THE CONTROL OF MENOPAUSAL FLUSHES BY VITAMIN E

BY

A. M. HAIN, D.Sc., Ph.D.

Institute of Animal Genetics, University of Edinburgh

AND

J. C. B. SYM, M.D., D.P.H.

It is the practice to treat a woman with menopausal flushes with some form of oestrogen, and as stilboestrol is so potent a form even when administered orally, stilboestrol dipropionate is commonly prescribed. Oestrogen treatment has several disadvantages, however—notably (a) that four or five days after stopping the pills the patient has a return of menstrual discharge, usually accompanied by general malaise; (b) if an oestrogen is taken over a prolonged period it may have a toxic action, may worsen any heart irregularity present, and may encourage any dormant tendency to cancer that exists. Regarding the first of these tendencies, it was the experience of Zondek and Bromberg (1942) that non-pregnant women showed toxic symptoms with doses of oestrogen which in their pregnant state were tolerated with ease. Regarding the last two possibilities, since the climacteric often sees the first symptoms of cancer and sometimes gives rise to various cardiac upsets, the importance of avoiding anything that may help to bring about either of these conditions is obvious.

The reason that vitamin E was given a trial in this connexion was the passing statement of Shute (1939) that, among other beneficial uses, wheat-germ oil relieves menopausal flushes and headache; no data were given in support of his statement, which seemed worth investigating. It was intended to secure the co-operation of several patients, but, as circumstances prevented this from being carried out with the completeness desired, data will be given of only two patients fully, and in other cases such facts as are available.

It is hoped that doctors will try this mode of therapy in preference to the use of oestrogens, and report their results. It should not be necessary to remark that a distinction should be drawn between true menopausal flushes and those due to other contributory causes.

Case A

The patient had had a hysterectomy done at 45 years of age for metropathia haemorrhagica. Menopausal flushes started in the summer of 1942, when she was almost 47. In October of that year she was having 11 to 13 flushes daily—i.e., in the 12 hours from 9 a.m. to 9 p.m. A record was kept each day for a week prior to the taking of vitamin E. As it was considered advisable to use a form of vitamin E of known strength, viteolin (Glaxo Laboratories Ltd.) was prescribed; this is standardized at 6 mg. of tocopherol per capsule. The patient started with two capsules daily, and was told to reduce these to one a day if the flushes showed a marked improvement. If they ceased the capsules were to be continued at the rate of one a day until a fortnight had elapsed without a single flush. The record, which was kept very conscientiously, was as follows:

TABLE I.—Case A: Results with Vitamin E

No. of Capsules Daily	No. of Flushes Daily						
	Tues.	Wed.	Thurs.	Fri.	Sat.	Sun.	Mon.
2	10	9	3	1	3	3	4
2	5	11	3	3	5	2	6
1	1	4	2	6	3	1	2
1	1	1	0	1	3	2	1
1	1	1	1	3	3	1	2
2	5	2	0	1	0	1	0
1	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
1	2						

The patient observed that although at the end of the first week of taking the capsules the flushes were not so numerous, they were getting stronger, and for this reason she continued to take two capsules daily. By the end of the second week the reverse had happened, and, although more numerous, they were weaker, and the

capsules were reduced to one a day. The data pertain to October to December. On Dec. 29 she wrote: "The flushes vary from none at all to one or two a day, and I have stopped taking the capsules. Do you know," she adds, "I found it a sort of relief to have those two flushes after more than a fortnight without them. They seemed to clear the brain!" And on Jan. 20, 1943: "I now have a flush only now and then—say one in three days during the last two weeks," during which time no viteolin was taken.

In Case A some of the general symptoms that accompany the climacteric were present, notably rheumatism (which was more severe than it had been at any time since she had rheumatic fever in childhood) and rapidly failing vision. Donald (1938) reported that a course of combined oral and injected oestrogens afforded the patient considerable relief of these symptoms. It is not clear what effect, if any, resulted from the use of vitamin E in our case, as remedial exercises were taken for the rheumatism and the carrying of heavy parcels was avoided.

Case B

This patient had a natural menopause at 50 years of age. Menopausal flushes had been experienced for a considerable time before treatment was begun in Oct., 1942, when she was 55. At this time the flushes, which were severe, numbered 7 to 9 a day, and she was put on stilboestrol dipropionate, 2 mg. daily. From the fifth day onwards her record was as follows:

TABLE II.—Case B: Results with Stilboestrol Dipropionate

No. of mg. Daily	No. of Flushes Daily						
	Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.
2	5	6	3	1	1	0	0
0	2	1	0	*	*	*	*
0	—	—	—	6	2	4	2

On the days marked with an asterisk a few drops of blood were passed and the discharge was accompanied by abdominal discomfort and headache, symptoms which would, of course, have been deferred had the stilboestrol been continued. The cessation of hormone therapy was followed by a return of the flushes, which in January of this year were as numerous and as severe as before hormone therapy was started. The patient was then treated with vitamin E, and took two capsules of viteolin daily for 18 days. There was no reduction in the number of flushes until the 16th day, when they fell to three and remained between two and four daily for seven days, for the last five of which she took only one capsule daily. During the whole of this period, and subsequently, the patient noticed that on the days when she did upholstery, which was strenuous work and necessitated stooping, the flushes were almost doubled—11 to 13 instead of 6 to 9 daily, as can be seen in Table III.

TABLE III.—Case B: Results with Vitamin E

No. of Capsules Daily	No. of Flushes Daily						
	Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.
2	—	—	—	—	—	5	3
2	6	12*	13	11	9	8	9
2	7	7	9	4	7	6	3
1	2	2	3	4	3	4	4
0	3	7*	10	9	9	11	8

* Upholstery was done on this and the four succeeding days.

In this case it is doubtful if the patient derived any benefit from vitamin E, as, unfortunately, therapy ceased just as a possible effect was manifesting itself. She certainly seems to have done better on oestrogen therapy.

Cases C and D

Case C had pruritus vulvae in addition to menopausal flushes, and this was now cured by viteolin after oestrogen therapy had been tried and had failed. As the flushes also ceased under this treatment the viteolin was stopped. Later on, the pruritus returned (but not the flushes), and viteolin had to be resumed. It appears to be advisable to continue small doses of vitamin E for some time after symptoms have ceased.

Case D had considerable relief, as flushes were reduced from 15 to 15 to 3 or 4 daily.

It would seem from the few cases examined that, before vitamin E can be said to have been given a fair trial, the patient should take two capsules daily for three weeks and one daily for the succeeding two months. As it is probable that long-standing cases respond less readily than others, the higher

dosage should preferably be continued by patients in this category until only one or two flushes are experienced daily.

Discussion

The facts given suggest that in vitamin E therapy we possibly have an alternative method to oestrogen therapy for combating menopausal flushes. If this be so—and the data are so few as to be merely suggestive—its mode of action is not clear. The changes which take place at the menopause lack uniformity and vary greatly in severity. It is unlikely, therefore, that an equal response will be obtained in all cases, and possibly one treatment will succeed where another has failed. As has been said, oestrogen is generally prescribed for menopausal flushes, the rationale being that, given in large doses, it depresses pituitary function at a time when considerable amounts of gonadotrophin are being excreted in the urine (Frank and Salmon, 1935; Jones *et al.*, 1937). The flushes are held to be an indication of oestrogen insufficiency, yet it has been demonstrated by Robson *et al.* (1934), Frank (1934), and others that in some cases oestrogens are recoverable from the blood and urine in considerable quantity for as long as 20 years after the menopause, although in other women there may be none at the end of three years.

The rationale for the employment of vitamin E in the control of menopausal flushes is all the more obscure as Shute (1939), its advocate, considers vitamin E to be anti-oestrogenic—a thesis which others, however, have failed to confirm (Drummond *et al.*, 1939).

It is always dangerous to cite effects on animals in an article dealing with the human subject, because of the similarity that such a reference tends to imply. Subject to this caution, and bearing in mind that the experimental results that have been obtained on animals do not indicate that the endocrine system is primarily responsible for the changes observed after feeding on an E-deficient diet (Mason, 1929; Drummond *et al.*, 1939), certain tangible results of E-deficiency stand out in a sphere in which many claims have too readily been made. Thus there is evidence of a reduction in the pituitary principle responsible for causing ovulation in vitamin-E-deficient rabbits (Rowland and Singer, 1936; Drummond *et al.*, 1939) and of thyroid deficiency in rats deprived of the vitamin (Singer, 1936; Barrie, 1937).

This latter finding may have some bearing on our problem, as a mild degree of myxoedema is commoner in menopausal women than states of true hyperthyroidism (Donald, 1938), and it is possible that one of the ways in which vitamin E acts is by relieving this condition, at the same time causing an improvement in the emotional and physical state. If this be so, such women are more likely to benefit by vitamin E therapy than those in whom menopausal flushes are combined with hyperthyroidism, who would benefit from oestrogen therapy rather than from vitamin E. The preferential response to stilboestrol in Case B may perhaps be explained on these lines, as she had manifest symptoms of hyperthyroidism, which were wanting in Case A, which responded well to viteolin. Relevant to this aspect is the fact that in the treatment of involutional melancholia in menopausal women Hemphill and Reiss (1940) noted that the patients who derived greatest benefit from oestrogen treatment were those in whom a lack of ovarian function was combined with a considerable degree of hyperthyroidism, whereas the symptoms seemed, if anything, to be aggravated in those with hypothyroidism. Since oestrogens inhibit the thyrotrophic action of the pituitary, their indiscriminate use may be harmful if thyroid insufficiency is present.

Arising out of this study, Reiss and Golla (1940) considered the possibility that the endocrines might have an influence on cerebral circulation, and their investigations suggest that in

trated animals the blood content in the brain is considerably lowered and can be increased by treatment with sex hormones. In our effort to ascertain if any similar action has been claimed for vitamin E we have encountered the statement by Wortis and Jolliffe (1941) that the vitamin "has a vasodilator action." If this can be substantiated we would have one property common to both substances—viz., a levelling-up of cerebral blood flow which would counteract sudden cerebral congestion.

(Side actions would be provided in a stimulus to muscular metabolism as well as a probable psychological effect.)

Reynolds (1939), on this aspect, states that the effect of oestrogens upon the venous pressure in ovariectomized women is to lower this appreciably within the short space of 6 to 8 minutes—a diminution which may be the result of a general increase in the size of the subcutaneous capillary bed, since capillary pressure diminishes coincident with the change in venous pressure. He considers it probable that the basis of the adjustment is a shift of part of the blood volume from the visceral regions to the somatic capillary bed as a moderate but extensive capillary vasodilatation takes place. Inevitably associated with this would be an alteration in the heat-regulating capacity of the individual, increasing the heat loss by radiation and conduction, and so minimizing the need for loss by evaporation. This, he avers, should minimize the amount of nervous activity of the sympathetic system which heat regulation by sweating entails. Such a peripheral vascular action of oestrogens would account for their relief of the acute menopausal disturbances on the basis of well-established physiological grounds through readjustment of normal heat-regulating mechanisms.

Conclusion

Although a case has not been made out for the alleviation of menopausal flushes with vitamin E, as claimed by Shute, the few cases described suggest lines along which patients might be selected for this mode of therapy, and it is hoped that it may be given a trial, especially where an idiosyncrasy for oestrogens exists.

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REFERENCES

- Barrie, M. M. O. (1937). *Nature*, **139**, 286.
 Donald, H. R. (1938). *British Medical Journal*, **1**, 727.
 Drummond, J. C., Noble, R. L., and Wright, M. D. (1939). *J. Endocr.*, **1**, 275.
 Frank, R. T. (1934). *N.Y. St. J. Med.*, **34**, 1009.
 — and Salmon, U. J. (1935). *Proc. Soc. exp. Biol.*, N.Y., **33**, 311.
 Hemphill, R. E., and Reiss, M. (1940). *J. ment. Sci.*, **86**, 1065.
 Jones, M. S., MacGregor, T. N., and Tod, H. (1937). *Lancet*, **1**, 320.
 Mason, K. E. (1939). *Vitamin E*, pp. 31 and 52, Society of Chemical Industry, London.
 Reiss, M., and Golla, Y. M. L. (1940). *J. ment. Sci.*, **86**, 281.
 Reynolds, S. R. M. (1939). *Physiology of the Uterus*, Hoeber, New York.
 Robson, J. M., MacGregor, T. N., Illingworth, R. E., and Steere, N. (1934). *British Medical Journal*, **1**, 888.
 Rowland, I. W., and Singer, E. (1936). *J. Physiol.*, **86**, 323.
 Shute, E. V. (1939). *Vitamin E*, p. 67, Society of Chemical Industry, London.
 Singer, E. (1936). *J. Physiol.*, **87**, 287.
 Wortis, H., and Jolliffe, N. (1941). *N.Y. St. J. Med.*, **41**, 1461.
 Zondek, B., and Bromberg, Y. M. (1942). *Lancet*, **1**, 381.

HEMIPLEGIA COMPLICATING WHOOPING-COUGH

BY

L. J. GRANT, M.B.

Flying Officer, R.A.F.V.R.; late Medical Officer, E.M.S.

AND

C. E. WILLIAMS, M.B.

Acting Senior Assistant Medical Officer, Eastern Hospital, L.C.C.

The occurrence of a complete and permanent hemiplegia during whooping-cough is a very unusual type of neurological complication: there is, in fact, no record of such a case at this hospital in 20 years. We feel, therefore, that the following case should be recorded, especially in view of the opinion of some authorities—e.g., Nelson (1939)—that it is desirable to report all cases of whooping-cough showing permanent neurological sequelae. The present case was further complicated by subcutaneous emphysema.

Case Report

A boy aged 5 was admitted on Sept. 25, 1941, with a history of cough for a month and occasional vomiting. He had first been heard to whoop three weeks before admission. On examination the child was found to be very ill; temperature was 102.8° F., pulse 130, respirations 60. He was cyanosed, the alae nasi were working, and there were recession and signs of a patchy pneumonia at both bases. Although next day the temperature had subsided to 100°, the pulse was still rapid and signs of bronchopneumonia became more extensive, involving the whole of the right lung and the major portion of