Eye (1989) **3,** 84–89

Probing Visual Function with Psychophysics and Photochemistry

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Summary
New methods using computer based measurements and image analysis techniques can improve and expand our ability to investigate non-invasively the function of the retina in patients. These can provide insight into the underlying mechanism of an abnormality and further our understanding of disease processes.

Clinical investigations of the function and malfunction of the retina are aided by the use of non-invasive techniques such as psychophysics and fundus reflectometry. Much can be learned about the underlying causes of the loss of vision from these new methods. It is vital to coordinate the different types of studies to answer these questions. For example, if we wish to know whether the loss of night vision in a retinal degeneration is entirely due to loss of rhodopsin in the photoreceptors or whether the defect involves a more proximal mechanism such as the neural elements of the retina, we must correlate the threshold elevation with the measured rhodopsin.

Techniques for improving the ease with which such information can be obtained from the patient have been greatly enhanced by recent technical developments. For psychophysical testing, automated static perimeters able to distinguish relative abnormalities of rod and cone function have been developed[1,2] and high resolution mapping provides more detailed information.[3–8] For photochemical measurements, an imaging fundus reflectometer (IFR), based on a modified 30 fundus camera coupled to a high sensitivity TV imaging system,[9–12] has been developed which makes it possible to obtain simultaneous information about the distribution of visual pigment within a large area of the retina. The video images of the fundus obtained from the camera are digitised and averaged by an image analysing system. The levels of visual pigment at chosen points within the area examined can then be compared with sensitivity measurements made psychophysically at the same loci.

Patients with retinitis pigmentosa (RP) have been extensively studied in terms of genetic type, clinical findings, retinal function measured electrophysiologically and psychophysically, and by fundus reflectometry. Several important findings have emerged both here and in the United States.[13–16] It is clear that within a given genetic type there are fundamentally different forms of the disease which are consistent among family members. One form of the autosomal dominantly (AD) inherited dis-

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ease shows diffuse loss of rod function ('D' type) throughout the retina while cone function may be nearly normal until late in the disease. In another form there is concomitant loss of rod and cone function in retinal regions ('R' type) with areas where rod and cone function can be nearly normal early in the disease coexisting with regions of severely abnormal rod and cone function. Further, as shown in Figure 1, there can be fundamental differences in the relation between rhodopsin and sensitivity.[12] In the 'D' type subjects

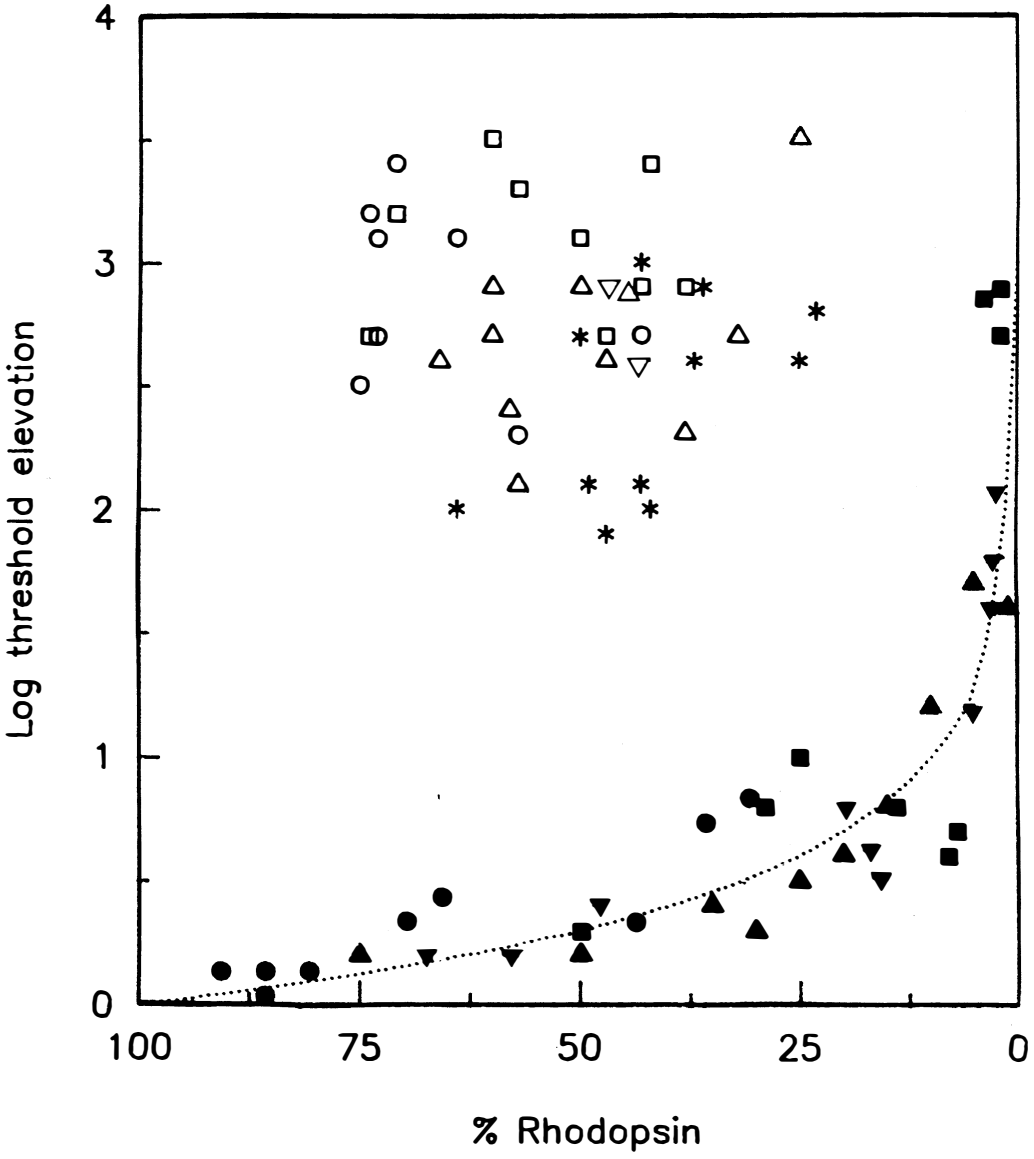

Fig. 1. *Relationship between log threshold elevation and rhodopsin levels measured with the imaging fundus reflectometer for four subjects with the regional form of AD RP (filled symbols) and five subjects with the diffuse form (unfilled symbols and *). The dotted curve is the relation which would be expected if threshold elevation were determined by the decreasing probability of quantal absorbtion resulting from reducing rhodopsin levels in the rods. (Reproduced with permission from reference 12).*

examined relatively substantial amounts of rhodopsin can be measured even where retinal sensitivity is severely reduced while in the 'R' type the loss of rhodopsin accounts entirely for the sensitivity loss. This suggests that while in the 'R' type the nightblindness can be attributed to the reduced quantity of rhodopsin in the patients' retinas, in the 'D' type the sensitivity loss is due to one or more factors beyond loss of rhodopsin. These findings suggest fundamentally different processes and it has become clear that the classification of RP families into pure RP type is vital for classifying disease mechanisms and for interpreting the results of blood and genetic studies.[17,18]

Further probing of retinal abnormalities has been accomplished on a microscopic scale using the newly developed technique of fine matrix perimetry to characterise further retinal function with higher resolution.[3–8] This has been made possible by new developments on the optics of retinal image formation, control of eye movements, and the use of video displays and computer generated graphics.[3–5,19,20] These measurements are made in conjunction with the rhodopsin density measurements to allow further characterisation of the retinal abnormalities on a microscopic scale, in particular at the edge of the advancing front of the degeneration and on the borders between nearly normal and severly affected retina.[21]

The retinal location tested is chosen based on funduscopic examination, fluorescein angiograms, fundus photographs, conventional visual fields, static perimetry and other considerations. The stimuli are formed on a video display and are typically 10 by 10 minutes of arc square, blue (450 nm), brief flashes. Thresholds are determined using the method of ascending limits at a series of positions on a 10 by 10 matrix. The values are passed through an image processing filter and plotted as maps of LOG (relative intensity) or threshold elevation relative to the normal value.

The improvements in the maps due to the image processing filter can be seen by comparing Figures 2 and 3. In Figure 2 are shown the unprocessed values over a small region of retina just under 7 degrees square in the superior field of a patient with retinitis pigmentosa. Figure 2a shows one set of measurements while Figure 2b shows a repetition made within the hour. Comparing 2a and 2b shows that it is clearly difficult to detect real, repeatable variations in sensitivity in the presence of these typical levels of noise. The

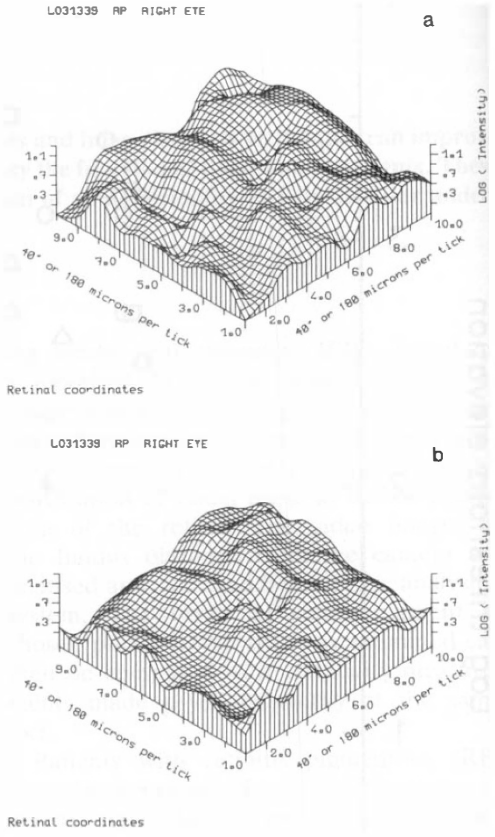

Fig. 2. *a. Threshold map centered at 15 degrees in the superior field (90 degree meridian) of an X–linked carrier of RP. The X– and Y– axes represent retinal or visual field location extending from about 12 to 18 degrees in the superior field and +3 to −3 degrees to either side of the 90 degree meridian. This corresponds to a location in the inferior retina about the same distance from the fovea as the centre of the optic nerve head and the extent of retina mapped (about 1.8 square mm.) is slightly larger than the size of the optic nerve head. This and the map in 2b have not undergone image processing. b. Repetition of the previous map showing how difficult it is to see consistent threshold differences in the presence of this level of noise without the use of image processing.*

noise in this unprocessed data is of the order of 0.5 log units which is similar to that of conventional perimetry.

The improvements resulting from application of image processing techniques are shown in Figure 3. Comparison of 3a to 3b is made easier with much of the spatially uncorrelated noise removed. It is now evident that the variation in retinal sensitivity on this scale extends from a threshold elevation of about

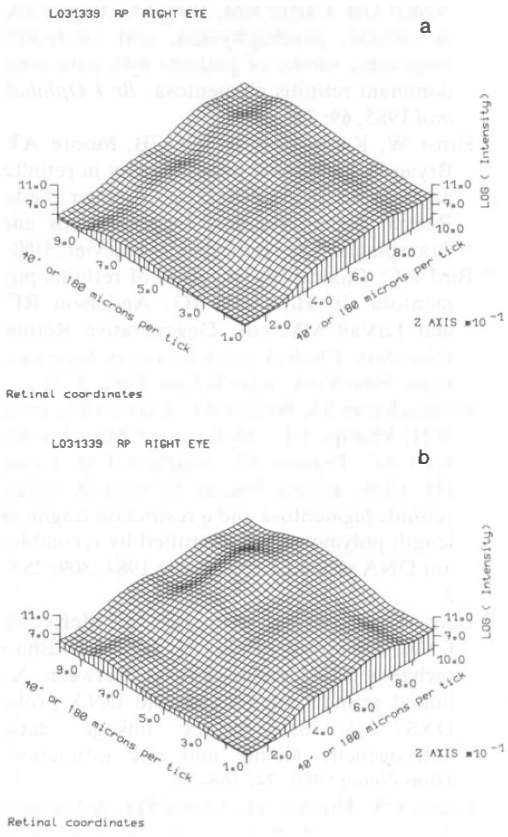

Fig. 3. *The same two data sets of the previous figure but which have now undergone image processing to reduce the effects of spatially uncorrelated noise. The image processing filter has a quantitatively predictable effect on image quality which allows its contribution to be calculated separately from the changes in retinal sensitivity. Comparison of map 3a with map 3b shows how reduction of noise allows detection of the real underlying spatial variations in sensitivity in this region where thresholds are elevated from 0.5 log units to 1.0 log units. Sensitivity differences of the order of 0.1 log units can be reproducibly measured.*

0.5 log units in the most sensitive area to nearly one log unit in the least sensitive region. Comparison of 3a and 3b shows how highly reproducible the results are.

These techniques allow the investigation of variations in retinal function on a 'microscopic' scale and are being used to measure the effects of opthalmoscopically visible features, the 'mosaic' of retinal function in heterozygotes for choroideremia and X-linked RP, and in following the changes at the edge of the spread of degeneration. They provide high resolution sensitivity maps for comparison with the results of rhodopsin measurements from imaging fundus reflectometry.

Severely delayed recovery of sensitivity during dark adaptation has been found in some patients with RP[22,23] and the use of these new techniques may help us understand the cause. It has been suggested that an abnormality in the balance between outer segment renewal and phagocytosis may be involved in RP[24] and these techniques may provide a means of indirectly measuring these processes in patients. The time course can be similar to that of the outer segment renewal mechanism and quantitatively consistent with abnormally shortened outer segments with normal renewal rates. Abnormal diurnal variation in visual sensitivity in patients with retinal oedema has been measured[25] and other reports of abnormalities in sensitivity with a daily variation[26] suggest that we may be able to measure this in patients. We may then be able to relate abnormalities in RP patients to animal findings of diurnal rhythms of outer segment renewal mechanisms which could be tested by manipulating the light-dark cycle in patients. We have measured changes in sensitivity over a period of days in several families with RP and have measured rhodopsin levels in the same location to provide further information about the potential role of these processes in patients with RP. Variations in delayed rates of dark adaptation have also been found in some regions of the retina of Sorsby's fundus dystrophy[8] and the mechanism, which appears to be related to the deposition of a yellow material in the fundus, is also currently being investigated.

The results of these measurements in patients, when considered in relation to new knowledge from animal studies and other investigations, can help our understanding of mechanisms of disorders of the retina and suggest further investigations to answer questions about the nature of the abnormalities.

We thank AC Bird, EL Chuang, AT Moore, GS Turner, PJ Polkinghorne, MRC Capon, SG Jacobson, DM Sharp, the late W Ernst, DJ Faulkner, P West, and G Joseph for their participation in this work and the National Retinitis Pigmentosa Foundation (U.S.A.), the British Retinitis Pigmentosa Society, the Wellcome Trust, the Medical Research Council, and Fight for Sight for financial support.

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