VITAMIN "E"

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HISTORY OF VITAMIN E

Discovery of vitamins had its origin in the attempt to explain the cause of specific diseases, for example, beriberi, scurvy, rickets, pellagra and others of equal and impressive nature. Some of these diseases arc now proven due to lack of particular vitamins in the diet. Today, In this era of enlightenment, we know that vitamins function not only as factors preventative or curative of certain diseases, but also as parts of enzymes or other compounds used by the body to accomplish metabolism of protein, fats or carbohydrates, as essential building material for certain diseases. In brief, we know now that vitamins are as essential in the diet of normal individuals as in the diet of the sick; that no diet for sick or well is adequate unless it provides in addition to calories, proteins, and minerals, definite amounts of specific vitamins.

The ever increasing knowledge of vitamins has also changed another concept of them. We used to differentiate them from hormones on the basis that they are regulatory compounds that must be supplied in food because, unlike hormones, the human body could not synthesize them. Today, we know that several of the important vitamins are actually manufactured in the human body, and that intestinal bacteria, under certain conditions, can meet some of the body's need of specific vitamins; a discovery resulting from the ability to eliminate the action of these bacteria by use of certain of the "sulfa" drugs.

Until only a few years ago, vitamins were primarily

of clinical interest in the treatment of specified deficiency diseases. It is now agreed that in correct dosages they can be used therapeutically in other conditions. Like hormones, vitamins can produce definite pharmacological effects which can be used therapeutically in subjects who are not suffering from a vitamin deficiency. Niacin, for example, has a powerful vasodilator action even in a normal person, a property which suggests its use in peripheral vascular disease. Both vitamin Bl and C stimulate metabolism, and the latter increases the oxygen intake of blood with a low oxygen tension, indicating that it might be useful in cases of accidents and injuries involving hemorrhage.

During the past year or so, there has appeared a flood of information and clinical findings dealing with the use of vitamin E, alone or in combination with other vitamins, in the treatment of various neuro-muscular disorders; more particularly of progressive muscular distrophy and of amyotrophic lateral sclerosis. In addition, claims have been made for vitamin E as an adjunct in circulatory diseases as well as conditions of the heart and blood vessels, male and female disorders, habitual abortion and a host of others. It is our intention to investigate these and other claims, and present

the accepted consensus of a mass of opinions from investigator; -- -in this country, and abroad. To do so we must begin at the beginning^ but before we do, may we point out that while it is a cliche' to say that "it is hazardous to apply facts gained from animal observations uncritically to human diseases, it is equally certain that all the precise knowledge that has been accumulated during the past few years as to the effects of vitamin E deficiency, has been derive: from experimental work with animals." These include rats, mice, guinea-pigs, dogs, chickens, ducks, turkeys, and pigeons. Work on monkeys is in progress in several laboratories, but only a very few scanty reports have appeared.

It was in the rat that classical studies first demonstrated that a new factor, most abundantly present in wheat germ oil, was needed for the successful completion of pregnancy in the female, and for continued fertility in the male. Herbert

McLean Evans, of California, will always have his name associated with vitamin E, partly because he and Bishop in 1922 demonstrated the existence of an anti-sterilitv vitamin, and partly because of subsequent developments which originated in their pioneer investigations. Evans and Bishop snowed that the foods richest in vitamin E were green leaves and the germ of seeds. Wheat germ and wheat germ oil were found to have a remarkably high content of E. Rats were the experimental animals employed, and with these animals it was proved that a deficiency of vitamin E leads to sterility in the male, and abortion, though not failure to conceive, in the female.

For a number of years, interest was exclusively centered on the role which this vitamin played in reproduction. We have since learned, that this was too narrow a definition of its varied functions. It was in 1928 that Evans and Burr reported that young rats, suckled by vitamin E deficient mothers, became paralyzed. The underlying cause of this paralysis of young rats escaped observation, and it was not until the publication of Olcott's paper that the symptoms were shown to be due to an intense and selective necrosis of the voluntary skeletal muscles. The lesions are those of hyaline necrosis, with segmentation of the fibers. In the early stages, there is intense inflammatory edema with a cellular reaction in which polymorphonuclears predominate. Later there is invasion by histiocytes, giant cell formation about the necrotic remains of the fibers which often become calcified; mitotic division of myocytes, and rapid regeneration of new fibers. If the animals survive, and about 60% of them do, there is restoration to normal within a week or so, even when no additional supplement of vitamin E is supplied. This is an interesting, yet still unsolved mystery.

In 1931, Goettsch and Pappenheimer showed that guinea-pigs and rabbits, when deprived of vitamin E, developed a primary muscular dystrophy histologically identical with the progressive muscular dystrophies of man. From Denmark, Ringsted, in 1935, and Einarsson and Ringsted in 1938, published careful and extensive research on the effects of lack of vitamin E on the central nervous system of adult rats. They pointed out that the neurological degenerations which were produced, resembled those of amyotrophic lateral

sclerosis, and tabes dorsalis in man.

It is a depressing demonstration of the lack of co-ordination between research workers and clinicians, that it was not until nine years after the discovery of vitamin E, that Vogt-Moller in Denmark first put it to anv useful purpose by treating sterility in cows. In the same year he treated two young women with habitual abortion with success, and six years later Young in England, and Shute in Canada, reported good results in the treatment of threatened abortion and pregnancy toxemias.

In 1938, seven years after the possible value of vitamin E in human muscular dystrophy had been implied by animal research, Bicknell in England, started to treat cases of muscular dystrophy and neurological degeneration, with vitamin E from wheat germ. The subsequent improvement in his cases was reported in 1940, the same year in which Stone and Wechsler, of the United States, reported cases of muscular dystrophy and amyotrophic lateral sclerosis successfully treated with vitamin E, but it was only in 1941 that the subject began to arouse wide clinical interest. The early promise, however, of the value of vitamin E in the treatment of muscular and nervous diseases, suggests that these diseases are probably caused by some complicated failure in the metabolism of the vitamin, which can only be corrected in certain instances by simple treatment with the vitamin alone.

The elucidation of the chemical structure of vitamin E has been rapid since 1936. In that year, Evans and Emerson isolated two alcohols from wheat germ; alpha- and beta-tocopherols, and from cotton seed oil, gamma-tocopherol, all of which has vitamin E activity. Further work by many investigators including Todd, Bergel and Drummond and their collaborators in England, Fernholz in America, and Karrer and John on the Continent, finally led to the synthesis of alpha, beta- and gamma-tocopherols and the elucidation of their chemical structure.

FUNCTION OF VITAMIN E

Since the definite claim for its existence was made about 1922, vitamin E has assumed several roles in metabolism. The first function associated with this food factor, was in connection with reproduction; it prevents resorption of fetuses in the female, and testicular degeneration in the male

laboratory rat maintained on a diet composed of purified food substance. Somewhat later, a disease

called encephalomalaciii (softening of the brain) was produced in chicks restricted to a diet deficient in vitamin E. This condition appears to be associated with imoairment of the blood vessels with the resultant cerebral ischemia (local anemia due to arterial contraction). By this time, vitamin E had been isolated and synthesized and the chemical name, alpha-tocopherol, was given it. Soon it was found that, in line with old observations in rats, paralysis could be produced in rabbits and several other laboratory animals. This experimental muscular dystrophy is now known to be a sequel of a lack of vitamin E. Various explanations have been offered to account for the foregoing observations, among them one which postulates that the tocopherols were believed to be natural protectors, or anti-oxidants for other essential substances, and to foster the integrity of the capillary walls.

As early as 1936 Martin and Moore called attention to still another phenomenon of vitamin E deficiency; in rats so prepared, there occurred a yellowish - brown coloration of the uterus, due to the collection of a pigment in the muscle of that organ. Skeletal muscle is similarly affected, and here the pigmentation is associated with dystrophy. According to Mason and Emmel, the ovarian pigment seems to be an abnormal product of metabolism, formed during cell degeneration in artretic follicles and in regressing corpora lutea. It is phagocytized by the tissue macrophages, giving rise to abnormal coloration of (lie tissue. Some of the macrophages escape to the lymph nodes, spleen and liver, where the abnormal pigments is also found. The pigment, resistant to strong alkalis, fat solvents and oxidizing agents, due;; not contain iron and has not been identified with any known biologic pigment. A determination of the chemical nature of this substance, might lead to an understanding of the cellular enzyme system in which vitamin E plays an important part. Although administration of large doses of tocopherol does not cause pigment to disappear from the ovary, the function of this organ does not appear to be disturbed by the accumulation of the pigment.

Another relationship between vitamin E and tissue

pigment has been reported by Granados and Dam. In rats, restricted to a ration deficient in alpha tocopherol but containing fat, there is a progressive loss of pigment from the incisors beginning at the gingival margin. This alteration is attributed to the action of the more highly unsaturated tally acids in the ameloblasts, in absence of vitamin E. Since tocopherol phosphate brings about a cessation of the greatly increased uptake of oxygen, from an animal lacking vitamin E in the diet, a further study of the abnormal pigmentation and depigmentation described, may lead to the implication of the tocopherols in some phase of the biologic, oxydative systems in the body.

PHYSIOLOGICAL ACTION OF VITAMIN E

The many symptoms which can be observed during a deficiency of vitamin E, points to the assumption that vitamin E is of importance to the tissues as a whole. Unconfirmed, experimental findings to the effect of the organism of vitamin E — depleted animals contains unsaponiliable material, which upon injection into rats causes symptoms of a Vitamin E deficiency, have tentatively been interpreted as indicating a disturbance of some metabolic processes, perhaps of the fat metabolism.

A possible relation of vitamin E to the amino-acid metabolism, is seen in the fact that during avitaminosis the creatine content of striated muscles is greatly reduced in rabbits and in rats, and that the urinary excretion of creatine is considerably increased, while the excretion of creatinine remains unchanged. A marked reduction of the creatine content in urine is observed following administration of vitamin E. No such changes have, however, been found in the urine of man suffering from progressive muscular dystrophy, amyotonia congenita and similar neuromuscular disturbances.

The primary physiological action of vitamin E apparently is to direct certain activities of the cell nucleus. This conception of the mechanism of the vitamin E action, although much disputed, has proved to be of extreme value in an attempt to correlate the various experimental facts and observations of the many different symptoms of vitamin E deficiency.

The role which vitamin E plays in the metabolic activities of the cell nucleus, cannot as yet be exactly defined. It seems that the vitamin function is more intimately concerned with the processes of cell maturation and differentiation than with mitosis. Thus the rate of growth of the Walker 256 mammary carcinoma is not essentially affected by continuous maintenance in vitamin E-deficient rats. On the Other hand, an increase in growth has been demonstrated in vitro experiments with liver, spleen, heart and periosteal tissue cultures upon the addition of vitamin E. Retarded growth has, as in the case of deficiencies of the other vitamins, also been observed during vitamin E deficiency. The considerable decrease in the weight of the testis, even when calculated in relation to the reduced body weight is, however, specific for this vitamin. In accordance with the conception that vitamin E is of special influence to all those tissues In which cellular proliferation and differentiation proceed at a high speed, it has been found that the application of this vitamin is especially useful, for example, to effect growth of prematurely born babies or to heal skin wounds in rats. Beneficial effects in the latter case have been observed upon oral or local applications.

The histopathological changes, which have been observed to occur in the testes of vitamin - E depleted rats, are largely responsible for conception of the function of vitamin E. The chromatin of the spermatozoa undergoes a typical change, a lysis, and the nuclei become crescentric. Upon further development of the deficiency disease, the mature and immature cells, the permatogonia, spermatocytes and spermatozoa, fuse into giant cells with many nuclei. Besides chromatolysis there appears to be an interference in the formation of chromatin.

Similar effects are observed in the fetus. The earliest signs of a vitamin E deficiency in the embryo is observed in the hematopoietic tissue, the growth of which is disturbed. The mesodermal tissues, where rapid cellular activity prevails, are similarly affected. The symptoms of vitamin E deficiency in nervous and degenerative lesions in the muscles, seem to be related to the cerebral cortrex, a tissue of high cellular activity.

All experimental evidences lead to the conclusion that, secondary to the lesions in the gonads and in the neuro-muscular system and probably as the result of these rather than

as their cause, abnormalities occur in the pituitary and thyroid glands. In young vitamin E-depleted rats, a change in the fur has been observed which is characteristic for hypophysectomized animals. In the anterior lobe, the acidophil and basophil cells degenerate and show no distinct granulation. The histological appearance of the anterior lobe is quite similar to the degeneration observed in the case of castrated animals. Actually, many of the Symptoms observed as a result of a vitamin E deficiency, resemble very closely, the syndromes of a hypophysectomy. The changes Observed in the tests are, however, dissimilar. Vitamin E deficiency causes a degeneration of the germinative tissue, whereas upon dysfunction of the pituitary, the interstitial tissue is degenerated. In male rata deprived of vitamin E, the pituitaries were found to contain a greater gonadotropic action than found in the glands of rata fed with vitamin E. In female rats deprived of vitamin E, the pituitary contains a decreased amount of luteinizing hormone. Nevertheless, the important symptoms of vitamin E deficiency, namely muscular dystrophy, gestation resorption and testicular degeneration, cannot be prevented or cured by administration of the hormones of the anterior lobe. The syndromes are, furthermore, not influenced by injection of the sex hormones. On the other hand, vitamin E, when administered to immature or hypophysectomized adult rats, does not exert any effect on the ovaries, uterus or vagina. In frogs, an interesting relation of vitamin E to the secretion of the hormones of the anterior lobe of the pituitary, has been observed. The glycogenotropic hormone could be detected in the livers only after an intake of vitamin E.

In the thyroids of vitamin E-depleted animal phypoplasia occurs. The vesicles are enlarged and filled with colloid. In the kidneys, a degeneration Of the epithelium of the convoluted tubules is observed. In the young of vitamin E deficient rats cretinism is observed.

Sterility in the Male

Male rats severly depleted in vitamin E from early life, show an irreversible degeneration of the seminiferous epithelium at the onset of sexual maturity, but no Injury during adolescence. The process may be delayed in proportion to pre-weaning storage or post weaning administration of vitamin E,

Opinions differ as to whether the alterations in the nuclear or in the cytoplasmic structure of the epithelial cells best reflect the deeply sealed metabolic disturbances, which precede demonstrable histopathological changes to such an extent that administration of vitamin E, as much as 10 to 15 days prior to the onset of the latter, usually fails to prevent or even retard the degenerative process. Within several weeks, practically no germ cells remain in the seminiferous tubules. The cellular changes will be described elsewhere. While there exists evidence that some restoration of the seminiferous epithelium may occur after prolonged periods of therapy, neither restoration of fertility nor the presences of mature spermatozoa in the epididymis has been reported; the ensuing sterility is truly permanent.

No testicular injury occurs in male mice reared for 400 days, or maintained through seven generations, on E-deficient diets which readily induce first pregnancy resorptions in mice and rats, and early testis degeneration in rats. This unusual finding suggests some unexplained difference in the metabolic demands of the seminiferous epithelium in these two closely related species. The Striking sex difference in E requirements of mice, has no parallel in rats. The male germ cells are unaffected in rabbits maintained In a prolonged state of chronic muscular dystrophy and in dystrophic guinea pigs. As mentioned before, this does not conclusively exclude the need of vitamin E for maintenance of germ cell integrity in these Species, whose musculature possesses such a high priority for the vitamin.

Testicular degeneration resembling that seen in the rat, but not yet proven to be irreversible, occurs also in the chick fed diets of natural food treated with ferric chloride to oxidize vitamin E present. Of particular significance are the recent observations that the male guppy fish reared on synthetic as well as iron-treated diets, reveals a suppression of the testicular development and similar degenerative chances in the mature germinal epithelium, together with dystrophy of the striated musculature, and unusual cell changes in certain visceral organs. These changes, which are much more difficult to induce in sexually mature fish, are preventable by pure a-tocopherol. Preliminary tests suggested an irreversible type of testis injury; the response of other tissues was not determined. On the other hand, tadpoles reared on the same diets, fail to metamorphose but show no suppression or

structural alteration of the gonads of either sex.

STERILITY IN THE FEMALE

In female rats deprived of vitamin E, the processes of estrus, ovulation, conception, and implantation of fertilized ova are entirely normal. However, the developing embryos and fetal membranes show abnormalities of development, resulting in intra-uterine death, followed by rapid autolysis and resorption of the products of conception. Administration of sufficient vitamin E, as late as the 10th day, will usually prevent the resorptive process. Repeated resorptions do not affect sexual functions or the ability to complete pregnancy, if sufficient vitamin is supplied, although prolonged depletion of E is associated with decreased fecundity and increased requirements of vitamin E, for the completion of gestation.

When sterile rats are given border-line doses of vitamin E, as used in routine, bio-assay tests, the implantation sites at any stage of pregnancy may exhibit all gradations between early resorption and viable fetuses. Fetuses which succumb during the last few days of pregnancy, are usually delivered dead; those which are viable at delivery, rarely survive more than a few days unless they, or the mother, are given an additional supplement of vitamin E. Efforts made to utilize this gradation in intensity of biological response as a criterion for bio-assay, have not given the results first anticipated.

The prolongation of gestation, reported by Barrie, in rats given critically low doses of vitamin E, must be attributed to experimental factors other than lack of vitamin E. Countless other investigations have demonstrated the almost Invariable occurrence of parturition between the 21st and 23rd days of pregnancy. An extensive series of rats fed border-line dose of E, and laparotomized during the last week of gestation, have shown no abnormalities of parturition. Barrie"s suggestion that resorption of some fetuses delays development in others and thus prolongs gestation, possibly through deficiency of anterior pituitary hormones, is not in accord with the observation that one or two fetuses surviving laparotomy in late pregnancy may be delivered, dead or living, at normal term.

The cause of fetal death and resorption in utero, has been generally attributed to a suppressed development of the mesodermal derivatives of the embryo, especially those of the hematopoietic tissues; blood islands of the yolk sac and embryonic liver. More recent studies based upon examination of

later (16 day old) fetuses, have revealed no serious depression of hematopoietic function in the low E embryo, but indicate that abnormalities of the vascular system, characterized by stasis, distention and thrombusis, (especially of venous channels) which lead eventually to the general ischemia and sometimes to frank hemorrhage, constitute the real causes of fetal death. These vascular changes, the incidence of which is indirectly proportional to the level of critical vitamin E dosage, are not influenced by separate administration of vitamin C or K. They have not yet been demonstrated in the mouse, in which the process of fetal resorption otherwise resembles that in the rat. These changes bear certain resemblance to the capillary thrombi of nutritional encephalomacia, the exudative diathesis of vitamin E deficient chicks, and the vascular lesions in the early chick embryo hatched from eggs containing vitamin E. Discovery of the fundamental cause of any one of these phenomena, should open the way to a better understanding of the others.

ABSORPTION, DISTRIBUTION AND FATE OF E

Bile appears to be necessary for the absorption of vitamin E. Brinkhouse and Warner report that, dogs with chronic biliary fistulae, develop within seven to nine months, both the nutritional muscular dystrophy and testicular degeneration typical of a deficiency of vitamin E. In one dog, the muscular dystrophy was arrested and improved when bile was fed by mouth. Greanes and Schmidt have obtained similar results in rats. (Liquid paraffin probably hinders absorption of vitamin E, as it does that of vitamins A, D and K).

Some vitamin E escapes absorption and appears in the feces of rats when the diet is very rich in the vitamin. The amount lost may lie a quarter of that eaten, males excreting more than females.

The fetus absorbs vitamin E from the mother as long as she has adequate stores, or receives it in her diet. If the mother is deficient in vitamin E, placental transfer is impaired, since Pappenhelmer has reported rabbits on a vitamin E deficient diet giving, birth to dystrophic young. Absorption through the placenta must be Insufficient In allow for storage, since the young born rats and rabbits on a deficient diet, develop muscular dystrophy only slightly sooner than do the young born of normal animals, when both are suckled by a vitamin *E*

deficient doe. The tissues from newly born rats of mothers on a normal diet, contain only small amounts of vitamin E.

The amount of vitamin *E* in milk depends on the maternal diet. Pappenheimer and others report that half of a single dose of 51 mg. of alpha-tocoplierol was excreted in the milk of nursing rats during the whole period of laction.

Whether vitamin E undergoes any change in the intestine during absorption is not clear yet. Many workers, among them Evans and Burr, Knowlton and others, have reported that vitamin E is active when injected for the prevention and cure of both sterility and muscular dystrophy.

STORAGE OF VITAMIN E IN THE TISSUES

Using a spectroscopic technique, Cuthbertson and others, found the greatest storage in body fat and some storage in muscle, but none in the liver, heart, kidneys, adrenals, tests, ovaries, and pituitary. Failure to find any vitamin E in so many organs, is presumably due to the technique being less delicate than the biological and chemical techniques used by other investigators already mentioned.

The contradictions in these various reports about the relative amounts of vitamin E stored in different tissues, are difficult to explain, but it may be that different mixtures of the tocopherols are not stored in the same manner, and that the rates of absorption by, and distribution from the various tissues differ, so that storage depends both on what form of tocopherol have been given, and how soon afterwards the tissues are examined. It has been suggested by Hines and Matill that, the high and very slowly depleted hepatic stores of the rat may explain why this animal is more resistant to lack of the vitamin than the rabbit, whose hepatic stores arc low, especially compared to those in the muscles.

DESTRUCTION AND EXCRETION OF VITAMIN E

The depletion of stores of vitamin E was shown by Evans and Burr, to continue at the same rate whether rats became pregnant or not, though vitamin E is excreted In milk. Thus it appears that vitamin E is used in the normal processes of the body, pregnancy not appreciably increasing the consumption.

It is improbable that the first stage in the destruction of vitamin E is its oxidation to tocopherylhydroquinine, which is biologically inert, though this has been suggested because the blood of dogs contain 0. 46 mg. per 100 c. c. and that of man 0. 31 mg. per 100 c. c. Hines and Matill, however, found none in

the liver, muscles and urine of rats consuming 100 mg. of vitamin E daily, which is a strong argument against vitamin E being oxidized to this substance.

Excretion of vitamin E in the urine and feces of rats only occurs when it has been consumed in very large amounts. It has not been found in human urine.

ALPHA TOCOPHEROL AND PROTEIN METABOLISM ITS INTERRELATIONSHIP

In 1048, Have reported that d, alpha tocopherol reduced weight loss in adult rats maintained on a 5% crude-casein diet for extended periods of time. It was pointed out that this result was in apparent contradiction to the work of Dam who had noted in 1944, no influence of alpha tocopherol on the body weight of rats, maintained until death, on | dn I oonlalnlnii approximately 5% protein from yeast. It occurred to the authors that the 4 week, rat-growth method originated by Osborne, Mendel, and Ferry in 1919 for determining protein quality, might be useful in resolving the divergent results. The results from 5 consecutive experiments showed that when the casein level in the diet of young rats was between 6 and 12 per cent, d, alpha tocopherol increased the utilization of casein protein for their growth. However, there was no benefit due to tocopherol at casein levels over 12 per cent or under 6 per cent in the 4-week test period. The average protein-efficiency ratio for the control groups was 1.88, as compared with 2.18 for the tocopherol-supplemental groups. The beneficial effect of alpha tocopherol was as evident on equalized feeding as on ad libitum feeding technics. The incidence of stomach ulcers and the bleaching of maxillary Incisors, which occur in rats maintained on low-casein diets, are reduced by d, alpha tocopherol. A yeast-protein concentrate, or 0.I per cent xanthine in the diet, is as effective as alpha tocopherol in increasing the utilization of casein protein.

This effect of tocopherol in improving efficiency of food utilization, has been noticed by Patrick and Morgan in chickens fed a synthetic diet containing casein protein. An explanation for the beneficial influence of tocopherol on food utilization efficiency, or on the protein-efficiency ratio, may be found in an experiment described by Bosshardt. As non-protein calorie intake increased, protein intake remaining constant, the protein-efficiency ratio was found to increase. Consequently, tocopherol

may be increasing the efficiency of fat metabolism, thus giving, in effect, a higher calorie intake and resulting indirectly in a higher protein-efficiency ratio.

The ability of alpha tocopherol or xanthine to improve casein utilization, may be related to the observations in the works of Schwarz that, these compounds prevented cirrhotic changes in the liver, and death rate of rats containing 15 per cent alkali-extracted casein. Traces of xanthine contained in crude casein would be removed by the alkali-extraction and a xanthine-free diet would result. Giri and Rao reported thai xanthine functions as an anti-oxidant in metal catalyzed oxidations, and it may be in this same capacity that it acts similarly and nonspecifically with alpha tocopherol in vivo.

Schwarz found dried yeast, 0. 5 Gm. daily, to be but slightly active, but results of the authors showed a yeast protein concentrate to be highly active. The active agent in the yeast preparation used by the authors may have been liberated, or formed precursors during the enzymatic digestion. Studies on this problem as well as the influence of other purine bodies and of folic acid are being pursued. In this regard Bosshardt, in working with mice, noted an increased utilization of casein protein produced by butanol extract of liver.

As mentioned before, tocopherol did not increase the protein-efficiency ratio in rats on diets with casein levels as low as 5 or 6 per cent, over the 4-week test period. In a previous experiment, rats kept on such diets for periods up to 20 weeks, showed a dramatic growth and survival benefit from alpha tocopherol. This difference may indicate that the interrelation between protein and alpha tocopherol follows separate and independent mechanisms under these two experimental conditions.

BLOOD PRESSURE OBSERVATIONS

How a deficiency in vitamin E effects a reduction in systolic blood pressure in rats is unknown. A search for the site of the disturbance in the vascular system has not been successful. Histological examination by Telford, of the hearts of 21 deficient animals, 12 to 26 months of age, tailed lo show any consistent pathological lesions. Although a few deficient animals showed definite myocardial damage, some of the normal controls also showed myocardial lesions to a similar degree. Thus the lesion was fell to be within normal limits.

A histological examination of the Larger vessels, such as the abdominal aorta, iliac, femoral and anterior tibial arteries, and corresponding veins, showed no abnormalities in six 22 month old vitamin E deficient animals.

There are, however, several observations that suggest that vitamin E is essential to the normal functioning of the vascular system. One pertinent point is that, the death of the fetuses in vitamin E deficient pregnant female rats has been attributed to any of three conditions. First, a suppression of the development of derivatives in the embryo, related to the hematopoietic function, as suggested by Evans, Burr and Urne. Secondly, defects in the vascular walls causing stasis and extravasation of blood into the tissues, suggested by Mason, and last a combination of both processes.

Another observation suggesting a vascular upset, is the presence of edema of the face in young rats suffering from an acute vitamin E deficiency. In the case of clicks, the vascular disturbances are much more evident and widespread than in the rat. Vitamin E deficient chicks manifest exudative diathesis, widespread edema, cerebellar lesions caused by arterial infractions and hemorrhage in the developing fetus.

The observation that two year old normal rats have a lower systolic blood pressure than year old animals, and that similar differences were found in E low rats, one and two years of age, raises a very interesting problem, since a rise in blood pressure would be expected in old age but not a reduction. In fact, Griffith, Jeffers and Roberts reported "in measuring the blood pressure of hundreds of rats of various ages, we have noted a tendency to a slight raise with age." However, rodents rarely develop the deposits of calcium and lipoid substances in the media or intima of a vessel. Rat studies substantiate this general observation. An explanation for the drop In blood pressure in normal 2-year old animals is, nevertheless, still lacking. The percentage difference is just as large, at the end of one year of vitamin E deficiency, as after a two year deficiency. The additional drop in blood pressure in the two year old deficient animals was due to an aging effect, and not aggravated by the continued deficiency state. The percentage difference between one and two year old deficient rats was 21.1 per cent. The difference between normal rats of corresponding age levels was 21.3 per cent reduction.

A resume of the foregoing observations and study results

would include the following conclusions:

a. One year old vitamin E deficient female rats showed a reduction of 29.4 per cent in their systolic blood pressure, when compared with normal rats of the same age.
b. In two year old vitamin E deficient rats, the reduction in blood pressure was essentially the same (29.2 %) as in the year old group. The systolic blood pressure for 2-year old vitamin E deficient rats and normal control rats was 61.7 mm. and 87.2 mm., respectively
c. A lowering of blood pressure in the second year of life is reflective equally in both experimental control groups. The reduction is therefore due to an aging effect and is not a manifestation of a dietary deficiency.
d. An histological examination of the hearts and large vessels of vitamin deficient rats, failed to demonstrate any consistent vascular lesions that might contribute to a reduction in blood pressure.
e. Variations in the room temperature, age and sex of the animal, and methods used in determining blood pressure are variables that influence the blood pressure readings in normal and experimental rats.

ANTIPURPURIC PROPERTIES OF ALPHA TOCOHEROL

Experimenting wild dogs, increased capillary fragility was produced by the Injection of stilbestrol intramuscularly and intravenously, in doses Of 10-20 mg. daily. This, according to Skelton, Shute, Skinner and Waud, produced a reduction in platelet counts and prolonged bleeding and clotting times, if the dosage was continued for 14-25 days, a true purpura developed. There is a possibility that this could lead to widespread large and small subcutaneous and visceral hemorrhages or even "hemorrhagic death. " Counteracting the effect of the synthetic female hormone with a male hormone, testosterone did not remedy the condition.

Daily administration of vitamin E hastened the restoration of the platelet count, and a return to a normal capillary fragility in these purpuric animals. There was a frank purpura, and definite vascular deficiencies, by the administration of alpha-tocopherol in the early stages.

Antipurpurogenic action of vitamin E has proven to be

effective in humans. The authors of these experiments quote five cases suffering from thrombocytopenic purpura, one of whom "had been helped by splenectomy." All of these were given 200 to 400 mg. alpha -tocopherol daily, and a rapid return to normal or near normal capillary fragility and platelet counts. There was a proportionate disappearance of clinical evidence of purpura.

One case had a terminal purpura and aplastic anemia, associated with an advanced lymphosarcoma, and showed a definite improvement in the clinical picture. "This effect of vitamin E at the above dosage appeared in 7 to 14 days, 'IU' " seems that the treatment must be continued for long periods of lime, if not permanently."

BIOLOGICAL FUNCTION OF VITAMIN E

Over a decade ago, at the conclusion of a long program of studies on the role of vitamin E in the physiology of reproduction in higher animals, Evans and Burr permitted E-low mother rats to attempt to suckle and, if possible, rear their young. Although they had been given but little more vitamin E than had proved necessary to insure birth of the living young, if vitamin B was high, lactation was not seriously interfered with and the young grew normally and, to all appearances, thrived. Suddenly, toward the end of the lactation period, a calamity intervened; the investigators were surprised to find that the majority of these well-nourished young developed a mysterious malady, characterized mainly by muscular paralysis. Half of the affected sucklings died from the malady — often so suddenly that there was no signs of wasting from under-nutrition.

The disorder was not due to constitutional inferiority of the young, through germinal impairment, or any 'inadequacy in their intrauterine life because, though diminished had the disease also occurred when young from normal, natural food mothers were allowed to suckle from these E-low mothers. The The disease was therefore unquestionably due to defect in the E-low mother's milk, and the final proof of this was secured by shifting her and and her own litter to natural foods, in which cases the paralysis never occurred, The researchers then began the addition of single nutritive elements to the diet of

other E-low mothers; these efforts were without effect until vitamin E was given them in the least contaminated form then available; wheat germ oil or concentrates from its non-sponifiable fraction. To put the cap on the proof, the direct administration of these substances to the young was similarly completely effective in preventing the disease. This previously unknown need for vitamin E in the economy of the developing young was remarkably limited in time, the paralysis were prevented if the substance was given as late as the fifteenth day of life; the disease otherwise developed by by the 25th day of life, so that this 10 day period is a critical one as regards to the need for vitamin E.

TREATMENT OF FIBROSITIS AND OSTEOARTHRITIS WITH VITAMIN E

A recent statement by Steinberg tends to support an earlier theory that, "primary fibrositis is a metabolic disorder resulting in disturbance of mesenchymal tissue function." Steinbeig has also reported that the blood vitamin E level in primary fibrositis usually normal, and the only exceptions found to date are a woefully inadequate diet or liver disease, which prevents absorption of the vitamin E from the gastro-intestinal tract.

Despite this, Ant and Appleton have shown that, in every case of fibrositis with continued symptomatology, the blood tocopherol levels were 35 per cent lower than the average normal. In the same series of patients, after administration of vitamin E, the blood tocopherol changes were noted in rheumatic disorders accompanied by digestive disturbances. Recently, Warter and co-workers stated that, "a majority of rheumatoid arthritis patients do not consume an adequate diet, consequently their reserves are called mi to make up the deficiency, resulting in a loss of weight and musle atrophy."

In three different series of cases, 92 cases of primary fibrositis in all, Steinberg has shown the value of vitamin E orally and intra-muscularly. In his research he had more than an adequate number of control cases in each series. Ingham too, reported on 12 cases of primary fibrositis with complete relief of symptoms in 3 to 4 weeks, on oral vitamin E therapy. Ant presented 32 cases of primary fibrositis in which vitamin E, in the form of wheat germ oil and in an Ointment, was used topically. Improvement was marked and definite In 20 cases, fair in nine and absent in three. The last

three cases, proved to be of non-fibrositic origin. Seventeen cases received Inunction therapy alone, and 12 of these (70%) showed marked or complete improvement. In the remaining five (30 *%),* the relief afforded was fair. It was postulated, in this report, that wheat germ oil is absorbed through the skin and has an affinity for fibrous connective tissue, acting as an insulator against hydremia which manifests itself in edema and swelling. Thus, basing opinions on the aforementioned reports, the conclusions appear to be:

a. Obstinate fibrositis and osteoarthritis were relieved by vitamin E, locally.

c.

b. Deep fibrostic changes were relieved by local, oral and injectable vitamin E, as evidenced by clinical follow-up. Continued treatment with this therapy had the desired metabolic effect.

d.

Cases of fibrositis accompanied by definite osteoarthritic changes, will respond to vitamin E, a therapy of distinct value.

PREVENTION OF ABRUPTIO PLACENTAE WITH VITAMIN E

Quite early in his Studies on vitamin E deficiency, it became apparent to Evan Shute, that uterine tenderness was almost always the first sign of vitamin E deficiency In human pregnancy; that it could always be relieved by the prompt administration of enough vitamin E, and that if it recurred, il was evidence of escape from vitamin E control. As extensive blood studies of the vitamin E estrogen equilibrium were continued, il was seen that, like spontaneous abortion, abruptio placentae, of either the classical degree of severity or of the mild degree described here, was usually associated with vitamin E deficiency and its comitant estrogen excess. We realize, of course, abruptio placentae of the most typical sort can occur in the absence of any of the major criteria; pain, tenderness, shock, external hemorrhage, toxemia, or a high blood estrogen value. When blood studies in early pregnancy revealed this vitamin E estrogen imbalance, it was at once anticipated that somewhere in the future of that pregnancy lay an abortion, miscarriage, premature delivery, noneclamptic toxemia, abruptio-placentae, or anomalous child. Much of the same idea suggested to Young,

the useful and graphic concept of the "abortion sequence. " The point to be stressed is, the danger of abruptio-placentae, classical or mild, can almost always be foreseen, and as what follows may indicate, can usually be prevented. A summation of case reports by Shute illustrate:

1. The first clinical sign ofl placental detachment is a localized area of uterine tenderness with or without bleeding or slight toxemia.
2. Abruptio placentae can often be foreseen even earlier In pregnancy by means of a blood estrogen assay.
3. If the early phenomena disappear the patient may go on to display classical abrutio placentae.
4. The early phenomena disappear promptly if enough vitamin E is administered at once.
5. The vitamin E must be a potent preparation. The dose usually rises as pregnancy proceeds and must always be the dose required to control symptoms in that particular woman's pregnancy, not just a standard dose. It must be given until delivery.

ALPHA TOCOPHEROL ITS EFFECT ON INSULIN REQUIREMENTS IN DIABETES MELLITUS

Both Dowd and Vogelsang noted that, if the insulin dosage was not reduced considerably after beginning the large dose: "I alpha tocopherol, the diabetic patient might suffer mild hypoglycemic reactions. Symptoms such as shakiness, chills, dizziness, creepy sensations and faintness were often noted. These symptoms, of course, disappeared when insulin dosage was adjusted at a lower level. This new level was maintained quite well, and none were obliged to return to the former high dosage unless the alphatocopherol was discontinued.

Molotchick has reported three cases of cardiac disease satisfactorily treated with alpha tocopherol. Case one of the series, a 55 year old male who had had coronary occlusion 10 10 years previously, showed a blood sugar level of 214 mgm. and 2.2% urinary glucose. On a relatively small daily dose of about 100 mgm. alpha tocopherol he obtained relief from his anginal distress.

What is almost as interesting is, that in approximately five months he had a blood sugar level of 125 mgm. and negative

urinary glucose. In retrospect one could wish that blood sugar and urine investigations had been recorded sooner than 5 months after therapy, as these might have shown such such results in 2 or 3 weeks time. This case illustrates the more or less "Immediate action" of alpha tocopherol on diabetes mellitus.

The cardiac status of many of the aforementioned cases have been observed for a protracted period of time by Vogeloang. After eight to twelve months of this therapy some of the diabetics in the series were able to stop the insulin altogether. Blood sugar and urinalysis then revealed normal glucose values. Vogelsang has treated numerous cases who had been diabetics, requiring both insulin and diet for several years and who now, after taking large doses (200 to 400 mgm.) of alpha tocopherol for many months, no longer need insulin. All these patients were over 48 years of age, and a partial list of case histories and results is now presented:

Case a: Mr. E. B. — white male, 68 years old. Complained of precordial pain and dyspnea. Gave a history of taking 20 units insulin per diem. He was diagnosed as coronary sclerosis with anginal syndrome. At start of therapy he was given 600 mgm. mixed tocopherols per day (200 Mg. alpha tocopherol) and promptly became more active, could indulge in favorite pastimes such as hill climbing, and soon all symptoms vanished. The 600 mgm. mixed tocopherol per day was continued for a year and a half during which time the insulin dosage was gradually reduced from 20 units to 16, 12, and 8 and then at the end of the first 6 months, discontinued entirely. At the conclusion of the 18 month period the patient was still off insulin.

Case b: Mrs. M. B. — housewife, 62 years of age. Had taken 20 units insulin daily for 12 years. Had severe rheumatic fever as a girl. Rheumatic heart disease with marked enlargement, aortic stenosis and hypertension. When she was given a daily dose of 375 mgm. alpha tocopherol she became compensated and no longer complained of dyspnea, precordial pain or ankle edema. Vitamin E was reduced to 300 mgm. after 9 days. Two days after first commencing treatment, patient's insulin was reduced to 15 units. Two days later to 10 units and in seven days discontinued entirely. Two weeks after treatment was instituted, she abandoned her diabetic diet and has continued free of sugar ever since.

Case c: Mrs. M.C. — age 77. Arteriosclerotic heart disease with moderate cardiac enlargement, regular sinus rhythm, mitral reguritation and anginal pain. She had had an anterior coronary occlusion seven years before. On 25 units of insulin daily, and a 2000 caloric diabetic diet. She showed 1 percent of glyosuria and 200 mgm percent of blood sugar. Eight days after beginning a daily dose of 300 mgm. alpha tocopherol, her urine became sugar-free and insulin dose was reduced to 20 units. On this regimen urine specimens remained free of glucose and the dose was then reduced to 15 units, and maintained at this level for eight months. At that time a slight reaction was noted and therefore the insulin was stopped altogether. She has shown no glycosuria or hyperglycemia since. The maintenance dose of alpha tocopherol now needed to keep her symptom-free and healthfully active is 240 mgm. per day.

Case d; Mr. A. B. — white, 79 years of age. Had been taking 30 units Protamin Zinc Insulin plus 10 units regular insulin for 10 years. When first seen he presented a picture of arteriosclerotic

heart disease with enlarged heart, coupling rhythm, mitral reguritation, pulmonary edema, paroxysmal nocturnal dyspnea and chronic, passive congestion Of the liver. Both legs were dark, purplish-red in color and showed three plus edema of a very soft character, very cold to I he touch. The large great toe was a dark brown color and quite Insensitive. There was no dorsalis pedis or posterior tibial pulsation in the left foot, and only a faint dorsali pedis in the right. The urine had remained free of glucose on frequent testing. A diagnosis of arte no-clerotic or diabetic gangrene was made. He was given 360 mgm. alpha tocopherol per day, the dosage of digitalis was continued and he was admitted to the hospital. The following day, his legs were free '>! edema and the color compatible with the rest of his body. The next day both dorsalis and posterior tibial arteries pulsated. The dosage of both Protamin Zinc Insulin, and insulin were continued for four days, then reduced five units for four days more and on the ninth day discontinued completely. For two days following, only a three and then a two percent urinary glucose was discernible, then none.

Even if the insulin requirements were not affected) the use of vitamin E in diabetes would be justified by virtue of the

success it has demonstrated in treating cardiovascular complications, Whatever the mechanism of the action of alpha tocopherol may be, the constancy of its effect on diabetes indicates that it should be "ad-ministered, in proper dosage, to every diabetic patient." (Vogelsang)

Alpha tocopherol, in doses of 200 to 400 mgms per day, radically lowers the insulin requirements in diabetes. After eight to twelve months of this therapy, many patients no longer require Inlsulin.

VITAMIN E THERAPY IN LEG ULCER

Multiple or single leg ulcers, with or without eczematization, occur commonly in the lower third of one or both Legs and not infrequently viewed as "stasis" or "varicose" ulcers, particularly if edema is present. In a group of seven cases of [eg ulcers successfully treated with tocopherols, both orally and by topical application, Burgess and Pritchard report that "this group seems to have a common pattern. The association of B more or less sclerotic condition of the legs in some patients only moderately apparent through 'feel', in others the skin being hidebound, resulting in limitation of ankle movements with or without varicosities, and these are often present to a minor degree, together with multiple or single ulcers of long duration or of frequent recurrence, often callous in type, makes up the clinical picture."

"It is our opinion that the primary and Important phenomenon probably is a subclinical degeneration of the collagenous tissue, resulting in the inability of the skin to withstand trauma of no

moment to the individual. Hather impressive has been the frequency with which biopsy wounds, away from the ulcer, have resulted in an inability to approximate the wound immediately, or the frequency with which the area often rapidly enlarged to reproduce an ulcer characteristic of that for which the patient sought treatment. "

Burgess and Pritchard made biopsies, in most cases, on tissue taken a distance away from any ulcerative process. After therapy had been completed, tissues for biopsy were taken close by the site of the earlier biopsy. Presuming that trauma was a

precipitating factor, it would appear that once infection is introduced in such ulcers, this in turn may well further intensify the sclerosing process as the leg, having the ulcerative process, shows the greater degree of thickening.

Experimental evidence in rats, shows that a muscular dystrophy of the lower extremities results after a prolonged vitamin E deficiency diet. It has been shown that the greatest concentration of vitamin E occur in the heart, lungs and spleen. It seems probable that the muscles of the lower extremities also require large concentrations of vitamin E, in order to maintain a relatively high metabolic activity. This may be of importance in the localization, predominantly in these areas of sclerosis with ulcer.

The pathogenesis and development of the lesions in these scleroses with leg ulcers, seems to be first a collagenous swelling in the corium, accompanied by vascular proliferation and often dilation commencing in the papillary zone and accompanied by lymphocytic infiltrations, diapedesis of red cells from the capillaries, and deposition of hemosiderin pigment. There then follows a secondary proliferative fibrosis in the corium, and the epidermis changes by becoming acanthotic and hyperkeratotic.

The primary collagenous changes are more marked and more extensive in lesions of short durations in the younger individuals, as compared with secondary, proliferative fibrosis and acanthosis with hyperkeratosis predominating in long-standing lesions in older people. This may explain, in part at least, why the response to therapy is more rapid in those cases showing lesser degrees of sclerosis. The very common association of excessive pigmentation in leg ulcers with sclerosis, together with the marked deposition of hemasiderin, may well be indicative of vitamin E deficiency, comparable to the observation of Mason in vitamin E deficient rats.

The report of Burgess and Pritchard continues, "Purposely, the cases treated in hospital were given intensive tocopherol therapy, with a view to its evaluation, and therefore we excluded, in many cases, the factor of rest, local dressings or other medication. Antibiotic therapy, together with other measures combined with tocopherol therapy, would seem to offer the possibility of more rapid cure. (Note — "other measures" included medication or surgical intervention). It should be noted here that, all of these cases were treated

simultaneously by the administration of tocopherols both by mouth and parenterally. It seems to us that either route of administration will probably give comparable results, depending on the amount aborsbed. Tocopherols in natural oils produce some pain and reaction when given intramuscularly. It is our observation thai bed patients have mild discomfort, but that ambulatory patients do sometimes complain of discomfort about the third or fourth day after Injections.

The considered opinion of these and Other eminent investigators would appear to be that, vitamin E Is of undoubted value in the treatment of sclerosis of the legs with associated leg ulcers. This effect is directed probably entirely towards regeneration of collagenous tissue, as demonstrated both clinically and Instopathologically. It has seemed probable to investigators that the tocopherols, in exerting their specific effect upon collagenous structures, may inhibit enzymes, such as hyaluronidase, within the cell body, but it is reasonable that this effect may well be linked up to its known anti-oxidant activity as in Its "sparing" function on vitamin *A* or other synergens. That the mixed tocopherols have little bactericidal activity is shown by its failure, when applied locally, to control bacterial content of several cases of ulcers.

"In moderate cases," advise Burgess and Pritchard, "a daily dosage of 100 to 300 mgm. of tocopherol by mouth is indicated, whereas in more marked case: a dosage of 600 mgm. of mixed tocopherols gives better results, preferably on an empty stomach and a relatively low fat diet. It would seem logical that a maintenance of tocopherol levels in the tissues is necessary in order to maintain its good health. Therefore, it is suggested that vitamin E be continued in 100 to 200 mgm. doses daily over a period of time. This might be added to by administration of non-defatted wheat germ by mouth.

VITAMIN E AND AMYOTROPHIC LATERAL SCLEROSIS

Amytrophic lateral sclerosis is a chronic disease involving, essentially, the old and new motor systems, namely the anterior horn cells and the pyramidal tracts. The disease, which affects older adults and persons past middle age, is regarded as a degenerative one of unknown etiology. It is relentlessly progressive. It generally begins in the upper extremities with loss of power, atrophies and fibrillations, and when it ascends,

as it generally does, to the medulla it terminates fatally. The duration Is from one to two years, longer if the disease begins in the lower extremities. As far as Is known, there are no remissions, no standardized, accepted treatment and no cure. The neurologic characteristic of the disease is a combination of paralysis and atrophy with increased, deep reflexes. In every other disease in which the anterior horn cells arc affected, the deep reflexes are invariably lost in the affected limb. In amyotrophic lateral sclerosis, because the pyramidal tracts arc also involved, the reverse is true. Because of its insidious nature, the patient at first pays no attention to the disorder or, is treated for a long time before it is recognized. This is the reason why the neurologist rarely sees early cases. When they come to him, they are usually fairly well advanced.

The following two cases are described because they are the first instances within the author's knowledge, in which amyotrophic lateral sclerosis yielded to treatment. (These facts were obtained after careful perusal of hundreds of papers and reports including assistance from the Neurological Service of Mount Sinai Hospital, New York City - author.) The results of treatment have been so spectacular as to make constraint almost impossible. Experimental work on animals has shown that, once the anterior horn cells are destroyed because of vitamin privation, they cannot be repaired, and the degeneration is progressive. If, however, the condition is recognized early and treated promptly, there is the possibility not only of arresting the process but of reversing it. This points to the need of treating amyotrophic lateral sclerosis in its early stages, before irreversible damage is done.

The treatment of amyotrophic lateral sclerosis with vitamin E, more particularly the alpha-tocopherol factor, was undertaken with the following considerations as a goal: It has been known for a long time, that the privation of vitamin K will cause atrophies and paralyses in young rats. The paralyses were observed in the course of experiments on sterility. More recently, Ringsted reported on paresis on old rats suffering from chronic avitaminosis. A year later, Lipshutz described degeneration of the nervous system as the result of privation of vitamin E. He showed that the posterior columns and pyramidal tracts, as well as the anterior horn cells and possibly those of the intermediolateral gray, were affected in vitamin E privation. In company with Einarsson, Ringsted raised several

interesting, practical and theoretical questions, among them the fact that the pyramidal tract in the rat is situated in the dorsal and not the lateral column of the spinal cord. What is Dertinent to our discussion is that, they demonstrated degeneration of the pyramidal tract and anterior horn cells, and spoke of the analogy to amyotrophic lateral sclerosis in man.

While it is known that vitamin E privation can cause paralyses of muscles, it was not known what the antisterility factor had to do with it. Einarsson and Ringsted raised the question whether there was not also another factor, the privation of which caused degeneration within the nervous system. Thanks to the work of Evans and his collaborators, it has become known more recently that whole wheat germ oil contains alpha and beta tocopherols, and that alpha probably has to do With the mUSCular atrophy.

Report of Cases

Case 1. A man, aged *52* complained of loss of power in the left hand and tiredness of both legs, He had been perfectly well up to the present illness, although lie stated that he had had an occasional tingling feeling in the left forefinger, and aches in the left scapular region for years. In July 1950, he began to have weakness of the left hand, the loss of power gradually becoming so marked that he practically lost the use of the hand. About a week or so before undertaking treatment on Oct. of the same year, his legs began to tire. There were no other complaints; no fever, no visual disturbances, no gastrointestinal symptoms, no urinary disturbances, no loss of libido, no history of trauma, no major or even minor illnesses.

Neurologic examination was entirely negative except for the following: The biceps, triceps, and wrist jerks were much more active on the left side than on the right, the left knee jerk was greater than the right and the left abdominals were weaker than those on the right, but the ankle jerks were equal, and there was no pathologic reflexes. The left planter reflex was not present. There was marked weakness of the fingers of the left hand, partial left wrist drop, and weakness of the muscles of the forearm and shoulder girdle. There was marked atrophy of the small muscles of the hand, the interoseei and the thenar and hypothenar eminences. The paresis was flaccid. A few fibrillations were seen occasionally in the left arm and shoulder muscles. There were no sensory disturbances. The cerebral nerves were entirely normal. There was asymmetry of the facies with slight lagging of the left corner of the mouth, actually of

no significance as the patient had it all his life. (He had been receiving vitamin B therapy for some time and with no effect).

He was admitted to the hospital (name omitted), where all the neurologic observations were confirmed. The serologic reactions were negative. The spinal fluid was normal and there was no block. The blood was normal, and X-ray examination of the skull, chest and cervical spine showed no pathologic conditions. A short time before coming to the hospital, the patient had been given whole wheat germ oil. As soon as studies were completed, he was given 300 mgm. of alpha-tocopherol, three times daily. Improvement began almost immediately. After a few weeks, the patient regained sufficient power to button his coat, make his tie and use his hand in eating. The wrist drop began to clear up. Once he ran out of the vitamin E and was without it for three days; weakness began to return, but immediate recovery set in at once on resumption of treatment. Four Weeks Later administration of the alpha-tocopherol was stopped on purpose for five days and again the weakness returned, only to disappear a: soon as the oil was: re-administered. Today he has good power in his hand, and the interosseous spaces and the thenar and hypothenar eminences are filling normally.

Case *2.* A woman, aged 36 was first examined in August 1950 with the complaint of weakness in both arms and legs of one year's duration. At first there was difficulty in walking; soon the hands and arms became weak, so weak in fact that she could no longer feed herself. Much later dryness of the throat, and difficulty in swallowing set in. There were no visual disturbances, no impairment Of urinary function and no other complaints. For years the patient had partaken of few green vegetables.

The positive neurologic observations were fibrillations in the muscles, extremities, trunk and tongue, and marked atrophy and loss of power in the muscles of the hands, feet, and tongue, and some of the arms and legs. All the deep reflexes were hyperactive and there was bilateral clonus. The spinal fluid, including dynamics, was normal, and so were the blood chemistry and the serologic reactions. X-ray examination of the spine was negative. There was no doubt of the diagnosis of amyotrophic lateral sclerosis.

The patient was given vitamin H and a diet fairly rich in all vitamins. Within one month she appeared to feel subjectively

better and the fibrillations seemed less. In October she was given alpha-tocopherol, 300 mgm. three time: daily, In addition to vitamin B. The difficulty in swallowing gradually subsided by the time of her discharge in November. When seen one month and two months later, the atrophy and fibrillations of the tongue had disappeared and her general strength increased to the extent that from being confined to bed, she could walk with assistance; in fact she returned for follow-up observation and advise alone and without help.

Although only two cases are cited, the prompt response to vitamin E, seems to be of unusual significance. It is of great importance that full recovery occurred in an early case, and that the atrophy of the tongue, which was the youngest symptom in the older case, yielded soonest. This is in accord with what has been observed in experimental animals. Of even greater significance is the fact observed on two occasions, when the administration of the tocopherols was stopped, that the weakness returned and, when treatment was resumed, recovery promptly resulted. This is almost a crucial physiologic and clinical experiment, indicating that the recovery was the direct result of the treatment.

There are a few theoretical questions worth considering. One i-the fact that aside from the pyramidal tract and anterior horn degeneration, there is also involvement of the posterior sensory columns in the experimental animals of Einarsson and Ringsted. Posterior column degeneration does not, as a rule, occur in amyolroohic lateral sclerosis, but it so happens that Wechsler reported cases In which there was posterior column involvement. Another point is that the pyramidal tract in rats is not quite comparable to the pyramidal tracts in man. It would therefore be necessary to try vitamin E privation in higher animals. Experiments are being undertaken with monkeys deprived of vitamin E and treatment with wheat germ oil and tocopherols instituted.

There seems to be good evidence of the relation of vitamin E privation to the dystrophies. The muscle degeneration in dystrophy differs from the atrophy which is secondary to loss of the anterior horn cells. It is possible, in view of the disappearance of cells from the Intermediolateral horns of the cord, that the trophic sympathetic nerves may have something to do with the dystrophies. In any case, treatment of the

dystrophies with vitamin E is definitely indicated in the hope of curing early stares, and arresting old ones.

Although the relapse in case number one, after withdrawing the vitamin E and the prompt recovery after re-administering it, it is almost absolute proof of the efficacy of the treatment. As of now, the treatment is being carried out on a large series and from present indications, results will be even more gratifying. It is of interest, first, that ordinary good diet may be deficient in vitamin E, that some persons, for various reasons, do not partake of those articles of diet which are rich in vitamin E, and that some individuals have gastrointestinal disturbances before the advent of the disease. This points to the probability of malabsorption despite adequate vitamin E in the diet. Indeed, some patients give a history of abdominal distress and restricted diet for a year preceding the onset of the illness. This parallels, more or less, the condition in vitamin E privation which results in neuropathies. It is therefore necessary to obtain complete dietary histories in every case, particularly as to likes and dislikes of food.

In view of the fact that there is, or seems to be, poor absorption from the gastrointestinal tract in cases of amyotrophic lateral sclerosis, and that one cannot in any event gage the amount it has absorbed, the need of administering vitamin E parenterally becomes extremely important.

COMBINED USE OF VITAMINS E AND C

A large number of individuals suffer from illness and physical incapacity which persists in spite of conventional or specific treatment. The Caul I Of many of these disabilities are unknown. It may be conjectured that some of them are on an infectious basis; Others may be metabolic or physiochemical disturbances not clearly understood. Still others may be due to chronic food or vitamin deficiences, or possibly one or more of these combined.

Recently, it has been suggested by Steinberg, that many muscular pains of long duration may be due to chronic deficiency of vitamin E, whether by failure to absorb, or failure to receive this vitamin from the diet.

The effect of minor deficiencies of very long standing has not been appreciated. Only recently has it been revealed that, persons in chronic ill health show a general reduction of oil-

soluble vitamins in the plasma fraction of the blood.

With these considerations in mind, it was thought desirable to try the effects of vitamins E and C (ascorbic acid was included because it, with tocopherols, is responsible for the chemical reducing power of the blood) on a number of patients who were suffering from long-persistent disorders of miscellaneous origin and character, the causes of which were not manifest, and who had these two important points in common: a reduction or displacement of diet over a long period; and muscular pain?: or aches, also of long duration.

To accomplish this, 14 such Individuals were subjected by Williams, of New York, to the long continued use of the vitamins E and C. These patients were grouped as follows:

Those with diabetes complicated by persistent pain in the arms or legs, or both, usually worse at night.

Non-diabetic individuals with similar pains.

Those with diabetes and osteoarthritis.

Nondiabetic individuals with arthritis and Heberden's nodes (hard nodules about the size of a pea or smaller, on the terminal phalanges of the fingers).

There was also a small group of miscellaneous maladies of unknown origin, long-resistant, and unrelieved by conventional treatment. Terminal arteriosclerotic disease, allergies, and fat dystrophy were the dominant physical signs of this group, which was used mainly for control purposes.

Each of these individuals was given, at breakfast, a polyvalent preparation which contained the accepted minimal daily requirement of vitamins A, D, C, and B. At noon each was given 25 mg. of Vitamin E and 50 mg. of vitamin C, and at the evening meal 40 mg. tocopherols. This dose represents a trebling of this estimated normal daily intake of vitamin E. The dose, however, is much smaller than the curative doses often recommended by Meller and Hosenberger (100 to 300 mg. per day). The treatment was continued in each case from one month to a year Or more. Routine clinical observations were made at monthly intervals, or more often when indicated.

In the group with diabetes plus neuromuscular pains, 20 cases were observed. Of these, 4 obtained definite but not complete relief, while in 5 cases there was complete relief of longstanding pain. In 11 cases the results were either negative or so slight as to be doubtful. Whether these cases would respond to larger doses is not established.

In the second group of non-diabetics with similar nerve, muscle pain, there were 6 cases. In 2 of these results were negligible, while in 4 cases the relief of pain was definite.

In the third group, diabetes complicated by arthritis, there were 4 cases, 2 of which obtained no relief, while 2 reported diminution of pain.

In the fourth and last group, of 5 cases with arthritis and Heberden's nodes, 3 cases were not benefited while in 2 the symptoms definitely subsided.

In this series just enumerated, there were 35 individuals suffering from illnesses, in most instances of several months' or years' duration, characterized by pain which seemed to be related to the neuromuscular system. A number of these secured partial or complete relief from pain, apparently from the addition of special vitamin preparations to the diet.

In some carefully controlled cases, the relief obtained was so dramatic and sustained as to afford highly suggestive evidence that the tocopherols plus ascorbic acid have helpful, therapeutic properties. In a number of similar cases, the relief from pain, although positive, was only partial and incomplete, suggesting the desirability of further study and possibly treatment with larger doses.

The main purpose for including this report is to call attention to the tocopherols as possible factors in certain obscure neuromuscular disturbances, which cause both pain and disability. It can scarcely be questioned that these painful neuropathies associated with diabetes are among the baffling mysteries of modern-day healing arts. And while, of course, it has not been established clearly, it is a hypothesis that the underlying cause is a deficiency disturbance. The use of large doses of vitamin B has yielded variable but usually disappointing results, according to Lawrence, Oakley and Mason. The fact that a small but significant proportion of these patients has been benefited from moderate therapy with vitamin E, suggests that deficiency of this vitamin may be one of the accountable factors in muscular pain.

VITAMIN E IN PHYSIOLOGY AND NUTRITION

The Strong but as yet, indirect evidence that vitamin E is important in practical nutrition, may be summarized in this simplified manner: (a) Cases have been found where traditional diets for domestic animals are low enough in vitamin E to

injure seriously their health, and vitamin E must be added to the purified or synthetic diets used for studying the nutrition of Laboratory animals; (b) The "requirement" of vitamin E by humans, estimated from the "requirement" Of vitamin E by laboratory animals, is about equal to the average quantity available in all food, but the unequal distribution of this vitamin makes it seem likely that many persons get very much less than the "requirement"; and (c) A group of underprivileged persons was found to have an average tocopherol blood level appreciably below that of normals.

The problem of studying the human requirements of vitamin E is complicated by the possibility that the need for this vitamin may be increased at certain periods during development. For example, Kaunitz has found, by measuring growth and testicular development, that rats have a critical requirement during the third week of life.

Like the rat fetus, the human fetus may have a very low content of tocopherol compared with that of the mother. It has been found by Varangot and by Kofler, that the blood level of tocopherol of the human fetus is much lower than that of the mother. The recent study of Straumfjord and Ouaife suggests that there may be a natural mechanism by which entry of tocopherol in the fetus is encouraged. They found, as did the other workers, that the vitamin E level of cord blood of infants at birth is one-fifth that of the level in the venous blood of the mothers. But the average plasma vitamin E level of mothers at term is 65 % higher than that of non-pregnant women.

The clinical importance of vitamin E with respect to reproductive troubles and muscular degenerations, is still of interest and is still disputed. Skelton and Shute found that experimentally produced purpura in dogs as well as human purpura, could be improved or cured with 200 to 400 mg. of a-tocopherol daily. Vogelsang and Shute, while studying this treatment of purpura, noticed an improvement in the heart condition of certain subjects. Further studies of the treatment of heart patients showed that tocopherol was distinctly beneficial to patients having congestive heart disease and the anginal syndrome; exercise tolerance was increased and anginal pain diminished or abolished. These disclosure have caused other workers to make similar studies, but while these are being carried out, it is interesting to I peculate on the high tocopherol content of normal heart tissue, the earlier mentioned

difference in enzyme action of normal and E-deficient rats found by Telford, and the report of Gullickson and Calverley thai many cattle on a vitamin E-free diet, died suddenly from heart failure.

VITAMIN E IN THE TREATMENT OF DUPUYTREN'S CONTRACTURE

Vitamin E is of great value in the treatment of early and moderately advanced Dupuytren's contracture (a form of fibrositis and contraction of the palmar fascia causing permanent flexion of one or more fingers). No surgery is required in these cases. It is indicated only in prolonged instances in which the contracture has produced permanent changes. This is particularly true if calcification has occurred and if such is the case, vitamin E should be used in conjunction with surgery. Steinberg recommends the optimum dosage of 300 mg. of vitamin E daily, given in divided doses of 100 mg. three times daily or until maximum improvement occurs, and then a maintenance dose of 1 mg. per kilogram of body weight. The blood plasma vitamin E level is normal in primary fibrositis, and the plateau curve obtained in vitamin E absorption experiments and the creatinuria indicate abnormal tissue utilization of the vitamin. Extensive liver disease, such as is found in portal cirrhosis, affects both the absorption and storage of vitamin E. Being a fat soluble vitamin, E behaves similarly to vitamin A, particularly when a liver condition is known or suspected to exist.

Dupuytren's contracture may be the result of an inadequate diet, low in vitamin E content, and as such should be carefully considered. Patients suffering from this disease have been administered vitamin E orally for terms of from three to four years, in a maintenance dose of 1 mg. per kilo with no untoward effects.

MUSCULAR DYSTROPHIES AND NERVOUS DISEASES

Among the great researchers responsible for recent discoveries and advances in the use of vitamin E, is Bicknell of England. His interest and work with children suffering from a host of muscular nervous diseases, are a matter of record, and because of the enormity of his efforts, we have decided to include? portions from this scientist's papers and notes, made over a

prolonged period.

In selecting in: lance "I unusual recoveries, wo have chosen to cite 26 cases treated by Bickneii, with vitamin E. Of these 26, 18 were Muscular Dystrophies, 4 were cases of Amyotrophic Lateral Sclerosis, 2 Tabes Dorsalis, 1 Peroneal Muscular Atrophy, and 1 a case of Amyotonia Congenita.

In the group "I the myopathies, the results of treatment with vitamin E were truly remarkable. Every patient who was treated for more than six weeks improved, except one who was mentally deficient. When it is remembered that these cases should have gotten worse, or at least remained the same, such definite improvement in 12 cases out of 13 must mean that this treatment promises success in a disease which has always, until now, "been hopeless. " 'Hie slowness, however, of the recovery and therefore the necessity for prolonged treatment must be emphasized. In one of the 26 Cases cited, recovery has continued for eighteen months and has Shown no sign of stopping. How far it can go remains to be seen, but there is no reason why patients in an early stage should not recover completely, provided that they continue to receive treatment. The diagnosis should be definite before treatment is begun; otherwise an apparently normal child may continue to be treated to guard against a relapse of a disease he may never have had.

Even bed-ridden patients have shown improvement. Since these children often have a long period of growth still before them, it seems possible that they may recover sufficiently to lead comparatively normal lives.

"Not enough patients with amyotrophic lateral sclerosis have been seen during treatment," states Bicknell, "for the results to be definite, but on the whole, I think they are promising. One case in whom the disease is arrested and who feels normal again, has no obvious involvement of upper neurones. Of the group, two patients who died had advanced bulbar involvement before treatment began. "

"The two cases of tabes were too advanced for the negative results to be of any value, but I still believe vitamin E will be found of value in this condition. The patient with peroneal muscular atrophy has not been treated long enough for any conclusions to be drawn. The very young girl with amyotonia congenita appears to have been greatly improved. " (Bicknell)

It seems reasonable to suggest that, in all degenerations of the

muscular or nervous systems, such as disseminated sclerosis, a large quantity of vitamin E should be of value, for though a deficiency may not be the cause, yet a sick cell should have an abundance of what is necessary for its life. It may also be that in children who have a diet rich in vitamin E the anterior-horn cells would be more resistant to infantile paralysis; hence, at least during epidemics, the vitamin should be used as a protection.

The clinical results observed by Bicknell, and reported here, strongly confirm the deductions which Einarsson and Ringsted made from their laboratory work. The discovery of the importance of vitamin E in the treatment of muscular and nervous diseases appears to be revolutionary. It opens up new lines of thought and treatment in many diseases. Indeed, it appears to be one of the great advances, in science, of the century.

VITAMIN E IN CARDIAC INSUFFICIENCY

Gatz and Houchin have shown that degeneration areas occur in the cardiac muscles of rabbits reared on vitamin E-deficient diets. A recent series of E-deficiency experiments in which vitaminD was supplied as cod liver oil in some series, confirms previous results obtained by these two researchers. Electrocardiograms of the experimental animals consistently show a reversal of the ORS interval in lead 1. (The different leads represent different views of the electrocardiogram, somewhat similar to a profile and full face photograph. In examining a tracing, we select the lead which shows most clearly the abnormalities of the wave or segment being studied, and pay less attention to those leads in which that particular complex is normal. For example, a ORS complex which is prolonged or reversed in lead 1, is abnormal even though it may be within normal limits in leads two and three.)

The portions of the heart which show necrosis of cardiac muscle are here listed according to the frequency and severity of the lesion; papillary muscles, columnar carneae, apex of heart, ventricular walls and septum infrequently atria. The Purkinje fibers appear to be unaffected. (Purkinje fibers consist of specialized cells which conduct stimuli more rapidly than does myocardial tissue, so that the bulky mass of centricular muscle is stimulated almost simultaneously and contracts more effectively as a unit.)

The affected cardiac muscle fibers may show wide contraction bands, hyaline degeneration, basophilia with the appearance of numerous droplets in the muscle fiber, and finally complete necrosis caused by the coalescence of the droplets.

Lesions which occur in the voluntary muscle of vitamin E-deficient rats were first described by Olcott, who reported that no pathology could be found in the heart. Spencer and Wilder found no change in the lipid content of the heart in dystrophic rabbits, although an increase in fat content is one of the most characteristic changes in the skeletal muscles. There are observations on record, which indicate that functional and metabolic changes may become apparent before pathological Changes appear. Hines and Knowlton found that the capacity for work could be reduced by as much as 50% in the gastrocnemius muscles of rats on a vitamin E deficient diet, at a time when only a few fibers showed hyaline changes. Numerous workers have demonstrated an increase in the resting oxygen consumption of dystrophic muscles from vitamin E deficient animals, amounting to 200 to 400 per cent in some cases. Recently, Kaunitz and Pappenheimer have shown that this increase becomes sizeable In the muscles of vitamin E deficient young rats before any pathological changes are detectable, and Houchin, in unpublished experiments, has found that the oxygen consumption of heart muscle slices from E deficient hamsters, may be increased as much as 40 per cent.

Recent observations in literature made available to this author, Suggest an explanation for the heart to resist functional deterioration, Until the dystrophy is well advanced in the skeletal muscles. Mason has shown that heart and lung tissue from normal animals may contain twice as much vitamin E as body fat, in which fat soluble substances might be expected to concentrate, or liver, which is notable as a storage reservoir for other vitamins. That the heart may be able to retain its more adequate supply in the face of depletion elsewhere, is indicated by Hines and Mattill, who found that tocopherol added to minced tissue could not be recovered quantitatively without the addition of sulfuric acid.

Eventually, experiments by Houchin and Smith, show the heart is reduced to the failing state through a cycle of events which we visualize as follows: Depletion of vitamin *E* leads to an increased oxygen demand and a reduced capacity for work. This increased oxygen requirement is obviously

Independent of heart volume, since it has been found to occur in isolated skeletal muscle and heart slices. The reduced capacity for work, however, leads to dilatation, which superimposes a further increase in oxygen requirement.

Thus the vitamin E deficient failing heart, becomes exceedingly sensitive to any reduction in its oxygen supply. Posterior pituitary extract, through the action of pitressin (circulatory stimulation), greatly reduces the coronary flow and precipitates the crisis already described.

It is generally accepted that the failing heart, particularly if it is dilated, is more resistant to the toxic effects of the cardiac glycosides than is normal, and that a dose of digitalis, which may be of some aid to such a failing heart, may have dangerous or even fatal consequences in normal individuals, due to a reduction of cardiac output or to disturbances of the normal cardiac rhythm. Since the majority of vitamin E deficient animals, used on this series of experiments, lived for several days beyond the predicted time of death, after receiving digoxin or ouabain, ,(the latter, an African arrow poison used as a substitute for digitalis) they were obviously benefited. The actions of digitalis to which this benefit may be ascribed are first^ direct stimulation to the myocardium with an increased cardiac output and a reduction of heart volume resulting from the greater strength of systole; second, an increase in efficiency which results in a greater work out-put at a given rate of oxygen utilization.

Since it is recognized that cardiac, function may be impaired in such deficiency syndromes as beri-beri and pellagra, "we (Houchin and Smith) are tempted to suggest that vitamin E, which has come to be recognized as a specific factor in the maintenance of normal metabolism in striated muscle, may also play a role of major importance in the maintenance of normal cardiac, function in man. "

Author's license

"A great deal has been done, and much has been said and written about vitamin E. Because of a multitude of conflicting factors, opinions and even predujudices, it becomes extremely obvious that in order for this humble effort to find acceptance, all facts and statements must have an 'authoritative' source. What the word 'authoritative' may be intended to imply depends on the readers views and subsequent interpretation.

As a result, the next significant and concluding chapter must

of sheer necessity be insured, as it were, of acceptance and credulity without the possibility of being underestimated, by inclusion of records, quotations, and personal remarks by men whose investigations and studies have established them as authorities. Unfortunately, most of the work done on HUMAN heart disease has been the effort of a small, intellectual group; a group of men who have defied ridicule, discouragement and attempted suppression. They are as eminent and proficient a group as can be found. Drs. Vogelsang, Shute, Skelton and Shute, the men who, in this author's considered opinion, have advanced the science and application of vitamin E therapy to HUMANS faster and further than any others, must here be accorded their rightful plaudits; it is without hesitation that we salute these gentlemen. The following excerpts, abstracts, implications, records and general remarks are based on the works of the aforementioned scientists. Be assured that all facts have substantial basis in truth. " (Author.)

HEART DISEASE AND VITAMIN E

In previous years, many hundreds of papers, reviews and published findings have pointed to the usefulness of large doses of vitamin E in the management of varied types of heart disease. The experiences of Vogelsang, Shute, et al., covers more cases than the one hundred twenty-six reported up to this date, but we are using the data of these papers for this further analysis, since later experience merely lends the weight "I confirmation. All records we shall present are those of private patients, personally studied and observed by Vogelsang, Shute and their co-workers. For sake of more concise, tabular summary, these results will be listed in Tables one, two and three, after a brief discussion of the more common symptoms and treatment methods employed.

Angina

The relief Of pain in anginal cases is usually both rapid and nearly or quite complete. Excessive exertion may still bring on cardiac pain, but the amount of activity required to do so is greatly increased. In a few instances, prolonged treatment was necessary before the pain was eliminated, but these patients were in the great minority. One patient responded only after five weeks of therapy, followed by a powerful intramuscular injection; the results which followed were then very good indeed.

One sixty-five year old patient with a history of two coronary occlusions, would feel severe boring precordial pain after such slight exertion as moving slowly from one chair to another. This pain would last up to one and a half hours and previous treatment, of necessity, included morphine lor temporary relief. He was given ten doses of 25 mgm a-tocopherol per day, and after ten days showed no relief. The treatment was then changed to ten doses of 50 mgm tocopherols and again experienced no relief. An increase to twelve doses was again without effect but when the dosage was increased to fourteen portions of 50 mgm daily, his relief was prompt and complete. This patient no longer experiences pain or discomfort provided he moves about with caution and without hurrying. It has been noted repeatedly, especially in anginal cases, that there is an optimal dose, perhaps a therapeutic threshold, for each patient; below that threshold little or no help is obtained. "This, " says Vogelsang, "reminds one of certain types of endocrine therapy. "

Table One:

Eighty-four cases having anginal pain as a common symptom.

	Cases	Percentage
Complete relief from pain	6	7
Marked improvement	38	45
Some improvement	37	44
No improvement	2	3
Demise	1	1
	84	
Total		

Cases of acute rheumatic fever, although few in this Vogelsang, Shute series, rank among the most striking results. Vitamin E combined with a mild hypnotic seemed to restore these patients to a clinical normal in a remarkably short time. "The final effect of our treatment upon heart enlargement and valvular disease cannot as yet be finally assayed," states Shute. " Probably little is to be expected of it in either of these respects for obvious reasons. But there have been indications of an improvement in cardiac contour and better myocardial function

in some of these patients who have been followed for several months. "

Table Two:

Twenty-eight cases of rheumatic heart disease with one active.

Main Signs and Symptoms	Cases
Precordial pain	8
Dyspnea	10
Auricular fibrillation	11
Cardiac enlargement	17
Valvular lesions	25
Pulmonary congestion	4
Ankle edema	7

	Number of cases
Complete relief of symptoms	0
Marked improvement	15
Some improvement	12
No improvement	1
Demise	0
Total	28

Hypertensive Heart

The hypertension present in these patients was, of course a limiting factor in end-results, as vitamin E appears to be of little or no benefit to hypertension per se. However, it is to be noted that in hypertensive heart disease the blood pressure was usually reduced slightly and on occasion very noticeably. The patient often experienced considerable relief from the type of symptoms usually ascribed to high blood pressure. The decompensated hypertensive heart appeared to respond as well as decompensation on any other etiological basis. The age of this group of patients and the duration of the hypertension were other factors strictly limiting the benefits which vitamin E therapy could offer them.

Table Three:

Sixty-six cases of hypertensive heart disease.

Main Signs and Symptoms

		Cases
Pain		39
Dyspnea		51
Aurlcu lar fibrillation		10
Cardiac enlargement		10
Pulmonary congestion		12
Ankle edema		32
	# of cases	Percentage
Complete relief of symptoms	0	0
Marked improvement	28	42
Some improvement	28	43
No improvement	2	3
Demise	8	
Total-66		
Arrythmias		

As might be expected, some degree of improvement in irregular pulses has been observed in patients receiving vitamin E therapy. Many cases of auricular fibrillation were unaffected. However, a fair number of individuals of this type exhibited long runs of regular pulse beats, with only an occasional break into the former rhythm; a few patients appeared to lose their fibrillation entirely. One such man who regained a regular rhythm, had had a known digitalis-resistant auricular fibrillation for five years. Although he was dying of decompensated rheumatic heart disease, his pulse rate became regular for two days when heavy dosage E was instituted.

A female patient, aged fifty-seven, who exhibited ectopic beats, quickly responded to vitamin E as administered by Dr. Shute, and almost any ratio of extra heart beat to regular pulse could be induced by simply varying her dosage. A few bradycardias were accelerated.

Electrocardiographic Studies

In nearly all of the cases studied by Vogelsang, Shute and

Shute, electrocardiograms were taken before therapy was begun, and at two, four and six weeks after treatment had been instituted. Except in two active rehumatic cases, no startling changes were noted. There were, however, certain slight changes in many instances, (a) Two cases showing a prolonged P-R interval reverted to an interval of less than .20 seconds, (b) Depressed S-T segments became less depressed or normal, (c) Inverted or isoelectric T waves showed respectively less inversion or became positive, (d) Three bundle branch blocks were unchanged.

One would scarcely expect marked changes to occur in such a short period of observation. It may be that changes will be seen in abnormal electrocardiograms in six months or a year's time.

Toxic Relations

Toxic reactions are very rare and mild, as could be expected of a fat-soluble vitamin, present to some degree at least, in every person' s diet.

In this extensive use of vitamin E in obstetrical work during the past twenty-three years, Evan V. Shute has seen many classic examples of a generalized maculopapular, itchy rash. This would disappear rapidly when the vitamin E was discontinued. There were no examples of such reaction in the cardiac series.

Some patients, notably women, complained of nausea when large doses were employed. Several developed diarrhea on vitamin E therapy, but this too was transient and responded quickly to a mild alkali.

One patient, as well as a doctor, reported an elevation of a previously normal blood pressure. Perhaps this is related to improved myocardial tone (?).

Five cases in this series developed rapid pulses on E-therapy, but returned to normal either with the help of small doses of digitalis, or with cessation of E administration and then a gradual return to larger doses.

Toxic reactions or idiosyncrasies appear to be very rare on the whole. Some of the patients have been given a daily dose of 600 to 700 mgm. of E for months, without any harmful effects appearing. One had 1400 mgm. per day for two months, with no untoward reactions. It should be noted that larger doses given to preeclamptic women at or near term, may be dangerous.

HOW DOES VITAMIN E AFFECT THE HUMAN HEART?

(a) It affects blood vessels: This was indicated by early biopsy studies by Shute, on leukoplakia vulvae, where massive K therapy seemed to be responsible for increased local circulation in the vulva, the local mobilization of degenerative material, and either the reopening of old capillaries or the proliferation of new.

The speed with which many anginal and coronary patients respond to E therapy suggests a vascular effect. Often this takes as little as four to seven daySi

Stuart reveals In a personal communication, that he has observed rapid Improvement In three cases of intermittent claudication treated will) vitamin E, Results by Shute, in several acute cerebral accidents, pointl in the same direction. He reports, "prompt and marked Improvement in the circulation in the legs of patients who had Incidental varicose ulcers and varicose eczema."

A most striking case was that of a woman, fifty-seven years of age, who had had Buerger's disease for more than eight years. During thai period her feet and legs were treated in a glass boot. She had repeatedly been threatened since that time, with gangrene of the toes of both pedal extremities. However, great care and regular Beurger exercises managed to avert frank gangrene. In the last two years there has been marked edema of both ankles,, and a constant cyanosis of the feet and ankles. On June 16, 1956 she was given 200 mgm.of vitamin E per day, orally. Within three days time she complained of such severe "pricking" sensations in all her extremities that she could not sleep. This tingling persisted for two weeks, gradually becoming less annoying. By the end of the first week, large purpuric areas began to appear on her thighs, legs, arms and trunk, but were more numerous on the extremities. It was equally obvious that the edema was decreasing rapidly and that the legs and toes were returning to normal color. Sensation returned to her feet and toes, and she was no longer obliged to sit on the floor to pick things up, but could kneel in a normal manner. This latter change was almost complete within five weeks time. Present status, normal.

It affects the myocardium: This affect, of course, may be secondary to an improvement in local capillary circulation,

but may also be due to a direct effect upon the cardiac muscle. Such an influence could be inferred from the pioneer work of Einarsson and Ringsted. The more recent observations of Steinberg, suggests that even fibrous tissue is affected by vitamin E; in scarred rheumatic or coronary hearts, this observation may be pertinent. Mason, has shown that the heart muscle has a higher concentration of E than even body fat and liver. Presumably the storage in this muscle bears some relation to its availability for function. Emmels and Mason, have demonstrated myocardial degeneration in the vitamin E-deficient rat, and have found that although this is also true for the monkey, vascular degeneration overshadows it in the latter species. Both types of degeneration are found in the vitamin E-deficient hamster.

It may influence the pace-maker of the heart: The effect vitamin E has upon certain disorders of conduction, such as lengthened P-R interval, or on ectopic beasts or fibrillation, while not consistent, is enough to point in this direction. It is possible, of course, that any such effects as do occur are due to changes in the fibromuscular tissues of the heart, or increased muscular tone.

(d) It may influence the thrombotic features of coronary disease by improving collateral circulation in the ischemic area: Skelton and Shute* s observations on the effect of vitamin E in controlling a thrombocytopenic purpura, open up a relevant line of thought. Paterson has postulated that, coronary and cerebral thrombosis begins at the site of small subintimal hemorrhages, in the coronary or cerebral vessels respectively. Perhaps some or many of such hemorrhages are on a purpuric basis. If so, and E can control certain purpuras, it may prevent the spread of such thromboses, promote their resorption, and even prevent their recurrence. Experience with acute and even months-old cerebral thrombosis, and with acute femoral thrombosis, lends support to these latter conceptions. There may even be a rapid resolution of thrombi directly due to vitamin E.

ALPHA TOCOPHEROL DOSAGE

RECOMMENDATIONS ACUTE CORONARY THROMBOSIS:

300 mg. per day started as soon as possible and maintained.

CORONARY THROMBOSIS:

300 mg. to 500 mg. daily.

ANGINAL SYNDROME:

Not less than 300 mg. per day. CHRONIC RHEUMATIC HEART DISEASE: ACUTE RHEUMATIC FEVER:
300 mg. daily.
PHLEBITIS — THROMBOPHLEBITIS:
300 to 600 mg. daily.
HYPERTENSIVE HEART DISEASE:
200 to 300 mg. daily.
DIABETES MELLITUS:
Same schedule as for cardiacs.

LATE TOXIMIA OF PREGNANCY:
For use in pre-eclamptic up to 150 mg.

ABHUPTIO PLACENTA:
150 mg. daily for 3 to 5 days. Thereafter 100 mg. daily.
LACTATION:
100 mg. daily.
THREATENED HABITUAL ABORTION:
100 mg. daily for 2 to 3 days. Thereafter at least 30 mg. daily until term.
FIBROSITIS — MYOSITIS:
1 50 mg. daily. PURPURAS:
300 to 900 mg. daily. INDOLENT ULCERS:
300 to 500 mg. daily. NEUROMUSCULAR DISORDERS:
200 to 400 mg. daily. DYSMENORRHEA:
30 mg. daily for one week or ten days before start of menses.

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