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ALPHA TOCOPHEROL IN THE MANAGEMENT OF SMALL AREAS OF GANGRENE*

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GANGRENE can develop suddenly and involve large areas. Fortunately, it usually begins gradually and affects small segments of tissue, its advance cephalad requiring an appreciable time, during which the body tries to throw up dykes against it. If this ischæmic process breaches the dyke and becomes extensive, amputation is demanded. But amputation must remain an admission either of medical unpreparedness or defeat. The question to be asked, and to be asked in good time, is: "What can be done to stay the relentless progress of local tissue ischæmia and necrosis?"

Vasodilating operations or drugs appear to be our hope, and accordingly both sympathectomy and administration of various vasodilators have come into widespread use. They have not been too satisfactory, perhaps because inadequate in themselves, perhaps because the impending disaster is often recognized too late; arterial occlusion may already be widely extended and almost complete when the first skin discoloration appears. How poor the final results may be, even in the ablest hands, can be gathered from two recent statistical reports.[1, 2] There would seem to be wide room for a new prophylactic and therapeutic agent in this field.

Alpha tocopherol is the most clinically effective factor in pharmaceutical preparations of vitamin E. Used in large doses it not only plays the supplementary role usually thought of in any vitamin medication, but it also has a pharmacodynamic effect all its own. For instance it is a vasodilator, at least of capillaries.[3-14] It enjoys an unrivalled role among physiological agents in its ability to improve tissue utilization of oxygen.[15-20] The classical demonstration of this is its ability to enable experimental animals to survive otherwise lethal degrees of anoxia.[21-23] It is rapidly able to produce collateral circulation about obstructed vessels, as has been experimentally demonstrated in animals by Enria and Fererro[24] after ligation of the femoral vein and by Dominguez and Dominguez in corresponding studies on arteries.[25] The latter workers mention that some of the collateral vessels so developed were as large as the original artery. It has other properties also which would recommend it for the current problem. It has been described as an antithrombin,[26-29] and certainly it is valuable in peripheral thrombosis.[30-43] As every surgeon knows, the march of gangrene is often facilitated by the onset of local thrombosis. Moreover, alpha tocopherol decreases abnormal capillary permeability.[44-52]

Duguid has lately revived Rokitansky's old theory that atherosclerosis itself is due to the organization of repeated mural thrombi.[53, 54] This suggestion has received very strong support from Levene,[55] who analyzed under the electron microscope the material taken from atherosclerotic plaques and found that it usually consisted of fibrin fibrils. If Duguid is correct, the prophylaxis of arteriosclerosis ultimately may depend on the early and prolonged administration of such an antithrombotic agent as alpha tocopherol, a substance which happens to be a common food factor and accordingly can be administered throughout the life span without difficulty.

With such considerations in mind the writers have been treating small areas of peripheral gangrene with massive doses of alpha tocopherol for several years past. The three main types treated have been those due to arteriosclerosis, diabetes mellitus and thromboangiitis obliterans. Several reports on this study have already appeared.[3, 56, 57] At the moment, our series includes 48 completed cases.† Although small, it numbers a good many patients regarded as worthy of amputation by competent and experienced surgeons. The salvage of a good percentage of such precarious extremities represents a distinct advance in the management of gangrene.

DATA

This is an analysis of 48 consecutive, unselected private patients (Table I). No study on human gangrene is ever "controlled", of course, partly because numbers are usually small, partly because there is such a wide variation in the clinical course of various cases of gangrene, and partly because the condition is so distressing, its prognosis so poor, and time runs out so quickly.

*From the Shute Institute, London, Ont.

†Now 59 completed cases.

Legend

Fig. 1	Case 4633, March 11, 1952	Case 1 in text
Fig. 2	Case 4633, March 23, 1952	
Fig. 3	Case 4633, May 25, 1952	
Fig. 4	Case PV609, July 25, 1952	Case 5 in text
Fig. 5	Case PV609, October 31, 1952	
Fig. 6	Case PV609, December, 1953	
Fig. 7	Case PV591, November 5, 1955	Case 2 in text
Fig. 8	Case PV591, November 9, 1955	
Fig. 9	Case PV591, March 3, 1956	
Fig. 10	Case PV513, July 28, 1955	Case 3 in text
Fig. 11	Case PV513, September 20, 1955	
Fig. 12	Case PV513, November 29, 1955	
Fig. 13	Case PV513, March 6, 1956	

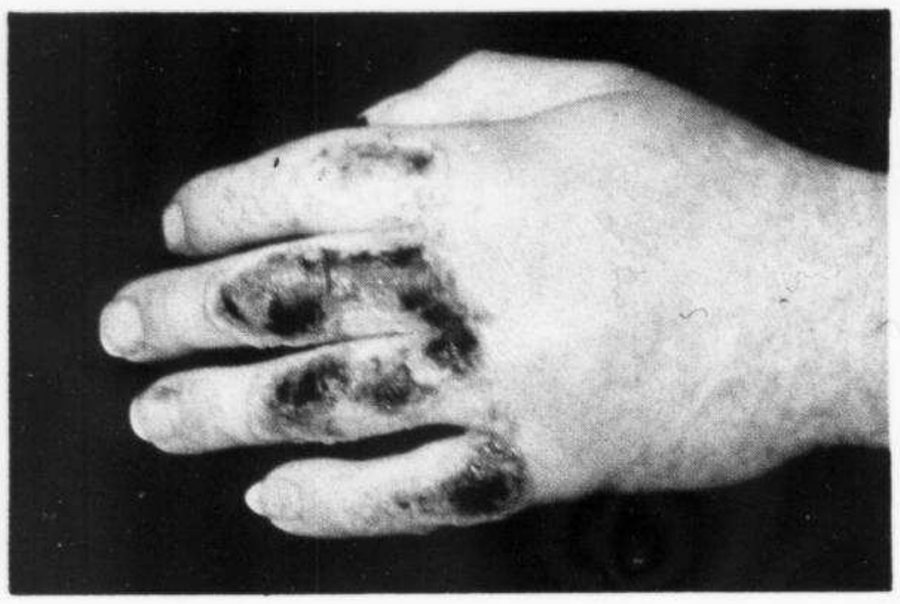


Figure 1.

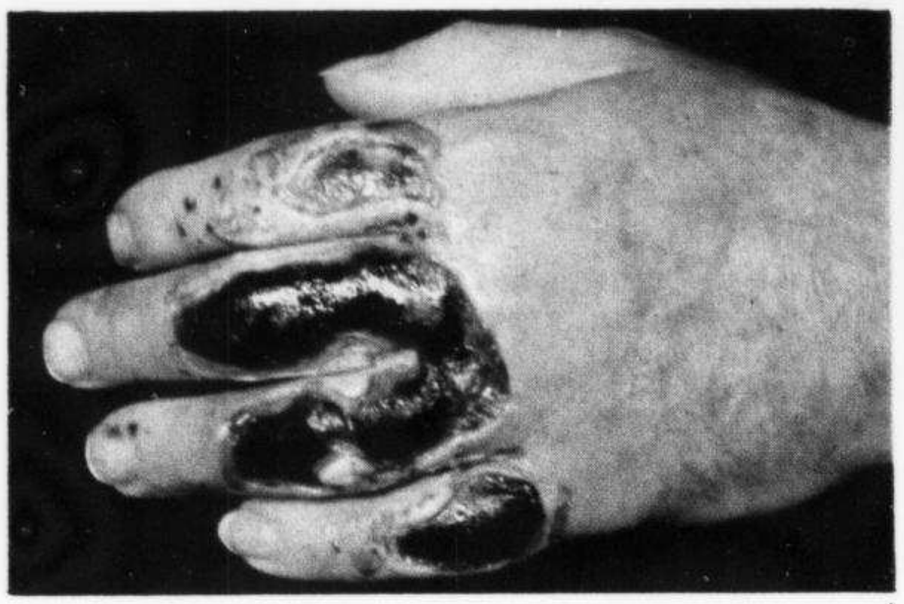


Figure 2.

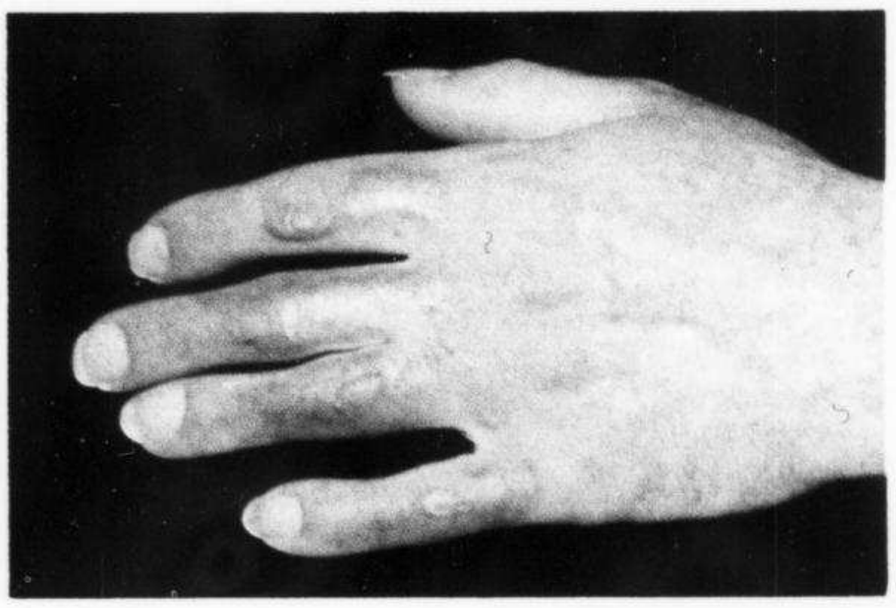


Figure 3.

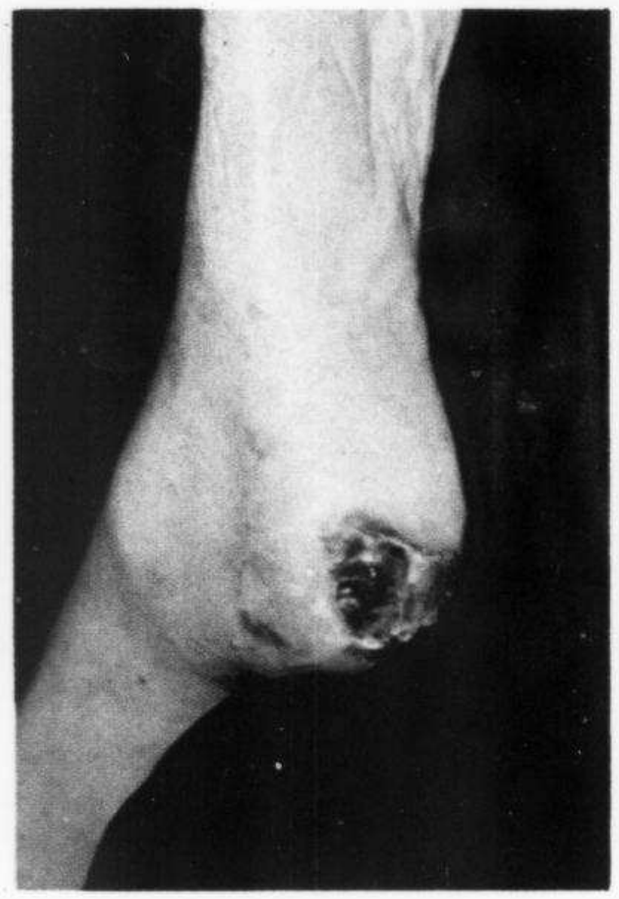
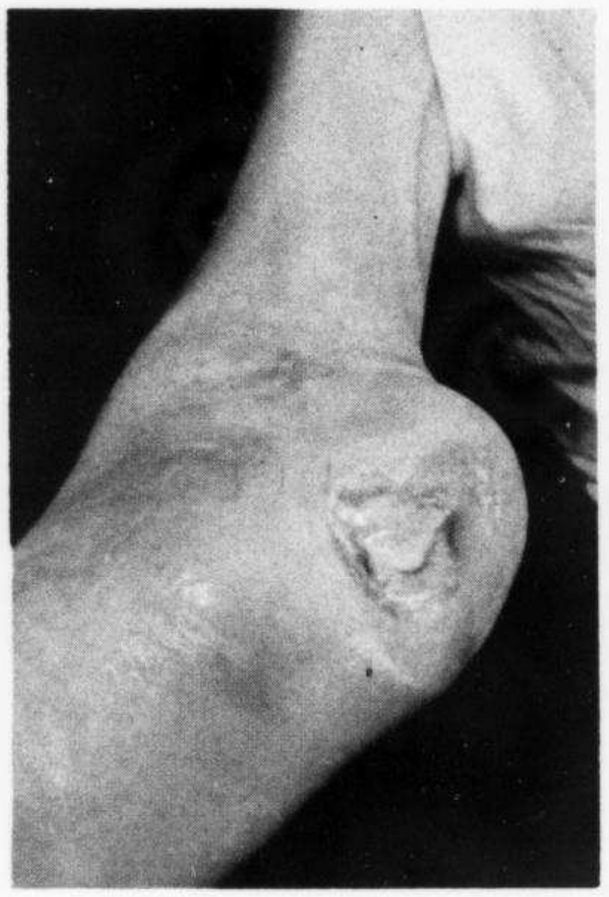


Figure 4.



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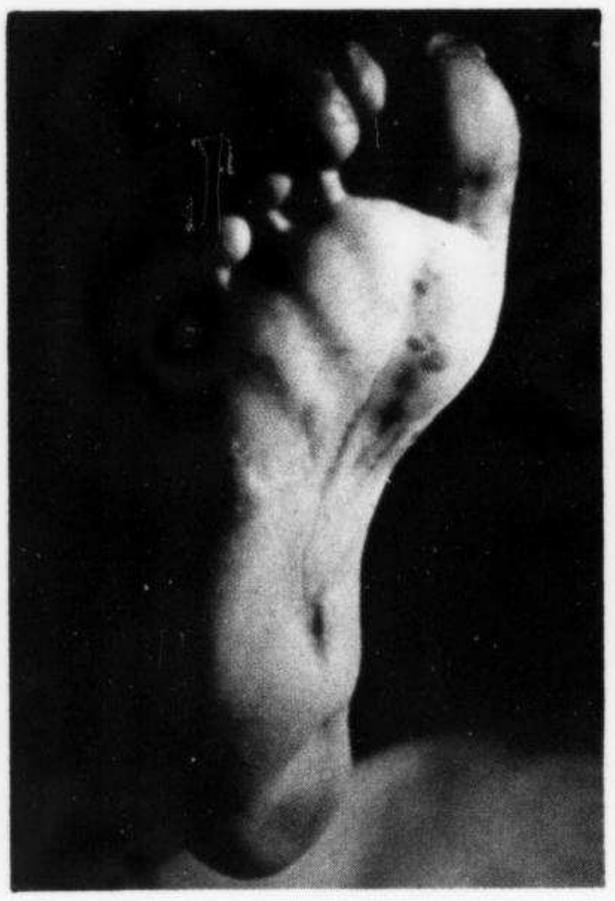

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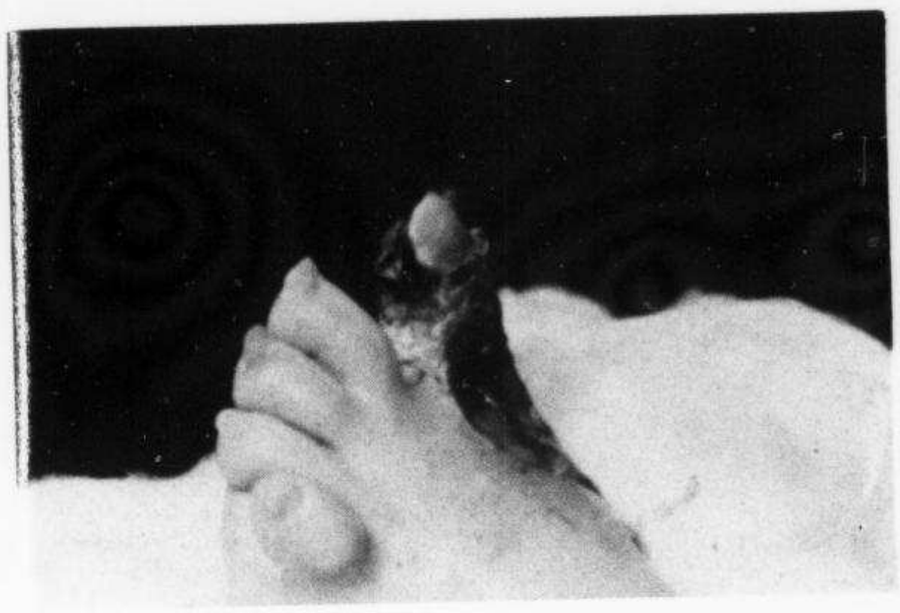

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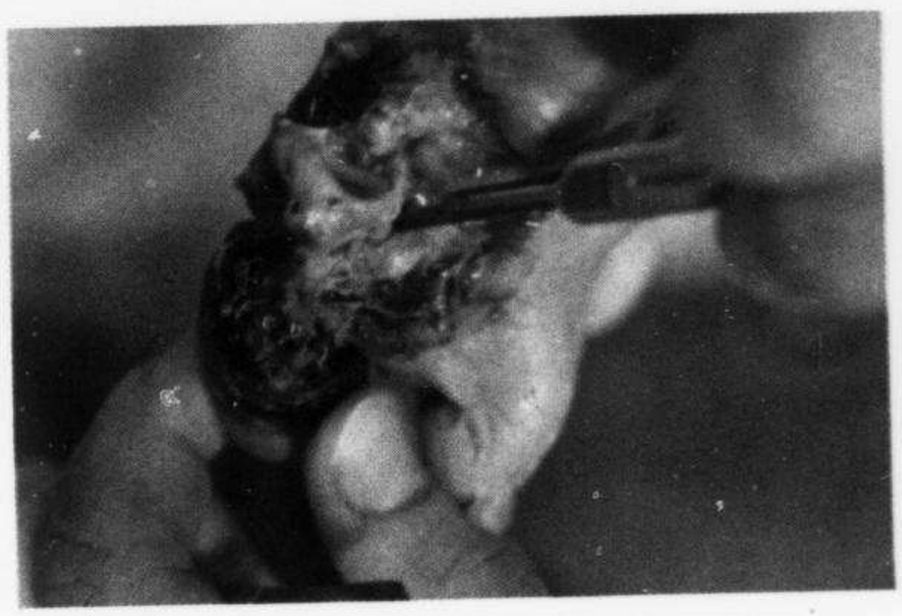

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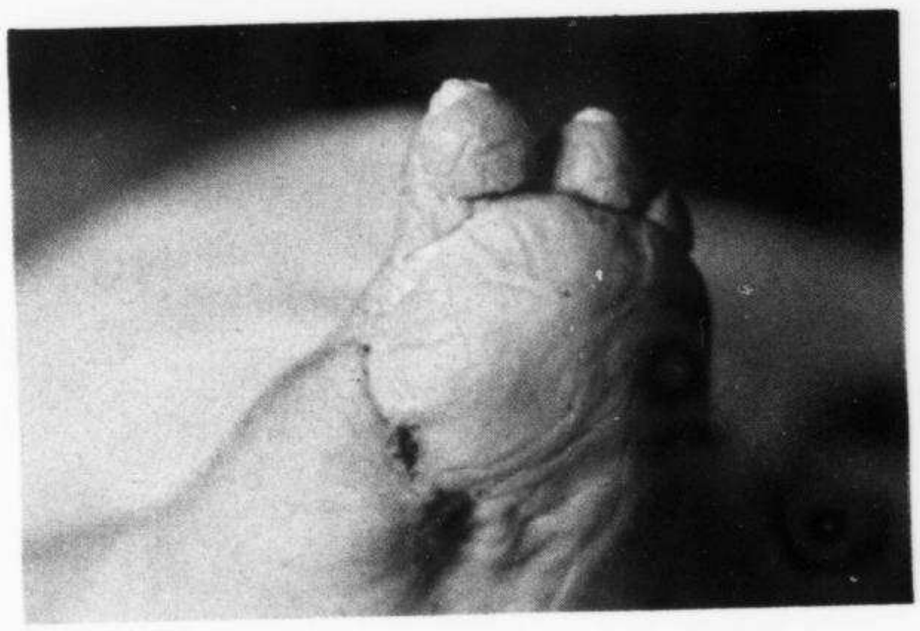

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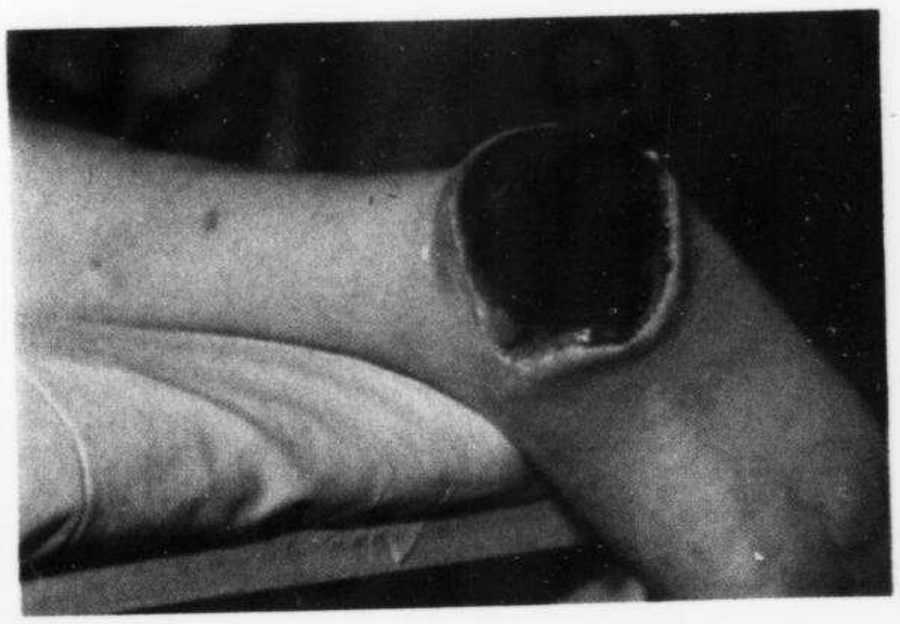

Figure 10.

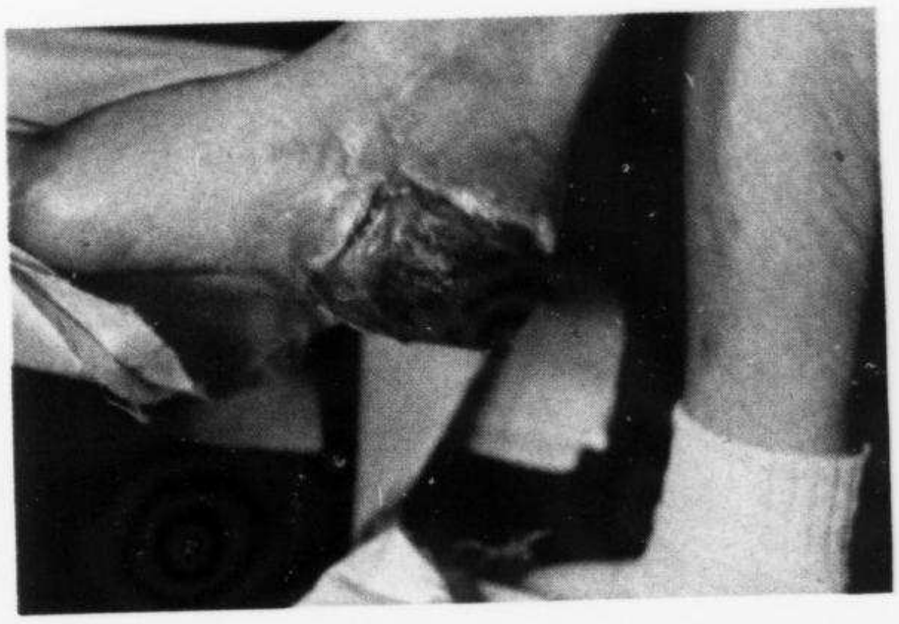

Figure 11.

Figure 12.

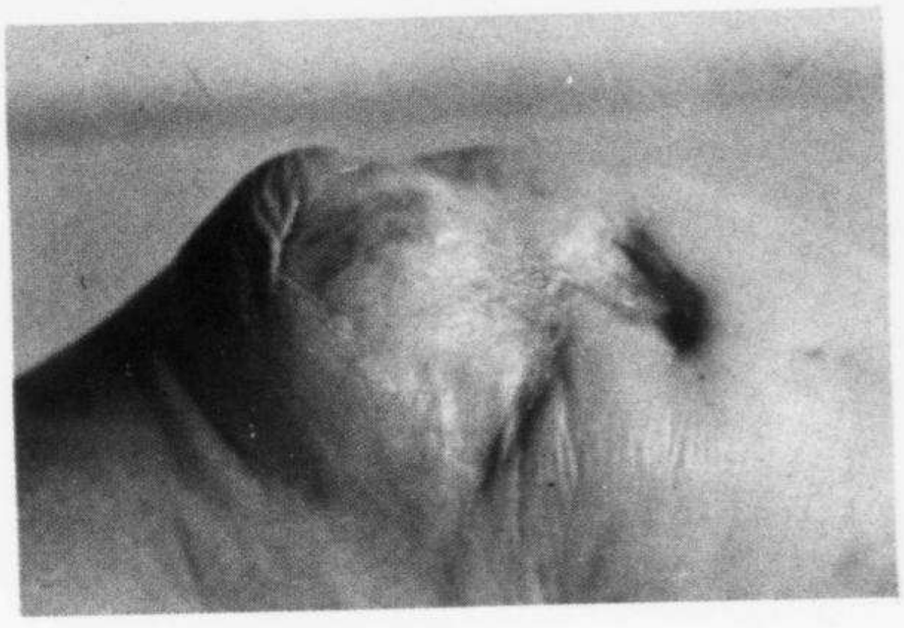

Figure 13.

TABLE I.

Cases	*Average age*	*Previous sympathectomies*	*Previous amputations*	*Complications when seen*	*Average dose of alpha tocopherol*	*Good*	*Results Fair*	*Poor*	*Insulin reduced*
				BUERGER'S DISEASE					
7	42	3 bilateral; 1 unilateral	3 multiple; 1 advised	all severe	600 i.u. (450-900)	3	1 (died of coronary disease in 3½ years)	3	
				DIAGNOSIS NOT CLEAR (Case 1 in case reports)					
1	29	0	0	Hypertension; coronary sclerosis	500 i.u.	1			
				ARTERIOSCLEROSIS					
25	71	2	2 amps.; 3 advised	Severe in 18	650 i.u. (225-1200)	9	4	12	
				DIABETES MELLITUS					
15	65	1	5 amps.; 2 advised	Severe in 8	700 i.u. (375-1200)	9	5	1	8

"Complications" include heart disease, cerebral accidents, cellulitis and such.
"Results" are classed as: (1) Good—restoration to normal activity without surgical intervention. (2) Fair—good temporary result, with later deterioration—or cure of gangrene itself without surgery, but unendurable pain. (3) Poor—amputation.

CASE REPORTS

Perhaps a better idea of what alpha tocopherol can accomplish in such patients is conveyed by the story of individual cases rather than by the table. Here are a few illustrative histories:

CASE 1.—Mr. E.O., aged 30 years. This man had twice before had gangrenous areas on the hand or forearm, each time healing readily with oral alpha tocopherol (400 i.u. daily). Unfortunately he was sensitive to almost every form of this therapeutic agent; he had not been able to continue the maintenance dose that we had advised in the hope of preventing a recurrence. He had coronary sclerosis as well. His blood pressure was 150/100 mm. Hg and his Wassermann reaction was negative.

He presented himself on March 11, 1952, with gangrene involving a large portion of the dorsum of the fingers of the left hand. He was immediately given 500 i.u. of alpha tocopherol by mouth, and tocopherol ointment was applied locally once a day. The gangrenous patches extended no further, and by March 23 they began to separate at the margins. The course of their healing is illustrated in the accompanying photographs (Fig. 1). No other therapeutic procedure but alpha tocopherol administration was used. Because the lesions were deep, the dorsal tendons of the fingers were caught in the scar when the gangrenous areas sloughed off. Healing was complete on May 25, 1952. The patient was left with some limitation of finger flexion.

CASE 2.—Mrs. D., aged 85 years. This woman was an unsuspected diabetic. Two weeks before we saw her, she began to develop gangrene of the left great toe. This spread rapidly as far as the web. Her blood pressure was 150/92 mm. Hg.

On October 9, 1955, treatment was begun by us with 600 i.u. of alpha tocopherol orally each day, as well as an 1800-calorie diet and 40 units of regular insulin (which was soon increased to 58 units).

The gangrenous process began to spread down the inside of the foot both dorsally and on the sole. Maggots appeared in the wound. The toe rapidly mummified and turned black. An abscess developed in the mid-plantar region where pus tracked down from the toe. This was drained, and irrigated through and through with saline.

On October 13, the dose of alpha tocopherol was increased to 1200 i.u. daily, the dorsal tendon was cut, and some debridement carried out. By October 18 the plantar abscess had resolved. Demarcation proceeded well, and finally on November 9, we amputated the great toe without anæsthesia (at home). By that time she needed only 15 units of insulin daily.

A tiny patch of gangrene developed on the heel. Pressure on it was relieved and it readily cleaned up. By February 4, 1956, the toe base was nearly healed and the heel was completely healed. The photographs appended (Fig. 2) illustrate the progress of this patient. She is still well, walks about, and takes 15 units of regular insulin daily as well as 800 i.u. of alpha tocopherol. She has been treated at home throughout.

CASE 3.—Mrs. L.M., aged 61 years. This woman from Michigan presented herself on July 21, 1955, with the story that an ulcer had developed on the right heel in August 1954. The ulcer had progressed slowly and a surgeon had advised amputation of the right leg just before she came to us. She had been a known diabetic since age 28, her condition worsening in the last two years. She had lately taken 35 units of regular insulin daily and adhered to an 1800-calorie diet. Her blood pressure was 165/85 mm. Hg and her Wassermann reaction was negative. She smoked heavily. There was an area of gangrene on the right heel about 5 cm. in diameter. She was at once given 900 i.u. of alpha tocopherol daily by us. Her blood sugar was 280 mg. %, although her urine was clear. Aureomycin ointment was applied locally. She was urged to stop using tobacco, but failed to do so. She was treated in the office throughout. Fig. 3 illustrates the original lesion and its progress under treatment.

By July 28 the gangrenous area was already beginning to demarcate. On August 8 there seemed to be no further progress and accordingly the dose of alpha tocopherol was increased to 1200 i.u. daily. She was now taking 10 units of N.P.H. insulin daily. On November 29, a large portion of the gangrenous area had loosened and could be cut away. Her blood sugar was now 150 mg. % on the same insulin dosage and the same diet (to which she failed to adhere). She smoked heavily again as the lesion healed. She also varied her

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dosage of alpha tocopherol on her own, averaging perhaps 900 i.u. daily. The lesion finally healed, as the photographs indicate, and she can now walk on a pad of elastic rubber. Her blood sugar has averaged 150 mg. % for several months past.

CASE 4.—Mr. R.G., aged 46 years. This man had been to a medical clinic in the United States and to a leading cardiovascular centre before presenting himself to us on January 20, 1949. His condition had been diagnosed as thromboangiitis obliterans; a lumbar sympathectomy, six months before, had failed to relieve his condition, and finally amputation of the left leg had been advised.

On examination no popliteal pulsation could be felt in either leg. The left extremity showed a dusky red great toe with a gangrenous tip where the nail had been removed. He had had claudication only in the left thigh. There was a slight cyanosis of the right hand. He had stopped using tobacco the previous year. His blood pressure was 188/116 mm. Hg. His Wassermann reaction was negative.

He was at once given 375 i.u. of alpha tocopherol daily and the foot was photographed. His electrocardiogram was normal, apart from some widening of the QRS complex.

When next seen on February 17, 1949, he was feeling a great deal of pain in the left foot and could scarcely sleep, and no local improvement could be made out. A radiograph revealed a spontaneous fracture of the distal phalanx of the involved toe. This fragment was promptly removed, the wound being left partially open. Once again healing was delayed unduly. A repeat radiograph revealed another spontaneous fracture of the tip of the terminal phalanx remaining. This fragment was excised too, and now the toe began to heal well under the influence of tocopherol ointment applied locally and the same dose of alpha tocopherol orally.

By May 25, 1949, he was sleeping well. On July 27, his blood pressure was 146/85 mm. Hg. His dosage of alpha tocopherol was increased to 675 i.u. per day, and the toe began to heal more rapidly. He promptly reverted to tobacco and we as promptly forbade this. He still had some aching in the affected foot at night, but his hands seemed normal, his other foot was in good condition and his ankle œdema had disappeared.

He was last seen on February 7, 1950, and his dosage of alpha tocopherol was increased to 825 i.u. daily, as his œdema had recurred and there was some local discharge from the toe. It was nearly healed. His wife had had a coronary attack on June 19, 1949, since which time he had done the cooking and nursing for her and had been on his feet nearly constantly.

We last heard of him in February 1953, by which time his wife had died. He had been working in a beverage room, where his employer described him as being "as active as a cricket", and was on his feet 12 hours daily. He had had no vitamin E for 1½ years, despite an attack of phlebitis and a stiff warning from us by letter. He had decided Priscoline and cigarettes were preferable and was on a routine of six Priscoline tablets and four cigarettes daily.

CASE 5.—Mrs. G.R., aged 55 years. This woman had had an amputation of the left foot, then of the left leg below the knee, then of the left knee, for arteriosclerotic gangrene in the six months prior to seeing us first on July 19, 1952. Three weeks before this she had developed a gangrenous area on the right heel, and at her visit this area was 6 cm. in diameter. There was a great deal of typical arteriosclerotic pain in the extremity, and therefore she habitually hung the right leg over the edge of the bed. As a result the right calf was greatly atrophied. She had much difficulty in sleeping. There was a small blister near the knee from the recent application of heat. The distal half of the right foot was a dull, purplish colour. She had smoked heavily till six months before seeing us. Radiographs revealed the anticipated osteoporosis, as well as slight cystic decalcification of the os calcis and slight calcification of the dorsalis pedis artery. Her blood pressure was 155/125 mm. Hg, and her Wassermann reaction was negative. Her fasting blood sugar was 68 mg. %. She had albuminuria.

She was promptly ordered to have 450 i.u. of alpha tocopherol daily, but by some error the nurses administered this for one day only; proper tocopherol medication was not initiated until August 1. Thereafter she made steady progress. The discoloration left the foot, her pain at rest steadily decreased, and the gangrenous patch began to detach as a superficial slough. She got out of bed on August 17. By September 25, she had no pain and was sleeping well. A small bedsore developed on July 29, as she was very bony. This responded slowly to the tocopherols taken orally and the local use of tocopherol ointment, and was gone by November 10.

By October 17, the gangrenous patch had almost completely separated, leaving a clean base. A tiny abscess had tracked down the sole from the heel. This was drained and cleared up rapidly.

She left hospital on December 20, 1952. She reported thereafter by letter, mentioning on April 7, 1953, that her foot had finally become warm. There was complete healing on July 28. She began to use crutches on August 8. She was photographed again on December 3 (Fig. 4).

DISCUSSION

Many of these patients came to us with fully developed gangrene and a long history. They had previously been treated by all the classical measures. The number and seriousness of their complications are worthy of mention. In the thromboangiitis group the multiplicity of operations they had undergone and the advanced stage of their disease previous to tocopherol treatment are striking.

From our data it would appear that alpha tocopherol is valuable in the management of small areas of peripheral gangrene. It is not completely successful, particularly in arteriosclerotic gangrenes, but it saves many toes and feet that otherwise would be sacrificed. Of course, the results it can achieve are demonstrated better by individual cases than by the over-all statistics. For it should be remembered that this series excluded no case of gangrene below the ankle, however serious when first seen. It was not "selected". Many obviously hopeless cases were deliberately treated palliatively with alpha tocopherol until amputation was compelled as an emergency. A "selected" series would have provided more optimistic data, but we have been eager to test our treatment on the most unfavourable cases in order to discover its limitations. The result was often better than we could have anticipated.

Several other well-known vasodilators [Priscoline (tolazoline,) Ilidar (azapentine) and Roniacol] were used in several desperate cases where

it was obvious that alpha tocopherol was failing to salvage the extremity. In none were these adjuvants obviously helpful. This is an unfair test of these substances, of course, but indicates that where alpha tocopherol fails they are not apt to help.

Cases of diabetic gangrene were more often salvaged than the other types, interestingly enough. Moreover, in a large percentage (50%) of these diabetics insulin requirement subsequently decreased,[57] something noticed in other studies of the tocopherol treatment of diabetes.[58-60] This frequently occurred long before the gangrenous process had resolved—twice within three days of initiating tocopherol treatment! In fairness we should add that several papers[61, 62] have appeared, denying the effectiveness of alpha tocopherol in diabetic patients.

No case in which the gangrenous process on the dorsum of the toes advanced more than one inch proximal to the toe webs was salvaged. On the other hand, several with discrete gangrenous areas half way along the sole, or even with extensive involvement on the plantar aspect of the heel, were rescued.

Only one case of gangrene of the hand is reported here. It was healed with minimal loss of skin only, although it had originally involved about 75% of the dorsal area of four fingers.

Some of these arteriosclerotics and two diabetics came to amputation for intractable pain only, although the gangrenous process apparently had been arrested or even improved.

Patients having Buerger's disease especially must be warned that their pain may be increased by tocopherol therapy as the circulation returns to ischæmic areas.[63] It resembles the painful thawing of a gelid extremity. This restoration of tingling circulation may be nearly indistinguishable for a time from the formication of ischæmia, but rarely is "burning" complained of by recovering patients.

Relief of pain at rest may be the first sign of improvement in the affected extremity. On the other hand, continuation of pain at rest despite obvious resolution of the gangrene is definitely ominous. Pain alone can defeat the attendant physician, as has been mentioned above.

We were unable to develop criteria by which we could recognize what cases were most likely to respond to treatment. We have seen the smallest areas of arteriosclerotic gangrene continue to worsen until amputation was demanded, and on the other hand large areas of diabetic gangrene which healed rapidly. A therapeutic trial in all cases seems indicated. The outcome is not long in doubt.

It would seem that alpha tocopherol may revolutionize the surgical prognosis of small areas of peripheral gangrene. A trial of this substance on frostbite, trench foot, and immersion foot should be undertaken by those who have the facilities for such a study.

CONCLUSION

Alpha tocopherol in high dosage can salvage small areas of peripheral gangrene, being more effective in diabetics than in arteriosclerotics and patients with thromboangiitis obliterans.

The writers desire to thank Webber Pharmaceuticals Limited of Toronto, Canada, for liberal supplies of the alpha tocopherol donated to many of these patients.

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BEHAVIOUR PROBLEMS IN JUVENILE DIABETICS

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FOUR QUESTIONS are dealt with in this paper:

Why be concerned with behaviour problems or emotional disturbances in juvenile diabetics?

Why is there an unusual incidence of behaviour problems in juvenile diabetics?

Were there many behaviour problems in the staff juvenile diabetics seen at the Children's Hospital?

What can be done about behaviour problems in juvenile diabetics?

QUESTION 1: *Why be concerned with behaviour problems or emotional disturbances in juvenile diabetics?*

DISCUSSION: *The significance of emotional disturbances in a diabetic.*

The importance of life experiences in the onset and course of diabetes mellitus has been a constant topic of discussion since Thomas Willis, 300 years ago, remarked upon the sweet taste of the urine of a few of his patients, and said that the disease was caused by prolonged sorrow.[18]

Meninger in 1935 pointed out a striking temporal correlation between changes in the diabetes and changes in the mental states of a number of psychotic patients.[18]

Hilde Bruch at Columbia[9] in a series of 37 juvenile diabetics found, preceding the onset of the diabetes, incidents of severe psychological stress in 10, infections in 12, and nothing in 15.

Rosen and Lidz[15] at Johns Hopkins studied, among a group of 50 diabetics picked at random, the 12 diabetics who had been readmitted in acidosis two or more times after their initial regulation. The average number of admissions in acidosis was 5½, and two had had more than 15 admissions. They found that almost every bout of acidosis was due to the patient's knowingly and purposefully disrupting the regulation of his diabetes. Many had gone out of their way to acquire infections; many had stopped therapy for several days prior to an infection precipitating the coma. All were seeking to escape from difficulties either by flight into the hospital or by ending their lives (10 of the 12 had attempted suicide at least once). Rosen and Lidz said, "It would be difficult to find 12 patients who had been grouped together for any reason other than being psychotic, who were so unstable."

Lawrence E. Hinkle[8-10] of Cornell University joined the staff of the Diabetic Clinic of the New York Hospital, where he took patients assigned to him in rotation. Over a period of several years he studied a group of 50 diabetics thoroughly from the psychiatric as well as the medical viewpoint. He found that in nearly every case the onset of the symptoms occurred in a setting of significant life stress. Exacerbations of the diabetes, associated with ketosis and coma, very frequently occurred during stressful life situations. Remissions of the diabetes, associated with reduced insulin requirements and hypoglycæmic reactions, occurred during periods of relative security. The latter statement was illustrated by reference to one patient whose insulin requirement fell from 130 units to 40 units when he was removed from a stressful situation at home. This patient's insulin requirement gradually rose again to 130 units when he returned home. Hinkle found that labile diabetics often