Rhodopsin and visual threshold in retinitis pigmentosa

H. Ripps, K. P. Brin, and R. A. Weale*

Rhodopsin kinetics and visual threshold were determined in three subjects with a dominant form of retinitis pigmentosa. The retinal areas studied showed varying loss of sensitivity, which correlated well with the reduction in the measured density of rhodopsin in the test region. Rhodopsin photosensitivity was normal, and there was no evidence that either rhodopsin or the cone pigments regenerated more rapidly than normal. The findings in these cases of retinitis pigmentosa, when compared with the threshold changes induced by vitamin A deficiency or photic bleaching, suggest that the disease produces an imbalance between disc removal and new disc formation, which results in a progressive shortening of the photoreceptor outer segments and, eventually, in their complete disappearance.

Key words: human retinitis pigmentosa, visual threshold, rhodopsin kinetics, fundus reflectometry, cone pigment regeneration

Our knowledge of the pathogenesis of heredodegenerative diseases of the human retina has been enhanced significantly by the development of animal models that exhibit many of the profound destructive changes characteristic of such diseases. Foremost among the advantages of this approach is the opportunity it affords to manipulate the genetic constitution of the animals and to analyze the consequences of these maneuvers with biochemical, histochemical, and electrophysiological techniques.

Man's mating behavior is not so readily controlled, and the human retina is far less accessible for laboratory investigation. Thus it becomes necessary to seek other means with which to probe the human visual system in order to study the nature of a disturbance and locate sources of defective function. Fortunately, there are available a number of quantitative, noninvasive experimental methods which can be brought to bear on some of these questions. The use of such procedures in the analysis of congenital night blindness has yielded new insights into the etiology of these disorders, and we are attempting now to apply similar methods to further our understanding of retinitis pigmentosa and other degenerative retinal diseases.

The patients we have examined in the present study include three family members suffering a slowly progressive form of pigmentary retinal degeneration and a fourth patient with a nutritional (surgically induced) vitamin A deficiency. The results, together with those obtained by Highman and Weale on more than a dozen cases of retinitis pigmentosa of varied inheritance, provide the first quantitative assessment of photopigment kinetics and visual sensitivity in this disease.
and may help to establish important facts concerning its nature. Indeed, the findings support the view that some forms of hereditary retinal disease produce initially a reduction in the rhodopsin density of the rod photoreceptors without affecting the functional integrity of these elements.

Methods

Two young women (23 and 25 years old) and their mother (48 years old) were the principal subjects of this study; they were referred to us by Dr. G. Fishman and were examined initially with a series of tests that comprise the routine diagnostic battery of our retinal clinic. Although no other family members are known to be affected, the pedigree suggests that the mode of transmission of the disease is autosomal dominant. However, since three generations of affected members are essential to establish dominant inheritance, neither pseudodominance nor recessive inheritance can be excluded as the possible mode of transmission. A more complete description of these cases will be given in a later paper (Carr et al., in preparation). Here it suffices to say that electrophysiological tests of retinal function (electroretinogram and electro-oculogram) were of subnormal amplitude and were more depressed in the older subject. Thus, compared with the recordings from normal subjects, the amplitudes of the scotopic responses to a blue, ganzfeld stimulus were reduced by 75% in the 48-year-old mother and by about 40% in the daughters. None of the responses exhibited significant delays in implicit time. As regards the electro-oculogram, a light dark ratio of 180% marks the lower limit of the normal range in our test configuration. The data for both the mother and older daughter were grossly abnormal, with values of 114% to 150%, respectively; the younger daughter was at the low end of the normal range, with an L:D ratio of 182% O.D. and 175% O.S. In addition, the fundi contained bone-spicule-shaped, pigmented deposits in the mid-periphery, and the perimetric data revealed regions of the visual field with apparent normal function, other regions with deep scotomata, and still others with sensitivities somewhere between these extremes. The most severely affected areas formed ring scotomata that extended from about 7° to 25° around the fovea, and here too the mother showed the largest field defects. We selected small areas within zones of varying sensitivity upon which to apply two test procedures: fundus reflectometry and the measurement of the final dark-adapted (i.e., "absolute") thresholds. It should be noted at the outset that the subjects were available for study for only a short time and that subject tolerance and humane considerations dictated the number of test procedures that could be applied within this period.

A fourth subject (S. K.) was a 37-year-old man who had undergone surgery to bypass a region of intestine extending from the upper end of the jejunum to the descending colon. The loss of intestinal tract mucosa reduced considerably the absorption of vitamin A, which led after a period of 4 years to night blindness. Other signs of vitamin A deficiency were present, but these, as well as the results of a more complete study of this unusual condition, will be reported in a future paper. Once again, our concern here was to estimate the rhodopsin content of a restricted region of the retina and to determine the subjective visual sensitivity of that particular area.

Fundus reflectometry. The technique employed has been described in detail in previous publications. Briefly, it involved the determination of density difference spectra (ΔDx for λ = 410 to 680 nm) from fundus reflectance measurements obtained under the following conditions of retinal adaptation: (1) after 30 min to 1 hr of dark adaptation; (2) after a 10 sec photic exposure that bleached more than 95% of the available rhodopsin; and (3) at various times after the bleaching light was extinguished. The density differences obtained between conditions 1 and 2 provide an estimate of the in situ density of rhodopsin, whereas the time-dependent increase in absorbance between conditions 2 and 3 is used in computing the rate at which the bleached rhodopsin was resynthesized. Unless otherwise noted, all reflectivity measurements were made with a circular test field that subtended an angle of 2° at the eye; the bleaching field was concentric with the test area but had an angular subtense of 4°30'. Depending upon the position of a small fixation target, the test region could be foveal or at any desired location in the peripheral retina.

Visual sensitivity. Absolute thresholds were determined for the same retinal loci that were examined by fundus reflectometry. The 510 nm interference filter of the reflectometer was locked in the test position, and a series of interchangeable, calibrated neutral-density filters were inserted in the optical path of the instrument. Subjective thresholds were measured in response to test flashes of 0.2 sec duration delivered through an electromagnetic shutter. Although some test regions required extremely divergent fixation an-
gles, the reduced image of the luminous source formed in the subject’s dilated pupil (Maxwellian view) never encroached upon the iris.

Results

Absorbance changes due to bleaching. Difference spectra for each of the affected female subjects of this study are graphed in Figs. 1 to 3 and show the maximal absorbance changes recorded at three retinal loci, the loci were selected on the basis of perimetric results to represent areas having different functional capacities. Thus 15° temporal to the fovea was for these subjects a deeply scotomatous region, and in each case the reflectometer was unable to detect the presence of any light-sensitive substance within the 2° test region. These data are shown only for Subject P. R. in Fig. 1 and for convenience have been omitted from Figs 2 and 3.

At 30° as well as 45° in the periphery, visual function was demonstrable by perimetry, and there was a significant change in the situation with regard to the visual pigment measurements. As shown in Fig. 1, for example, the youngest subject (P. R.) gave a density difference of 0.023 unit at the $\lambda_{\text{max}}$ of $\sim 510$ nm for a test spot located 30° temporal to the fovea and an even greater absorbance change ($0.077$) at 45°.

For Subjects D. P. (Fig. 2) and A. M. (Fig. 3), density changes of smaller magnitude were obtained at both of the more peripheral loci. Thus the 30° data for D. P. showed a maximum change in absorbance of 0.01 density unit, and the 45° data, one of 0.068 density unit. A further reduction in measurable pigment density was observed with Subject A. M. The density difference due to bleaching was about 0.01 at 30°, whereas a $\Delta D_{\text{max}}$ of only 0.032 unit was recorded at the 45° mark. It should be noted that except for the data obtained at 30° for Subjects D. P. and A. M., the spectral curves peaked in the region of 510 nm, indicating that rhodopsin was the principal photopigment being measured. In the former instances, on the other hand, the $\lambda_{\text{max}}$'s were shifted to longer wavelengths, pointing to the likelihood that cone pigments contributed to the absorbance difference spectra.\(^{16}\)

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*Fig. 1. Density difference spectra for Subject P. R. from three regions of the temporal retina. The absorbance changes in this and in subsequent figures indicate values for double transit through the retina. In each experimental run, the retinal illuminance of the photic exposure was 7.3 log scotopic troland-sec, sufficient to bleach more than 95% of the available rhodopsin.*

*Fig. 2. Density difference spectra for subject D. P. Results for 15° temporal retina gave no absorbance change, due to bleaching, and have been omitted. Note shift in $\lambda_{\text{max}}$ to longer wavelengths at 30°. Bleaching exposure same as in Fig. 1.*

*Fig. 3. Density difference spectra for Subject A. M. See legend to Fig. 2 for further details.*
The difference spectrum for the vitamin A-deficient subject is shown in Fig. 4. The data, recorded at 15° temporal to the fovea, show a maximum density change of 0.097 unit—a value that is significantly greater than any obtained from the subjects with pigmentary retinal disease. However, the special feature of this case, and the rationale for incorporating the findings in the present report, is the extreme sensitivity loss associated with this seemingly moderate decrease in rhodopsin content (see below).

Visual sensitivity of the peripheral retina.

Table I, which presents the absolute threshold data for the four observers, shows that sensitivity varied markedly with retinal locus in the cases of retinitis pigmentosa. Although rod-mediated vision could not be demonstrated in the test region centered at 15° (where the retina appeared to be devoid of rhodopsin), thresholds were elevated by only 1 to 1.7 log units in regions where visual pigment densities were less than 20% of the normal values. Moreover, the fact that thresholds were raised well above the cone plateau at 15° indicates that the cone mechanism was severely affected in this region of the retina. Note also that a very different situation was encountered in the fully dark-adapted eye of our vitamin A-deficient sub-

**Table I.** Retinal illuminances (in scotopic troland-sec) for absolute threshold at different loci in the temporal retina

<table>
<thead>
<tr>
<th>Subject</th>
<th>15°</th>
<th>30°</th>
<th>45°</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. R.</td>
<td>$4.5 \times 10^{-5}$</td>
<td>$1.5 \times 10^{-2}$</td>
<td>$1.3 \times 10^{-4}$</td>
</tr>
<tr>
<td>D. P.</td>
<td>$1.44^*$</td>
<td>$4.8 \times 10^{-3}$</td>
<td>$2.4 \times 10^{-4}$</td>
</tr>
<tr>
<td>A. M.</td>
<td>$3.02^*$</td>
<td>$9.5 \times 10^{-4}$</td>
<td>$6.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>S. K.</td>
<td>$7.9 \times 10^{-5}$</td>
<td>—</td>
<td>(80)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses give the log increment above the average normal threshold of $-4.02$ log scotopic troland-sec.

Fig. 4. Density difference spectrum for S. K., a subject with surgically induced vitamin A deficiency. Bleaching exposure same as in Fig. 1.

Fig. 5. Change in log threshold as a function of the percent rhodopsin present in the dark-adapted retina as determined by fundus reflectometry. Threshold elevation is relative to a mean absolute value of $-4.02$ log scot td-sec; 100% rhodopsin refers to a measured density of 0.13 unit. Threshold values that lie above the cone threshold line show that visual sensitivity was measurable, but that it was subserved by the cone mechanism. Large symbols are for the four subjects of this study; they can be identified by reference to Figs. 1 through 4. Small filled circles are data from Highman and Weale\(^1^2\) replotted on this scale of coordinates. The continuous curve is the relationship expected if threshold is determined by the probability of quantal absorption; the dashed line shows the linear relation between log threshold and bleached rhodopsin obtained by Rushton.\(^1^8\)
Rhodopsin, visual threshold in RP

It is apparent that the data for our subjects with pigmentary retinal disease do not deviate markedly from this probability function. In addition, we have replotted on the same coordinates the earlier results of Highman and Weale to illustrate how well the probability curve fits the data for their cases of retinitis pigmentosa. The familial histories of these patients indicated that some cases were typical of the carrier state (heterozygote) of the X-linked disease and that others inherited the disease as either an autosomal dominant or an X-linked disorder.

In addition to the reduction in rhodopsin density that occurs in retinitis pigmentosa, the rhodopsin content of the rods can also be reduced directly by photolysis or indirectly by vitamin A deprivation. However, it should be noted that the loss of rhodopsin due to either of the last two causes raises the visual threshold far more than is predicted solely by the loss of quantal absorption. The dashed line of Fig. 5 illustrates the relation between bleached rhodopsin and visual threshold that was obtained by Rushton on a “rod monochromat.” The absence of cone function in this subject enabled him to measure rod-mediated thresholds well above the usual scotopic range and to demonstrate that the threshold was raised, e.g., by more than 4 log units, when the rhodopsin content of the rods was reduced by only 25%. An equivalent loss

Fig. 6. Bleaching of rhodopsin as a function of the log retinal illuminance. The continuous curve is a plot of equation 1, and the arrow points to the value of $E_c$, the retinal illuminance that bleaches $(1 - e^{-1})$ of the available rhodopsin.
Fig. 7. Regeneration of visual pigment in retinitis pigmentosa. Filled symbols show data for the resynthesis of rhodopsin as measured at 45° in the temporal retina after exposure to 7.3 log scot td-sec. The open squares represent the regeneration of cone pigments measured in the fovea of Subject D. P.; the bleaching intensity was 7.0 log td-sec, and the test field of the reflectometer was reduced to 1.3° of visual angle for the foveal measurements. The curves are exponential functions with time constants of 5.8 min (continuous line) and 2.7 min (dashed line).

of rhodopsin due to vitamin A deficiency probably induces a corresponding elevation of threshold, although the true value may be masked by the presence of photopic (cone) function. Thus the data point (open circle) for the vitamin A-deficient subject approaches the bleaching curve but falls short of it owing to the intrusion of the cone mechanism, the threshold for which now lies below that of the rod system.

**Bleaching and regeneration of rhodopsin.** There is the possibility that abnormalities of the pigment epithelium-photoreceptor complex in retinitis pigmentosa alter the kinetic properties of the rhodopsin cycle. In the normal retina the bleaching of rhodopsin is described adequately by the expression:

\[
\left( \frac{\Delta D_H}{\Delta D_{\text{max}}} \right)_\lambda = 1 - e^{-\alpha y t}
\]

where \(\Delta D_H\) is the absorbance change at wavelength \(\lambda\) due to an intensity \(I\) delivered for time \(t\); \(\Delta D_{\text{max}}\) is the maximum change in absorbance after a full bleach, and \(\alpha y\) is the photosensitivity, defined as the product of the extinction coefficient \(\alpha\) and the quantum efficiency \(y\). It is evident that the retinal illuminance \(E_c\) that bleaches \((1 - e^{-1})\) of the available rhodopsin provides a measure of the photosensitivity, i.e., \(E_c^{-1} = \alpha y\). Expressed in troland-sec, \(E_c \approx 10^7\) td-sec in the normal human retina.

The value of \(E_c\) was determined for one subject (D. P.) only, and the results are shown in Fig. 6; measurements of \(\Delta D_H/\Delta D_{\text{max}}\), expressed as the percent of rhodopsin bleached, are plotted as a function of the log retinal illuminance delivered by 10 sec exposures of various intensities. The good agreement between the four data points and the curve of equation 1 (solid line) is evidence that the photolysis of rhodopsin in this subject follows the usual exponential form, whereas the position of the curve on the scale of abscissa indicates that the value of \(E_c\) is 6.8 log troland-sec.

The temporal course of rhodopsin regeneration was determined for two of our subjects (D. P. and P. R.). The data shown in Fig. 7 represent the percent recovery of visual pigment at various times after a photic exposure that bleached more than 95% of the available rhodopsin; for Subjects D. P. and P. R. the \(\Delta D_{\text{max}}\) was 0.06 and 0.072 density unit, respectively. The results for both subjects, recorded at 45° in the peripheral retina, agree reasonably well with an exponential growth curve having a time constant (\(\tau\)) of 5.8 min; that is, the half-time of regeneration is approximately 4 min.

The regeneration of foveal cone pigments was also measured, but only in Subject D. P. These data, the unfilled symbols of Fig. 7, show that cone pigment regeneration proceeds at more than twice the rate of rhodopsin synthesis. The exponential curve (dashed line) has a time constant of 2.7 min, with a half-time of 1.9 min.

**Discussion**

The results of this study, and of that reported earlier by Highman and Weale, provide conclusive evidence that in some forms of heredodegenerative retinal dystrophy there is a reduction in the measured
density of rhodopsin within areas of the retina that exhibit visual impairment (cf. Figs. 1 to 3). Moreover, the data of Fig. 5 indicate that the loss of scotopic (rod) sensitivity can be attributed directly to the reduced efficacy of quantal absorption that accompanies the fall in optical density; thresholds rise in direct proportion to the fractional loss of rhodopsin. It is likely therefore that the rod photoreceptors are affected in each of these cases; that is, abnormalities of the proximal retina cannot be implicated as the source of the visual defects.

It seems difficult at first glance to reconcile the retention of rod-mediated vision with a loss in rhodopsin content amounting in some retinal regions to more than 80% of normal. Rushton has shown that rod thresholds lie above the cone plateau when only about 15% of the available rhodopsin is in the bleached state. And a similar situation is seen after vitamin A deprivation in experimental animals, where the rise in threshold due to the depletion of rhodopsin parallels the results obtained with bleached rhodopsin. Note also that in the case of night blindness due to vitamin A deficiency (Fig. 5, open circle) the threshold is elevated above the cone plateau despite the presence in this patient's retina of about 75% of the normal complement of rhodopsin. Thus, in each of these instances, the threshold rise associated with the loss of rhodopsin is far greater than predicted by the assumptions underlying the probability function. Instead, log threshold rises linearly with the decline in rhodopsin content of the rods (dashed line of Fig. 5).

The fact that bleached rhodopsin or vitamin A deficiency exerts a profound effect on visual sensitivity is hardly surprising. Rhodopsin is the major protein constituent of the disc membranes of the rod outer segment, and it is well known that the photic isomerization of rhodopsin causes significant changes in the physical state of these membranes as well as in the ionic permeability of the cell. In vitamin A deficiency, Dowling and Gibbons have described in great detail the progressive deterioration of the visual cells that begins with the pigment-bearing membranes of the outer segments (see also Witkovsky et al.). It appears therefore that any upset in the integrity of the cell membrane of the photoreceptor will disrupt its functional capacity.

We doubt whether this type of defect is likely to be involved in the forms of pigmented retinal degenerations which are of concern here and in which there is a relatively modest decrease in visual sensitivity associated with a marked loss of rhodopsin. Indeed, of the various possibilities that we have considered, it seems most likely that the disease process in our patients leads to a progressive shortening of the outer segments of the rod receptors, which in other respects retain their normal functional properties. The loss in axial density produced by this shortening reduces the fraction of incident light absorbed by the photoreceptors, and there is a proportionate drop in visual sensitivity. If the process proceeds long enough, the outer segments disappear, the cells die, and pigment epithelial changes ensue. In its early stages, the situation appears to be the reverse of that seen in the developing photoreceptor; as visual cells mature, the outer segments increase in length, and provided that the in situ density does not exceed about 0.2, the photic sensitivity of the receptors increases proportionately with the increase in visual pigment.

Our views on how (or whether) the rods continue to shorten and lose the discs of their outer segments are necessarily conjectural, but the vital interplay between cell growth and degradation is not. In a series of elegant tracer studies, Young and his co-workers have demonstrated the delicate balance that exists between the growth of rod outer segments, disc shedding, and the phagocytic action of the pigment epithelium. The lamellar discs of vertebrate rods are being renewed continually; they are assembled at the base of the outer segment, are gradually displaced along the outer segment, and are then removed at the distal ends and phagocytized by the pigment epithelium. If the latter fails to fulfill its phagocytic role (as occurs in rats with retinal dystrophy), there is an over-
Table II. Density readings for normal subjects at various loci in the temporal retina

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>15°</th>
<th>30°</th>
<th>45°</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. A.</td>
<td>M</td>
<td>48</td>
<td>0.144</td>
<td>0.107</td>
<td>0.091</td>
</tr>
<tr>
<td>B. C.</td>
<td>M</td>
<td>45</td>
<td>0.145</td>
<td>0.104</td>
<td>0.075</td>
</tr>
<tr>
<td>L. M.</td>
<td>M</td>
<td>34</td>
<td>0.118</td>
<td>0.092</td>
<td>0.076</td>
</tr>
<tr>
<td>S. M.</td>
<td>F</td>
<td>34</td>
<td>0.123</td>
<td>0.095</td>
<td>0.093</td>
</tr>
<tr>
<td>B. P.</td>
<td>F</td>
<td>32</td>
<td>0.101</td>
<td>0.084</td>
<td>0.096</td>
</tr>
<tr>
<td>I. S.</td>
<td>M</td>
<td>48</td>
<td>0.100</td>
<td>0.095</td>
<td>0.080</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>0.122</td>
<td>0.096</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Density values are for the peaks of the difference spectra at $\lambda = 510$ nm.

There was either an overproduction of outer segment material or excessive phagocytosis by a greedy pigment epithelium. Excessive phagocytic activity is obviously one of the ways in which a progressive shortening of rods could come about.

Perhaps we should stress that neither this nor the earlier study has revealed any evidence of an overproduction of rhodopsin like that reported for pigmentary degeneration in RCS rats. This statement may seem inconsistent with some of the reflectometric data shown in Figs. 1 to 3, in particular the density measurements obtained at 45° in the peripheral retina. It will be recalled that the only measurements reported for that eccentricity in a normal retina are those of Campbell and Rushton. Their results, obtained on Rushton's eye, are not given in density units, but they do indicate that at 45° temporal to the fovea the relative rhodopsin density falls to about 20% to 30% of the maximum recorded at 16° in the temporal retina. Now 20% of the average maximum for our normal observers ($D = 0.13$) is only 0.026, a density value that is exceeded by all our affected subjects. Without dwelling on the possible causes for the extremely low rhodopsin content obtained by Campbell and Rushton (e.g., failure to dark-adapt between successive measurements at various retinal loci), we can report that our data for normal subjects show a far more gradual decline in pigment content between 15° and 45°. Shown in Table II are the results of reflectometry on six normal observers (32 to 48 years old) at 15°, 30°, and 45° in the temporal retina. Comparing these findings with those of our patients indicates that at 45° the latter are at or below the low end of the range of normals; none of the patients shows evidence of having more than the normal concentration of rhodopsin at any of the retinal locations tested.

There is yet another hypothesis that cannot be dismissed on the basis of the evidence cited, for the findings seem compatible also with the notion that there could be a mosaic within the affected area formed by two popu-
lations of cells: one consisting of entirely normal visual cells and the other composed of cells in various stages of disintegration. The disruption of even a large percentage of the percipient elements would not grossly alter visual sensitivity, and there would be a fall in the measured rhodopsin density of the affected area. But if there are degenerating cells, whatever the degree of breakdown, the upset to the cell membranes would render the elements functionally inactive at the very onset of the degenerative process (as in vitamin A deficiency). On the other hand, it is unlikely that the rhodopsin measurements would be correspondingly affected (being a function of the degree of deterioration), and we would not expect the results to lie on the probability curve. Indeed, it can be argued that almost any disturbance that affects the functional properties of the rod mechanism (e.g., a rise in intrinsic noise, defects in neural transmission, or a change in the cable properties of the receptor) would significantly alter the correlation between threshold and percent rhodopsin that is shown by the solid curve of Fig. 5. It is interesting that Berson et al.36 also rejected the concept of a mosaic in favor of a generalized reduction in the rhodopsin content of the rods to account for the abnormal rod-mediated electrical responses recorded in dominantly inherited retinitis pigmentosa.

Another question that needs to be considered in the present context relates to the kinetic properties of the visual pigments in heredodegenerative diseases of the retina. Data from measurements of the early receptor potential37. 38 (ERP) suggest that the regeneration of visual pigment may be accelerated in some forms of retinitis pigmentosa, and Reading20 has inferred from various biochemical findings that rats with retinal dystrophy possess a visual pigment of an unusually labile nature, i.e., an increased photosensitivity. As regards the latter, a comparison of the bleaching kinetics of rhodopsin in normal and dystrophic rats by Chaitin and Williams39 failed to provide confirmatory data; the present findings suggest that rhodopsin kinetics are normal in human retinitis pigmentosa as well. The photosensitivity measurement (Ee = 6.8 log scotopic troland-sec) obtained from Subject D. P. (Fig. 6) is compatible with the range of values reported40. 41 for normal observers, i.e., 6.86 to 7.1. And with regard to the rate of regeneration of bleached rhodopsin, the data (Fig. 7) agree well with an exponential curve having a time constant (τ) of 5.8 min. This value falls within the range (τ = 4 to 6.6 min) reported for normal observers.40. 42 It should be noted, however, that our data were recorded at an eccentric location (45° from fixation), and it is obviously premature to draw any conclusions until more results are accumulated from peripheral regions of normal and diseased retinas.

As for the regeneration of cone pigments, there is no evidence in the one patient (D. P.) on whom foveal data were obtained that the rate of regeneration is faster than normal. In fact, the time constant (2.7 min) of the regeneration curve (Fig. 7) is slightly longer than the value obtained by reflectometry16. 43. 44 of the normal fovea, i.e., τ = 2 min. However, it is important to consider the differences in experimental method, the retinal locus tested, and patient classification between our study and that of Berson and Goldstein37; the ERP data of the latter work were obtained with test stimuli that subtended a visual angle of 45° (a test of peripheral cones), and the recordings were from patients with dominant retinitis pigmentosa with complete penetrance.

We are indebted to Dr. Gerald Fishman for having referred the patients with retinal dystrophy and to Drs. Fishman, R. E. Carr, and J. Maggiano for their cooperation throughout the course of this study. Special thanks are due Miss Jane Zakovicus for assistance in the preparation of the manuscript and to Drs. G. B. Arden and I. M. Siegel for helpful suggestions. R. A. W. thanks New York University for financial help toward expenses.

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