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VITAMIN-E THERAPY IN NEUROMUSCULAR DISORDERS

A symposium on vitamin E which was published in 1939[1] was largely concerned with its endocrine and obstetric actions, though Vogt-Möller referred briefly to its employment in disease of the nervous and muscular systems. The value of vitamin E in the prevention of abortion—its original application in man—remains unproven, and during the last two or three years interest has been focused on its action in neuromuscular disease. The occurrence of nervous and muscular disorders in experimental vitamin-E deficiency has been known since 1928, when Evans and Burr[2] reported paralysis in the offspring of rats which had been kept on a diet lacking this vitamin. In these animals Lipshutz[3] demonstrated degeneration affecting chiefly the ascending and descending vestibular, tecto-spinal, rubro-spinal, and dorsal ascending tracts. Several workers subsequently observed a muscular dystrophy, without nervous changes, in young rabbits, guinea-pigs, and dogs reared on a diet deficient in vitamin E. These dystrophies could be prevented, and in the earliest stages cured, by adding the vitamin to the diet. Ringsted[4] in 1935 and Burr, Brown, and Moseley[5] in 1937 reported the appearance of paresis in adult rats deprived of vitamin E: a full clinical and pathological account of this disorder was given by Einarson and Ringsted[6] in 1938. They described pronounced flaccid paralysis and wasting of the hind limbs, with ataxia, some hypo-aesthesia, and loss of hair and trophic ulceration over the hind quarters. Administration of vitamin E could arrest the paralysis in its earliest stages only, without bringing about recovery; in the later stages it had no effect on the progress of the disease. Einarson and Ringsted compared the early changes to those arising in tabes dorsalis, and the later ones to those in amyotrophic lateral sclerosis and progressive muscular atrophy. The purely muscular dystrophy unaccompanied by nervous changes seen in young rabbits and guinea-pigs deprived of vitamin E may be compared to the juvenile muscular dystrophies of man. Antopol and Unna's[7] observation of foci of muscle atrophy in vitamin-B_6-deficient rats, and the production of tremors and convulsions from overdose of it, led to the suggestion that deficiency of this vitamin also might play a part in the pathogenesis of muscular dystrophies.

The resemblance of these experimental disorders to spontaneous nervous and muscular diseases in man was so striking that clinical trial of vitamin E was not only appropriate but imperative. It is true that in the experiments on animals treatment had been disappointing in so far as vitamin E had not cured the disorders once they were established. In adult rats and in puppies the dystrophies can be arrested only in the early stages, though in young rabbits and rats advanced cases of muscular dystrophy have responded to *a*-tocopherol, the active principle of vitamin E, and Morris[8] has reported the cure of muscular dystrophy in adult rabbits with the same substance. Moreover, in cases of muscular and nervous atrophy in man there are usually no signs of dietary deficiency, and Denker and Scheinman[9] could obtain no evidence of this in their cases of amyotrophic lateral sclerosis. Bicknell,[10] on the other hand, maintains that many people consume a diet deficient in foods which are rich in vitamin E. He gave half an ounce of fresh dried whole-wheat germ twice daily to eighteen patients with muscular dystrophy, four with amyotrophic lateral sclerosis, two with tabes, one with peroneal muscular atrophy, and one with amyotonia congenita. Nine of his cases of muscular dystrophy improved after treatment for two to eighteen months, one relapsing when the treatment was stopped. In the other nine there was little or no improvement after treatment for six to sixteen weeks. Only one of his cases of amyotrophic lateral sclerosis clearly showed improvement (after seven months' treatment); in one the improvement was doubtful; and two of the patients died. In the other diseases no effect was observed after eight weeks' treatment, though the patient with amyotonia congenita seemed rather stronger. Wechsler, after a preliminary report[11] on five cases of amyotrophic lateral sclerosis, in two of which improvement had followed treatment with *a*-tocopherol, reported[12] twenty more cases of this disease. He gave 50 to 100 mg. of *a*-tocopherol, partly by mouth and partly intramuscularly, and a diet rich in vitamin E; six cases were unaffected, three were arrested, and eleven were improved. In some cases the improvement was considerable, as in one practically bedridden woman aged 36, with a year's history of illness, who became able to walk and even do some housework after ten months' treatment. Stone[13] reported improvement in five patients with muscular dystrophy treated with 2 c.cm. wheat-germ oil daily: he also gave vitamin B_1 and thought that this helped. He stated that in one case of old anterior poliomyelitis there was lessening of muscular atrophy with the same treatment.

To many readers of these papers the results seemed too good to be true, and time has unfortunately confirmed their scepticism. Later reports have been so uniformly negative as to suggest that these earlier successes can be explained by the remittent nature of neuromuscular disorders and by the psychological stimulus of new therapy. Shelden, Butt, and Woltman[14] treated eight cases of muscular dystrophy, six of amyotrophic

[1] *Symposium on Vitamin E*, by the Society of Chemical Industry, London, 1939
[2] *J. biol. Chem.*, 1928, **76**, 273.
[3] *Rev. neurol.*, 1936, **65**, 221.
[4] *Biochem. J.*, 1935, **29**, 788.
[5] *Proc. Soc. exp. Biol.*, N.Y., 1937, **36**, 780.
[6] *Effect of Chronic Vitamin E Deficiency*. Oxford University Press, 1938.
[7] Unpublished work cited by Antopol, W., and Schotland, C. E., *J. Amer. med. Ass.*, 1940, **114**, 1058.
[8] *Science*, 1939, **90**, 424.
[9] *J. Amer. med. Ass.*, 1941, **116**, 1893.
[10] *Lancet*, 1940, **1**, 10.
[11] *J. Amer. med. Ass.*, 1940, **114**, 948.
[12] *Amer. J. med. Sci.*, 1940, **200**, 765.
[13] *J. Amer. med. Ass.*, 1940, **114**, 2187.
[14] *Proc. Mayo Clin.*, 1940, **15**, 577.

lateral sclerosis, and four of progressive muscular atrophy with 180 c.cm. wheat-germ oil by mouth daily, and with 100 mg. of *a*-tocopherol intramuscularly twice weekly, for periods of three to five months, but none of their cases showed any improvement. Denker and Scheinman[9] treated eleven cases of amyotrophic lateral sclerosis with 55 to 175 mg. *a*-tocopherol daily, partly orally and partly by intramuscular injection. In no case was any improvement noticed. One of their cases was very mild and of only six months' standing, but was not helped any more than the others. They add a note on four other more recent cases treated with 250 mg. *a*-tocopherol and 100 mg. vitamin B_6 daily, but the results were equally disappointing. Ferrebee, Klingman, and Frantz[15] treated thirteen patients with progressive muscular dystrophy, seven with progressive muscular atrophy, and six with amyotrophic lateral sclerosis: they gave two tablespoonfuls of wheat-germ cereal, 70 to 100 mg. *a*-tocopherol, and 10 to 30 mg. pyridoxine hydrochloride (vitamin B_6) daily by mouth, and 100 to 200 mg. *a*-tocopherol intramuscularly once or twice a week. The period of treatment extended over two to fifteen months. In none of these cases was there significant improvement; in ten of the cases of muscular dystrophy and six of progressive muscular atrophy there was no deterioration. Two important investigations in this country, both of which gave negative results, have been published this summer. Worster-Drought and Shafar[16] treated twenty-five cases of motor-neurone degeneration with vitamin E in the form of synthetic *a*-tocopheryl acetate or wheat-germ oil. The cases included bulbar paralysis, progressive muscular atrophy, and amyotrophic lateral sclerosis; only two showed definite improvement, and progressive deterioration occurred in all nine cases of bulbar paralysis. The authors point out that, though the prognosis of motor-neurone degeneration is always grave, the rate of progress varies, and periods during which no advance of the disease takes place are by no means uncommon in the absence of specific treatment. Fitzgerald and McArdle[17] treated ten cases of muscular dystrophy and ten of motor-neurone disease with either vitamin E or vitamin B_6, or with a combination of the two, without obvious improvement. Their results are of particular value because they were controlled by the estimation of the daily output of creatine and creatinine. In diseases of muscle creatine is found in excess in the urine, the amount depending on the bulk of improperly functioning muscle. Rabbits with nutritional muscular dystrophy excrete an abnormal quantity of creatine, which falls dramatically within a few days of the administration of *a*-tocopherol. No such improvement occurred in the human cases treated by Fitzgerald and McArdle.

When these and other figures in the literature are summed up the clinical statistics of vitamin-E therapy in neuromuscular disease are indeed disappointing and reveal no significant difference from the course of the untreated disease. No biochemical evidence has been produced of any action of vitamin E, natural or synthetic, on neuromuscular disease in man. It is probable that the place of vitamin E in the index of treatment will not finally be decided until simple means are available for analysing the amount of the vitamin in the body fluids and tissues. We do not doubt that vitamin E is an important food factor, but we find nothing yet to persuade us that any human disease, or any disturbance of childbearing or locomotion in man, is due to deficiency of vitamin E or is alleviated by treatment with it. Similar provisional judgment must be passed on vitamin B_6, now known as pyridoxine, which has been advised in Parkinson's syndrome and in a number of other neurological disturbances in addition to those already discussed; here, too, the early promise has not been confirmed.[18 19]

[15] *J. Amer. med. Ass.*, 1941, **116**, 1895.
[16] *Lancet*, 1941, **2**, 209.
[17] *Brain*, 1941, **64**, 19.

ECONOMY IN DRESSINGS

It is a pity that the Select Committee on National Expenditure cannot be persuaded to look into the use of surgical dressings in wartime. Its comments might be pungent and informative. The amounts of cotton and other imported materials used for surgical dressings must bulk as large as the imports of drugs, but so far they have not been subject to the same carefully planned economy. It is perhaps inevitable that the treatment of wounds should be on a cost plus percentage basis, but certainly more might be done to communicate to the surgeon a sense of the cost of dressings in money to the patient, hospital, or insurance fund, and in imports and irreplaceable stocks to the country. It is inexcusable that materials should still be wasted in techniques which are discredited or superseded. M.R.C. War Memorandum No. 3 says laconically that boric acid in boric lint is wasted. Nevertheless we have it on reliable authority that 44% of all prescriptions for lint are for boric lint and that prescriptions for boric lint constitute over 6.5% of all the prescriptions for dressings under the National Health Insurance Act. It is perhaps misleading to say that the boric acid is wasted, for when the doctor orders two ounces of boric lint the patient actually gets only just over an ounce of lint and the rest boric acid. But to weight lint with boric acid, which must be imported, seems both extravagant and foolish in wartime, for there can be few who now seriously believe in the antiseptic or healing virtues of boric acid. Nor has any pharmacologist the slightest doubt that the belladonna in belladonna plaster is wasted, and that the same green colour and psychological effect could be produced by an extract of lawn mowings, yet an important proportion of our supplies of this precious drug is still being diverted to this purpose. The surgeon is entitled to reply that no up-to-date casualty department ever uses boric lint or belladonna plaster, but his own foibles are equally susceptible to criticism. The hospital treatment of burns has been debated with almost religious fervour, but we have no figures for the relative cost in time, money, and materials of treating a burnt hand with plaster-of-Paris, Bunyan bag, sulphonamide and saline packs, or the antiseptic pellicles of which sulphadiazine in triethanolamine is the latest example. Few hospitals go to the trouble of sorting soiled dressings from dirty dressings so that the merely soiled may be used again.

[18] *J. Amer. med. Ass.*, 1941, **116**, 2148.
[19] *Proc. Soc. exp. Biol.*, N.Y., 1940, **43**, 97.