

A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa

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• **Objective.**—To determine whether supplements of vitamin A or vitamin E alone or in combination affect the course of retinitis pigmentosa.

Design.—Randomized, controlled, double-masked trial with 2×2 factorial design and duration of 4 to 6 years. Electroretinograms, visual field area, and visual acuity were measured annually.

Setting.—Clinical research facility.

Patients.—601 patients aged 18 through 49 years with retinitis pigmentosa meeting preset eligibility criteria. Ninety-five percent of the patients completed the study. There were no adverse reactions.

Intervention.—Patients were assigned to one of four treatment groups receiving 15 000 IU/d of vitamin A, 15 000 IU/d of vitamin A plus 400 IU/d of vitamin E, trace amounts of both vitamins, or 400 IU/d of vitamin E.

Main Outcome Measure.—Cone electroretinogram amplitude.

Results.—The two groups receiving 15 000 IU/d of vitamin A had on average a slower rate of decline of retinal function than the two groups not receiving this dosage ($P=.01$). Among 354 patients with higher initial amplitudes, the two groups receiving 15 000 IU/d of vitamin A were 32% less likely to have a decline in amplitude of 50% or more from baseline in a given year than those not receiving this dosage ($P=.01$), while the two groups receiving 400 IU/d of vitamin E were 42% more likely to have a decline in amplitude of 50% or more from baseline than those not receiving this dosage ($P=.03$). While not statistically significant, similar trends were observed for rates of decline of visual field area. Visual acuity declined about 1 letter per year in all groups.

Conclusions.—These results support a beneficial effect of 15 000 IU/d of vitamin A and suggest an adverse effect of 400 IU/d of vitamin E on the course of retinitis pigmentosa.

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Retinitis pigmentosa is the name applied to a group of hereditary retinal degenerations with a worldwide prevalence of about 1 in 4000.¹⁻¹⁰ Patients typically report night blindness in adolescence and lose vision in the midperipheral and then the far-peripheral visual

field in adulthood due to progressive loss of both rod and cone function.¹¹⁻¹³ Most patients have reductions in central vision by age 50 to 80 years. Findings on fundus examination usually include attenuated retinal arterioles and intraretinal pigment around the midperiphery. Visual function testing^{11,12} and histologic studies^{14,15} have led to the conclusion that visual loss occurs because of degeneration of rod and cone photoreceptors across the retina.

In 1945, patients with retinitis pigmentosa were found to have reduced or nondetectable (ie, $<10 \mu V$) electroretinograms (ERGs), even when they retained some peripheral field and preserved central vision.^{16,17} Advances in signal detection technology allowing measurement of responses down to $1 \mu V$ ^{18,19} or less^{20,21} have made it possible to record ERGs from most patients with remaining vision and thereby monitor objectively the course of their disease. ERG amplitudes were reported to decline exponentially as the disease progressed.²⁰

See also pp 751 and 754.

Therapeutic trials for the common forms of retinitis pigmentosa have used vasodilators,²² placental tissue,²³ vitamin A therapy for several months to 3 years,²⁴⁻²⁶ vitamin E therapy for 1 year,²⁴ hydrolysate of yeast RNA,²⁷ and other treatments²⁸; in none of these trials was a beneficial effect established. Moreover, all previous attempts at treating this disease were conducted without a randomized, controlled, double-masked protocol and without an objective measure of retinal function, such as the ERG, as the outcome measure.

While studying the natural course of retinal degeneration in the common forms of retinitis pigmentosa from 1979 to 1983,²⁰ we noted a subgroup of patients aged 18 through 49 years who reported that they were treating themselves with a separate capsule of vitamin A and/or vitamin E each day, often with other nutritional supplements. Combining observations made over 2 years, we found that the percentage of patients with a decline in ERG amplitude from baseline was lower among those taking vitamin A (two [11%] of 18 patients) or vitamin E (four [21%] of 19 patients) than among

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those taking only a multivitamin supplement (18 [34%] of 53 patients) or no vitamin supplement (37 [41%] of 91 patients). More than half of these self-treated patients reported taking both vitamin A and vitamin E, so we could not determine whether these trends were associated with one vitamin only or with the combination. A food-frequency questionnaire completed by this population also suggested intake-response relationships; patients with the highest estimated intake of preformed vitamin A ($>16\,500$ IU/d) or vitamin E (>200 IU/d), including both diet and supplements, had the lowest incidence of loss of ERG function (three [19%] of 16 patients for each vitamin), whereas those with the lowest estimated intake of these vitamins (<2200 IU/d for vitamin A or <5 IU/d for vitamin E) had the highest incidence of loss of ERG function (14 [52%] of 27 and 11 [44%] of 25 patients, respectively). These preliminary findings as well as the known roles of vitamins A and E in maintaining normal photoreceptor function and structure²⁹⁻³² prompted this randomized, controlled trial to determine whether daily supplements of these vitamins alone or in combination would halt or slow the progression of the common forms of retinitis pigmentosa.

METHODS

Overview of Design

In this trial we screened patients with retinitis pigmentosa for eligibility according to visual, dietary, and medical criteria. We performed a baseline examination on eligible patients within 6 weeks of the screening examination; at baseline these patients were randomly assigned to one of four treatment groups: supplement of 15 000 IU/d of vitamin A, 400 IU/d of vitamin E, both, or only a trace dosage of both. Patients were followed up annually. Since we had found the ERG to be a more sensitive indicator of change than visual field area or visual acuity in patients with retinitis pigmentosa²⁰ and since our preliminary findings were based only on ERG data, we decided a priori to quantify ERG amplitude as the outcome measure in this trial. We calculated a sample size based on the expected rate of decline in ERG amplitude for patients not taking supplements²⁰ and an estimated reduction in the rate of decline per year by 4% among patients taking supplements that would preserve a detectable ERG response for 5 additional years. We calculated that a sample size of 601 patients would be needed to detect a treatment effect over 4 to 5 years using a two-sided test at $\alpha=.05$ with more than 95% power when comparing the two groups receiving vitamin A, 15 000 IU/d, with the two groups not receiving this dosage or when comparing the two groups receiving vitamin E, 400 IU/d, with the two groups not receiving this dosage, assuming no interaction. We calculated that the power would be greater than 80% for this sample size when comparing each active treatment group with the group receiving trace amounts. Visual field areas and visual acuities were also monitored as additional measures of visual function, although we had no expectation that we could detect significant treatment effects with these measures over the course of this study. The project was approved by the appropriate institutional review boards.

Study Population

Patients were recruited by letter from the files of the Berman-Gund Laboratory, Boston, Mass, from the registry of the Retinitis Pigmentosa Foundation Fighting Blindness, Baltimore, Md, and from names and addresses provided by private ophthalmologists. From May 1984 through June 1987 we examined 1051 patients from across the United States and Canada to identify 601 patients with the common forms of retinitis pigmentosa who met a preset list of eligibility criteria. All were initially thought to come from separate families. In seven instances two patients were subsequently found to be first or second cousins; in one instance two patients were siblings. All eligible patients had retinal arteriolar attenuation, elevated dark adaptation thresholds, and reduced ERGs with delayed b-wave implicit times^{33,34}; 94% of eligible patients had intraretinal pigment in the midperipheral fundus. Patients were included if they had a best corrected Snellen visual acuity of 20/100 or better, a central visual field diameter on the Goldmann perimeter with V-4-e white test light of 8° or greater, and an ERG amplitude of 2.5 μ V or greater in response to 0.5-Hz white light or of 0.12 μ V or greater in response to 30-Hz white flickering light in at least one eye. Patients with partial hearing loss (ie, Usher's syndrome type 2) were included. Patients were not included if they had posterior subcapsular cataracts with an area more than 11% of the total lens area in both eyes as quantitated with an adjustable slit-lamp beam. We did not include patients with atypical forms of retinitis pigmentosa (including paravenous retinitis pigmentosa, clumped pigmentary retinal degeneration, sector retinitis pigmentosa, or unilateral retinitis pigmentosa), the carrier state of X-linked retinitis pigmentosa, Refsum disease, the Bardet-Biedl syndrome, or Usher's syndrome type 1 (ie, retinitis pigmentosa with profound congenital deafness), because of a lack of preliminary data suggesting that vitamin A or vitamin E therapy could modify the course of these forms. Patients with retinitis pigmentosa associated with hereditary abetalipoproteinemia (ie, Bassen-Kornzweig syndrome) were excluded, as previous reports have indicated a beneficial effect of vitamin A and vitamin E therapy on this rare form.^{35,36}

Patients were also excluded for the following reasons: less than 18 or more than 49 years of age (because our preliminary findings were based on patients in this age range); weight lower than the fifth percentile of weight for a given age, sex, and height³⁷; serum retinol level of 3.50 μ mol/L (100 μ g/dL) or greater, or of 2.80 μ mol/L (80 μ g/dL) or greater with the percentage of retinyl esters greater than 35% of the serum retinol level; serum α -tocopherol levels greater than the normal range adjusted for serum triglyceride level, total cholesterol level, and sex³⁸; total estimated intake of preformed vitamin A in diet plus pills assessed by a food-frequency questionnaire to be greater than 11 500 IU/d, or total estimated intake of vitamin E in diet plus pills greater than 40 IU/d; average vitamin A capsule intake greater than 5000 IU/d or average vitamin E capsule intake greater than 30 IU/d either in separate capsules or in a multivitamin preparation; pregnancy or

lactation; or a systemic disease that might affect the absorption or metabolism of vitamins A or E. Patients who asked to know the contents of the supplement were advised that disclosure of this information could influence their pattern of intake and thereby bias the results of the study; if they insisted on knowing the contents, they could not take part in this study. All patients signed an informed consent form prior to the screening examination and, if eligible, prior to the baseline examination as well.

Techniques for Evaluation

At each visit patients arrived after fasting for 12 hours, and blood was obtained for a complete blood cell count, serum laboratory chemistry scan, and serum retinol and α -tocopherol determinations. Serum retinol and α -tocopherol concentrations were determined using high-performance liquid chromatography.³⁹ Urine was obtained for routine urinalysis. After breakfast the patients completed medical and food-frequency questionnaires. Heights and weights were measured by a clinical coordinator.⁴⁰ At follow-up visits beginning in May 1987, the patients completed a questionnaire on whether they could walk unaided or drive during the day or night and on whether they were currently employed.

After the questionnaires were completed, best corrected visual acuities were determined using transilluminated Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a distance of 3.2 m.⁴¹ The ETDRS charts contained five letters of comparable difficulty on each line; adjacent lines differed in letter size by 0.1 log unit. A separate chart was used for each eye to reduce the likelihood of memorization. The ETDRS visual acuity was scored as the total number of letters identified. Kinetic visual field areas were then measured for each eye with V-4-e white test light on a white background of 31.5 apostilbs in a Goldmann perimeter, bringing test lights from nonseeing to seeing areas. Visual fields were plotted with a digitizing tablet, and, using a computer, the area of field was quantified in degrees squared for total field and for field contiguous to the center (ie, excluding peripheral islands). Patients then had both pupils maximally dilated with topical phenylephrine hydrochloride and cyclopentolate hydrochloride and wore eye patches for 45 minutes.

ERGs were then recorded with a bipolar contact lens electrode placed on the cornea, which was topically anesthetized with proparacaine hydrochloride. Responses to brief (10 μ s in duration) full-field flashes of light were amplified, summed on a computer (sweep duration, 200 ms), displayed and photographed on an oscilloscope, as described previously.²⁰ First, single flashes of white light (3.8 log foot-lamberts) presented every 2 seconds (ie, 0.5-Hz flashes) were used to elicit mixed cone-rod responses, then flashes of the same white light presented at 30 per second (30 Hz) were used to obtain cone-isolated responses. Responses to 0.5-Hz flashes were summed as two waveforms of 32 responses each by the computer; amplitudes as low as 1 μ V could be detected. Responses to 30-Hz flashes of flickering light were recorded as eight consecutive waveforms of 256 summations each; testing

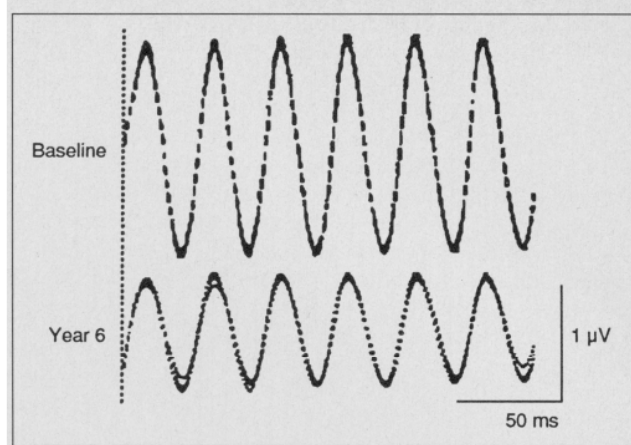


Fig 1.—Computer-averaged full-field cone electroretinograms in response to 30-Hz flashes (n=256) from a representative patient with retinitis pigmentosa at baseline and at year 6. Three response averages are superimposed. The broken vertical line indicates the onset of the train of flashes.

required an average of 8.5 minutes to allow for amplitude stabilization, which occurred in practically all cases.⁴² With the use of a narrow bandpass filter tuned to the stimulus frequency, 30-Hz responses could be recorded at amplitudes as small as 0.05 μ V. The two waveforms for the 0.5-Hz condition and three of the last four for the 30-Hz condition were quantified with respect to peak-to-peak amplitudes. The photographed responses were later evaluated by a separate examiner masked to treatment group assignment and were included for analysis only if the range of amplitude was less than 2:1 for a given test flash condition. Five hundred seventy-five patients (96%) had measurable 30-Hz responses at screening or baseline compared with only 366 patients (61%) with measurable 0.5-Hz responses; therefore, the 30-Hz responses were used as the ERG outcome variable consistent with our sample size calculation of 601 patients. Typical computer-averaged 30-Hz ERG responses used in these analyses from a patient at baseline and 6 years later are illustrated in Fig 1.

Treatment Groups

Using a 2×2 factorial design, we randomly assigned 601 patients to one of four treatment groups as follows: vitamin A, 15 000 IU/d, plus vitamin E, 3 IU/d (group A) (n=146); vitamin A, 75 IU/d, plus vitamin E, 3 IU/d (trace group) (n=149); vitamin A, 15 000 IU/d, plus vitamin E, 400 IU/d (group A+E) (n=151); and vitamin A, 75 IU/d, plus vitamin E, 400 IU/d (group E) (n=155). Vitamin A was provided as retinyl palmitate and vitamin E as *dl*- α -tocopherol in soft gelatin capsules (Hoffman LaRoche, Nutley, NJ). Each bottle contained 100 capsules labeled with a lot number and instructions for storage at room temperature but not labeled as to content. Patients were given four bottles at each visit and advised to take one capsule daily after breakfast.

The procedure for randomization took into account the estimated dietary intake and genetic type at the screening evaluation. The technique of block randomization (block size, eight) was used to ensure that an approximately equal number of patients was assigned

to each treatment group within each of the strata defined by vitamin A (5000 to 11 500 IU/d or <5000 IU/d in diet and pills), vitamin E (10 to 40 IU/d or <10 IU/d in diet and pills), and genetic type (dominant, recessive, X-linked, isolate, or undetermined). Accordingly, 20 strata (ie, $2 \times 2 \times 5$) were defined. A separate set of randomization assignments was maintained for each stratum based on a computer-generated set of random numbers to facilitate the above randomization. Treatment group assignments were placed in a record separate from that used for ocular examinations as part of masking those in contact with the patients.

Masking

All members of the staff in contact with the patients, including the principal investigator (E.L.B.), were masked as to the treatment group assignment of each patient. Each ocular examination and ERG was performed without review of previous records. All serum samples were analyzed without knowledge of treatment group assignment. Patients did not know the contents of the supplements under study or their group assignment and also agreed not to know the course of their retinal degeneration until the end of the study.

Compliance and Toxicity

Compliance was evaluated by measuring serum α -tocopherol levels because these levels are correlated with intake of vitamin E, whereas serum retinol levels are only weakly related to intake of vitamin A.³⁸ Compliance was also monitored by monthly calendars mailed to us by the patients and by counts of returned capsules.

Possible vitamin A or vitamin E toxicity was monitored by a symptom questionnaire administered at each examination and by serum measurements of liver function. Patients with symptoms or signs suggesting possible toxicity (for example, hair loss, persistent headaches, elevated aspartate aminotransferase or alanine aminotransferase concentrations, or joint pain) were referred to a consulting internist who was masked with respect to treatment group assignment. In the case of vitamin A, serum retinyl ester concentrations were evaluated by reverse-phase high-performance liquid chromatography⁴³ in any patient whose serum retinol concentration exceeded 2.80 $\mu\text{mol/L}$. As a precaution, women were instructed not to take the capsules if they learned they were pregnant.

Data Analysis

Data on ERG amplitudes and visual field area were transformed to the log_e scale to approximate a normal distribution.⁴⁴ Data for a given patient for each visit represented the average of test results from both eyes or from a single eye if data for the other eye could not be quantitated. Test/retest data were obtained by comparing results from the screening and baseline measurements performed within a 6-week interval. The average of these two visits was used as the initial measure of ocular function prior to treatment.

Using the 2×2 factorial design, we evaluated main and interaction effects of vitamins A and E based on the following formulas:

$$\text{Vitamin A Main Effect} = [\text{Mean (Group A - Trace Group)} + \text{Mean (Group A+E - Group E)}] / 2$$

$$\text{Vitamin E Main Effect} = [\text{Mean (Group E - Trace Group)} + \text{Mean (Group A+E - Group A)}] / 2$$

$$\text{Interaction Effect} = \text{Mean (Group A - Trace Group)} - \text{Mean (Group A+E - Group E)}$$

This design has been used by others to evaluate the effects of two medications in a single study with a sample size smaller than that required to evaluate the separate effects in independent studies.⁴⁵⁻⁴⁷ The effect of vitamin A was evaluated as an average of the difference between group A and the trace group and the difference between group A+E and group E. The effect of vitamin E was evaluated as an average of the difference between group E and the trace group and the difference between group A+E and group A. The interaction effect was evaluated to determine whether the effect of one vitamin differed in the presence or absence of the other. If a significant ($P < .05$) interaction was found in a factorial analysis, analyses of treatment effects were restricted to the comparison of each active treatment group with the trace group.

Over the 3-year enrollment period it became evident that patients in the lowest quintile of initial 30-Hz ERG amplitude ($<0.34 \mu\text{V}$) had larger intervisit variability between the screening and baseline visits than patients in the upper four quintiles. The coefficients of variation were, from lowest to highest quintile, 17.3%, 12.8%, 11.7%, 11.2%, and 9.3%; the lowest quintile differed significantly from the upper four quintiles (F test, $P < .01$). Therefore, in accord with the Data Safety and Monitoring Committee, we defined a group of 354 patients who had initial 30-Hz amplitudes at least twice the lowest quintile ($\geq 0.68 \mu\text{V}$) so that we could maintain as large a sample size as possible and consider measurements at follow-up that would be above the lowest quintile in most instances, even if the responses declined by 50% (ie, our criterion for failure in survival analyses; see below). Data analyses performed on all randomized patients were also performed on this group of 354 patients.

Additional justification for defining this subgroup of 354 patients based on initial 30-Hz ERG amplitude from the 575 patients who had measurable 30-Hz responses at screening or baseline was provided at the end of the study by comparing the rate of change in the trace group among those included (ie, initial amplitudes $\geq 0.68 \mu\text{V}$ [$n=354$]) with the rate of change in the trace group among those excluded ($n=221$). The rate of decline per year for those included was 10.0%, which was significantly different from zero ($P < .001$), while the rate of decline per year for those excluded was 0.5%, which was not significantly different from zero ($P = .62$). Since the measurable rate of decline for excluded patients with initial amplitudes lower than $0.68 \mu\text{V}$ was essentially zero, we could not expect to detect effects of vitamins A and E in slowing progression for patients with initial amplitudes this small. Thus, we could estimate the effects of intervention more precisely from the 354 patients with initial 30-Hz ERG amplitudes of $0.68 \mu\text{V}$ or greater. We designated this group of 354 patients the "higher-amplitude cohort."

A repeated-measures regression analysis encompassing the data from all follow-up visits was performed to compare rates of decline of ERG function among treatment groups for all randomized patients as well as for the higher-amplitude cohort. The general linear model with intraclass correlation^{48,49} was used to perform slope analyses. This method allows for differences in the number and timing of visits among patients as well as for differences in mean baseline values among treatment groups. Log_e ERG amplitude in a given year was regressed on time, indicator variables for treatment group, and cross-product terms of time by the indicator variables. Equal correlations were assumed among error terms for retinal function of the same patient at different years. Based on these analyses, an average rate of change could be defined for each treatment group, taking into account the intrapatient correlation across visits. We compared rates of change between those receiving vitamin A, 15 000 IU/d, and those not receiving this dosage (ie, vitamin A main effect) and between those receiving vitamin E, 400 IU/d, and those not receiving this dosage (ie, vitamin E main effect) with factorial analysis of variance methods using linear contrasts of the cross-product terms.⁴⁴ Similar analyses were performed for visual field area and ETDRS visual acuity. Since the area of total field showed no significant decline in the trace group over the course of the study (0.4% per year, $P=.50$) while the area of field contiguous to the center did show a significant decline in the trace group (5.9% per year, $P<.001$), we restricted our assessment of treatment effects with respect to visual field to analyses of area of visual field contiguous to the center.

We performed survival analyses for 30-Hz ERG responses on the higher-amplitude cohort of 354 patients. A change score was computed in the log_e scale for each individual for each year of follow-up by subtracting the mean of screening and baseline for that individual from his or her follow-up score. In these analyses treatment was considered as failing at the visit when a patient first had a decline in 30-Hz amplitude of at least 50% relative to the mean of screening and baseline. The validity of choosing a 50% decline in 30-Hz amplitude as a criterion for failure was reinforced by our finding that only one patient who had failure according to this criterion subsequently recovered (ie, had at least one subsequent visit when the 30-Hz amplitude was within 25% of the original value and had no subsequent failure). The log-rank test was used to compare survival curves among the four treatment groups.⁵⁰ Relative risks for failure for those receiving vitamin A, 15 000 IU/d, vs those not receiving this dosage and for those receiving vitamin E, 400 IU/d, vs those not receiving this dosage were calculated as described previously.⁵¹ In addition, the Cox proportional hazards model⁵² was used to control for other baseline covariates, including age, sex, baseline visual function, baseline serum levels of retinol or α -tocopherol, and baseline dietary intake of vitamin A or E.

To provide additional information on year-specific changes in function, we also evaluated mean change from initial values in 30-Hz ERG amplitude. A change score was computed in the log_e scale for each individ-

ual for each year of follow-up by subtracting the mean of screening and baseline from his or her follow-up score. Factorial analysis of variance was used to evaluate main and interaction effects of vitamins A and E based on these change scores.

To evaluate the dose-response relationship between estimated vitamin A or E intake and change in retinal function, we also divided the higher-amplitude cohort into quintiles by total intake of vitamin A or E over the entire follow-up period based on both assigned supplements and dietary intake. One-way analyses of variance were performed⁵³ to assess the change in 30-Hz ERG amplitude as a function of total intake of vitamin A or E; comparisons of specific groups were performed with the least significant difference method using two-sided tests based on a significance level of .05.⁵⁴

To help assess the clinical significance of the ERGs recorded from these patients, we performed logistic regression analyses that related the frequency of positive response with respect to walking unaided, driving, or being employed to 30-Hz ERG amplitude while controlling for age and sex. These analyses were performed on data from the eye with the larger ERG amplitude, which was expressed as a continuous variable. Analyses were based on responses of 586 patients from the first visit for which data were available from both the questionnaire and the ERG. In addition, to assess the reproducibility of responses to these questions on activities of daily living, we compared responses to each question on the first 2 consecutive years for which they were available (585 patients) using the κ statistic.⁵⁵

Study Duration

The trial was originally planned to allow for 4 years of follow-up for each patient. However, recruitment was less rapid than anticipated and required 3 years. Moreover, the progression of the disease in all treatment groups was less rapid than had been expected from our previous natural history study.²⁰ Therefore, follow-up was continued on all patients until the last randomized patients had completed their fourth year of follow-up. The Data Safety and Monitoring Committee recommended cessation of this protocol in September 1991 because all patients had completed their fourth year of follow-up by that time and additional follow-up data would probably not lead to substantially more precise conclusions. The smaller sample sizes at year 5 ($n=472$) and year 6 ($n=261$) reflect the fact that the study was stopped after the last fourth-year follow-up visit. The mean duration of follow-up was 5.2 years both for all randomized patients and for the higher-amplitude cohort.

RESULTS

Randomization

The Table shows demographic and ocular characteristics for all randomized patients and for the group with larger initial ERG amplitudes, designated the higher-amplitude cohort. In accord with the criteria for randomization, the four treatment groups had comparable percentages of patients with each genetic type of retinitis pigmentosa and comparable dietary intakes of vitamins A and E at baseline. The groups were also

Demographic and Ocular Characteristics								
	All Randomized Patients (n=601)*				Higher-Amplitude Cohort (n=354)*			
	Group A (n=146)	Trace Group (n=149)	Group A+E (n=151)	Group E (n=155)	Group A (n=84)	Trace Group (n=90)	Group A+E (n=88)	Group E (n=92)
Genetic type, No. (%)†								
Dominant	45 (31)	40 (27)	40 (26)	40 (26)	31 (37)	27 (30)	23 (26)	29 (32)
Recessive	22 (15)	22 (15)	26 (17)	29 (19)	13 (15)	15 (17)	18 (20)	13 (14)
X-linked	15 (10)	17 (11)	12 (8)	12 (8)	5 (6)	10 (11)	4 (5)	6 (7)
Isolate	59 (40)	62 (42)	62 (41)	63 (41)	32 (38)	30 (33)	38 (43)	41 (45)
Undetermined	5 (3)	8 (5)	11 (7)	11 (7)	3 (4)	8 (9)	5 (6)	3 (3)
Dietary intake, IU/d‡								
Vitamin A	3559±180	3536±183	3766±185	3624±192	3798±259	3406±220	4076±244	3837±256
Vitamin E	11.7±0.6	11.6±0.6	11.8±0.6	12.5±0.7	12.5±0.9	10.6±0.7	12.2±0.9	13.0±0.9
Multivitamin use, No. (%)	28/145 (19)	28/149 (19)	35/151 (23)	27/154 (18)	18/84 (21)	13/90 (14)	20/87 (23)	17/90 (19)
Serum values, µmol/L‡								
Retinol	1.74±0.03	1.74±0.03	1.77±0.03	1.75±0.02	1.74±0.03	1.74±0.03	1.73±0.04	1.78±0.03
α-Tocopherol	20.9±0.5	21.1±0.5	21.8±0.5	21.6±0.5	20.9±0.5	21.1±0.5	21.6±0.5	21.6±0.5
Age, y‡	32.5±0.7	32.2±0.7	32.3±0.6	31.5±0.6	32.4±0.9	32.1±0.9	32.0±0.8	30.8±0.8
Baseline ocular function								
ERG amplitude, µV§								
30 Hz	0.25±0.13 (1.3)	0.29±0.12 (1.3)	0.27±0.12 (1.3)	0.10±0.11 (1.1)	1.20±0.12 (3.3)	1.16±0.11 (3.1)	1.15±0.13 (3.2)	0.94±0.12 (2.6)
0.5 Hz	2.13±0.11 (8.4)	2.15±0.11 (8.6)	2.16±0.11 (8.7)	1.94±0.11 (7.0)	2.28±0.12 (9.8)	2.30±0.11 (10.0)	2.36±0.12 (10.6)	2.08±0.12 (8.0)
Visual field area, degrees¶ (area)	7.28±0.13 (1445)	7.42±0.13 (1669)	7.43±0.12 (1678)	7.48±0.13 (1765)	7.80±0.17 (2453)	7.94±0.16 (2805)	7.94±0.16 (2808)	8.03±0.16 (3080)
[equivalent diameter]	[43]	[46]	[46]	[47]	[56]	[60]	[60]	[63]
ETDRS visual acuity, letters‡	47.5±0.7	47.1±0.7	48.3±0.7	48.0±0.7	50.0±1.0	48.4±0.9	50.1±1.0	49.2±0.9

*The treatment groups were group A: vitamin A, 15 000 IU/d, plus vitamin E, 3 IU/d; trace group: vitamin A, 75 IU/d, plus vitamin E, 3 IU/d; group A+E: vitamin A, 15 000 IU/d, plus vitamin E, 400 IU/d; and group E: vitamin A, 75 IU/d, plus vitamin E, 400 IU/d.

†Percentages may not add to 100% because of rounding.

‡Values are mean±SE. For retinol, 1.74±0.03 µmol/L=49.7±0.8 µg/dL. For α-tocopherol, 20.9±0.5 µmol/L=0.90±0.02 mg/dL.

§Values are mean log₁₀±SE; geometric means are given in parentheses and equivalent diameters in brackets. The lower norm for 30-Hz electroretinographic (ERG) amplitude is 50 µV; the lower norm for 0.5-Hz ERG amplitude is 350 µV; and the lower norm for visual field area is 11 399 degrees² or 120° equivalent circular diameter.

||The lower norm for Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity is 60 letters. An ETDRS visual acuity of 46.9 letters is equivalent to a Snellen visual acuity of 20/35.

balanced with respect to serum retinol and α-tocopherol levels as well as for age. The study population was 62% male and 38% female with a comparable distribution in all treatment groups for all randomized patients and for the higher-amplitude cohort. The patients came from across the United States and Canada, with the majority from outside New England and New York. Twelve percent reported partial hearing loss, with no significant differences in the frequency of partial hearing loss among the four treatment groups. The Table also gives baseline ocular function by treatment group; values represent the mean of the screening and baseline examinations prior to the institution of treatment. We observed no material differences in these measures of visual function among treatment groups. Sixty-seven percent of patients had a posterior or subcapsular cataract in at least one eye at baseline, with comparable percentages in all four groups.

Serum Values

Percentage changes in serum retinol concentrations for all randomized patients by treatment group from baseline to the mean of all follow-up visits were: group A, +8.8%; trace group, +0.3%; group A+E, +5.3%; and group E, -1.0%. Serum retinol values were significantly elevated ($P<.001$) for those receiving vitamin A, 15 000

IU/d (ie, groups A and A+E), compared with those not receiving this dosage (ie, trace group and group E). Percentage changes in serum α-tocopherol concentrations for the same population were: group A, +10.2%; trace group, +11.9%; group A+E, +78.6%; and group E, +82.7%. Serum α-tocopherol values were significantly elevated ($P<.001$) and serum retinol values were significantly depressed ($P=.03$) for patients receiving vitamin E, 400 IU/d (ie, groups A+E and E), compared with those not receiving this dosage (ie, group A and trace group). We observed comparable differences for the 354 patients in the higher-amplitude cohort.

Longitudinal Regression Analyses

A repeated-measures regression analysis that encompassed all available follow-up examinations for all randomized patients showed that rates of decline of remaining 30-Hz ERG amplitude per year by treatment group were: group A, 6.1%, trace group, 7.1%; group A+E, 6.3%; and group E, 7.9% (Fig 2, top). Patients receiving vitamin A, 15 000 IU/d (ie, groups A and A+E), showed a slower rate of decline on average than those not receiving this dosage (ie, trace group and group E) ($P=.01$) (Fig 2, bottom). No significant differences were observed when patients receiving vitamin E, 400 IU/d (ie, groups A+E and E), were compared with those not

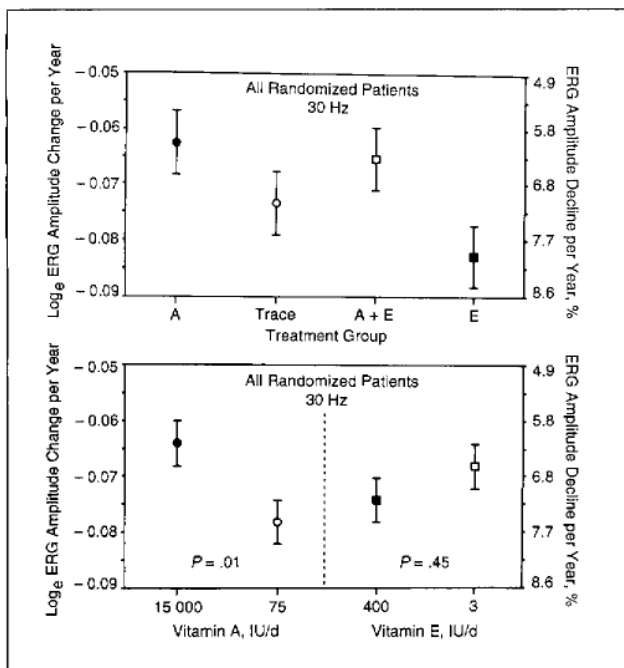


Fig 2.—Mean $\pm$ SE change per year in 30-Hz electroretinogram (ERG) response, based on longitudinal regression analysis for all randomized patients by treatment group (top). Sample sizes were: group A, $n=135$; trace group, $n=143$; group A+E, $n=145$; and group E, $n=152$. Those receiving vitamin A, 15 000 IU/d, are compared with those receiving vitamin A, 75 IU/d (bottom left); and those receiving vitamin E, 400 IU/d, are compared with those receiving vitamin E, 3 IU/d (bottom right). Vertical bars indicate SEs.

receiving this dosage (ie, group A and trace group).

For the higher-amplitude cohort, rates of decline of remaining 30-Hz ERG amplitude per year were: group A, 8.3%; trace group, 10.0%; group A+E, 8.8%; and group E, 11.8% (Fig 3, top). Patients receiving vitamin A, 15 000 IU/d, had a slower rate of decline on average than those not receiving this dosage ($P<.001$), while patients receiving vitamin E, 400 IU/d, had a faster rate of decline than those not receiving this dosage ($P=.04$) (Fig 3, bottom). In addition, group A had a significantly slower rate of decline than the trace group ($P=.03$), while group E had a significantly faster rate of decline than the trace group ($P=.02$). We found no significant differences in treatment effects among the different genetic types.

Rates of decline of remaining 0.5-Hz ERG amplitude per year among the 61% of all randomized patients with measurable responses ($n=366$) were: group A, 8.7%; trace group, 9.6%; group A+E, 9.1%; and group E, 10.6%. We observed a significant vitamin A main effect ($P=.04$) but no significant vitamin E main effect. For those in the higher-amplitude cohort with measurable 0.5-Hz responses ($n=307$), rates of decline per year by treatment group were: group A, 8.1%; trace group, 9.4%; group A+E, 8.4%; and group E, 10.9%. We found a significant vitamin A main effect ($P<.001$) but no significant vitamin E main effect. No significant interaction effects between treatment groups were observed in any of the ERG longitudinal regression analyses.

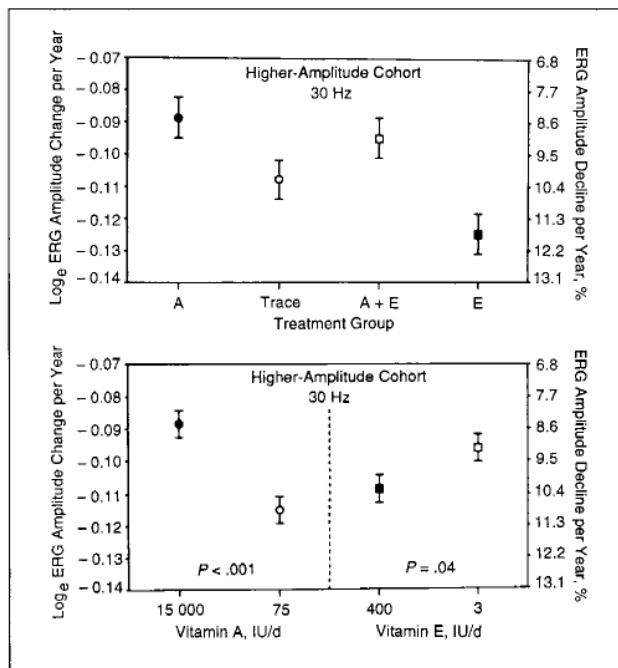


Fig 3.—Mean $\pm$ SE change per year in 30-Hz electroretinogram (ERG) response, based on longitudinal regression analysis for the higher-amplitude cohort by treatment group (top). Sample sizes were: group A, $n=84$; trace group, $n=90$; group A+E, $n=88$; and group E, $n=92$. Those receiving vitamin A, 15 000 IU/d, are compared with those receiving vitamin A, 75 IU/d (bottom left); and those receiving vitamin E, 400 IU/d are compared with those receiving vitamin E, 3 IU/d (bottom right). Vertical bars indicate SEs.

Survival Analyses

Survival fractions by year are illustrated in Fig 4. Patients receiving vitamin A, 15 000 IU/d, maintained their initial amplitude longer than patients not receiving this dosage ($P=.01$, log-rank test). The relative risk was 0.68 (95% confidence interval, 0.50 to 0.92); that is, patients given vitamin A, 15 000 IU/d, were 32% less likely to experience failure in a given year than were those given vitamin A, 75 IU/d (Fig 4, top). Conversely, patients not receiving vitamin E, 400 IU/d, maintained their initial amplitude longer than patients receiving this dosage of vitamin E ($P=.03$, log-rank test). The relative risk was 1.42 (95% confidence interval, 1.04 to 1.93); that is, patients had a 42% greater chance of experiencing failure in a given year if 400 IU/d of vitamin E were taken rather than 3 IU/d (Fig 4, bottom). At year 6, the percentages of patients surviving with less than a 50% decline in 30-Hz ERG amplitude from baseline were: group A, 62%; trace group, 48%; group A+E, 50%; and group E, 27%. Results similar to those using the log-rank test were obtained when proportional hazards models were used to control for baseline variables. Interaction effects between vitamins A and E were considered both in the context of the log-rank test and in the context of the proportional hazards model and were not statistically significant.

Mean Change Analyses

The effects of these treatments by year for the higher-amplitude cohort are plotted in Fig 5. The mean

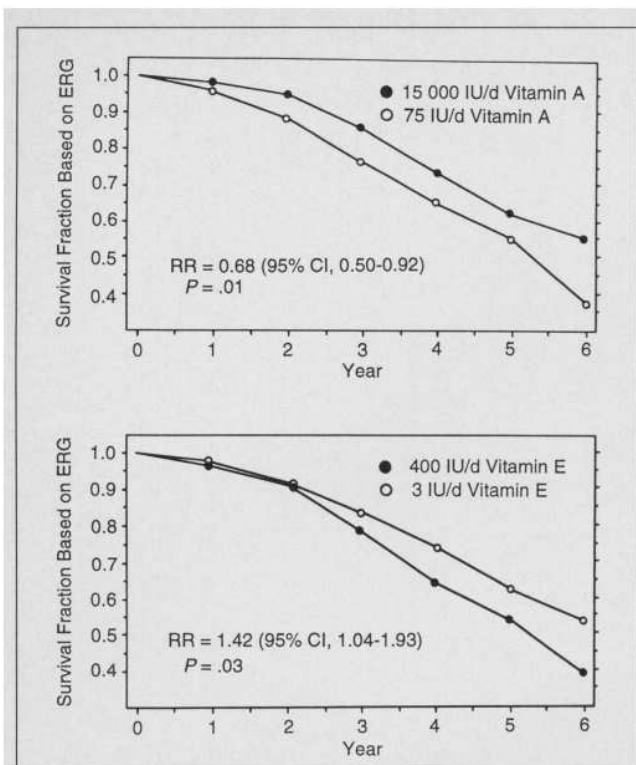


Fig 4.—Survival fractions by year based on a decline from baseline of less than 50% in 30-Hz electroretinogram (ERG) amplitude in the higher-amplitude cohort. Top, Patients who survived the previous year and were available for analysis for years 1 through 6, respectively, were $n=172$, $n=165$, $n=159$, $n=143$, $n=97$, and $n=46$ for patients receiving vitamin A, 15 000 IU/d, and $n=182$, $n=174$, $n=156$, $n=133$, $n=85$, and $n=42$ for patients receiving vitamin A, 75 IU/d. Bottom, Patients who survived the previous year and were available for analysis for years 1 through 6, respectively, were $n=180$, $n=170$, $n=159$, $n=135$, $n=84$, and $n=39$ for patients receiving vitamin E, 400 IU/d, and $n=174$, $n=169$, $n=156$, $n=141$, $n=98$, and $n=49$ for patients receiving vitamin E, 3 IU/d. RR indicates relative risk; CI, confidence interval.

decline in 30-Hz ERG amplitude from baseline values was least for group A in 5 of the 6 years of follow-up and was greatest for group E in all 6 years. The greatest separation among treatment groups occurred at years 5 and 6 (Fig 5, top). The patients receiving vitamin A, 15 000 IU/d (ie, groups A and A+E), had on average significantly smaller declines from baseline than those not receiving this dosage (ie, trace group and group E) at years 1, 2, 5, and 6 ($P \leq .01$ in each of these years) (Fig 5, center). The patients receiving vitamin E, 400 IU/d (ie, groups A+E and E), had on average significantly greater declines in retinal function than those not receiving this dosage (ie, group A and trace group) at years 1, 3, and 6 ($P \leq .03$ in each of these years) (Fig 5, bottom). No significant interaction effects were observed in these mean change analyses.

Progression by Total Intake

To evaluate the dose-response relationship between vitamin A or E intake and change in retinal function, we measured the change in 30-Hz ERG amplitude from baseline by quintile of total preformed vitamin A or E intake (diet plus supplements) irrespective of randomization assignment. For the higher-amplitude cohort,

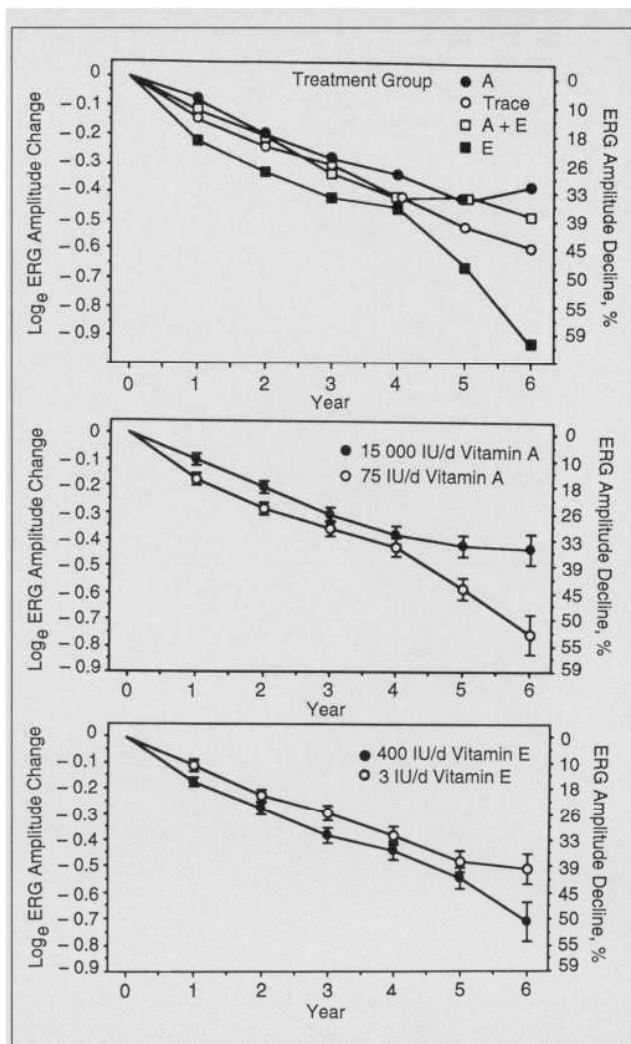


Fig 5.—Mean change from baseline over 6 years in 30-Hz electroretinogram (ERG) amplitude in the higher-amplitude cohort by treatment group (top), by vitamin A main effect (center), and by vitamin E main effect (bottom). Sample sizes for years 1 through 6, respectively, were $n=171$, $n=167$, $n=168$, $n=164$, $n=123$, and $n=59$ for patients receiving vitamin A, 15 000 IU/d, and $n=178$, $n=182$, $n=172$, $n=171$, $n=125$, and $n=64$ for patients receiving vitamin A, 75 IU/d. Sample sizes for years 1 through 6, respectively, were $n=178$, $n=177$, $n=173$, $n=168$, $n=122$, and $n=61$ for patients receiving vitamin E, 400 IU/d, and $n=171$, $n=172$, $n=167$, $n=126$, and $n=62$ for patients receiving vitamin E, 3 IU/d.

the average percentage decline in amplitude for all follow-up visits was greatest for those with daily vitamin A intake lower than 2428 IU (ie, lowest quintile), intermediate for those with intake between 2428 and 16 946 IU (middle two quintiles), and least for those with intake of 16 947 IU or greater (upper two quintiles) (Fig 6). A significant difference was found among these three groups by analysis of variance ($P < .05$) and between the lowest quintile and the upper two quintiles by the least significant difference method ($P = .02$). An analysis of variance for vitamin E showed no significant dose-response relationship, but the range of intake was narrow for those not randomized to the high vitamin E dosage.

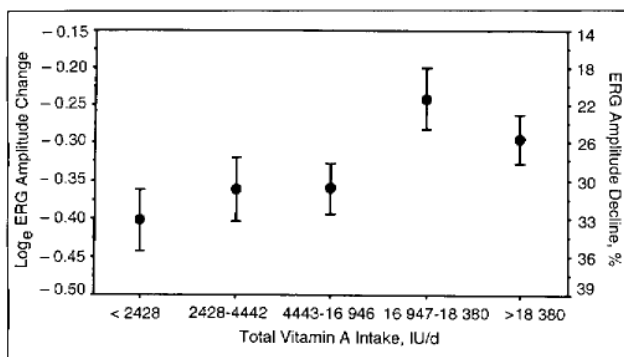


Fig 6.—Mean $\pm$ SE decline from baseline in 30-Hz electroretinogram (ERG) amplitude by total vitamin A intake (diet plus capsules) irrespective of randomization assignment for all patients in the higher-amplitude cohort. The mean decline was calculated as the mean of screening and baseline minus the mean of all follow-up visits by quintile of total vitamin A intake averaged over all visits. Sample sizes were $n=69$, $n=72$, $n=74$, $n=65$, and $n=74$ for the lowest to highest quintiles of total vitamin A intake. Vertical bars indicate SEs.

Analyses of Visual Field and Visual Acuity

For all randomized patients, percentage declines per year of remaining visual field area by treatment group were: group A, 5.6%; trace group, 5.9%; group A + E, 6.2%; and group E, 6.3%. For the higher-amplitude cohort, rates of decline were: group A, 6.3%; trace group, 7.2%; group A + E, 7.3%; and group E, 7.8%. No significant vitamin A or vitamin E main effects or interaction effects were observed in these analyses of field area. For all randomized patients, declines in ETDRS visual acuity were: group A, 1.1 letters per year; trace group, 0.9 letter per year; group A + E, 0.7 letter per year; and group E, 0.9 letter per year. For the higher-amplitude cohort, declines were: group A, 0.8 letter per year; trace group, 0.8 letter per year; group A + E, 0.7 letter per year; and group E, 0.7 letter per year. For all randomized patients, the factorial analysis revealed a significant interaction effect ($P=.008$); comparison of each treatment group with the trace group revealed no significant differences. For the higher-amplitude cohort, no significant vitamin A, vitamin E, or interaction effect was observed.

Significant correlations were observed between change in visual field area and change in 30-Hz ERG amplitude from baseline to the mean of all follow-up visits for all randomized patients ($r=.21$, $P<.001$) and for the higher-amplitude cohort ($r=.19$, $P<.001$). No significant correlations were found between change in ETDRS visual acuity and change in 30-Hz ERG amplitude for all randomized patients ($r=-.06$, P , not significant) or for the higher-amplitude cohort ($r=-.004$, P , not significant).

Relationship of ERG to Routine Activities Utilizing Vision

Among the 586 patients who responded to a questionnaire on routine activities utilizing vision, 30-Hz cone ERG amplitude was significantly related to the probability of a patient driving during the day ($P<.001$) or night ($P<.001$), walking unaided at night ($P<.001$),

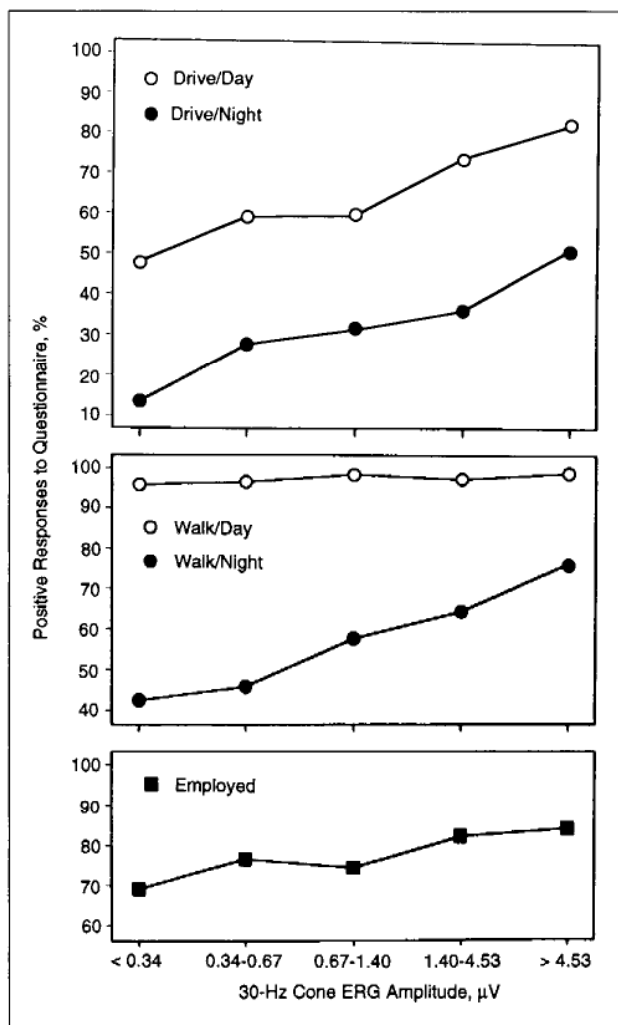


Fig 7.—Frequency of positive responses on questionnaire as a function of 30-Hz cone electroretinogram (ERG) amplitude for 586 patients with retinitis pigmentosa. Groups were defined based on quintile of ERG amplitude: $<0.34 \mu\text{V}$ ($n=132$); 0.34 to $0.67 \mu\text{V}$ ($n=125$); 0.67 to $1.40 \mu\text{V}$ ($n=117$); 1.40 to $4.53 \mu\text{V}$ ($n=109$); and $>4.53 \mu\text{V}$ ($n=103$).

or being presently employed ($P=.001$) after controlling for age and sex (Fig 7). No significant relationship was observed between ERG amplitude and walking unaided during the day. These relationships remained when these analyses were performed on those patients ($n=435$) with visual acuity of 20/40 or better. The reproducibility of responses to the questionnaire as measured by the κ statistic was: driving during the day, .83; driving at night, .78; walking during the day, .34; walking at night, .64; and being employed, .65. These findings indicate good ($.40 \leq \kappa \leq .75$) to excellent ($\kappa > .75$) reproducibility⁵⁵ of the responses to our questionnaire for the four activities that were significantly related to 30-Hz cone ERG amplitude. Since this questionnaire was not administered prior to treatment, the percentage of positive responses to each question was not used as an outcome variable with which to assess the effects of vitamin supplementation in this trial.

Compliance

Only 5% (29/601) of patients failed to complete this study; four of these patients died and 25 patients declined to continue participation, most after the fourth year. Missed visit rates for all randomized patients were 2% (13/596) for those scheduled for visits at year 4, 7% (32/472) for those at year 5, and 12% (32/261) for those at year 6. Capsule counts indicated that at least 94% of capsules were consumed in any given year, and monthly calendar reports indicated that 88% of patients consumed more than 90% of capsules. No significant differences were noted in any of the above parameters among treatment groups. No evidence of systemic illness or toxicity attributable to these capsules could be established during the course of this study based on blood tests, urinalyses, patient responses to a symptom questionnaire, and, in some cases, examination by a consulting internist.

COMMENT

The present study supports the hypothesis that a 15 000-IU supplement of vitamin A taken daily will slow the progression of the common forms of retinitis pigmentosa as monitored by ERG testing. The beneficial effect of vitamin A was substantiated by a repeated-measures regression analysis on all randomized patients that showed that those receiving vitamin A, 15 000 IU/d (ie, groups A and A + E), had a significantly smaller average rate of loss of remaining ERG amplitude per year than those not receiving this dosage (ie, trace group and group E). Survival and mean change analyses on the subgroup of patients with larger initial 30-Hz cone ERG amplitudes, designated the higher-amplitude cohort, showed that those receiving vitamin A, 15 000 IU/d, retained more retinal function than those receiving vitamin A, 75 IU/d. Furthermore, a repeated-measures regression analysis on these patients corroborated the vitamin A effect seen in all randomized patients and also showed that the rate of decline for group A (8.3% per year) was significantly slower than the rate of decline for the trace group (10.0% per year).

The findings also suggest that a 400-IU supplement of vitamin E taken daily may have an adverse effect on the course of the common forms of retinitis pigmentosa. Survival and mean change analyses on the higher-amplitude cohort revealed that those taking vitamin E, 400 IU/d, had greater loss of retinal function than those taking vitamin E, 3 IU/d. A repeated-measures regression analysis on these patients showed that those receiving vitamin E, 400 IU/d, had a faster rate of decline than those receiving vitamin E, 3 IU/d, and that the rate of decline for group E (11.8% per year) was significantly faster than the rate of decline for the trace group (10.0% per year). However, no significant adverse vitamin E effect was seen in the analyses performed on all randomized patients.

The clinical significance of daily intake of a supplement of 15 000 IU of vitamin A or 400 IU of vitamin E can be best estimated (see the "Methods" section) from the ERG rates of decline for the higher-amplitude cohort (group A, 8.3%; trace group, 10.0%; group A + E,

8.8%; and group E, 11.8%). We found that more than 50% of patients in this trial who had a 30-Hz ERG near 0.05 μ V were legally blind (defined as visual acuity $\leq 20/200$ or a central visual field diameter $\leq 20^\circ$ in both eyes), while fewer than 10% of patients who had a 30-Hz ERG near 1.3 μ V were legally blind. Assuming that the above rates were sustained over the long term, the estimated time for the ERG to become nondetectable (ie, $<0.05 \mu$ V) for the average patient with an ERG amplitude of 1.3 μ V at age 32 years (Table) would be 38, 31, 35, and 26 years for groups A, trace, A + E, and E, respectively. Stated in another way, the average patient who starts taking vitamin A, 15 000 IU/d, would be expected to have a nondetectable ERG at about age 70 years (ie, 32 + 38 years), whereas the average patient who starts taking the trace dosage would be expected to reach this level at about age 63 years. In contrast, the average patient who starts taking vitamin E, 400 IU/d, would be expected to have a nondetectable ERG at about age 58 years. Since the likelihood of driving, walking unaided at night, and being employed were each positively correlated with ERG amplitude, it would be expected that patients taking vitamin A, 15 000 IU/d, would have a higher probability of retaining the capacity to perform these activities at a given age than patients in the trace group or group E.

Although we did not observe any significant treatment effects with respect to visual field area, the average rate of loss of remaining field area showed trends similar to the ERG data, with group A showing the smallest rate of loss per year and group E the largest. We did observe a significant positive correlation between change in visual field area and change in 30-Hz ERG amplitude for all randomized patients as well as for the higher-amplitude cohort. Therefore we anticipate that patients receiving vitamin A, 15 000 IU/d, would show a slower rate of decline of visual field area over the long term than those not receiving this dosage. Visual acuity was comparably preserved among all treatment groups. We have no data to predict a beneficial effect of vitamin A on the rate of decline of visual acuity over the long term.

It must be emphasized that this trial was conducted on a population aged 18 through 49 years in good general health with the common forms of retinitis pigmentosa. Women who became pregnant during the study were directed to stop taking the supplement during pregnancy because of the possibility of birth defects in children born to women taking high doses of vitamin A.^{56,57} We also did not include patients under age 18 years, those with known liver malfunction, or patients in the lower 5th percentile of weight for a given age, sex, and height,³⁷ because of the possibility that taking vitamin A, 15 000 IU/d, would lead to toxic side effects over the long term; therefore, we cannot draw conclusions for such patients. We must also emphasize that our conclusions are based on group averages, and therefore we cannot provide assurance that a specific patient will benefit from this treatment. We found no evidence that the beneficial effect of vitamin A was confined to one or another genetic type. It remains to be established whether vitamin A supplementation will have the same

effect on retinal function in all groups of patients with recently discovered subtypes of retinitis pigmentosa defined through molecular genetic analysis.⁵⁸⁻⁶⁴

The results must be interpreted with caution for patients with the more advanced stages of disease who were ineligible for this study. In addition, the low dosage of vitamin E, 3 IU/d, was not trivial in relation to the dietary intake of the study patients, which averaged about 12 IU/d and raised serum levels of α -tocopherol by about 12%. For this reason we cannot assess the effects of the large supplement we used (400 IU/d) compared with no supplement at all or whether small supplements of vitamin E (within the recommended daily allowance of 15 IU) have any influence on the progression of retinitis pigmentosa.

We observed no toxic side effects of vitamin A supplementation of 15 000 IU/d for 4 to 6 years in our study patients, who had an average intake of vitamin A by diet of about 3600 IU/d (Table). Since we have no evidence that intake of vitamin A of more than 18 380 IU/d will provide any greater benefit (Fig 6) and because total vitamin A intake (ie, diet plus supplement) of 25 000 IU/d or greater has been reported by others to be associated with potentially harmful side effects, including liver disease, when taken over the long term,^{56,57,65} we would not advise patients to take a vitamin A supplement that exceeded the 15 000 IU/d used in this study. Furthermore, we would also advise patients taking a daily supplement of vitamin A of 15 000 IU to maintain a regular diet without specifically selecting foods containing high levels of preformed vitamin A.

The mechanism by which vitamin A supplementation affects the course of retinal degeneration in retinitis pigmentosa remains to be clarified. A common denominator in this group of diseases is loss of rod and cone photoreceptors; it is not unreasonable to hypothesize that vitamin A acts on some final common pathway, resulting in preservation of photoreceptor function. It is possible that some patients with this condition have a diminished capacity to retain vitamin A in the retina due to impaired rods and cones or that they have one or another carrier protein^{66,67} that is abnormal, so that vitamin A is not efficiently transported from the serum to the retina. In any event, the daily intake of a vitamin A supplement may

provide protection against possible transient decreases in serum retinol concentration that may adversely affect photoreceptor function. With respect to vitamin E, we speculate that a daily dosage of 400 IU might affect the course of retinal degeneration in retinitis pigmentosa at least in part by inhibiting the absorption or transport of vitamin A, as we observed that patients receiving vitamin E, 400 IU/d, had slight but significant ($P=.03$) decreases in serum retinol concentration compared with those not receiving vitamin E, 400 IU/d.

In summary, based on ERG results, the course of retinal degeneration in retinitis pigmentosa was slower on average among patients receiving a daily supplement of 15 000 IU of vitamin A than the course among those not taking this dosage. Our results also suggest that the course might be faster on average among patients receiving a daily supplement of 400 IU of vitamin E than the course among those not receiving this dosage. Based on these findings and the analysis of decline of ERG amplitude as a function of total vitamin A intake, it is recommended that most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A, 15 000 IU/d, under the supervision of an ophthalmologist and avoid the use of high-dose supplements of vitamin E, such as the 400 IU/d used in this trial.



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