

SURGERY

GYNECOLOGY AND OBSTETRICS

VOLUME 86

JANUARY, 1948

NUMBER 1

THE INFLUENCE OF VITAMIN E ON VASCULAR DISEASE

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IN 1942 Mason (2) reported that the classical fetal resorption in E-deficient pregnant rats was due to such vascular abnormalities in the uterine wall as stasis, distention, and thrombosis (notably venous). Occasionally these conditions terminated in ruptures into the decidua with frank hemorrhage. In E-deficient chicks analogous phenomena are also seen, and there is some evidence in them, too, of functional alteration of the capillary walls.

At about the same time Shute (6) stated that senile vulvovaginitis treated with high doses of the tocopherols often was clinically improved. Biopsy of vulvar tissue after such treatment revealed an appearance suggesting either the proliferation of new capillaries or the reopening of old collapsed capillaries. But the definite lag of 2 to 4 weeks before improvement showed itself suggested the former as being the more likely. On *a priori* physiological grounds it was the more tenable explanation, too.

Mason (3) has also pointed out that in both the monkey and hamster vascular degeneration is a prominent feature in the picture of prolonged vitamin E deficiency. Shute (8) has recently reported the rapid response to intensive tocopherol therapy of 3 patients with acute hemorrhagic nephritis, indicating an ef-

fect on the glomerular capillaries. Other observations (7, 11) we have made on the purpuras indicate that the tocopherols decrease capillary permeability and increase low platelet counts. However, it was the influence of the tocopherols on coronary thrombosis and other cardiac processes (1, 3, 14, 15) that recently turned our attention directly to the effect of tocopherols upon pathological conditions of the vascular system. It was noted that many arteriosclerotic cardinals given tocopherols reported that feet and hands that had been cold and numb for years had suddenly become warm again. Many had had small indolent ulcers which now healed rapidly. We could scarcely fail to investigate certain types of peripheral vascular disease in following up such clues.

CLINICAL STUDIES

What follows is an account of our experiences with tocopherol therapy in a series of patients having vascular disease.

Thrombophlebitis and phlebothrombosis. Twenty-two cases of this condition have been studied. Three typical examples will be described briefly.

CASE 1. Miss M. (courtesy Dr. R. Schram), aged 20 years. This girl developed an acute left femoral thrombophlebitis May 28, 1946, the third day postpartum. The area involved was about 4 inches long in the left midthigh, and there was at the same time a phlebitic mass 3 centimeters in diameter in the left

This publication was made possible by grants from the Shute Foundation for Medical Research.

groin. There was a fever of 100.4 to 101.6 degrees, and a platelet count of 80,000. After May 31 the patient was given a daily oral dose of 200 milligrams of α tocopherol acetate. The temperature fell to normal and remained normal after June 1. By June 3 the phlebitic area in the thigh looked as one would expect it to appear after 10 to 14 days of the classical therapy with heat, elevation, and rest. The redness, and almost all the heat and tenderness, had disappeared from the inflamed area. The mass at the groin was then only half its original size and much less red and tender. The platelet count was 136,000 on June 6. Improvement in the phlebitic thigh was rapid and continuous, but not so rapid in the mass in the groin. Her platelet count on June 10 was 176,000. After 2 more weeks the mass in the groin had disappeared, however, and the patient went home on June 26, 1946.

This was the first case of thrombophlebitis treated by us.

CASE 2. Mrs. R., aged 26 years. This woman had suffered from severely varicosed legs for years. On February 24, 1947, in the 8th month of her fifth pregnancy, she presented herself with the most severe and extensive antepartum thrombophlebitis ever seen by us. The femoral and internal saphenous veins of the left lower extremity were involved from mid-thigh to midleg, and a thrombosed, inflamed varix just above the knee was as large as a man's clenched fist. An area of redness extended for 2 inches on each side of the vein in the thigh. Her temperature was 98 degrees, her platelet count 96,000. She was promptly sent to hospital. In 3 days' time she was greatly improved and left the hospital in good condition in 10 days. Her platelet counts were 96,000 on February 25, 1947 and 132,000 on March 1. She went home with a sedimentation rate of 86, however. Her sole treatment throughout was bed rest, and 250 to 300 milligrams of α tocopherol per day by mouth. She was sent home on 100 milligrams per day. She delivered normally on March 21, 1947. At labor her platelet count was 100,000. There was no recurrence of her phlebitis afterward, perhaps because she was given 300 milligrams of α tocopherol per day during her puerperium.

CASE 3. Mrs. F., aged 37 years. At 36 weeks of her second pregnancy this woman appeared to have a huge hydramnios. It was impossible to induce her *per vaginam* because of an almost inaccessible, rigidly closed cervix. At cesarean section on March 3, 1947 the uterus was found to be small, however, and a child weighing 5 pounds 6 ounces was delivered. But an enormous malignant right pseudomucinous cystadenoma of the ovary (secondary in nature!) was found filling the whole right side of the abdomen, extending up to the liver and far across the left side of the midline. It was adherent generally to the whole ascending colon, much of the inferior aspect of the liver, and to numerous loops of the ileum posteriorly. The patient ran a comparatively easy and afebrile postoperative course for 10 days, although she was

flatulent. On March 13 the platelet count was 266,000. That day she developed an acute sepsis; and repeated daily blood cultures showed a hemolytic *Bacillus coli*. On the same day the whole left lower extremity suddenly developed a typical phlebothrombosis. There was no local heat or redness but some linear tenderness, some edema, and Homans' sign. At once she was given α tocopherol orally in doses of 300 milligrams per day. At the end of 3 days there was absolutely no evidence that there had ever been a thrombosis of that extremity, and the patient moved it in bed with maximum freedom. Because she was nauseated, the tocopherol was discontinued. The next day she suddenly developed a pulmonary embolus in the right base, accompanied by severe dyspnea necessitating an oxygen tent. Her platelet count on March 17 was 200,000. She remained so nauseated that she refused all food and medication, and was carried along for several days on transfusions, intravenous saline and streptomycin. Two days after the tocopherol was discontinued both legs became very edematous generally, with some slight tenderness over the left calf. The platelet count was 156,000 on March 21. In a few days she began to eat and could take tocopherol capsules again. She made a tedious recovery, however. The legs suddenly returned to near normal appearance on April 4 and at the same time her low-grade fever disappeared. On April 6 her platelet count was 360,000. She was sent home taking tocopherol, but no iron of course. Her legs have been normal since. On April 16 she got out of bed for the first time.

All the other patients did as well as those described above.

We have ascribed the results achieved in thrombosis of the veins, with or without attendant inflammation, to a direct effect of the tocopherols on thrombi. There seems to be little doubt that in a fresh thrombosis the clot itself is directly attacked. It can literally melt away, as in the last patient described above. But in thrombophlebitis a thick thrombus can be felt long after all evidences of inflammation other than an elevation of the sedimentation rate have disappeared. Resolution always seems to begin and to progress uniformly over thrombotic areas of any length. Any associated fever usually falls promptly. The possibility of embolism following unduly rapid resolution of a fresh phlebothrombosis must be borne in mind, of course. Perhaps in such cases a small dose of tocopherols and a more gradual response would be desirable.

Fresh thrombi are often associated with a low platelet count, as if the fresh fibrin plug had formed a screen to take a large share of

the platelets out of circulation. Clinical improvement in these patients is coincident with a rise in platelet count and an apparent resorption of the fibrin mesh. On the other hand, older and organized thrombi are usually associated with higher platelet counts, do not seem to screen out platelets, and do not respond to the same dosage of tocopherols. Perhaps double the usual dose is required—often as high as 600 milligrams of the alpha form. Can it be that tocopherols attack fibrin directly by a proteolytic process? A decrease of platelets and a persisting high sedimentation rate on tocopherol therapy is an indication either of recurrence or extension, and demands an increased dose.

The bearing of these observations upon our views on cerebral and coronary thrombosis is too obvious to be labored here, of course.

Should all puerperal women be given tocopherols in an effort to avoid thrombosis? Such therapy might also promote lactation in a few such women (5), but of course should not be instituted until the third day, at least in toxemic mothers, for fear of precipitating eclamptic convulsions (9). Many herniotomies and pelvic operations might benefit similarly from prophylactic dosage.

Indolent ulcers of the leg and ankle. We have studied 13 of these and will describe 4 typical examples:

CASE 4. Mr. H., aged 63 years, a railway news agent. His right leg had been ulcerated at the ankle off and on for 19 years. There was considerable generalized arteriosclerosis, and a normal blood sugar. The present exacerbation dated from 1945. When first seen by us on September 16, 1946, he had been in bed for a month with the right leg literally covered from toe to knee with old and recent open ulcers of all sizes up to 2 inches in diameter. During that month he had been treated with local applications with little or no relief. He was promptly given 250 milligrams of α tocopherol per day by mouth. He began to show improvement in 7 days' time, was nearly healed in 8 weeks, and was completely healed in 10 weeks. He returned to work November 16, 1946, and has been well since, working on the railroad again.

CASE 5. Mrs. C., aged 76 years, a widow living alone. For 18 years she had had recurrent varicose ulcers of both lower legs. She came under our observation on December 13, 1946, for a fundus carcinoma. It was incidentally noticed at that time that her left leg was in an Unna's boot. Both shins were

badly scarred from old ulcerations. She had had an indolent varicose ulcer over the left internal malleolus for the previous 6 months, and had worn an Unna's boot during that period of time without much benefit.

The boot was removed, she was curetted and given deep roentgen therapy, and kept in bed. After December 14 she was given 300 milligrams of α tocopherol per day by mouth. In 10 days' time the old ulcer had greatly improved and in 17 days was well healed. The leg has remained well since. She was discharged February 2, 1947. She is now quite active, doing her own housework.

CASE 6. Mrs. A., aged 82 years, had suffered from varicose veins of both legs since 20 years of age. She had had varicose ulcers occasionally since 30 years of age, the last one appearing in 1938. The present episode began in August, 1946. When first seen by us on December 7, 1946, there was a typical varicose ulcer over the internal malleolus of the left ankle. It was 3 centimeters in diameter with a dirty, sloughing base. Several tiny ulcers were to be seen over the external malleolus of the same leg. Her urine was normal. She was put to bed for 9 days and given 300 milligrams per day of α tocopherol. There was so much improvement in the ulcer in that time that she was allowed up. By the 23rd day of treatment the ulcers were greatly improved and healing was complete on the 29th day. She has been well and active since.

CASE 7. Mrs. C., aged 54 years. This woman had been troubled with varices in the left leg since 1922. At that time she had had a venous ligation done. She had had phlebitis five times since, once in both legs. In 1941 an ulcer developed over the left internal malleolus and it had never healed completely since. For the past 3 years it had covered the mesial and anterior aspect of the lower leg and when she presented herself it was about 4 inches in diameter, square in contour, with a stinking, sloughing base.

She was admitted to hospital March 8, 1947. Her blood and urine were normal. She was afebrile. The usual local treatment was applied and penicillin was used as well, both intramuscularly and locally. On March 18 one of us suggested that the penicillin be discontinued and that she be given 375 milligrams of α tocopherol per day by mouth. She made steady and rapid progress thereafter, getting out of bed after March 21. By March 25 the slough had all cleared away from the surface of the ulcer, the odor had gone, fresh granulation covered the whole base, and peninsulas of epithelial tissue had grown in over the granular surface for as much as 1 centimeter in many places. By March 30 the epithelialization had progressed considerably, in some places encroaching 3 centimeters or more into the ulcerated area. She was discharged from hospital on April 12.

She was next seen on April 26 at which time the ulcer was well healed except for an area at the center 3 centimeters in diameter. This was reduced to half this size by June 3. On July 20 the ulcer was completely healed.

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All the other patients did as well as those described here.

The response achieved in these patients was both prompt and lasting. It was ascribed to an improvement in local arteriolar circulation and to better oxygen utilization by the local tissues. During treatment the affected extremity sometimes became warmer than its mate.

These studies may bear on the problems of plastic surgery.

Early gangrene of the extremities. We have studied 3 such cases and will describe one of them in detail:

CASE 8. Mr. McK. (courtesy Dr. W. Hambly) aged 74 years. He was admitted to hospital in London on March 19, 1947, displaying small areas of dry gangrene on the dorsum of both feet and legs, large, deep, gangrenous areas $1\frac{1}{2}$ inches in diameter in front of, and behind, the left external malleolus, and a large area of dry gangrene over the right tendo achillis. Both legs were inflamed, discolored, and edematous half-way to the knees. The patient said he had been "sloshing around" in the fluid in his boots for several days before admission. His hands were a dusky, cyanotic color. The blood sugar was normal, but the nonprotein nitrogen was 43 milligrams per cent and his sedimentation rate 76. X-ray studies of his legs showed considerable calcification of the posterior tibial artery, much more marked in the left leg. The left popliteal did not pulsate and the right pulsated only very faintly.

Beginning on March 23 he was given 300 milligrams of α tocopherol acetate per day by mouth. On the 26th he complained of "pins and needles" in his feet, and a change for the better was apparent at the upper limit of his lesions. His feet and legs were no longer edematous. His hands were no longer cyanotic. On the 28th a pulsation in the left popliteal artery was first palpable. By the 30th most of the epidermis of the legs and the dorsum of the feet had sloughed off, leaving normal pink skin underneath. At this time the more superficial gangrenous areas were rapidly healing under loosening scabs. By April 6 several of these had been cast off, and a pulsation could be detected in both posterior tibial arteries for the first time. By April 18 his right leg and foot were almost normal in appearance. On the left foot only a few of the deeper scabs remained. On April 23 his nonprotein nitrogen was 43, creatinine 1.1, and sedimentation rate 35. The corresponding values on May 2 were 43, 1.1, and 17. By April 28 both feet were healed and the patient began to walk about.

When he went into hospital amputation of both legs above the knee seemed to be the treatment of choice. Amputation is no longer necessary. He still takes 100 milligrams α tocopherol per day.

The first case of early gangrene of an extremity treated with tocopherols was a woman of 76 years of age, who was admitted to hospital December 8, 1946, for an acute diverticulitis which was promptly operated upon. Her left leg at that time showed early but discrete and superficial gangrenous areas extending as high as the knee. She was a mild diabetic under good dietary control, but with arteriosclerosis. After December 11 she was given 100 milligrams of α tocopherol per day by mouth, and soon showed great improvement in the affected leg. She was discharged from hospital on December 22, 1946 and has led an active life ever since, doing her own housework. She still takes 25 milligrams of α tocopherol per day as a prophylactic measure. There has been no recurrence of her lesions.

What would tocopherol therapy do for frostbite, "immersion foot," and similar conditions? Others with better clinical opportunities may provide the answer.

Thromboangiitis obliterans and related vascular conditions. We have thoroughly studied one verified and one dubious case.

CASE 9. Miss M. T., aged 56, single. She has never used tobacco. She began to complain of pains in her toes in 1938. The toes became dusky red, at times almost purple, and gangrene was feared as their condition became progressively worse. At that time a glass boot and other such measures in hospital over a period of 15 weeks gave temporary relief. With Buerger's exercises and careful avoidance of overexertion and heat (this has always bothered her more than cold!), she maintained an approximate *status quo* until July of 1946, although frequently during these intervening 8 years the toes were ulcerated. The greatest care was required to avoid a major foot infection and to heal these small ulcers. Once, in 1942, she almost developed dry gangrene of several toes of both feet and was forced to spend 7 weeks in bed. The toes have been numb for years, as has also been true of the feet and lower legs. When she wanted to pick up anything from the floor she could not kneel steadily because of the numb feet, but sat down in order to do so. She often awakened in the night "to see if her feet were still there." There had been considerable edema of the feet and lower legs during these years, and this was not altered appreciably by a salt-free diet.

On June 12, 1946, she was given 200 milligrams of α tocopherol acetate per day—our first case of peripheral vascular disease treated with the tocopherols. On the 15th she "could scarcely sleep for the

tingling in her arms and legs," and in the next few days purpuric areas of all sizes appeared over the trunk and extremities, accompanied by sensations of "pins and needles." She had had these purpuric manifestations at her x-ray menopause 10 years before, but not in the interim. In 10 days' time her edema decreased considerably, and her toes felt warm and had practically returned to normal color. By July 23 her feet and toes were no longer numb. She now could kneel on the floor to work or pick things up. Trauma to the toes was now felt as pain. On three or four occasions she stopped her tocopherol therapy or reduced the dose, but each time her edema and other difficulties recurred promptly. Her chiropodist could always detect changes in her dosage. Her corns began to trouble her again as soon as sensation returned to her toes, and they regained their usual color. Actually it seemed to her that the corns grew faster than before. She is now leading a very active life as a practical nurse on a difficult case.

We are well aware of the fact that the diagnosis in this case is questionable, and that to call it Raynaud's disease might be more accurate. However, the vascular relief achieved provides our reason for presenting it.

CASE 10. Mr. S. K., aged 48, a veteran of the last war. In the winter of 1944, he experienced a good deal of pain in his fingers and toes. They often felt intensely cold and would assume a dead white appearance. In June, 1945, he was sent into hospital for a stubborn ulcer on the ball of the left thumb. The palmar aspect of the right thumb then displayed extensive areas of dead white skin, and ached. His toes also were white, but not as white as the thumb. They, too, were cold to the touch and ached. His other fingers ached constantly too. When the ulcer on the thumb healed, other ulcers appeared on the tips of other fingers, some of them on the other hand. A diagnosis of Raynaud's disease was made. In October of that year the ring finger of his left hand was ulcerated at the tip. Neither detailed examination by a neurologist nor laboratory studies were helpful.

On a later hospital admission in September 1946 an x-ray examination of the hands revealed osteolytic reaction involving particularly the distal end of the distal phalanx of the third right finger and the distal phalanx of the right index finger. His feet showed similar changes involving the distal phalanx of the 2nd right and 2nd left toes, and both 4th toes. The right 5th toe showed some proliferations and cystic areas, suggesting a response to vascular occlusion. Two weeks later gangrene of the second right toe appeared, with swelling and redness of that toe and foot. Only an occasional dorsalis pedis pulsation could be felt. The right popliteal was palpable. Injection of 8 milligrams of mecholyl produced a temperature elevation of as much as 1.2 to 2.1 degrees only in the first right toe, 4th right toe, and in 1st, 3rd, 4th, and 5th left toes. In the remainder, the flushing response was less than one degree. On Oc-

tober 25, 1946 the right lower extremity was amputated by the Gritti-Stokes method. As the stump failed to heal, skin grafts were attempted in November, 1946, and January, 1947, but both failed to take.

The pathological report on the amputated leg revealed thickened vessels, showing in one place an old organized, canalized thrombus. There was intimal hyperplasia, a lymphocytic infiltration of the media, and a thickened adventitia. The small vessels showed either marked narrowing of the lumina or organized blood clot filling them. There was no evidence of calcification anywhere.

The condition of the other leg rapidly became worse, and, when first seen by us, on February 13, 1947, he had been sent home on 2 weeks' leave before returning to consider its amputation. The site of the unhealed skin grafts was a raw ulcer. For a fortnight he was given 300 milligrams of a tocopherol acetate per day by mouth, but not required to reduce his cigarette consumption. By the 4th day of treatment he began to feel improvement. On the 8th day increased urination developed and he no longer experienced pain in his extremities. By February 24 his phalanges were normally warm and of good color. The recalcitrant stump ulcer was now completely healed and felt normally warm. On March 14 he was able to walk on his artificial leg for 4 hours without discomfort, and his hands and remaining foot seemed nearly normal. He bought a truck and decided to begin a trucking business. However, he was unable to get tocopherol capsules for a 2 week period in April. When he next reported, on May 1 he showed a recurrence of the stump ulcer. He was promptly given tocopherols again and the ulcer healed as promptly as at first. He was working as a trucker when last heard from at the end of May.

Another typical case has had a fine result. It should be mentioned that these patients often suffer a good deal as their circulation improves. During that time they may be difficult to maintain on treatment.

Our former colleague, Dr. C. K. Stuart, has treated with tocopherols 4 patients displaying intermittent claudication, the results being excellent in 3 of them.

Our friend, Dr. George Dowd, has treated 4 such patients between the ages of 48 and 63 years. Three of the patients became asymptomatic and one was markedly improved on doses of 400 to 1100 milligrams of mixed tocopherols daily. We have had a good result in the only case we have treated ourselves.

Cerebral thrombosis. After what has been said above on the subject of thrombosis in general, little need be added here. One of the more puzzling phases of our studies has been the trivial influence the tocopherols usually

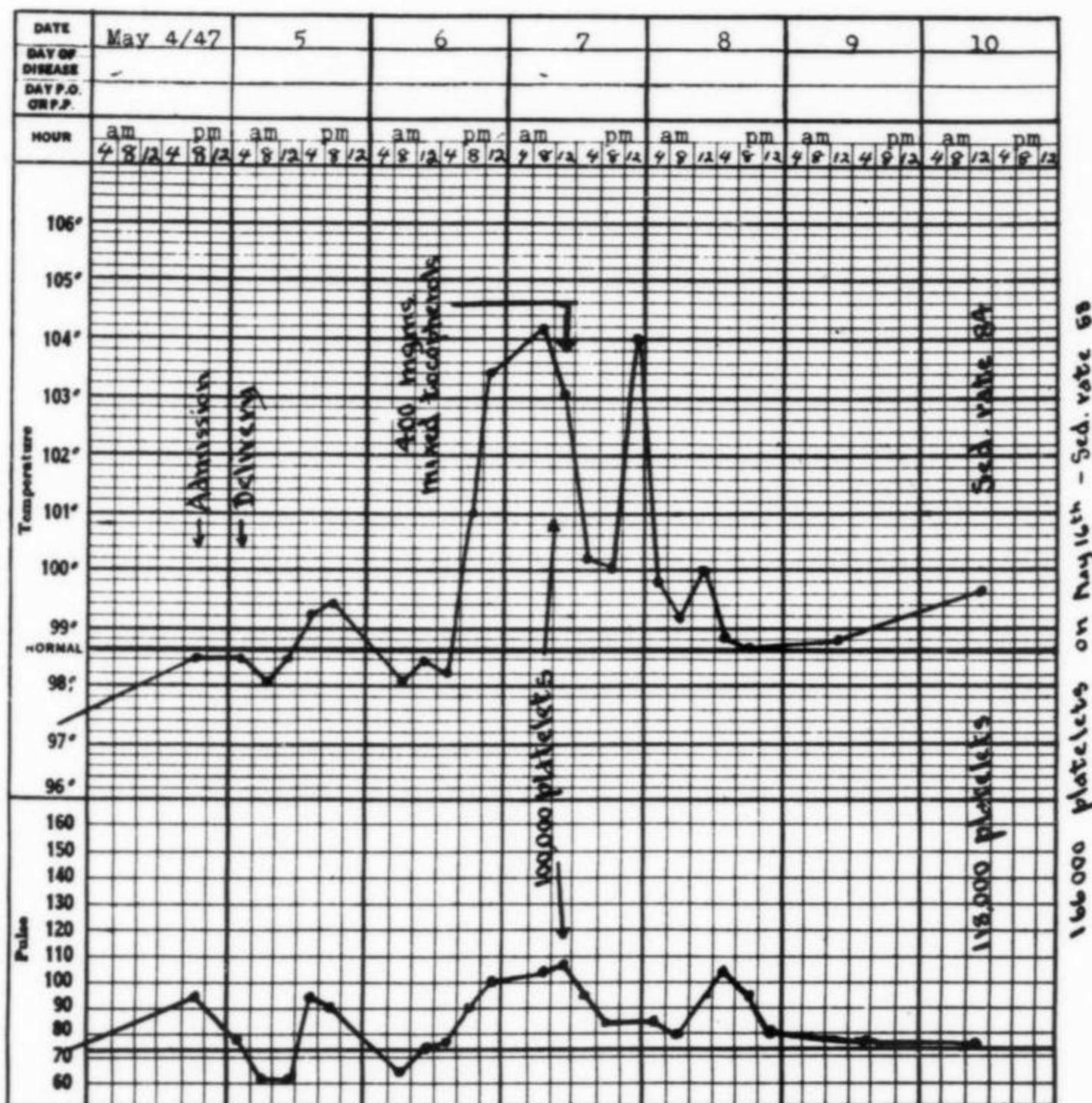


Fig. 4. Graph showing results of treatment with tocopherols only in a case of puerperal thrombophlebitis.

exert on hypertension *per se*, but the fact that in hypertensive heart disease there may be a small initial rise of both systolic and diastolic blood pressures coincident with increased cardiac tone and relief of decompensation, which is often followed by a drop as compensation occurs. The symptoms ascribable to hypertension are often relieved out of all proportion to the improvement thus achieved. This parallels the experience of Smithwick with his surgically treated hypertensives.

We have studied a score of cases of cerebral thrombosis, most of them of months' or as long as $2\frac{1}{2}$ years' standing. Even in the old cases some improvement was often achieved. As would be anticipated, the patients treated most promptly did best. Generally speaking, from 10 to 75 per cent of the disability has disappeared in the group as a whole. This gain was made principally within the first 3 weeks,

after which improvement went on much more slowly. It is very difficult, of course, to prove how much of what was gained was ascribable to tocopherol therapy and how much was spontaneous. Others must settle that point whose opportunities are superior to ours. We merely discuss the topic here for its suggestive value and because it is pertinent to this whole problem. But Dowd tells us he has seen definite improvement in a woman whose stroke occurred 6 years previously. If cerebral thrombosis occurs in end vessels, as medical texts have long contended, the theoretical interest of this type of case is further enhanced. One of our most interesting cases was that of an elderly lawyer who had experienced his accident in 1944, 2 years before he was first seen by us. His outstanding complaint was a central scotoma of the right eye, thought by his ophthalmologist to be on an arteriosclerotic

basis. His blurred vision dramatically improved in 3 weeks' time. Before treatment he could distinguish a person standing 6 feet away but not his features. Afterward he could differentiate all his major features.

The benefit these patients experienced may have been strictly analogous to that seen in thrombosis elsewhere. Or gliosis itself may have partially responded, as in Steinberg's cases of fibrosis and fascial contracture. Both Davison and Dowd suspect that some damaged nerve cells live in a twilight state, neither dead nor yet fully alive, until such a reparative stimulus as the tocopherols reach them and enable them to regain at least a portion of their former function.

If every hypertensive were given tocopherols would the incidence of apoplexy be reduced?

DISCUSSION

The number of patients studied in each of these groups is small, but the results are of such interest, developed so promptly, and have such an important bearing on the great problem of heart and kidney disease in general that it was felt they should be reported now.

The color photographs appended illustrate the rapidity and extent of some of the changes described.

One cannot but suspect that the surgical and medical possibilities of the field we have stumbled into will prove both fascinating and rewarding to investigators who have better opportunities than we have. Generally speaking, the tocopherols should be helpful wherever improved arteriolar circulation or better oxygen utilization in tissues is desired (10).

It would seem that when tocopherols are administered thrombosed veins relax to permit a circulation over and past the thrombus, as Pereira has clearly shown can occur with sympathetic block in like cases. The analogies of our treatment to sympathectomy are of real interest.

The need for continued treatment at high dosage levels in so many cardiovascular conditions is analogous to the situation encountered in hormone substitution therapy, for example in hypothyroidism or in diabetes. It suggests that one is either replenishing a rapid wastage of tocopherols in these particular peo-

ple or combatting the continued production of some noxious bodily antagonist. Our work with the purpuras would perhaps suggest the latter and may even point to that agent as being the estrogens—another indication of the truth of our old thesis that vitamin E is anti-estrogenic, whatever else it is.

The matter of dosage is fundamental in tocopherol therapy. About 200 to 300 milligrams of α tocopherol per day seems to be the average therapeutic level. The fact that it is α tocopherol that is required should be stressed. In cases of acute cerebral thrombosis we have used parenteral tocopherols with success. Patients so treated seem to react in one-half to one-third of the usual time taken when tocopherols are administered by mouth. To achieve the best results in such cases it is important to saturate the patient as early as possible in order to minimize brain cell damage adjacent to the thrombus or embolus.

Inorganic iron should not be given with the tocopherols (10).

We have even been so bold as to hazard the guess—and it can only be that in the present state of our investigations—that the tocopherols may be at least as valuable in the prophylaxis of certain vascular accidents and conditions as in their therapy. In this connection it should be pointed out that many of these conditions soon recurred after healing unless tocopherol therapy was continued at a high level permanently.

For too long, medical men have considered the vitamins to be mere food accessories, things we could either take or leave alone. But surely the time is approaching when some of them, at least, will rank as true chemotherapeutic agents, to be administered in doses comparable to those of the sulfonamides or penicillin, and for indications quite as strict and clearly understood. It may even prove that Nature thought of them as being prophylactic before we thought of them for cure, just as she left medicinal molds lying about for those to pick up who could see them under their feet.

SUMMARY

In such vascular diseases as indolent varicose ulcers of the legs, thrombophlebitis, early gangrene of the extremities, and even thromb-

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angiitis obliterans, tocopherol therapy may be helpful.

Lately, several important companies in this field are labeling their tocopherols according to a new spectrophotometric assay. This means that if their products are to be used in dosage comparable to ours as high as four times as much of their product must be employed.

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