phenomena. We have termed these: X, the proliferation of basal epithelial cells; Y, the contribution to the cell mass by centripetal movement of peripheral cells; and Z, the epithelial cell loss from the surface. Corneal epithelial maintenance thus can be defined by the equation: X + Y = Z, which simply states that if the corneal epithelium is to be maintained, cell loss must be balanced by cell replacement.

The presence of the X component has been established by tritiated thymidine labeling of epithelial cells, identifying the actively dividing basal cells. However, there remain numerous questions to be answered with regard to X. Does the mitotic rate change in response to increased or decreased epithelial attrition? Is the rate under neuronal or pharmacologic control? What happens to the rate of basal cell proliferation in a variety of clinical circumstances, eg, inflammation, drug toxicity, denervation, or metabolic stress from contact lenses?

The Y component is an ongoing, slow, centripetal cell movement that occurs even in the absence of an acute defect. It is important not to confuse Y with another phenomenon, the rapid movement of peripheral cells in response to an acute central defect. While as yet not proven, there is both direct and indirect evidence for such an ongoing movement, even in the absence of a defect. Analysis of the sex chromatin in donor corneal epithelium shows that there is a loss of donor epithelium from corneal grafts, even when there is no acute rejection, but that this replacement of donor by host epithelium takes many months. Indirectly, clinical observation of centripetal movement of epithelial dots after grafting, and the observation that epithelial graft reactions were not seen more than 13 months after keratoplasty (presumably because no donor epithelium remained to react) also indicate an active Y component. These observations have been made on surgically treated eyes. However, recent studies showing a radial pattern of hemidesmosome alignment along the basement membrane of normal murine eyes are also consistent with the concept of centripetal