# THE SCOPE OF VITAMIN E.

*By*

The Staff of THE LEE FOUNDATION FOR NUTRITIONAL RESEARCH

Received for Publication, December 1, 1955

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## HISTORICAL DEVELOPMENT

The discovery of a new nutritional factor in the galaxy of vitamins, later to become known as vitamin E, was made by Evans and Bishop in 1922. It was first defined as a necessary element in reproduction. Its absence brought sterility in the male and abortion in female rats.[1] In the same year, Sure independently also made the identical discovery.

At that time, wheat germ oil was the only source of supply of this valuable complex which may yet be regarded as the most brilliant constellation in the vitamin universe as its range of clinical activity and application continues to widen. Four vitamin factors have been isolated in the course of time from the E complex — alpha, beta, gamma and delta tocopherol. Of these the alpha form has been found the most powerful and is often erroneously considered as the whole vitamin E. Actually the term "vitamin E" should only be used in reference to the element which occurs in foods as in its entirety it includes factors not present in alpha tocopherol alone.

This has led to some confusion and a wide disparity of results in clinical applications and experimental observations. In addition, the action of the tocopherols also vary markedly with different species. Because vitamin E was first tested on rats with a marked effect on reproductive powers, it was originally regarded as a stimulant to fertility. As a result, for years its use was limited to the obstetrician and gynecologist in the treatment of habitual abortion.

E. V. Shute, however, recommended its use for threatened but not for habitual abortion.[2] He later extended this to the prophylaxis of abruptio placentae; in most of the late toxemias of pregnancy; to improve the sperm of husbands whose wives habitually aborted; for senile conditions of the female genitalia; for the prevention of premature births and for the menopause. Dr. Wilfred Shute found it valuable in the treatment of nephritis.

These clinical uses were only a logical development of researches on rats deprived of vitamin E. Hens react to the same deficiency with encephalomalacia. Had early therapeutic trials then followed only this indication, the use of vitamin E would have been limited to neurology. In cattle and sheep, vitamin E deficiency produced still another manifestation—myocardial failure. This could have led to its use primarily in cardiovascular diseases.

On the other hand, vitamin E deficiency cannot be produced in goats possibly because they metabolize their own supply. In this instance an in-

vestigator could have been led into a blind alley or, if instead of the tissues, the effects of vitamin E or its derivatives had been studied on the blood, its relation to red blood cell hemolysis would have limited its application to hematology.

It is probably because of these widely varying results, the often confusing manifestations of its physiological activity, as well as administering fractions instead of the entire vitamin, there has been so much controversy and misunderstanding about vitamin E. As its application was extended to further fields in the course of international recognition with reports of its value ranging from enthusiastic praise to cold skepticism, many disputes arose because of the widely conflicting opinions.

Progress in therapeutics was therefore not very rapid. It was only after the first International Congress on vitamin E in London, England, in 1939, that advances became notable. The first observations of the value of the alpha tocopherol in cardiovascular diseases were made by Santacroce, Spampinato and Butturini in Italy. Their work was limited in scope, and not pursued very actively. It attracted little attention until 1947.

The Doctors Shute and associates initiated the most significant clinical evaluations of vitamin E derivatives in cardiovascular diseases and diabetes mellitus. They identified the alpha form of the tocopherols as the most potent, and the beta, gamma and delta forms as of lesser strength. They administered dl-alpha tocopherol acetate, the most readily synthetized and standardized form of the factor.

The first studies of the Shute group were not pursued with the completeness the work deserved because of various difficulties they encountered. Besides the demands of their medical practice, they were hampered by a lack of experimental facilities and the indifference of their medical colleagues. Continuing despite these handicaps, in 1942 Dr. E. V. Shute attributed vascular disturbances to E-deficiency in the diet and found the vitamin brought excellent results in therapy. At the same time Mason of Rochester made the same discovery.

Though the Shutes and their associates continued to demonstrate many significant clinical results with alpha tocopherol, the ensuing years brought strong opposition from the orthodox faction of the medical profession. Their work was denied recognition and their claims ridiculed. Patients, however, were being helped considerably and the work went on despite the active opposition of a great majority of Canadian physicians.

So great was this resistance, that the Doctors Shute acknowledged becoming resigned to being denied a chance to present their views in any official medical publication. The National Research Council of Canada declined to accept their manuscripts for registration. Nevertheless, the Doctors Shute continued to compile their clinical results with alpha tocopherol, publishing their findings in their own medium.

The Shute Foundation for Medical Research was formed and within a decade over 10,000 cardiovascular cases were treated with massive doses of alpha tocopherol. In 1947 the use of this factor was extended to vascular

conditions, including Buerger's disease and peripheral thrombosis. This work finally attained an authoritative medical endorsement in which Italy led the way. In their native land, however, the Shutes were still confronted with united antagonism. The controversy has been thoroughly aired in the pages of a lay magazine.[3] The author of the magazine article disclosed that unofficially and secretly many doctors were using vitamin E for themselves and their families, while refusing to prescribe it for their patients.

Opponents of alpha tocopherol therapy in heart conditions had only the classical methods of treatment to offer. None of these were very hopeful; the standard advice of absolute rest for heart patients has proven harmful rather than ameliorative. New drugs such as heparin, dicumarol, and tromexan proved dangerous and toxic to various degrees. The dismal prognosis of three heart attacks and three years of life was about all that the classical treatment had to offer. Yet one of the most noted proponents of such therapy said in the hearing of Dr. E. V. Shute that vitamin E was useless and he had never used it.

The second International Conference on Vitamin E held by the Section of Biology of The New York Academy of Sciences met April 15 and 16, 1949. The intervening ten years since the first conference had seen important advances in vitamin E research and therapy. As Dr. Mason of Rochester wrote in his foreword to the published proceedings:

> "No other vitamin has received such special honor and consideration. No other vitamin has presented such a challenge to students of nutrition."[4]

In 1954 the Doctors Shute and their collaborators, Butterini, Khoo, Pin, Faust, Lambert and Prosperi published their monograph, *Alpha Tocopherol (Vitamin E) in Cardiovascular Disease*. To date this volume is the most comprehensive, thorough and valuable publication on the subject, the fruits of their vast clinical and investigative experience. This publication heralds an extremely revolutionary principle, one that the die-hards of the medical profession have refused to recognize, namely, that most major diseases can be traced to nutritional deficiencies brought about by current commercial and agricultural food processing. The biochemical approach to the study of therapeutics is slowly but surely coming to the forefront as the most fruitful and promising in the cure and prevention of disease.

## ASSAY

In 1937 Fernholz[5] stated the chemical formula for the nutritional factor whose deficiency was responsible for sterility in male and abortion in female rats. Subsequently four such vitamin factors have been chemically isolated; alpha, beta, gamma and delta tocopherol. In commercial quantities, alpha tocopherol is secured chiefly from wheat germ, cotton seed and soya beans.

In 1940 the League of Nations officially adopted synthetic racemic dl, alpha tocopherol acetate as the International Standard. One international unit of vitamin E is that amount which is contained in 0.1 gram of a solution in olive oil. No official method of biological assay, however, has as yet been

adopted. Evans and Burr used a method of bioassay for vitamin E based on the prevention of fetal resorption in the female rat.[6] Other investigators modified this method in their bioassays. In 1943, Gottlieb and associates suggested a method of assay based on the weight increase of rats during gestation.[7] This method was proposed as more economical and more sensitive than the others suggested.

Despite the League of Nations standard unit, there are four substances now being somewhat carelessly designated as "vitamin E" or "alpha tocopherol." These are:

a) d, alpha-tocopherol (natural alpha tocopherol) processed from vegetable oils and supplied in the form of a concentrate of mixed tocopherols. One of these concentrates contains 34 per cent tocopherols of which half (17 per cent) is d, alpha tocopherol.

b) d, alpha-tocopheryl acetate (natural alpha-tocopheryl acetate) also processed from vegetable oils. One such product available comes in a concentrate containing 25 per cent d, alpha tocopheryl acetate with a small but variable amount of other tocopherol acetate.

c) dl, alpha-tocopherol (synthetic alpha-tocopherol). This is the synthetic product.

d) dl, alpha-tocopheryl acetate (synthetic alpha-tocopheryl acetate) also produced synthetically. The International Standard Vitamin E reference material is a selected preparation of dl, alpha tocopheryl acetate.

According to Harris and Ludwig[8] d, alpha tocopheryl acetate is more active biologically than the others, whose potency they calculate as follows:

One I.U. is supplied by 1.087 mg. d, alpha tocopherol (a)
One I.U. is supplied by 0.735 mg. d, alpha-tocopheryl acetate (b)
One I.U. is supplied by 1.470 mg. dl, alpha-tocopherol (c)
One I.U. is supplied by 1.000 mg. dl, alpha-tocopheryl acetate (d)

Obviously there is a wide range in the potency and cost ratios of the various purported vitamin E's on the market. The potency can range from 46 to 136 International Units. In this respect, d, alpha tocopheryl acetate (b) is consequently the best available because it is 36 per cent higher in potency than the standard equivalent but only 29.5 per cent higher in price. The greatest disproportion exists in the synthetic preparation (c) which has only 68 per cent of the potency of an international unit, though it costs almost four times as much.

## PHYSIOLOGICAL ACTIVITY

"The fundamental or biochemical action of Vitamin E is probably to inhibit or restrain oxidation in all the tissues of the body. It must be admitted that this view of its action does not explain why some tissues are more affected by lack of the vitamin than others, nor why different tissues are affected in different species unless it is postulated, which would seem reasonable, that some tissues, differing from species to species, have a prior claim on whatever amounts of vitamin E are available or can utilize antioxidants other than vitamin E."[9]

In this connection, the authorities quoted above, Bicknell and Prescott,

believe that E *in vitro* is an anti-oxidant and this activity works to protect vitamin A and carotene against oxidation not only while they are still within the lumen of the gut but also after their absorption when they are circulating in the blood. They state further:

> "In a similar way, vitamin E protects biotin and the vitamin B complex against destruction by rancid fats. Vitamin E is the only anti-oxidant in body fats and it plays the same role in at least some fish liver oils."

Besides this role in oxidation, vitamin E is also known for its highly polyfunctional activities, probably exceeding that of any other known vitamin. It participates in many phases of metabolism and is present in many of the two thousand known enzyme systems of which a great number contain vitamins. Each of the twenty known vitamins consequently participates in many different forms of metabolic activity simultaneously.

Those vitamins working simultaneously in several systems are known as conditioning vitamins. Of these, vitamin E is probably the most important. Though primarily designed to inhibit oxidation, it can also promote oxidation when the occasion demands. The tocopherols are also unique in being capable of bridging any gap between interlayers of fat and protein.

Therefore, to the English authorities, Bicknell and Prescott, vitamin E is best administered in conjunction with other vitamins, particularly the B complex. Other vitamins will also tend to destroy an excess of E. They also believe there should be a proportionate increase in the intake of supporting vitamins when vitamin E is administered because of this highly integrative action.

Another important function of vitamin E is its protection of the mixture of lipid and protein that constitutes most operative animal tissue.[10] Still another of its basic functions is to prevent muscle disintegration. Steinberg believes E maintains an optimum condition in the collagen matrix in which the cells are imbedded, important in rheumatoid and collagen metabolic diseases.[11] Hickman affirms that 10 mg. of vitamin E per kilogram of muscle are necessary to maintain life in such tissue; "to maintain optimum health the requirements are much higher."[10]

Unquestionably vitamin E is bound up with the basic physiological chemistry of the cell. Some E-deficient conditions are irreversible and cannot be remedied; impaired spermatogenesis in the rat becomes permanent. In the female rat, however, E-deficiency conditions not too severe can be reversed by adequate intake.[12]

Both the vascular system and the activity of the sebaceous glands are affected strongly by vitamin E, which stimulates the excretion of lubricating fluid for the skin. Possibly it also helps to eliminate excess cholesterol which might otherwise not be excreted. Experimental animals show alterations in muscle and nerve due to poor oxygenation following E deficiency. Heart tissue from normal animals contains twice as much vitamin E as does body fat. Oxygen consumption of heart muscle slices from E-deficient hamsters was as much as 40 per cent above normal, indicating that E is necessary to utilize oxygen efficiently.[13]

Alpha tocopherol has been shown to have a specific action on the red blood cells and also possibly on other formed elements in the blood. Deficiency conditions have been experimentally shown to cause generalized structural weakness in the vascular system, contributing to stagnation of the blood. It is also a proven antithrombin in the circulating blood and hence an effective agency for preventing thrombosis.[12]

The relationship of vitamins A and E is highly interesting. Both reveal common characteristics in being fat soluble and essential to reproduction. Both also prevent degenerative changes in tissue which proliferate rapidly, such as epithelial and muscle tissue.[14] Since the chromatin elements of the cell nucleus govern the growth and formation of the cells, these vitamins must be highly essential to the formation of the chromatin. In the opinion of Rosenberg who observed degeneration of the chromatin in E-deficient rats, this is the primary physiological action of vitamin E in directing the various activities of the cell nucleus. He states:

> "Besides chromatolysis, there appears to be an interference in the formation of chromatin in the germinal cells in E-deficiency. In the young of vitamin E deficient rats, cretinism is observed."[15]

In view of a chromatin activity relationship, the importance of vitamin E is apparent, for the chromosomes which carry the blueprint for the reproduction of the cell are formed from chromatin. It is, therefore, quite obvious why A and E deficiencies result in sterility—the necessary agency to create the chromatin for making the germinal cell is absent. In partial deficiencies, the blueprint becomes distorted and monsters result because a true replica of the parent is impossible without adequate materials.

Cancer is now suspected to be a result of chromosome damage and the failure to regulate the proliferation of cells which multiply at a greatly accelerated rate. Dr. Zwick of the University of Cincinnati discovered that the epithelial cell changes preceding cancer were apparently identical with those changes resulting from A deficiency.

One theory of cancer is that it is a disease arising out of changes in the nuclear integrity of the cell. It seems definite that a deficiency of vitamins A and E specifically contribute to such changes. If a lack of vitamin E can cause dissolution or lysis of the chromatin, as stated by Rosenberg,[15] it is quite obvious that the first symptom of disease the victim will notice is an alteration in the nature of some characteristic of the tissue involved. If the skin is affected, these changes are quite obvious. If the chromatin is damaged, the cells cannot reproduce their exact replica and the skin becomes rough, characteristic of eczema or dermatitis. For example, oil dermatitis results when industrial workers are constantly exposed to fat soluble materials which rob the skin of vitamins. Often the use of the right kind of vitamin E will rapidly heal this type of dermatitis.

The type of vitamin E which prevents sterility, not the synthetic alpha tocopherol, is necessary to correct such skin disorders. The refined tocopherols evidently lose some associated factor which carries a necessary component. Pure tocopherol in the experiments with dogs as completed by Professor

Voegt-Moeller of Denmark aggravated rather than cured symptoms of vitamin E deficiency.[16] Only the entire wheat germ was effective; evidence of the complex nature of the vitamin as naturally supplied in green leafy vegetables or wheat germ. In testing the action of the vitamin on dogs suffering with muscular degeneration, the natural vitamin E complex produced highly beneficial results.

## EXPERIMENTAL OBSERVATIONS

Because of the variation in biochemical elements in the various forms of the tocopherols and the vitamin E complex, there is understandably a variation in experimental observations and results. The greater effectiveness of wheat germ oil over the synthetic tocopherols was conclusively proven by the Voegt-Moeller test on dogs.[16]

Previous observers, Martin[17] and Goertsch and Ritzmann[18] had suggested that possibly several factors beside the tocopherols were involved in the curative results effected in neuromuscular disturbances. In seeking to clarify the effectiveness of synthetic products in comparison with the whole E complex, Voegt-Moeller experimented with dogs infected with the distemper virus which usually develops typical neuromuscular symptoms. These dogs were fed on a uniformly balanced diet until all had developed the initial symptoms of distemper which usually precede the onset of neuromuscular disturbances. Voegt-Moeller then divided his 90 dogs into three groups of 30 each, using one group as a control, a second group to be injected with 10 milligrams daily of alpha tocopherol and the third group with 5 c.c. of wheat germ oil containing approximately 10 milligrams of alpha tocopherol.

In this control group, untreated with either the synthetic or natural vitamin, 10 of the 21 dogs developing neuromuscular symptoms died and 3 died without developing symptoms. In the alpha tocopherol group, 11 of the 23 dogs likewise developing the symptoms died, and 4 died before such symptoms developed. In the wheat germ group, however, only 2 of the 5 dogs developing symptoms died and 10 died before such symptoms developed.

Levin further suggests that before any conclusive evidence of the effectiveness of wheat germ oil is possible, a number of points must be established.[19] The nature of the oil, whether it was "cold pressed" or solvent extracted, the temperature involved during the process, the type of solvent used and the age of the oil must all be known. Each of these factors would have a great bearing on the stability of the oil, as well as the presence of factors other than the tocopherols.

Shute contended that after 8 days, pressed wheat germ oil was valueless for treating habitual abortion unless kept under refrigeration.[20] Other workers, notably Currie of England employed a solvent extracted oil, as did Hain and Sym in their treatment of menopausal flushes. The difference between such oils can be measured if they originated in a stable source. If the original wheat germ oil was not stable because of a high free fatty acid content or high peroxide value, various synergistic factors would be absent, leaving no accurate basis for comparing therapeutic effectiveness.

Levin's point that studies involving vitamin E and wheat germ oil should

carefully specify the manner of preparation, its form, source and stability of the material used seems well founded. Throughout experiments, checks on the stability of the substances used would appear imperative. Only in this way could some uniformity and reliability in experiments be achieved. Because vitamin E and its associate factors are involved in reproduction, the muscular and vascular systems, the endocrine glands and the formations of neurological lesions, such determinations as Levin suggests are fundamentally necessary.

Undoubtedly this variation in stability, processing, temperature, etc., has led to the confusion arising from the widely diverging results of animal experimentation. The deficient states produced by lack of vitamin E can exhibit a multiplicity of structural and functional alterations true of no other vitamin. E also produces widely diverging manifestations during deficiencies in closely related species, such as the rat and mouse, while often unrelated species will show corresponding responses.

Deficiency states of other vitamins produce more uniform changes in cells and tissues and can be more readily appraised. Vitamin E deficiencies are more complex and the pattern of change is not confined to a specific type of cell or tissue and corrective administration of the vitamin is not followed by an orderly process of structural repair.

The effects of E deficiency in disorders of the reproductive system are better understood than its other manifestations. Such studies through which the existence of the vitamin was first discovered have been confined for the most part to the rat. E deficiency in the rat affects both male and female, though in different ways. There is definite interference with the development of the embryo, while oestrus, ovulation, conception and implantation of fertilized ova proceed normally. It is the embryo which develops the degenerative changes ending in resorption. Restoration of vitamin E to the diet before the first half of pregnancy or earlier usually enables the female to bear offspring.

Martin and Moore,[21] however, report that prolonged deprivation in the female eventually produces permanent effects. The oestrus cycle becomes abnormal and the animal becomes sterile. The failure to achieve pregnancy is attributed by Bicknell and Prescott[9] to possible changes in the uterine wall. The uteri of E deficient rats who did become pregnant were often large, deformed and unhealthy.

The foetuses in deficient E females appear to succumb to abnormalities of the vascular system such as stagnation of the blood, distention and thrombosis of the veins leading to anemia and hemorrhage; the actual causes of death in the foetus. Only vitamin E appears to be able to correct these blood changes which do not respond to therapy with either vitamin C or K.

In the male rat lack of vitamin E causes direct and irreversible damage to the tissue of the gonads, interfering with the production of sperm and bringing on a permanent sterility. These changes occur at the beginning of sexual maturity with no observable effects during adolescence. In the mouse, the female is affected somewhat like the rat in vitamin E deficiency, though

apparently it does not affect the male in any way. Male chicks and guinea pigs, however, also suffer testicular injury from vitamin E deficiency.

Evans and Burr[22] discovered that vitamin E deficiency extended beyond the reproductive system. Mother rats were maintained on a bare subsistence level of vitamin E which was only sufficient to produce young and maintain lactation. The young appeared to thrive until the end of the lactation period when suddenly a majority of them contracted a mysterious disease, characterized primarily by muscular paralyses. Half of them died, often so suddenly there were no signs of malnutrition. The cause of this quickly fatal disorder was traced to a deficiency of vitamin E in the mother's milk, confirmed when the young of normal mothers were transferred to E deficient mothers for suckling and consequently developed mild forms of the disease. Administering a wheat germ oil concentrate to the nursing females or directly to the young prevented the diseases, thus proving the need for vitamin E was vital in the developing young.

Other studies by Goettsch and Pappenheimer[23] produced dystrophy of the voluntary muscles in vitamin E deficient rabbits and guinea pigs. The mysterious disease of the suckling rats noted by Evans and Burr was identified ten years later as the same dystrophy. In subsequent experiments, it also developed in a wide variety of animals, including sheep, goats, mice, ducks, geese, hamsters and dogs.

The most thorough evidence that E deficiency is the sole cause of muscular dystrophy was provided by Mackenzie and others.[24] Animals fed on rancid food had proven susceptible to muscular dystrophy but alphatocopherol was given separately from rancid food to avoid destruction of the vitamin and prevented muscular dystrophy. Wheat germ from which vitamin E had been extracted (defatted wheat germ) had no preventive effect. Further, alpha-tocopherol cured animals who had taken no "water soluble factor" which proved the cure was not due to body stores of the latter.

It was also shown that animals who received wheat germ oil mixed with the rancid ration would become dystrophic. If defatted wheat germ was added as well, however, dystrophy did not occur. Apparently the defatted wheat germ protected vitamin E from oxidation. This conclusively proved that vitamin E could prevent muscular dystrophy and that the superiority of wheat germ over vitamin E alone lay in its protection of vitamin E from destruction by rancid fats. According to Bicknell and Prescott:[9]

> "This, of course, does not mean that other vitamins contained in wheat germ, such as the vitamin B complex, may not be necessary for the proper utilization of vitamin E in the body, in the same way as vitamin E is necessary for the utilization of vitamin A. The animals discussed above were all on diets containing an abundance of all the vitamins except E."

In the cure of muscular dystrophy in animals, it has been found that vitamin E both cures and prevents the affliction in rabbits, guinea pigs and various other species but can only prevent, not cure, dystrophy in adult rats. In these therapeutic trials vitamin E acts with amazing rapidity. Within 24 hours the creatine in the urine of the animal may drop, becoming normal in a few days. The appetite and weight of animals improve as the creatine

falls, with a normal rate of growth re-established in one or two weeks. Even when the animals were too weak to stand or feed themselves, vitamin E led to a rapid return of strength in one or two days and a disappearance of the dystrophy symptoms in a few weeks. However, in children recoveries required years and did not always occur.

Gullickson[25] reported at the Second International Vitamin E Conference (1949) that although a vitamin E deficient diet in dairy cattle did not hinder reproduction, sudden deaths often occurred during pregnancy or just after calving. Gullickson believed death was brought on by the accelerated need for vitamin E during the last months of pregnancy. In contrast to the rat, in dairy cattle the mother is sacrificed rather than the foetus.

In the discussion following this paper, Dr. Evan Shute commented that it was well known among obstetricians and gynecologists that pregnancy is the supreme test of cardiac function and vitamin E deficiency could be fatal during delivery.

Besides its effects in the reproductive, muscular, vascular and nervous systems, vitamin E has been known to exert an effect on endocrine activity. Levin, Burns and Collins[26] demonstrated this relationship in experiments with wheat germ oil on immature female rats, adult spayed female rats and immature hypophysectomized female rats.

The interesting feature of these experiments is that the preparations were given orally. Demonstrable estrogenic, androgenic, and gonadotrophic activity was effected with wheat germ oil solvent extracted at low temperatures. Rancid wheat germ oil could not produce these effects nor would the tocopherols.

In an experiment with hypophysectomized male rats at the age of 40 days, Levin was also able to demonstrate authentic gonadotrophic effects comparable to those demonstrated on the female hypophysectomized rats. The males exhibited increase of seminal vesicle weight, prostate weight and even production of spermatozoa. In the female, corpora lutea was produced in the ovaries and the "clumping" of the theca cells, usual after removal of the pituitary, was repaired and brought back to normal.

Vitamin E is evidently closely related to the functioning of the endocrine glands as it also has a direct relationship to metabolism. The thyroid seems to be particularly affected, as marked histopathologic effects can be observed as a result of E deficiency. These effects give rise to a hypofunctional state of the thyroids.[27]

In conclusion, it is, therefore, quite obvious that vitamin E plays a prominent role in every vital system, including the reproductive, endocrine, nervous, vascular and muscular. Experimental observations have produced a wealth of evidence to support this view and to confirm the polyfunctional nature of vitamin E.

## VITAMIN E IN FOODS

The alarming increase in cardiovascular diseases began with the introduction of flour bleaching and the milling which robs our breads and pastries

of wheat germ, the most potent source of vitamin E. Being highly susceptible to the changes which produce rancidity, the wheat germ is removed from flour by commercial millers.

Wheat germ and green leafy vegetables, among which lettuce holds a prominent place, are the only rich sources of vitamin E. Wheat germ is a valuable feed for live stock and under our present economy the nutrition of pigs rather than human beings has become more lucrative. Consequently the removal of the wheat germ from flours has taken away the cheapest and only universal food source of the vitamin.

Unfortunately the finicky state of modern appetites also excludes other sources of vitamin E. Brown rice and ordinary steel cut oatmeal both contain the germ but they are not eaten regularly, in fact, as supplied in stores are stale and rancid. Rose hips are very rich in vitamin E present in the seeds.

Authorities emphasize that vitamin E is necessary to the proper utilization of carotene and vitamin A. Indeed, the value of the carotene in vegetables depends greatly on the amount of vitamin E which they contain.[28]

Foods which should also contain a small amount of vitamin E are milk, eggs, butcher's meat and fat. However, the E content of milk and eggs depends on the animal's diet, and when cows are stall fed and chickens are kept cooped on egg farms, this is undoubtedly low.

Rancidity takes a heavy toll of vitamin E. Since modern processing and storaging brings to our tables foods no longer fresh and also with much fat, the vitamin E content is lost even though a rancid smell is not present. The variation in taste between fresh and storage meats is due to the chemical processes which precede marked rancidity.

Pasteurized milk, too, is often older and staler than the consumer realizes, as is butter. Consequently foods supposedly containing some vitamin E have lost it by the time they are consumed. Fortunately cooking does not destroy a large amount of vitamin E unless rancid fat is used. Not much is known about the E content of canned and preserved foods. There are proofs that dried and pasteurized milks are devoid of vitamin E and since these are prescribed for infants, the well known greater disease susceptibility of artificially fed infants in comparison to the breast fed can to some extent be attributed to the lack of the vitamin in their milk.

Since vitamin E is stored in animal tissues, the quality of cattle food is of direct concern in human nutrition. The amount of vitamin E in the wheat germ will vary with the freshness of the wheat, the conditions in which it is stored and used, humidity and many other factors. The same holds in the case of alfalfa and vitamin A, though this plant also contains vitamin E as well.

Tests quoted by Pacini[29] illustrated the rapid disappearance of E from fresh wheat germ, which was allowed to stand after being freed from bran. Daily checks were taken in the bins for thirty days. On a basis of 100 per cent for the original content, at the end of the second day 10 per cent was lost, third day 16 per cent, fourth day 30 per cent, sixth day 60 per cent. From the sixth to the fourteenth day the loss increased to 90 per cent where

it remained practically constant. Therefore, in a week wheat germ in bins lost almost half of its vitamin E content; in another week only 10 per cent remained. For this reason cattle raisers have been forced to supplement their feeds with more dependable sources of vitamin E.

A study of the tocopherol content of food was done in Holland during World War II.[30] Spinach, endive, kale and other green vegetables had a high content. Colorless vegetables such as onions, potatoes and beets were poor sources, as were dairy products, confirming Bicknell's findings in England. Vegetable oils excepting coconut and olive oil were also found to be good sources of vitamin E though the purified oils usually offered to the public had sustained considerable losses.

During the war the Dutch were forced to look for other sources of vitamin E rich foods. Rape seed, linseed and poppy-seed oil were found to be moderatey supplied. An excellent substitute for wheat germ and wheat germ oils during the war was found in pine needles and seeds of cord grass growing in muddy salt marshes bordering on the North Sea.

This search for natural vitamin E is therefore an indication of the awareness of some nations of the vital importance of nutrition to the national welfare. It is, of course, ironical that governments ignore the richest and cheapest source of vitamin E, the wheat germ which is eliminated by modern milling practices. The difference in flavor in stone ground wheat as it ages is highly noticeable from day to day. Insuring the means of preserving the wheat germ content in our breads and bakery goods could be an invaluable boon to the public health, yet in just this direction our Food and Drug Administration has lamentably failed.

## VITAMIN E IN THERAPEUTICS

Every revolutionary advance always meets antagonism, denunciation and attempts to sabotage its development. This is also true of vitamin E which has had a stormy therapeutic history. In addition to opposition, there has also been the aforementioned confusion arising from widely varying results due to a lack of uniformity in preparation and biological assay, which has been unfortunate.

Nevertheless, vitamin E appears to have achieved solid gains. Therapeutic results are highly convincing. Vitamin E has been tried in the crucible of the clinic and survived many severe tests. The credit for much of this advance is due to the Doctors Shute and their associates for their long, hard and unremitting struggle to win recognition of vitamin E. Their monograph is by all odds the most complete, well documented and authentic discussion of the subject available today.

A summary of the therapeutic effectiveness of vitamin E, as is probably most suitable, should begin in the field of its first application—obstetrics and gynecology. In 1937, Dr. E. V. Shute recommended alpha tocopherol in the treatment of even mild forms of abruptio placentae in the belief it would help provide a better anchorage to the uterine wall.[2] This belief has been confirmed by excellent results with both human subjects and experimental animals.

Shute is inclined to believe that the slight tearing pains, tenderness and bleedings early in pregnancy are forewarnings of the severe pain, rigidity and shock typical of complete abruptio placentae near the end of the pregnancy, and that early administration of alpha tocopherol can prevent such catastrophes. Even in cases where there were major though incomplete detachments of the placentae in vitamin E administered mothers, possibly because of inadequate dosage, he reported mother and baby invariably thrived in spite of these mishaps.

In a discussion at the New York Academy conference in 1949, Dr. E. Shute observed that vitamin E is 72 per cent effective in abortions and premature births, but fully 85 per cent preventive in miscarriages. In habitual abortions, however, he could attribute no value to alpha tocopherol beyond improving the semen of the husband. As for pre-eclampsias, a condition due to estrogen deficiency, he maintained vitamin E was contraindicated and could actually tend to bring on convulsions.

In menopausal flushes and headaches, however, vitamin E was found extremely effective. These conditions are believed the results of excess estrogen and E corrected through its anti-estrogen properties. This, therefore, indicated to Dr. E. Shute that the value of alpha tocopherol in miscarriages and allied conditions is not due to a relieving deficiency but to overcoming an excess of estrogen in the system.

Probably the most fruitful and brilliant results of alpha tocopherol treatment has been attained in cardiovascular diseases. These results are the strongest possible reasons for discarding the old classical cardiac therapy which was merely a method of alleviation of complications without any effect on the underlying pathology. The commonly used digitalis, quinidine, mercurial diuretics and ammonia chloride all have toxic properties and require extremely careful administration in heart conditions. They are not curative and are of value only as adjuncts to treatment with vitamin E, according to the Doctors Shute.

Even the sentence of six weeks absolute bed rest in severe heart conditions has in recent years come to be regarded as wholly unnecessary and even harmful. Levine initiated the armchair treatment based on mild activity for heart patients and succeeded in showing a greatly decreased mortality, as well as eliminating cases of thrombophlebitis or pulmonary embolism which usually occurred in over one-third of the bedfast cases.

The alarming feature of heart disease is its sudden prevalence in recent decades. Coronary thrombosis became highly noticeable with the advent of bleaching flour. In England it has increased seven fold in the last half century, and was rarely described in the older medical literature. According to W. E. Shute:[2]

> "We must look for the underlying pathological change responsible for coronary thrombosis in something affecting one of the normal clotting constituents of the bloodstream during the last four decades, a factor not active before 1900. It may be the naturally occurring antithrombin that is deficient, as Kay has suggested. He and his co-workers have found alpha tocopherol to be an effective antithrombin. Zierler has reported that alpha tocopherol is a naturally

occurring antithrombin in the human blood stream and moreover that in normal concentration it prevents thrombosis there. Since refined cereals entered general table use some forty years ago, there has been widespread and more or less marked deprivation of tocopherols in our diets. Is it purely coincidence that that era has become the coronary epoch? No one has offered any other equally plausible suggestion."

Moreover, the mortality in coronary thrombosis has been extremely high when treated by the old classical methods. White[31] reported mortality of 50 per cent in 82 cases; Levine that the initial attack claimed a mortality of 53 per cent.[32] Many other authorities, all of whom were committed to the classical form of therapy, had about the same high mortality.

These high death rates are also typical in the treatment of coronary sclerosis, rheumatic heart disease, and hypertensive heart disease. No helpful therapy existed which warranted hope in recovery before the advent of vitamin E. Recommendations were invariably made which restricted physical exertion and reduced the patient to the status of a semi-invalid. Symptoms continued to develop in a losing battle against the heart affliction, and nothing had been developed in classical treatment to reverse the course of the disease or prevent its occurrence.

The treatment for the patient with signs of valvular and myocardial damage without heart disease was really nothing beyond advice to avoid exertion, exposure and respiratory infections. In the young, this advice was wholly unwarranted as it prevented them from building up their strength and resistance to disease through exercise.

Almost 800,000 deaths from cardiovascular diseases occur in the United States each year, which is about 44 per cent of the national mortality. It is estimated that about 9 million Americans, including 500,000 school children, have heart disease. Consequently no greater field for a promising dynamic therapy could possibly be imagined. It was in this field that vitamin E has found its greatest scope of therapeutic effectiveness but also met the greatest and most inexplicable opposition to its use. In view of the inane results achieved by classical methods, this opposition should be regarded as one of the most unjustified in the annals of medicine.

In coronary sclerosis with its symptoms of dypsnea or angina pectoris, or both, due to decreased blood supply of the myocardium, alpha tocopherol has achieved almost miraculous alleviation, report the Doctors Shute. Oxygen requirements are immediately reduced, thus quickly relieving pain; E also acts as an anti-coagulant. As a major antithrombin, when present in the human blood stream in normal amounts it will prevent the plugging of blood vessels.[33]

With the threat of thrombosis hanging over almost half the population over forty, this is indeed most promising. Alpha tocopherol also increases the exercise tolerance of patients, permitting them greater activity and amusement. Another advantage has been found in the ability of the vitamin to prevent or relieve arterial spasm. It may also halt or even reverse damages in the walls of blood vessels. In brief, the administration of alpha tocopherol

in coronary sclerosis has been found to remedy and prevent many of the pathological changes brought by the disease.

In coronary occlusion, the same pattern of increased incidence correlated with our modern flour processing is noticeable. Before our modern era it was comparatively rare; today it is overwhelmingly prevalent, yet it was first identified only as recently as 1896 by George Dock.

In treatment of acute coronary thrombosis, alpha tocopherol has been shown to be fibrinolytic, to remove fresh thrombi and to help in canalization.[34] Clots tend to crumble easily after vitamin E is administered; by-passes about sites of vascular blocking are opened up, thus increasing circulation. Capillaries also tend to dilate. There are many other established beneficial effects, including reversing increased capillary permeability characteristics around areas of infarct (important to revival of life in badly damaged cells) and limiting the formation of excessive scar tissue around injuries.

In comparison with a mortality of about fifty per cent after three years of classical therapy, the Shutes have been able to report a mortality of only about 3 per cent in their coronary thrombosis cases. Some of these deaths were from other causes. Individual case histories of patients over fifty and sixty years of age recounted almost full recovery and return to normal occupations and activities. In cases of coronary occlusion, to quote verbatim:

> "Alpha tocopherol is uniquely valuable in the treatment and prophylaxis of coronary occlusion. It is simple, cheap, can be self administered indefinitely and rarely requires even initial hospitalization. It has no rivals. Even the anticoagulants in common use are not comparable in any sense, whether in safety, price or effectiveness. The mortality rate achieved by its use is perhaps the best argument for it—a rate only a fraction of that attainable by the best modern treatment of any other type. The degree of clinical improvement is also dramatic in many instances."[2]

In the acute and early stages of rheumatic heart disease, alpha tocopherol achieves some of its most dramatic and instant effects. In the early stages, tissue destruction in the heart muscle and in the endocardium is not advanced. Consequently alpha tocopherol institutes (a) reduced capillary permeability which reinstates normal cellular exchange of fluids and enables the heart to overcome infective and toxic agents; (b) small thrombi do not spread and are rapidly dissolved; (c) tissue anoxia is lessened or disappears; (d) normal healing is promoted. When alpha tocopherol is administered at the onset of rheumatic fever, it disappears in a few weeks; sometimes in a few days. Such cases must be maintained on the vitamin until all chance of a recurrence has disappeared.

In chronic cases of rheumatic fever where treatment has been instituted only after there has been great tissue damage, the results are, of course, not so gratifying but improvement can be effected and the patient can often lead a more tolerable existence. In very young patients, complete cures even of chronic conditions can be brought about, though it is naturally impossible in older patients. In chronic cases, adjuvants to vitamin E therapy are needed and great caution is required against overdosage of digitalis.

Alpha tocopherol has also extended its usefulness to treatment of con-

genital anomalies of the heart, bringing about increased exercise tolerance, greater immunity to infection and other benefits, strongly indicating alpha tocopherol has a direct effect upon the cardiac muscle. As a pre-operative medication for patients with congenital heart defects, it has proven excellent.

In the management of hypertensive cases, especially with heart complications, alpha tocopherol is also beneficial. However, great skill must be exercised by increasing dosage very gradually, even in the numerous cases in which E fails. The vitamin can be a prophylactic agent against cerebral and coronary accidents in such cases.

Butturini of Italy, one of the pioneers in alpha tocopherol treatment, has investigated its value in cases of diabetes with heart complications.[2] He believes the vitamin acts on diabetes in two specific ways:

1) on its enzyme metabolism in normalizing the glucose metabolism thus eliminating factors noxious to the vascular system;

2) by a trophic influence on the arterial and capillary walls which is occasionally protracted after treatment stops and glycosuria has returned.

As a whole, Butturini reported satisfactory results with diabetics, especially in intermittent claudication, the earliest gangrene of the extremities, mild myocardial sclerosis, in coronary disease and in capillary fragility.

Other conditions which have proven fruitful fields of application for alpha tocopherol are: indolent ulcers, in which improvement is effected by oral and local applications; in the treatment of arteriosclerosis of the extremities with incipient gangrene. In such cases the vitamin is of even greater usefulness as a prophylaxis, which is also true in the treatment of thromboangiitis obliterans. In the kidney diseases of infancy alpha tocopherol is also indicated, either alone or with vitamin C, and in the severe cases should be combined with antibiotics and other measures. Possibilities of cure are then considered excellent.

According to E. V. Shute, alpha tocopherol has a limited effect in collagenosis of the extremities, and cannot resolve the condition.[2] He justifies its continued use for the present because nothing of comparable value is yet available. Another fruitful field of application is in the treatment of senile conditions where alpha tocopherol helps to prevent the degenerative changes characteristic of old age.

As a prophylaxis in general, E. V. Shute advocates alpha tocopherol for the prevention of many nutritional disturbances such as beri-beri, peripheral neuritis, pellagra, scurvy, rickets and hemorrhagic diseases of the newborn. Modern dietary conditions have produced less recognizable forms of the above diseases which are only exhibited when deficiencies are specific and severe.

In general, the Doctors Shute believe alpha tocopherol must be classified as a vital substance which is as necessary to the maintenance of health and prevention of disease as it is to the cure of conditions which arise because of its absence. They believe arteriosclerosis, rheumatic fever, hypertension, and coronary disease can be prevented by an adequate intake. Even congenital

defects can be avoided, they maintain, because alpha tocopherol can improve the sperm of the male and produce defect-free offspring.

Other fields where alpha tocopherol has been applied with optimal results are: Ophthalmology, in the treatment of choroiditis, rare cataract, hypertensive retinitis, interstitial keratitis and other conditions. Vogelsang[35] found that diabetics over 25 years of age showed a marked decrease in insulin requirements after two months on vitamin E and almost all were able to abandon the use of insulin after a year. None of his cases became comatose and insulin reactions were usually extremely mild, with quick recovery possible after taking a little whiskey and sugar. Often a short rest alone proved sufficient. Gangrene and perforating ulcers in diabetics began to heal a few days after Vogelsang's cases started treatment and healing was usually complete.

Alpha tocopherol has been established as a connective tissue vitamin; its value in rheumatic diseases would therefore be demonstrable. Amt and Di Cyan reported[36] on 100 cases of rheumatic diseases, all of whom had rheumatic diseases, with some coexisting disturbances such as anemia, diabetes, hypertension, hyperthyroidism and other metabolic conditions. Employing vitamin E intramuscularly, orally and topically, these investigators reported amelioration of pain, mitigation or disappearance of physical stigmata and increased mobility of the joints. Conjunctive agents included with vitamin E were one or more of high vitamin E foodstuffs in the diet, calcium preparations intravenously and liver and vitamin B complex intramuscularly.

Steinberg[37] suggests that E deficiency in abnormal metabolism of fibrous connective tissue characteristic of rheumatic diseases, may occur for a number of reasons. These may be lack of vitamin E intake and a normal absorption of E but lack of utilization of tissues of the vitamin (a common condition) and normal intake with poor absorption (in cirrhosis of the liver) resulting in a low blood level of all the fat soluble vitamins including E.

## SUMMARY AND CONCLUSIONS

The therapeutic scope of vitamin E appears to be boundless. This viewpoint is encouraged by the results reported from the many investigators in the treatment of so many differing ailments. Undoubtedly this wide range of application arrives because vitamin E is bound up with the basic physiology of every type of cell in the body.

Vitamin E is therefore highly intricate, perhaps the most intricate of all complexes. In a natural source, such as wheat germ oil, it is associated with a number of synergists. As observed, the four commonly known factors of vitamin E—alpha, beta, gamma and delta tocopherol—should be regarded only as factors and not as the entire E complex. Wheat germ oil is undoubtedly the most effective means of administering vitamin E because of the inherent associated factors, as substantiated by experimental results.

The confusion, the wide disparity in reports on the use of vitamin E and the many disputes over its effectiveness are due to differing methods of extraction, varying potency, the presence or absence of necessary associated

factors, the effects of temperature, storage, supplementary diets and other influences.

It is also patent other vitamins in wheat germ, such as the B complex, are necessary for the proper utilization of vitamin E, just as E is important to the adequate utilization of vitamin A. The factors synergistic with vitamin E are not only necessary to attain the best therapeutic results but also to guarantee the greatest amount of safety in avoiding untoward effects.

Despite the fact that advocates of the synthetic tocopherols contend they are as effective as the natural complex, great caution is imperative. An excessive intake of the synthetic tocopherols can be just as dangerous as an excessive intake of vitamin D. The good results reported with the synthetic tocopherols could well be due to a diet which contained the necessary associated factors. That the dosage must be limited to fit the patient, as recommended by the Shute report,[2] tends to support this concept. The sex hormone precursors demonstrated by Levin[26] also show that the value of the natural complex is not limited to the tocopherol content alone.

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