

The FELIX Letter

A COMMENTARY ON NUTRITION

NO. 9

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I. A VITAMIN E SCARE

For some time, I had heard rumors of a significant article describing the dangers of large doses of vitamin E. When I finally ran it down a few months ago, it proved to be Dr. Hyman J. Roberts' "Perspective on Vitamin E as Therapy," featured prominently in the Commentary section of the July 10, 1981 JAMA (*Journal of the American Medical Assoc.*). A similar more detailed paper by Dr. Roberts was published in *Angiology*, March 1979. The disorders ascribed to vitamin E were alarming and Dr. Roberts' references were numerous, so I'm devoting the August and September issues to evaluating his material, current information on vitamin E, and what I learned in talking to several prominent scientists in the field.

Vitamin E has been the "stormy petrel" of nutrition research since the 1940's, when its experimental use which, since its discovery in 1922, had been confined largely to animals, began to be accelerated in humans. Much of medicine's pique against "self-prescription" of vitamins has been centered on vitamin E. The work of the Canadian physician-brothers, Evan and Wilfrid Shute, who had written of their successful treatment of thousands of heart patients for over 25 years with large doses of vitamin E, has been repeatedly challenged by the medical establishment. It received so much acclaim, however, by word of mouth and in the healthfood literature, that non-prescription sales of the vitamin rose over the last 20 years to now include possibly as many as 20 million persons yearly.

A New Danger?

The safety of large doses was thought to be well established, so there have been relatively few warnings in the literature on the toxic effects of overdosage that are routinely issued



for vitamins A and D. In addition to the popular literature's espousal of megadoses of the vitamin, a number of physicians who are convinced of its usefulness have also been prescribing amounts far greater than the current Recommended Dietary Allowance of 10 milligrams a day for adult men (equivalent to 15 International Units, or 15 IU). Hence, Dr. Roberts' data could have serious implications for people taking vitamin E "in excess of 100 to 300 units," Dr. Roberts' definition of a megadose.

The following are a group of the lesser but still unpleasant side effects listed by Dr. Roberts: severe fatigue, headache, dizziness, nausea, diarrhea, intestinal cramps, muscle weakness, visual complaints, hypoglycemia, sore mouth, chapped lips, hives.

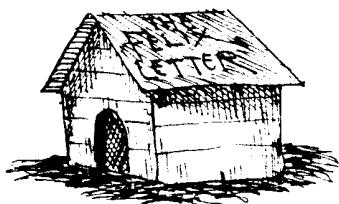
According to the references he gives, these symptoms occurred largely as isolated cases rather than as common side effects of controlled studies using vitamin E. A researcher in vitamin E at Hoffman-La Roche in New Jersey told me that one of his associates has reviewed a huge number of case studies, and "basically, the number of side effects you get with vitamin E is the same as you get with a placebo or untreated population. If you look at enough people, you're going to get things like headaches, muscular fatigue, and so on, but the numbers we have seen are no different from a control population."

(In my own experience, several individuals have found that large doses can sometimes cause intestinal gas and discomfort.)



Caution in Hypertension

Dr. Roberts describes "hypertension" (high blood pressure) as a side effect he has noted in some of his patients who had self-medicated with vitamin E in high dosages. Many physicians and individual users who swear by its benefits also have found that persons with rheumatic heart disease or high blood pressure may get a rise in pressure initially unless they take the vitamin in low doses, e.g., 30 IU, and gradually build it up over a period of months. Responsible popular literature usually cautions diabetics and persons with overactive thyroids, hypertension, or heart disease to take the vitamin only with medical supervision, since it has been known to interfere with medication; but there is no question that a lot of popular writing ignores or minimizes this risk.



Lumpy Breasts and E

Among the more serious complaints attributed by Dr. Roberts to overdosing are swollen breasts (gynecomastia) in both men and women, sore breasts, and cystic mastitis ("lumpy breasts", or mammary dysplasia). Contrary to Dr. Roberts' findings, there are a lot of anecdotal reports, both medical and popular, of the vitamin's usefulness in relieving cystic mastitis and breast tenderness. Recently, Dr. Robert London did a controlled trial on 26 patients with "lumpy breast" disease and 8 normal women as controls, giving all of them 600 IU of vitamin E per day for eight weeks. In ten patients, the lumps and soreness disappeared. Twelve women showed moderate improvement; the remaining two did not respond.

In noting that laboratory tests of the women showed vitamin E to have affected the levels of certain hormones produced by the adrenal and pituitary glands, Dr. London makes this pivotal observation:

I think the important thing is that vitamin E has profound effects on the homeostatic mechanism both in normal women and in women with mammary dysplasia . . . It may change your lipids; it may . . . alter some of your steroid hormones. At least at the dosage levels we prescribed, which weren't all that high, vitamin E is not a benign vitamin that you can take like vitamin C if you think you're getting a cold. It is — and we need to stress this — a pharmacologic agent.

He also adds:

[they found] absolutely no side effects in terms of clinical derangements, and it worked in a high percentage of patients. If the clinicians can get symptomatic relief in patients with something as benign as vitamin E, I think it's a reasonable therapy. The other therapies are all more dangerous or have more side effects.

Nevertheless, we need to be aware that in pharmacological amounts — that is, in amounts much higher than can readily be found in foods — vitamin E may have "profound effects". For this reason, I don't want to minimize the complaints reported by Dr. Roberts. For example, he refers to "vaginal bleeding" in which one or two episodes of menstrual-like bleeding took place, one in a menopausal and the other a near-menopausal woman (his own patient), that appeared to be related to vitamin E intake. Unless a rash of similar cases appears, the ones cited by Dr. Roberts don't seem to represent a common ongoing problem. Nevertheless, a cautious approach is certainly warranted if a woman has any suspicion that bleeding episodes after menopause might be related to high doses of vitamin E.

An Unwarranted Caution

Another effect attributed by Dr. Roberts to vitamin E overdosage is "decreased rate of wound healing (in experimental animals)." A careful reading of the detailed study given as reference, however, would lead to a different understanding. Certain substances in the body such as testosterone and vitamin A are known to speed up healing of wounds by their

ability to stimulate collagen production. (Collagen is the main structural protein in the body.) Other natural body substances, such as corticoid hormones produced in the adrenal glands, are known as "anti-inflammatory agents" which retard the body's production of collagen.

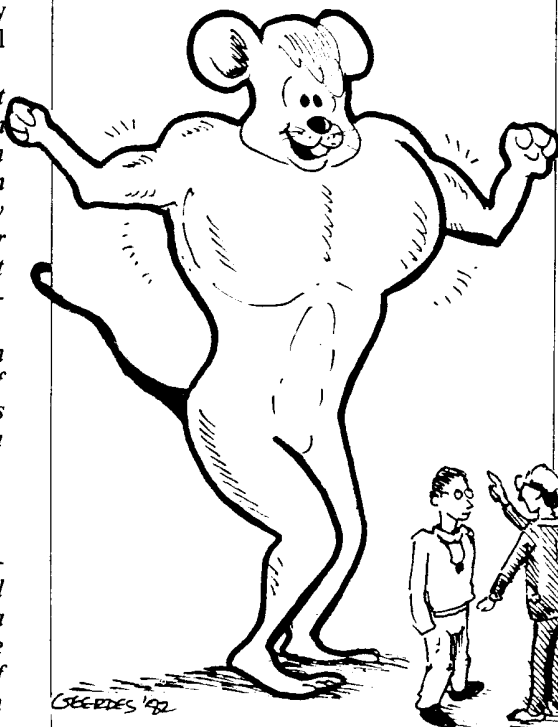
Together, the anti-inflammatory agents and the collagen-stimulating agents spur the processes necessary for wound healing. The results of the experiment indicated that vitamin E fell into the *anti-inflammatory* category, like the corticoid hormones, and as such, tended to slow down production of collagen. The usefulness of this, as explained by the researchers, is that by retarding the rapid accumulation of collagen, vitamin E "may have clinical value in modifying scar formation. In this respect, it could prove superior to corticoids by virtue of its lesser side effects."

There are burn units in hospitals routinely using vitamin E precisely *because* it reduces pain and inflammation and discourages heavy scar formation. I don't feel Dr. Roberts' use of a "warning" in this instance is valid.

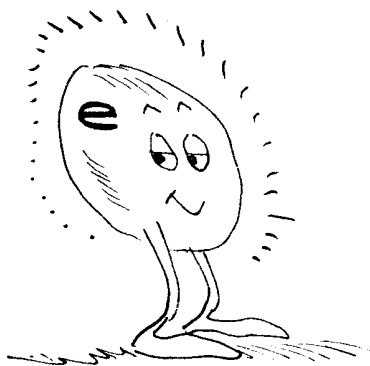
Metabolic Effects

Besides the clinical problems noted, Dr. Roberts also lists a number of "laboratory abnormalities induced by vitamin E." Careful reading of his reference papers, however, reveals the "abnormalities" to be phrases from a number of studies, many ascribing favorable effects to the vitamin. One, for example, suggests vitamin E increases activity of an important enzyme system in our liver that detoxifies cancer-causing substances, insecticides, and other toxic materials. Several indicate that it enhances antibody production and increases immunity to disease. For his list of "laboratory abnormalities," Dr. Roberts excerpts those phrases demonstrating that vitamin E has an effect on metabolic functions as determined by laboratory tests.

In this respect, he may be doing us a service by stressing that in pharmacological doses vitamin E can have significant consequences in the body and that its use in this way should not be entered into casually. The approach he uses is not entirely straightforward, however, since a number of the "laboratory abnormalities" actually represent beneficial effects of the vitamin.



SMEDLEY! HOW MANY TIMES DO I HAVE TO TELL YOU TO KEEP YOUR RATS OUT OF THE VITAMIN E?

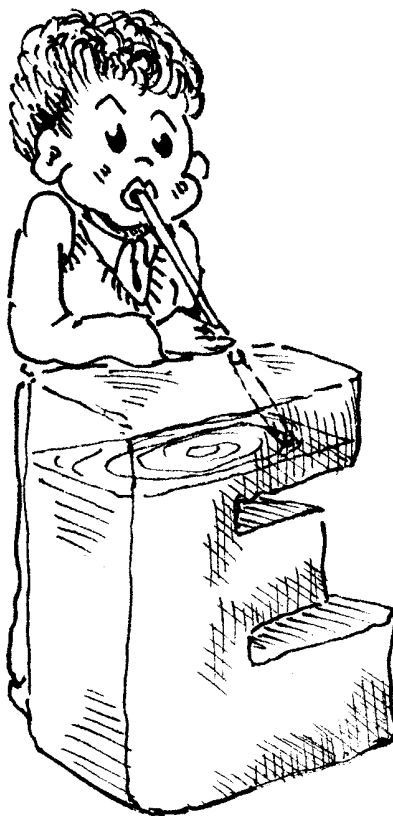


Thrombophlebitis from E?

The heart of Dr. Roberts' caveat is his observation that over a period of about 12 years he has seen more than 80 patients suffering from thrombophlebitis, a serious ailment involving blood clots and inflammation in deep veins of the legs, which had been "caused or aggravated by self-medication with vitamin E in high dosages." A number also developed pulmonary embolism, a life-threatening condition where blood clots lodge in an artery of the lungs. (Along with the epidemic of heart disease of modern life, America has seen an alarming rise in cases of thrombophlebitis and pulmonary embolism.) At first, he says, he was reluctant to ascribe these illnesses to the use of the vitamin which, as he notes, has been "enthusiastically recommended" for managing thrombophlebitis. As time went on, however, he felt that he had obtained a "sufficient data base" to warrant the report. In two cases, the ailment had arisen within two months of self-medication with vitamin E. In another, thrombophlebitis developed in a woman who had been taking 1600 IU daily for years. Four weeks after the dose was reduced to 400 IU, her symptoms markedly lessened.



Generally, in all the thrombophlebitis cases, he notes that, *presenting features in the lower extremities generally abated following the cessation of vitamin E and the administration of conventional conservative measures for thrombophlebitis. The latter included bed rest, local heat, supporting bandages or properly fitted 'antiembolism' hose, and the avoidance of other possible aggravating factors (e.g., the wearing of tight clothes and habitual leg crossing).*



Estrogen and Thrombosis

Dr. Roberts, who is a specialist in internal medicine and a Fellow of the American College of Angiology [angiology: the study of blood and lymph vessels], has published extensively in the field of blood vessel and heart diseases. Among the factors he believes contributing to the epidemic of thrombophlebitis and pulmonary thromboembolism are *high dosages of estrogens and contraceptive drugs, and chronic illnesses such as high blood pressure, heart disease, diabetes, and liver disease.* The latter disorders "predispose to small-vessel disease, platelet aggregation, and thrombosis, especially if estrogens have been or are being taken."

The 80 patients, he notes, had been suffering from a number of these serious chronic illnesses. (It is assumed their self-dosage with vitamin E was prompted by the hope of improving their health.) A group of them, he writes, also had been given estrogen, presumably before he saw them as patients. The ones who took vitamin E in large doses must represent only a fraction of the cases of thrombophlebitis that Dr. Roberts, an angiologist and cardiologist, has seen over the 12-year period. Given the epidemic nature of the disease, what would the chances be of patients with chronic heart disease, diabetes, etc. developing thrombophlebitis if they had *never* taken supplements of the vitamin? One wonders how Dr. Roberts separates cause and effect under these circumstances.

He dismisses any possibility of vitamin E having an "anti-thrombin" action, saying that rather than playing a preventive role, large doses of the vitamin may actually precipitate thrombus (abnormal clot) formation in patients already suffering from heart disease and other serious metabolic disorders. Yet there is good information about its effectiveness in preventing abnormal clots; and one of the references he lists describes a medically well-known danger of vitamin E supplementation; that taken simultaneously with potent anti-clotting medication given for certain kinds of heart disease, it may potentiate the effect to such a degree that small hemorrhages may occur.

Of course, this further reinforces our understanding of vitamin E as a potent substance which can interfere with medication being given for serious ailments when it is taken in pharmacological doses. In Part II, I'll tackle the matter of pharmacological versus natural amounts based on the new, extensive tables of vitamin E values in foods, which will be incorporated into the next edition of *Agricultural Handbook No. 8* of nutrient values in foods — the nutritionists' bible!

A Doctor's Reaction

Nevertheless, it helps to explain why Dr. Roberts' observation of vitamin E as a precipitating factor in thrombophlebitis is puzzling to a number of clinicians. Over the

telephone, I spoke with Dr. Marvin Bierenbaum about Dr. Roberts' findings. He is a cardiologist with the Atherosclerosis Research Group at St. Joseph's Hospital and Medical Center in Montclair, New Jersey, who has directed a number of research projects, one of which involving megadoses of vitamins C and E was recently completed. He told me, "For a period of 8 months, we used 800 IU of vitamin E per day in one group, and the second group had the same amount of vitamin E plus 2000 or 1600 milligrams of vitamin C, with no side effects — so I'm mystified by the large number of side effects Roberts reports."

At my request that he share his views on this matter with *Felix Letter* readers, he sent me the letter he wrote to the *New England Journal of Medicine*, which they chose not to publish:

To The Editor:

Apparently in response to an editorial by Oski in the *Journal* which strongly defended the use of vitamin E, Roberts (JAMA, July 10, 1981) cautions against the current widespread usage of vitamin E because of the many problems that he has encountered seemingly to have been caused or aggravated by self medication with vitamin E in high dosages. He cites 80 cases of thrombophlebitis, pulmonary embolism or both among an almost amazing list of complications that he and others have observed. This data appears to be an extension of an earlier monograph where he reported 50 thrombophlebitis cases most of whom were on 800 IU or more of vitamin E for months to years and 20% of whom were currently or recently on some form of estrogen therapy.

Our group recently studied the effect of 2000 IU/day of vitamin E, first in a 2 week double-blind cross-over study of 25 normal, 15 coronary, and 15 diabetic subjects¹, and then in a 12 week study of 25 adult onset diabetic subjects².

The dosages used here achieved the highest blood levels of vitamin E yet reported in the literature. There was a significant reduction in serum glucose levels of both groups of diabetics and a reduction in blood pressure level for all groups in both studies. In contrast to an earlier report, the entire thyroid pro-

file was unaffected by vitamin E in the experiment. A table of the side effects noted in the second study is included below.

EFFECTS REPORTED (3000) PERSON DAYS

	Vitamin E	Placebo
General Feeling of		
Well Being	6	2
GI Symptoms	1	0
Impotency	0	0
Other	1	0

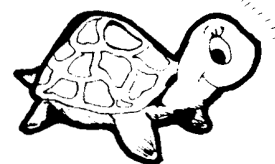
There were no reports of thrombophlebitis or any of the clinical disorders attributed by Dr. Roberts in table 1 of his monograph. These side effects were of no significance other than biological variation. These data raise some question as to the somewhat biased view being expressed by Roberts. The accumulation of 30 cases of thrombophlebitis and/or pulmonary embolism in so short a time as 2 years (from 1979-1981) when our group saw none over a 3 month study is quite amazing. In addition, a reference to finding no beneficial effect on platelet aggregation by vitamin E was in a study of one week's duration utilizing 1000 IU/day and made no comment as to the brevity of this trial. These are only a few of the more outstanding exceptions that one might take with Roberts "perspective" but they serve to point up problems with it.

We can take no umbrage with the stand against unsupervised usage of an agent with potentially widespread metabolic effects, particularly in large doses. It is a disservice, however, to raise such a strong warning about so many possible side effects still requiring substantiation, that investigators will be dissuaded from continuing evaluation of this potentially useful food supplement. We fully intend to continue our studies* in the near future using the "megadose" 800 IU/day (over an eight month period) with careful surveillance and anticipate no serious complication, while examining its potential beneficial effects.

Marvin L. Bierenbaum, M.D.
FACP, FACC

¹Bierenbaum, ML, Fleischman, AL, Machlin, LJ, Stier, A, Watson, PB, Urbach, D, Naso, A: Effects of short-term treatment of post coronary and diabetic subjects with high levels of vitamin E. *V International Symposium on Atherosclerosis* 241: 1979.

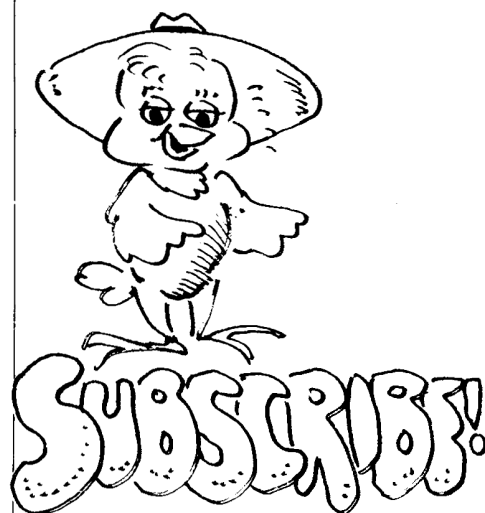
²Bierenbaum, ML, Noonan, FJ, Machlin, LJ, Machlin S, Stier, A, Watson, PB, Somol, H, Naso, A: The effect of supplemental vitamin E upon serum parameters in diabetics. *American Heart Association CVD Epidemiology Newsletter* 30: 1981.



Cause for Optimism

*The studies Dr. Bierenbaum refers to were those he described over the telephone as being recently completed. A research colleague of his told me that they demonstrated with "good, hard data" that peripheral circulation (blood flow to legs, feet, etc.) measurably improved in patients with atherosclerotic arteries, during the eight months of megadose therapy with vitamins C and E. No thrombophlebitis was seen either in this study or in "almost hundreds of clinical trials we've conducted over the years, where nothing like the adverse effects Dr. Roberts reports has ever shown up."

Part II in the September *Felix Letter* will conclude the vitamin E controversy with an update on research, and a guide to the best nutritional sources based on the newest, most complete tables of vitamin E content in foods that have ever been available. ■



Illustrations are by Clay Geerdes.