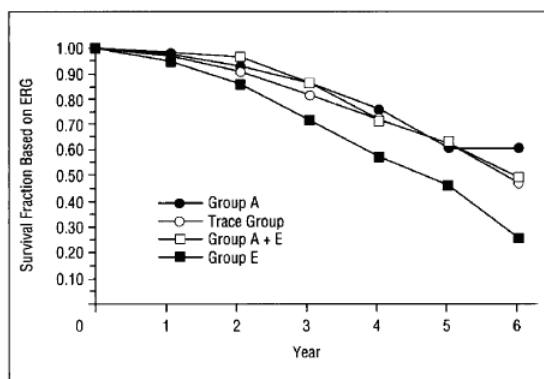


A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa

As a member of the Data Safety and Monitoring Committee for the recent study by Berson et al,¹ I have difficulty accepting the conclusions that "These results support a beneficial effect of 15 000 IU/d of vitamin A . . ." for several reasons.

First, in the study design, patients were assigned to one of four treatment groups as follows: 15 000 IU/d of vitamin A, plus 3 IU/d of vitamin E (group A); 75 IU/d of vitamin A, plus 3 IU/d of vitamin E (trace group); 15 000 IU/d of vitamin A, plus 400 IU/d of vitamin E (group A+E); and 75 IU/d of vitamin A, plus 400 IU/d of vitamin E (group E).

The data through years 4 and 5 show no significant difference between group A and the trace group (**Table** and **Figure**). The authors fail to address these data. Instead, the analysis combines group A and group A+E and



Survival fractions of the four treatment groups as randomized, based on a decline from baseline of less than 50% in 30-Hz electroretinogram (ERG) amplitude in the higher-amplitude cohort. 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. Patients who survived the previous year and were available for analysis for years 1 through 6, respectively, were n=84, n=82, n=77, n=71, n=49, and n=21 for group A; n=90, n=87, n=79, n=70, n=49, and n=28 for the trace group; n=88, n=83, n=82, n=72, n=48, and n=25 for group A+E; n=92, n=87, n=77, n=63, n=36, and n=14 for group E.

Survival Analysis for 30-Hz ERG Amplitude by Treatment Group as Randomized*

Group†	Time Interval, y	Fall, No.‡	Success, No.	Total	Survival	
					Censored§	Fraction
A	0-1	1	83	84	0	0.99
	1-2	5	77	82	1	0.93
	2-3	6	71	77	0	0.86
	3-4	8	63	71	0	0.76
	4-5	9	40	49	14	0.62
	5-6	0	21	21	19	0.62
Trace	0-1	3	87	90	0	0.97
	1-2	5	82	87	0	0.91
	2-3	8	71	79	3	0.82
	3-4	8	62	70	1	0.73
	4-5	6	43	49	13	0.64
	5-6	7	21	28	15	0.48
A+E	0-1	2	86	88	0	0.98
	1-2	1	82	83	3	0.97
	2-3	9	73	82	0	0.86
	3-4	12	60	72	1	0.72
	4-5	6	42	48	12	0.63
	5-6	5	20	25	17	0.50
E	0-1	5	87	92	0	0.95
	1-2	8	79	87	0	0.86
	2-3	13	64	77	2	0.71
	3-4	12	51	63	1	0.58
	4-5	7	29	36	15	0.47
	5-6	6	8	14	15	0.27

*Based on patients whose average electroretinogram (ERG) amplitude over screening and baseline was at least two times the lowest quintile.

†See text and Figure legend for description of the groups.

‡A patient fails in a given time interval if their ERG amplitude declines by at least 50% from baseline to the end of the time interval.

§Patients are shown as censored if they were successes up to the beginning of the specified time interval and had no subsequent visits.

compares these two groups with the trace group and group E. This distorts the data for the trace group because group E from year 2 onward consistently performed poorer than the other three treatment groups. This difference is addressed in the "Conclusions" section of the abstract: ". . . and suggest an adverse effect of 400 IU/d of vitamin E on the course of retinitis pigmentosa."

Second, 601 patients were entered into the study and 95% completed 4 years. Of the higher-amplitude cohort, which is the basis of the analysis, 78% were followed up for 4 years, only 51% were followed up for 5 years, and only 25% were followed up for 6 years. As a member of the Data Safety and Monitoring Committee, I wanted all data reported. The 6-year data, however, should not have been included in the statistical analysis because it is not representative of the entire group.

This excellent study provides useful information for future investigators, but it fails to scientifically establish a significant beneficial effect for vitamin A in the treatment of RP.

Edward W. D. Norton, MD
Miami, Fla

1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993; 111:761-772.

In their recent report, Berson et al¹ conclude that vitamin A has a beneficial effect and that vitamin E has an adverse effect on RP. On critical reading of the data, however, these conclusions may be less war-

ranted than is intimated in the text. Several members of the Data Safety and Monitoring Committee (myself included) have had reservations about the interpretation of the findings.

The study was planned to include 600 patients to obtain sufficient statistical power to draw conclusions, but because of slow recruitment, 596 patients were followed up for 4 years, 472 were followed up for 5 years, and only 261 were followed up for 6 years. The 6-year data represent the first group of patients recruited and a "leading edge" of the dataset as patients accumulated at each year of follow-up. A glance at Figure 5^{1(p768)} shows that the positive effects of vitamin A and the negative effects of vitamin E appear to be greatest at years 5 and 6, which seems to suggest that the curves are diverging and that treatment effects would become more prominent with time. However, this "leading edge" effect was apparent throughout the study, and every year it disappeared as the full cohort of patients became incorporated into the dataset. For this reason, I believe that the 6-year data represent an atypical sample of the population and I question the appropriateness of combining these data with those from earlier years of follow-up.

The Data Safety and Monitoring Committee recommended that analytic results be shown for all four treatment groups. This was done in Figure 5 (top), which shows (with the exception of years 5 and 6) remarkably little difference among the four treatment groups. A similar analysis of the data in Figure 4^{1(p768)} (see the Figure in the accompanying letter by Norton) shows virtually no difference among the groups, with the exception of patients receiving vitamin E alone who did worse. I find it difficult to look at these two graphs and conclude that there is any clinically meaningful effect of vitamin A, regardless of whether a few points may be mathematically "significant." The vitamin E result could, as Berson et al¹ point out in the "Comment" section, be explained simply by a modest interference with vitamin A absorption.

Figures 2 and 3^{1(p767)} appear to show the effects of vitamin A independent of vitamin E. Since "amplitude change per year" is an averaged parameter analogous to an overall slope of signal loss, we cannot judge how these results may have been influenced by the divergence of curves in years 5 and 6. The authors should show data to answer whether the result in Figures 2 and 3 would be the same if the analysis were limited to 4 years of follow-up on all patients.

Berson et al¹ recommend that patients should receive 15 000 IU/d of vitamin A palmitate, since that is the form of vitamin A that was studied. There are good reasons for patients not to use beta-carotene supplementation, since conversion to vitamin A is regulated in the body and may not be predictable, and since large doses may yellow the skin. However, there appears to be no scientific reason to prefer vitamin A palmitate over acetate or other ester forms of vitamin A.

Because of these concerns, I am far less convinced than Berson et al that this study shows a beneficial effect of vitamin A on RP. At best, the data are suggestive and the effect of vitamin A is very small. There is also no analysis to indicate whether certain individuals responded unusually well to vitamin A (a possibility that must be considered given the genetic heterogeneity of the disease). Even the deleterious effect of vitamin E, which seems more definitive than the effect of vitamin A from the graphic data, may represent only competitive absorption rather than a direct pharmacologic effect on the disease.

This study was meticulously designed and extraordinarily well performed, and it represents an important scientific contribution; however, I would argue that its message should be one of caution more than enthusiasm. Patients should be informed that vitamin A may be only marginally beneficial if it helps at all, and this fact must be weighed against a somewhat uncertain risk of liver or other toxic side effects after many years of vitamin A supplementation at 60% of reportedly "toxic" dose levels.²⁻⁴ Patients with RP may elect to receive vitamin A supplementation in the absence of other options for this disease, but they should do so with full awareness of the benefits and risks.

Michael F. Marmor, MD
Stanford, Calif

1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993; 111:761-772.
2. Herbert V. Toxicity of 25,000 IU vitamin A supplements in 'health' food users. *Am J Clin Nutr*. 1982;36:185-186.
3. Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL. Evaluation of vitamin A toxicity. *Am J Clin Nutr*. 1990;52:183-202.
4. Geubel AP, DeGalsosy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology*. 1991;100:1701-1709.

The article¹ published in the June 1993 issue of the ARCHIVES demands a response from one "guinea pig" who believes that his experience with the study has not been accurately portrayed.

First, the article states that "There were no adverse reactions." On the contrary, I, after 4 years of taking the maximum dose of vitamins A and E, was told by research staff that I had high levels of liver enzyme in my blood and should consult a physician. I was then surprised to learn that I was having extreme reactions (nausea, dizziness, and fatigue) to alcohol the day after consumption. I quit drinking once I figured out the relationship, but the fatigue factor did not go away. I quit taking supplements, but for an entire year I was no longer able to work out three times a week. It was a full 2 years before I was back to my normal routine of exercise and feeling good, including the moderate

Name: Clowes, Dennis		Treatment Group: 15000 IU Vitamin A+ 400 IU Vitamin E (Group AE)					
D.O.B: 9-25-56		Genetic Type: X-Linked					
		Screening Baseline*	Year 1	Year 2	Year 3	Year 4	
Date of Visit		4-22-85	6-4-85	6-6-86	6-5-87	6-6-88	6-9-89
Test	Eye+						
Visual Acuity (Best Corrected)	OD	20/70	20/50	20/70	20/70	20/70	20/80
	OS	20/200	20/100	20/200	20/200	20/200	20/400
Visual Field Diameter in Degrees** (Normal ≥ 120)	OD	74.60	73.41	67.33	61.62	76.07	61.36
	OS	78.57	85.07	68.15	69.96	67.27	65.34
Full Field Erg Amplitude in Microvolts to White Light Single Flash (Lower Norm=350)	OD	NA	NA	NA	NA	NA	NA
	OS	NA	NA	NA	NA	NA	NA
Full Field Erg Amplitude in Microvolts to White Flickering Light (Lower Norm=50)	OD	0.56	0.60	0.52	0.34	0.20	0.26
	OS	0.35	0.25	0.33	0.26	0.14	NA

* Capsules Started After This Visit
+ OD=Right Eye; OS=Left Eye
** Equivalent Circular Diameter From Area of Central Field and Peripheral Islands if Present to V-4E White Test Light
NA Not Available=Too Variable to Quantitate
ND Not Detectable as Tested

Visual examination results over 4 years for a patient with retinitis pigmentosa participating in the research program conducted by Berson et al.¹

use of alcohol. Hepatitis was suspected by the research staff, but no evidence ever showed up in the numerous medical tests that I underwent. Frankly, I think it was the vitamin A. In a telephone conversation with Berson, he mentioned another study participant who had "hepatitis."

Second, the article states that "Follow-up was continued on all patients until the last randomized patients had completed their fourth year of follow-up." My last visit was June 1989, yet the study was halted in September 1991. Is this deliberate deception?

Third, presenting such rudimentary science as treatment is extremely premature. The idea for the study came from observations of a few patients taking vitamins whose vision appeared to be declining slower than those who were not. The authors attempted to validate their observations by getting a large study group together to "prove" their point. They do not claim to know why or how vitamin A affects RP, and I would submit that a working hypothesis should be present before we start treating people with a substance that has at least some toxic side effects.

Fourth, the article claims only to slow the decline by 20%. In other words, you lose 80% of what you would anyway in the short term, and all of it eventually. Owing to the "spurt" nature of RP vision loss, I submit that monitoring patients over 4 years, picking up a marginally slower rate of decline in one group over the other, and then trumpeting this as treatment

is absurd. My vision loss during the study period was dramatic (I have included a copy of their data documenting the decline I experienced) (**Figure**).

This study cost me much in time, money, and I believe, health. The purpose of this letter is to share my honest views with fellow sufferers of RP and those trying to assist them. It pains me to tell you that this horrible nightmare will continue for all of us.

Dennis D. Clowes
Minneapolis, Minn

1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993; 111:761-772.

Based on the findings reported recently in the ARCHIVES by Berson et al,¹ the National Retinitis Pigmentosa Foundation and the RP Foundation Fighting Blindness have begun national campaigns that will probably persuade most patients with RP to begin a lifelong regimen of vitamin A supplementation. This media blitz was launched despite important and compelling uncertainties raised in an accompanying editorial by Massof and Finkelstein.² The authors of this editorial discuss at length three reservations, including the use of an electrophysiologic parameter (ERG [electroretinogram] amplitude) to measure clinical impact.

We wish to raise an additional concern. In reality, Berson et al¹ measured three variables—ERG amplitude, visual acuity, and visual fields. Had any one of these three shown a response to therapy, would they have interpreted this finding as a successful outcome? Furthermore, Berson et al measured clinical impact for two agents (vitamins A and E), and they performed additional tests on a subgroup of patients with higher ERG amplitudes. Thus, the authors performed multiple statistical comparisons in their examination of the null hypothesis, and yet they do not describe any adjustment in the threshold *P* value to allow for these multiple comparisons. If such adjustments had been made, would their important therapeutic finding still be significant?

In addition to this apparent failure to adjust for multiple comparisons, the authors also appear to set the threshold value at *P*=05. This value may not be significantly rigorous for a study of this size and importance.

Combining our concerns with those of Massof and Finkelstein,² it is apparent that the therapeutic impact of vitamin A on RP has not been established. Although this issue warrants further study, the report by Berson et al does not appear to provide sufficient evidence to

justify a lifetime of potentially toxic therapy for thousands of patients who already suffer from this visual disability.

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Charles C. Barr, MD
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1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol.* 1993; 111:761-772.
2. Massof RW, Finkelstein D. Supplemental vitamin A retards loss of ERG amplitude in retinitis pigmentosa. *Arch Ophthalmol.* 1993;111:751-754.

In the June 1993 edition of the ARCHIVES, Berson et al¹ reported a beneficial effect of vitamin A supplementation on the cone ERG amplitude in RP. Surprisingly, no visual functions were measured and in an accompanying editorial, Massof and Finkelstein² expressed a number of concerns. They questioned the basis of this ERG finding and even offered alternative explanations for the purported effect of vitamin A on cone function.

In their final paragraph, Berson et al recommended "that most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A.¹ It comes as no surprise that this statement immediately caught the attention of sufferers of RP. It was inevitable because this prestigious journal considered these results of sufficient import to expedite publication ensuring that they reached the public domain with the least possible delay.

Therefore, with understandable alacrity, the RP Foundation Fighting Blindness issued a missive in the form of "questions and answers about . . ." to sufferers of RP. Here are a few extracts. Although not a cure, "it may be a help for many" and "the average patient taking vitamin A could expect to keep retinal function for several years longer. If vitamin A supplements were started by the average patient at age 32 years, legal blindness could be delayed by as much as 7 years." "Should I be encouraged by the discovery of this treatment?" "Yes, indeed! This breakthrough is a concrete reward for the many years of research that preceded it. Daily vitamin A supplementation is the first discovered means to partially control RP that is proven useful and safe for most patients." The article by Berson et al is quoted in detail, and while the editorial is cited, the full reference is not given, nor is there any mention of its critical content.

The consequences of the article by Berson et al were wholly predictable, because it offers hope for a condition that blinds; but raising false hopes is a crude manipulation of the sufferers of RP. It is unfortunate,

therefore, that the final paragraph of this otherwise excellent article was published. It reflects poorly on the ARCHIVES and is not entirely mitigated by the accompanying editorial. Extravagant speculative statements do not reflect well on clinical ophthalmology. It is easy to be wise after the event, but this expensive project (\$5 million according to RP Foundation Fighting Blindness literature) still leaves us with the question: "Does, or does not vitamin A have a significant and beneficial effect of photoreceptor function in RP?" This sequence of events will not facilitate future RP research, and broadening the outcome parameters as suggested in the editorial² would have obviated this unsatisfactory result.

Incidentally, the British Retinitis Pigmentosa Society has adopted a suitably cautious approach more in keeping with your excellent editorial.

Alistair R. Fielder, FRCS
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John Marshall, PhD
London, England

1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol.* 1993; 111:761-772.
2. Massof RW, Finkelstein D. Supplemental vitamin A retards loss of ERG amplitude in retinitis pigmentosa. *Arch Ophthalmol.* 1993;111:751-754.

In reply

We are pleased by the interest generated by our article¹ in the June 1993 issue of the ARCHIVES and welcome the opportunity to reply.

In response to Drs Fielder and Marshall, the ERG is an indicator of visual function in RP for the reasons enumerated in our response to the editorial by Drs Massof and Finkelstein.² Thus, we cannot accept their statement that our publication raises "false hopes." Instead, vitamin A therapy should be accepted for what the data show—a means to slow, in modest degree, the mean rate of decline of remaining retinal function for adults afflicted with RP.

Dr Norton's comments emphasize individual group comparisons while ignoring the factorial design of the study. The factorial study design has been widely used in major clinical trials sponsored by the National Institutes of Health to evaluate two treatment effects in one study with the smallest possible sample size. In our study, this design was chosen a priori, and sample size was calculated accordingly, so that we would have more than 95% power in detecting significant differences when comparing the two groups receiving 15 000 IU/d of vitamin A or 400 IU/d of vitamin E, respectively, with groups not receiving these doses. Our conclusions, when statistical interaction effects are not present (see "Methods" section of our article),¹ are based on factorial analyses. While comparisons of each of