

TOCOPHEROLS

GRASS Review

NOV 26, 1973

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HOFFMANN-LA ROCHE INC.

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November 26, 1973

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Bureau of Foods
Food and Drug Administration
GRAS Review Branch (BF-335)
200 C Street, S. W.
Washington, D. C. 20204

Gentlemen:

Re: Tocopherols -- GRAS Review

In accord with the notice published in the Federal Register of July 26, 1973, Volume 38, No. 143, page 20053, attached please find additional pertinent published data which should be included in considering the safety of tocopherols.

Under separate cover, ten copies of this information are being supplied to:

Select Committee on GRAS Substances
Federation of American Societies for
Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

The original and two copies are enclosed herein.

Sincerely,

HOFFMANN-LA ROCHE INC.



Raymond E. McKinley, V.D.D.
Assistant Director
Drug Regulatory Affairs

REM:kr
Attachment
HLR No. 731219



Tocopherols

A bibliography of literature references in which Tocopherols were given either in high dosage or for a protracted period of time. These references are intended to supplement the compilation by Informatics Inc. Document #PB-221337.

Compiled: November 1, 1973

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Tocopherols

I. Clinical Studies

Anson, P. J.

New Treatment for Varicose Ulcers.

Landarzt 26: 262, 1950; Abstract: Annotated Bibliog. Vitamin E. 3: 141, 1952-1954.

Patients with leg ulcers showed remarkable improvement when treated with large amounts of vitamin E, 200 to 400 mg. daily, for long periods of time. In two cases a coincident coronary insufficiency was also improved during vitamin E therapy.

Ant, M.

Vitamin E in Rheumatism and Arthritis.

Rheumatism 6: 114-121, 1950; Abstract: Annotated Bibliog. Vitamin E 2: 59, 1950-1951.

Vitamin E in daily doses of 600 to 1,000 mg. alpha-tocopheryl acetate orally for several weeks, followed by maintenance doses of 200 mg. daily, was employed. Also, vitamin E as wheat germ oil in a hydrophilic base was used for topical application twice daily. Parenterally, a concentrate of natural mixed tocopheryl esters in oil was used and injected intragluteally in doses of 200 to 500 mg. twice weekly. The blood plasma level of tocopherol was found to parallel the development and recession of rheumatic symptoms.

Ardissone, G.

Clinical Observations on Use of Vitamin E in Cardiac Diseases.

Rass. Intern. Clin. e Terap. 35: 345-351, 1955; Abstract: Annotated Bibliog. Vit. E. 4: 169, 1955-1957.

A case of cardiac sclerosis with pulmonary insufficiency and a case of mitral insufficiency with pulmonary edema were each treated with 600 mg. vitamin E orally daily for 1 month and 2 months, respectively. Improvement was noted in each case although previous therapy with classical treatments had been unsuccessful.

Ayres, S., Jr. & Mihan, R.

Leg Cramps (Systemma) and "Restless Legs" Syndrome -- Response to Vitamin E (Tocopherol).

Calif. Med. 111 (2): 87-91, 1969

Nearly all of the twenty-six patients with leg cramps received prompt and gratifying relief from their symptoms while taking vitamin E in the form of d-alpha-tocopheryl acetate, 100 I.U. three times a day before meals. Treatment lasting for up to 18 months was not reported to have any adverse effects.

Ayres, S., Jr. & Mihan, R.

Keratosis Follicularia (Darier's Disease). Response to Simultaneous Administration of Vitamins A and E.

Arch. Dermatol. 106: 909-910, 1972.

A young man with a severe eruption of keratosis follicularis (Darier's disease) of long duration had failed to respond to continuous administration of vitamin A in large doses over a 5-year period. Seven months after adding vitamin E in a dose of 1,200 I.U. daily and continuing vitamin A, the eruption had improved approximately 75%. It is speculated that the striking improvement in this recalcitrant case was due to a synergistic action of vitamin E with vitamin A, previously demonstrated experimentally. If these results can be duplicated, it would suggest that advisability of the combined administration of these vitamins in those conditions where vitamin A is indicated, thus facilitating its utilization and lessening the danger of hypervitaminosis A by reducing the amounts required for a therapeutic effect.

Ayres, S. & Mihan, R.

Effective Dose of Vitamin E?

Lancet 2: 139, 1972.

The correspondents commenting on reported failure of "high dose" of vitamin E in recurrent psychotic illness (Cosling et al, Lancet II: 1084, 1971) feel that 140 mg/day of alpha-tocopherol is not an adequate dose. Their own experiences have shown that where vitamin E is indicated in therapeutic amounts, an effective dose would be certainly not less than 400 I.U. daily, and, more likely, 800-1600 I.U. daily. They have obtained excellent results in a limited number of patients with intractable dermatological conditions, such as Raynaud's phenomenon, both systemic and morphea types of scleroderma, lichen sclerosus et atrophicus, and several other dermatoses, as well as in the control of nocturnal leg cramps and the "restless legs" syndrome. These benefits turned up as unexpected side-effects when vitamin E was given in several dermatological conditions.

Ayres, S., Jr. & Mihan, R.

Yellow Nail Syndrome. Response to Vitamin E.

Arch. Dermatol. 108: 267-268, 1973.

The yellow nail syndrome includes slow-growing, opaque yellow nails with exaggerated lateral curvature, lymph-edema, and chronic respiratory disorders such as chronic bronchitis, pleural effusions and chronic sinusitis. A case is described in which the classical yellow nails, of 11 months' duration, returned to normal with 6-1/2 months after oral treatment with vitamin E in the form of d-alpha-tocopheryl acetate, 800 international units daily was begun, and with parallel improvement of an associated chronic bronchitis and chronic sinusitis.

Baer, S., Heine, W. I. & Gelfond, D. B.
The Use of Vitamin E in Heart Disease.
Am. J. Med. Sci. 215: 542-547, 1948.

Alpha-tocopherol, 300 to 400 mg. daily, was used to treat 22 patients with angina pectoris, congestive failure, or hypertension for periods of 10 days to 6 months. In no case was there any demonstrable effect on the electrocardiogram, orthodiagram, or blood pressure. None of the patients was markedly or moderately improved. Six were questionably improved, and the remainder showed no change or became worse.

Baker, S. J., Pereira, S. M. & Begum, A.
Failure of Vitamin E Therapy in the Treatment of Anemia of Protein-Calorie Malnutrition.
Blood 32: 717-725, 1968.

Sixteen children aged 1 to 4 years, showing the edema, apathy and other associated features of protein-calorie malnutrition were included in the study. After 1 to 2 weeks baseline observation, the children were given, d,l-alpha-tocopherol 100 mg. daily by intramuscular injection and 100 mg. d-alpha-tocopheryl acetate as a water miscible preparation orally, three times a day for 5 to 7 days. Two showed a very delayed rise in reticulocyte count and six had a peak reticulocyte response 5 to 8 days after starting therapy. None of the patients showing reticulocyte responses had a sustained rise in hemoglobin or packed cell volume. In none of the cases did the marrow become normoblastic following therapy and in five the marrow abnormalities became more marked. (No adverse effects are reported.)

Baum, G. L. & Stein, W.
Vitamin E Therapy in Heart Disease.
Wisconsin Med. J. 48: 315-317, 1949; Abstract: Annotated Bibliog.
Vitamin E 1: 139, 1940-1950.

The majority of 22 patients with heart disease showed no significant change in the determinations of body weight, arm-to-tongue circulation time, vital capacity, and blood pressure before and after oral administration of vitamin E in doses of 200 to 600 mg. daily for periods of 9 to 150 days (average 65 days).

Bayer, R.
Zur Behandlung der primären und sekundären essentiellen Infertilität mit hohen Vitamin-E-Dosen.
Geburtsh. Frauenh. 16: 396-405, 1956.

The successful treatment of essential infertility, i.e., habitual abortion, by means of prolonged administration of massive doses of vitamin E is reported. The effects are slow to appear, and treatment for at least 10 months with a total dosage of 12,000-20,000 mg. vitamin E is required. Even daily oral administration of 100 mg. EPHYNAL forte did not produce any side effects.

Beckmann, K. H.

Vitamin Therapy of Sudeck's Syndrome.

Chirurg 26: 57-62, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 161, 1955-1957.

Vitamin D (35,000 to 40,000 I. U. daily) influences calcium metabolism and vitamin E (300 to 600 mg. daily for 3 weeks, followed by 100 mg. daily) stimulates the diencephalohypophyseal system. Of 16 patients treated with vitamins for 6 to 14 weeks, 10 were cured, 4 showed improvement, and 2 showed an arrest of the process.

Beckmann, R. & Teirich-Leube, H.

Die progressiven Muskeldystrophien und Moeglichkeiten ihrer Behandlung. Therap. Gegenw. 109: 648, 650-651, 654-656, 1970

In a review of progressive muscular dystrophy and its treatment, the authors suggest vitamin E 200-300 mg. daily per os for 6 weeks combined with Laevadosin (nucleosides/nucleotides mixture).

Berger, H.

The Failure of Vitamin E to Alleviate the Signs and Symptoms of Congestive Heart Failure.

N. Y. State J. Med. 50: 441-443, 1950.

Vitamin E, EPHYNAL ACETATE, in this small but adequately controlled experiment in which each of 12 patients served as his own control, had no beneficial effect in congestive failure, p.o. 400 mg/day for 4 weeks.

Bernhardt, H.

Behandlung von Zahnfleischerkrankungen mit Vitamin E.

Zahnaerztl. Praxis 6: 1-4, 1955

Therapeutic effects of EPHYNAL in various odontological disorders tested in 150 patients for approximately 18 months. Treatment: 30 mg. and 300 mg. i.m., 100 mg per os. Favorable effects. Edema and Oleoma at site of injection. Oral administration well tolerated over long periods (up to 18 months); patients report general feeling of well-being, in two cases only "increased activity" (hyperactivity?).

Block, M. T.

Vitamin E in the Treatment of Diseases of the Skin.

Clin. Med. 60: 31-34, 1953; Abstract: Annotated Bibliog. Vitamin E 3: 155, 1952-1954.

Vitamin E relieved a variety of dermatologic conditions, hitherto considered not amenable to therapy. It is imperative to use large doses of vitamin E, e.g., 100 mg. orally three times a day plus 150 mg. vitamin E in aqueous solution by intramuscular injection twice a week. In some cases, ever larger doses are needed, e.g., 600 mg. vitamin E daily orally, and 450 mg. vitamin E weekly, parenterally.

Bonaccorsi, R. & Vicari, F.

Medical Therapy of Peripheral Arteritis with Special Reference to Vitamin E.

Riv. Patol. e Clin. 7: 469-486, 1952; Abstract: Annotated Bibliog. Vitamin E 3: 144, 1952-1954.

A series of cases of endoarteritis obliterans in various stages was treated with alpha-tocopheryl acetate. Doses were given intramuscularly in amounts varying from 400 to 1000 mg. daily over periods ranging from 40 to 60 days. Eight cases were reported in detail and of these, 3 were definitely improved, 2 showed subjective improvement, while 3 remained unimproved. A criticism of the use of vitamin E treatment of arteriopathy was that patients showed so much subjective improvement that they tended to discontinue reporting for continued observations. Thus control of the case by the physician could be lost with potential undesirable consequences for the patients.

Bottiglioni, E., DeJaco, M. & Vannini, P.

Changes in Tests for Colloidal Lability, Serum Albumin and Globulin Fractions and Cholesterolemia in Patients Suffering from Liver Diseases Treated with High Doses of Vitamin E.

3 Congr. Intern. Vitamin E 1: 59, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 166, 1955-1957.

Administration of 600 mg. vitamin E daily for 7 to 10 days to each of 15 patients suffering from liver disease with enlarged but insufficiently functioning livers resulted in increased cholesterolemia and improved colloidal lability concomitant with increases of serum albumins and beta-globulins and a decrease of gamma-globulin. Treatment with vitamin E is suggested for trophometabolic liver diseases.

Bottiglioni, E. & Sturani, P. L.

Clinical Use and Pharmacological Actions of Vitamin E.

3 Congr. Intern. Vitamin E 1: 39-40, 1955; Annotated Bibliog. Vitamin E 4: 103, 1955-1957.

The clinical usefulness of vitamin E is dependent on the pharmacological actions which can be attained by parenteral administration of 60 to 100 mg. The administration of high doses of tocopherol is followed by hypoglycemia, arterial and venous hypotension, and slow decrease in the size of the spleen.

Bousquet, F. P., Jr. & Laupus, W. E.

Studies on the Pathogenesis of Retrolental Fibroplasia.

Am. J. Ophthalmol. 35 (Part II): 64-68, 1952.

Premature infants. Oral vitamin E 150 mg/day to infants of less than 1,650 g. (No adverse effects reported by the authors).

Boyd, A. M. & Marks, J.

Treatment of Intermittent Claudication. A Reappraisal of the Value of Alpha-Tocopherol.

Angiology 14: 198-208, 1963.

Three month treatment at 400 mg/day in 34 patients. (No adverse effects reported).

Boyd, A. M. & Marks, J.

Vitamin E and the Cardiovascular System.

In H. von Kress & K. U. Blum, [eds.], Vitamin A, E. und K --
Klinische und physiologisch-chemische Probleme. F. K. Schattauer
Verlag, Stuttgart/New York, pp. 353-359, 1969.

The administration of large doses (400-600 mg/day 4-6 months) of alpha-tocopherol for a prolonged period has a significant beneficial effect in the therapy of certain peripheral vascular diseases particularly those associated with tissue anoxaemia.

Bronte-Stewart, B., Antonis, A., Eales, L. & Brock, J. F.

Effects of Feeding Different Fats on Serum-Cholesterol Level.

Lancet 1: 521-526, 1956.

The administration of 1000 mg. vitamin E daily to a subject fed a saturated fatty acid fraction was not accompanied by an immediate fall in the serum cholesterol levels such as was seen with unsaturated oils, although a moderate decline occurred 6 days later.

Burgess, J. F. & Pritchard, J. E.

Noduloulcerative Granuloma of Legs; Treatment with Tocopherols.

Arch. Dermatol. Syphilol. 57: 605-614, 1948.

A case of nodulo-ulcerative granuloma of the legs associated with necrobiotic changes together with lipid deposition (necrobiosis lipoidica diabetorum) responded rapidly to treatment with vitamin E. Doses of 250 mg. of mixed tocopherols were administered daily for 10 days by intramuscular injection. Thereafter 100 mg. of tocopherols were given daily by mouth. Improvement and healing were noted within 1 week. After 4-1/2 months a biopsy specimen showed no evidence of necrobiosis but showed completely reconstituted collagen.

Burlina, A.

The Effect of Vitamin E in Protecting the Liver.

Clin. Terap. 9: 1, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 166, 1955-1957.

General improvement in health resulted in 30 persons with chronic liver disease who received 200 mg. alpha-tocopherol intramuscularly daily for 40 days. Hepatomegalia responded particularly well. Liver function tests showed improvement in many cases.

Calvi Zampetti, A.

Arterial Retinal Spasms and Vitamin E.

3 Congr. Intern. Vitamin E 1: 71-72, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 187, 1955-1957.

Administration of 600 mg. vitamin E daily for two 6-day periods separated by a 3-day interval to 7 patients suffering from spasm of the central retinal artery or some of branches relieved the spasm appreciably and improved the field of vision.

Ceresa, A.

The Adrenals and Vitamin E.

Vitamina E, Atti 3 Congr. Intern. 258-274, 1956; Abstract: Annotated Bibliog. Vitamin E 4: 190, 1955-1957.

Seven normal subjects were given ACTH (25 units IV) before and after treatment with 600 mg. tocopheryl acetate orally daily for 6 days. There was no change in plasma 17 hydroxycorticosteroids or of 17-ketosteroids. However, vitamin E influenced the metabolism of dehydroisoandrosterone, slowing the oxidative transformation to delta 4-androstene-3,17-dione.

Cohen, H. M.

Fatigue Caused by Vitamin E?

Calif. Med. 119: 72, 1973.

The correspondent reports that weakness and fatigue resulted from the intake of 800 IU of vitamin E daily. The symptoms disappeared after withdrawal of the drug.

Colucci, C. F. & Marra, E.

Peculiar Case of Werlhof's Disease Subjected to Splenectomy and Treated with Vitamin E.

Riforma Med. 65: 829-834, 1951; Abstract: Annotated Bibliog. Vitamin E 2: 73, 1950-1951.

A detailed account is given of an 18-year-old girl with idiopathic thrombocytopenic purpura. After 5 months during which all types of therapy had been given in vain all treatment was stopped and vitamin E was administered, 300 mg. alpha-tocopherol intramuscularly daily for 15 days, then 600 mg. daily for 20 days. The menorrhagic and gingival bleeding and subcutaneous hemorrhages were reduced. One week after cessation of tocopherol treatment severe bleeding started again. Vitamin E therapy was reinstated and after one month splenectomy was performed and the postoperative course was good. Administration of tocopherol, part parenterally and part orally, was continued and the patient has remained well.

Coxon, M. W.

Experiences with Retroental Fibroplasia in Oxford.

Proc. Roy. Soc. Med. 45: 863-865, 1953.

Premature babies born during one year were treated from 1 week to 6 months of age with 150 mg. alpha-tocopheryl acetate daily. Five developed retroental fibroplasia and there was no evidence that treatment lessened its severity.

Cuervo Garcia, C.
New Therapeutic Orientation of Vitamin E.
Med. Espan. 25: 345-357, 1951; Annotated Bibliog. Vitamin E 2: 73,
1950-1951.

Three cases of severe hyperthyroidism were treated with alpha-tocopherol, 200 mg. daily by intramuscular injection for 1 to 2 months. Nervousness, exophthalmos, basal metabolic rate, and other systems returned to or toward normal. More than 100 patients with gastric disturbances and ulcers were given vitamin E, 100 to 200 mg. was daily injected for 1 month, then 40 mg. orally each day. There was rapid improvement in all patients with complete remission of symptoms in many.

Dainow, I.
Vitamin E. in the Treatment of Endocrine Skin Disorders.
Dermatologica 112: 468-470, 1956; Abstract: Annotated Bibliog. Vitamin E 4: 181, 1955-1957.

Three female patients with psoriasis or paronychia particularly severe prior to menstruation were each given 400 mg. alpha-tocopherol orally daily. Cure was essentially complete in 4 to 6 months.

Dalla Torre, L. & Boldrini, R.
Alpha-Tocopherol Acetate in the Treatment of Peripheral Vascular Diseases.
Clin. Nuova (Rome) 12: 617-624, 1952; Abstract: Annotated Bibliog. Vitamin E 3: 145, 1952-1954.

Two cases of senile arteritis, a case of Buerger's disease, and a case of intermittent claudication were improved after treatment with high doses of alpha-tocopherol, 300 to 600 mg. daily, administered for 2 to 3 months.

Dalle Coste, P. & Klinger, R.
Alpha Tocopherol in Diabetic Diseases of the Veins.
Riforma Med. 69: 853-856, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 170, 1955-1957.

Forty-four patients were given 300 to 500 mg. alpha-tocopherol daily orally for 2 months to 3 years. Improvement was seen after 30 days in 9 cases with varicose ulcers, with 7 being healed completely. The other 35 patients had postphlebotic or varicose lesions and all were helped. Edema, congestion, and pain were decreased after 20 days. Hypertensives were also helped. Carbohydrate metabolism was not altered and no side effects were observed.

Darby, W. J., Cherrington, M. E. & Ruffin, J. M.

Plasma Tocopherol Levels in Sprue.

Proc. Soc. Exptl. Biol. Med. 63: 310-312, 1946.

Three patients with sprue in relapse or early remission showed very low plasma tocopherol levels. Also, their response to a single oral dose of 600 mg. of tocopherol as measured by tolerance tests showed decreased efficiency of absorption of vitamin E compared with normal subjects.

De Campos Magalhaes, M. J. & Figueiredo Barbosa, A. J.

Treatment of Amyotrophy of the Hands of Leprous Patients with Local Injections of Vitamin E.

Medico (Porto) 9: 97-101, 1958; Abstract: Annotated Bibliog. Vitamin E 5: 142, 1958-1960.

Leprosy patients with amyotrophy of the small muscles of the hands were treated with injections of 30 or 300 mg. vitamin E into each atrophic muscle once or twice weekly. After 5 to 10 injections all 6 cases showed improvement in muscular strength.

De Hoff, J. B. & Ozazewski, J.

Alpha Tocopherol to Treat Diabetic Retinopathy.

Am. J. Ophthalmol. 37: 581-582, 1964.

The empirical use of EPHYNAL ACETATE, in dosage from 300 mg. to 600 mg. p.o. every day for protracted periods, had no demonstrable effect on the progression of diabetic retinopathy, as observed in 12 patients. After several months' administration of the drug, there were no complaints due to side-effects.

Del Giudice, A.

Massive Doses of Vitamin E as a Factor in Mental Improvement.

Dia Med. (Buenos Aires) 29: 1814-1817, 1957; Abstract: Annotated Bibliog. Vit. E 5: 144, 1958-1960.

Doses of 600 to 800 mg. alpha-tocopherol daily were given to a large series of psychotic patients. In many, mental improvement was observed, and there was a good effect on motor coordination and muscular tone. Occasional benefit was observed in patients with amenorrhea. Large doses exerted a slight sedative effect, and there was occasional diarrhea, but smaller doses were ineffective therapeutically.

Del Giudice, A.

Large Doses of Vitamin E as a Factor in the Mental Improvement of Subnormal Children.

Summary 12: 21-22, 1960; Semana Med. (Buenos Aires) 116: 46-47, 1960; Abstract: Annotated Bibliog. Vitamin E 5: 144, 1958-1960.

With no adverse side effects, large doses of tocopherol (2 g. daily for years) have produced physical and mental benefit in many cases of mental and neurotic incapacity. This pharmacodynamic action may be due to regulatory effects of alpha-tocopherol on endocrine glands and central nervous system.

Della Thammasa, F.

Alpha-Tocopherol Therapy in Patients with Sequelae of Rheumatic Hemorrhagic Exanthema.

Policlinico, Sez. prat. 59: 933-936, 1952; Abstract: Annotated Bibliog. Vit. E 3: 145, 1952-1954.

A patient with a severe, chronic ulceration of the leg was treated with alpha-tocopheryl acetate; 200 mg. was injected subcutaneously daily for 45 days. The leg ulceration was cured.

De Souza, P. A. & Jardim, M. L.

Emprego de vitamina "E" nas amiotrofias leproticas.

Bol. Serv. Nac. Lepra 1970: 69-76 .

The authors report good results in the treatment of myopathy associated with leprosy. The 5 patients were given 300 mg. of EPHYNAL i.m. 2 times per week for 8-20 weeks; no adverse effects reported by the authors.

Dorman, J. D., Engel, W. K. & Fried, D. M.

Therapeutic Trial in Amyotrophic Lateral Sclerosis. Lack of Benefit with Pancreatic Extract and DL-Alpha Tocopherol in 12 Patients.

J. Am. Med. Assoc. 209: 257-258, 1969.

Eleven of the 12 patients with amyotrophic lateral sclerosis (ALS) showed no apparent change in their rate of progressive decline in strength while being treated with pancreatic extract and DL-alpha-tocopherol, regardless of whether or not the dietary regulation was also followed. Four deaths due to ALS occurred in patients receiving the therapy. Therapy consisted of pancreatic extract 6.3 gm daily and DL-alpha-tocopherol (Aquasol E) 1,500 international units daily (administered for 7 months). No adverse effects of vitamin E therapy reported.

Dowd, G. C.

Massive Dosage of Alpha-Tocopherol in Alleviation of Multiple Sclerosis.

Ann. N. Y. Acad. Sci. 52: 422-424, 1949.

Seven patients, ages 32 to 47, who have been afflicted 21 to 240 months, were treated for 3 to 14 months. The chief difficulties were ataxia, spasticity, muscle weakness, hyperesthesia, speech and visual difficulties, and deafness. Each patient was given 300 mg. of injectable vitamin E over a period of a week, then 600 to 1000 mg. of alpha-tocopherol by mouth daily. After 3 weeks, corrective therapy was instituted in an effort to obtain muscle relaxation and re-education. Two cases reverted to virtual normality after 5 and 9 days of therapy. These were acute types, which were seen a few days after onset. The remaining 5 cases were chronics. After 2 to 14 months of corrective therapy, along with maintenance doses of tocopherols, ataxia, spasticity, and muscular strength have been moderately improved in 3 patients. Two severe cases remained uncured.

Eisen, M. E. & Gross, H.

Vitamin E in Arteriosclerotic Heart and Peripheral Vascular Disease.
N. Y. State J. Med. 49: 2422-2424, 1949.

Twenty-one patients with arteriosclerotic heart disease, 12 with arteriosclerotic peripheral vascular disease, and 2 with thromboangitis obliterans were treated with vitamin E for periods of 2 to 12 months. Doses ranged from 150 to 800 mg. of tocopherol daily. No benefits were observed as the result of this therapy. Electrocardiographic studies before and after exercise, with and without vitamin E therapy, showed no significant differences in ST segments and T waves.

Falcon, J. H.

Sclerema of the Newborn.

Semana Med. (Buenos Aires) 106: 935-937, 1955; Abstract: Annotated Bibliog. Vit. E. 4: 158, 1955-1957.

An 1800 g. girl born prematurely showed generalized acute scleroderma on the 9th day of life. Breast feeding and treatment with heat and a series of 12 daily injections of vitamin E cleared the scleroderma within a month.

Faust, F. B.

Anticoagulation and alpha-tocopherol.

Med. Times 81: 386-391, 1953; Abstract: Annotated Bibliog. Vitamin E 3: 149, 1952-1954.

During 4 years use of dicoumarol or Tromexan to increase prothrombin time in coronary thromboses (7 cases), lower extremity thromboses (5), pulmonary thrombosis (1), and cerebral thrombosis (1), prothrombin time would fluctuate widely and administration of the anticoagulant would be exceedingly tedious and embarrassing. However, administration of 300 to 600 mg. alpha-tocopherol in divided doses caused the prothrombin times to level off and become quiescent. Water-soluble vitamin E by injection or alpha-tocopheryl acetate orally were used.

Feissly, R.

On the Treatment of Hemophilia.

Acta Haematol. 6: 267, 1951; Abstract: Annotated Bibliog. Vitamin E 4: 168, 1955-1957.

Alpha-tocopherol (500 mg.) given over a 20 day period had no effect on blood coagulation.

Fleshko, E. A.

[Successful Vitamin E Treatment of Scleroderma and Hypertensive Disease].
In *Voprosy serdechno-sosudistoi patologii Barnaul*. 74-76, 1965; BA 47:
81872, 1966.

This reports the successful treatment with 200 mg. of vitamin E daily given intramuscularly for a course of 30 injections of a 73-year-old patient suffering from "macrofocal" scleroderma, hypertensive disease, and cerebral sclerosis. The blood pressure decreased to 140/80 mm Hg. Supplementary courses of treatment were carried out on an out-patient basis.

Gerloczy, F.

The Importance of Vitamin E in Pediatrics.

Orvosi Hetilap. 45: 1606-1615, 1959; Abstract: Annotated Bibliog.
Vitamin E 5: 138, 1958-1960.

Of 320 prematures with scleredema treated with tocopherol (10 mg. or less/day) many were cured. Tocopherol exerted a diuretic effect, and mortality dropped from 75% to 15 to 27%.

Goisis, M. & Ferruzzi, M.

Dyshormonal Hepato-Endocrine Syndromes: Liver and Menstrual Function.
Ann. Ostet. Ginecol. 76: 243-268, 1954; Abstract: Annotated Bibliog.
Vit. E 3: 165, 1952-1954.

Ten patients suffering from premenstrual pain and showing serum protein changes indicating liver dysfunction were treated with 150 to 300 mg. tocopherol daily by injection and orally until the 6th or 7th day before the next cycle. The serum albumin and globulin value returned to normal and the dysmenorrhea symptoms disappeared.

Graul, E. H.

Pathogenesis, Clinical Manifestations and Therapy of Induratio Penis Plastica.

Strahlentherapie 98: 104-118, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 162, 1955-1957.

Different forms of therapy are discussed. Best results are obtained by means of fractionized roentgen irradiation and daily doses of 300 to 500 mg. vitamin E until a total of 20 to 30 g. have been given.

Gros, H.

Investigations of Metabolism in Erb's Progressive Muscular Dystrophy.
3 Congr. Intern. Vitamin E 1: 49-50, 1955; Abstract: Annotated Bibliog.
Vitamin E 4: 162, 1955-1957.

The accelerated excretion of intravenously administered hippuric acid in cases of Erb's progressive muscular dystrophy is restored to normal by daily treatment with 400 mg. vitamin E orally for 3 months.

Gross, S. & Guilford, M. V.
 Vitamin E-Lipid Relationships in Premature Infants.
 J. Nutr. 100: 1099-1104, 1970.

A study was conducted with 36 premature infants to determine the effect of body weight 4 to 12 days after birth and supplementation with vitamin E on the distribution of lipids between plasma and erythrocytes. The infants were grouped into two groups, the larger (> 1600 g) and the smaller (< 1600 g). The larger infants responded to the addition of vitamin E by a significant rise in the red blood cell/plasma lipid ratio. In the smaller infants this did not occur. Dose: 50 units/day - 4 days-per os.

Haeger, K.
 Long-Time Treatment of Intermittent Claudication with Vitamin E
 Int. Vitamin E Conf., Sept. 26-27, 1973, Minneapolis, Minn., 1 p., 1973
 Forth-seven male patients (mean age 67, range 43-82 years) were followed during 2 to 5 years with intervals of 3 - 6 months. All patients fulfilled the following criteria: (1) total occlusion of femoral or femoro-popliteal arteries (2) intermittent claudication of at least grade 2, (3) an arterial flow to the lower leg of max. 14 ml/100 gm/min. Venous occlusion plethysmography and a standardized walking test were performed with intervals of 4 to 7 months. The series was divided in one group receiving d-alpha-tocopherol (600 mg/day) and one control group. In the control group the alternative therapy was either dicoumarine treatment or vasodilator drugs. Otherwise the series were similarly treated as regards exercise, diet, etc. It was shown that there was a significant difference in the improvement of the walking test, the alpha-tocopherol group showing better results already after 4 to 6 months ($0.001 < p < 0.01$). Fifty-four per cent of the treated group reached the test limit of 1000 m. uninterrupted walking distance, as compared to 23 per cent in the control group. Also the arterial flow was significantly better in the treated group. This improvement, however, did not appear until about 12 to 18 months after the start of the treatment. After a period of 20 to 25 months the arterial flow to the lower leg increased with approximately 34 per cent, whereas no change was noted in the control group. There were no side reactions worthy of remark.

Hamilton, M., Wilson, G. M., Armitage, P. & Boyd, J. T.
 The Treatment of Intermittent Claudication with Vitamin E.
 Lancet 1: 367-370, 1953.

The effect of natural vitamin E in intermittent claudication was investigated in 41 patients, divided at random into control and treatment groups. The controls received capsules containing arachis oil, and the treatment group received capsules identical in appearance but containing alpha-tocopheryl acetate. The daily dose was 450 I.U., the equivalent of 450 mg. of tocopherol, and was continued for twelve weeks. (No adverse effects reported by the author.)

Heinsen, H. A. & Scheffler, H.

Vitamin E and Peripheral Circulatory Disturbances.

Med. Klin. 46: 909-911, 1951; Abstract: Annotated Bibliog. Vitamin E 2: 74, 1950-1951.

Two patients with arteriosclerotic changes of the leg arteries as the result of endangiitis obliterans of long duration were treated successfully with vitamin E. Initial doses of 1200 mg. alpha-tocopherol were given intramuscularly, then daily doses of 50 to 300 mg. alpha-tocopheryl acetate were given orally. Improvement in one patient was noticed within 4 days and it continued throughout the period of clinical observation. Circulating eosinophils decreased with vitamin E treatment.

Helwing, H.-P., Hochrein, H. & Helwing, B.

Vitamin E in der Behandlung der Digitalis-Intoxikation.

Arzneimittel-Forsch. 21: 335-342, 1971.

With undiminished level of glycoside and constant digitalis maintaining dose, vitamin E caused remission of toxic digitalis symptoms. The antitoxic dose of vitamin E is 200-700 mg. Occurrence of toxic effects or side effects was not observed in the therapy with vitamin E up to doses of 700 mg. i.v..

Hochrein, H. & Helwing, H.-P.

Klinische und experimentelle Befunde ueber einen kardialen. Vitamin-E-Effekt.

In H. von Kress & K.-U. Blum, [eds.], Vitamin A, E und K -- Klinische und physiologisch-chemische Probleme. F. K. Schattauer Verlag, Stuttgart/New York, pp. 337-352, 1969.

Experiments in heart-lung preparations of guinea pigs showed that even at highest doses (500 mg/100 ml tocopherol acetate) there is no toxic or hemodynamic effect in normal nonfailing hearts. Clinical observations in cardiac patients stress the effect of vitamin E in digitalis-intoxication. Higher doses of digitalis could be used under the protection of vitamin E. Vitamin E given at daily doses of 300 mg for up to 9 months.

Horwitt, M. K.

Tocopherol Requirements of Man.

Federation Proc. 18: 530, 1959.

Preliminary analyses of data obtained during a five year controlled study of human tocopherol needs have produced the following tentative conclusions: (1) The tocopherol levels of tissues can be related to the amounts of oxidizable lipid consumed. (2) The feeding of an unsaturated lipid which has been slightly oxidized to remove tocopherol quite unexpectedly produced gastrointestinal erosions that were diagnosed as peptic ulcers and which responded to treatment. (3) The recovery of erythrocytes in their response to the peroxide hemolysis test when rapid return of plasma tocopherol to pre-experimental levels. (4) The administration of 200 mg. of D-alpha-tocopherol acetate produced a small but significant increase in reticulocytes in those experimental subjects whose hemoglobin levels were 13.0 gm. per cent or less.

Jensen, H. P.

Vitamin E in der Behandlung der Rueckenmuskelverspannung.
Therapiewoche 13: 447, 1963

EPHYNAL combined with physical therapy brought about improvement of vertebral syndromes in 58% of acute and 93% of chronic cases in a total of 242 patients treated. Four hundred mg/p.o./day for 6-8 weeks. (No adverse effects reported by author).

Jones, G. E. S., Delfs, E. & Stran, H. M.

The Effect of Alpha-Tocopherol Administration on Pregnanediol Excretion.
J. Clin. Endocrinol. 9: 743-748, 1949.

The urinary pregnanediol excretion during 20 menstrual cycles of 6 apparently normal individuals has been studied. Eleven were control cycles and 9 were during periods of vitamin E administration. No regular variation in pregnanediol excretion was noted when alpha-tocopherol was administered in doses of 50 to 150 mg. per day for one month.

Jordan, P. & Wulf, K.

Erythematosus Treated with Vitamin E.

Hautarzt 1: 233, 1950; Abstract: Annotated Bibliog. Vitamin E 4:
179, 1955-1957.

Ten patients who had been resistant to treatments of various types, were given daily intramuscular injections of 600 mg. or more of alpha-tocopherol. Although septic foci were cleared up, none showed completely satisfactory results after 6 months.

Kadaner, V. Ya.

[The Mechanism of Action of Vitamin E.]

In: Patologiya gepato-pankreatoduodenal'noi zony i rasstroistva krovoobrashcheniya, Moscow, pp. 61-62, 1965; B. A. 47: 47489, 1966.

The patients were given 2 courses of treatment separated by an interval of 6-8 months, consisting of 25 intramuscular injections (200 mg of vitamin E). The vitamin E exerted an antiedematous, anti-inflammatory, and anti-allergic action, prevented the development of destructive-necrotic changes in the connective tissue, made possible the restoration of connective-tissue elements, returned permeability to normal, and improved the oxidative processes. Vitamin E is recommended for the treatment of relapsing rheumatism. (No adverse effects reported by the author).

Kinsey, V. E. & Chisholm, J. F., Jr.
 Retrolental Fibroplasia. Evaluation of Several Changes in Dietary Supplements of Premature Infants with Respect to the Incidence of the Disease.

Am. J. Ophthalmol. 34: 1259-1268, 1951.

Administration of dl-alpha-tocopherol acetate therapeutically in daily doses ranging from 30 to 150 mg. to premature infants at the time the eyes showed vascular changes characteristic of the early stages of retrolental fibroplasia did not reduce the incidence of the severe form of the disease significantly. Fifty-six percent of the premature infants given 50 mg. of dl-alpha-tocopherol acetate prophylactically from birth three times a day developed vascular changes, and 40% also developed vitreous and retinal changes associated with retrolental fibroplasia. Five percent of the infants given dl-alpha-tocopherol acetate from birth developed the severe form of the disease involving membrane formation, compared with 11% who did not receive dl-alpha-tocopherol acetate prophylactically. This difference in incidence is of doubtful significance.

Kirk, J. E. & Chieffi, M.

Tocopherol Administration to Patients with Dupuytren's Contracture; Effect on Plasma Tocopherol Levels and Degree of Contracture.
 Proc. Soc. Exptl. Biol. Med. 80: 565-568, 1952.

Treatment with 300 mg. of alpha-tocopherol acetate daily was given to 19 old patients with Dupuytren's contracture for a period of 300 days. Following discontinuation of the treatment the patients were followed for another 350 days. The alpha-tocopherol administration resulted in a slow but steady rise of the mean plasma tocopherol level from 0.55 to 1.37 mg. %. (No adverse effects reported by the authors).

Krohn, B. C. & Pottenger, F. M., Jr.
 Allergic Rhinitis: Tocopherol Therapy.

Ann. West. Med. Surg. 6: 484-487, 1952

EPHYNAL, 100-400 mg/day p.o. for 1-4 months. No adverse effects.

Laupus, W. E. & Bousquet, F. P., Jr.

Retrolental Fibroplasia. The Role of Hemorrhage in Its Pathogenesis.
 Am. J. Diseases Children 81: 617-626, 1951.

The high incidence of serious ophthalmologic abnormalities, despite supplementation with vitamin E, challenges the prophylactic role attributed to the tocopherols in treatment of this disease. All except two infants received vitamin E, 50 mg., three times daily. Sixty-five infants were given an aqueous dispersion of dl-alpha-tocopherol acetate (EPHYNAL acetate) beginning with the first sign of fundus abnormality. This medication was continued until examinations had conclusively shown the fundus to be normal or to have consistent irreversible pathologic changes. High serum tocopherol levels were found in all instances when the determination was made. No adverse effects mentioned by the authors.

Lee, P. F.

Alpha Tocopherol in Ocular Diseases.

Summary 8: 85-93, 1956; Abstract: Annotated Bibliog. Vitamin E 4: 189, 1955-1957.

Forty-four cases of a variety of ocular diseases were treated with alpha-tocopherol for periods ranging from 2 to 7 months. Three did not return for examination. The daily dosage was increased from 100 to 200 mg. for the first 2 weeks to 200 to 400 mg. for the next 2 weeks to 200 to 600 mg. for as long as necessary. Seven of 14 cases of hypertensive retinopathy, 3 of 3 cases of diabetic retinopathy, 7 of 9 cases of senile macular degeneration, 1 of 4 cases of retinitis pimentosa, 1 of 4 cases of vitreous degeneration and opacity, and one case of retrobulbar neuritis showed improvement ranging from increased vision to complete recovery. No benefit was noted in 6 glaucomatous patients. No side reactions or toxic effects were observed during treatment.

Levitan, B. A.

Clinical Observations on the Effects of Injectable Rutin, Esculin, Adrenoxyl, and Vitamin E on the Capillary Fragility of Diabetic Retinopathy.

Am. J. Med. Sci. 221: 185-189, 1951.

In five subjects, 300 to 400 mg. of vitamin E daily, alone or in combination with large doses of ascorbic acid and rutin, for periods of 14 to 35 days failed to elicit any sustained improvement in capillary strength. No adverse effects mentioned by the author.

Levy, H. & Boas, E. P.

Vitamin E in Heart Disease.

Ann. Internal Med. 28: 1117-1124, 1948.

Thirteen patients with heart disease were treated with 200 to 800 mg. of alpha-tocopherol daily for periods of 3 weeks to 3 months. Four of the patients had had chronic angina pectoris for from 5 to 16 years. The others had either active angina pectoris, chronic heart failure secondary to myocardial infarction, or chronic heart failure due to chronic rheumatic cardiovalvular diseases. Absorption of the drug was excellent in all those whose plasma levels were tested and values roughly paralleled the dosage. Aside from symptoms of headache, dizziness, and vertigo on the higher dosages, there was remarkably little change or effect from this drug.

Lewis, J. S., Pian, A. K., Baer, M. T., Acosta, P. B. & Emerson, G. A. Effect of Long-Term Ingestion of Polyunsaturated Fat, Age, Plasma Cholesterol, Diabetes Mellitus, and Supplemental Tocopherol Upon Plasma Tocopherol.

Amer. J. Clin. Nutr. 26: 136-143, 1973.

No plasma tocopherol values less than 0.3 mg/100 ml were found for the 217 subjects studied. No adults or normal children had plasma tocopherol levels below 0.6 mg/100 ml. No significant difference was found between the means of plasma tocopherol levels of children on high poly-unsaturated fat diets since birth and of children on normal diets. Plasma tocopherol levels were significantly correlated to age and significantly correlated to cholesterol levels. Mean plasma tocopherol levels of non-obese diabetics were not significantly different from those normal non-obese subjects of the same age and sex. Plasma tocopherol values for the same individual varied little from day to day or month to month. Supplements of d-alpha-tocopherol acetate did not significantly change plasma cholesterol levels. Supplements of 200 and 600 I.U. of d-alpha-tocopherol acetate increased plasma tocopherol levels only from 50% to 60%, and plasma levels returned to presupplementation levels within 4 days.

Livingstone, P. D. & Jones, C.
Treatment of Intermittent Claudication with Vitamin E.
Lancet 2: 602-604, 1958.

The series consisted of 40 non-diabetic male patients with obliterative vascular disease who complained of intermittent claudication, 20 of whom received vitamin E, 20 served as controls. The usual daily dose was 600 mg. EPHYNAL tablets given over a period of 40 weeks.

Loos, S.
Vitamin E und parodontale Erkrankungen.
Oesterreich. Z. Stomatol. 52: 526-535, 1955

Use of vitamin E is evaluated on the basis of observations made during the past 9 years. Parodontal disease of inflammatory-edematous character was found to respond best to relatively high dosage vitamin E therapy. The following dosage schedule proved most favorable: 300 mg. tocopherol in 1 cm³ oily solution given i.m. every other day for a total of 5 injections; this followed by 8 days of oral tocopherol acetate 300 mg/day. Oral medication to be continued at gradually reduced dosage for 2 more weeks. Doses of 500 mg/day orally or parenterally were tolerated well, but did not produce notably better results. Other treatment schedules tried: 300 mg/daily per os for 14 days or 300 mg. intragluteally every other day or a combination of both. Other authors have reported adverse local and general reactions to intragluteal injections of large doses, i.e. 600 mg. (irritation at injection site, pustules, painful infiltrates, occ. oil cysts). These effects were not seen by the author in his experience (approximately 5,000 intragluteal vitamin E injections). In conclusion, the author warns that high doses of vitamin E may lower blood pressure, may have vasodilator and anti-estrogenic effects - caution is indicated in certain cardiac disorders. No other side effects are known even if the drug is used in excessive amounts.

Losowsky, M. S. & Leonard, P. J.

Evidence of Vitamin E Deficiency in Patients with Malabsorption or Alcoholism and the Effects of Therapy.

Gut 8: 539-543, 1967.

Eleven subjects with evidence of vitamin E deficiency secondary to poor diet or malabsorption have been studied. It was found that low plasma vitamin E levels, abnormal hemolysis of red cells by hydrogen peroxide, and creatinuria were reversed by administration of EPHYNAL administered intramuscularly and orally for the first seven days (total daily dose 300 mg.), followed by oral doses of 200 mg/day.

Lowe, L. B., Jr.

Hereditary Epidermolysis Bullosa.

Arch. Dermatol. 95: 587-595, 1967

In one of the cases presented, no sustained improvement was achieved with vitamin E therapy (1600 I.U. per day for 6 months) nor with other types of treatment, e.g. combination of antimalarial agents or coricotropin. No adverse effects reported by the author.

Lubich, T. & Caragnoni, A.

Glycine and Alpha Tocopherol in Cardiac Therapy.

Giorn. Clin. Med. (Parma) 35: 1294-1307, 1954; Abstract; Annotated Bibliog. Vitamin E 4: 168-169, 1955-1957.

Treatment of 25 patients with 6 to 10 g. of glycine and 600 to 800 mg. of alpha-tocopheryl acetate orally daily is described. Serial electrocardiograms were taken. Clinical improvement was noted in 5 of 6 cases of coronary sclerosis, 2 of 4 cases of coronary infarctions, myocarditis associated with metabolic disturbances and 4 of 6 cases of valvular disease. One severe case of pericarditis and 2 of pancarditis died. The clinical improvement was associated with improvement of electrocardiograms except in the cases of coronary infarctions. Treatment must be continued 4 to 6 weeks as a minimum.

Mantero, O.

Association of Tocopherol and Diethylstilbene in Cardiovascular Therapy. Osp. Maggiore 38: 638-649, 1950; Abstract: Annotated Bibliog. Vitamin E 2: 70, 1950-1951.

Thirty-three patients with various types and degrees of cardiovascular symptoms were treated with vitamin E, 300 to 400 mg. either orally or parenterally. Some were given diethylstilbene and hexanitromannitol in addition. Favorable results were obtained in cases of thrombophlebitis of the legs, Buerger's disease, and acute rheumatic fever. An increase of blood level of tocopherol and, in some cases an improvement in electrocardiographic and oscillometric findings were determined.

Marcacci, M.

Vitamin E Action on the Blood Coagulation in the Light of the Results Obtained with the Most Modern Methods. A. In Vitro. B. In Vivo. 3 Congr. Intern. Vitamin E 1: 25, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 171, 1955-1957.

The oral administration of 600 mg. alpha-tocopheryl acetate daily for 3 consecutive days to normal individuals had no effect on the levels or activity of plasma prothrombin, Factors V or VII, AHG, or PTC.

Marks, J.

Critical Appraisal of the Therapeutic Value of Alpha-Tocopherol. Vitamins & Hormones 20: 573-598, 1962.

Review article. Use of alpha-tocopherol in high dosage 400 mg. - 600 mg. per day for at least 12 weeks, up to 40 weeks in intermittent claudication. Long range follow-up by nine investigators showed survival in the tocopherol series to be better than in non-treated patients. (No adverse effects mentioned by authors).

McLaren, H. C.

Vitamin E in the Menopause.

Brit. Med. J. 2: 1378-1382, 1949.

Vitamin E in the form of alpha-tocopherol temporarily relieved severe menopausal flushing in 30 patients (64%) and failed to in 17. The dose required is variable, but averaged 18.5 g over 37 days with the highest dosage amounting to 60 g. over a period of 83 days. Vitamin E produces no sudden change in the clinical appearance of the lower genital tract, although prolonged and heavy dosage seemed to cause healing in 50% of senile vulvar and vaginal lesions (including doses of 28.7 g over 112 and 42.0 g over 42 day periods.) Cell changes were observed in 7 out of 21 urethral smears by massive doses of vitamin E. As in the vagina, therefore, there is no sharp reaction in all urethral smears, and it is possible that the changes observed were the result of faulty technique - e.g., in failing to pick up cells. Side-effects were few: one case developed dermatitis; two cases menstruated, one developing a hemorrhagic leucal cyst.

Melhorn, D. K. & Gross, S.

Vitamin E-Dependent Anemia in the Premature Infant. I. Effects of Large Doses of Medicinal Iron.

J. Pediat. 79: 569-580, 1971.

Alpha-tocopherol acetate 25 I.U./day orally from the 8th to the 42nd day; no adverse effects reported by the author.

Minkowski, A.

On the Prevention of Cerebromeningeal Hemorrhages in Prematures by Administration of Anti-Vascular Fragility Compounds to the Mother During Labor.

Arch. Franc. Pediat. 6: 276-280, 1949; Abstract: Annotated Bibliog. Vitamin E 3: 126, 1952-1954.

Vitamin E was given in doses of 300 to 600 mg. to each mother in the first hours of premature labor in 45 cases. A similar series of control cases received no vitamin E. The vascular resistance of these premature infants was measured. It was found that vitamin E, given in large amounts, increases the vascular resistance of the premature newborn and helps to prevent cerebromeningeal hemorrhages, a frequent cause of death in infants weighing less than 2 kg.

Minkowski, A., Neumann, J. & Caillebotte, N.

Effect of a Supplement of dl-alpha-Tocopheryl Acetate Given to the Mother During Labor Upon the Level of Tocopherol in Cord Blood.

Etudes Neo-Natales 2: 33-37, 1953; Abstract: Annotated Bibliog. Vitamin E 3: 128, 1952-1954.

Twenty-eight women received supplements of 300 to 1,500 mg. alpha-tocopherol during labor. Tocopherol levels in the cord blood were determined for this and for a control group of 28 subjects. Values in the control series varied widely (75 to 970 $\mu\text{g}/100$ cc plasma). The mean level of the tocopherol-supplemented group was increased over that of the control series (526 vs. 390 $\mu\text{g. \%}$). The difference was statistically significant. Previous findings, concerning the amelioration of vascular fragility in the premature, and the results of this study suggest that large doses of alpha-tocopherol should be given during labor to those women who give birth prematurely.

Muller, D. P. R. & Harries, J. T.

Vitamin E Studies in Children with Malabsorption.

Biochem. J. 112 (4): 28P, 1969.

Vitamin E deficiency was greatest in a beta-lipoproteinaemia. Initially vitamin E could not be detected in the serum of the four patients studied and red-cell hemolysis was considerably raised. After treatment with massive doses (up to 1.5 g/day) of a water-miscible preparation of the vitamin, serum concentrations became detectable (up to 0.2 mg/100 ml) and hemolysis returned to normal. Twelve children with obstructive jaundice were studied. Administration of large doses of vitamin E (water- or fat-miscible preparations) to these patients has so far failed to raise serum concentrations or decrease hemolysis. In patients with deficiency of pancreatic enzymes due to cystic fibrosis, impaired lymph flow due to intestinal lymphangiectasis and mucosal damage due to gluten-induced enteropathy, studies suggest that repletion of these patients by oral administration of the vitamin is likely to be more successful. No adverse effects reported by the authors.

Muller, D. R. P., Harries, J. T. & Lloyd, J. K.
 Vitamin E Therapy in A-Beta-Lipoproteinaemia.
 Arch. Diseases Childhood 45: 715, 1970.

The vitamin E status of 6 children with a-beta-lipoproteinemia was investigated. Oral administration of large doses of vitamin E resulted in rapid correction of the abnormal hemolysis. Serum vitamin E remained undetectable for approximately 6 months in 4 children who received doses varying between 25 and 75 mg/kg/day, whereas in 2 children who received even larger doses (100 mg/kg/day) serum vitamin E was detectable after 1 and 3 months, respectively. The maximum level achieved by oral therapy was 0.24 mg/100 ml (normal - 0.44 mg/100 ml) which approached the peak levels of 0.3 mg/100 ml obtained in 2 children who received a large, single intramuscular load. Since the natural history of the condition is toward progressive deterioration, and as no other form of therapy was introduced during administration of vitamin E, it seems likely that this vitamin has contributed to the improvement. No adverse effects mentioned by the authors.

Nano, H., Gilabert, N., Scenna, M. & Baron, H. G.
 Vitamin E in Ophthalmology.
 Ann. Oculist 186: 987-994, 1953; Abstract: Annotated Bibliog. Vitamin E 3: 163, 1952-1954.

Alpha-tocopheryl acetate given in daily doses of from 150 to 600 mg. for 20 days to 6 months was effective in treating 4 out of 7 patients with diffuse sclerosis of the choroid vessels, 4 out of 7 with macular abnormalities, and 9 out of 11 with degenerative myopia. The most prompt and impressive effects were seen in 5 patients with abnormalities of the papilla or retrobulbar nerve.

Nikkila, E. A. & Pelkonen, R.
 Serum Tocopherol, Cholesterol, and Triglyceride in Coronary Heart Disease.
 Circulation 27: 919-928, 1963.

Serum lipids were estimated in 175 male myocardial infarct survivors, 214 blood donors, and 70 healthy persons. They were given a tocopherol loading test of 2 g. of tocopherol acetate. (No adverse effects reported by author).

Nikolowski, W. & Adam, W.
 Zur Therapie der Oligo- und Asthenospermie.
 Proc. World Congr. Fertility and Sterility, 2nd., 729-735, 1956.

EPHYNAL for oligospermia: Case 1: 10 x 300 mg. i.m. in the course of 5 weeks; Case 2: 400 mg/day for 3 months, 600 mg/day for 1 month; Case 3: 1,000 mg. EPHYNAL; Case 4: 2,000 mg. EPHYNAL.
 No adverse effects reported by the authors.

O'Connor, V. R.

Correspondence (Letter to the Editor).

Summary 11: 71-72, 1959; Abstract: Annotated Bibliog. Vitamin E 5: 146, 1958-1960.

Case report of a 39-year-old man, weighing 252 lbs., with generalized edema and acute nephritis. Improvement was evident within 5 days after daily administration of 675 I.U. alpha-tocopherol began; edema disappeared, albuminuria decreased, and sedimentation rate returned toward normal. On a maintenance dose of 450 I.U. alpha-tocopherol daily, the patient remained symptom free.

Oski, F. A. & Barness, L. A.

Vitamin E Deficiency: A Previously Unrecognized Cause of Hemolytic Anemia in the Premature Infant.

J. Pediat. 70: 211-220, 1967.

The late anemia of some premature infants has been found to be due to hemolysis at six to ten weeks. This anemia is correctable by administration of vitamin E. The vitamin E deficiency is probably induced by low vitamin E stores at birth, and dietary insufficiency, or by factors in the diet causing increased use of vitamin E. Eleven infants weighing 1,100-1,920 g. received total doses of 200-800 mg. of vitamin E p.o. (No adverse effects mentioned by the authors.)

Owens, W. C. & Owens, E. U.

Retrolental Fibroplasia in Premature Infants. II. Studies on the Prophylaxis of the Disease: The Use of Alpha-Tocopheryl Acetate.

Am. J. Ophthalmol. 32: 1631-1637, 1949.

For a period of 10 months, alternate infants admitted to the premature nursery with birth weights of three pounds (1,360 gm) or less were given supplements of dl-alpha-tocopheryl acetate. The dose used was 150 mg. daily, given orally in 50 mg. doses every eight hours between feedings. During this 10-month period, 11 infants received vitamin E supplements and none developed retrolental fibroplasia. Fifteen infants in the control group did not receive vitamin E, and five of these developed retrolental fibroplasia. The average serum tocopherol level in the unsupplemented group of premature infants was 0.25 mg. percent. On a dosage of 50 mg. of dl-alpha-tocopheryl acetate every eight hours, the average serum tocopherol level rose to 4.12 mg. percent. No adverse effects reported by the authors.

Pennock, L. L. & Minno, A. M.

Vitamin E in Treatment of Leg Ulcers.

Angiology 1: 337-350, 1950.

In these trials alpha-tocopherol, in doses of 300 to 1000 mg. daily, failed to improve the healing time of various leg ulcers.

Pillokat, A.

Is the Treatment of Induratio Penis Plastica with Vitamin E an Advance?
Supplement to the Paper by Suesse and Aurig.

Deut. Gesundheitsw. 7: 1227-1228, 1952; Abstract: Annotated Bibliog.
Vitamin E 3: 133, 1952-1954.

A 44-year-old man was treated with 200 mg. of alpha-tocopherol, part orally and part intramuscularly, for 10 weeks. He reacted to the injections and also showed aggravation of his Peyronie's disease. He later responded to x-ray therapy. Vitamin E treatment was rejected as irrational.

Pratesi, G. & Serafini, U. M.

Vitamin E and Fragility of the Small Blood Vessels.

Boll. Soc. Ital. Biol. Sper. 27: 1664-1667, 1951; Abstract: Annotated
Bibliog. Vitamin E 2: 75, 1950-1951.

Five subjects with various disease and with evidence of increased vascular fragility were given single doses of 150 mg. alpha-tocopherol intramuscularly. No improvement in vascular strength resulted as measured 5 hours after treatment by the Hecht test (formation of petechiae under negative pressure). Five similar subjects were injected with 600 mg. alpha-tocopherol, also without measurable improvement. Five of the patients were given 150 to 300 mg. alpha-tocopherol daily for 7 to 10 days and then were tested for capillary fragility. Only one of the five showed a definite decrease in fragility.

Pratesi, G. & Serafini, U. M.

Research on the Action of Vitamin E in Some Collagen Diseases.

3 Congr. Intern. Vitamin E 1: 54, 1955; Abstract: Annotated Bibliog.
Vitamin E 4: 163, 1955-1957.

Patients with various collagen diseases showed no change in capillary fragility 5 hours after a dose of 150 or 600 mg. alpha-tocopherol. Capillary permeability decreased appreciably in individuals with acute rheumatic fever and slightly in cases of rheumatoid arthritis, acute lupus erythematosus, dermatomyositis, and sclerodermic arthritis.

Prosperi, P.

Vitamin E in the Treatment of Hemophilia.

Summary 4: 1-6, 1952; Abstract: Annotated Bibliog. Vitamin E 3" 147,
1952-1954.

Twelve cases of hemophilia and two cases of acquired pseudo-hemophilia were treated with 100 to 400 mg. vitamin E daily by mouth. In all cases the coagulation time was lowered, from initial levels as high as 3 hours, to normal, or even to subnormal values, following treatment with vitamin E. If vitamin E therapy is used, it must be given constantly at levels of 50 to 100 mg. daily during periods of well-being with normal coagulation time. The dose must be rapidly increased to 300 to 500 mg. daily in cases of articular pain, or if grave hemarthrosis develops.

Prosperi, P. & Dell'Orso, S.
 Vitamin E in the Prophylaxis of Neonatal Hemorrhage in Newborn.
 Riv. Clin. Pediat. 52: 501-511, 1953; Abstract: Annotated Bibliog.
 Vitamin E 3: 129, 1952-1954.

Thirty-two women were injected intramuscularly with tocopherol (approx. 500 mg.) just prior to parturition. Coagulation times and bleeding times were decreased and prothrombin time was decreased in 72% of the women. Hemorrhagic conditions did not appear in any of the babies born to mothers treated with tocopherol. Prothrombin times of the umbilical cord blood were invariably reduced below the values of normal controls..

Raskin, I. M. & Estrin, E.I.
 [Vitamins A and E in the Treatment of Coronary Atherosclerosis.]
 In Materialy XV Nauchnoi sessii Instituta pitaniya Akademii
 Meditsinskikh Nauk SSSR, 1964, Moscow 1: 49-50, 1964; BA 47:
 11275, 1966.

When 45 male patients with coronary atherosclerosis were treated with vitamin E at 50-70 mg intramuscularly in combination with vitamin A at 50,000 units by mouth per day for 20 days, along with the usual spasmolytics and sedative. Improvement was noted in 37. However, the improvement was less marked and less prolonged than after treatment with vitamin E alone.

Ratcliffe, A. H.
 Vitamin E in Intermittent Claudication.
 Lancet 2: 1128-1130, 1949.

Forty-one cases of obliterative vascular disease leading to intermittent claudication were treated with vitamin E (alpha-tocopheryl acetate, 400 mg. daily). After 3 months, 34 of those treated were improved whereas only 5 of a control group of 25 were improved. The results are highly significant. One of the striking observations was the delay before improvement was noticed. This was 4 to 8 weeks, an average of 6 weeks. Negative results with doses of less than 400 mg. of alpha-tocopherol or treatment periods less than 3 months should be considered inadmissible.

Raverdino, E.
 Vitamin E and Vascular Disorders of the Eye.
 Vitamina E, Atti 3 Congr. Intern. 420-444, 1956; Abstract: Annotated
 Bibliog. Vitamin E 4: 188, 1955-1957.

Patients with thrombosis in the vessels of the eye had slightly subnormal levels of tocopherol in their blood. In cases where the central or peripheral vessels were partly closed, administration of high doses of vitamin E (450 mg. alpha-tocopherol) daily markedly reduced both edema and hemorrhages in the area surrounding the thrombotic vessel and the area supplied by the vessel. In cases where complete vascular occlusion had occurred, neither vitamin E nor heparin administration was effective.

Reifferscheid, M. & Matis, P.
 Vitamin E in the Treatment of Hemorrhagic Injuries, Dupuytren's
 Contracture and Thromboses.
 Med. Welt 20: 1168-1172, 1951; Annotated Bibliog. Vitamin E 2:
 75, 1950-1951.

Vitamin E therapy was found to be definitely protective against thromboembolic occurrences. Doses of 300 to 600 mg. alpha-tocopherol daily seemed necessary. Early circumscribed diabetic gangrene (5 cases), Raynaud's disease (9 cases), moderately severe Dupuytren's contracture (7 cases), and hemorrhagic diseases (14 cases) all yielded to tocopherol treatment. Rabbits injected with 150 to 300 mg. alpha-tocopheryl acetate daily showed an increase in plasma antithrombin. In human subjects about 50% showed an increase in plasma antithrombin following vitamin E treatment.

Richards, H. J.
 Dupuytren's Contracture Treated with Vitamin E.
 Brit. Med. J. 1: 1328, 1952.

A series of 46 cases of Dupuytren's contracture were treated; 24 had bilateral lesions. Vitamin E was the sole form of treatment, and in no case was any improvement noted. EPHYNAL, 100 mg. twice daily, was administered orally for a minimum period of 3 months. This dosage and the period of administration seemed reasonable for the purpose of producing a response, should any be likely to occur. On this dosage no toxic effects were noted.

Rinzler, S. H., Bakst, H., Benjamin, Z. H., Bobb, A. L. & Travell, J.
 Failure of Alpha-Tocopherol to Influence Chest Pain in Patients with Heart Disease.
 Circulation 1: 288-293, 1950.

Effects of EPHYNAL acetate and a placebo were compared by the blind-test method in 41 ambulatory patients with chronic chest pain and heart disease (chiefly arteriosclerotic and hypertensive). EPHYNAL acetate was given to 19 patients by mouth in daily doses of 200 mg. for about 2 weeks, and 300 mg. thereafter. A similar number of placebo tablets was given. The average duration of administration of the vitamin was 16 weeks (10 to 20 weeks) and of the placebo 16.6 weeks (10 to 20 weeks). No toxic effects of these doses of alpha tocopherol were noted. The effects of medication on chest pain and on objective measurements of cardiac and skeletal muscle function were similar for the group given alpha-tocopherol and for the controls who received the placebo.

Ritchie, J. H., Fish, M., Brady, J., McMasters, V. & Grossman, M.
Edema and Anemia in Premature Infants, a New Syndrome Due to Vitamin E Deficiency: Elucidation of the Nature of the Anemia.
Clin. Res. 16: 155, 1968.

Abstract of paper. A study of 8 premature infants with widespread edema, anemia, reticulocytosis, and thrombocytosis is presented. The edema cleared and the hematologic abnormalities were corrected in 5 infants who were treated with 50-100 mg. of vitamin E daily p.o. for at least one week.

Ritchie, J. H., Fish, M. B., McMasters, V. & Grossman, M.
Edema and Hemolytic Anemia in Premature Infants. A Vitamin E Deficiency Syndrome.
New Engl. J. Med. 279: 1185-1190, 1968.

Widespread edema, anemia, reticulocytosis, thrombocytosis and vitamin E deficiency were noted in 7 premature infants during the second month of life. When vitamin E (alpha-tocopherol acetate), 75 to 100 I.U. daily (given in three or four 25 mg. doses daily), was given separately by mouth to 5 infants available for treatment and study, serum tocopherol level rose, reticulocyte count fell to normal and erythrocyte survival time lengthened; this was followed by correction of the anemia, clearing of the edema and subsidence of the thrombocytosis.

Rizzi, C.

Action of Vitamin E on the Ocular Tension.

3 Congr. Intern. Vitamin E 1: 73, 1955; Annotated Bibliog. Vitamin E 4: 188, 1955-1957.

Each of 7 male individuals were given 450 mg. vitamin E daily during two 6-day periods separated by a 3-day interval. Blood tocopherol levels increased from an average of 1.07 mg. % to an average of 1.91 mg. % during treatment but responses of ocular tension and ocular tonus varied from an evident decrease to an evident increase.

Rodriguez Guerrero, F. A.

Effect of Alpha-Tocopherol on the Blood Sugar of Apparently Healthy Subjects.

Folia Clin. Intern. 7: 83-90, 1957; Abstract: Annotated Bibliog. Vitamin E 4: 197, 1955-1957.

Blood sugar levels before and 24 hours after intramuscular injection of 300 mg alpha-tocopheryl acetate averaged 77.13 ± 1.27 mg. % and 70.22 ± 1.86 mg. %, respectively, for 22 women, and 80.60 ± 5.55 mg. % and 73.50 ± 5.48 mg. %, respectively, for 10 men.

Sack, G. M.

Neue Wege in der Behandlung der Mastopathie.

Medizinische 1955 (20/30): 1052-1053.

Vitamin E (EPHYNAL) was successfully used in the treatment of 16 patients. In the author's opinion this treatment is efficacious only if high enough doses of the vitamin are used. His dose schedule is 400 mg. per day for at least 3-4 months, then 100 mg. per day for at least 1/2 - 1 year (Total dosages of 60 g. over a 1-year period tolerated without any adverse effects).

Schmidt, L.

The Influence of Vitamin E on Cardiovascular Disorders:

Med. World 72: 296-298, 1950; Abstract: Annotated Bibliog. Vitamin E 2: 71, 1950-1951.

Fifty-one patients with cardiovascular disease, rheumatic heart, coronary thrombosis, angina pectoris, myocardial insufficiency, and hypertensive heart were treated with vitamin E with excellent results. Clinical improvement occurred promptly and was followed in most cases by electrocardiographic evidence of improvement. The vitamin E therapy consisted of oral administration of 300 to 450 I.U. alpha-tocopherol daily for periods of three or more months.

Schmitt, A. & Luzius, H.

The Effects of Vitamin E Medication on Skin Temperature.

Aerztl. Forsch. 8: 45-50, 1954; Abstract: Annotated Bibliog. Vitamin E 3: 168-169, 1952-1954.

Forty-one persons, 15 to over 60 years of age, were given daily doses of 300 mg. of alpha-tocopherol, orally or parenterally, for periods of 10 to over 60 days. Skin temperatures were measured with thermocouples at 6 points of the head, 6 on the body, 3 on the fingers and toes, and 4 on back of hands and foot. The temperatures varied greatly but the averages showed an initial rise, a secondary fall, then an increase to a level above the original level prior to alpha-tocopherol administration.

Schneider, E.

Specific Therapy of Bradytrophic Tissue with Massive Doses of Vitamin E.

Langenbecks Arch. Klin. Chir. 273: 809-816, 1952-1953; Abstract: Annotated Bibliog. Vitamin E 3: 133, 1952-1954.

Patients with epichondylitis and showing fatigue and decalcification, were treated with tocopherol; 600 mg. alpha-tocopherol daily by intramuscular injection for 14 days, then 300 to 600 mg. daily by mouth for 14 days. Clinical improvement was observed within two weeks; swelling was relieved and decalcification stopped.

Schneider, E.

Treatment of Skeletal System Diseases.

Therapiewoche 3: 467, 1953; Abstract: Annotated Bibliog. Vitamin E 4: 160, 1955-1957.

Fifty patients with epicondylitis were treated with 300 to 600 mg. alpha-tocopherol orally per day. After about 8 days, pain decreased and after 3 to 4 weeks, deposition of calcium ceased. One case of painful damage to a tibial joint capsule was described in detail. So long as the patient continues her alpha-tocopherol therapy she is free of pain and swelling and the ankle retains its mobility. Plastic operations on joints were formerly accompanied by danger of thrombosis and slow (6 months) healing of the implants. Alpha-tocopherol administration greatly shortened the period of convalescence and patients now are able to move the joint in about 3 weeks.

Seidenari, R., Mars, G. & Morpurgo, M.

Vitamin E in Hypertensive Arteriosclerotic Retinopathy.

Acta Gerontol. 1: 55-78, 1951; Abstract: Annotated Biblio. Vitamin E 3: 162, 1952-1954.

Oral and parenteral treatment with 200 to 400 mg. alpha-tocopheryl acetate was given to 20 patients, aged from 51 to 78 years, with retinal changes due to hypertension and arteriosclerosis. Treatment lasted at least one month. The eye condition was definitely improved in 12, slightly improved in 5, and not improved in 3. There was some subjective improvement. The effect is considered to be pharmacological. Some case histories are given. Treatment must be maintained or relapse is likely to occur.

Serafini, U. M. & Pratesi, G.

Modification of Capillary Permeability in Humans Following Administration of Vitamin E During Various Disease.

Boll. Soc. Ital. Biol. Sper. 27: 1660-1663, 1951; Absr.: Annotated Bibliog. Vitamin E 2: 75, 1950-1951.

Sixteen patients with evidence of abnormal capillary permeability, as measured by the method of Landis, were treated with a single intramuscular injection of either 150 or 600 mg. alpha-tocopherol. Five hours later the permeability tests were repeated and a definite protective effect was observed in those who had received 150 mg. doses and a greater beneficial effect in those given 600 mg.

Shute, E. V.

Vitamin E for Menopausal Complaints.

Summary 2: 34-37, 1950; Abstract: Annotated Bibliog. Vitamin E 2: 81, 1950-1951.

The senile pruritus vulvae or ani which is often associated with menopause was relieved only by large doses, 300 to 600 mg. vitamin E. Twenty-three of 34 cases of pruritus ani and 20 of 32 patients with pruritus vulvae were helped by vitamin E therapy. Treatment must be persisted in because no effect is observed for 2 to 4 weeks after commencing therapy.

Shute, W. E.

Fragilitas Ossium—Two Brief Case Reports.

Summary 5: 1-2, 1953; Abstract: Annotated Bibliog. Vitam E 3: 136, 1952-1954.

Administration of 200 I.U. of alpha-tocopherol daily to a child from her 4th to 13th month of age completely changed the course of the disease, fragilitas ossium, a rare condition in which the bones are unusually fragile but in which fractures heal rapidly. Under alpha-tocopherol treatment, no fractures occurred although in this period the child learned to crawl and sustained several falls from chairs.

Shute, W. E.

Acute Nephritis Treated with Alpha-Tocopherol.

Summary 5: 2-4, 1953; Abstract: Annotated Bibliog. Vitamin E 3: 140, 1952-1954.

Three boys, 4, 6, and 14 years of age, suffering from acute nephritis, were treated with 300 to 450 I.U. of alpha-tocopherol daily. The patients responded rapidly. Hematuria, albuminuria and edema disappeared and body temperature returned to normal within one week.

Shute, E. V.

Premature Rupture of the Membranes as an Indication for the Use of Alpha-Tocopherol.

Summary 6: 15-17, 1954; Abstract: Annotated Bibliog. Vitamin E 3: 158, 1952-1954.

Thirty-two consecutive and unselected cases of threatened premature labor or miscarriage because of prematurely ruptured membranes were given identical care except that some were given 75 to 600 I.U. of alpha-tocopherol daily. Eighty-eight percent of the women with threatened premature labor who were receiving alpha-tocopherol supplementation continued on to term. Only 20% of the untreated controls did so. In the threatened miscarriage group 88% of the vitamin E treated women continued for several weeks longer or to term in contrast to only 38% of the untreated patients.

Shute, E.

Alpha-Tocopherol for Pruritus Ani.

Summary 7: 15-16, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 180, 1955-1957.

Daily doses of 400 to 600 I.U. of alpha-tocopherol were very helpful in treating 23 cases of pruritus ani of the degenerative type. Increased local vascularity, restoration of normal color and tissue turgor, and healing of cracked skin resulted from the treatment.

Shute, E. V.

Vitamin E in Cardiovascular Diseases.

Vitamina E, Atti 3 Congr. Intern. 393-403, 1956; Abstract: Annotated Bibliog. Vitamin E 4: 173, 1955-1957.

M. Lee, England, during discussion reported on results obtained with vitamin E in a large varicose ulcer clinic. Doses of 400 mg. alpha-tocopherol were used in a double-blind type study on 57 patients with long-existent, treatment-resistant ulcers. Healing was more rapid in the vitamin E supplemented group. Considering only the patients with a history of deep venous thrombosis prior to ulceration, the average time of healing was 9.9 weeks for the vitamin E treated vs. 15.8 weeks for the placebo controls. There seemed to be no correlation between the rate of healing and the levels of plasma tocopherol.

Shute, E. V.

Alpha Tocopherol in the Management of Chronic Phlebitis and the Post-Phlebitic Syndrome.

Can. Med. Assoc. J. 80: 189-194, 1959.

All the 166 patients received no other therapy to the vascular system than large doses of alpha tocopherol (300 to 2000 I.U. daily). (No adverse effects reported by the author).

Shute, W. E., Shute, E. V. & Vogelsang, A. B.

Vitamin E in Heart Disease. I. The Anginal Syndrome.

Med. Record 160: 91-96, 1947; Abstract: Annotated Bibliog. Vitamin E 1: 135, 1940-1950.

A series of 84 unselected, consecutive cases manifesting anginal pain as one of the major symptoms were treated with alpha-tocopherol in doses of 200 to 600 mg. daily. The majority responded favorably.

Shute, E. V., Vogelsang, A. B., Skeleton, F. R. & Shute, W. E.

Influence of Vitamin E on Vascular Disease.

Surg. Gynecol. Obstet. 86: 1-8, 1948.

Vascular diseases such as thrombophlebitis, indolent varicose ulcers of the legs, early gangrene of the extremities, and thromboangitis obliterans which have yielded to alpha-tocopherol therapy were described using detailed case records and color photographs. About 200 to 300 mg. of alpha-tocopherol daily was required for effective therapy. Parenteral administration was preferred in cases of acute cerebral thrombosis for rapid action, 2 or 3 times faster than by oral administration.

Solomon, A.

Moderne und konservative Methoden zur ambulanten Behandlung des Uleus cruris.

Ars Medici 46: 547-552, 1956

On the basis of treatment with massive doses of EPHYNAL in 15 patients with ulcers of the legs, the author concludes that healing and regeneration are very favorably influenced, particularly by parenteral administration. Dosage: 300 mg. EPHYNAL per day twice per week intramuscularly, on other days orally. In general, well tolerated; some patients complained of dizziness, two complained of mild palpitations of the heart, which disappeared on reducing dose to 150-200 mg. Some patients exhibited very marked improvement of their general state of health as well as local improvement. Following intramuscular treatment, more marked secretion of the wound which is considered prognostically favorable.

Souza Araujo, H. C. de

Efficacy of Vitamin E in Amyotrophia of Leprosy.

Arquiv. Mineiros Leprol. 17: 110-113, 1957; Abstract: Annotated

Bibliog. Vitamin E 4: 165, 1955-1957.

Ten patients with amyotrophy of hands due to leprosy were given 30 to 300 mg. vitamin E injected into the atrophied muscles at intervals from 1 to 3 weeks. Total dosage ranged from 300 to 5,400 mg. All patients showed partial or complete function recovery. The volume of muscles increased progressively. Muscle tone and muscular movements of hands improved.

Stachler, F., Babe, G. & Hopp, W.

Experimentell Untersuchungen ueber die Beziehungen des Fertilitetsfaktors E (Tokopherol) zur inneren Sekretion der Ovarien und der Hypophyse.

Arch. Gynaekol. 174: 236-258, 1942.

Further studies on tocopherol as fertility factor have shown that, in the castrated rabbit, the corpus luteum hormone can be replaced by tocopherol acetate if the latter is given in abnormally high doses (2500 g.). Ovaries of young rats (100-130 g.) weighed on the average 25.2 mg. after 10 days of tocopherol acetate treatment (1000 mg.) compared to 20.6 in control animals. Young rabbits mature more rapidly than controls after 4-6 weeks on 9 mg. tocopherol acetate/day. Female rats given 100 mg. tocopherol acetate/day for 4 weeks became sterile earlier than their untreated controls. Two castrated women were given 21000 mg. of alpha-tocopherol acetate per os without resulting adverse effects.

Steinberg, C. L.

Tocopherols (Vitamin E) in Treatment of Primary Fibrositis.

J. Bone Joint Surg. 24: 411-423, 1942; Abstract: Annotated Bibliog. Vitamin E 1: 119, 1940-1950.

All of 12 patients given 200 mg. of synthetic alpha-tocopherol in corn oil intramuscularly at weekly intervals and observed for 2 to 4 months were definitely relieved.

Steinberg, C. L. R.

A New Method of Treatment of Dupuytren's Contracture, a Form of Fibrositis.

Med. Clin. N. Am. 30: 221-231, 1946.

Vitamin E is of value in the treatment of early and moderately advanced Dupuytren's contracture. The optimum dosage is 300 mg. of vitamin E daily given in divided doses of 100 mg. three times daily until maximum improvement occurs and then a maintenance dose of 1 mg. per kilogram of body weight. No untoward effects have been obtained from oral vitamin E given over a period of three to four years in a maintenance dose of 1 mg. per kilo.

Stuettgen, G., Betzler, H. & Witte, W.

Assay of Vitamin E in Serum and Skin Fat with Phosphomolybdic Acid.

Arzneimittel-Forsch. 7: 407-408, 1957.

Oral doses of 2 or 4 g. alpha-tocopherol raised human blood levels 350% and 500% respectively, but caused no increase of tocopherol in skin fat. Cutaneous application had no effect on the blood level.

Suardi, L.

The Influence of Prolonged Administration of Tocopherol on the

Sympathetic Tissues and on the Endocrine Organs of the Hypophysectomized Rat.

Gazz. Intern. Med. e Chir. 64: 1245-1255, 1959; Annotated Bibliog.

Vitamin E 5: 72, 1958-1960.

Hypophysectomized rats were treated with 20, 50, or 100 mg. vitamin E daily for 15 days. Such treatment caused no appreciable modifications of the histological changes found in untreated hypophysectomized animals in the spleen, lymph nodes, adrenals, testes, ovaries, thyroids, or parathyroids. The pancreas in the animals treated with vitamin E showed slight insular hyperplasia. The role of the hypophysis in the mechanism of action of vitamin E on the endocrine gland is discussed.

Thomas, P.

The Effects of Vitamin E on Some Aspects of Athletic Efficiency.
Thesis, Univ. of Southern California, Los Angeles, 54 pp, 1957;
Abstract: Annotated Bibliog. Vitamin E 4: 197, 1955-1957.

The effect of vitamin E on athletes in training was investigated with 30 male students. Fifteen were given 450 I.U. of alpha-tocopheryl acetate daily for 5 weeks and then given placebos for 5 weeks. The other group received placebos first, followed by vitamin E. Measurements at 0, 5, and 10 weeks of reclining pulse rate, resting respiratory rate, speed sit-ups, vertical jump, and of pulse rate and respiratory rate immediately after activity showed no differences between the groups during either test period. In addition, no changes were observed in temperament, disposition, or general feeling of well-being.

Tolgyes, S.

The Outlook for Life in Intermittent Claudication Patients Treated with Alpha Tocopherol.

Summary 11: 9-14, 1959; Abstract: Annotated Bibliog. Vitamin E 5: 159, 1958-1960.

A total of 30 consecutive patients with intermittent claudication due to arteriosclerosis, diabetes, or Buerger's disease are reviewed in relation to their prognosis for life. All have been on alpha-tocopherol therapy for 5 years or more. No other vasodilator has been used. Excellent functional results were obtained in 30% of the patients. Figures given in 4 references regarding such patients show 5-year survival of 72 to 84% (average, 75%). In this study survival rate was 90%. In respect to both survival and relief of symptoms, alpha-tocopherol in doses of 120 to 800 I.U./day apparently has much to offer cases of intermittent claudication.

Vogelsang, A.

Alpha-Tocopherol (Vitamin E) in Obliterative Arterial Disease.
Intern. Rec. Med. 164: 353-357, 1951; Abstract: Annotated Bibliog.
Vitamin E 3: 144, 1952-1954.

Of 42 cases of arteriosclerotic gangrene and indolent ulcers, 41 responded beneficially. No other treatment was used; in cases of Buerger's disease smoking was not stopped. Dosage was 600 to 700 I.U. alpha-tocopherol by mouth daily in all cases except the diabetics which were given 300 units daily. In sufficient dosage, alpha-tocopherol exerts a capillary-dilating effect in those areas in which the blood supply has been inadequate. By an effect which encourages the growth of new capillaries into old sclerotic fibrous tissue promoting resorption of scar tissue, the collagenous tissues are repaired. To maintain the improvement, the medication must be continued at a high level indefinitely, and when the medication is halted, the symptoms will reappear.

Vogelsang, A.

Ten Years' Experience in Using Alpha-Tocopherol in Certain Cardiovascular Conditions.

3 Congr. Intern. Vitamin E 1: 61, 1955; Abstract: Annotated Bibliog. Vitamin E 4: 173-174, 1955-1957.

Ten years experience with alpha-tocopherol in some degenerative cardiovascular conditions indicates doses of 300 to 400 I.U. daily for congestive failure with pulmonary and/or peripheral edema, 400 I.U. daily for coronary thrombosis and coronary insufficiency, 600 to 900 I.U. daily for the first few weeks in arteriosclerosis obliterans and in thromboangiitis obliterans followed by 400 I.U. daily, and 600 I.U. daily for 3 weeks only in acute thrombophlebitis. Alpha-tocopherol is not so effective in aortic regurgitation and should not be given to hyperthyroid heart cases.

Vogelsang, A.

Twenty-Four Years Using Alpha-Tocopherol in Degenerative Cardiovascular Disease.

Angiology 21: 275-279, 1970.

The author reviews use of alpha-tocopherol in degenerative heart disease based on his experience in approximately 5,000 cases. He warns that problems may arise from the synergism between alpha-tocopherol and digitalis products. The usual maintenance dose of digitalis has been what we used to know as the "cat unit". This is equivalent to 1.5 gr of digitalis folia, 0.1 mg of digitoxin, or 0.25 mg of digoxin. When used alone with alpha-tocopherol the maintenance dosage should not exceed one-half of the above dosage or electrocardiographic, electrolyte (potassium) depletion and clinical evidence of digitalis intoxication will probably ensue. No patient with hyperthyroid heart should be given alpha-tocopherol. Any iron medication will effectively erase the beneficial effect of the alpha-tocopherol. Laxatives containing mineral oil have a tendency to coat the gastrointestinal tract. Since alpha-tocopherol is oil-soluble the medication may be carried away by the oil without being absorbed. He suggests doses of up to 600 mg. for prolonged periods in coronary insufficiency, also in coronary thrombosis, Buerger's disease, acute thrombophlebitis and prevention of thrombophlebitis, intermittent claudication and decubitus ulcers.

Vogelsant, A. B.

Thrombocytopenic Purpura Treated with Vitamin 'E'.

Med. World 64: 448-449, 1946; Abstract: Annotate Bibliog. Vitamin E 1: 134, 1940-1950.

A 67-year-old male with severe thrombocytopenic purpura was given 200 to 600 mg. of alpha-tocopherol daily for 5 months. His blood platelet count increased to normal and purpuric areas disappeared. Iron salts administered orally during vitamin E therapy seems to vitiate the beneficial action of alpha-tocopherol.

Wallis, K., Gross, M., Zaidman, J. L., Julsary, A., Szeinberg, A. & Kook, A. I.

Tocopherol Therapy in Acanthocytosis.

Pediatrics 48: 669-671, 1971.

In the case presented, intramuscular administration of large doses of tocopherol (100 mg. twice a week then reduced to once a week) resulted in a significant clinical improvement of muscular and neurological disturbances confirmed by electromyographic examination and muscle biopsy after six months of treatment, though no improvements in field vision and retinal function were observed.

Weber, F. & Weiser, H.

Vitamin E-Bedarf.

Wiss. Veroeffentl. Deut. Ges. Ernaehrung 16: 137-145, 1957.

Under average conditions of nutrition, the daily requirement is between 5 and 30 mg. of vitamin E. Approximately 1 mg. of vitamin E per gram of polyunsaturated fatty acids should be ingested with the food in order to cover the increased vitamin E requirement.

Wechsler, I. L.

Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E.

Arch. Neurol. Psychiat. 45: 873-878, 1941; Abstract: Annotated Bibliog. Vitamin E 1: 128, 1940-1950.

Twelve of 37 patients showed improvement when the dose of vitamin E was large enough. Some who did not do well on 100 mg. daily began to improve on 150 to 300 mg. intramuscularly and 200 mg. by mouth. As much as 1,000 mg. of tocopherol intramuscularly and the same amount orally was given to some patients every day.

Wegner, A.

Treatment of Ulcus Cruris with Massive Doses of Vitamin E

Dermatol. Wochschr. 123: 385-389, 1951; Annotated Bibliog. Vitamin E 2: 76, 1950-1951.

Ten patients with obstinate varicose ulcers were treated with 300 mg. vitamin E daily for 8 to 55 days either orally or intramuscularly. Response was quite variable but some healing was promoted particularly in those cases given local therapy combined with vitamin E administration.

Wenig, H. & Westphal, J.

Treatment of Scleroderma in New born with Vitamin E.

Zentr. Gynaekol. 80: 1673-1677, 1958; Abstract: Annotated Bibliog. Vitamin E 5: 151, 1958-1960.

In 2655 births between 1956 and 1957, sclerema neonatorum occurred in 26 infants (7 female and 19 male). Treatment was 15 mg. alpha-tocopherol intramuscularly daily for 2 or 3 days. Increased excretion of urine occurred 3 or 4 days after the first tocopherol injection and continued until edema disappeared. Excretion of 17-ketosteroids in urine, which significantly increased during development of sclerema, decreased to original levels following tocopherol treatment.

Zacherl, H.

On the Menopause and Its Treatment.

Wien. Klin. Wochschr. 64: 569-571, 1952; Abstract: Annotated Bibliog. Vitamin E 3: 160, 1952-1954.

Intensive vitamin E therapy consisted of a course of five injections of 300 mg. alpha tocopheryl acetate given on alternate days, and oral administration of 150 mg. alpha-tocopheryl acetate on the intervening days. Patients then received 150 mg. alpha-tocopheryl acetate orally daily for about a month, and then 100 mg. daily as a maintenance dose. It is concluded that vitamin E therapy during the menopause is advantageous because of its lack of harmful side-effects.

Vitamins for Mental Illness?

Amer. Drug 166: 39-40, 1972.

Over the past 5 years, Dr. David R. Hawkins, Director of the North Nassau Mental Health Center, in Manhasset, New York has treated almost 5,000 schizophrenia patients with massive doses of vitamins C and E, niacin, and pyridoxine and he claims that he achieved significant improvement in more than 4,000 of them. His regimen included in addition to the large doses of vitamins a high protein-low carbohydrate diet, mineral supplements, tranquilizers, antidepressants, and supportive psychotherapy. But the psychiatrist emphasizes that the "megavitamin" therapy is the key element in the treatment program. According to Dr. Hawkins, he usually gives his schizophrenic patients the following oral doses of vitamins every day: about 4 g of ascorbic acid, 4 g of niacin or the equivalent in niacinamide, between 50 mg. and 200 mg. of pyridoxine, between 1,000 international units and 1,600 I.U. of alpha-tocopherol. He usually supplements the above oral doses with three-times-weekly injections of vitamins for speedier response in hospitalized patients.

Side-Effect of Vitamin E Therapy. (Letter to the Editor).

Brit. Med. J. 1: 493, 1950.

An interesting side-effect observed during vitamin E therapy is recorded. A patient has a duodenal ulcer, comparatively quiescent, together with an early Dupuytren's contracture. The latter complaint was treated with tablets of alpha-tocopheryl acetate. Half an hour after taking the first two tablets the patient developed severe epigastric pains and vomiting, which lasted for about an hour. On taking the next two the same thing occurred. He again took only one tablet, but this caused the pain and vomiting. On stopping administration of the tablets there was no further trouble. The symptoms could not be produced by giving other tablets, such as aspirin or phenobarbitone.

**Problems of Cardiovascular Diseases in an Ageing Population.
A Symposium.**

Brit. Med. J. 2: 112-113, 1951.

Lumbar ganglionectomy gave excellent results and alpha-tocopheryl acetate, 400 mg. daily, gave similar results but took 3 to 4 months to do so.

Intermittent Claudication.

Lancet 2: 59-61, 1950.

Of the various drugs which have been tried at the Manchester clinic, the only one which has given encouraging results, as regards both claudication and nutrition of the leg, is vitamin E by mouth. The optimal dosage is 400 mg. daily, and benefit is usually observed within 6 to 8 weeks.

Daily Vitamin E Check Poisoning from Digitalis.

Med. Tribune 9 (2): 2, 1968.

Dr. H. Hochrein reported that initial intravenous injection of 200-400 mg. vitamin E followed by daily oral administration of 200-300 mg., successfully checked digitalis intoxication in 80% of cases, without necessitating withdrawal of cardiac glycosides. He also stated that in guinea pig heart-lung preparations, even very large doses of vitamin E have neither toxic or hemodynamic action. Studies of myocardial electrolyte and water metabolism, however, have shown that load capacity of the heart is increased under the in vitro action of vitamin E. In the isolated heart, digitalis toxicity is halved by large doses of vitamin E. Drs. J. Marks and A. M. Boyd report that a daily dose of 400 mg. vitamin E for six weeks is the required minimum for influencing peripheral arteriosclerotic processes manifesting themselves as intermittent claudication. This is described as a pharmacodynamic effect rather than a "vitamin" action.

Editor, Medical Tribune.

Med. Tribune 12 (43): 15, Nov. 3, 1971, (Reprint).

The correspondent reports control of restless legs syndrome (6 cases) by continued usual of d-alpha-tocopherol acetate with dosage of 400 I.U. one or two times per day. He points out that it is important to remember that simultaneous use of iron or mineral oil may interfere with beneficial effects.

World Health Organization
Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants.
WHO Tech. Rept. Series No. 228: 102-104, 1962; Bibliography on Vitamin
E 6-7: 1040, 1960-1967.

Human Requirement.

In Mitchel, H. S., Rynbergen, H. J., Anderson, L. & Dibble, M. V.
Nutrition in Health and Disease, 15th ed., J. B. Lippincott Co.,
Philadelphia and Toronto, p. 90, 1968.

The Food and Nutrition Board states that vitamin E requirement varies between 10 and 30 mg. per day for adults, depending on both the level of PUFA in the diet and the amount of other substances (such as selenium) which may spare vitamin E. For infants, a level similar to that found in human milk (0.5 mg/kg) is suggested.

II. Animal Studies

Bottiglioni, E. & Sturani, P. L.

Histological Aspects of the Thyroid in Rats with Vitamin E Deficiency and Treated with Tocopheryl Acetate.

Endocrinol. e Sci. Costituz. 23: 176-182, 1956; Annotated Bibliog.

Vitamin E 4: 94, 1955-1957.

The thyroid was studied in rats in which vitamin E deficiency was induced by o-cresyl acetate or which were treated with increasing doses of alpha-tocopheryl acetate. Generally, decreased functional activity occurred in animals injected for 10 days with a daily dose of 2 or 20 mg., whereas a dose of 100 mg. daily proved much less active in bringing about this effect. In animals with vitamin E-deficiency, the changes observed were not typical and indicated functional activation.

Braginskii, B. M. & Mirzoev, I. M.

[Effect of Certain Vitamins on Excretion of 17-Keto Steroids and Chlorides with the Urine in Local Inhabitants of Eastern Pamir.]

Tr. Tadzhiksk. Med. Inst. 62: 64-68, 1963. CA 63: 6073b, 1965.

A single intake of 100 mg. vitamin E increased 17-keto steroids excretion by approximately 1.5 times; after a 7-day treatment with vitamin E, 17-keto steroids excretion approximately doubled.

Bruce, R. A. & Tobin, C. E.

Effects of Sesame Oil and Fractions of Sesame Oil on Adrenalectomized and Other Experimental Rats.

Endocrinology 27: 956-970, 1940.

Eleven primiparous rats were adrenalectomized on the 15th to 19th day of gestation. Two controls received 0.1 cc. of depleted sesame oil injected subcutaneously on the first postoperative day. The remaining 9 were injected subcutaneously with 2.5 to 10.0 mg. of synthetic alpha-tocopherol that was dissolved in 0.10 to 0.45 cc. of depleted sesame oil. All females gave birth to living young, except one which delivered 12 dead fetuses with intact membranes. Of the 9 females that were given alpha-tocopherol, only 2 weaned any of their young. These 2 weaned 80% and 89% of their litters, a total of 12 young rats. In view of the fact that 7 of the 9 females lost weight during lactation and failed to wean any of their litters, it is suggested that alpha-tocopherol is toxic to adrenalectomized rats during lactation. The alpha-tocopherol was also toxic to immature adrenalectomized male rats.

Butturini, U.

Diphtheritic Paralysis and Vitamin E. VI. Action of Vitamin E on Body Weight, Peripheral Neuritis, and Creatinuria in Experimental Diphtheria Infections.

Giorn. Clin. Med. (Bologna) 24: 7 pp., 1943; Abstract; Annotated Bibliog. Vit. E, 4: 101, 1955-1957.

In acute poisoning of guinea pigs with diphtheria toxin, alpha-tocopherol in daily oral doses of 20 mg. prior to infection and 40 mg. after infection neither increased survival time nor lessened the anatomical symptoms. Under conditions of chronic poisoning, one group of guinea pigs (I) received no vitamin E, one group (II) was given 20 mg. alpha-tocopherol/day for 8 days prior to infection, one group (III) was given 40 mg. vitamin E/day for 10 days after infection followed by 10 mg/day for 53 days, and one group (IV) was given a combination of treatments II and III. Vitamin E maintained creatinuria within normal limits in groups III and IV, and permitted normal growth in group IV. The development of peripheral neuritis was retarded in all supplemented groups and significantly decrease in group IV. It was suggested that vitamin E may be beneficial in improving the glycogen reserve of the muscle.

Castellani, L. & Bertola, G.

Influence of Vitamin E on Free Liver Methionine of Normal and Carbon Tetrachloride-Poisoned Guinea Pigs.

Arch. "E. Maragliano" Patol. e. Clin. 10: 849-853, 1955; Abstract: Annotated Bibliog. Vit. E. 4: 104, 1955-1957.

Daily treatment of guinea pigs with 75 mg. of vitamin E/kg. body weight raised the average methionine content of liver from 1.73 to 2.58 mg/100 g. fresh tissue. When the guinea pigs breathed carbon tetrachloride 10 minutes daily for 20 days, similar treatment with vitamin E raised the average methionine content of liver from 0.81 to 1.29 mg/100 g. fresh tissue.

Chakravarti, R. N., Balkrishna, & Zaidi, S. H.

Effect of Alpha-Tocopherol on Experimental Atherosclerosis.

Indian J. Med. Res. 48: 356-362, 1960; Abstract: Nutr. Abstr. & Revs. 31: 462, 1961.

Four groups of 6 rabbits of average weight 1 kg fed on stock diet were given, by stomach tube daily, olive oil 5 ml alone or with cholesterol 0.5 g, or olive oil and cholesterol and, by intramuscular injection, DL-alpha-tocopheryl acetate 15 mg., or nothing. After 12 weeks they were killed, total and free cholesterol were estimated in samples of heart, aorta and liver. Alpha-tocopheryl acetate considerably increased total and doubled free cholesterol content of aorta, did not affect that of heart, and decreased total and halved free cholesterol, compared with tissues of rabbits given olive oil and cholesterol only. It increased extent of atherosclerosis of aorta and greatly increased its severity as measured by plaque thickness. With olive oil only, biochemical values remained within normal limits and atherosclerosis did not appear.

Chatelier, G. G. du

Does dl-alpha-Tocopherol have a Protective Action Comparable to That of Vitamin P Factors Toward the Adrenaline of the Tissues?

Ann. Pharm. Franc. 9: 203-210, 1951; Annotated Bibliog. Vit. E 2: 77, 1950-1951.

Alpha-tocopheral at high dosage (50 mg/kg) sensitized the guinea pig to the action of histamine, uniformly causing death due to shock. At low doses no sensitization was observed. It did not prolong the time required for the animal to succumb to asphyxiation. However, it protected against an aerosol high in histamine content.

Durack, D. T., Gubbay, S. S. & Kakulas, B. A.

Electrophysiological Studies in the Rottnest Quokka with Nutritional Myopathy.

Australian J. Exptl. Biol. Med. Sci. 47: 581-588, 1969.

The nutritional myopathy of the Rottnest quokka (Setonix brachyurus) was investigated by electromyography and electrocardiography and the finding were correlated with microscopic changes in the skeletal and cardiac muscles. The animals were sedated with 30-40 mg. of VALIUM, given intramuscularly 10 minutes before examination. Complete reversion of the electromyogram to normal occurred following treatment with EPHYNAL 100 mg/week for 10 weeks. No adverse effects reported by the authors.

Dyer, I. A.

Vitamin E for Beef Cattle.

Feedstuffs 39 (12): 20, 1967.

Interest in vitamin E nutrition has increased due to reports of improved performance when this vitamin was fed or injected. Two experiments were initiated with calves to: (1) determine the effects of injected vitamin E in the presence of vitamin A, stilbestrol and phosphorus on performance, and (2) determine the effect of this vitamin with different dietary hay-grain ratios on performance. Data obtained in the two tests show that 500 I.U. (1 mg. dl-alpha-tocopherol acetate equals 1 I.U. vitamin E) vitamin E per calf (injected) was beneficial.

Epstein, S. S., Joshi, S., Andrea, J., Forsyth, J. & Mantel, N.
The Null Effect of Antioxidants on the Carcinogenicity of 3,4,9,10-Dibenzpyrene to Mice.

Life Sci. 6 (Part 1): 225-233, 1967.

A study was made of the effects of life-long feeding of a wide variety of antioxidants, including vitamin E and compounds with vitamin E biopotency, on the response of mice to a polycyclic carcinogen. None of the antioxidants, at any of the concentrations tested, produced any significant decreases in average body weight after 10 weeks of feeding, any significant decreases in average tumor incidence or, finally, any significant increases in average time to tumor-induced death. (Vitamin E given 5% w/w in diet).

Forni, P. V.

Renal Histological Lesions in Experimental Hypervitaminosis.
 Vitaminologia (Turin) 9: 16 p, 1953; Annotated Bibliog. Vitamin E,
5: 81, 1958-1960.

Various hypervitaminoses were induced in male rats and the animals were killed after 15 days. Subcutaneous administration of 1.12 g. tocopherol/kg. body weight did not affect kidney weight and caused no macroscopic changes. Histological examination revealed a mild turbid swelling of the convoluted tubules and of the descending tract. Glomeruli were enlarged and turbid in some cases and shrivelled in others. No stones were observed although the control casein-based diet seem to predispose to formation of renal deposits.

Forni, P. V., Codeca, M. & Fubini, A.

Experimental Hypervitaminosis and Endocrine Organs.
 Ormonologia 15: 23 p., 1955; Annotated Bibliog. Vitamin E, 5: 81,
 1958-1960.

Young male rats given a total of 90 mg. alpha-tocopherol subcutaneously in 3 doses at intervals of 4 days were considered to be hypervitaminotic. Vitamin E decreased thymus weight and increased adrenal weight, but had no effect on body weight, testes weight, or pancreas weight. Histologic examination showed no effect of vitamin E on pituitary, parathyroid, pancreas, adrenals, or testes. The thyroid showed signs of hypofunction, and the thymus showed ill-defined alterations.

Forni, P. V., Guglielmo, R. & Ortone, G.

Weight Changes in Experimental Hypervitaminosis.
 Ipervitaminosi (Vitaminologia) 10: 12p, 1953; Annotated Bibliog.
 Vitamin E, 5: 81, 1958-1960.

Various hypervitaminoses were induced in young male rats fed 8 g. daily of a casein-based diet for 15 days. Compared with control animals, hypervitaminosis E (90 mg. of alpha-tocopherol given subcutaneously in 3 doses at intervals of 4 days) reduced gain in body weight, had no effect on the growth of liver, lung, and kidney but significantly increased the size of the spleen.

Francesconi, G., Perelli-Ercolini, M. & Frontino, G.

The Action of [High Dosages of] Vitamin E on Rooting of Free Skin Autografts and Homografts.

Atti Accad. Med. Lombarda 18: 86-91, 1963; CA 59: 15751d, 1963.

Vitamin E was given as oily solution (150 mg/kg/day subcutaneously) to 56 of 180 adult female Wistar rats (average weight 200 g.) of different breeding, fed a restricted diet. Grafts were performed as previously indicated and the Scotharne and of Tough method was used. A graph of average injection times of vitamin E vs. days (19 as total) shows a rapid penetration of dye 3-5 days after the graft. Vitamin E shortened blood-flow time in grafts and vitamin E activity was probably due to its effect in improving vascular development, but capillary-protective and antihyaluronidase effects were also appreciable.

Fritz-Niggli, H.

Chemical Protection from Radiation Injury. (Studies with Vitamin E).
Muench. Med. Wochschr. 103: 2191-2194, 1961; Abstract: Nutr. Abstr.
& Revs. 32: 1140, 1962.

Mice - 10 mg. dl-alpha-tocopherol acetate for 5 days. (No adverse effects reported by author).

Gialdrone-Grassi, G., Grassi, C. & Sprovieri, L.

About Some Aspects of E-Hypervitaminosis in the Normal and the Tuberculosis Guinea Pig.

Giorn. Ital. Tuberc. 8: 207-210, 1954; 3 Congr. Intern. Vitamin E, 1: 75, 1955; Annotated Bibliog. Vitamin E 4: 112, 1955-1957.

Daily administration to guinea pigs of 250 mg. tocopherols for 105 days reduced adrenal ascorbic acid, increased adrenal cholesterol, and suppressed the increase in body weight. Concurrent infection with tuberculosis accentuated the unfavorable influence of hypervitaminosis E although adrenal cholesterol decreased

Guarino, A. M., Mendillo, A. B. & De Feo, J. J.

Toxic and Inflammatory Properties of Two Antibiotics: Muconomycin A and B.

Biotechnol. Bioeng. 10: 457-467, 1968.

Vitamin E reversed the creatinuria induced by muconomycin. Rats which had received high doses (25 or 100 mg/kg daily per os) of the vitamin displayed a low level of creatinuria during treatment with muconomycin. On the other hand, rats which had received only 10 mg/kg of the vitamin, or none at all, displayed a high level of creatinuria.

Hochrein, H. & Zaqqa, Q.

Myocardstoffwechael, Herzfunktion und Digitalis-Wirkung unter dem Einfluss von D1-alpha-Tokopherolacetat.

Arzneimittel-Forsch. 15: 489-493, 1965.

High doses of vitamin E (5 g/liter of the perfusion liquid) do not evoke toxic effects and do not cause hemodynamic reactions in the normal heart of guinea pigs. Exposure to vitamin E causes a decrease in the water content and intracellular sodium content of the normal myocardium. Consequently, the development of intracellular edema during the initial stages of cardiac insufficiency is avoided.

Imbesi, A.

Effect of Tocopherol on the Absorption of Vitamin A Through the Lymphatics.

Arch. Ital. Sci. Farmacol. 6: 238-240, 1956; Abstract: Annotated Bibliog. Vit. E 4: 128, 1955-1957.

Administration of 5 mg. alpha-tocopheryl acetate/kg. body weight to dogs favorably influenced intestinal absorption, lymphatic transport, and hepatic storage of vitamin A acetate (1 mg/kg), but did not affect blood vitamin A. Absorption was greater when the vitamins were given in oil solution than when they were given as emulsions or as aqueous dispersions. However, the absorption of axerophthol under the same conditions was greater and faster when aqueous dispersions were used.

Lewis, M. R.

Nile Blue Staining of Adrenal Glands of Living Mice.

Anat. Rec. 102: 37-44, 1948.

Addition of tocopherols to food containing Nile blue did not result in fewer cells containing blue bodies at the junction of the cortex and the medulla of the adrenals (representing amount of brown degeneration pigment) of the treated mice either in young or old animals. Large amounts (2.5% to 3%) of tocopherol proved to be toxic to the mice.

Maess, J.

Weitere experimentelle Untersuchungen an wachsenden Haehnen zur Frage einer Vitamin-E-Hypervitaminose mit DL-alpha-Tocopherolazetat und D-gamma-Tocopherol.

Diss. Hanover, 1964; Abstract: Intern. Z. Vitaminforsch. 35: 437, 1965.

Controlled studies in growing male chickens have shown that intramuscular injections (0.1 g.) of DL-alpha-tocopherol acetate caused low-grade inflammations of the site of injection but had no adverse effects on weight gain or development of secondary sexual characteristics.

Marusich, W., DeRitter, E. & Rubin, S. H.

Hemoglobinuria Induced in the Vitamin E-Deficient Rat by Massive Infections of Water-Soluble Vitamin K.

Federation Proc. 15: 562-563, 1956.

An oral dose of 20 mg. of alpha-tocopherol given to deficient rats 4 hours prior to injection of the vitamin K protected completely from hemoglobinuria.

Maske, H., Wolff, H., Stampel, B. & Baumgarten, F.
 Beobachtungen ueber den Zinkstoffwechsel beim alloxandiabetes.
 Arch. Exptl. Path. Pharmakol. 216: 457-472, 1952.

In dogs, alpha-tocopherol acetate prevented alloxan hemolysis.
 Optimal dosage of 2 x 300 mg. of alpha-tocopherol acetate i.m. prior
 to alloxan treatment. Doses of 50-60 mg. of alpha-tocopherol acetate
 proved ineffective; one or more doses of more than 1,000 mg. led to
 hemolysis and above normal serum zinc values.

Peres, G., Jouanneteau, J. & Zwingelstein, G.
 Action of Alpha-Tocopherol and Alpha-Tocopherylquinone on Rat Adrenal Glands.
 Therapie 14: 271-274, 1959; Presse Med. 67: 352, 1959.

Daily subcutaneous administration of 220 mg. of alpha-tocopherol/
 100 g body weight for 6 days caused no change in the weight of the
 adrenal glands or in their ascorbic acid level. At the same dose,
 alpha-tocopherylquinone decreased adrenal weight and increased the
 ascorbic acid level. A daily dose of 440 mg. of alpha-tocopherylquinone
 for 21 days increased both adrenal weight and ascorbic acid level, but
 caused occasional deaths.

Raymondi, G.
 The Influence of Vitamin "E" on the Adrenal Cortex.
 Gazz. Intern. Med. e Chir. 63: 899-908, 1958; Annotated Bibliog.
 Vitamin E, 5: 71, 1958-1960.

Daily parenteral administration to rabbits of 75 mg. vitamin E/kg.
 body weight for 40 days improved growth compared with the nonsupplemented
 controls. Blood sugar levels were similar in both groups. Histological
 examination of the adrenal cortex showed a clear influence of vitamin
 E, particularly in the glomerular and fasciculate zones, with cortical
 changes related to hyperemia. The action of vitamin E is comparable to
 that of ACTH.

Salvi, F. & Mentasti, P.
 The Protective Action of Vitamin E on Lesions Due to Marcumar.
 Acta Vitaminol. 10: 17-26, 1956; Abstract: Annotated Bibliog. Vit. E,
4: 108-109, 1955-1957.

Groups of 6 rabbits each were given 5 mg/kg body wt/day of
 3-(alpha-phenylpropyl)-4-oxycumarin (MARCUMAR) alone or with 20 mg.
 alpha-tocopherol/kg. body wt/day or the tocopherol for 24 days followed
 by both. Average survival times after starting administration of
 MARCUMAR were 9, 14 and 18 days, respectively. Alpha-tocopherol had
 little effect on prothrombin activity, but appeared to inhibit strongly
 the hyaluronidase-like effect of the anticoagulant. The vitamin also
 inhibited the degenerative changes in the liver which were caused by
 MARCUMAR.

Selye, H., Tuchweber, B. & Gabbiani, G.
 Further Studies on Anacalciphylaxis.
 J. Am. Geriat. Soc. 12: 207-214, 1964.

In experiments on Holtzman rats, it was found that the progeria-like syndrome induced by chronic intoxication with dihydrotachysterol (DHT) can be duplicated with vitamin D₂ (500 µg in 0.5 ml of corn oil, by stomach tube) or even vitamin D₃ (100 µg in 0.5 ml of water, subcutaneously). Vitamin E (250 mg in 2 ml of water by mouth twice daily) inhibits the progeria-like syndrome produced either by DHT or vitamin D₂. On the other hand, vitamin D₃ intoxication is quite unresponsive to Vitamin E prophylaxis.

Studer, A., Zbinden, G. & Uehlinger, E.
 Die Pathologie der Avitaminosen und Hypervitaminosen. G. Toxikologie der Vitamine (Hypervitaminosen). III. Toxikologie der uebringen Vitamine.

Handbuch Allgemeinen Pathol. 11 (Part 1): 982-988, 1962.

It is stated that a real E-hypervitaminosis is unknown; it appears however, that large doses of vitamin E interfere in some manner with internal secretion balance, but the exact mechanism of the effects remains unexplained. Published data are cited to support these observations (see Huter, Strahler, Winkler). Studer, et al. (unpublished data) indicate that vitamin E is well tolerated when given intravenously to dogs in doses of 20 x 10 or 20 x 20 mg/kg.; no impairment of hepatic functions, no abnormalities in the blood picture nor histopathology or organs.

Suardi, L.

Effect of Tocopherol on the Pituitary-Adrenal System and the Lymphopoietic Parenchyma of the Normal Rat.

Gazz. Intern. Med. e Chir. 63: 1877-1889, 1958; Annotated Bibliog. Vitamin E 5: 72, 1958-1960.

Normal rats were given 0, 20, 50, or 100 mg. of vitamin E daily for 15 days. Adrenal weight was increased only by the highest dose. Increasing the dose reduced the depth of the fasciculate zone, decreased the granule content of cells in the reticular zone, and induced hyperplasia in the glomerular zone. The pituitary showed no microscopic changes with increasing levels of vitamin E but showed increasing numbers of basophilic cells and loss of chromophobic cells. In most cases the spleen and lymph glands were atrophied and hyperplastic.

Suardi, L.

The Influence of the Administration of Tocopherol on the Lymphatic Tissues and Endocrine Tissues and Endocrine Organs of the Adrenalectomized Rat.

Gazz. Intern. Med. e. Chir. 64: 972-983, 1959; Annotated Bibliog. Vitamin E 5: 72, 1958-1960.

Rats subjected to bilateral adrenalectomy were treated with 20, 50, or 100 mg. vitamin E daily for 15 days. The resultant hyperplasia of the spleen and lymph nodes was less in the treated animals than in untreated controls. Basophilic cells in the pituitary and intra-follicular cells in the thyroid increased more in number in treated animals than in controls. Testes were normal in treated animals; spermatogenesis decreased in controls. Hyperplasia of the corpus luteum was somewhat less in controls. No changes were noted in parathyroid or pancreas.

Torii, T.

Effects of Vitamin E Administration on the Anterior Pituitary of the Immature Mouse.

Okjimas Folia Anat. Japon. 35: 91-105, 1960; Annotated Bibliog. Vitamin E 5: 72, 1958-1960.

The delta and theta cells of the pituitary glands in male and female mice, injected with 1 mg. vitamin E/g. body weight every other day from 10 days of age, showed early differentiation. After 60 to 80 days of age pituitaries of treated animals were similar to those of controls. Beta cells showed less early differentiation. No changes occurred in the acidophils or basophils.

Volterrani, U. & Guglielminetti, A.

Hypertocopherolemia, Insulin Hypoglycemia and Adrenalin Hyperglycemia. Vitaminologia 10: 304-316, 1955; Annotated Bibliog. Vitamin E 4: 94, 1955-1957.

Ten mg. alpha-tocopherol/kg. body weight given intramuscularly to rabbits accentuated the hyperglycemia induced by adrenalin and attenuated the hypoglycemia induced by insulin.

Webb, R. W., Marion, W. W. & Hayse, P. L.
Effect of Tocopherol Supplementation on the Quality of Precooked
and Mechanically Deboned Turnkey Meat.
J. Foo Sci. 37: 853-856, 1972.

Turkeys were administered orally or subcutaneously the equivalent of 10 or 100 I.U. of alpha-tocopheryl acetate (vitamin E) per pound of ration consumed from 8 weeks of age to market age. Samples representing turkey breast and thighs and mechanically deboned turkey racks were tested for storage stability. Tocopherol supplementation was effective in retarding oxidative rancidity development during cooking and frozen storage of precooked whole turkey parts, and during storage of meat from mechanically deboned turkey racks at 5°C. Weekly subcutaneous injections of tocopheryl acetate were most effective in retarding rancidity development, but the addition of 100 I.U. of tocopheryl acetate per pound of ration was effective enough to also warrant its recommendation. Even with these positive results, vitamin E supplementation to the live turkey does not appear to be the complete answer in stabilizing mechanically deboned turkey. Samples from turkeys receiving the tocopherol showed off-odor and off-color development after only 3 or 4 days of storage at 5°C.

Wulzen, R. & Krueger, H.
Local Reaction to Alpha Tocopherol in Guinea Pigs Deficient in the
Anti-Stiffness Factor.
Amer. J. Physiol. 167: 840, 1951.

Guinea pigs were injected weekly for three months with 0.1 ml of sesame oil containing 20 mg. alpha-tocopherol or with sesame oil alone. Alpha-tocopherol produced pronounced swelling and hardening of the tissues in the vicinity of the injection site. Often hard and rough concretions, extending from the knee to the pelvis and from the elbow to the shoulder, were formed.

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