

# Retinal function of the diabetic retina after argon laser photocoagulation assessed electroretinographically

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**SUMMARY** Electroretinographic (ERG) responses were measured in diabetic patients before, during, and after panretinal photocoagulation treatment with argon laser. The laser applications reduced considerably the amplitudes of the a and b waves of the ERG. Moreover, the relationship between the amplitude of the b wave and that of the a wave was severely affected, resulting in ERG responses of abnormal pattern. The b waves were smaller than expected from the a waves. These findings indicated that the photocoagulation treatment not only destroyed the retinal areas directly illuminated by the laser beam, but also affected the functional integrity of adjacent areas. These additional effects resulted in subnormal signal transmission from the photoreceptors to the proximal retina.

Panretinal photocoagulation (PRP) has become an accepted treatment for diabetic retinopathy aimed at reducing the risk of blindness.<sup>1</sup> The intention of this therapy is to destroy a substantial portion of the peripheral retina in order to reduce the difference between oxygen demand and oxygen supply and thus to reduce the stimulus for neovascularisation.<sup>2</sup> The extent of retinal destruction by the PRP treatment may determine its effectiveness. The electroretinogram (ERG) reflects retinal activity as a mass response and is generally used as an objective index of retinal function.<sup>3,4</sup> Therefore many investigators have measured the electrical responses of the diabetic retina after photocoagulation.<sup>5–10</sup> In these studies the amplitudes of the a and b waves were used as criteria for retinal destruction. There was no agreement among the different studies. In one report a 10–95% b wave deterioration was observed in different patients who were treated similarly.<sup>6</sup> This variability was explained by variability in the extent of the effective retinal ablation. Similar lack of direct relationship between the number of laser applications and the reduction in the ERG amplitude was reported by others.<sup>7</sup> Another report concluded that the a wave was reduced more than the b wave,<sup>8</sup> thus supporting the notion that the laser application

destroyed primarily the photoreceptors. These findings were later challenged in a study where both the b wave and the a wave were proportionally reduced.<sup>9</sup> Furthermore, some of the studies concluded that the ERG responses were reduced more than expected on the basis of the coagulated area,<sup>6,8,10</sup> while others stated that ERG reduction was proportional to the coagulated retinal area.<sup>5,9</sup>

In this study the ERG responses were measured in diabetic patients before, during, and after treatment with argon laser. The relationship between the amplitude of the b wave and that of the a wave was used as an index of retinal function.<sup>11</sup> This relationship was used to determine the integrity of signal transmission from the photoreceptors to the proximal retina.<sup>11</sup> Moreover, this method of ERG analysis circumvented problems arising from differences, between experimental sessions, of the flash intensities reaching the retina, due, for instance, to differences in pupil dilatation.<sup>11</sup> The data indicated that the photocoagulation treatment destroyed a substantial portion of the peripheral retina, causing a severe reduction in the ERG responses. In addition the laser treatment affected adjacent retinal areas and caused deterioration of signal transmission from the photoreceptors to the proximal retina. This finding explained previous reports of larger reductions in the b wave amplitude than expected on the basis of the coagulated area.

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## Materials and methods

### SUBJECTS

Electroretinographic responses were measured in 23 diabetic patients ranging in age from 30 to 70 years. In 16 patients ERG records were obtained only after panretinal photocoagulation (PRP) with argon laser. In these patients both eyes underwent PRP treatment. In seven patients the effects of the PRP treatment were followed in detail by recording the ERG responses before, during, and after treatment. In these subjects the ERG was also measured one week, one month, and if possible also six months after treatment, in order to ensure reliable recordings without the possible effects from retinal oedema caused by the laser treatment. These seven patients underwent PRP treatment in only one eye, either because the fellow eye had been treated before or because treatment was not mandatory.

### ELECTRORETINOGRAM

The procedure for ERG recordings has been reported previously.<sup>11</sup> The electrical signals were recorded between a Henkes-type contact lens electrode (Medical Work Shop) and a reference electrode attached to the subject's forehead. The ground electrode was placed on the ear lobe. Uniform illumination of the retina by the test flash was achieved with a -100 dioptre lens attached to the contact lens electrode. An electronic camera flash was used for photostimulation. The intensity and colour of the test flash were controlled by 'neutral' density filters and broad-band colour filters (Schott).

The subject's pupil was maximally dilated by 0.5% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride. The ERG responses were first recorded in the light-adapted state with background illumination of 11 foot-lamberts (38 cd/m<sup>2</sup>). After 25 minutes of dark adaptation the ERG responses evoked by flashes of different intensities were recorded. Rod function was measured by a dim blue test flash.

ERG analysis included comparison of the a and b wave amplitudes measured in each response. The a wave amplitude was measured from the baseline to the trough of the a wave. The b wave amplitude was measured from the trough of the a wave to the peak of the b wave.

### PANRETINAL PHOTOCOAGULATION

Panretinal photocoagulation in diabetic patients suffering from either preproliferative or proliferative diabetic retinopathy was performed in the usual manner with the pulsed argon laser (Britt). An average of 2500 applications was done, divided into five to six sittings. For each patient the laser beam was

adjusted to produce similar retinal burns. The laser beam parameters were within the following ranges: energy, 300 mW to 1.8 W; duration 0.02 to 0.1 second; and spot size, 200 to 500  $\mu$ m. PRP was performed in a scattered pattern, beginning by encircling the posterior pole and then covering a quadrant per session from the nasal side and clockwise. Some of the patients were admitted to hospital and treated daily until satisfactory coverage of the whole retina was achieved. Others were treated on an outpatient basis, with intervals of some days between sittings. Eyes were selected for PRP treatment either if they showed preproliferative retinopathy where areas of non-perfusion could be demonstrated by fluorescent angiography or if they showed neovascularisation on the disc (NVD) or neovascularisation elsewhere (NVE). Patients who underwent treatment in only one eye were chosen only on clinical considerations. In these cases the degree of retinopathy differed significantly between the two eyes. In all cases the untreated eye was treated, if necessary, at a later date.

## Results

The ERG responses shown in Fig. 1 were recorded from one diabetic patient who underwent panretinal photocoagulation treatment of the right eye. Each pair of responses contains the ERG response recorded from the left (upper trace) and the right (lower trace) eyes. The responses in Fig. 1 were obtained before photocoagulation treatment was started (first column), after 900 laser applications to the right eye (second column), after treatment to the right eye was completed (third column), and six months after PRP was completed (fourth column). This patient was admitted to hospital and therefore received laser applications almost daily. ERG measurements were done in this and in other patients in hospital 24 hours after completion of each photocoagulation session. Since in this study we were interested in retinal function based on the entire dynamic range of the ERG, only dark-adapted responses were considered and are illustrated in Fig. 1. The responses in the first row were obtained by dim blue flash (4 log units attenuation) and therefore represented rod function. The responses in the second and third rows were evoked by white flashes attenuated by either a 3 log unit (second row) or a 1 log unit (third row) filter. As is evident in Fig. 1, the ERG responses of the right (treated) eye decreased significantly in amplitude after the laser treatment, while the responses measured from the left (untreated) eye varied only slightly between different experimental sessions. In all seven patients studied the ERG responses of the untreated eye were characterised by normal pattern and amplitude. However, normality was not satisfied

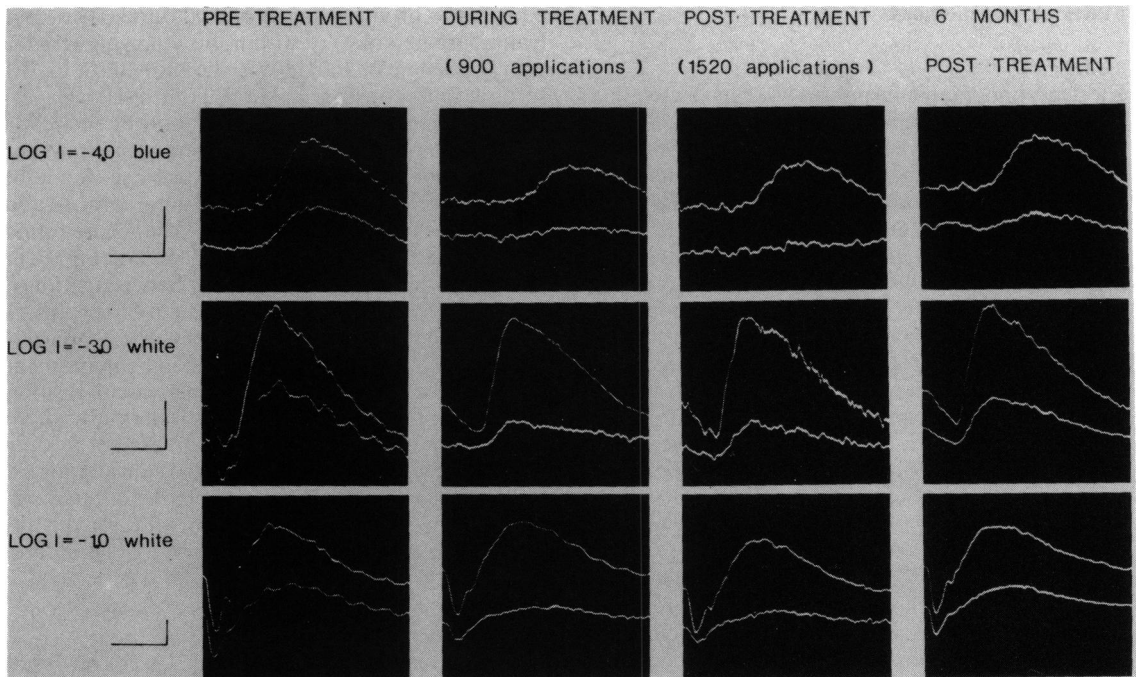


Fig. 1 Dark-adapted ERG responses measured in one diabetic patient. Each pair of responses (OS: upper trace; OD: lower trace) was evoked by either dim blue flash (upper row), white flash of moderate intensity (middle row), or bright white test flash (lower row). The relative intensity of the flash is described by the 'neutral' density attenuation to the left of each row of responses. The ERG responses were obtained before PRP treatment (first column), during treatment after 900 laser applications had been delivered (second column), immediately after treatment (total of 1520 applications) was ended (third column), and six months after the PRP treatment (fourth column). The calibration bars to the left of each row of responses have a height of 200  $\mu$ V and a length of 50 ms.

by every parameter; the oscillatory potentials were usually subnormal.

Fig. 2 shows the effects of the photocoagulation treatment on the ERG responses. The reduction in the ERG amplitude was calculated from either the post-treatment/pretreatment amplitude ratio (Fig. 2A) or the treated eye/untreated eye amplitude ratio (Fig. 2B). The data are given as a function of the number of laser applications. In order to minimise the possible contribution of retinal oedema to the reduction in the ERG amplitude, ERG data were also measured one week, one month, and six months after completion of the PRP treatment and are shown in Fig. 2. The reduction of the ERG amplitude was calculated from responses evoked by flashes of different intensities. Reduction in the rod function was obtained from responses evoked by blue flash attenuated by a 4 log unit filter (open triangles). The white flashes used were bright enough to evoke responses containing both a and b waves. Therefore the reduction in these waves was calculated separately. In Fig. 2 open symbols describe b wave data, while solid symbols describe a wave data. Two different white

flashes were used, one attenuated by a 3 log unit filter (circles) and the other by a 1 log unit filter (squares). It is apparent that the degree of retinal destruction calculated from ERG data strongly depended on the intensity of the test flash used to evoke the ERG responses. Estimates of retinal destruction also depended on whether the a wave or the b wave was used for its calculation. No consistent differences were found here between a and b wave reductions, contrary to previous findings of larger reduction in a wave than in b wave.<sup>8</sup>

Detailed examination of the ERG data after PRP treatment revealed that the b wave was usually reduced to a value which in the normal retina was not expected to be preceded by an a wave. To illustrate this observation the relationship between the b wave and the a wave for one diabetic patient is plotted in Fig. 3. The continuous curve bounded by the two dotted curves describes the normal mean  $\pm$ SD obtained from ERG data measured in 20 volunteers with normal retinal function.<sup>11</sup> The data points were obtained from ERG responses measured before treatment (circles), during treatment (triangles), and

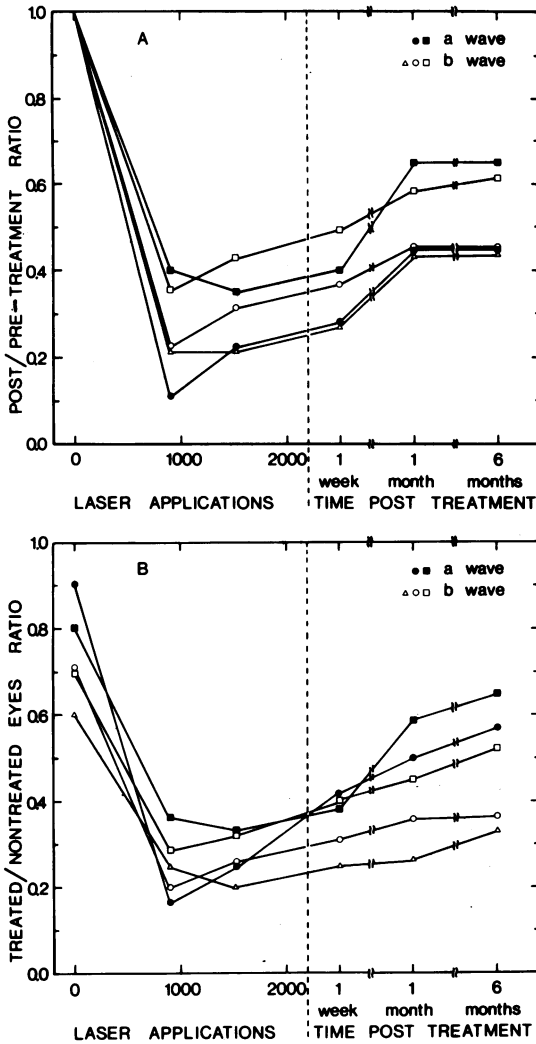


Fig. 2 The effect of PRP treatment on the amplitude of the ERG responses. The reduction in the ERG is described either relative to the pretreatment values of the treated eye (A) or by comparing the treated eye to the untreated one as measured in each experimental session (B). The reduction in the ERG is shown first as a function of the number of laser applications delivered and then as a function of time after the PRP procedure was finished. The data points describe the reduction of the a wave (solid symbols) and the b wave (open symbols). The ERG responses used to construct the figure were elicited by dim (4 log units attenuation) blue flashes (open triangles), white flashes attenuated by a 3 log unit filter (circles), and white flashes attenuated by a filter of 1 log unit (squares).

one month after PRP treatment had been completed (squares). The b wave/a wave relationship of the untreated eye (open symbols) was within the normal range or slightly above it and did not change signifi-

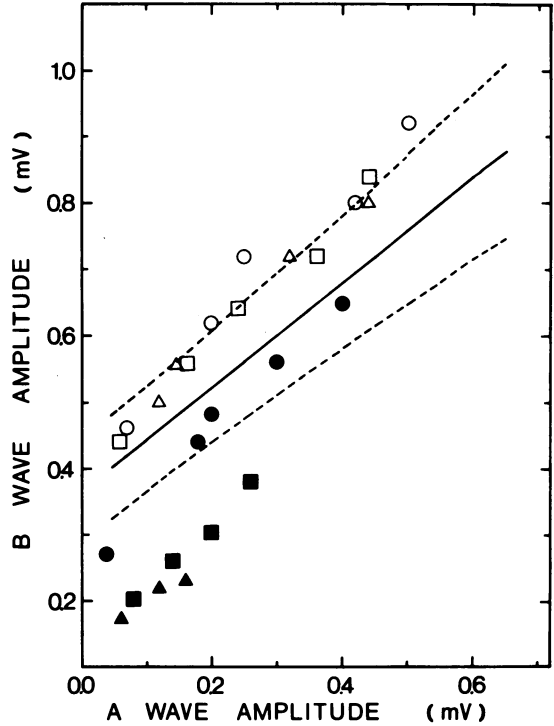
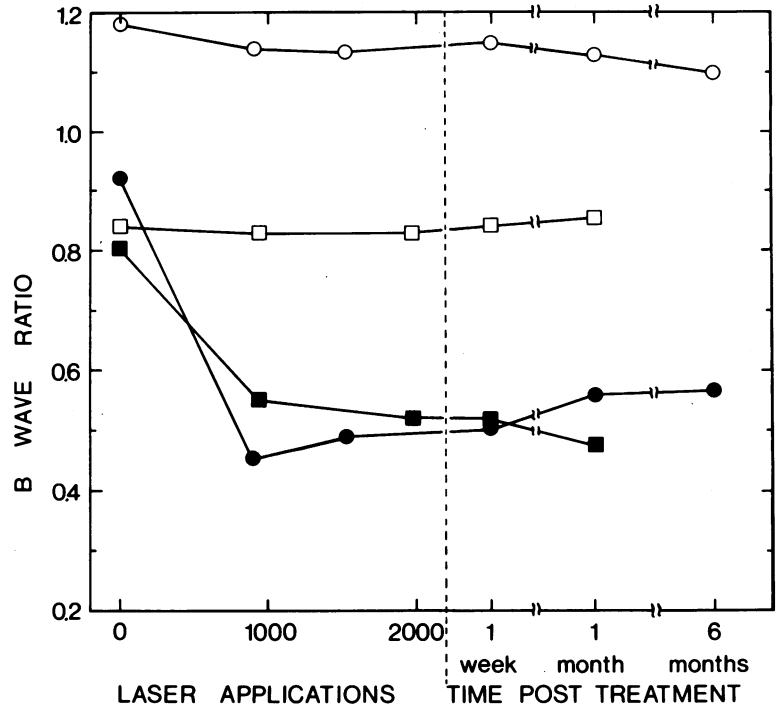


Fig 3 The relationship between the b wave amplitude and the a wave amplitude. The mean normal relationship (continuous curve) is bounded by two dashed curves which describe the normal range ( $\pm 2$  SD). Data are given for the treated (solid symbols) and untreated (open symbols) eyes of one diabetic patient. Each set of symbols describes one experimental session. The ERG responses were measured before PRP treatment (circles), during the treatment period (triangles), and one month after termination of treatment (squares).

cantly between different experimental sessions. Data from the treated eye obtained before treatment (solid circles) were significantly different from the untreated eye data (open circles) but still within the normal range. ERG responses recorded from the treated eye in the middle of the treatment period (solid triangles) and one month after completion of the treatment (solid squares) showed not only reduction in the amplitude of the ERG but also a significant change in its pattern. The b wave/a wave relationship reduced significantly—that is, the b wave measured was significantly smaller than the value expected from the a wave amplitude.

This finding was quantified by using the a wave as the independent variable that depended only on the light intensity reaching the retina and the functional integrity of the photoreceptors. Thus for each ERG response the measured a wave was used to obtain the amplitude of the b wave expected from a normally

Fig. 4 The effect of PRP treatment on the functional integrity of the retina. The b wave ratio is the ratio between the measured b wave and the value expected according to the a wave. The expected b wave was obtained from the normal b wave/a wave relationship. Each data point describes the average b wave ratios calculated for the individual ERG responses recorded from one eye in one experimental session. The b wave ratio is given as a function of the number of laser applications and also as a function of time after the PRP treatment was completed. The data were measured from both the treated (solid symbols) and the untreated (open symbols) eyes of two diabetic patients (squares and circles).



functioning retina (Fig. 3, continuous curve). The ratio between the measured amplitude of the b wave and the expected value was averaged for all the responses obtained in each experimental session from one eye. This average, defined as the b wave ratio, was used as a quantified measure of the function of the diabetic retina. In Fig. 4 the b wave ratios for the treated (solid symbols) and untreated (open symbols) eyes are shown for two diabetic patients. Each data point was calculated from one ERG session from all the ERG responses measured in one eye that contained both a and b waves. The b wave ratio was calculated as a function of the number of laser applications from the ERG responses recorded at different stages of the PRP treatment. Data were also obtained one week, one month, and six months after completion of the treatment. The b wave ratios calculated for the two eyes before treatment differed significantly in one patient (circles) and slightly in the other one (squares). This was expected, since the eyes suffered from different degrees of retinopathy. The eye chosen for laser treatment was suffering from more advanced retinopathy than the fellow eye.

In all seven patients studied the eye scheduled for PRP treatment, based on clinical criteria, was also characterised by a smaller b wave ratio—that is, there was a correlation between the fundus appearance and the ERG data. Laser photocoagulation

significantly reduced the b wave ratio to a level that stayed relatively constant throughout the treatment period and even six months after treatment had been completed. The b wave ratios of the untreated eyes varied slightly between experimental sessions. Comparison between the b wave ratios calculated for the treated and untreated eyes of six diabetic patients is given in Table 1. One patient who was studied here had previously undergone PRP treatment in one eye, and therefore his data were excluded from Table 1. Before PRP treatment both eyes showed normal b wave ratios, indicating normal signal transmission in the retina. After treatment was completed the b wave ratio of the untreated eye did not change, while that of the treated eye declined significantly, indicating inferior signal transmission from the photoreceptors to the proximal retina.

Retrospective examination of ERG data from 23 diabetic patients who underwent PRP treatment in both eyes revealed an average b wave ratio of  $0.509 \pm 0.111$  (SD). This value was significantly below the

Table 1 B wave ratio for treated and untreated eyes in six diabetic patients

	Treated eye (mean $\pm$ SD)	Untreated eye (mean $\pm$ SD)
Pretreatment	0.861 $\pm$ 0.069	0.867 $\pm$ 0.167
Post-treatment	0.563 $\pm$ 0.062	0.859 $\pm$ 0.173

normal value of  $1.01 \pm 0.1$  (SD) obtained from 20 volunteers with normal retinal function. These diabetic patients were examined electroretinographically because they either were scheduled for vitrectomy or had severe visual loss which could not be explained based on clinical data. These findings therefore supported the conclusion that photocoagulation by argon laser reduced signal transmission in the retina.

## Discussion

The ERG responses were measured before, during, and after unilateral PRP treatment with argon laser in seven diabetic patients. The ERG parameters usually used to determine retinal function are the amplitudes of the a and b waves. However, it has been shown here that evaluation of the extent of retinal destruction could not be done reliably by comparing either the b wave or the a wave amplitude with the values measured in the treated eye before treatment or to the values obtained from the untreated eye. The extent of retinal damage thus calculated depended on the flash intensity used to evoke the ERG responses. In general the brighter the flash used the smaller the reduction observed in retinal function.

An additional parameter for the ERG analysis, the b wave/a wave relationship, was found most useful in evaluating the loss of retinal function induced by the laser treatment. This relationship is based on the assumption that the a wave depends on the light intensity reaching the retina and the functional integrity of the photoreceptors. The b wave depends on the a wave and on signal transmission from the photoreceptors to the proximal retina.<sup>11</sup> Therefore any interference limited to the light pathway or to the photoreceptor function is not expected to affect the b wave/a wave relationship.<sup>11</sup> It has been shown in this report that laser applications significantly reduced the b wave/a wave relationship of the treated eye (Fig. 3). The b wave ratio of the treated eye was found to be within the normal range before treatment started, suggesting a normal signal transmission in the retina. The reduction in the b wave ratio caused by the laser treatment indicated that the non-coagulated retina responded abnormally to light stimuli and that this impairment was expressed by a significantly smaller b wave than expected from the measured a wave. This observation is supported by data published previously.<sup>9</sup> In Table 5 of that report scotopic ERG data were given for eyes treated with argon laser. In all the patients the post-treatment responses showed a subnormal b wave/a wave relationship, while most cases (7 of 10) showed a normal b wave/a wave relationship before treatment. These

findings suggested that the argon laser applications had two major effects on the retina: the laser pulses destroyed retinal tissue directly illuminated and also reduced signal transmission in adjacent retinal areas. Histological support for this conclusion has been obtained from a checkerboard coagulation applied to the rabbit retina, where degeneration of the retina was also observed between coagulated areas.<sup>12</sup>

The conclusion that the laser applications also affected the non-coagulated retinal areas explains previous reports in which the b wave reduction was found to be larger than expected from the estimated area of the coagulated retina.<sup>6,8,10</sup> The b wave, which is a summed response of the entire retina, is severely reduced by PRP treatment, owing to direct destruction of retinal tissue. The additional reduction in the b wave, which cannot be accounted for by the coagulated retina, is caused by defective signal transmission in the non-coagulated areas. Another observation that can be explained by the data presented here was the finding that the a wave was more affected than the b wave by the photocoagulation treatment.<sup>8</sup> This observation contradicted Granit's general comment that any interference (with the exception of alcohol) with the retina would affect the b wave more than the a wave.<sup>13</sup> It was argued that the selective effect of the laser treatment on the a wave reflected its direct destructive effects on the photoreceptors.<sup>8</sup> Similar conclusions could be drawn here from the data presented in Fig. 2A. Examination of the ERG responses evoked by flash intensity of  $-3.0$  log relative units revealed that the a wave (solid circles) was reduced by the photocoagulation treatment to a larger extent than the b wave (open circles). This differential effect was apparent only when the amplitudes of the b and a waves were considered separately and were compared with the pre-treatment values without account being taken of the relationship that existed between these waves in the normal ERG. In view of the normal b wave/a wave relationship (Fig. 3), a 50% reduction of the a wave—for instance, from 200  $\mu$ V to 100  $\mu$ V caused by destruction of photoreceptors only—is expected to cause a reduction of the b wave from 524  $\mu$ V to 444  $\mu$ V, namely, by about 15%. If the b wave is reduced to a greater extent, as was found here and previously,<sup>5-10</sup> it implies that the b wave is more affected by the laser treatment than is the a wave. It can be concluded, therefore, that the reduction in the a wave due to the direct destructive effects of the laser upon the photoreceptors should cause only a proportional reduction in the b wave, according to the normal b wave/a wave relationship. The additional reduction observed in the b wave is due to subnormal signal transmission from photoreceptors to the proximal retina in non-coagulated areas.

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