

pression or inhibition, since it cannot be assumed that the occlusion of the fixating eye resulted in a reorientation of the retinal elements of the amblyopic eye.

The other thought is this: In the past I have assumed, as have others, that in patients in whom intensive attempts at re-educating the visual acuity of the amblyopic eye were not successful in improving the acuity of that eye beyond a certain level, we were faced with an amblyopia of pathologic origin, even though we were unable to discover any fundus anomalies with the ophthalmoscope. Ever since the work of Bangerter and Cüppers became known, a number of my friends interested in the amblyopia problem have pointed out to me that there was no such thing as a pathologic strabismic amblyopia and that my assumption was simply based on my inability to diagnose small degrees of eccentric fixation.

Dr. Enoch's work opens up the possibility of reviving the concept of a pathologic strabismic amblyopia. The question arises then, how can a mal-orientation of the retinal elements occur, such as Dr. Enoch believes to be present? Many years ago, stimulated by a case of what we then called pachymeningitis hemorrhagica, the eyes of which I had an opportunity to study histologically. I examined a number of eyes of newborn children ophthalmoscopically and was struck by the frequency with which retinal hemorrhages, often rather large and numerous ones, were seen in these infants. These hemorrhages disappeared without leaving a trace and had no appreciable effect on the function of the eyes. It is quite conceivable that such hemorrhages, if they occurred at the posterior pole of the eye, while not affecting the eye grossly might produce a disarrangement in the orientation of the sensory retinal element and result eventually in such phe-

nomena as the ones which Dr. Enoch has described for us.

I have just one question to ask Dr. Enoch. It was not clear to me why Dr. Enoch felt that in his last case in which the patient had to blink to "restore" the brightness of the adapting field, the seat of the lesion was central to the receptors.

I wish again to congratulate Dr. Enoch on his excellent presentation of a beautiful piece of work.

DR. ENOCH (closing): I certainly want to thank Dr. Burian for his kind remarks. I shall endeavor to answer the questions raised as best I can.

Any factor which will introduce obliquity of incidence of the light, or of the receptors (relative to each other) should result in the findings described above to some degree.

There is no doubt that the amblyopia of subject D.S. consisted of more than one factor. The same may be said of subject R.W. This is why it is important to develop a more complete etiology of amblyopia, in order that we may predict the results of training, and to direct our attention to the specific needs of the patient. Where training or other procedures are not yet possible, such a breakdown of amblyopias will serve to guide our research. This study is but a first step in such a breakdown.

In the case of the subject who restored field brightness by blinking, one cannot say that the fault lay in the photochemical response mechanisms of his receptors. From our knowledge of dark adaptation, a brief blink is not sufficient to restore photochemical concentrations. Further, the tests completed in this series show that retinal response is normal (as defined above). Rather, it would seem that this defect would be in the excitation transmission system or in the interpretive centers. In terms of the tests performed, one cannot tell at this time at which level this defect is mediated.

THE EFFECT OF TWIN FLASHES AND OF REPETITIVE LIGHT STIMULI ON THE HUMAN ELECTRORETINOGRAM*

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The size and shape of the electric responses of the retina depend, aside from physical factors of the stimulus and technical factors of recording, on biologic factors, the state of the retina. Illumination of the

retina by a flash of light produces changes in the state of the retina which last beyond the duration of the flash. Thus twin flashes, and the use of repetitive light stimuli, offer a

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tool for the study of the effect of photic stimulation on the retina.

The effect of twin flashes on the retina of animals has been investigated by a number of physiologists. Studies in man were done by Dodt¹ and Mahneke.² Repetitive stimuli have proved useful not only in physiologic experiments but also in clinical electroretinography.

The present report deals with a study in which we employed twin flashes of four intensity levels, but equal for each set of flashes, separated by 15 to 150 msec. intervals, and repetitive stimuli with comparable intervals.

TECHNIQUES AND PROCEDURE

Experiments were performed on five subjects, students between the ages of 20 and 24 years, without significant ocular anomalies.

The light source was provided by a PS-2 Grass Photo Stimulator: Intensities 1 (I_1), 4 (I_4), and 16 (I_{16}) were employed. In addition, a fourth, low intensity was obtained by a neutral filter consisting of an exposed X-ray film, giving a reduction by two log units. It was used in conjunction with I_1 (I_1F_2). The photo stimulator could be operated manually or automatically by a Hunter Timer, delivering one flash every four seconds.

The active electrode was a Burian-Allen³ speculum electrode; the indifferent electrode, a silver cup electrode, was fastened to the supraorbital area of the eye to be tested; grounding was provided by two electrodes, one fastened to each earlobe of the subject.

Recording was done simultaneously with a Grass 4-channel EEG pen-writer and a Dumont oscillograph and Grass camera. The paper and film records were correlated by a lapse time indicator (Arnott⁴). The details of the experimental arrangement will be described in a forthcoming publication.

The experimental procedure was as follows. After the subject was prepared, he was light adapted for five minutes to the light reflected from a bowl painted with non-

glossy white paint. He was then dark adapted for 10 minutes and the automatic light flashes were started. The intensity remained unchanged during each experimental session. To maintain a steady level of adaptation, a flash was delivered automatically every four seconds throughout the whole session, except at the end when repetitive stimuli were used. After the first minute of delivering the flashes, recording of single flashes were made for one-half minute. At the 12th minute double flashes of 15 msec. flash interval were delivered for one-half minute, followed again by one-half minute of single flashes. The procedure was repeated in exactly the same fashion with double flashes of 20, 30, 40, 60, 70, 80, 90, 100, 120, 150 msec. intervals. At the conclusion of this series repetitive light stimuli with frequencies of 1, 2, 4, 6, 7, 8, 10, 12, 15, and 20 stimuli per second were delivered.

A few exploratory experiments were discarded. One experimental series on each eye of each subject was utilized for this report. For each stimulus situation in each series three electroretinograms were measured and the measurements averaged. These averages were then again averaged for the whole group.

ANALYSIS AND DISCUSSION OF RESULTS

The results will be analyzed under four headings: (1) The single flash electroretinogram; (2) the effect of twin flashes on the first electroretinogram; (3) the second electroretinogram with twin flashes; (4) the electroretinogram with repetitive flashes.

1. THE SINGLE FLASH ELECTRORETINOGRAM

While the data obtained with single flashes do not add essentially new information, they furnish a clear and consistent picture of the differences in the size and shape of human electroretinograms obtained with stimulating flashes of four intensity levels.

In most of our electroretinograms the four typical components of the electroretinogram resulting from flashes of brief duration, a

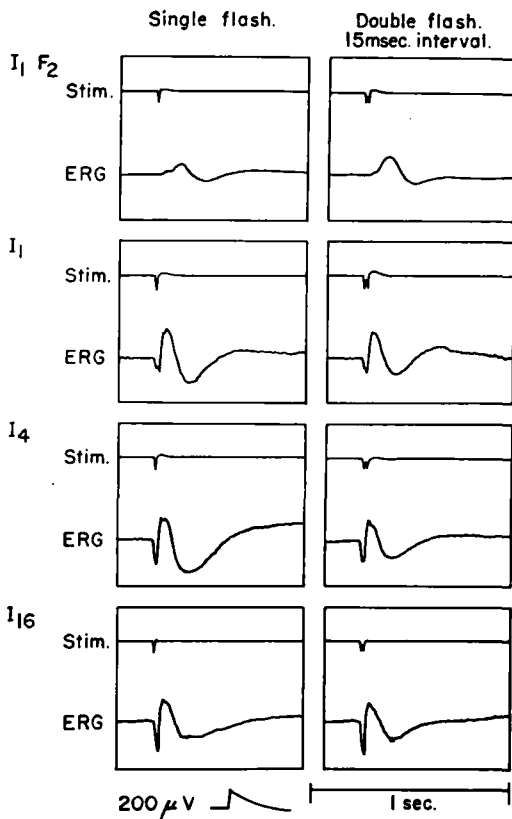


Fig. 1 (Burian and Spivey). Electroretinograms obtained with single flashes of four stimulus intensity levels (left hand column) and with double flashes having a 15-msec. interval (right hand column). Note the small positive hump early in the response with I_1F_2 and the difference in size of the responses with I_1F_2 of the single flash and the double flashes. Note also the difference in shape of the electroretinograms with single and double flashes at the higher intensities, demonstrating the reduction in the scotopic component with the double flashes.

double a-wave and a double b-wave, were clearly discernible, with the exception of the electroretinograms produced by I_1F_2 flashes which never gave an a-wave (fig. 1). In some of the electroretinograms the positive elevation was represented by a plateau rather than by two distinct peaks, but in the majority of them two peaks could readily be measured.

We shall speak of the four components of the electroretinogram as of the first and second negative and positive elevations and designate them as a_1 , a_2 , b_1 , and b_2 . Such a

designation, being purely descriptive, avoids any theoretic implications and should be preferable even to the designation a_p , a_s , b_p and b_s , suggested by Johnson⁵ to avoid the existing terminologic confusion, where the subscripts p and s stand for photopic and scotopic, respectively.

The summary of the averages of the measurements obtained (table 1, fig. 2) permits the following conclusions.*

1. Stimulation with low intensity (I_1F_2) resulted in electroretinograms from which the a-wave was always absent. There was, however, in all of the electroretinograms a small first positive elevation which had a peak time of 65 msec. which we believe to correspond to the b_1 -wave of the electroretinograms obtained with more intense flashes (fig. 1).

2. With intensity I_1 an a_1 and a_2 -wave, and a b_1 and b_2 wave were obtained, with the first negative and positive components being *smaller* than the second ones.

3. With intensities I_4 and I_{16} the situation was reversed, the first negative and positive deviations being *larger* than the second ones.

4. The absolute values of the b_1 - and b_2 -waves were somewhat smaller for I_{16} than for I_4 .

5. The peak times of a_1 and of a_2 were the same for all intensities, whereas with the higher intensities there was a reduction in the peak time of b_1 and especially of b_2 , the peak time of b_2 for I_{16} being only one half of that for I_1F_2 .

These findings summarize and confirm the results obtained with many different methods in this laboratory and in others. They clearly support the assumption that a_1 and b_1 are essentially expressions of the *photopic* process: at a given level of dark adaptation they are smaller for low stimulus intensities and larger for high stimulus intensities than their counterparts a_2 and b_2 . These latter com-

* In evaluating the mean deviations it should be understood that they relate to the differences between subjects. For measurements in the individual subjects the deviations were generally much smaller.

TABLE 1
AVERAGE AMPLITUDES (A) AND PEAK TIMES (t_p) OF THE FOUR COMPONENTS OF THE ELECTRORETINOGRAM WITH SINGLE FLASHES OF FOUR INTENSITY LEVELS

	a ₁		a ₂		b ₁		b ₂	
	A μ V	t_p msec	A μ V	t_p msec	A μ V	t_p msec	A μ V	t_p msec
I ₁ F ₂	—	—	—	—	33 \pm 3	65 \pm 7	123 \pm 14	110 \pm 4
I ₁	97 \pm 19	13 \pm .1	107 \pm 19	22 \pm .1	373 \pm 24	45 \pm 4	403 \pm 16	61 \pm 3
I ₄	230 \pm 18	15 \pm 2	233 \pm 8	20 \pm 1	479 \pm 24	43 \pm 2	443 \pm 13	60 \pm 2
I ₁₆	276 \pm 17	18 \pm 2	263 \pm 29	22 \pm 2	456 \pm 47	43 \pm 3	433 \pm 63	53 \pm 5

ponents would then be the expressions of the *scotopic* process.

The fact that b_1 and b_2 have smaller absolute values for I₁₆ than for I₄ bears out an old observation made in this laboratory (Burian⁶) that supramaximal stimuli tend to reduce the b-wave, whereas the a-wave is not so affected.*

There is no difference of opinion regarding the existence of a double b-wave, or for that matter of a double a-wave, but it is not clear whether the first positive elevation can be equated under all circumstances with the so-called x-wave. Auerbach and Burian⁷ assumed this to be the case. Schubert⁸ summarily rejected their interpretation, stating that the differential construction of the electroretinogram suggested by them was wrong because of faulty measurement (Ausmessung) of the x-wave.

Best⁹ has confirmed the findings of Auerbach and Burian, using red stimuli of increasing intensity, and following up, as they did, the behavior of the electroretinogram throughout dark adaptation with a white stimulus light. While Best is, therefore, inclined to agree that the first positive elevation is in fact the x-wave, he points out correctly that the continued increase in size of the first positive elevation during dark adapta-

tion, and especially the rapid change in rate of this increase after the 11th minute, would indicate that both the photopic and the scotopic activity contribute to the appearance of the x-wave. However, if this explanation is correct, it introduces another complication, namely that we must assume the existence of quick acting scotopic responses in addition to the well known slow acting ones.

One wonders what elements might be giving this response. Also, it will be hard to answer the question, when the first positive ele-

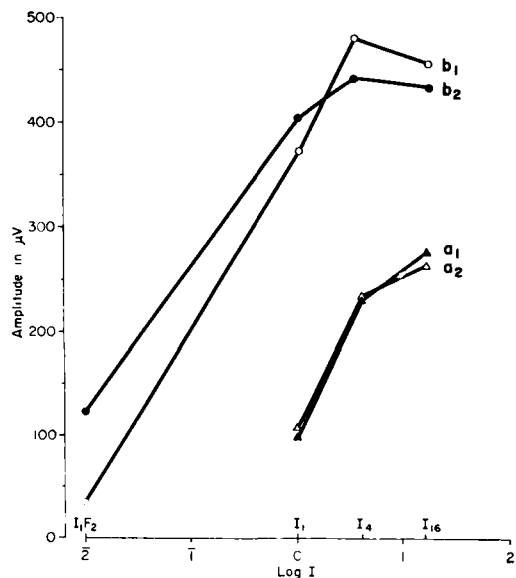


Fig. 2 (Burian and Spivey). Plot of average amplitudes of the components of the single flash electroretinograms at four intensity levels of the stimulus. Note the inversion of the quantitative relationship of the components of the I₄ and I₁₆ level, compared to levels I₁F₂ and I₁.

* It must be pointed out that at the time this observation was made we measured the b-wave from the iso-electric line, not from the trough of the a-wave. When it is done in the latter fashion—and this has now been our practice for quite some years—the effect is not invariably found.

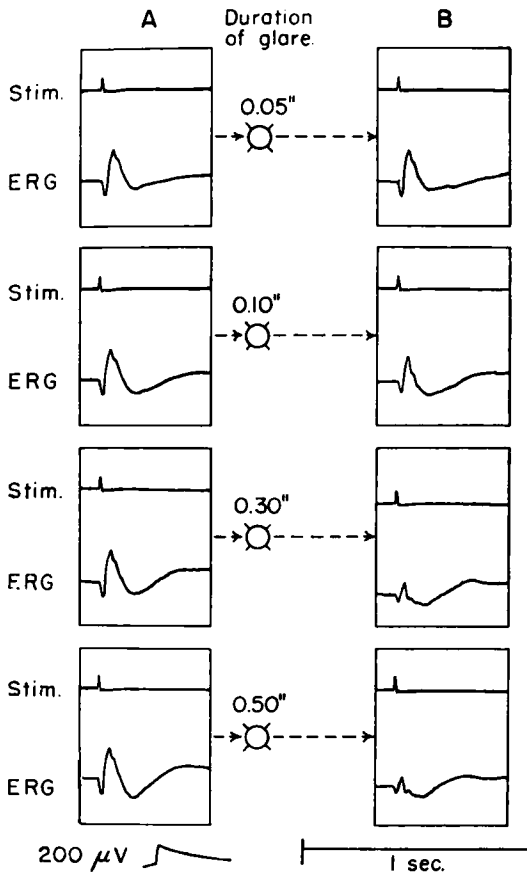


Fig. 3 (Burian and Spivey). Tracings demonstrating effect of light adapting flashes of short duration on electroretinograms of normal dark-adapted human eye. Column A: last electroretinogram prior to flash. Column B: first electroretinogram following the flash. Note progressive reduction of b_2 -wave, as well as of a - and b_1 -waves, with corresponding progressively "photopic" appearance of electroretinogram and "isolation of x-wave."

vation becomes an "x-wave," unless it is true, as Armington¹⁰ thinks, that the x-wave is a specific "red" response, not an over-all photopic response. Consider for example such an experiment as the one reported by Burian,¹¹ in which dark adaptation was interrupted by light adapting flashes of varying duration (0.05" to 0.5"). The first electroretinogram following the bright flash showed a definite change in size and shape compared with the last electroretinogram preceding the flash. With increasing duration of the light adapting flash the "photopic" character of

the electroretinogram following it became increasingly prominent (fig. 3). Has the b_1 -wave already become an "x-wave" with the light adapting flash of 0.1" or only with the 0.3" flash?

Regardless of the solution to this problem, there is ample evidence that the b-wave is composed essentially of two peaks and that these peaks can be differentially affected, depending on the condition and state of adaptation of the eye and on the parameters of the stimulating light.

2. EFFECT OF TWIN STIMULI ON THE FIRST ELECTRORETINOGRAM

At no intensity could a second electroretinogram be elicited by twin flashes with a 15 and 20 msec. delay interval; very much

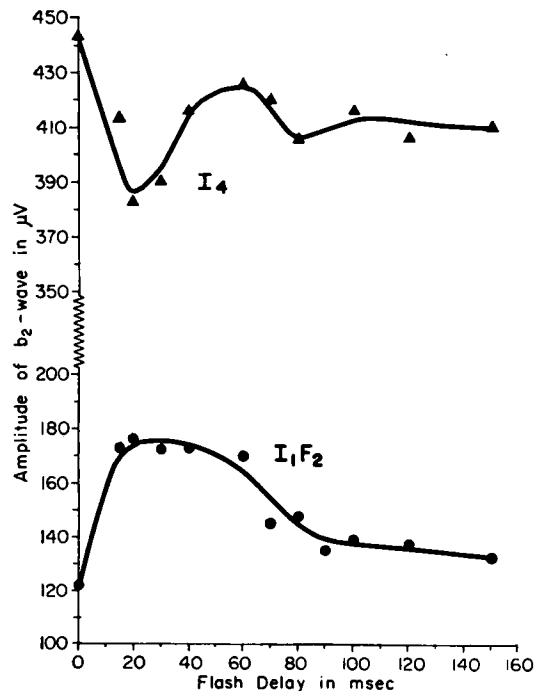


Fig. 4 (Burian and Spivey). Plot of average amplitudes of b_2 -waves of first electroretinogram with single flash and with double flashes of increasing flash delay at intensities I_1F_2 and I_1 . Note that for double flashes with short flash delays there is an increase in effective light intensity causing flashes at intensity I_1F_2 to increase the amplitude of the b_2 -wave, whereas such flashes at intensity I_1 reduce the amplitude of the b_2 -wave.

TABLE 2

AVERAGE AMPLITUDES IN μV OF COMPONENTS OF FIRST ELECTRORETINOGRAM AND OF B-WAVE OF SECOND ELECTRORETINOGRAM FOR STIMULUS INTENSITY I_1F_2

First Electroretinogram				Second Electroretinogram
Single flash		33 \pm 3	122 \pm 14	
Flash delay in msec.	15	40 \pm 4	173 \pm 21	—
	20	33 \pm 4	176 \pm 19	—
	30	37 \pm 4	172 \pm 17	—
	40	30 \pm 6	173 \pm 15	—
	60	40 \pm 9	170 \pm 24	—
	70	31 \pm 5	145 \pm 19	—
	80	33 \pm 6	148 \pm 17	—
	90	30 \pm 0	135 \pm 6	—
	100	37 \pm 7	139 \pm 11	27 \pm 6
	120	33 \pm 7	137 \pm 22	47 \pm 9
	150	33 \pm 10	135 \pm 23	83 \pm 10

longer intervals were needed to obtain a second electroretinogram with the two lower intensity levels. However, even when no second electroretinogram appeared, twin stimuli had a definite effect on the first electroretinogram (fig. 1, tables 2 to 5).

At I_1F_2 the electroretinograms produced by 15 to 50 msec. delay interval flashes showed a considerable increase in the amplitude of the b_2 -wave (maximal over 50 percent, fig. 4); the b_1 -wave was not affected.

At I_1 there was an increase in the b_1 -wave with 15 and 20 msec. flashes and a decrease in the b_2 -wave; at I_4 and I_{16} there was under these circumstances a decrease of both the b_1 and b_2 -waves.

As the interval between the flashes was lengthened, the b_2 -wave tended to return al-

most fully to its original amplitude with I_1F_2 stimuli (fig. 4); with the three higher intensities it fell at first and then rose slowly, but never reached its original height, possibly because of the light adapting properties of the stronger stimuli (fig. 4). The b_1 -wave fell at I_4 and I_{16} with flashes of 15, 20, and 30 msec. delay intervals and then remained throughout on the same level.

One may conclude from these findings that twin flashes with short delay intervals simply act by effectively increasing the stimulating light intensity. Thus such twin flashes produce a larger b_2 -wave with low intensities (but are not strong enough to affect the b_1 -wave or to cause the appearance of an a-wave); they inverse the relationship of the first and second positive components for

TABLE 3

AVERAGE AMPLITUDES IN μV OF COMPONENTS OF FIRST ELECTRORETINOGRAM AND OF B-WAVE OF SECOND ELECTRORETINOGRAM FOR STIMULUS INTENSITY I_1

First Electroretinogram						Second Electroretino-gram
		a ₁	a ₂	b ₁	b ₂	
Single Flash		97 ± 19	107 ± 16	373 ± 24	403 ± 16	—
Flash delay in msec.	15	97 ± 13	120 ± 11	403 ± 11	383 ± 20	—
	20	83 ± 14	107 ± 10	392 ± 22	370 ± 24	—
	30	87 ± 12	90 ± 10	370 ± 10	370 ± 25	—
	40	90 ± 11	100 ± 10	363 ± 17	376 ± 8	—
	60	83 ± 8	107 ± 6	390 ± 23	386 ± 16	—
	70	87 ± 15	100 ± 9	393 ± 19	399 ± 20	13 ± 13
	80	90 ± 14	103 ± 8	393 ± 18	393 ± 12	23 ± 18
	100	87 ± 22	103 ± 13	376 ± 23	380 ± 27	43 ± 28
	120	87 ± 9	97 ± 10	396 ± 25	380 ± 27	73 ± 24
	150	87 ± 8	100 ± 9	386 ± 24	383 ± 21	103 ± 14

TABLE 4
AVERAGE AMPLITUDES IN μV OF COMPONENTS OF FIRST ELECTRORETINOGRAM AND OF
B-WAVE OF SECOND ELECTRORETINOGRAM FOR STIMULUS INTENSITY I_4

First Electroretinogram						Second Electroretinogram
		a_1	a_2	b_1	b_2	
Single Flash		230 ± 18	233 ± 86	479 ± 24	443 ± 13	—
Flash delay in msec.	15	223 ± 13	240 ± 6	459 ± 27	413 ± 42	—
	20	213 ± 10	230 ± 6	446 ± 24	383 ± 50	—
	30	206 ± 15	214 ± 8	436 ± 28	390 ± 60	—
	40	213 ± 15	220 ± 5	443 ± 30	416 ± 32	23 ± 10
	60	206 ± 10	206 ± 5	446 ± 30	426 ± 53	31 ± 17
	70	213 ± 14	216 ± 10	446 ± 33	420 ± 53	50 ± 30
	80	203 ± 18	213 ± 11	446 ± 26	406 ± 59	63 ± 31
	100	209 ± 12	216 ± 13	450 ± 30	416 ± 64	93 ± 41
	120	200 ± 20	210 ± 18	446 ± 33	406 ± 68	133 ± 43
	150	216 ± 5	220 ± 7	450 ± 24	410 ± 53	170 ± 43

intermediate intensities, and create supra-maximal stimuli for high intensities. These results may again be interpreted in terms of a differentiation of the photopic and scotopic components of the electroretinogram.

An intensity effect of twin flashes is also evident from the series of electroretinograms for the "dark-adapted" eyes reproduced by Mahneke,² although he draws no attention to this fact. Judging from his reproductions, the b-wave measured for very short flash intervals roughly $500 \mu\text{V}$, whereas for flash intervals of over 100 msec. it measured about $330 \mu\text{V}$.

3. THE SECOND ELECTRORETINOGRAM

The appearance of a second electroretino-

gram with twin flashes in relation to the duration of the delay interval depends upon the intensity of the flashes: the *weaker* the intensity, the *longer* must be the interval (tables 2 to 5 and fig. 5).

At intensity I_1F_2 a second electroretinogram was recorded in all records with a 100 msec. flash delay; in two records there was evidence of a second electroretinogram with a 70 msec. flash delay and in four with a 80 msec. flash delay.

At intensity I_1 a second electroretinogram was recorded in all records with a 70 msec. flash delay; in four records there was evidence of a second electroretinogram with a 60 msec. flash delay.

At intensity I_4 a second electroretinogram

TABLE 5
AVERAGE AMPLITUDES IN μV OF COMPONENTS OF FIRST ELECTRORETINOGRAM AND B-WAVE
OF SECOND ELECTRORETINOGRAM FOR STIMULUS INTENSITY I_{16}

First Electroretinogram						Second Electroretinogram
		a_1	a_2	b_1	b_2	
Single Flash		276 ± 17	262 ± 29	456 ± 47	433 ± 63	—
Flash delay in msec.	15	266 ± 25	240 ± 43	410 ± 67	406 ± 57	—
	20	280 ± 16	273 ± 18	423 ± 60	403 ± 43	—
	30	270 ± 17	260 ± 32	426 ± 50	396 ± 70	—
	40	276 ± 21	263 ± 27	409 ± 80	406 ± 80	24 ± 4
	60	266 ± 16	253 ± 22	400 ± 70	403 ± 47	50 ± 32
	70	256 ± 28	250 ± 32	393 ± 80	400 ± 80	47 ± 28
	80	270 ± 22	250 ± 25	403 ± 83	403 ± 57	63 ± 34
	100	263 ± 19	253 ± 22	393 ± 83	390 ± 60	90 ± 32
	120	273 ± 24	269 ± 29	396 ± 84	396 ± 50	130 ± 24
	150	273 ± 21	260 ± 31	396 ± 83	403 ± 80	160 ± 22

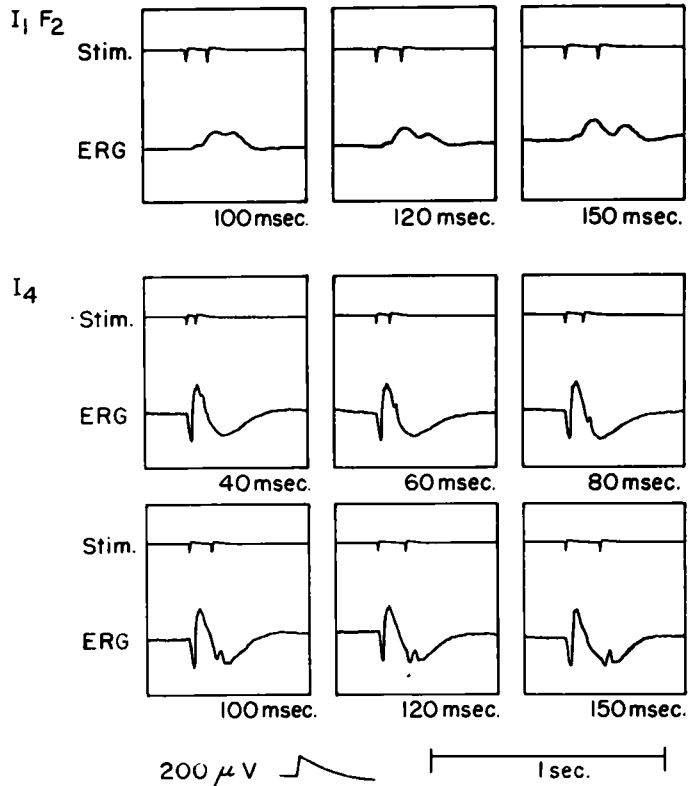


Fig. 5 (Burian and Spivey). Second electroretinogram produced with twin flashes at intensity $I_1 F_2$ (upper row) and I_4 (second and third row). Note that the shapes of the second electroretinograms remain essentially unchanged at $I_1 F_2$ whereas their shape differs greatly from the first electroretinograms at I_4 .

was recorded in all records with a 40 msec. flash delay; in three records there was evidence of a second electroretinogram with a 30 msec. flash delay.

At intensity I_{16} a second electroretinogram was recorded in all records with a 40 msec. flash delay; in four records there was evidence of a second electroretinogram with a 30 msec. flash delay.

The character of the second electroretinogram was always essentially photopic, consisting of a single positive elevation with a sharp rise for the higher intensities but for flash delays of 120 and 150 msec. a very small positive elevation could be seen following the first sharp rise, representing most likely the first indication of a b_2 -wave. The amplitude of the second electroretinogram increased with prolonged flash delay, except for intensity $I_1 F_2$ where the amplitude remained at the same low level for the relatively short flash delays of 100, 120, and 150 msec. (fig. 6).

Why must the flash delay be greater for low intensities than for high ones, in order that the second flash may give rise to an

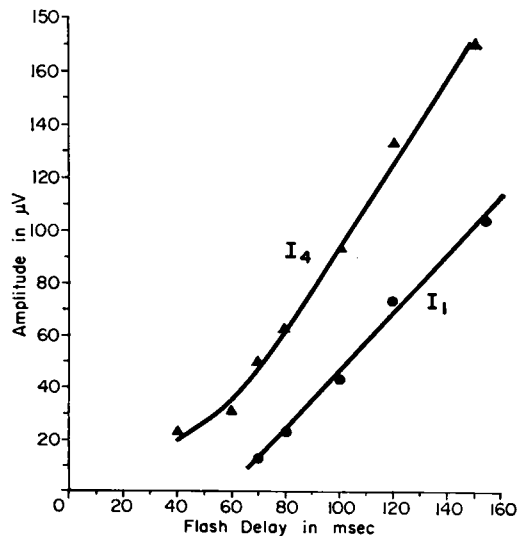


Fig. 6 (Burian and Spivey). Average amplitude of b-wave of second electroretinogram with stimuli of intensities I_1 and I_4 .

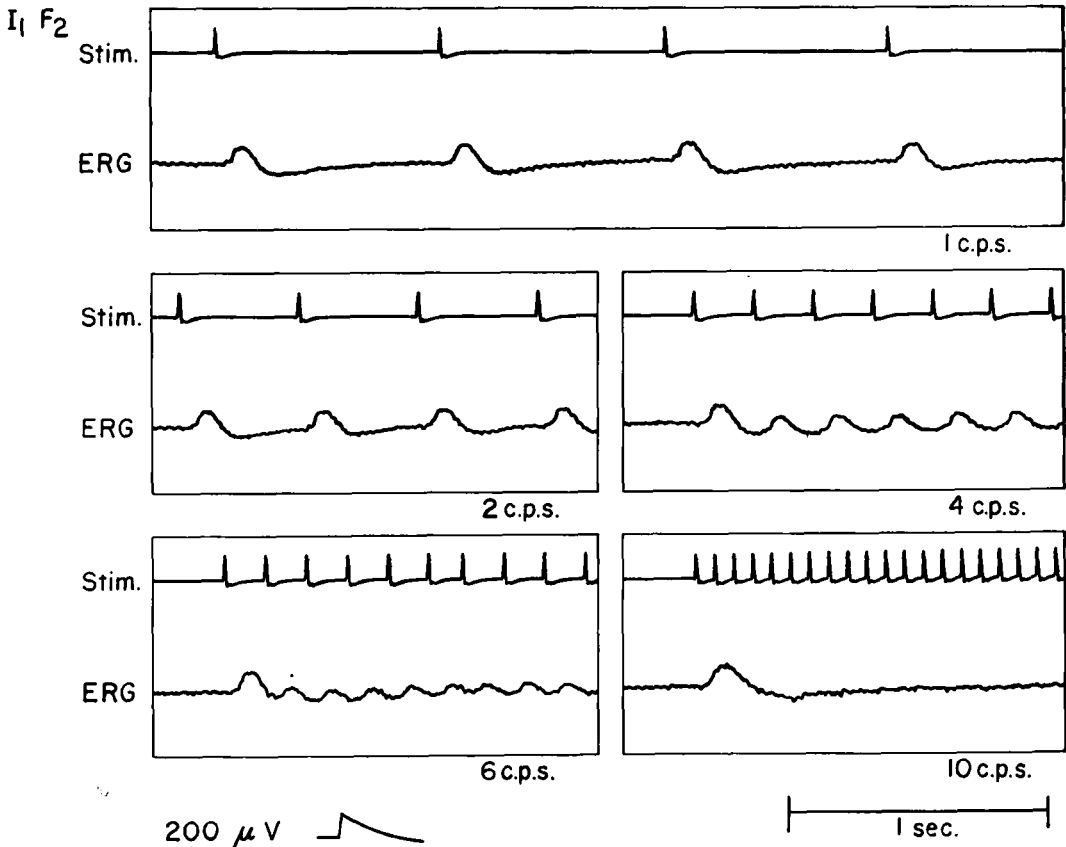


Fig. 7 (Burian and Spivey). Electrophysiological recordings obtained with repetitive light stimuli at intensity $I_1 F_2$. Note that there is no change in shape, but only a reduction in size, with increasing stimulus frequency. Note also the larger size of the one and only electroretinogram at frequency 10 cps which in this case represented the fusion frequency.

electroretinogram response? Low light intensities stimulate presumably the slower scotopic mechanism, whereas high light intensities stimulate the faster photopic mechanism. It is known from the study of electroretinograms produced with repetitive flashes that the scotopic mechanism cannot follow fast stimulus frequencies and that the fusion frequency is very much lower for low intensity flashes than it is for high ones. The requirement of a larger flash delay for low intensities, to elicit twin electroretinograms, would seem to be readily explained on this basis. Nevertheless, this greater flash delay requirement raises certain questions which will be discussed in the following sec-

tion dealing with the electroretinograms obtained with repetitive light stimuli.

4. THE ELECTRORETINOGRAM WITH REPETITIVE FLASHES

Electroretinograms were obtained with repetitive stimuli ranging in frequency from one stimulus per second to 20 stimuli per second, that is, with intervals between stimuli from 1,000 to 50 msec.

We shall in this presentation pay particular attention to the electroretinogram following the first stimulus and to the shape of the subsequent stimuli.

For all recordings, regardless of the stimulus frequency, the first electroretinogram

was always of considerably larger amplitude in all its component waves than were the subsequent electroretinograms. This was particularly evident for the second electroretinogram and increasingly so for higher stimulus frequencies. The second electroretinogram not only was lower in amplitude, but had a definitely "photopic" character for the higher intensities. The subsequent electroretinograms depended for their shape and amplitude on the intensity of the stimulus and on its frequency.

At I_1F_2 (fig. 7) there was, with a stimulus frequency of one and two cps, essentially no difference in either amplitude or shape between the first electroretinogram and the subsequent ones. From the beginning a steady response was obtained. With a frequency of four cps the second electroretinogram was notably smaller than the first, and all subsequent electroretinograms were equal to the second. No difference in shape between first and subsequent electroretinograms could be noted. With increasing frequency the electroretinograms which followed the first one became progressively smaller and fusion was soon obtained—with eight or 10 cps. This is consistent with the low flicker fusion frequency of the scotopic mechanism. It should also be noted in Figure 7 that the amplitude of the one and only electroretinogram obtained with 10 cps, elicited in response to two stimuli, is considerably larger than the amplitude of the electroretinogram obtained with lower frequencies.

The electroretinograms elicited by repetitive stimuli of I_1 , I_4 , and I_{16} are much more complex than the ones elicited with I_1F_2 . With all the higher intensities the second electroretinogram became the smaller, the faster the flicker, and for the frequencies corresponding to those employed in producing twin flashes, the second electroretinograms encroached upon the first electroretinogram and were quite comparable to those described in the preceding section of this paper. However, after three, or at the most five, flashes

the electroretinograms attained a size and shape characteristic for the particular intensity and particular frequency. It is essential to note that this steady response could be maintained indefinitely.

As has been mentioned before, this steady response was indistinguishable from the first electroretinogram for frequencies of one and two cps with I_1F_2 ; for higher frequencies it differed only in the size of the electroretinogram. The steady responses with I_1 still had some "scotopic" characteristics: a small a-wave and a rounded b-wave (fig. 8). With I_4 the a-wave was comparatively larger; the b-wave became a sharp, narrow peak. At lower frequencies of repetitive stimuli a double b-wave could still be made out, but the second peak quickly disappeared with increase in frequency (fig. 9). Finally, with I_{16} the a-wave was larger still, the b-wave further reduced in height, and a trend toward a positive elevation preceding the a-wave could be made out (fig. 8).

The existence of a refractory period which determines the delay in the appearance of the second electroretinogram with twin flashes, and the observations made with repetitive stimuli, require an explanation.

Granit¹² concluded on the basis of his beautiful experiments on single fibers of the optic nerve of animals that the refractory period and the reduction in the b-wave were due to postexcitatory synaptic inhibition, whereas the appearance of larger a-waves with multiple stimulation resulted from a pre-excitatory inhibition of the off-effect. Dodt¹ has taken over these concepts of Granit's and enlarged them by applying them to human electroretinography. In particular, he has shown that by suppressing the scotopic activity of the human retina by means of flicker the photopic activity can be brought out, including the presence of an off-effect.

Adrian¹⁸ offered a different explanation. Calling attention to the reduction in the size of the scotopic component after the first response, observed in flicker experiments, he

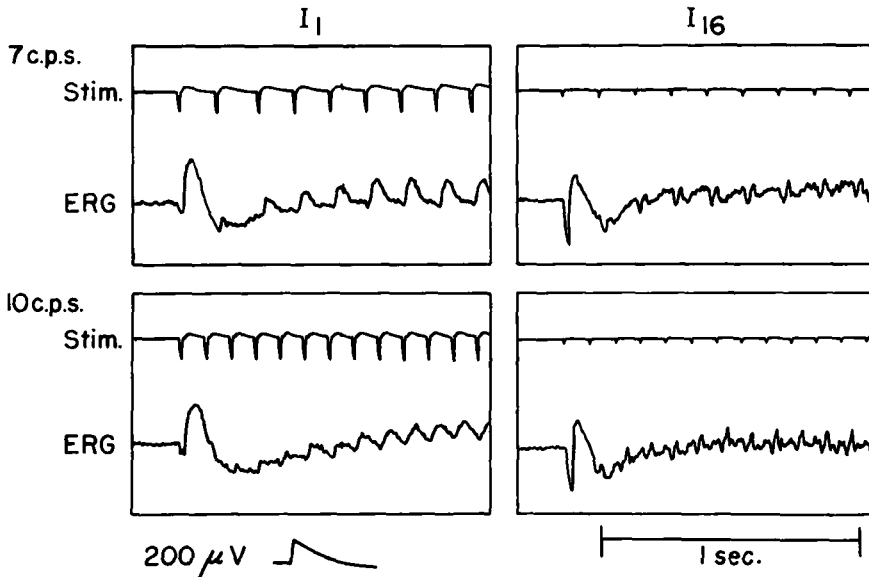


Fig. 8 (Burian and Spivey). Electrophoretograms obtained with repetitive light stimuli at intensities I_1 (left column) and I_{16} (right column). Note in the I_1 records the relatively small a-wave and the relatively large b-wave which is rounded in shape (prevalence of b_2 -wave). At I_{16} the a-wave is larger, the b-wave smaller, more peaked in shape (prevalence of b_1 -wave).

stated that it was presumably due to the light-adapting effect of the first flash. This finding suggested to Adrian a dependence on photochemical factors. He added, however, that the rate of recovery might well depend on neural factors also. Adrian found furthermore that with the use of blue light the responses did not become progressively smaller, but that after the first few flashes the responses attained a steady value "as though the retina discharged its accumulated reserves at the first stimulus, but could then revert to a state of dynamic equilibrium where the supply keeps pace with the demand."

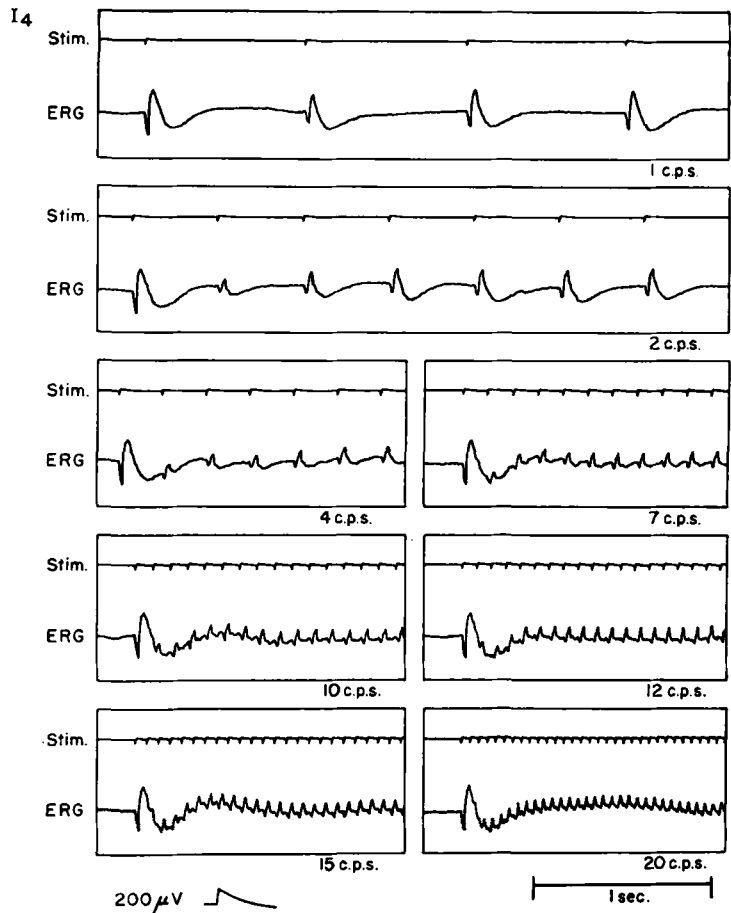
This view has much to attract the ophthalmologist, fitting, as it does, so well with what we know about the origin of the retinal potentials and with many observations in clinical electroretinography. Experimentally, a close correlation of photochemical processes and size and shape of the electroretinogram has been demonstrated in the recent work of Dowling and Wald¹⁴ who showed that there exists a remarkable parallelism between the

electroretinographic threshold and the rhodopsin content in the retinas of vitamin A-deficient rats.

One feels justified, therefore, to explain the observations with twin flashes of light and with repetitive light stimuli by the content in photopigments of the retinal sensory elements.

The amount of photopigments in the sensory retinal elements available under specified conditions would seem to be fully capable of accounting for the observations made with double light flashes and repetitive light stimuli. The delay required for the appearance of the second electroretinogram, the reduction in size and change in shape of the second electroretinogram are readily explained by it. The attainment, with repetitive stimuli, of the steady dynamic equilibrium spoken of by Adrian,¹³ characterized by electroretinograms typical for each level, having larger a-waves and smaller b-waves with progressively higher intensities and greater frequencies, causing an ever more light adapted state of the eye, further indicate that

Fig. 9 (Burian and Spivey). Electroretinograms obtained with repetitive stimuli at intensity I_4 . Note that a constant response is established in each record after one (one cps) to six or seven (15 and 20 cps) stimuli following the first stimulus. Note, furthermore, the almost immediate reduction in the b_2 -wave, as well as the steady reduction in size of the a- and b₁-waves, with progressively higher frequencies of stimulation. Note, lastly, that the second electroretinogram with seven, 10, 12, 15, 20 cps agrees well with the electroretinograms obtained with the double flashes of the roughly corresponding flash delays of 150, 100, 80, 70, 50 msec.



the size and shape of the electroretinogram depend on the level of available photopigments, resulting from their bleaching and re-synthesis.

In considering the results of our study, it must be kept in mind that it was performed with stimuli of extremely short duration (10 microseconds, according to the manufacturer) and very high intensity. This may well explain discrepancies between our findings and those of other observers. Dodt¹ found it necessary, for instance, to reduce the scotopic activity by flicker, in order to obtain maximal a-waves of 100 μ V. A-waves of comparable size were never observed by him either with single or double flashes. With our photo stimulator a-waves of 100 μ V are commonplace and with higher intensities we obtain

frequently a-waves of 200 to 250 μ V in normal eyes. Also, Dodt stated that the optimal frequency to elicit the maximal a-wave was eight to 10 cps. Greater or smaller frequencies would give a-waves of smaller size. Dodt has explained this observation by the fact that the optimal condition for the production of an a-wave is given when the second stimulus arrives at the peak of the off-effect, basing himself on Granit's view that the a-wave is an expression of the pre-excitatory inhibition of the off-effect. From our results it would appear that the size of the a-wave with repetitive stimuli may very well also be simply a function of stimulus intensity. A comparison of the a-waves obtained with light flashes of I_1 , I_4 , and I_{16} (figs. 8 and 9) would certainly point in this direction.

SUMMARY

This report is concerned with a study of twin light flashes and repetitive light stimuli on the human electroretinogram of five young subjects.

An analysis of the electroretinogram obtained with the single flashes allows one to attribute once again the first and second positive elevations to the photopic mechanism, the second negative and positive elevations to the scotopic mechanism.

To elicit a second electroretinogram with twin flashes longer flash delays are required for low intensities than for higher ones. Even if no second electroretinogram is produced by twin flashes with short delay intervals, the second flash does have an effect on the first electroretinogram: at low flash intensities the second flash caused the total

intensity to be effectively increased; at intermediate flash intensities the quantitative relationship of the first and second positive and negative components of the electroretinogram was reversed; at high intensities supramaximal stimuli were created.

After the first few flashes, repetitive stimuli give rise to a steady response which is characteristic for each level of intensity and frequency. In general, the electroretinograms obtained with higher stimulus intensities and greater stimulus frequencies are more complex and tend to assume a more and more "photopic" character.

The authors favor an explanation of the observed phenomena based on the dependence of the electroretinogram on photochemical processes.

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