Pigmentary degeneration of the retina: Early diagnosis and natural history

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Twenty-five patients were examined by means of several tests of visual function to determine tests best suited for early diagnosis, for evaluation of progression, and for analysis of visual capabilities. Nine patients were tested two or more times during intervals ranging from one to 34 years. In the incipient stage cone function is usually normal. Measures of the light threshold of the dark-adapted eye in a number of locations from center to periphery of the retina detect localized areas of deficient rod vision. At a later stage conventional perimetric examination of the light-adapted eye detects areas in which both cone and rod function are impaired. At a far-advanced stage the field is reduced to a small patch and visual acuity is significantly reduced. Quantitative tests of ability to read continuous text determine whether or not ordinary print can be read with ease and, if not, whether magnification can provide useful reading vision. The rate at which visual function is lost varies markedly even among members of the same family.

Precise information concerning the earliest manifestations of pigmentary degeneration of the retina, its various stages of deterioration, and the rate at which such changes occur might contribute to a better understanding of this disease. Early diagnosis is also of importance in the search for and evaluation of methods of arresting the visual impairment. The clinical material of this investigation was obtained from detailed studies of 25 patients. Nine of the 25 were members of the second and third generations of the V. family with a dominantly inherited form of pigmentary degeneration of the retina. The pedigree of this family is shown in Fig. 1. The third generation provided patients for investigation of the incipient stages of retinitis pigmentosa and for comparative evaluation of tests for its early diagnosis.

The five affected members of the second generation were first examined more than 25 years ago by one of us. Three of the five have recently been retested to provide data on the natural rate of progress of the disease. Other patients with pigmentary degeneration of the retina, followed for times ranging from one to 34 years, provide additional data on the progress of visual impairment.

Methods of examination

Study of the patients included routine ophthalmoscopic examination, measurement of the field of vision, and of the corrected visual acuity. Tests of near vision, with the use of graded sizes of continuous text, were given to those with impaired reading ability. Electroretinographic (ERG) tests were given to four patients who were at a very early stage of retinitis pigmentosa, according to other tests.

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Special emphasis was placed on detailed studies of the light sense by means of the instruments and techniques developed in this laboratory. Two types of light-sense tests were employed: (1) measurement of the rate of dark adaptation in a single region of the retina after preadapation to a high brightness, and (2) measurement of the light thresholds of the fully dark-adapted eye from center to periphery in the horizontal meridian of the visual field. The graph showing the variation in threshold with retinal location is referred to in this laboratory as the threshold gradient. Recently it has been called a retinal profile by others. For both tests we normally use a white stimulus subtending a visual angle of 1 degree.

The dark-adaptation curve is of value primarily for study of an early stage of impairment, at which it is sometimes possible to obtain separate measures of cone and rod function. This use of the adaptation curve is illustrated in Figs. 2A and 2B, which give data for three patients with visual impairments differing in severity. The adaptation curves of E. Z., tested at age 10 and at age 15, show two independent sections, the first of which measures cone thresholds and the second, rod thresholds. On the first date the cone thresholds were still within the normal range, the rod thresholds about 1.2 log units above the average normal level. Five years later the cone thresholds were about 1 log unit, the rod thresholds about 2 log units, above average normal. Data on the threshold gradient and visual fields of this patient are given later.

The adaptation curves of R. L. and E. C. (III in Fig. 1) are typical of the findings at a more advanced stage of retinitis pigmentosa. The final cone thresholds are, respectively, 1.7 and 0.5 log units above the average normal value. Neither patient has a bipartite curve because, even after 40 minutes of dark adaptation, the rod threshold lies above that of the cones and therefore cannot be measured. Such determinations of the rate of
dark adaptation are time consuming, and provide information about the sensitivity to light of only a single region of the retina. Measurement of the final thresholds of the dark-adapted eye, from center to periphery in the nasal and temporal fields, takes less time and provides far more information. In the early stages of pigmentary degeneration of the retina, when the visual fields are often essentially normal, we find the threshold gradient the most generally useful test of visual function. At more advanced stages the light thresholds are often too high to measure except within a few degrees of the fovea. In such cases visual field studies and tests of reading vision provide important additional information as to the degree of visual impairment.

Results
This section illustrates typical data on the light sense, visual fields, and reading vision of patients with early, moderate, and advanced pigmentary degeneration of the retina.

Typical findings in incipient stage of pigmentary degeneration of the retina. Four third-generation members of the V. family illustrate findings characteristic of an early stage. Although the fundi are abnormal in all, cases only one, C. G. (III2 in Fig. 1), has the classical bone-corpuscular forms of pigment deposits. The others have such abnormalities as narrowed arteries, blurred disk margins, or fine dust-like pigmentation.

The threshold gradients of these patients are shown in Figs. 3A, 3B, 3C, and 3D. Each graph gives for comparison two
curves drawn in solid lines to show the range of rod thresholds in dark-adapted normal eyes. The single curve drawn with a dotted line in each graph shows the dark-adapted cone thresholds of a normal eye, as determined by the location of the first plateau in the bipartite adaptation curve. The data are from a previous study. They are for only one subject because of the time-consuming tests required to locate the cone plateaus for a series of retinal locations from center to far periphery.

It is apparent from the graph that T. J. H. (III in Fig. 1) has a slight but significant impairment of rod function. Her thresholds are within normal limits only in the far periphery. In all other regions they are outside the range of normal rod thresholds, but well below the thresholds of normal dark-adapted cones. Her younger sister, C. H. (III in Fig. 1), shows more severe impairment. In a central area within 10° of fixation her thresholds lie above those of normal dark-adapted rods but below those of normal dark-adapted cones. Outside this central area the thresholds are about 1 log unit above normal cone thresholds. Except in the central field, therefore, rod thresholds are too high to measure and there is also impairment of cone function. C. G. and E. G. (III and III in Fig. 1) have light thresholds above those of normal cones in all retinal locations from center to periphery. Rod function is therefore not measurable and could conceivably be completely lost. The ERG findings in these four patients are closely related to the degree and extent of rod impairment indicated by the light-sense test. T. J. H., who has only slight impairment of rod function in the midperiphery and normal rod thresholds in the far periphery, has a normal ERG. C. H., with measurable rod function in only a central field of 10° radius, has a subnormal ERG. Extinguished ERGs were found in the two patients whose rod thresholds are everywhere too high to measure (because they lie above the threshold gradient of the dark-adapted cones).

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Fig. 4. Visual fields of three of the four patients (A, C. H.; B, C. G.; C, E. G.) whose threshold gradients are shown in the previous figure.
To obtain additional information concerning the extent of impairment of cone function, the visual fields of C. H., E. G., and C. G. were measured on the Ferree-Rand perimeter with white and blue test objects. (In this instrument the background luminance to which the eye is adapted is 0.7 ml.) The results are shown in Figs. 4A, 4B, and 4C. C. G. has the most definite evidence of a visual-field defect, with a slight generalized concentric contraction of the isopters for white and blue test objects. C. H. shows slight constriction of the limits for 6/330 white, but only in the lower temporal quadrant. E. G. had normal fields on August 27, 1965, and a slight contraction in the temporal field 9 months later. In order of severity these early field defects, therefore, correspond to the degree of elevation of the thresholds above those of normal dark-adapted cones. Although the visual fields can be normal when rod function is significantly impaired, perimetric studies are nevertheless useful in detecting the onset and progression of impaired cone function, as will be seen from data to be presented in the next section.

Typical findings at an intermediate stage of visual impairment. Well-marked defects in the visual field for a 6/330 or 3/330 white test object can be found at an intermediate stage of retinal degeneration. When the far periphery is most severely affected a more or less concentric contraction of the field is observed. When there is selective involvement of the midperiphery a ring scotoma is usually found. Illustrative findings typical of the intermediate stage are shown in Figs. 5 to 7.

The visual fields of K. B. for 6/330 white and blue test objects (Fig. 5) show a generalized contraction. The threshold gradient confirms the marked loss of function in the far periphery. The fact that all the thresholds are higher than those of normal dark-adapted cones indicates that there is slight impairment of cone function in the central field also.

Fig. 6 illustrates, for W. W., loss of function primarily in the midperiphery as manifested by the incomplete ring scotoma for 3/330 white and the marked elevation of the thresholds in localized regions in the nasal and temporal field. In the far periphery the thresholds are above those of nor-

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**Fig. 5.** Visual field and threshold gradient of K. B. The light thresholds show significant impairment of cone function at all locations.
Fig. 6. Visual field and threshold gradient of W. W. The light thresholds show impairment of cone function in a midzone corresponding to the ring scotoma.

Fig. 7. Visual field and threshold gradient of S. J. The thresholds show impaired cone function only in the temporal field.
nal rods but below those of normal dark-adapted cones. In the central field the thresholds show no evidence of impairment of either cone or rod function because they fall within the normal range. Results for another patient, S. J., with an incomplete ring scotoma are shown in Fig. 7. Impairment of rod vision is more marked than in the previous case because all of the thresholds from center to periphery are outside the normal range.

Typical findings in advanced stages. Fig. 8 illustrates the transition to an advanced stage in which the ring scotoma is beginning to extend to the far periphery. The field for an 18/330 white test object shows a scotoma extending, in the horizontal meridian, from 10° to 54° nasally and from 10° to 66° temporally. The light thresholds are well above those of normal dark-adapted cones except in the far periphery (at 50° in the nasal field, and from 70° to 90° in the temporal field).

Many patients at an advanced stage of pigmentary degeneration of the retina have a visual field consisting of only a central patch about 5° to 10° or smaller in radius. This type of field is illustrated by the data for one of the members of the V. family, C. W. H., age 12 (III, in Fig. 1). The visual field and the threshold gradient of the left eye are shown in Fig. 9. An 18/330 white test object was seen only in a central field of 8° to 10° radius. The fact that a 3/330 blue test object was recognized as blue in this central area and the fact that visual acuity was 20/30 indicate fairly good cone function in the central field. The light thresholds measured at the fovea and at 6° and 10° from fixation are, however, more than 2 log units above the thresholds of normal dark-adapted cones.

It is of interest that C. W. H. at age 12 shows far greater impairment than his two sisters, T. J. H. and C. H., tested at about the same age (see Figs. 3, A and B; and 4, A). His rate of deterioration also appears to have been far more rapid than that shown by his mother, T. V. H. (II, in Fig. 1), who was first examined at ages 14 and 16. The findings for T. V. H. are reported in detail in a previous paper.  

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![Fig. 8. Visual field and threshold gradient of D. F. The light thresholds show marked impairment of cone function at all locations.](downloaded_from_http://iovs.arvojournals.org/pdfaccess.ashx?url=data/journals/iovs/933621/ on 06/24/2017)
Fig. 9. Visual field and threshold gradient of G. W. H., a member of the V. family, showing marked loss of both rod and cone function at an early age.

Fig. 10. Threshold gradient of T. V. H. (mother of G. W. H., C. H., and T. J. H.) at ages 14 and 16, and visual fields at ages 16 and 40.
which she is reported as Case 7. The data shown in Fig. 10 indicate a slight degree of impairment similar to that of her daughter C. H. at about the same age. At age 40, however, T. V. H. has an advanced defect similar to that shown by her son at age 12.

Patients whose fields are reduced to a small patch centered on the fovea may, like G. W. H., have normal or only slightly impaired visual acuity, and can therefore read ordinary print at a conventional distance of about 40 cm. Even when acuity is significantly reduced, reading is often possible with the aid of a magnifier. Magnification is less helpful when the central field, in relation to the magnified image of the text, is so small that only two or three letters fill the entire field.

It is often difficult to obtain reproducible and reliable measures of the extent and location of the small remaining visual field characteristic of advanced retinitis pigmentosa because of the patient's inability to maintain fixation. Measures of the light threshold are unreliable for the same reason. These tests are therefore of limited usefulness in the study of patients at a far-advanced stage of pigmentary degeneration. Tests of visual acuity give more reproducible data and are helpful in following the progress of the visual impairment. A conventional measure of the acuity for isolated capital letters is, however, of little value in deciding whether or not a magnifier can provide useful reading vision. The simplest and most direct way to answer this question is to have the patient attempt to read graded sizes of continuous text viewed from a fixed distance. The reading cards described in previous papers provide reliable measures of the most suitable amount of magnification. These cards are particularly helpful in the examination of the patient with reduced acuity combined with a small field, because they determine not only the lower limit of required magnification but also an

![Fig. 11. Visual fields of four patients with an advanced defect. Three of the four were able to read with the aid of a suitable magnifier.](image-url)
upper limit of useful magnification set by the angular size of the visual field.

The following case reports of five patients illustrate the use of the reading cards in the selection of magnifiers for patients who can no longer read with conventional spectacles. Fig. 11 shows the visual fields of four of the patients, C. S. and R. M., in spite of low acuities of 7/100 and 6/100, had fairly extensive central fields for a 3/330 white test object. C. S. could read 7M print with ease at the standard distance of 40 cm.; R. M. could read 10M print. (These print sizes are respectively 7 and 10 times that of ordinary newsprint.) C. S. was able to read the newspaper with a magnifier suited to her level of reading vision. R. M., who was not interested in reading for pleasure, was provided with a magnifier of sufficient power to enable him to read the addresses on packages as required by his job.

E. W. and J. C. with somewhat better acuities of 10/100 and 13/100, had much smaller fields than the first two patients. At 40 cm. E. W. was able to read 7M and 10M print, but considerable effort was required because she saw only three or four letters at a time. As would be expected from her small field of vision, an increase in the size of the print to 14M made reading worse rather than better. It was not possible to find a reading aid acceptable to this patient.

J. C., with slightly better acuity but with a smaller field than E. W., preferred 7M to larger or smaller print at the standard distance of 40 cm. Although he could see only two or three letters at a time, a magnifier suitable for a 7M reading level was accepted by this patient as a useful aid. He reports that with its help he reads for about an hour and a half at a time.

The fifth patient, E. F. (39-year-old brother of D. F.), has a visual acuity of 20/100 and a very small field. It could not be measured accurately, but was estimated to be about 2° in diameter when examined with a 3/330 white test object. A confirmatory measurement was obtained by having the patient approach a 20/200 letter to find the distance at which it just filled his field of vision. This occurred at five feet, i.e., when the letter subtended a visual angle of 3.3°. At the standard reading distance of 40 cm. he read 4M and 5M print more easily than smaller or larger sizes, but saw only one letter at a time. As a dictaphone typist he finds it necessary to use a standard medical dictionary to determine the correct spelling of unfamiliar words. He is able to read the bold-faced type by removing his myopic distance correction of -3 diopters and by accommodating about 2 diopters in order to view the book from a distance of 20 cm. Use of the dictionary is easier with the help of a planoconvex stand magnifier. This allows him to relax his accommodation and to hold the book at a distance of 33 cm. With the stand magnifier he can also read newsprint.

Rate of progress of visual impairment.

There are no published reports in which the same tests of visual function were used in long-term studies of the natural history of pigmentary degeneration of the retina. Such information could be helpful in advising the patient as to how long he is likely to maintain useful reading vision. It is also of interest to know more about the early stages of visual impairment to learn whether there are significant periods of time during which the light thresholds and visual fields remain essentially constant and whether spontaneous temporary improvement ever occurs. Such information is needed for evaluation of the many forms of therapy that are proposed from time to time.

This section presents data on patients followed for periods of time ranging from 1 to 34 years. Figs. 12A and 12B show changes in the threshold gradient of two members of the V. family, R. V. G. and J. V. (III, and II 4 in Fig. 1). They are represented by Cases 5 and 8 in a previous paper. J. V. had moderate elevation of the light thresholds at age 13 and corrected acuity of 20/30. At age 38 the thresholds were too high to measure in the far periphery beyond 40°, and showed a
moderate increase in more centrally located areas. Since the foveal threshold has increased only 0.4 log unit during this time, the reduction in his visual acuity from 20/30 to 16/100 is probably attributable to the lens opacity noted at age 38. He works at a gas station and his only visual complaint is foggy vision in bright sunlight. His sister, R. V. G., had at age 18 the characteristic U-shaped threshold gradient (Fig. 12, B) associated with a small central field. The foveal threshold of the dark-adapted eye was at this time almost within normal limits and visual acuity was 20/15. Twenty-two years later, all thresholds were significantly higher; the foveal threshold, for example, was increased about 2 log units. Since her ocular media were perfectly clear at the time of the second examination, the reduction of acuity to 14/100 must, in this case, be associated with impaired function of the foveal cones. The central visual field was 6 to 8° in radius for a 6/330 white test object and about 4° in radius for a 1/330 white object. It is important to note that this field is large enough to permit her to read ordinary newsprint with the assistance of her 11 diopter hand lens.

R. V. G., who shows an earlier onset and a greater degree of visual impairment than her brother, presents a second example of the fact that members of the V. family differ as to the age at which they reach the advanced stage of retinitis pigmentosa. In the previous section, similarly, it was shown that G. W. H. at age 13 had greater visual loss than his sisters or his mother at about the same age.

The next case, R. L. S., provides another example of a patient who, having an advanced defect at age 18, still had useful reading vision at age 42 in spite of a gradual constriction of the fields and elevation of the light thresholds (Figs. 13A and 13B). The foveal threshold, well within normal limits at the time of the first examination at age 18, was 3 log units higher 22 years later. Visual acuity, however, had decreased only from 20/30 to 20/50 and she had no difficulty in reading with a +1.25 add. If one considers, for example, only the decrease in visual field between ages 18 and 25, or the increase in light thresholds between ages 25 and 29, it is of interest that the evidence for loss of visual function is very slight. For this patient, therefore, data based on intervals of time of seven years or less could be misinterpreted as representing a stationary defect rather than a slowly progressing one.

The next patient, S. B., examined at ages 25 and 32, provides another illustration of very slight loss of function in an interval
of seven years (see Figs. 14A, 14B, and 14C). This patient is atypical in that the degeneration involves primarily the lower retina. The visual fields were almost the same on the two dates and show relatively little defect except in the upper field. A threshold gradient measured in the vertical meridian confirmed the advanced defect in the upper field and, at the time of the second examination, showed evidence of a beginning rise in threshold in the lower field. The threshold gradient for the horizontal meridian was within normal limits at age 25. Seven years later the light thresholds were increased in the near temporal field just beyond the blind spot, corresponding to the slight extension of the field defect in this area. The findings for these four patients suggest that the downward course of untreated pigmentary degeneration of the retina can be a relatively slow process, and that useful reading vision can be maintained for 20 years or more.

The next two patients, who are brothers, have been followed to the point at which reading became difficult or impossible because of the very small field of vision. R. M. F. was examined at ages 20, 33, and 49. At 34 he was treated with injections of cod-liver oil without any apparent benefit. Cataract extractions were performed several years later. Visual fields of the right eye are shown in Fig. 15. At age 20 a 6/330 white test object was seen in a field 10° to 30° in radius and visual acuity was 20/50. At age 33 the field for this test object had decreased to a radius of 5°. Red and blue 6/330 test objects were not seen and the acuity was 20/200. At age 49 the 6/330 white test object could still be seen at the fixation point. The exact size of the very tiny patch of field was impossible to determine. Isolated 20/200 letters could be recognized when the patient could find them. Reading of continuous text was not possible because, when large enough to be identified, one letter almost filled the entire field of vision. The visual fields of P. F.'s right eye at ages 30, 34, and 64 are shown in Fig. 16. At age 30 he had a field for 6/330 white of about the same extent as that of his brother, R. M. F., at age 33. Better visual function in this central area is, however, indicated by the fact that 3/330 blue and red were recognized, and the visual acuity was 20/40. At age 32 this patient (P. F.) had a cervical sympathectomy, which perhaps accounts for the slightly wider fields and slight improvement...
in acuity (from 20/40 to 20/30) noted at the time of the second examination. (He is reported as Case 1 in a paper by Walsh and Sloan\cite{6} describing the results of this operation.) When about 58 years old this patient had bilateral cataract extractions, followed by removal of the left eye for absolute glaucoma. When next seen by us at age 64 he had a very small oval field for 6/330 white, with a horizontal radius of about 3°. At the fixation point a 6/330 red test object was identified correctly and a 6/330 blue was reported as either green or blue. Visual acuity was 20/80. Reading continuous text was difficult because of the small field, but by using his finger as a guide he was able to read ordinary print at 25 cm. with a +4 diopter add. There is little doubt that P. F. has fared somewhat better than his younger brother. It is, however, impossible to say whether the cervical sympathectomy was of influence in retarding the rate of visual impairment. Members of the V. family, who received no treatment, nevertheless differed significantly in the rate of decline. The data for these six patients indicate that visual function, as measured by the threshold gradient or the visual field, shows considerable variation in the rate of its downward progress and, on occasion, periods of apparent arrest.

Study of three patients at a very early stage of the disease suggests that spontaneous temporary improvement in the light thresholds can occur. The best-documented evidence of such transient improvement is provided by E. Z., whose father had well-advanced pigmentary degeneration of the retina. When first seen at age nine, E. Z. had a few typical pigment deposits in the far periphery. Fig. 17 shows, during an interval of eight years, changes in the average value of the light threshold (the numerical average of the thresholds at 19 locations in the horizontal meridian). Six tests between the ages of 9 and 11 gave evidence of a gradual rise in threshold during the first year, followed by a decrease during the second year. That

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**Fig. 14.** Threshold gradients (A and B) and visual fields (C) of S. B., who has severe impairment only in the upper field and shows little change in seven years.
Fig. 15. Visual fields of R. M. F. at ages 20 and 33.

Fig. 16. Visual fields of P. F., brother of R. M. F., at ages 30, 34, and 64.
this was a significant improvement is more clearly evident in Fig. 18, which gives the complete threshold gradients for ages 10 and 11. The marked decrease in threshold was only temporary, and was followed by a steady rise up to the last examination at age 17. Fig. 19 shows the light thresholds at ages 10, 15, and 17, and the visual field at age 17.

Two other patients, M. J. J. and F. V., followed for only a short time, showed similar evidence of spontaneous improvement in the light thresholds (Figs. 20A, 20B, and 21). Both have normal fundi and only a questionable contraction of the peripheral fields. M. J. J. has an aunt with established pigmentary degeneration of the retina. F. V. is III, in the V. family pedigree. M. J. J. had in the right eye a marked elevation of the thresholds in the nasal field, which was not present four years later. The slightly abnormal thresholds of the left eye were essentially the same on both dates. Only the right eye of F. V. was tested. The thresholds were outside the normal range in three tests given during an interval of nine months. The marked elevation of the gradient in the nasal field found in the first examination was, however, not present in later tests.

In interpreting these findings it must be remembered that measurement of the light threshold is a subjective test, and that reproducibility varies in different patients. It is possible, therefore, that the apparent improvement is simply a practice effect. Re-
Fig. 19. Threshold gradients of E. Z. at ages 10, 15, and 17, showing increasing impairment. Visual field at age 17.

Fig. 20. Threshold gradients of M. J. J. at ages 24 and 28. The left eye (A) shows no significant change; the right eye (B) shows improvement.

gardless of the interpretation, the fact that such improvement can occur indicates that adequate controls are essential in the evaluation of any therapy which claims to arrest or to reverse the progress of the disease.

Comments

It is clearly evident that pigmentary degeneration of the retina shows marked individual variation in its natural history. Spontaneous improvement in rod function may occur in the incipient stage. This may be followed by periods of rapid downhill progress interspersed with intervals of several years in which there is no significant change in the visual status. The variability in the course of the disease, which was observed even in members of the same family, suggests that some environmental fac-
tor might possibly play a role in hastening the degenerative process. In this connection it is of interest that Dowling has found that the rate of progress of inherited retinal dystrophy in the rat is markedly influenced by the amount of exposure of the retina to light.

Conclusions

1. Measures of the light threshold in the dark-adapted eye at a number of retinal locations from center to periphery provide a sensitive method of detecting localized areas of impaired rod vision. Since the rod mechanism is the first to be affected in pigmentary degeneration of the retina, this type of test is of particular value in early diagnosis of the disease.

2. In the incipient stage at which only rod vision is impaired, the patient's sole complaint is of inability to find his way about in dim illumination. As the defect progresses to an intermediate stage and impairs cone as well as rod function, his visual handicap is somewhat greater and is best evaluated by examination of the visual field of the light-adapted eye.

3. At the advanced stage in which a marked visual field loss is combined with reduced acuity, the patient's remaining visual capabilities are best assessed by special tests of ability to read continuous text. Some patients maintain useful reading vision for many years and are therefore able to meet the visual requirements of sedentary clerical jobs with the assistance of a reading magnifier if this proves necessary and helpful.

4. The rate of visual deterioration varies in different individuals and in the same individual at different times. This variation makes it difficult to evaluate the possible benefit from any form of therapy.

REFERENCES