THE PHYSIOLOGICAL AND BIOCHEMICAL BASIS FOR THE USE OF VITAMIN E IN CARDIO-VASCULAR DISEASE*

By W. E. SHUTE, B.A., M.D., E. V. SHUTE, B.A., M.B., F.R.C.S.(C), and ARTHUR VOGELSANG, B.A., M.D., *London, Canada*

VITAMIN E first came to medical notice as a preservative of precarious pregnancies, whether habitual [1] or threatened abortions.[2, 3] Its rôle in the maintenance of normal gestation was later emphasized with respect to premature placental detachment [4] and non-eclamptic toxemias.[5] Certain uses in gynecology, such as in the menopause,[6, 7] in senile vulvitis [8, 9, 10] and even in male sterility,[11] were also reported. But, fundamentally, for the first 25 years of its existence it did justify the appellation of "fertility vitamin" which now seems so misleading.

That this vitamin played a much more significant rôle than this "bit part" could have been inferred even long before 1945 from the studies of Madsen, Mason, Hickman and Harris, Houchin and Mattill and others. For example, the musculature proved to be a major site of involvement in the E-deficient hamster, rabbit or guinea pig, the vascular system in the monkey, and the heart in the monkey, rabbit and cow. "The association of vitamin E with the reproductive process, therefore, is largely due to a laboratory accident, and it is almost time, 25 years later, that we broke the unfortunate linkage produced in most medical minds by those first aborting rats." [12] For vitamin E, to quote Hickman and Harris, is "the most versatile and active of all the vitamins."

Seen through the eyes of the biochemist, vitamin E plays a still larger rôle. It is even an anomaly among fat-soluble vitamins, since it "behaves as a water-soluble vitamin that requires a lipid carrier for transport." It is one of the two great stabilizers of the blood during the digestive journey." It is the balance-wheel of the oil-soluble vitamins and the unsaturated fats. It is implicated in phosphorus metabolism—and its effects extend to the utilization of oxygen and the aging of the whole animal organism." [13] It is both oxidant and anti-oxidant. Indeed a more versatile participant in the bodily mechanism could scarcely be imagined, and it is not too surprising, therefore, that drastic changes develop in many tissues and systems in the face of E-poverty.

As internists in general, and cardiologists in particular, may not be fully aware of the more relevant animal experimentation in this field, it can be briefly summarized here in order to illustrate the broad basis on which our studies now stand, and to encourage perusal of the original papers, notably Govier's.

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Madsen[14] first showed that myocardial scarring developed in rats after prolonged deprivation of vitamin E. Mason and Emmels[15] confirmed this, and observed gross cardiac enlargement in a large series of such animals coming to autopsy. The pigment found in their heart muscles seemed to be identical with that found in brown atrophy in the senile human heart. Gatz and Houchin[16] reported analogous findings in the hearts of E-deficient rabbits, an observation lately confirmed by Bragdon.[17]

Electrocardiographic changes similar to those seen in failing hearts in man have been found in E-low rats by Butturini,[18] and by Martin and Faust[19] in rats and rabbits, but not by Ensor[20] in rats. Mason and Telford[21] report that E-deficient monkey hearts showed myocardial fibrotic areas, although in the macaque vascular degenerations seemed to preponderate. Holman[22] has also done interesting work relating vitamin E to vascular lesions in dogs.

The study of Gullickson and Calverly[23] on the hearts of E-deficient cattle bids fair to become a veterinary classic. We understand that these authors possess a great wealth of unpublished material, accumulated from a study of over 10 years' duration. Fundamentally, their observations pointed clearly to E-deprivation in cattle producing death from heart failure, with electrocardiographic changes resembling those seen in myocardial damage in man, and with postmortem myocardial foci suggestive of those seen in rheumatic affections in the human.

An interesting piece of clinical work in the veterinary field was reported by Lambert.[24] Dogs and cats in undoubted heart failure were restored to good functional efficiency on the administration of vitamin E. This clinical work on dogs and cats has been widely substantiated, we might add, and some of these veterinary cases have come to our personal attention.

This extensive animal work, some of it antedating our own clinical observations, lays a strong a priori basis for the relationship of vitamin E to cardiovascular lesions in man, should humans ever be suspected of E-deficiency.

That the average American diet is often inadequate in available vitamin E has been clearly demonstrated by the careful calculations of Harris et al.[25] and by Quaife and Harris.[26] A very good exposition of how this can develop is given by Hickman[27] in a recent letter to the Lancet. It would appear that the average American industrial worker gets only from 10 to 90 per cent of his daily requirement of tocopherols. This deficiency is further aggravated by large intakes of milk, butter, white bread and root vegetables, as well as of rancid and unsaturated fats. This deficiency is at least as marked in the upper economic strata as in those less fortunate. The assimilation of vitamin E in healthy persons is less than 50 per cent, and in deficients may be much less.

Govier et al.[28] as well as Spaulding and Graham,[29] have carried out extensive studies on the enzyme systems of heart muscle. "Anoxia in heart muscle is the accepted cause of congestive failure." It is known that in states

of cardiac anoxia coenzyme I is broken down, although it is needed for the proper metabolism of lactate, the preferred substrate of heart muscle. Now alpha tocopherol both inhibits coenzyme I nucleotidase and can also inhibit succinoxidase and lactic dehydrogenase. Govier suggests that if heart muscle in congestive failure is E-deficient, as its low creatine content resembling that of other E-deficient muscles might suggest, this deficiency would permit coenzyme I nucleotidase to act in a system already anoxic and thus produce that breakdown of coenzyme I which is known to occur in such heart muscle. This breakdown of coenzyme I would seriously derange heart metabolism. It is noteworthy that digitoxin seems to prevent such breakdown of coenzyme I in E-deficient muscle, and that alphatocopherol also seems able to prevent its destruction, by inhibiting coenzyme I nucleotidase. Govier has more recently concluded, we understand, that the somewhat similar results in these enzyme systems are accomplished differently, the one substance increasing production of coenzyme I and the other retarding its destruction.

Our own observations [30-33] on the value of alpha tocopherol as a therapeutic agent in various types of cardiac and renal disease we do not propose to review here, as they are rapidly becoming too extensive for convenient summary. Our electrocardiographic studies should soon appear.[34, 35] We ought to emphasize, however, that our conclusions were originally pragmatic, not based on any of this animal work or dietary analysis, and stand or fall by themselves as clinical observations.

Vitamin E therapy in our hands is not substitution therapy, but a form of chemotherapy. This is a point that deserves emphasis. The doses we use are larger than nutritional studies would demand, but usually smaller dosage is ineffectual. We think of alpha tocopherol as a chemical compound which also happens to be a food constituent, but whose dosage level in established cardiac disease is not closely related to that coincidence. The analogy to the modern use of vitamin D is suggestive. A small dosage of E gives but little hint of what it can accomplish in massive dosage. What could be hoped for from a small and more nearly physiological dose administered over a period of years is, of course, quite a different consideration and one on which we have little evidence as yet, although it is a problem of vital importance.

Summary

The physiological and biochemical evidence supporting the use of vitamin E in cardiovascular disease is reviewed.

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