Experimental and therapeutic aspects of photic damage to the retina

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For 99 per cent of patients with hereditary retinitis pigmentosa, no treatment is known. This paper presents a treatment plan based on long periods of light exclusion, and supporting evidence is reviewed.

Key words: retinitis pigmentosa, light, dark, electroretinogram, rod, cone, early receptor potential, retina, hereditary, vitamin A.

Approximately 100,000 people in this country have retinitis pigmentosa, and the overwhelming majority will go blind from this disease, some as early as age 15. I would expect that every ophthalmologist at this meeting can think of at least one such patient. The rare patient with abetalipoproteinemia and early pigmentary retinal degeneration has a reversible retinopathy; but for over 99 per cent of patients with the other types of hereditary retinitis pigmentosa, no treatment is known. I have come to this symposium to present a plan of treatment. This plan is described in the May, 1971, issue of Archives of Ophthalmology and is based on the hypothesis that long periods of almost complete light exclusion will benefit patients with early stages of hereditary retinitis pigmentosa.

First, I will review the facts that support this hypothesis, and then discuss the therapeutic considerations for achieving complete light exclusion.

The facts that led to this hypothesis are as follows:

1. Minimal light stress accelerates photoreceptor outer segment turnover in the rat.

2. Light exposure is required to produce photoreceptor abnormalities when visual pigment synthesis is disturbed in vitamin A–depleted rats.

3. Some abnormality in visual pigment function has occurred in patients with retinitis pigmentosa to explain their abnormal early receptor potential (ERP) amplitudes and their faster-than-normal ERP recovery rates.
GROUND SQUIRREL (CITELLUS TRIDECEMLINEATUS)

Pure-cone retina

GROUP A. Normal diet

GROUP B. Vitamin A free diet
Plus limited vitamin A supplement

GROUP C. Vitamin A free diet
Plus retinoic acid supplement

1. Cyclic dim illumination 0.1 - 10 foot-candles
2. Cyclic moderate illumination 50 - 500 foot-candles

Fig. 1. Experimental groups for study of vitamin A deficiency and light on ground squirrel retina. Illumination conditions (1 or 2) obtained with 40 watt fluorescent bulbs (cool-white). Environmental temperature in cages was 27° C. in dim illumination and 28° C. in moderate illumination.

4. Retinal oxygen utilization and glycolysis are abnormally increased in human 12 and animal 13 - 14 retinas with hereditary retinal dystrophy. These results as well as the ERP studies indicate that the degenerating retina becomes hyperfunctional.

5. Complete light exclusion does preserve retinal structure and function in rats with hereditary retinal dystrophy. These results as well as the ERP studies indicate that the degenerating retina becomes hyperfunctional.

6. Light exposure is required to produce cone photoreceptor abnormalities in the vitamin A-depleted thirteen-lined ground squirrel. 15

Because cone defects are present in the earliest stages of all types of hereditary retinitis pigmentosa, 6, 8, 26 - 29 we have been studying the thirteen-lined ground squirrel which has a pure-cone retina. 24 - 26 Dowling and Wald 1 and Noell and co-workers 4 have demonstrated the effects of vitamin A depletion and light on the rod-dominated rat retina. We have worked on the effects of vitamin A depletion and light on the all-cone squirrel retina. 19

Squirrels born in the laboratory received either a normal diet (Group A), a diet free from vitamin A and supplemented with limited vitamin A (Group B), or a diet free from vitamin A and supplemented with retinoic acid (Group C). Liver assays confirmed that the vitamin A-free Group C became totally depleted of vitamin A, while the other two groups maintained liver stores of vitamin A (Fig. 1). In one experiment, animals from these groups were exposed to cyclic (12 hours on, 12 hours off) dim illumination (range 0.1 to 10 foot-candles, average 4 foot-candles) for 32 to 44 weeks. Then some animals from these three groups were exposed to cyclic moderate illumination (range, 50 to 500 foot-candles, average 200 foot-candles) for up to 12 weeks, while others from these three groups continued to remain in cyclic dim illumination. All squirrels were studied with electrophysiologic testing and were put to death so that light and electron microscopic examination of the retinas could be made. These squirrels (Groups A, B, and C) in cyclic dim illumination had a normal appearance to their fundi and a normal electroretinogram (ERG). The squirrels with liver stores of vitamin A (Groups A and B) placed in cyclic moderate illumination retained a normal fundus appearance and a normal ERG. In contrast, the squirrels with essentially no liver vitamin A (Group C) developed an abnormal fundus appearance and had abnormal ERG's within four weeks after exposure to cyclic moderate illumination. These squirrels had multiple discrete round white deposits in the deep retina near the level of the pigment epithelium that were particularly noticeable in the midperiphery of each eye. The abnormal fundus greatly resembled the human retinal degeneration, retinitis punctata albsccens. 19 The ERG thresholds in these animals were elevated on the average 0.7 log units above normal, and ERG spectral sensitivity data indicated that both cone mechanisms were abnormal. 27 Light microscopic examination showed that no abnormalities were visible in the vitamin A-depleted animals kept in cyclic dim illumination (Fig. 2A) or in
Fig. 2A. Representative section from midperipheral retina of vitamin A–depleted thirteen-lined ground squirrel kept in cyclic dim illumination for 45 weeks. Architecture of retina appears normal. Fixation, two per cent paraformaldehyde, two per cent glutaraldehyde; postfixation, one per cent osmium tetroxide. (Toluidine blue. ×500.)

Fig. 2B. Representative section from midperipheral retina of vitamin A–depleted thirteen-lined ground squirrel kept in cyclic dim illumination for 38 weeks and then cyclic moderate illumination for eight weeks. Abnormal deposits are visible at photoreceptor–pigment epithelial cell interface and extend into inner segment layer. Largest deposit is 20 × 40μ. Fixation and stain as in Fig. 2A. (×500.)
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Fig. 3. Representative ERP's for a normal (N) and eight patients with dominantly inherited retinitis pigmentosa (Families W, B, and F). Responses recorded to single flashes of white light after patient had been dark adapted for a minimum of one hour. Amplitudes (from cornea-positive peak, R1, to cornea-negative peak, R2) for each patient are expressed as a percentage of average normal response of 191 /urv. Averages are based on 10 to 20 responses for each patient except F1 and F2 which are based on two to three responses. Stimulus onset is at beginning of trace. Calibration symbol, lower left, is 50 /uv vertically and 0.5 msec horizontally.

animals with normal stores of vitamin A kept in cyclic moderate illumination. In contrast, multiple focal deposits could be seen at the photoreceptor-pigment epithelial cell interface in the vitamin A-depleted squirrel kept in cyclic moderate illumination (Fig. 2B). Some of these deposits extended to the level of the inner segments and measured 20 x 40 /m. Electron microscopic studies are in progress to define further the nature of these deposits.

These studies show that light is required to produce cone abnormalities in the vitamin A-depleted thirteen-lined ground squirrel and are consistent with the findings of Noell and associates that light is required to produce rod abnormalities in the vitamin A-depleted rat. However, the illumination found to damage the cone retina of the squirrel is greater than that (0.5 to 1 footcandle) required to produce photoreceptor abnormalities in the rod-dominated rat retina. The illumination (200 footcandles) that led to cone photoreceptor abnormalities in the vitamin A-depleted squirrel was about 50 times below that measured from a white surface in ordinary outdoor sunlight conditions.

These findings on the effects of light on cone function and structure are particularly important when we consider the electrophysiologic abnormalities in early retinitis pigmentosa. Electrophysiologic testing of young patients with all known genetic types of retinitis pigmentosa has revealed in every instance a cone ERG and/or a cone ERP defect, as well as a rod ERP defect at the time that the patients were first evaluated for night blindness. Although these patients often first show bone spicule pigmentation at the retinal equator and loss of peripheral field, the marked changes in the temporal aspects of the ERG's can be best explained by the fact that not only all the rods but also all the cones across the entire retina are affected in the earliest stages of most of these degenerations.

The diminution or disappearance of the ERG a-wave in early stages as well as the histopathologic studies of advanced stages have indicated that the defect in different types of retinitis pigmentosa involves the photoreceptors and/or the pigment epithelium. Recent studies on the ERP in young patients with dominant and sex-linked retinitis pigmentosa who have abnormal ERG's have revealed that the amplitudes of the ERP also become diminished very early in these conditions. The abnormal ERP amplitudes localized a defect in the receptor outer segments, even at a time when some of these affected children had 20/20 visual acuity, full visual fields with conventional perimetric testing, and minimal or absent changes on ophthalmoscopic examination. This change in photoreceptor outer segment function implies, in turn, that the relationship of the pigment epithelium to the photoreceptors has become altered in

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Fig. 4. Average ERP recovery curves for four normal subjects (solid circles), two siblings—(B1) age 16 and (B2) age 14—in Family B (open squares), and three siblings—(W1) age 18, (W2) age 13, and (W3) age 11—in Family W (solid triangles), after a yellow (λ > 500 nm) bleaching flash at time zero. ERP amplitudes for each subject are responses to white light flashes and are expressed as a percentage of response of dark adapted eye. Curve N is based on average of four normal subjects, Curve B on average of B1 and B2, and Curve W on average of W1, W2, and W3. Data for each patient were based on average of two to four responses at 30 seconds, one minute, two minutes, and four minutes after bleaching flash. Only one white light test flash was presented after the bleaching flash in each sequence of recordings, and the patient was dark adapted for a minimum of one hour between each sequence. Average variation from the mean for each determination for each patient and normal subjects was ± five per cent. Recovery curves could be described by exponential functions (normal subjects, \( t_{1/2} = 1.6 \) minutes; Family B, \( t_{1/2} = 35 \) seconds; Family W, \( t_{1/2} = 1.0 \) minute). Since final level of recovery for normal subjects was about 97 per cent, all exponential curves were calculated to asymptote at this level.8

In summary, the ERP abnormalities indicate that some defect has occurred in visual pigment function in the receptor outer segments. The abnormal ERP recovery rates can be best explained by an abnormally fast rate of cone pigment regeneration.8, 9, 11 When visual pigment function is abnormal in the vitamin A–depleted ground squirrel, ordinary light is the "catalyst" that produces structural and functional changes in the cones.19 These squirrels develop a picture that resembles retinitis punctata albescens, and it is well known that many patients with retinitis pigmentosa also have the fundus change of retinitis punctata albescens. Furthermore, a hyperfunctional state must exist in the degenerating retina to explain the faster-than-normal ERP recovery rates during dark adaptation of human retinas and the increased oxygen utilization of human and animal retinas with hereditary retinal dys-

Fig. 5. ERP for normal subject (N), B1, and W2 for white light flashes presented to dark-adapted eye prior to bleaching flash (DA) and 0.5 and two minutes after bleaching flash. Responses are representative for those used to construct ERP recovery curves in Fig. 4. Calibration symbol (lower left) signifies 50 µv vertically and 0.5 msec. horizontally.
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Fig. 6. A, Front and side view of flush-fitting opaque scleral contact lens. Back surface is laminated with black plastic so no light can be seen through lens when flashlight is held against front or back surface. B, Scleral lens in place on subject’s left eye (right in photograph). Lens is comfortable, cosmetically acceptable, and protects eye almost completely from light. Reflections from flashbulb appear as two white spots in region of each pupil. C, Subject is looking up to show 1 mm fenestration located just above lower lid margin. When subject looks straight ahead, fenestration is at or just below lower lid margin. Fenestration in this position had no effect on rod psychophysical thresholds or ERG amplitudes illustrated in Figs. 7 and 8.

trophy. Both ERP recovery rates as well as rates of oxygen utilization are increased by a factor of two. The hypothesis is that light could further aggravate this hyper-functional state and lead to further destruction of both the cone and rod photoreceptors in patients with hereditary retinitis pigmentosa.

All of the above evidence, taken together, provides the scientific basis for a therapeutic trial of complete or almost complete light exclusion. Complete or almost complete light exclusion of one eye for at least 10 to 14 hours per day for many years cannot be accomplished simply. Long-term patching is impossible as patients develop a dermatitis from the adhesives or become annoyed with the constricting headbands necessary to hold the patch in place; and some light inevitably leaks through or around these patches. Attempts with sunglasses have been unsatisfactory because the darkest sunglasses equipped with side shields do not protect patients sufficiently to achieve a state of almost complete dark adaptation. Furthermore, young asymptomatic patients do not remember to wear the glasses all the time. Miotics are unsatisfactory because the retina still remains light adapted in ordinary daylight. Tarsorrhaphy will not eliminate light and is also cosmetically unacceptable in these young children. A corneal black contact lens, 10 to 11 mm. in diameter, has also been tried without success because the patient does not become dark adapted due to either light leakage around the lens or due to trans-scleral illumination of the retina (unpublished observation).

Constant and almost complete light exclusion can be best accomplished in a clinically feasible manner with a flush-
fitting opaque scleral contact lens with a back surface laminated with black plastic (Fig. 6, A, B, and C). We have shown with psychophysical (Fig. 7) and electrophysiological (Fig. 8) testing that an opaque scleral lens could be used to protect the eye almost completely from light.4 A properly fitted, molded44 scleral lens can be worn for ten to 14 hours each day. Our first patient is wearing the lens 11 hours each day with no complications. The lens moves with rotation of the globe and can be made cosmetically acceptable. If it is necessary to improve the circulation of tears in this type of lens, a 1 mm. fenestration can be placed in that part of the lens in apposition with sclera just at or below the lower lid margin so that no significant light leak results. Channels placed radially to the limbus on the back surface of the haptic portion of the lens provide another possibility for venting without fenestration and eliminate the risk of a light leak.40

Light exclusion with a flush-fitting scleral lens is a feasible long-term treatment for young, healthy patients, particularly because no systemic side effects can be anticipated. The eye under cover must be observed to make certain that a strabismus does not develop, but this would seem unlikely since the patient will use binocular vision at least for a few minutes each day prior to insertion of the lens. Amblyopia ex anopsia should not be a problem, since a scleral lens will usually be fitted at a time when these patients have fully developed central vision. If patients are treated at an early time in life when they still have relatively full visual fields in both eyes, the obstruction of one eye with an opaque lens will not offer any serious visual handicap.

Patients considered for a trial of constant light exclusion with a scleral lens should be those with the earliest stages of retinitis pigmentosa. Pigmentary migration35, 36, 46 represents an advanced stage of retinal degeneration in which widespread areas of the neuroepithelium are already irreversibly damaged, and the ERG's in these instances are invariably small or not detectable.31, 33

Although light exclusion could be attempted in these patients, treatment of retinas with loss of function and architecture would seem to have a much smaller chance of success. The best candidates for this treatment would be patients under the age of 25 who retain moderate retinal function, reduced but measurable ERG signals, and minimal or absent changes on ophthalmoscopic examination.8, 20, 21, 29 The patients may have minimal or no symptoms, and the disease is often detected only after the ophthalmologist has insisted on ERG testing of younger asymptomatic siblings and off-spring of patients with advanced retinitis pigmentosa. A diagnosis of retinitis
Fig. 8. ERG responses for normal totally dark-adapted subject (top row), normal subject exposed to white light adapting field (390 footlamberts) without scleral lens protection (center row), and normal subject exposed to same adapting field with scleral lens protection (bottom row); responses elicited with full-field (ganzfeld) system as described previously. First column is responses to suprathreshold blue (λ < 470 nm.) light flashes; second column, to suprathreshold red (λ > 600 nm.) light flashes; third column, to suprathreshold white (8 footlambert) light flashes. ERG's in first two columns are responses to lights scotopically matched (i.e., matched in brightness for rod system); arrows point to rod b-waves in these recordings. Subject without lens (center row) after five minutes of dark adaptation had a small oscillatory response to long wavelength light flashes but not to scotopically matched short wavelength flashes, so this oscillatory response is from the cone system. Responses from normal dark-adapted subject and subject protected with scleral lens are almost identical. Subjects who wore dark sunglasses with side shields were tested under similar condition, and their ERG amplitudes were well below normal dark-adapted ERG responses, indicating that sunglasses did not provide much protection. Calibration symbol (lower right corner) signifies horizontally 50 msec, for all tracings, vertically 100 μV for columns 1 and 2, and 200 μV for column 3. Stimulus onset is vertical hatched line. Stimulus flash duration is 10 msec. Corneal positivity represents an upward deflection; two or three successive responses to same stimulus are superimposed.

Pigmentosa can be established on the basis of an abnormal ERG, usually in early childhood.

The amplitudes of the ERG signals in affected children can be used as the objective measure for stabilization or progression in a therapeutic trial. Since both eyes have identical ERG's and are symmetrically involved in the majority of patients with hereditary retinal degenerations, the eye exposed to light will serve as the control for the eye under cover in the same patient. The therapeutic trial will be continued only if electrical activity, dark adaptation thresholds, visual fields, and visual acuity are better preserved in the eye under the scleral lens than in the eye exposed to light.

The long-term beneficial effect of almost complete light deprivation of one eye for any individual patient is difficult to predict at this time. An observation, perhaps pertinent, is that rats with inherited retinal dystrophy that were reared in complete darkness gave ERG responses up to 120 days after birth, while litter mates reared under ordinary lighting conditions did not give ERG responses beyond 60 days. These experiments in the rat support the idea that retinal function in the eye under cover could be prolonged by as much as a factor of two. Another observation that should be considered is histologic evidence that some retinal deterioration continues in these rats, even with complete light exclusion. Noell found that rats with hereditary retinal dystrophy first reared in complete darkness for many days, then exposed...
to ordinary light for one day, and then replaced in complete darkness showed a considerable advance in their retinal degeneration compared with litter mates reared in complete darkness; their retinal function did remain better than that of litter mates reared under ordinary lighting conditions. If human retinal degenerations behave similarly to that of the rat, then almost complete light exclusion would appear critical, and the eye under cover in man cannot be expected to remain completely unchanged. Furthermore, the possible effects of sudden abrupt changes in light adaptation on the eye under cover are not known. Taking these available facts, one would speculate that if a patient keeps one eye in almost complete darkness and begins this therapeutic trial early in life, then retinal function in the covered eye could be maximally prolonged for twice the period of time that retinal function remains in the uncovered eye.

The widespread involvement of both receptor systems early in these degenerations as well as the frequent family history of an older affected relative who became blind indicates that total blindness is inevitable in the overwhelming majority of these young patients with night blindness. The grim prognosis for these young patients who still have considerable retinal function but who have abnormal cone and rod ERG's emphasizes the urgency for an attempt at therapy. Almost complete light exclusion of one eye with a flush-fitting opaque scleral contact lens is the most reasonable approach to try to preserve retinal function in young patients with early retinitis pigmentosa until a better therapy is available. If light deprivation will stop or markedly delay the degeneration, it may be possible to double the patient's visual lifetime by keeping one retina in reserve in darkness while the other retina functions but degenerates in light.

REFERENCES

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