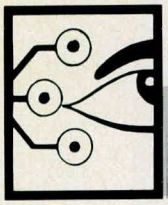

CLINICAL RESEARCH

# Electrical Indices of Rod Dysfunction

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**Abstract**

*Patients presenting with night time vision difficulties and a family history of retinitis pigmentosa require special testing procedures even in the absence of typical functional deficits or ophthalmoscopically visible retinal disease. The authors discuss various theoretical aspects of electroretinography and their practical clinical applications in objectively identifying the physiological defect occurring in retinitis pigmentosa.*

**Abrégé**

*Les personnes souffrants de certaines difficultés de la vision nocturne et ayant une histoire familiale de "RP" exigent l'application de tests spécifiques même dans l'absence de déficience sensorielle ou des signes concrets de lésions rétiniennes. Ce travail traite de certains aspects théoriques de la "electroretinography" et de leur application clinique dans un dépistage objectif de ce défaut physiologique dans un cas de RP.*

## Introduction

Differential diagnoses for patients having difficulty with night time vision include simple night myopia, refractive aberrations resulting from positive spherical aberrations, vitamin A deficiency, and various disorders of retinal function associated with defective rod photoreceptors. Among the retinal disorders resulting in defective night time vision are congenital stationary night blindness, Oguchi's disease, retinitis punctata albescens, and retinitis pigmentosa. One of the most commonly encountered causes of night vision disorders is retinitis pigmentosa (RP)[2]. A definitive diagnosis of RP relies on funduscopic signs, restrictions of the visual fields, elevated rod and/or cone thresholds in dark adaptometry, and reduced or extinguished electroretinograms (ERGs). Neither the absence of the classical bone spicule pigment deposition in the peripheral fundus nor the maintenance of normal or near normal visual fields exclude a possible diagnosis of RP. In the experience of one of the authors (JVL), RP is detectable electrophysiologically despite the retention of normal visual fields. Thus, in the absence of fundus and visual field changes, an early diagnosis of RP can be made on the basis of the ERGs elicited under controlled testing conditions.

## Case History

A 13 year old male Caucasian and his 17 year old brother were referred to the Electrodiagnostic Clinic for evaluation of retinal function because of a family history of RP. The results of an oculovisual assessment and special testing procedures will be presented in detail for the younger patient only. The patients' deceased maternal grandfather and great uncle both had suffered from RP with only light perception remaining at the time of their deaths. An earlier ophthalmological consultation had not yielded any information concerning the possible occurrence of RP in either patient. The main concern at that time for the younger patient was for the optical correction of a relatively large amount of bilateral myopia and astigmatism. Although the younger patient did not complain of any significant difficulties with mobility at night time, his father indicated that he did have difficulties identifying people from a distance at night time. However, both parents attributed this difficulty with nocturnal resolution to inadequate street lighting in their home town. The mother was generally sceptical of the possibility that either son could have RP. As far as the mother could judge, neither patient exhibited any difficulties with colour vision of a blue-yellow nature which is frequently a precursor of manifest retinitis pigmentosa.

## Clinical Findings

### Refraction

| | Prescription | Visual Acuity (6M) |
|---|---|---|
| Right Eye | -10.00/-3.75x020 | $6/24^{-2}(20/80^{-2})$ |
| Left Eye | -9.25/-4.00x165 | $6/21^{-2}(20/70^{-2})$ |
| Both Eyes | | 6/21 (20/70) |

Visual acuity could not be improved with either single or multiple pinhole apertures.

Near-point visual acuity was difficult to quantify with a standard reading chart. However, with considerable effort, the patient was able to attain a 0.75m acuity level in each eye using +8.00D reading adds and holding the reading material approximately 10cm from the facial plane.

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**Binocularity**

Standard cover test procedures for detecting a phoria or tropia were not useful because of the patient's reduced near-point and distance visual acuity. The Hirschberg corneal light reflex technique indicated a constant left esotropia of approximately 10 prism diopters for a 40cm observation distance.

**Visual Fields**

Monocular confrontation fields suggested only a slight restriction of the inferior visual field in each eye. A standard tangent screen procedure for central visual fields could not be done because of the patient's reduced visual acuity. When a 5mm white target was used at a 1M distance, the visual fields for each eye were shown to be roughly symmetrical and approximately 20° to 25° in diameter.

**Electrodiagnostic Evaluation**

Accommodation was relaxed and the pupil of each eye dilated with 1% cyclopentolate hydrochloride while the patient dark adapted for approximately 40 minutes. Each eye was tested separately after dark adaptation. The right side of Fig. 1 illustrates scotopic ERGs elicited for the patient's right eye by scotopically matched blue and red light flashes and a white flash presented within a ganzfeld stimulator[3]. The ERG was extinguished for the blue flash test condition. On the other hand, the red light elicited a measurable ERG but with a "b" wave composed of a single peak as opposed to the expected double peak found in normals. The ERG in response to the white flash was of low amplitude with a longer than normal implicit time for the "b" wave. These abnormalities clearly indicated a gross rod dysfunction. Similar results were obtained for the patient's left eye.

When an abnormality of rod function is indicated by blue, red and white flashes, retinal function is further evaluated by scotopic ERGs in response to red and blue flashes of increasing intensity. Fig. 2 presents a typically normal pattern of ERG responses to blue and red flashes of increasing intensity. Note in particular that testing for graded rod activity by increasing the blue flash intensity causes the amplitude of the "b" wave to increase and the implicit time to decrease systematically. Similarly, increasing the red flash intensity causes the amplitude of the double peak "b" wave to increase and the implicit time of the rod component to decrease. The implicit time of the cone portion of the "b" wave remains unchanged for all stimulus intensities. Fig. 3 illustrates the ERG responses to blue and red flashes of increasing intensity for the patient: None of the normal stimulus-response relationships described above were observable in the patient. The red flashes elicited ERGs whose small "b" wave tended to increase in amplitude with stimulus intensity. However the slower rod portion of the "b" wave was totally absent. Note the development of oscillations of decreasing amplitude in the falling portion of the "b" wave at the higher flash intensities. In sharp contrast, blue flashes of increasing intensity failed to elicit any retinal response at low and moderate intensities and only a small signal for the brightest flash.

One additional test to further confirm the absence of rod activity was performed for this patient. Under dark adapted conditions, presenting blue or red flashes of increasing frequency elicits single and then "flicker" ERGs[4-6] (a series of ERGs resembling a sinewave) whose amplitude decreases with increasing flash frequency (Fig. 4). As the rod photoreceptors are incapable of responding to flash stimuli beyond approximately 25 to 30 Hz., the "b" wave amplitude flash frequency function for a normal individual (stimulated with a flashing red light) is characterized by a "rod-cone break" at approximately 25 to 30 Hz (Fig. 5). The solid upper line in Fig. 5 indicates a rod-cone break typical for an individual with normal retinal function. It should be noted that at a flash frequency of approximately 60 to 80 Hz., the amplitude of the "flicker" ERGs reduces to zero. This represents the electrophysiological counterpart of the psychophysically determined critical fusion frequency (CFF). This biphasic "b" wave amplitude-flash frequency function occurs because the red flash is effective in eliciting a response from both rods and cones. The portion of the curve for flash frequencies between 1Hz. and approximately 25Hz. is largely due to rod activity. Since rods reach their fusion frequency at about 25Hz the second arm of the red flash responsive curve is a function of cone activity exclusively. Note that the patient's "b" wave amplitude-flash frequency function for red flash did not show a rod-cone break. In fact, it tended to saturate at a flash frequency below 60Hz. which under the testing conditions employed is somewhat low. This latter observation implies that the rod dystrophy evident on ERG testing has likely involved the cones as well.

RP is very often associated with an extinguished ERG in the light or dark adapted retina. However, in early cases of autosomal recessive (AR) or autosomal dominant (AD) RP small amplitude ERGs with prolonged "b" wave latencies are recordable. This patient showed reduced amplitude and prolonged latency flicker ERGs for both photopic and scotopic conditions, (Fig. 6) suggesting an AR or AD mode of inheritance. A detailed family tree would be required to determine the exact hereditary mode of transmission.

In summary, the patient showed extinguished ERGs to constant or graded intensity flashes of blue light, and an ERG with a missing peak in response to

scotopically matched flashes of constant or graded intensity red light. Also, he did not show the typical rod-cone break in the "b" wave amplitude-flash frequency function. Given these results and family history, one must conclude that this patient is suffering from a widespread rod dysfunction, likely RP. A diagnosis of retinitis albescens punctata can be eliminated on the basis of the fundus appearance. Fig. 7 presents composite fundus pictures for the patient's right and left eyes. Note the absence of any of the commonly reported bone spicule pigmentation in the periphery of the fundus, as well as the absence of any well defined white spots characteristic of retinitis punctata. The overall appearance is that of a normal fundus, with relatively scant RPE and choroidal pigmentation. The family history of eventual blindness in the grandfather and great uncle, and the patient's current reduction in visual acuity, despite a full optical correction for myopia and astigmatism, indicate an unfavourable visual prognosis.

## Discussion

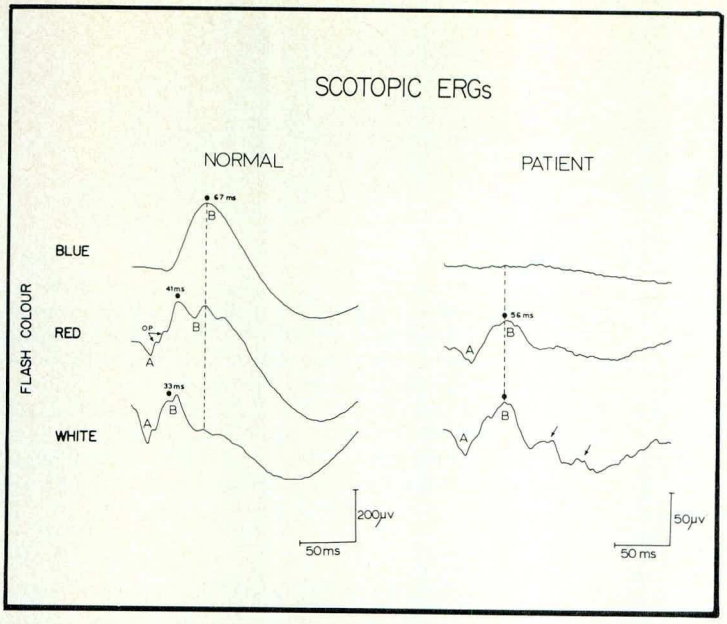
### ERG Evaluation of Rod-Cone Function

The human retina is composed of two types of photoreceptors, the cones and rods. The former class of neuron is primarily responsible for acute day time vision while the latter is maximally sensitive for night time vision. Under controlled light conditions, it is possible to isolate cone from rod activity and identify any physiological dysfunction of either class of photoreceptor. The standard testing procedure for assessing rod function at the University of Waterloo Electrodiagnostic Clinic involves the evaluation of ERGs elicited by scotopically matched red and blue light flashes as well as white flashes[1]. The intensities of the red and blue flashes are matched so that for a standard observer with normal retinal function the ERGs will have "b" waves of nearly equal amplitude. In addition, the ERG elicited by a diffuse flash of red light will be characterized by a "b" wave with two peaks. The first major positive peak corresponds to the faster responding cone system, while the second major positive peak identifies the slower reacting rod system[2]. A white flash will elicit a short latency ERG with a "b" wave amplitude greater than that elicited by either the red or blue flash. The implicit time or "peak" time of the "b" wave of ERGs elicited in dark adaptation (Scotopic ERGs) varies with the test flash. Normally, the implicit time of the scotopic ERG elicited by a dim blue flash is longer than the implicit time of the "b" wave for a scotopically matched red flash, which in turn is longer than the implicit time of the "b" wave for a white flash. Averaged Scotopic ERGs elicited from a juvenile with normal retinal function are illustrated on the left side in Fig. 1. Note that the ERG elicited by the blue flash is primarily composed of a positive (upward) going "b" wave while the ERG in response to a red flash is composed both of a small negative going (downward) "a" wave following by a positive going "b" wave. The ERG in response to a single diffuse flash of white light is composed of a large "a" wave followed by a very large "b" wave. However, an averaged white flash ERG such as the one shown in Fig. 1 will have a smaller "b" wave than a single flash ERG because of progressive photoreceptor pigment bleaching on repeated stimulation with intense white flashes.

When an optometrist is confronted with a patient with a family history of RP, but without any of the typical fundus signs, it is incumbent on him or her to obtain an electrodiagnostic evaluation of retinal function before deciding on the presence or absence of any cone or rod dysfunction.

This report is presented to emphasize the value of objective, electrophysiological indicators of abnormalities in rod or cone function before a definitive diagnosis is made. Psychophysical test procedures, such as dark adaptometry, that are used to assess retinal function are occasionally invalidated by poor patient compliance or ability to respond appropriately in the testing procedure. In the present case, visual field testing gave no clear indication of an advanced photoreceptor dysfunction. Nor did the patient present with any of the symptoms typical of the field losses normally reported by patients with advanced retinitis pigmentosa. Perhaps the expected symptoms of difficulty with night time vision and mobility were somewhat confounded by the parents' belief that any nocturnal resolution abnormalities were related to poor street lighting. It is somewhat surprising that the one ophthalmological consultation a few years prior to this referral apparently did not include an electrodiagnostic evaluation of retinal function because of the family history of RP. Perhaps normal retinal function was assumed because of the relatively normal appearance of the ocular fundus. Clearly, however, there may be pronounced physiological disorders, despite a normal looking fundus as in the case reported here.

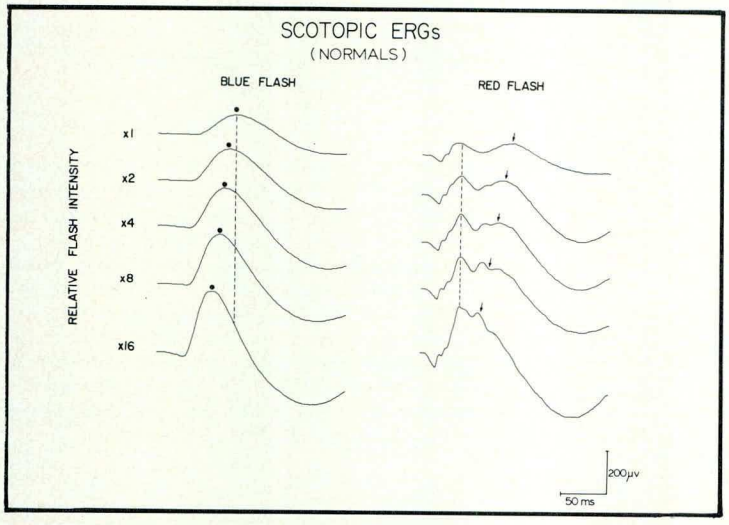
One interesting aspect of this case is that the patient's progressive increase in myopia over the last few years may have been interpreted as the cause of his difficulty with night time vision or generally inferior vision for all visual tasks. Without electrodiagnostic testing, one might assume, incorrectly, that there is residual amblyopia related to uncorrected myopia from an early age. However, ERG testing indicated without any doubt that a severe rod dysfunction was present. Furthermore, the deterioration of retinal function appears to be progressing towards central retinal mechanisms as judged by the reduction in the cone following frequency and delayed photopic flicker ERGs to red




◀Fig. 1

Left side: Scotopic ERGs for a patient with normal retinal function. The blue and red flashes were scotopically matched (equated for intensity to give approximately equal amplitude "b" wave responses). Each record is the average of 20 consecutive ERGs recorded with a Burian-Allen corneal electrode. The vertical dashed line was drawn to emphasize the differences in the implicit time of the "b" waves. Note that the implicit time for the "b" wave is progressively shorter for the blue, red and white flashes. The small black dots specify the place in each ERG where the implicit time of the "b" wave is measured. The amplitude of the "b" wave is measured from the trough of the "a" wave to the peak of the "b" wave. "OP" refers to oscillatory potentials found on the early rising component of the "b" wave.

Right side: Scotopic ERGs for the patient in this case, under the same test conditions. Note the absence of a retinal response to the dim blue flash which is used to elicit exclusively rod responses. The ERG corresponding to the red flash is delayed, has a very low amplitude, and is missing the second major positive peak which is attributed to rod activity. The white flash ERG is also delayed and of low amplitude. The vertical dashed line is drawn at the approximate location where the rod component of the scotopic blue and red flash ERGs should have occurred. The small arrows indicate decaying oscillations of the "b" wave frequently recorded for RP patients.




◀Fig. 2

Figure illustrating the normal response pattern in averaged scotopic ERGs (n=20) elicited by scotopically matched blue and red light flashes of increasing intensity. Note that at low flash intensity the red flashes elicit an ERG whose "b" wave is composed of two peaks. The first peak is due to cone activity while the second slower peak is due to rod activity. The vertical dashed line drawn through the cone portion of the "b" wave emphasizes the fact that the implicit time of this peak does not change with stimulus intensity but does show a progressive increase in amplitude. The rod peak shows a progressive increase in amplitude and decrease in implicit time as the intensity of the flashes increases. The small inverted arrows identify the rod portion of the "b" wave. For blue flash test conditions, the small black dots mark the implicit times of the "b" waves. The vertical dashed line highlights the changes in the implicit times with flash intensity.

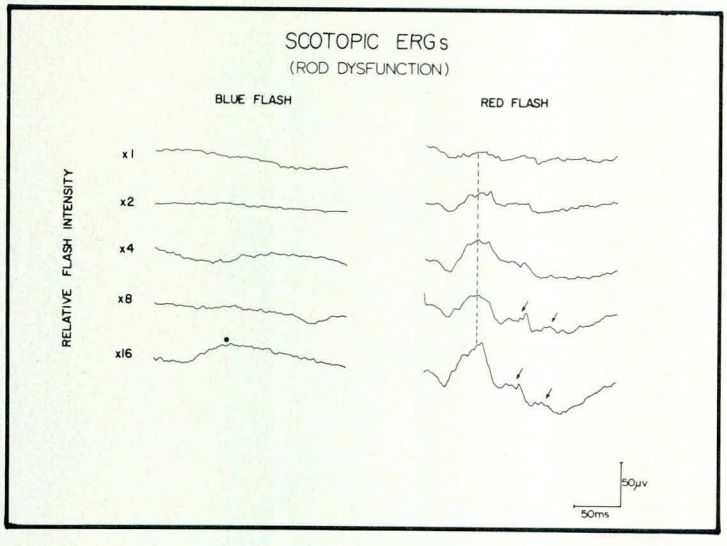



Fig. 3

Averaged scotopic ERGs (n=20) obtained for the patient in this case for the same conditions described for Fig. 2. It is noted that the red light flashes elicited an ERG with a "b" wave composed of a single peak. This peak, attributed to cone function, showed a progressive increase in amplitude with an increase in stimulus intensity. The second peak indicative of rod activity is completely absent. The small inverted arrows locate decreasing amplitude oscillations of the "b" wave at the higher flash intensities. A blue light flash of increasing intensity failed to elicit any significant ERG. A severe rod dysfunction was indicated.

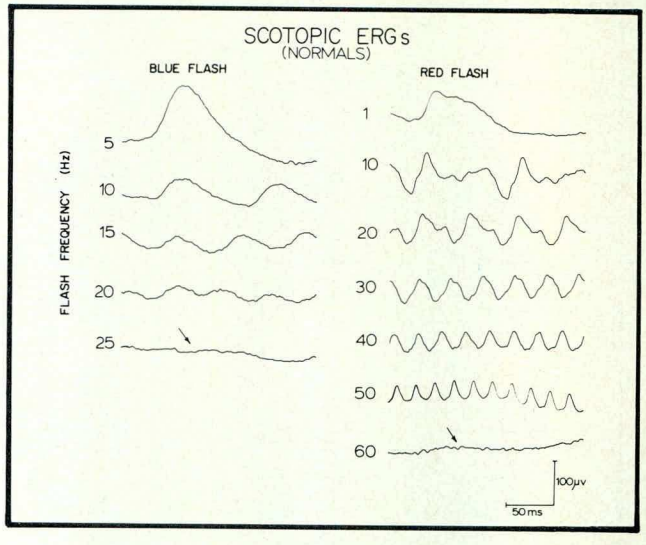



Fig. 4

Figure showing the normal change in the averaged scotopic ERG waveform and amplitude as a function of flash colour and frequency. For blue light (activating only rods) the flicker ERG response reduces to zero at flash frequencies near 25Hz. Red flashes (activating rods and cones) elicit flicker ERGs far above 25Hz, frequently reducing to zero value only at flash frequencies exceeding 60Hz. The fusion frequency for blue and red flashes is indicated by small oblique arrows.

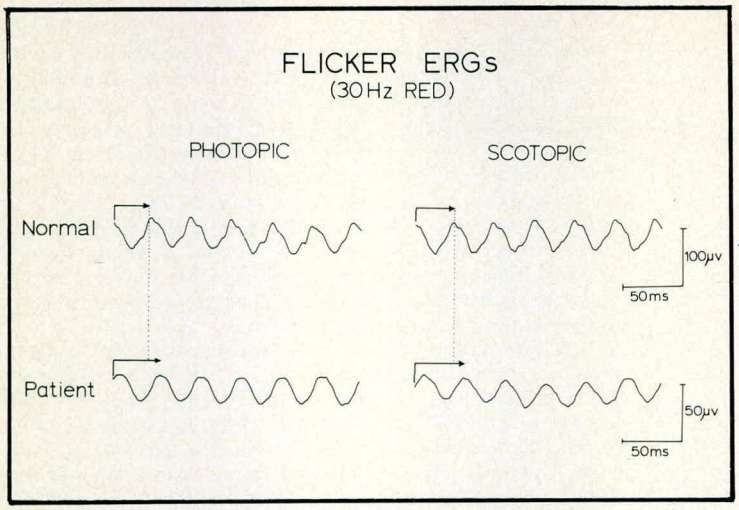



**Fig. 5**

**Graph illustrating the "b" wave amplitude as a function of stimulus frequency for red flashes scotopically matched to blue light flashes for a normal observer (solid lines) and for the patient in this case (broken lines). Note that for red flashes the normal observer demonstrates a biphasic amplitude/frequency function that "breaks" at approximately 30Hz.. The ERG fusion frequency for this normal observer was approximately 80Hz.. In direct contrast, the patient in this case demonstrated a low amplitude ERG response at low flash frequencies, no rod cone break at 25-30Hz., and a reduced flash fusion frequency.**

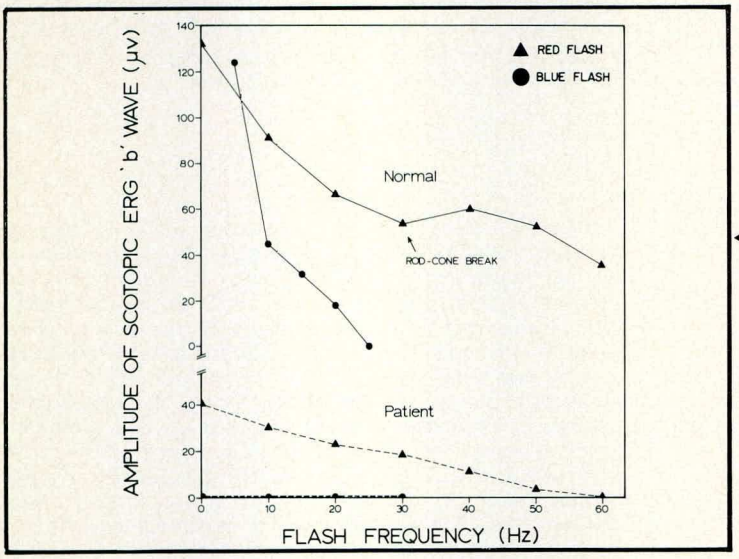



**Fig. 6**

**Comparison of photopic and scotopic flicker ERGs of a normal patient to those obtained from the right eye of the patient in this case. Similar results were found for the patient's left eye. These records are the averaged responses of 20, 200 m.sec. responses to red flashes presented 30Hz. A sinewave response with 6 peaks is expected since only one fifth (200 m.sec.) of the responses to 30 flashes per second are recorded for easy resolution of the flicker ERG waveform. Note the delayed flicker response of the patient shown as a misalignment of the peaks for the flicker ERG of a patient with normal retinal function. The vertical dashed lines highlight the delayed response. Note also that this patient's response amplitude was about half that for the normal.**

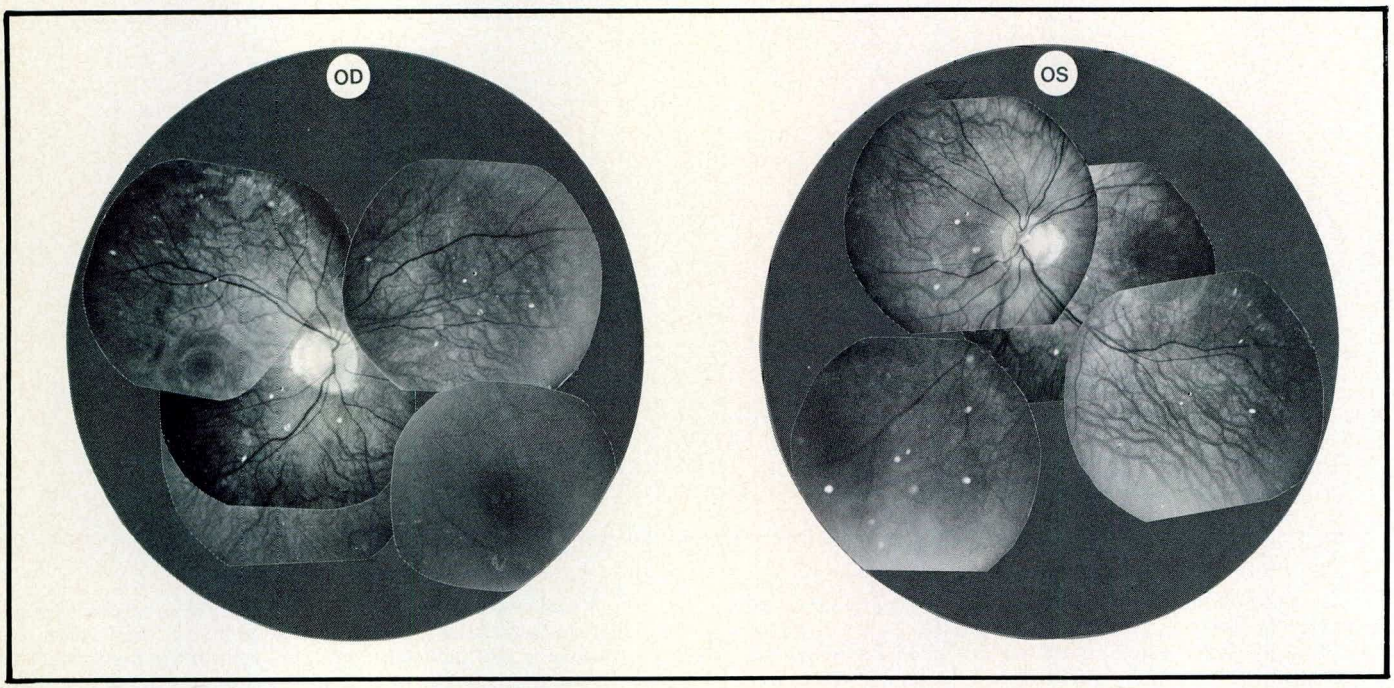



**Fig. 7**

**Composite fundus pictures of the patient's right and left eye. These figures illustrate an absence of any abnormal fundus signs characteristic of RP. The small white spots in these pictures are photographic artifacts. A prominent myopic conus is evident near the optic nerve head of each eye. Except for the slight pallor of the entire fundus and the myopic conus, all fundus signs appear within normal limits. These fundus pictures emphasize that severe physiological dysfunctions may occur in a relatively normal appearing ocular fundus.**

flashes. This latter observation provides an adequate explanation for bilaterally reduced central visual acuities.

A further noteworthy point in this case was that the patient's older brother demonstrated virtually identical abnormalities in the ERG to each of the tests applied, yet retained a 6/9 (20/30) visual acuity level in each eye with an optical correction for moderate myopia and astigmatism. This latter refractive finding had been stable for a number of years. Given the very similar electrodiagnostic findings for both brothers, and the significant difference in refractive error, it cannot be argued that the abnormality of the retinal response for the thirteen year old patient was directly attributable to his highly myopic condition. The fundus appearances for the older brother were the same as those shown in Fig. 7.

Another noteworthy point about the older brother was that he failed to detect (with either eye) any of the diagnostic numbers present in the Ishihara colour plates, yet had a nearly perfect score on the Panel D-15 colour test. (Neither test indicated a well defined colour deficiency in the younger patient). More comprehensive colour vision testing by such tests as the FM 100-hue test or the Nagel anomaloscope may have disclosed some colour anomaly. This finding cautions that the results of colour vision testing alone are not diagnostic, and may, at times, be totally invalidated either because of reduced visual acuity or retinal dysfunction of a general nature. Thus, RP should still be a possible diagnosis even in the absence of a blue-yellow colour defect.

In view of the parents' scepticism over a possible diagnosis of retinitis pigmentosa, they were encouraged to attend part of the ERG evaluation. We believe they found the experience informative and convincing with regard to the likely diagnosis. In view of the eventual diagnosis of RP, the parents were advised that an annual examination to re-evaluate retinal function would be worthwhile in order to determine whether the condition is stabilized or progressive. The parents were also informed that should vision continue to deteriorate, there were low vision devices which would likely be helpful for reading purposes. Finally, the parents were counselled not to expect any improvements in their son's vision, and to be highly selective in the guidance given him with respect to future occupational possibilities. A re-evaluation of retinal function has been scheduled in twelve months.

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