Abstracts of Current Literature

VITAMIN E

The most potent vitamin E compound is alpha-tocopherol. The synthetic alpha-tocopherol acetate is the standard for vitamin E activity, 1 mg. representing the international unit of the latter. The physiologic action in man is not known but in animals a variety of changes are observed in vitamin E deficiency states. The administration of large amounts of unsaturated fats has been shown to reduce vitamin E activity in man and in experimental animals. In animals, this deficiency is a cause of encephalomalacia; it is possible that the same effect may be observed in man.

Relationship Between Vitamin E in the Free and Acetate Form Present in the Plasma After Parenteral Administration of Tocopherol Acetate. G. Rindi and V. Perri. *Internat. Ztschr. Vitaminforsch.*, 28: 274, 1958.

A single dose of 300 mg. of DL-alpha-tocopherol acetate in aqueous emulsion, administered intramuscularly to a human subject, engenders a rapid increase of the plasma esterified tocopherol content which continues until the eighth hour following the injection, and drops thereafter until the forty-eighth hour.

The free tocopherol instead increases manifestly only from the eighth hour up to the thirty-second hour, and remains unchanged at the levels reached up to the forty-eighth hour.

It is concluded that aqueous emulsions of alpha-tocopherol are a much better form of parenteral application of vitamin E than are oily solutions as they produced a significant rise of the serum level of vitamin E.

AUTHORS

Ineffectiveness of Factor 3—Action Selenium Compounds in Resorption-Gestation Bioassay for Vitamin E. P. L. Harris, M. I. Ludwig and K. Schwarz. *Proc. Soc. Exper. Biol. & Med.*, 97: 686, 1958.

Purified factor 3, which is characterized by an organic substance containing selenium, prevents certain deficiencies attributed to lack of vitamin E, such as degeneration and necrosis of liver, heart, muscle and kidney particularly of rodents, and exudative diathesis of birds. Since resorption of fetuses during pregnancy is thought to be specifically due to vitamin E deficiency, a gestation bioassay was made in rats in order to determine whether or not the selenites might counteract the lack of tocopherol. Weanling female rats were fed a diet low in vitamin E; when they had reached a weight of 150 gm. they were mated with males fed a stock diet and given supplements of either tocopherol or high doses of test substances such as selenocystin, sodium selenite or selenium acid on each of five consecutive days of pregnancy. The animals were killed on the twentieth day of gestation. While tocopherol counteracted the harmful effect of the deficient diet, no effects were observed after administration of the selenium compounds. Thus factor 3-selenium is not identical with tocopherol, although both are essential for a complete diet.

M. SILBERBERG

Vitamin E deficiency in animals produces degenerative changes of germinal epithelium; in females, there is an increase in stillbirths and a resorption of fetuses. Degeneration of striated muscles and cardiac muscle with creatinuria occurs with prolonged deprivation. The dystrophic changes observed in animals have been compared to muscular dystrophy in man.

Effect of Vitamin E Deficiency on Creatine Phosphokinase of Heart and Skeletal Muscle. W. O. Read and S. Nehorayan. *Am. J. Physiol.*, 196: 1286, 1959.

A quantitative determination of creatine phosphokinase activity of heart and skeletal muscle has been

made in early and severe vitamin E deficiency in the rabbit. This study revealed that early vitamin E deficiency resulted in an increase in creatine phosphokinase activity of skeletal muscle but decreased the enzymatic activity of the heart. Severe vitamin E deficiency resulted in a decrease in creatine phosphokinase activity of both skeletal and heart muscle. 17-Hydroxycorticosterone, administered in small doses, resulted in an increase in enzymatic activity of skeletal muscle but no change in heart muscle. Large doses of 17-hydroxycorticosterone caused a decrease in the creatine phosphokinase activity of both heart and skeletal muscle. Normal male rabbits exhibited a lower enzymatic activity than female animals, a difference which, in part, was due to testosterone. AUTHORS

Effects of Selenium and Vitamin E on White Muscle Disease. O. H. Muth, J. E. Oldfield, L. F. Remmert and J. R. Schubert. *Science*, 128: 1090, 1958.

White muscle disease is a myopathy in lambs and calves which results when legumes from certain areas are fed during gestation. When 100 International Units of alpha-tocopherol were fed daily to the animals on a basal ration, sixteen of the twenty lambs were affected with white muscle disease. However, when 0.1 part of selenium per million was given, it appeared that selenium had a definite protective pharmacodynamic effect in this disease under the conditions of the experiment. As the authors suggest, a more comprehensive and critical investigation should be made of the role of this element in white muscle disease and other myopathies in animals and in man. S. O. WAIFE

Effect of Short-Term Vitamin E Deficiency on Guinea Pig Skeletal Muscle Myoglobin. A. D. Bender, D. D. Schottelius and B. A. Schottelius. *Am. J. Physiol.*, 197: 491, 1959.

Myoglobin concentration was determined in gastrocnemius and masseter muscles of guinea pigs maintained up to fifteen days on vitamin E-deficient and vitamin E-supplemented diets. A statistically significant increase in myoglobin was noted in muscles of animals on the deficient diet for fifteen days. That the increase was real and not apparent was attested by studies of total nitrogen, non-collagen nitrogen, percentage of solids and muscle wet weight, all of which were the same in control and experimental muscles. Histological sections and creatine excretion studies confirmed the impression of mild, incipient nutritional dystrophy. AUTHORS

Serum Proteins, Lipoproteins and Glycoproteins in Muscular Dystrophy of Vitamin E Deficiency. H. Oppenheimer, S. Shulman, S. Roberts and A. T. Milhorat. *Proc. Soc. Exper. Biol. & Med.*, 97: 882, 1958.

An investigation was made to determine whether or not the changes in serum lipid patterns known to be produced in animals by vitamin E deficiency are associated with changes in serum proteins. Rabbits were fed a vitamin E-deficient diet from which all traces of the vitamin had been removed by oxidation with ferric chloride. Control animals received the same diet with supplements of DL-alpha-tocopherol, 6 to 7 mg. in oil, twice weekly. Similar doses were used to treat established deficiency which was manifest by biochemical changes and muscular dystrophy.

Vitamin E-deficient animals showed an increase in the beta-lipoprotein and a decrease of the alpha-lipoprotein level in the serum with parallel changes in cholesterol and phospholipid concentrations. There was an over-all increase in the serum cholesterol and phospholipid levels. The increase in the free cholesterol was greater than that of the esterified fraction. The total serum protein level remained constant but there was a small decrease in the albumin and an increase in beta-globulin. The concentration of serum protein-bound carbohydrate increased slightly. All these changes, as well as the increased ratio of urinary creatine to creatinine which accompanied the muscular dystrophy, were reversed by the administration of DL-alpha-tocopherol. G. WALKER

Favorable reports upon treatment of vascular insufficiency due to atherosclerosis with vitamin E have emerged sporadically for the past decade. The failure to confirm these reports by other investigators has dampened enthusiasm for this form of therapy. The following study indicates that further studies are required.

Treatment of Intermittent Claudication with Vitamin E. P. D. Livingstone and C. Jones. *Lancet*, 2: 602, 1958.

There is no agreement about the value of vitamin E in cases of intermittent claudication, and judgment is often impossible because of the difficulty of grading and classifying cases and the tendency for the condition to improve spontaneously in some cases.

Forty males without diabetes, who had had this disability for at least five years, were divided into two groups with approximately the same age distribution and the same grading of the condition by Boyd's classification. One group was given 600 mg. of vitamin E daily for forty weeks, the other group was given dummy tablets.

Three of each group dropped out of the trial; of the remaining seventeen taking vitamin E, thirteen felt great improvement; this was confirmed by exercise tolerance tests. In the control group only two of the seventeen men showed subjective and objective improvement; one recovered completely for no obvious reason, the other had popliteal aneurysms unknown at the time of selection.

Two important points emerge from this trial: (1) large doses of the vitamin are necessary, and (2) no improvement may occur for as long as several months

after treatment begins. The improvement seemed to be lasting. F. E. HYTTEN

The following contributions seem to indicate that vitamin E may function as a co-factor in several biochemical reactions. Whether these effects are the result of its well known antioxidant activity or other unknown actions remains to be determined.

Vitamin E Deficiency in the Monkey. III. The Metabolism of Sodium Formate-C^{14}. J. S. Dinning and P. L. Day. *J. Biol. Chem.*, 233: 240, 1958.

Nutritional muscular dystrophy developed in rhesus monkeys in ten months when kept on a tocopherol-deficient diet. Nucleic acids isolated from bone marrow and skeletal muscle from tocopherol-deficient monkeys injected with sodium formate-C^{14} incorporated greater amounts of radioactive carbon than the same nucleic acids from control animals. Resupplementation of the animals for three months following a ten-month depletion period resulted in a complete reversal of this lesion in bone marrow, but only a partial reversal in skeletal muscle. The rate of uptake of formate-C^{14} into desoxyribonucleic acid of bone marrow was elevated sixfold in vitamin E-deficient monkeys, but was restored to normal by resupplementation. Considerable increases were also seen in the incorporation of labeled formate into the acid-soluble purines, nucleic acid purines and creatine of skeletal muscle from deficient animals. From these results, as well as from previous studies in rats and rabbits, the authors claim that vitamin E has a role in regulating nucleic acid metabolism. M. K. HORWITT

The Role of Lipides in Electron Transport. IV Tocopherol as a Specific Cofactor of Mammalian Cytochrome c Reductase. K. O. Donaldson, A. Nason and R. H. Garrett. *J. Biol. Chem.*, 233: 572, 1958.

The experiments described in this paper indicate that the lipide co-factor of cytochrome c (glycol monopalmitate, -oleate and -stearate) isolated from bovine heart muscle acts by releasing endogenous vitamin E to "active sites" on the enzyme. Extractions of cytochrome c reductase with iso-octane causes a 90 per cent reduction in the enzyme activity while removing only 10 per cent of the total vitamin E. This amount of vitamin E is insufficient to restore the activity of the enzyme. However, several natural and synthetic lipides as well as the heart co-factor were capable of restoring enzyme activity. The same lipide substances which restored activity to the extracted fresh enzyme were also capable of increasing the amount of tocopherol removed from the enzyme by iso-octane extractions, suggesting that these substances mobilize the endogenous tocopherol. When the enzyme was aged and extracted, thereby removing a much greater amount of endogenous tocopherol, activity was restored specifically by tocopherol, while the lipide co-factor and other lipides which were capable of reactivating the fresh extracted enzyme were now ineffective. The same lipides were now inactive in potentiating the removal of tocopherol from the aged tocopherol-specific enzyme. Vitamin E, therefore, appears to be a co-factor of cytochrome c reductase. M. K. HORWITT

Inter-relationship Between α-Tocopherol (Vitamin E) and 5-Hydroxytryptamine (Serotonin). A. Meyer. *Internat. Rev. Vitamin Res.*, 29: 77, 1958.

Contrary to certain other views, experimental evidence indicates that vitamin E exerts not only a general non-specific antioxidant effect, but also a specific effect as a vitamin. It appears, like tyroxine, the substance promoting basic metabolic exchanges, to have a protective action on 5-hydroxytryptamine (serotonin) and so to prevent its premature destruction. AUTHOR

The Curative Action of α Tocopherol and of Protein Upon the Incisor Teeth of Vitamin E-Depleted Rats. J. T. Irving. *J. Dent. Res.*, 37: 732, 1958.

The incisors of young rats maintained on a vitamin E-deficient diet for thirty days showed the typical degenerative changes previously reported as attributable to vitamin E deficiency. All incisor teeth observed grossly were white and, upon histologic study, the dialuric acid test was found to be positive with a practically complete or complete absence of iron in the ameloblasts. Fibrous tissue containing large numbers of macrophages replaced the ameloblasts. In rats which received a daily supplement of 3 mg. of alpha-tocopherol throughout the experiment, the incisors remained the normal orange-yellow color and were normal histologically with negative dialuric acid tests.

In rats that were fed 3 mg. of alpha-tocopherol for varying periods from ten to eighty days after a preliminary vitamin E-depletion period of thirty to forty days, the first sign of recovery was a reappearance of iron in the ameloblasts about ten days after therapy was begun. Macrophages decreased in number as the period of therapy increased. The first appearance of the yellow pigment at the gingival margin occurred between twenty-nine and sixty-four days after therapy was begun. The dialuric acid test was faintly positive after ten days of therapy but was consistently negative thereafter. In a fourth group of rats, the protein content of the diet was increased from 9.3 to 18.8 per cent after the usual thirty- to forty-day vitamin E depletion period. The reparative results of the protein increase were virtually identical with those that had been seen in the alpha-tocopherol treated rats except that the dialuric acid test remained positive throughout the entire experimental period.

The discussion contains interesting comments on the reparative process and possible reasons for the prolonged repair period required by the enamel organ and the role of protein in substitution for vitamin E. J. H. SHAW