VITAMIN E IN PROPHYLAXIS AND TREATMENT OF THROMBO-EMBOLIC DISEASES

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Vitamin E was discovered to be a fertility vitamin, in rats in 1922 by Evans and Bishop[1], and since then, it has been known generally for this activity. But actually, several years after its discovery some researchers proposed that it had different activities in other animals. Pappenheimer and Goettsch[2] showed that chicks fed on E-deficient diets developed nutritional encephalomalacia, and Dam and Glavind[3] found an alimentary exudative diathesis in E-deficient chicks. Muscle dystrophy in rabbits and guinea-pigs fed on diets low in vitamin E, was first seen by Goettsch and Pappenheimer[4]. Shute[5] declares that if another test animal had been used by the first investigators it might be that quite other properties would have been attributed to it.

Since Evans[6] and Emerson[7] achieved chemical separation of alpha, beta and gamma tocopherol from wheat germ oil and Karrer[8] completed synthesis of alpha tocopherol in 1938, further investigators have demonstrated that vitamin E has very wide and confusing biological activities. Its well known activities are as follows; anti-sterility action and control of menopausal disorders, acceleration of growth, repair of fragile blood vessels, and the treatment of certain types of cardiac failures, muscular dystrophy and collagene diseases.

First investigation for its activity in blood coagulation was made by Adamstone[9], who reported obstruction of the blood vessels in the yolk sac of chicks from hens on E-deficient diets. Mason[10] reported that the resorption of the fetus in E-deficient pregnant rats was due to venous thrombosis in the uterine wall. Since then, many studies have been made on the correlation of vitamin E and blood coagulation or intravascular clot formation.

At the same time, the surgeon's interest in postoperative thrombosis has been rapidly increasing. As Ochsner[11] has said, two of the top ranking causes of postoperative death, shock and infection, have become less important because of great improvement in their prevention and control. Postoperative thrombosis, however, because it sometimes results in fatal complications such as pulmonary embolism, has become relatively more important, but its detailed pathogenesis is still obscure.

During the last decade, the efficacy of vitamin E for thrombo-embolic diseases has been studied by many researchers. But there are many contradictory results and its mechanism of action is still uncertain. The following animal experiments and clinical studies show that vitamin E (alpha tocopherol) can

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have an excellent effect on several vascular diseases and especially on post-operative venous thrombosis.

MATERIALS AND METHODS

Solid food for rabbits: RC-7 (Oriental yeast Industry and Co., Japan)

A solid dry food. Its main component is grass, but contains all kinds of nutritional elements for rabbits, and is a standard food. Ordinary chows are irregular in their components and not suitable for nutritional experiments.

Vitamin E-deficient diet

It was based on Young's[12] diet. Casein was refined with ether. Phillips-Hart's[13] salt mixture was used. Components of diet are as follows.

Casein	15 g	Pyridoxine hydrochloride	0.5 mg
Sucrose	39.3 g	Thiamine chloride	0.5 mg
Corn starch	36.0 g	Riboflavin	0.5 mg
Lard	3.0 g	Calcium pantothenate	1.0 mg
Cod liver oil	3.0 g	Folic acid	0.5 mg
Salt mix	3.0 g	Biotin	0.005 mg
Inositol	0.1 g	2-methyl-naphthoquinon	0.025 mg
Choline chloride	0.1 g	Vitamin B_{12}	4.5 γ
Nicotin amide	20 mg		

Vitamin E preparations

Juvela-tabs (Eisai Co. and Ltd., Japan)

Each tablet contains alpha tocopherol acetate 20 mg.

Juvela-inj. (Eisai Co. and Ltd., Japan)

Each 1 ml ampule contains alpha tocopherol 100 mg in sesame oil.

Vita-E tabs (Webber pharmaceuticals, Canada)

Each tablet contains alpha tocopherol succinate 50 I.U. (equivalent to 50 mg of the acetate).

Thrombin (Mochida Pharm. Mfg. Co., Japan)

Thrombin Topical. One vial contains 500 I.U. of bovine thrombin.

Fibrinogen (Mochida Pharm. Mfg. Co., Japan)

One vial contains 10 mg of bovine fibrinogen.

Sodium morrhuate (Eli Lilly and Co., U.S.A.)

Each 2 ml ampule contains 0.1 g of Sodium morrhuate in alcohol solution (3%). Used for making experimental thrombosis.

Silicone coating

Silicone KF-99 (Shinetsu Chemical Co., Japan) was used.

Test tubes, needles and syringes were soaked in 2% silicone-benzol solution. After drying, they were heated on 150° C for 30 minutes. Removal of silicone was made by soaking in concentrated NaOH solution for one day.

Coagulation time of whole blood.

Lee-White's glass tube method was used. Test tubes were 8 mm in

diameter, and coagulation was observed in 37° C water bath.

Recalcified plasma clotting time

According to Tocantins' method[14], clotting mixture was 0.1 ml of plasma, 0.1 ml of 0.85% NaCl and 0.1 ml of 0.02 M $CaCl_2$. Clot formation was observed in glass test tubes in 37° C water bath.

Prothrombin time

Quick's one stage method was used. Thromboplastin was made of the brain of rabbits.

Prethrombotic index (Kay)

Kay[15] proposed this test for the recognition of a prethrombotic state.

The exact procedure is as follows;

1) Place in a siliconized test tube 1.4 ml of 1.85% solution of $K_2C_2O_4$.
2) Add 10 ml of blood as soon as it is withdrawn (needles and syringes are silicone coated) and mix well.
3) Centrifuge at 1500 RPM for 10 minutes.
4) Remove the supernatant plasma.
5) Make a serial dilution of the plasma, as follows:
   a. Place 10 tubes in rack; add 0.5 ml distilled H_2O to all except No. 1.
   b. Place 0.5 ml of plasma in tube No. 1 (1 : 1).
   c. Place 0.5 ml of plasma in tube No. 2 and mix well (1 : 2).
   d. Place 0.5 ml of the mixture from tube No. 2 into tube No. 3, and mix well (1 : 4).
   e. Continue to dilute the plasma in the manner described untill 10 tubes have been prepared. The dilution in the tenth tube is 1 : 512.
6) Add to each tube exactly 0.1 ml of thrombin solution in distilled water. It is diluted so that each cubic centimeter contains 0.01 unit of thrombin.
7) Shake the tubes well, then incubate them in a water bath at 37.5° C for 30 minutes.
8) Add to each tube 0.1 ml of 3% bovine fibrinogen solution, from which profibrin has been removed by freezing. The solution is prepared by weight and contains 40–50% sodium citrate.
9) Incubate the tubes again in the water bath for 60 minutes.
10) Observe each tube for the last trace of fibrin formation, recording the greatest dilution at which it ceases to occur. The fibrin frequently appears as a fine precipitate occurring in decreasing amounts.
    In normal plasma, fibrin formation ceases to occur when the plasma dilution is between 1 : 32 and 1 : 128.

EXPERIMENTS

1. Animal experiments concerning alpha tocopherol: Large doses and deficiency

The following experiments were made to determine the effect of alpha tocopherol on the circulatory system.

A. Large doses of alpha tocopherol

Twenty male rabbits (1.5–2 kg weights) were given 200 g of the standard diet (RC-7) and 100–150 g of water daily. And they were divided into 4 groups.

A-group: five were given only the standard diet.

B-group: five rabbits fed 200 mg of alpha tocopherol acetate (Juvela-tabs) added daily to the standard diet.

C-group: five were injected 2 ml of sesame oil (the solvent of alpha tocopherol), intramuscularly.

D-group: five were injected 2 ml (200 mg) of alpha tocopherol in sesame oil (Juvela-inj.) i.m. every day. Thus, groups A and C serve as controls for the alpha tocopherol treated groups B and D. All animals took their food well.

The increase of body weight in the alpha tocopherol group was more rapid than in the control group (Fig. 1). Recalcified plasma clotting time and prothrombin time were determined before and every two weeks after administration, but no significant differences were noted between the two groups (Fig. 2). The rabbits were sacrificed after eight weeks and their heart and vascular system were studied histologically. The hearts of the tocopherol group showed hypertrophy of the cardiac muscle fibers which were stained more deeply by eosin, and their nuclei were larger and the intermuscular space was narrowed (Fig. 3). The muscle fibers in the media of peripheral arteries of these animals were hypertrophic, and showed a closely packed structure, as compared with the control groups. And they were stained more deeply both by eosin and PAS*, and showed more metachromatic substance by toluidine blue than the control groups, as illustrated in Fig. 4. This hypertrophy and good stainability, particularly the increase of PAS positive substance and metachromatic substance or acid muco polysaccharide of muscle fiber, observed both in the hearts and blood vessels suggest that alpha tocopherol has some effects upon the metabolism of heart and blood vessels.

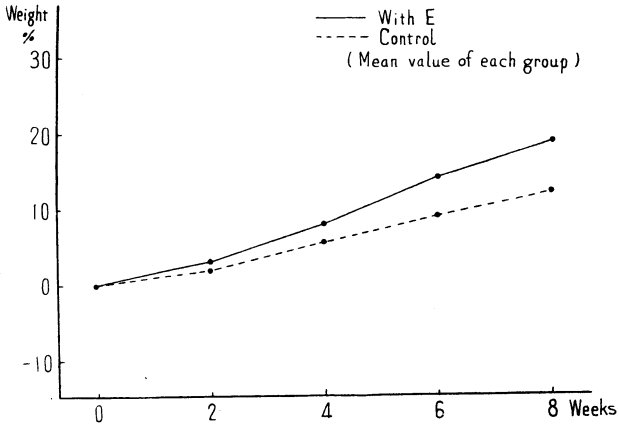


FIG. 1. Change in body weight of E-given rabbits.

* PAS=Periodic Acid Schiff.

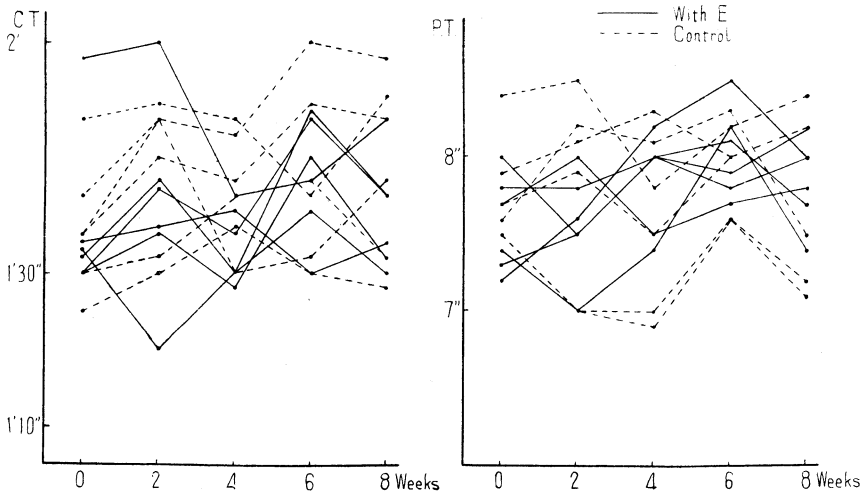


FIG. 2. Recalcified plasma clotting time and prothrombin time in E-given rabbits.

There was no significant difference between the alpha tocopherol injected group and alpha tocopherol acetate orally given group. The sesame oil injected group showed the same findings as the group which received only the standard diet.

B. Vitamin E deficient diet

Fifteen male adult rabbits were divided into three groups.

A-group (five): received 150 g of E-deficient synthetic diet daily.

B-group (five): 10 i.u. of alpha tocopherol succinate (Vitamin-E tabs) added every other day to E-deficient diet.

C-group (five): received 200 g of the standard diet (RC-7), daily. 100 to 150 g of water added daily to each group. Rabbits took their synthetic diets well after initial bewilderment.

The changes of body weight are shown in Fig. 5. Rabbits of group C increased in weight normally and those of group B also after an initial loss caused by the strange diet. Group A, however, showed a marked loss of weight, and showed falling off of the hair and muscular dystrophy in the third week, and four of them showed distinct paralysis of the hind legs. Fig. 6 shows an emaciated, rough haired and paralysed E-deficient rabbit after 8 weeks of the vitamin E deficient diet, compared with a normal. The change of blood coagulability is shown in Fig. 7. The control groups showed no significant change in recalcified plasma clotting time, prothrombin time and prethrombotic index, but the deficient group showed many instances in which the prethrombotic index fell to a "Dangerously low" level and the plasma clotting time was reduced. This showed the acceleration of blood coagulability.

Sacrificed after 8 weeks, the cardio-vascular system was histologically studied. Group B showed generally a normal picture as did group C. But group A, deficient animals, showed some pathological changes. Thrombi were

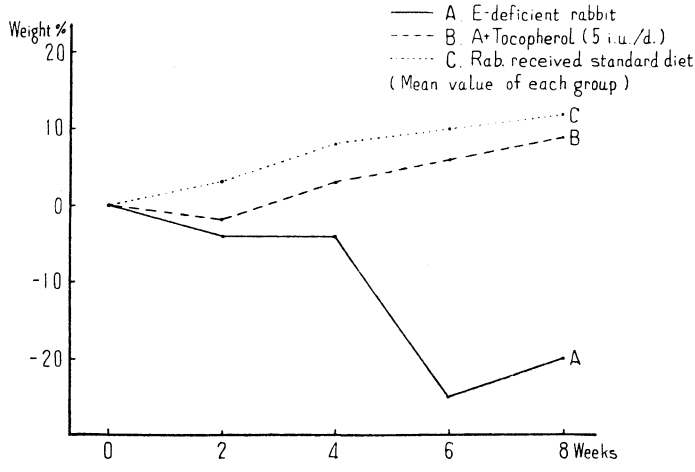
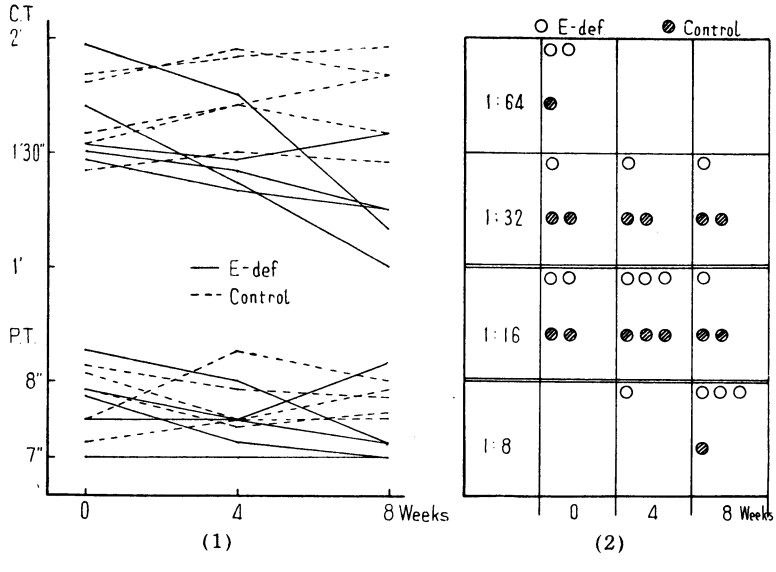


FIG. 5. Change in Body weight of E-deficient rabbits.



EIG. 7. Blood coagulability in E-deficient rabbits.
(1) Recalcified plasma clotting time and prothrombin time.
(2) Prethrombotic index.

observed in cardiac ventriculi in 3 cases of this group (Fig. 8). These thrombi showed clearly a structure of a separating thrombus. The intima at these sites was somewhat edematous, and the small vessels and capillaries among the myocardial fibers were dilated, with some interstitial hemorrhage. The striations are minute and not clear by PAS stain. The peripheral arteries (Fig. 9) showed atrophy of intimal cells, fading of subintimal connective tissue and atrophy of muscle fibers in the media with small vacuoles and spaces between

them. Throughout the entire series of E-deficient rabbits, atrophy and high fragility of heart muscle and blood vessels were observed.

Comments: Many investigators have described some of these changes in the cardiovascular system of animals deprived of vitamin E. Olcott[18] reported that in the E-deficient rat with muscular dystrophy, sudden death might be caused by heart failure, in spite of the absence of pathological changes in the heart muscle. Also in E-deficient rabbits, Bragdon and his coworkers[19] described acute myocarditis and electrocardiographic changes, with muscular distrophy. Gatz and Houchin[20] showed that the affected myofibrils in the heart of E-deficient rabbits became hyaline in appearance and exhibited basophilia. Further, Houchin and Smith[21] proposed that vitamin E might be important in the nutrition of human heart and its lack might be a factor of cardiac failure in beriberi. Shute and Shute[5] reported that massive doses of alpha tocopherol were effective in cardiac degenerations and especially angina pectoris, although Makinson[22], Rinzler[23] and Bicknell *et al.*[24] did not agree with them. However, according to the author's observation, myocardial atrophy was similar to that of skeletal muscles in deficient animals, and the cardiac muscles of animals to which large doses had been administered showed a marked increase in stainability. Therefore, the author must agree with Houchin, Smith and Shute that vitamin E does seem to be related to heart function. Markees and Mason described the high fragility of blood vessels in deficient animals, and this was also confirmed in the author's experiment. But there are scarcely any reports of histologically studied peripheral blood vessels of animals receiving massive doses of alpha tocopherol. It is interesting that good stainability of muscle in the media, which may show good function, was observed in this experiment.

2. Alpha tocopherol in the treatment of experimental thrombosis

The following animal experiment was carried out to observe the effect of alpha tocopherol upon the thrombus. Ten adult male rabbits, weighing 1.5 to 2.8 kg were injected with 0.01 ml of 5% sodium morrhuate. The injection was made into a 2 cm section of the femoral artery isolated by 2 previously placed silk ligatures. After two days, the ligatures were removed, all isolated segments showing thrombus formation. From the 7th day five of the rabbits were injected with 100 mg of alpha tocopherol intramuscularly every day, for one month. The other five served as controls, receiving no treatment. All animals were sacrificed after one month, and the affected femoral arteries were removed.

In control animals, the arteries had become a hard cord and formed strong adhesions with the surrounding tissues. In the treated group, the arteries were grossly softer and showed little adhesion. When histologically studied, the arteries in the control group (Fig. 10) showed a highly advanced exudative endoarteritis: the lumen being filled with a thrombus composed of many lymphocytes and some polymorphonuclear leucocytes and closely adherent to the muscle of the media whose fibers were sparse, with marked round cell infiltration in the adventitia. In the treated group, there was little evidence of any exudative inflammation. The lumen was filled with granulation tissue which consisted of fibroblasts and endothelial cells. There were several spaces

in the granulation tissue lined with new endothelium indicating recanalization after obstruction (Fig. 11). The original arterial wall showed an irregular structure-muscle layer of media and the internal elastic layer was partially destroyed.

Comments: By this experiment, it was clearly shown that alpha tocopherol accelerates the healing of arteritis and recanalization. Enria and Ferrero[25] reported the effect of vitamin E upon experimental phlebothrombosis. They traumatized the femoral or axillary veins of dogs by pinching, and treated them with 140 mg of vitamin E per day. Phlebography was carried out and a very rapid development of collateral venous channels was observed, while histological examination showed only minimal degenerative and inflammatory lesions in the vessel wall. By concomitant use of tromexan with alpha tocopherol, canalization occurred more rapidly. Piana[26] used vitamin E with calcium gluconate and mesoinositol as a prophylaxis of thrombosis in the traumatized saphenous veins of dogs. He reported that it was effective. Dominguez and Dominguez[27] reported that massive doses of alpha tocopherol after obstruction of the femoral artery produced in rabbits by double ligation, were effective in developing good collateral arterial channels. In the author's experiments, even though such a strong agent as sodium morrhuate was used to produce not only thrombosis but a high degree of inflammation, alpha tocopherol stopped the inflammation and stimulated the reopening of blood flow. This is a significant observation.

3. Prophylaxis of postoperative thrombosis

The etiology of thrombosis has been clarified by Aschoff when he enumerated the following factors: changes in the coagulability of blood, changes in the blood elements (particularly in the power to agglutinate), changes in the blood flow both in regard to speed and the formation of eddies, and change in the vessel wall. Prophylaxis of thrombosis has, therefore, followed his theory: use of anticoagulants for lowering the coagulability of blood, and early ambulation or exercise of the lower extremities for the acceleration of blood flow.

Many investigators have reported the changes in postoperative blood coagulability. Gray and his coworkers[28] observed that shortening of coagulation time was caused by bleeding, and Bergquist[29] found a sharp fall in coagulation time in the early postoperative period. Warren *et al.*[30] reported that the plasma prothrombin activity decreased, the circulating platelets decreased in the early and increased in the late, and plasma fibrinogen was increased in the postoperative period. An increase of thrombin postoperatively in the circulating blood flow was found by Reich[31] and Sternberger *et al.*[32], Zierler[33] demonstrated that alpha tocopheryl phosphate was antithrombic both *in vitro* and *in vivo*. Based on this result, Ochsner[34][35] and Kay[36][37][38] undertook several experiments and found that alpha tocopherol appear to have an antithrombic activity at concentrations in normal human plasma, and might be an antithrombin. Then, they proposed to use it in the prophylaxis of postoperative thrombosis as in that condition the coagulability of blood was accelerated.

The following clinical study was carried out to find the effect of alpha tocopherol on the prophylaxis of thrombosis. The coagulation time of whole blood, prothrombin time and prethrombotic index were determined from the preoperative period to the end of the second week postoperatively in a series of 80 surgical patients. Half of them randomly selected were given alpha tocopherol for 2 weeks. Because of the inability of some patients to take medication orally in the immediate postoperative period, all 40 of these patients were given 100 mg of alpha tocopherol intramuscularly every 8 hours for the

TABLE 1. Types of Operation

	With tocopherol	Without tocopherol	Total
Appendectomy	13	7	20
Enterotomy	9	7	16
Gastrotomy or gastrectomy	3	7	10
Operative treatment in fracture	2	5	7
Pulmonary resection	2	3	5
Herniotomy	2	1	3
Amputation of breast	1	2	3
Anal operation	1	2	3
Nephrectomy	2		2
Cholecystectomy		2	2
Amputation of limb	1	1	2
Venectomy	1		1
Removal of ureteral stone	1		1
Castration	1		1
Removal of jaw	1		1
Nephropexy		1	1
Thyroidectomy		1	1
Removal of aneurysm		1	1
Total	40	40	80

TABLE 2. Change in Clotting Time in Surgical operations

Clotting time	Before operation		After operation			
			With tocopherol		Without tocopherol	
<5′	2	2.5%	1	2.5%	2	5.0%
5′–10′	76	95.0	36	90.0	35	87.5
10′<	2	2.5	3	7.5	3	7.5
Total	80		40		40	

TABLE 3. Change in Prothrombin Time in Surgical Operations

Prothrombin time	Before operation		After operation			
			With tocopherol		Without tocopherol	
12.1″–14″	26	32.5%	3	7.5%	12	30.0%
14.1″–16″	49	61.3	34	85.0	22	55.0
16.1″–18″	5	6.2	3	7.5	6	15.0
Total	80		40		40	

TABLE 4. Change in Prethrombotic Index in Surgical operations

Prethrombotic index	Before operation		After operation			
			With tocopherol		Without tocopherol	
Safe	65	81.2%	22	54.0%	9	22.5%
Borderline	12	15.0	15	37.5	11	27.5
Dangerously low	3	3.8	3	7.5	20	50.0
Total	80		40		40	

first 3 day, and thereafter 300 mg of alpha tocopherol acetate every day by mouth. Intravenous calcium gluconate was concomitantly used in ten of these patients. Types of operation are shown in Table 1. The change of clotting time is illustrated in Table 2, and the change of prothrombin time in Table 3. No significant differences are found between the two groups. The prethrombotic index, however, is markedly different (Table 4). In the tocopherol administered

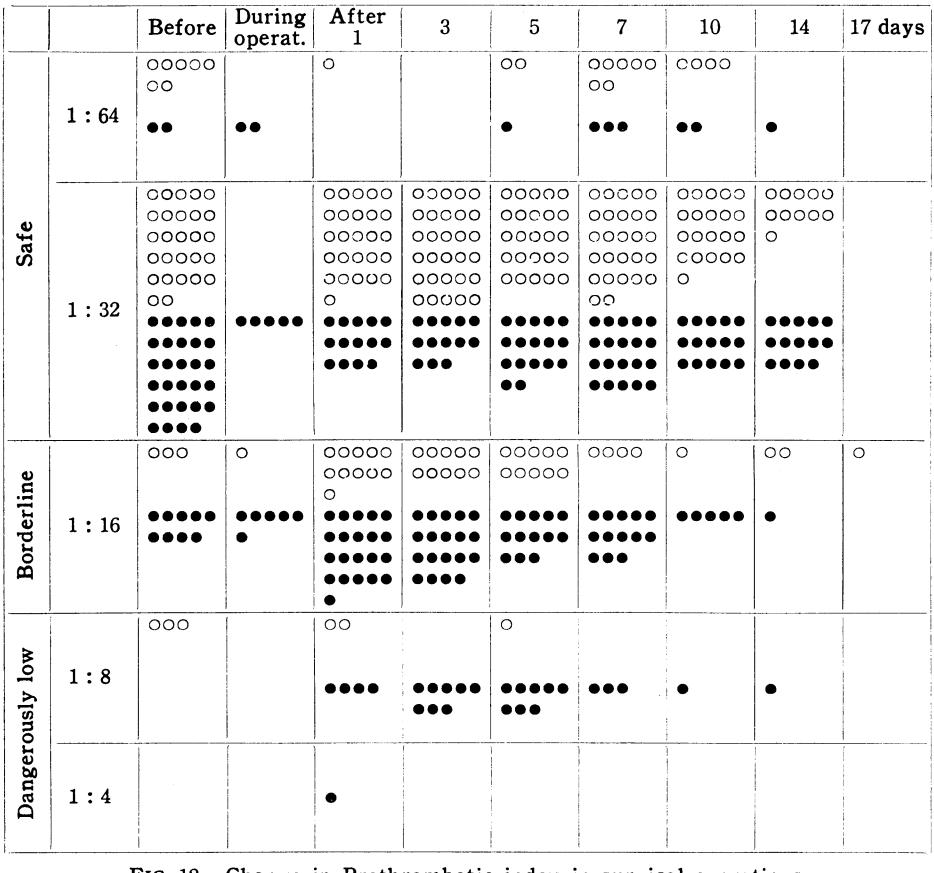


FIG. 12. Change in Prethrombotic index in surgical operations.
○ V. E given group ● Control g

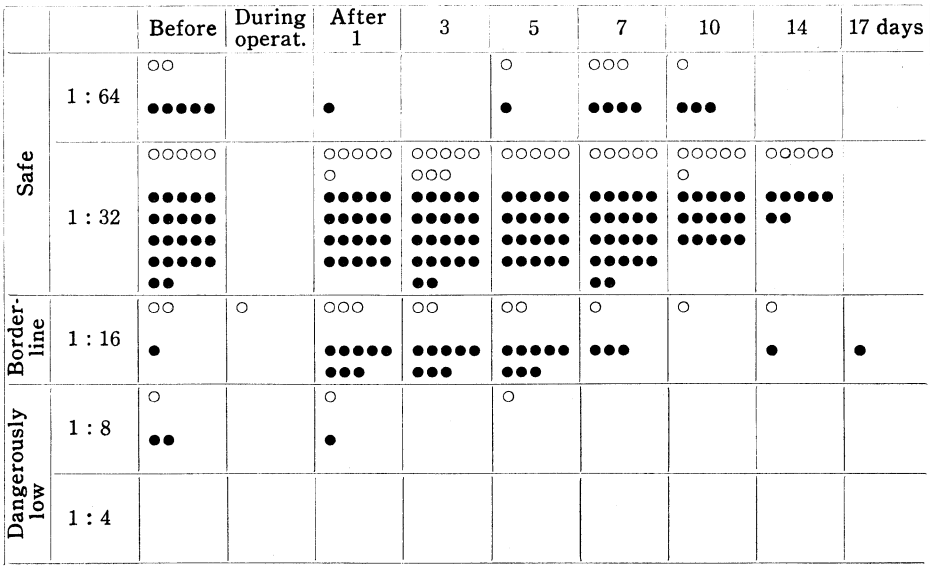


FIG. 13. Influence of additional calcium administration.
○ V. E + Ca ● V. E alone

group, the index is so stable that there are only three cases which show a "dangerously low" level postoperatively, but in the control group, twenty cases, 50%, show such a level. When examined as to time, most of them fall to their level by the fifth day as illustrated in Fig. 12. One of the control group, a 63 year old man, showed a 1 : 8 level on the third day after the operation for fracture of the left tibia, and recovered to 1 : 16 level on the seventh day, when he complained of fever, swelling of the right leg and tenderness of calf, namely, thrombophlebitis. No clinical thrombosis was found in the tocopherol administered group. There was no significant difference between the tocopherol alone group and calcium added group, shown in Fig. 13.

Comments: The first trial of alpha tocopherol in the prophylaxis of postoperative thrombosis was based on Zierler and Kay's observation that it had an antithrombic action. Kay initially offered his test as a plasma antithrombin determination, but Wright[39)40)] and Coon[41)] asserted that the Kay test could not measure the true antithrombin titres. Afterwards, Kay himself[15)] agreed with them and proposed that his test was of value in the recognition of the prethrombotic state, and named its result "the prethrombotic index". The single case of thrombosis in the author's series showed a low level of this index. McLachlin[42)] used the Kay test in seriously ill patients and no correlation was obtained between the index and the postmortem pathological findings, and he concluded that this test could not predict thromboses. However, he used the simpler test which did not use fibrinogen, and therefore did not truly evaluate the present more specific Kay test. The combination of alpha tocopherol and calcium gluconate was used initially by Kay, based upon *in vitro* work which

showed the inactivity of alpha tocopherol, because it combines with blood fibrinogen, when administered alone. The following writers examined this method. Moorman[43] reported that with adequate alpha tocopherol and calcium dosage very few thromboembolic diseases developed, but with alpha tocopherol alone results were worse and with no alpha tocopherol at all there was a *much* higher incidence of both thromboembolic disease and fatal pulmonary embolism. Wilson[44] experienced a lower incidence of thrombosis and no severe thromboembolic disease and pulmonary embolism in his alpha tocopherol and calcium gluconate treated group. Crump[45] reported only six mild cases of phlebothrombosis in alpha tocopherol and calcium gluconate treated group, though there were 31 cases of thrombosis including one death by pulmonary embolism, in the control group. Bauer[46] also reported that he could reduce the incidence of postoperative thrombo-embolic complications to one tenth of the usual incidence by using alpha tocopherol and calcium, even though he reduced the number of calcium injections by one half. Shute[5] proposed that alpha tocopherol alone was sufficient to prevent thrombosis and no additional calcium was necessary. In the author's small series, ten of the alpha tocopherol treated group were given calcium gluconate intravenously every day, but no significant difference was noted in the prethrombotic index.

There are many contradictory reports on the correlation of alpha tocopherol and blood coagulation. Zierler, Ochsner and colleagues and Masure[47] reported that alpha tocopherol acted as an antithrombin, and Reifferscheid[48] also described an increase in plasma antithrombin following alpha tocopherol treatment. Fleischhacker[49] reported that it possesses heparin-like activity in some respects; and an antagonistic action for histamin on blood coagulation, namely an anticoagulant action, was demonstrated by Wagner[50]. These investigators all proposed that alpha tocopherol has an anticoagulant action, but entirely opposite reports have been presented. Namely, DeMatteis and coworkers[51] reported that alpha tocopherol accelerated the coagulation of blood. Wright[39] and Paul *et al.*[54] observed no change in blood coagulability following alpha tocopherol administration, and Heyman[55] also reported no modification in the thrombelastogram with alpha tocopherol. Thus, these numerous studies have produced confusing and contradictory results. According to the author's observation, the definite difference between the alpha tocopherol given group and the control group as regards blood coagulation, illustrated in Table 4, seems to show clearly that alpha tocopherol does influence some phase of the blood coagulation mechanism. But as the author[56] previously reported, no change was observed in the blood coagulation time, prothrombin time, or in the prethrombotic index either *in vitro* (when aqueous alpha tocopherol succinate was added to human blood) or *in vivo* (when massive doses of alpha tocopherol were administered to healthy volunteers). These results may suggest that alpha tocopherol is not a common anticoagulant of blood. And such peculiarity of action that appears after surgical operations or in other stresses may be due to a more complex mechanism of activity in the organism.

4. Alpha tocopherol for the treatment of several thromboembolic diseases

As good effects of alpha tocopherol were observed in the treatment of experimental arterial thrombosis, the author used alpha tocopherol in the treatment of the following thrombo-embolic diseases and other vascular disorders.

Phlebothrombosis and thrombophlebitis: Twenty-one cases were treated with alpha tocopherol alone: namely, 16 cases of postoperative and posttraumatic thrombophlebitis (13 of which were acute or subaute and 3 chronic) and 5 spontaneous. 100 to 500 mg of alpha tocopherol were given daily mostly orally but sometimes parenterally. Total amount administed was 6.3 to 36 g. Results are illustrated in Table 5. Fourteen (67%) were successfully treated, 5 (24%) showed some effect and 2 cases (9%) no effect. Generally, treatment begun early enough and in adequate dosage was relatively successful. Case 13, a 22 year old female, with fever, and tenderness in her left thigh and calf 7 days after appendectomy (Fig. 14), was given daily 400 mg of alpha tocopherol acetate from the 10th day after operation. The calf tenderness decreased markedly on the second day of administration, and thereafter the fever and swelling improved and she was dramatically cured by administration for two weeks. Case 17, a 69 year old male, was given daily injections of 400 mg of alpha tocopherol on the 7th day of the disease. Pain in the right leg was reduced on the next day, and all symptoms improved markedly. But case 6, a spontaneous thrombophlebitis, who was given alpha tocopherol treatment 2 years after the onset of illness, in a dose of 300 mg of alpha tocopherol acetate every day for 30 days, showed no improvement.

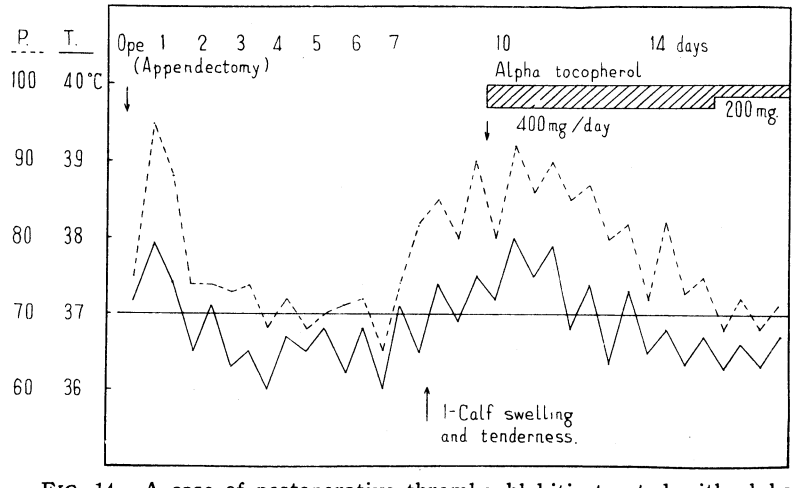


FIG. 14. A case of postoperative thrombophlebitis treated with alpha tocopherol.
H. O., 22 years, F (Case 13).

Arterial thrombosis and Buerger's disease: Two cases of arteriosclerotic thrombosis and 15 of Buerger's disease were treated with alpha tocopherol.

TABLE 5. Effect of Alpha Tocopherol Upon Phlebothrombosis

Case No.	Name	Sex	Age	Diagnosis	Symptoms	Duration before tocopherol treatment	Tocopherol treatment (duration and dosis)	Another treatment	Results (effect of alpha tocopherol)	
1	F.N.	F	28	Postope. th.-ph. (left leg)	Swelling, pain and fatigue in left leg	3 mon.	300 mg×2 mon.	Trypsin	Pain and fatigue reduced	Good
2	T.K.	M	19	〃	Swelling and pain in left leg	3 mon.	300 mg×1 mon.	Indione	Swelling and pain disappeared	〃
3	T.S.	M	22	Spontan. th.-ph. (left leg)	〃	7 years	300 mg×3 wks.		Pain reduced	Satis-factory
4	Y.M.	M	32	〃 (both legs)	Swelling in both legs	6 mon.	400 mg×1 mon.	Heparin	Swelling reduced (espec. in right)	Good
5	S.S.	F	31	Postope. th.-ph. (left leg)	Swelling and tenderness in left calf	2 mon.	300 mg×3 mon. 150 mg×2 mon.	Indione	Swelling reduced	Satis-factory
6	S.T.	M	27	Post-traumatic th.-ph.	Swelling and pain in left leg	2 years	300 mg×1 mon.	〃	No change	Poor
7	S.H.	F	39	Postope. th.-ph. (left leg)	Swelling in left leg and tenderness in calf	2 mon.	300 mg×6 wks.	Unna's paste	Swelling and tenderness much reduced	Good
8	T.F.	F	33	Spontan. th.-ph. (left leg)	Swelling and pain in left leg	1 mon.	300 mg×1 mon. 150 mg×1 mon.		Swelling disappeared pain reduced	〃
9	T.Y.	F	37	〃 (both legs)	Swelling and fatigue in both legs	1 mon.	300 mg×6 wks.		Swelling and fatigue much improved	〃
10	M.A.	F	24	Postope. th.-ph. (right leg)	Swelling and pain in right leg	2 wks.	500 mg×1 mon. 300 mg×2 mon.	Unna's paste	Swelling reduced and pain disappeared	〃
11	S.M.	F	44	〃 (left leg)	Swelling and fatigue in left leg	2 mon.	500 mg×3 wks. 300 mg×2 mon.	〃	Swelling much reduced	〃
12	M.A.	F	25	〃	〃	2 mon.	300 mg×1 mon.		Swelling almost disappeared	〃

13 H.O.	F	22	Postope. th.-ph. (left leg)	Fever, swelling in left leg and calf tenderness	3 days	400 mg×6 days 200 mg×2 mon.		Swelling and calf tenderness disappeared	Good
14 K.M.	F	27	〃 (right leg)	Swelling in right leg	1 mon.	300 mg×2 mon. 120 mg×2 mon.		Swelling reduced	〃
15 K.K.	F	19	Spontan. th.-ph. (both legs)	Swelling and fatigue in both legs	1 year	300 mg×1 wk. 200 mg×1 mon.	Trypsin	No change	Poor
16 M.F.	M	41	Posttraum. th.-ph. (left leg)	Swelling in left leg	2 wks.	300 mg×1 mon. 200 mg×2 mon.		Swelling slightly reduced	Satisfactory
17 K.M.	M	69	〃 (right leg)	Swelling and calf tenderness in right leg	1 week	400 mg×2 wks. 200 mg×2 mon.	Heparin	Swelling, pain and redness reduced	Good
18 S.I.	M	38	Postope. th.-ph. (left leg)	Swelling and pain in left leg	2 mon.	300 mg×1 mon. 200 mg×2 mon.	Sintrom	Swelling and pain much reduced	〃
19 S.Y.	F	38	〃	Swelling in left leg and hardness of walking	1 year	500 mg×1 mon. 300 mg×1 mon.	Predonine	Swelling reduced	Satisfactory
20 M.M.	F	16	〃 (right leg)	Swelling in right leg	1 year	300 mg×1 mon.	Unna's paste	Swelling slightly reduced	〃
21 T.S.	M	17	〃 (left leg)	Swelling and calf tenderness in left leg	3 wks.	300 mg×2 wks. 150 mg×1 mon.		Swelling and tenderness much improved	Good

TABLE 6. Effect of Alpha Tocopherol Upon Arterial Thrombosis and Buerger's Disease

Case No. Name	Sex	Age	Diagnosis	Symptoms	Duration before tocopherol treatment	Tocopherol treatment (duration and dosis)	Another treatment	Results (effect of alpha tocopherol)	
1 K.S.	M	57	Arteriosclerotic thromb. (left leg)	Pain and fatigue in left leg	1 year	300 mg×1 mon.	Both side lumb. sympath.	Pain reduced	Satisfactory
2 S.I.	M	58	〃	Intermittent claudication and pain and coldness in left leg	2 mon.	300 mg×1 mon.	Left lumb. sympath.	Claud. improved and pain reduced	Good

TABLE 6. (*Continued*)

Case No.	Name	Sex	Age	Diagnosis	Symptoms	Duration before tocopherol treatment	Tocopherol treatment (duration and dosis)	Another treatment	Results (effect of alpha tocopherol)	
3	S.G.	M	47	Buerger's disease (left leg)	Cyanosis and ulcers in left toes	3 mon.	400 mg×1 mon.		Ulcers much improved	Good
4	T.S.	M	30	〃 (right leg)	Coldness in right leg, ulcer and necrosis in toes	3 years	500 mg×1 mon. 300 mg×3 wks.	Right lumb. sympath.	Coldness reduced	Satisfactory
5	I.A.	M	44	〃	Numbness in right foot	1 year	300 mg×3 mon.	Both side lumb. sympath.	Feeling improved	〃
6	J.S.	M	48	〃	Intermittent claudication and fatigue in right leg	6 years	300 mg×2 mon.		〃	〃
7	M.N.	M	22	〃 (left leg)	Pain and coldness in left leg	1 year	300 mg×3 wks.	Left lumb. sympath.	Pain and coldness reduced	Good
8	K.I.	M	38	〃 (right leg)	Necrosis in right 5th toe	1 year	300 mg×1 mon.	Right lumb. sympath. and resection thromb. art.	Coldness somewhat reduced	Satisfactory
9	E.A.	M	33	Buerger's disease	Pain and ulcer formation in both sides toes	1 year	400 mg×1 mon.		Ulcers almost healed and pain reduced	Good
10	B.Y.	M	30	〃 (right leg)	Coldness in right leg	1½ year	300 mg×2 mon.	Right lumb. sympath.	No change	Poor
11	T.T.	M	47	〃 (left leg)	Pain and coldness in left leg	2 years	300 mg×1 mon.	Left lumb. sympath.	Pain reduced	Satisfactory
12	Y.K.	M	45	〃 (right leg)	Coldness in right leg, and pain and ulcer in toes	15 years	300 mg×1 mon.	Trypsin	Ulcer reduced	〃
13	T.S.	M	41	〃 (left leg)	Pain and ulcer formation in left leg	6 years	400 mg×2 mon. 300 mg×3 mon.	Left lumb. sympath.	Ulcer reduced and pain improved	Good
14	S.M.	M	30	〃	Hardness of walking and coldness in left leg	6 mon.	300 mg×1 mon.	〃	Coldness slightly reduced	Satisfactory

15 S.H.	M	33	〃 (right leg)	Fatigue in right leg	1 year	300 mg×2 wks.	Right lumb. sympath.	No change	Poor
16 S.K.	M	36	(both legs)	Coldness and ulcer formation in both legs	4 years	300 mg×1 mon.	Amputation of right leg	〃	〃
17 S.K.	M	26	〃 (both legs)	Ulcer formation in left leg	3 years	300 mg×2 mon.	Amputation of left leg	〃	〃

TABLE 7. Effect of Alpha Tocopherol Upon Several Vascular Diseases

Case No. Name	Sex	Age	Diagnosis	Symptoms	Duration before tocopherol treatment	Tocopherol treatment (duration and dosis)	Another treatment	Results (effect of alpha tocopherol)	
1 I.K.	F	40	Raynaud's syndrome	Coldness and cyanosis in extremities	6 years	300 mg×1 mon. 200 mg×2 mon.	Both side thorac. and lumb. sympath.	Coldness reduced	Satisfactory
2 H.K.	F	21	〃	Coldness and cyanosis in both hands	6 mon.	300 mg×2 mon.	Both side thorac. sympath.	No change	Poor
3 S.Y.	M	25	〃	Pain in left lower extremity	3 years	300 mg×2 mon.		〃	〃
4 S.K.	F	43	〃	Coldness and pain in both hands, ulcer in left-fgs.	3 years	300 mg×1 mon.	Both side thorac. sympath.	Pain reduced	Satisfactory
5 T.M.	F	33	〃	Pain and coldness in left foot and toes	3 years	300 mg×2 wks. 200 mg×1 mon.	left lumb. and right thor. sympath.	No change	Poor
6 K.S.	F	42	〃	Coldness in both side of lower extrem.	10 years	300 mg×3 wks.	Both side lumb. sympath.	〃	〃
7 T.M.	F	57	Varicose veins in both legs	Swelling and hypesthesia in both legs	10 mon.	300 mg×6 wks.	Resection of varicose veins	〃	〃
8 H.S.	M	64	〃	Right leg ulcer	7 mon.	300 mg×3 wks.	〃	Ulcer improved	Satisfactory

The results shown in Table 6, were less marked than in thrombophlebitis. But case 3 showed disappearance of the feeling of coldness of the affected leg and reduction in size of the ulcer of the second toe after one week of treatment, with almost complete healing after three weeks. Fig. 15 shows the excellent effect of alpha tocopherol on an ulcer of the foot which had failed to heal with other medicines, case 13. After 1 week of treatment the reduction in size of the ulcer was conspicuous the size being reduced to one tenth after 16 weeks of treatment.

Other peripheral vascular diseases

As illustrated in Table 7, 6 cases of Raynaud's syndrome and 2 of varicose veins were treated, but the only effect observed was the subjectively increasing warmth in the affected extremities of 2 patients.

Comments: During the last decade, many researchers have tried to treat cardiovascular diseases with alpha tocopherol. Shute and his coworkers[57)58)] studied the effect of alpha tocopherol upon several peripheral vascular diseases, especially thrombosis, for a long time, and asserted its excellent efficacy. Regarding venous thrombosis, there are many reports which indicate the good effects of alpha tocopherol. Ochsner[34)], Kay *et al.*[15)] and others reported on its efficacy. Kraus[59)] described two cases in whom other treatments had failed, but showed much improvement with alpha tocopherol. Generally, treatment in the early stage has much more value, as many investigators[43)60)61)] have reported. In the author's experience, good effects can not be expected in chronic cases of more than two years. However, Sturup[62)] reported a single case of thrombophlebitis, five years after onset, which was almost healed with 150 mg of alpha tocopherol daily. The only use of alpha tocopherol in the treatment of thrombophlebitis in Japan, which I could find, is that reported by Manabe[63)] in six cases.

Several investigators tried to examine the effects of alpha tocopherol in arteriosclerotic diseases. Baguena[64)] *et al.* showed that alpha tocopherol caused a significant decrease in blood cholesterol level. Comi and Nesi[65)] used alpha tocopherol in arteriosclerosis and Buerger's disease with much help in all. One arteriosclerotic ulcer of the ankle for which amputation had been advised, was almost healed with alpha tocopherol, as Hagerman[66)] reported. Vogelsang[67)] also reported two successfully treated cases. Leinwand[68)], Heinsen[69)], Butturini[70)] and Schmid[71)] described the good effects of alpha tocopherol in Buerger's disease. There is scarcely a writer who ascribes any effect in Raynaud's syndrome, and even Shute[72)] obtained only 20% good results in his cases. This is not surprising, for the pathogenesis of Raynaud's syndrome is quite different from that of thrombosis or angitis As for varicose veins, Block[73)] reported some effects of alpha tocopherol in such ulcers, but the author found little improvement in his 2 cases.

Massive doses must be given until a satisfactory result is gained. Initially, 300 to 500 mg were given per day, and gradually decreased, observing the effects, and for long periods, 100 to 150 mg were maintained. Sometimes parenteral administration was more convenient for large doses, but oral adminis-

tration was used usually. Kamimura[74] tried alpha tocopherol treatment in several skin diseases, and concluded that the oral use was satisfactory. No side reaction was observed. A little pain after intramuscular injection was complained of in a few cases. In two cases of phlebothrombosis, patients complained of a prickling sensation with increasing warmth in the affected leg. This has been reported by Chia[75] and Walther[76], too. This feeling may reflect the increasing blood circulation.

DISCUSSION

In the prophylaxis and treatment of thrombosis the effects of anticoagulants such as heparin, coumarin or phenylindandione are definite, as many researchers have suggested. But these have a common serious defect, namely the danger of bleeding. In spite of their excellent effects on thrombosis, they cannot be used during or immediately after common operations. An absolute advantage of alpha tocopherol treatment lies in this. It may be used for the prophylaxis of postoperative thrombosis with no anxiety, while experimental angitis caused by sodium morrhuate was found to improve very rapidly with alpha tocopherol. This may be another advantage. But in chronic thrombosis, especially with an already organized thrombus, the effect of alpha tocopherol is poor, and other therapies such as surgical treatment must be used in conjunction.

Through-out these experiments the polyhedral action of alpha tocopherol upon the circulatory system and blood was found. Kamimura[77] reported its action to increase the resistance of peripheral blood vessels, and so was effective in chilblains. His is an interesting study of the protective action on blood vessels.

In the consideration of its chemical structure, an antioxidant action can be easily suspected. But it is difficult to explain such complicated activities by antioxidant action only. On the other hand, large amounts of tocopherol are contained in the pituitary body and adrenal gland, as Beckmann[78] has shown, and therefore, it may be surmised that they are the centers of tocopherol metabolism. Barrie[79] observed clear degenerative changes in the anterior lobe of the pituitary body in the E-deficient rat. And Roy[80] proposed that alpha tocopherol stimulated the secretion of cholesterol-degrading hormone from the anterior lobe of the pituitary body, and degraded cholesterol to a steroid hormone. Gomirato-Sandrucci[81] observed increasing 17-KS excretion with alpha tocopherol administration. Itai[82] asserted that the mechanism of action of alpha tocopherol has a close connection with pituitary-adrenal cortical function from his E-deficient experiments. Further, Heinsen[69] observed a decrease in eosinophiles of blood after tocopherol administration, and suggested tocopherol has a cortisone-like action. But when the author treated another group of experimental thrombosis with hydrocortisone, the inflammatory substance was absorbed rapidly and was not replaced by granulation tissue, and the appearance of healing was quite different from that with alpha tocopherol. Thus, the similarity of alpha tocopherol to cortisone was not observed in this experiment.

Actually, many physiological activities of alpha tocopherol are well known,

and these show that the mechanism of action is very complicated and remains still obscure. Just as it was called "vitamin X" in an early era, its action has not yet been clarified yet. And, vitamin E may be an eccentric vitamin. For Ochsner wrote that this acted not as a vitamin but as a medicine. When the action of vitamin E is completely cleared as regards its mechanism, the essence of these interesting effects which have been observed here may be clearly explained.

SUMMARY AND CONCLUSION

1. Massive doses of vitamin E were given for 8 weeks to rabbits. The coagulability of blood showed no change. Hypertrophy and good stainability of heart muscle and the middle coat of blood vessels were found by histological studies. On the other hand, rabbits fed for 8 weeks on a vitamin E deficient diet showed acceleration of blood coagulability and high fragility of blood vessels and formation of intraventricular thrombi.

2. Artificial thrombosis and arteritis were produced with sodium morrhuate in the rabbit's femoral artery. When treated with alpha tocopherol, acceleration of healing of exudative arteritis and reopening of blood flow were observed.

3. In 80 surgical patients clotting time, prothrombin time and prethrombotic index were examined before and after operation. Postoperatively one half of them were given alpha tocopherol every day. The tocopherol given group showed relatively stable coagulability of blood, in spite of marked increased coagulability in the control group. One thrombosis developed in the control group but none in the tocopherol group.

4. 20 cases of phlebothrombosis, 2 of arterial thrombosis, 14 of Buerger's disease, 6 of Raynaud's syndrome and 2 of varicose veins were treated with alpha tocopherol. Results with phlebothrombosis were most successful, followed by that with Buerger's disease.

From these animal experiments and clinical studies, the author demonstrated that alpha tocopherol a) has some effects upon the metabolism of the heart muscle and the wall of blood vessels, b) accelerates the healing of arteritis, c) keeps postoperative blood coagulability stable and d) improves blood circulation.

Therefore, the use of alpha tocopherol in the prophylaxis and treatment of thrombo-embolic diseases is suggested.

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REFERENCES

1. EVANS, H. M. AND K. S. BISHOP. *Science* **56**: 650, 1922.
2. PAPPENHEIMER, A. M. AND M. GOETTSCH. *J. Exp. Med.* **53**: 11, 1931.
3. DAM, H. AND J. GLAVIND. *Nature* **143**: 810, 1939.
4. GOETTSCH, M. AND A. M. PAPPENHEIMER. *J. Exp. Med.* **54**: 145, 1931.
5. SHUTE, E. V. AND W. E. SHUTE. *Alpha Tocopherol in Cardiovascular disease.* Toronto: The Ryerson Press, 1956.
6. EVANS, H. M. *ET AL. J. Biol. Chem.* **113**: 319, 1936.
7. EVANS, H. M. *ET AL. Science* **83**: 421, 1937.
8. KARRER, P. *ET AL. Helv. Chim. Acta* **21**: 520, 1938.
9. ADAMSTONE, F. B. *J. Morphol.* **52**: 47, 1931.
10. MASON, K. E. *Yale J. Biol. Med.* **14**: 605, 1942.
11. OCHSNER, A. *ET AL. Annals Surg.* **131**: 652, 1950.
12. YOUNG, J. M. *ET AL. J. Biol. Chem.* **193**: 743, 1950.
13. PHILLIPS, P. H. AND E. B. HART. *J. Biol. Chem.* **109**: 657, 1935.
14. TOCANTINS, L. M. *The Coagulation of Blood.* New York: Grune and Stratton, 1955.
15. KAY, J. H. *Yale J. Biol. Med.* **23**: 515, 1951.
16. QUICK, A. J. *Hemorrhagic Diseases.* Philadelphia: Lea and Febriger, 1957.
17. HASHIMOTO, Y. *J. Jap. Soc. Surg.* **58**: 939, 1957 (Japanese).
18. OLCOTT, H. S. *J. Nutrit.* **15**: 221, 1938.
19. BRAGDON, J. H. AND H. D. LEVINE. *Am. J. Path.* **25**: 265, 1949.
20. GATZ, A. J. *ET AL. Anat. Record* **110**: 249, 1950.
21. HOUCHIN, O. B. AND P. W. SMITH. *Am. J. Physiol.* **141**: 242, 1944.
22. MAKINSON, D. H. *ET AL. Lancet* I, 102, 1948.
23. RINZLER, S. H. *ET AL. Circulation* **1**: 288, 1950.
24. BICKNELL, F. AND F. PRESCOTT. *The vitamins in Medicine.* London: Heinemann Med. Books Ltd., 1953.
25. ENRIA, G. AND R. FERRERO. *Arch. per la Scienze Med.* **91**: 23, 1951.
26. PIANA, G. *Gazz. Med. Ital.* **112**: 51, 1953.
27. DOMINGUEZ, J. P. AND R. DOMINGUEZ. *Angiologia* **5**: 51, 1953. (Cited from *The Summary* **5**: 33, 1953.)
28. GRAY, H. AND L. K. LUNT. *Am. J. Physiol.* **34**: 332, 1914.
29. BERGQUIST, G. *Acta Chir. Scandinav.* **92**: 1, 1945.
30. WARREN, R. *ET AL. Arch. Surg.* **61**: 419, 1950.
31. REICH, T. *ET AL. Surg. Gynec. and Obst.* **102**: 463, 1956.
32. STERNBERGER, L. A. *J.A.M.A.* **150**: 1591, 1952.
33. ZIERLER, K. L. *ET AL. Am. J. Physiol.* **153**: 127, 1948.
34. OCHSNER, A. *ET AL. Annals Surg.* **134**: 405, 1951.
35. OCHSNER, A. *ET AL. J.A.M.A.* **144**: 831, 1950.
36. KAY, J. H. AND S. B. HUTTON. *Bull. Tulane M. Fac.* **9**: 122, 1950.
37. KAY, J. H. *ET AL. N. Orleans M. and S. J.* **103**: 116, 1950.
38. KAY, J. H. *ET AL. Surgery,* **28**: 24, 1950.
39. WRIGHT, I. S. *Circulation* **5**: 161, 1952.
40. WRIGHT, I. S. *The Pathogenesis and Treatment of Thrombosis.* New York: Grune and Stratton, 1952.
41. COON, W. W. *Surg. Forum* p. 536, 1953.
42. MCLACHLIN, J. *ET AL. Surg. Gynec. and Obst.* **93**: 1, 1951.
43. MOORMAN, R. H. *ET AL. Arch. Surg.* **67**: 137, 1953.
44. WILSON, M. G. *ET AL. Lancet* **266**: 486, 1954.
45. CRUMP, W. E. AND E. F. HEISKELL. *Texas State J. M.* **48**: 11, 1952.

46. BAUER, R. *Wien Klin. Woch.* **31**: 552, 1951.
47. MASURE, R. *ET AL. Rev. Belge Path. Med. Exp.* **22**: 73, 1952.
48. REIFFERSCHEID, M. AND P. MATIS. *Med. Welt.* **20**: 1168, 1951.
49. FLEISCHHACKER, H. *Wien Med. Woch.* **27**: 493, 1953.
50. WAGNER, H. *Aerztl. Woch.* **7**: 248, 1952.
51. DEMATTEIS, FE. AND C. MARENZANA. *Minerva Med.* **43**: 1152, 1952.
52. SALVINI, L. AND G. SCARDIGLI. *Clin. Terap.* **2**: 357, 1952.
53. PROSPERI, P. *Proc. 3rd Internat. Cong. Vit. E* p. 275, 1955.
54. PAUL, R. M. *ET AL. Can. J. Biochem. and Physiol.* **32**: 347, 1954.
55. HEYMAN, A. AND O. STAMM. *Gynaecologia* **140**: 224, 1955.
56. KAWAHARA, H. AND H. HIBI. *J. Jap. Soc. Surg.* 59, 1958 (Japanese).
57. SHUTE, E. V. *ET AL. Surg. Gynec. and Obst.* **86**: 1, 1948.
58. SHUTE, E. V. *ET AL. J. Ob. and Gynec. Br. Emp.* **58**: 843, 1951.
59. KRAUS, H. H. *Zentralbl. Gyn.* **75**: 1249, 1953.
60. SUFFEL, B. *Can. Med. Ass. J.* **74**: 715, 1956.
61. DEOLIVEIRA, D. *Hospital, Rio de Jan.* **36**: 135, 1949.
62. STURUP, H. *Nordisk Med.* **43**: 721, 1950.
63. MANABE, S. *Clin. Surg. (Japan)* **10**: 37, 1955 (Japanese).
64. BAGUENA, M. B. *ET AL. Arch. Med. exptl. Madrid* **14**: 47, 1951.
65. COMI, G. AND C. NESI. *Riv. Crit. di Clin. Med.* **50**: 214, 1950.
66. HAGERMAN, G. *Archiv. f. Dermat. Syphil.* **191**: 637, 1950.
67. VOGELSANG, A. *ET AL. Med. Record* **161**: 88, 1948.
68. LEINWAND, I. *N.Y. State J. Med.* **48**: 1503, 1948.
69. HEINSEN, H. A. AND H. SCHEFFLER. *Med. Woch.* **46**: 909, 1951.
70. BUTTURINI, U. *Gior. de Clin. Med.* **31**: 1, 1950.
71. SCHMID, S. *Wien Klin. Woch.* **64**: 128, 1952.
72. SHUTE, W. E. AND V. E. SHUTE. *The Summary (Canada)* **6**: 42, 1954.
73. BLOCK, M. T. *Clin. Med.* **57**: 112, 1950.
74. KAMIMURA, M. *Shinyaku to Rinsho (Japan)*, **5**: 363, 1956 (Japanese).
75. CHIA, W. *Thesis-U. of San Marcos*, 1949. (Cited from *The Summary* **6**: 23, 1954.)
76. WALTHER, H. *Hautarzt* **2**: 526, 1951.
77. KAMIMURA, M. *Shinyaku to Rinsho (Japan)* **4**: 114, 1955 (Japanese).
78. BECKMANN, R. *Zschr. Vitam. Horm. Fermentforsch.* 7, 1955.
79. BARRIE, M. M. O. *Lancet* **233**: 251, 1937.
80. ROY, A. B. *Schweiz. Med. Woch.* **80**: 1030, 1952.
81. GOMIRATO-SANDRUCCI, M. *Minerva Pediat.* **5**: 859, 1953.
82. ITAI, T. *J. Jap. Soc. Physiol.* **15**: 564, 1948 (Japanese).

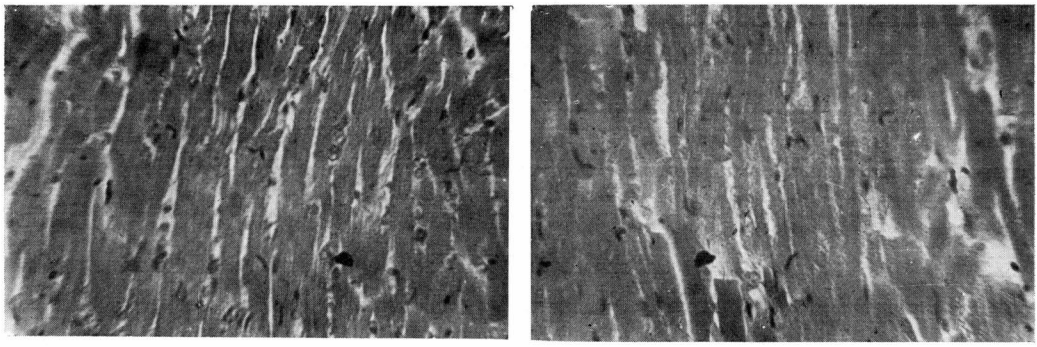


FIG. 3

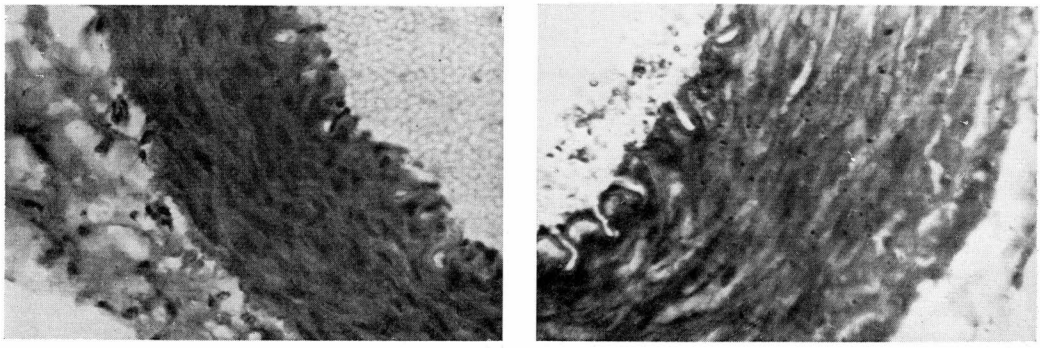


FIG. 4

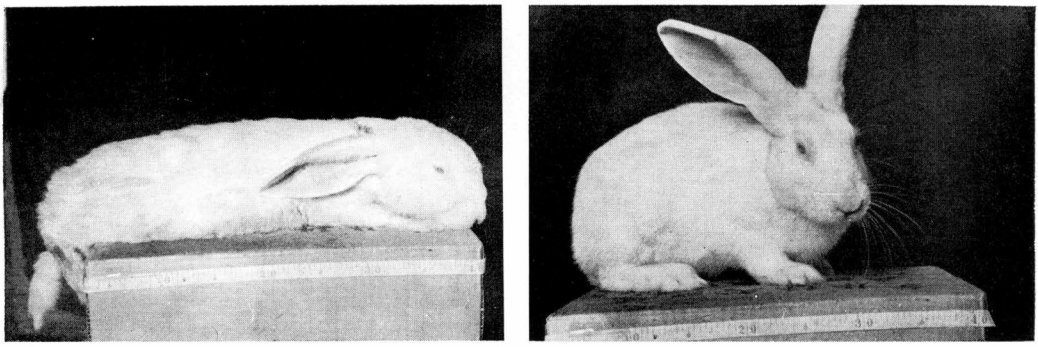


FIG. 6

FIG. 3. Photomicrograph showing cardiac muscle fibers of a rabbit which received massive doses of alpha tocopherol (left), compared with the control (right). Hematoxylin-Eosin double stain. ×320.

FIG. 4. Photomicrograph showing femoral artery from a rabbit which received massive doses of alpha tocopherol (left). Compare with the control (right). PAS stain. ×320.

FIG. 6. Rabbit which received a diet deficient in vitamin E for eight weeks (left) is shown; right shows a control rabbit.

FIG. 8

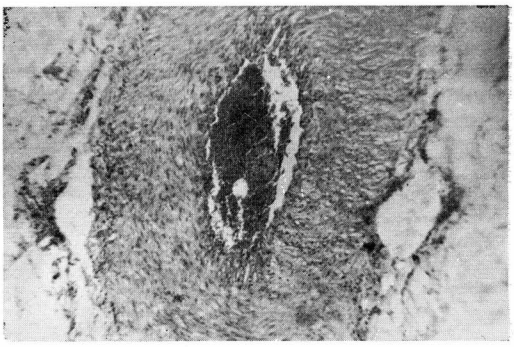


FIG. 9

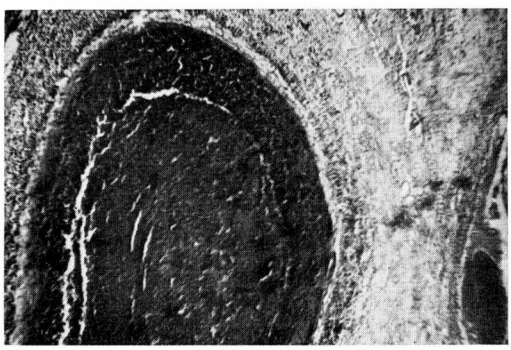


FIG. 10

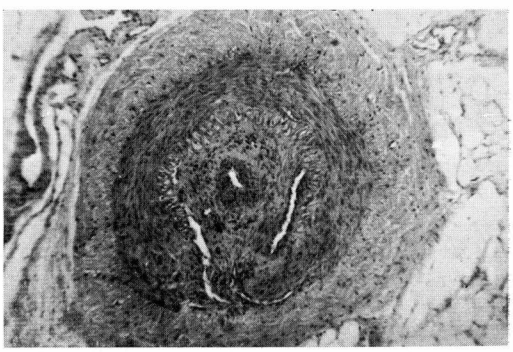
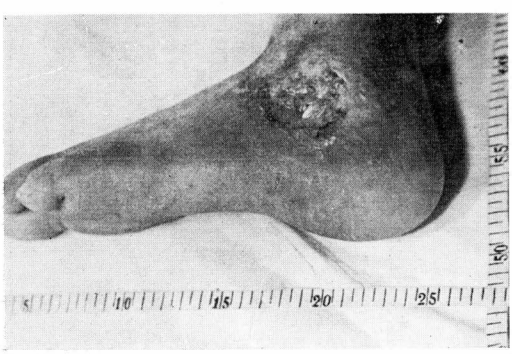


FIG. 11



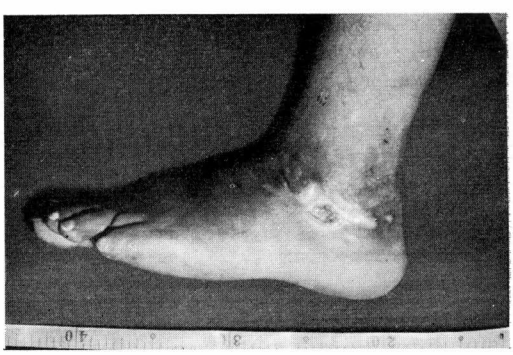


FIG. 15

FIG. 8. Photomicrograph of a separating thrombus in cardiac ventriculus from a rabbit on a diet deficient in vitamin E. H-E double stain. ×80.

FIG. 9. Photomicrograph of femoral artery from a rabbit which received a diet low in vitamin E for eight weeks. H-E double stain. ×80.

FIG. 10. Photomicrograph showing an artificial thrombus in femoral artery from a control rabbit. H-E double stain. ×100.

FIG. 11. Photomicrograph showing an artificial thrombus in femoral artery from a rabbit which was given alpha tocopherol for one month. H-E double stain. ×100.

FIG. 15. A case of Buerger's disease with foot ulcer (left) and same patient after eight weeks tocopherol therapy (right). Case 13, a 41 year old male.