VITAMIN E IN THE MENOPAUSE*

BY

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Menopausal flushing and sweating can usually be controlled by oestrogens, but the stimulating effect of these hormones on the genital tract and breasts sometimes contraindicates their use—for instance, after radium treatment of cancer or before cessation of menstruation. Although oestrogens promote cancer development in animals there is so far no proof that they do so in man (Gemmell and Jeffcoate, 1939; Gardner, 1947). Nevertheless, "cancer-like" areas are quite often a troublesome finding in curettings from patients whose oestrogen-withdrawal bleeding has necessitated curettage (Gusberg, 1947).

Vitamin E was first used by Evan Shute (1937) to control flushings, and several confirmatory reports have followed

The Investigation

Clinical Material.—In view of the cost (£7 per case), treatment was given only to patients seriously disabled by drenching sweats, flushings, loss of sleep, and so on. The incidence of severe flushing after cessation of menstruation is about 17%, while after radium or surgical castration the figure is 50% (McLaren, 1941). Vitamin E in the form of alpha-tocopherol ("ephynal") was given to 47 patients with severe flushings; these included four regarded as new cases, although in fact they had relapsed after successful treatment with vitamin E. Forty cases had not been previously treated, while three had resisted stilboestrol. The 47 cases fall into the following categories:

	Cases
Radium menopause (two years approximately)	25
Deep x-ray (one year approximately)	9
Hysterectomy and double oophorectomy	10
Hysterectomy and one ovary	2
Spontaneous menopause	1

As a control before vitamin E, 18 cases were treated as follows. After completion of her case history and pelvic examination the patient was given blank tablets and a card to record the number of flushes at each period of the day.

TABLE I.—Effect of Vitamin E on Flushing

No. and Class	Vitamin E (mg.)	Days	Result	Blanks before Treatment		Blanks after Treatment		Spontaneous Relapse
				Days	Result	Days	Result	
778 Spont. M.	14,000	35	Fail					
732 X-ray	35,000	35	Part cure	12	Fail	28	Cure	Unknown
720 "	35,000	35	Fail	14	"			
701 "	35,000	35	"	14	"			
722 X-ray	28,000	28	"	10	"			
725 "	54,600	21	Cure	10	"			Unknown (Case 3)
736 "	14,000	14	"	14	"			Cure (Case 4)
743 "	25,200	35	Fail	12	"			
730 "	35,000	35	Cure	14	"	49	Relapse	
745 "	21,000	21	"	19	"	28	Cure	Relapse 4/52
734 Castrate	35,000	35	"	14	"	35	Relapse	
739 X-ray	28,000	28	Part cure	24	"	35	Cure	Relapse 3/52
754 Castrate	28,000	21	"	19	"	21	Relapse	
578 "	14,000	14	Cure	21	"	28	Cure	Relapse 4/52
466 Rad. M.	17,500	49	"					After oophorectomy relapse
573 " ovary	30,700	65	"			14	"	Relapse 3/52
562 Rad. M.	12,600	26	Fail					
464 "	8,300	35	Cure			106	"	Unknown
450 "	13,500	56	"			28	Relapse	
585 "	4,200	14	Fail					
452 "	32,200	43	"					
615 Castrate	42,000	42	"					
668 Rad. M.	4,200	14	Cure	14	"	28	Cure	Cure 14/52
561 "	15,400	42	Part cure					Relapse 4/52
561B "	14,000	14	Fail					
293 Castrate	28,750	98	Cure			21	Relapse	
46 Rad. M.	5,110	42	"			63	Cure	Cure 10/12
112 "	3,360	28	"					Unknown
355 Castrate	5,600	14	"			21	"	Relapse 3/52
355B "	10,000	21	"	42	"			Part relapse 4/52
263 Rad. M.	3,360	14	"			14	"	Relapse 74/52
307 Castrate	18,060	56	Fail					
269 " ovary	6,860	49	Part cure			21	Relapse	
106 Rad. M.	4,200	28	Fail					
108 "	60,600	83	Cure	40	"	21	Cure	Relapse at once
176 "	1,400	14	"					Unknown
324 "	17,300	42	Fail					
451 "	9,450	56	Part cure			14	"	Unknown
45 "	8,400	63	Fail					
583 "	12,600	21	Cure	21	Cure (40%)	28	Relapse	
172 "	5,880	63	"			21	Cure	Cure 12/12
227 "	1,680	14	Part cure					Relapse at once
514 "	21,000	41	Fail					
47 "	4,116	38	"					
149 "	5,600	56	"					
225 "	10,640	47	Cure					
157A Castrate	15,750	80	"			84	"	Relapse at once
647 "	—	—	—	32	Cure	—	—	Cure 5/12

Spont. M. = Spontaneous menopause. X-ray = X-ray menopause. Castrate = Hysterectomy and bilateral salpingo-oophorectomy. 1 ovary = Hysterectomy and unilateral salpingo-oophorectomy. Rad. M. = Radium menopause. Part cure = Patient not completely relieved. Bracketed cases = Relapsed and retreated cases.

(Shute *et al.*, 1938; Hain and Sym, 1943; Christy, 1945; Ferguson, 1948; Finkler, 1949). In this study special attention has been paid to the genital tract to ascertain if vitamin E is inert and therefore a substitute for oestrogens or stilboestrol in cases in which stimulation of the genital tract is undesirable.

After intervals up to 42 days (average 19 days) only one case was cured (No. 647), while another was somewhat improved but was still in need of treatment.

The results of treatment of flushing by vitamin E are shown in Table I: 23 were completely cured, 7 were markedly improved, and 17 were failures. The dosage given was as follows: lowest, 1,400 mg.; highest, 60,000 mg.; average 18,500 mg.

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Effect of Placebos.—Of 23 cured or improved cases, 22 were given placebos for periods varying from 14 to 106 days (average 35 days). Fifteen cases (68%) maintained their improvement, while seven relapsed. Flushing reappeared in four and partially reappeared in two cases, while 16 (73%) maintained the cure. Of 17 cases questioned up to a year after completion of treatment 12 had relapsed partially or completely, but five were completely free from symptoms. No information was available from the remaining six cases.

Analysis of Failures.—There was apparently no special "type" of menopause resistant to treatment—viz., radium menopause, 10 cases; hysterectomy and double oophorectomy, three cases; deep x-ray, three cases; spontaneous menopause, 1 case. In an attempt to overcome the resistance to treatment doses up to 60 g. (average 20.745 g.) were given over an average period of 36 days, but without success. The 17 "failures," however, were quickly cured of their flushings by small doses of stilboestrol.

Vitamin E and Sex Function

A recent survey of the effect of the radium menopause on sex function led to the belief that it speedily causes many patients to lose their normal libido and the ability to achieve the orgasm. Ten out of 100 cases, moreover, suffered from dyspareunia after radium (McLaren, 1949).

It was impossible to interview every patient, and often the information was quite obviously inaccurate—e.g., when the patient alleged satisfactory coitus yet on examination proved to have a painful lesion of the vulva or vagina. Accordingly only 22 out of 43 patients were considered to be giving reliable evidence, but from this number we concluded that vitamin E had little effect in restoring libido or on the achievement of orgasm. As will be described later, vitamin E has a slow effect in curing painful senile lesions in the genital tract, and to this extent it must contribute to improved sexual relations, although in this it does not compare with stilboestrol.

Effect of Vitamin E on the Genital Tract

The clinical material was drawn from patients who some two years previously had had the menopause induced by radium. Senile lesions in the genital tract are then quite common—e.g., bleeding spots were observed in the vagina on speculum examination in 11 out of 68 patients whose ages averaged 45, an incidence which would not be unusual in normal women 15 or 20 years later (McLaren, 1941, 1949). We therefore had the opportunity of testing the curative effect of massive doses of alpha-tocopherol on these and other senile genital lesions. Cell-smears were also studied to ascertain if the drug was in fact inert or caused any cell division or differentiation.

Shute *et al.* (1938) and Shute (1942) have reported healing in a proportion of cases of senile vulvo-vaginitis after vitamin E, while Rubenstein (1948) and Finkler (1949) both comment on the inert or poorly developed type of vaginal smear which follows vitamin E as compared with the high degree of maturation of cells which follows stilboestrol.

In 28 to 112 days slow but definite healing was observed in four senile vulvar lesions, while two cases were unchanged (Table II). Case 134 will be reported under "toxic reactions," for dermatitis compelled us to stop treatment. In this case we first noted a remarkable softening of the indurated vulva, then a diminution in pruritus, and, finally, almost complete healing, which was still maintained a year later.

TABLE II.—*Effect of Vitamin E on the Vulva and Introitus*

No. and Class	Disease	Dose (mg.)	Days	Result
45 Radium menopause	Red introitus bled easily	8,400	82	Very much improved
134 Carcinoma of body	Vulvitis, pruritus, excoriation	38,680	112	Almost cured, but skin reaction. (See below)
269 Hysterectomy and 1 ovary removed	Red tender introitus	6,860	28	No improvement
293 Hysterectomy and bilateral salpingo-oophorectomy	Patches of red (raw) areas at vulvo-vaginal junction	28,750	110	Cured
355 Radium menopause	Red introitus, tender caruncle	5,600	35	No improvement
263 " "	Introitus red, tender periurethral oedema	3,360	35	Healed

Effect of Vitamin E on the Vagina

In all, 30 cases were examined by a Cusco speculum before and after treatment. Twenty-two normal cases were unchanged, showing no undue vascularity or "blueing" such as one normally sees after stilboestrol. The remaining eight cases (Table III) had senile vaginitis; of these,

TABLE III.—*Effect of Vitamin E on Senile Vaginitis*

No. and Class	Disease	Dose (mg.)	Days	Result
269 Hysterectomy and 1 ovary removed	Senile vaginitis	6,861	49	No effect; bleeding spots persisted
*45 Radium menopause	Senile vaginitis (acutely) inflamed	8,400	82	Healed; no red or bleeding spots
615 Subtotal hysterectomy and two ovaries removed	Senile vaginitis	42,000	42	Cervix healed; little effect in vagina
*46 Radium menopause	Mild vaginitis	5,110	102	Improved, but still several bleeding spots
*106 " "	" "	4,200	56	No effect
*112 " "	" "	3,360	28	Healed
263 " "	" "	3,360	35	"
293 Hysterectomy and two ovaries removed	Red vagina (split and bled with small speculum)	28,750	112	"

* "Spots" also present on the portio cervicis.

two were apparently the result of a simple speculum examination using 30% "dettol" cream. After prolonged treatment with alpha-tocopherol four were cured and four were only slightly affected. It is possible, however, that simple hygienic measures with sexual abstinence would also have affected a cure.

As in the case of the vulva, therefore, vitamin E has a slow healing effect, but in no way compares with stilboestrol as a healing agent in senile vaginitis.

Effect of Vitamin E on Vaginal Smears

Certain types of vaginal smears are capable of giving a fairly accurate forecast of the state of development of the underlying mucosa—for instance, after stilboestrol therapy in a 70-year-old woman adult flat squamæ replace small immature cells and leucocytes. It is necessary, however, to set a limit on what can be "read" from vaginal smears. For instance, in a previous report 138 biopsies and smears were correlated, but only adult smears and senile (small-cell) smears gave an accurate forecast of the epithelial maturity or senility. The remaining and most numerous smears with large squamæ, spinosum cells, and small (immature) cells could not be "read" with accuracy (McLaren, 1941). With these limitations in mind, and aware that only gross changes such as "stilboestrol effects" (or perhaps ovulation) (Papanicolaou and Traut, 1943) could be "read," 36 smears were taken. The classification III down to I represents grades of increasing senility.

Total number of vaginal smears	36
Grade III, mainly squamæ	1 } Adult
Grade IIIM, menopausal clumping	12 }
" mixed, spinosum, squamæ, and deep cells	7 } Increasing
" II (spinosum cells) (40 μ diam.)	9 } senility
" I (small basal cells)	7 }

TABLE IV.—Changes in Vaginal Smears after Vitamin E

No. and Class	Grade	Dose (mg.)	Effect
47 Radium menopause	IIIM (adult)	4,116	I—i.e., depressed
176 " "	III (full adult)	1,400	II?I—i.e., depressed
466 " " (Figs. 1, 2, 3)	Mixed	17,500	IIIM, "luteal clumps"—i.e., higher differentiation
736 X-ray menopause	II	14,000	IIIM—i.e., a higher differentiation
743 " "	Mixed	25,200	IIIM—i.e. (very full); almost stilboestrol effect; differentiated
615 Hysterectomy and both ovaries removed	II (vaginitis)	42,000	IIIM—i.e., a higher differentiation

Only six out of 36 smears therefore showed definite alteration in maturity, and this parallels the lack of clinical change after alpha-tocopherol. Case 47 (Table IV) had had dienoestrol up to the beginning of treatment with alpha-tocopherol, and the smears simply depict a sudden loss of ovarian hormone or its equivalent, dienoestrol. Case 466 is mentioned later, since here the development of an intensely clumped smear not only resembled a pregnancy smear but on laparotomy a luteal cyst was discovered (Fig. 4). The changes in Case 736 were quite sharp, so that a guess was hazarded that this patient might menstruate, and, as described below, this actually happened.

Effect of Vitamin E on the Cervix

Thirty-four speculum (Cusco) examinations following doses up to 60 g. of alpha-tocopherol failed to show any increase in bulk, softening of the portio, or increased mucus secretion. Four out of five cases with bleeding punctate spots on the portio, however, were cured by vitamin E; in three this was part of the general healing of the vaginal mucosa.

Twenty-six cell-smears were taken before and after treatment, but there was no sharp alteration with use of vitamin E. The motley collection of cells typical of a menopausal cervix persisted—namely, leucocytes, endocervical cells, long (120 μ) fibre cells, and so on. There was no sudden diminution in the number of cells and their replacement by clear mucus such as follows stilboestrol therapy.

FIG. 3.—Case 466. After 17.5 g. vitamin E. Haemorrhagic luteal cyst coexisted. Intermediate cells apparently being desquamated in sheets.

FIG. 4.—Case 466. After 17.5 g. vitamin E. Corpus luteum distended with blood.

It is clear, therefore, that neither the cervix nor its secretion or cytology is altered by massive doses of vitamin E. It may be, however, that just because it does not stimulate cell division and mucus secretion vitamin E may prove to be safer than stilboestrol in the control of flushings which follow irradiation of the pelvis.

Urethral Smears after Vitamin E

Although no patient had urinary symptoms, Hanley's (1944-5) work in menopausal urethritis and trigonitis, and Zuckerman's (1940) observations on the male macaque urethra, suggested that it might be worth while to observe the cytological changes in the urethra.

A dry swab often fails to pick up urethral cells, and only 21 specimens were obtained. A typical well-differentiated smear contains ovoid epithelial cells about 40 μ in diameter; free nuclei, leucocytes, and small clumps of flattened squamæ complete the picture. Fourteen typical (differentiated) smears were not altered by vitamin E—i.e., there was no further building up or desquamation of the epithelium. The changes observed in seven smears are shown in Table V.

As in the vagina, therefore, there is no sharp reaction in all urethral smears, and it is possible that the changes observed were the result of faulty technique—e.g., in failing to pick up cells. Only in Cases 736 and 47 was a corresponding change observed in the vagina—namely,

FIG. 1.—Case 466. Radium menopause one year. Small "castration" cells mixed with more mature squamæ. Stain: Papanicolaou and Traut.

FIG. 2.—Case 466. After 4.5 g. vitamin E. Heaped up smaller cells with larger squamæ emerging from deeper layers. This smear resembles mid-pregnancy or the "luteal" phase.

TABLE V.—Changes in Urethral Smears

No. and Class	Dose E. (mg.)	Urethral Smear	
		Before	After
263 Radium menopause	3,360	Small undifferentiated cells	Larger, differentiated
45 " "	3,400	Degenerate epithelial cells (? poor fixation)	Loss of leucocytes (inflamed introitus also healed at this time)
47 " "	4,116	Normal smear	Degenerate epithelial cells. (Effect of loss of dienoestrol?)
736 X-ray menopause	14,000	Scanty cells	Abundant large differentiated cells
743 " "	25,200	Granular debris	Many adult transitional cells
754 " "	28,000	Scanty debris	Well-differentiated cells; free nuclei
466(b) Radium menopause	42,000	Debris	Adult cell smear

maturation, Case 736; senility, Case 47. From this small number of specimens, therefore, it seems possible that vitamin E may cause development and desquamation of the urethral epithelium, although in most cases no cellular alteration is detectable.

Case Reports

Dermatitis and Uterine Bleeding After Vitamin E

Case 1.—Mrs. A, aged 66, developed a generalized itching dermatitis which spared only her face. In the neck the skin became raised in silvery folds, but in the abdomen the rash was rather blotchy and red. Twelve years previously the patient had panhysterectomy with supporting vaginal radium for carcinoma of the corpus, and for a year previously she had suffered from intense pruritus. The vulva was excoriated and had many small areas of lichen simplex. Under vitamin E the vulvar condition almost completely healed. The labia majora and introitus became soft and elastic, but after 16 weeks (36,640 mg. alpha-tocopherol) the rash stopped treatment. The generalized skin condition took eight weeks to settle, but the vulvar pruritus and vulvitis did not relapse, and a year later the patient was practically symptom-free although on examination four very small areas of vulvar excoriation were present.

Post-menopausal Luteal Cyst

Case 2.—A widow aged 42 (No. 466) had radium menopause 10 months ago. Three months ago a 10-weeks course of stilboestrol (1 mg. b.d.) was completed with temporary control of flushing and no withdrawal bleeding. After 5.4 g. of alpha-tocopherol she had 12 days' uterine bleeding preceded by breast-tingling and dysmenorrhoea. Flushings, however, persisted almost unabated, and treatment was continued for 43 days, with control of her flushings. After 17 g. of vitamin E (49th day) she developed sudden right iliac pain with nausea and vomiting. Laparotomy revealed a normal appendix but a left luteal cyst distended with blood. The uterus on its peritoneal aspect resembled a coarse type of liver cirrhosis, being irregular and nobbly to the touch.

Histologically, the luteal cyst from the left ovary was of simple haemorrhagic type, measuring 2 in. by $\frac{1}{4}$ in. (5×1.8 cm.) (Fig. 4). The right ovary (10 months after radium) contained no recent follicles or corpora lutea but numerous corpora albicans. Vaginal smears: Figs. 1 to 3 show the movement in the cell pictures under vitamin E. No further uterine bleeding followed removal of the right and most of the left ovary, although flushings recurred and were once again controlled by vitamin E (31 g. in 35 days).

"Collapse" of the Breasts

Case 3.—(No. 725.) Aged 46. After 54 g. of alpha-tocopherol the patient complained that her breasts felt slack. Unfortunately we were unable to compare the size of the breasts before and after treatment, but it seems likely that little change in size had occurred. (They were small and pendulous.) No corresponding alteration in cell smear was observed.

Resumption of Menstruation

Case 4.—(No. 736.) Aged 44. X-ray castration one year ago. This patient began to menstruate five weeks after 14 g. of vitamin E. Unfortunately she also had completed a course of 20 mg. of amphetamine sulphate, so that it is doubtful which drug (if any) caused resumption of bleeding. Premenstrual curettings showed intense stromal vascularity and simple gland formation.

Comment

Vitamin E can apparently control severe menopausal flushing in more than 50% of cases, and, although not quite inert, its activity on the genital tract in no way compares with that of stilboestrol.

How vitamin E brings about its therapeutic effect on menopausal flushings is quite obscure, and will probably remain so until the mechanism which causes flushing is understood. This lack of knowledge of the therapeutic action of vitamin E applies to other fields of medicine (*Symposium on Vitamin E*, 1939; *Lancet*, 1949) where alpha-tocopherol has been on trial—e.g., in the treatment of primary amenorrhoea (Massenbach and Heinsen, 1948, 1949; Massenbach, 1949), cardiovascular disease (Shute *et al.*, 1948a, 1948b), abortion (Vogt-Moller, 1933), and so on.

When it is available in a cheaper form alpha-tocopherol may replace natural oestrogens and stilboestrol in the control of menopausal symptoms, for, even if only 60% of cases respond, the worry of oestrogen-withdrawal bleeding and the (theoretical) risks of genital cell-stimulation are avoided.

Summary

Vitamin E in the form of alpha-tocopherol temporarily relieved severe menopausal flushing in 30 patients (64%) and failed in 17. The dose required is variable, but averaged 18.5 g. over 37 days (£7 per cure).

Failures did not respond to prolonged and heavy doses, but were quickly relieved by stilboestrol.

Of 17 cases followed up after successful treatment 5 remained cured, 12 had further flushings.

Vitamin E is not an aphrodisiac, but dyspareunia may be relieved in time by the healing of senile lesions in the lower genital tract.

Vitamin E produces no sudden change in the clinical appearance of the lower genital tract, although prolonged and heavy dosage seemed to cause healing in 50% of senile vulvar and vaginal lesions.

Vaginal smears seldom alter, and no parallel exists between cell maturation and the cure of symptoms.

The cervix is not stimulated to mucus secretion.

Cell changes were observed in 7 out of 21 urethral smears.

Side-effects were few: one case developed dermatitis; two cases menstruated, one developing a haemorrhagic luteal cyst.

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TREATMENT OF DUPUYTREN'S CONTRACTURE WITH VITAMIN E

BY

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Since the preliminary report (Thomson, 1949) on the effect of vitamin E in a case of Dupuytren's contracture further cases have come under review and have yielded promising results. In fact, the general response has been so good that to assert that vitamin E has a specific effect on Dupuytren's contracture does not appear to be unduly reckless. The mode of action is unknown, but the work of Steinberg (1946) on the action of the tocopherols on fibrous tissue renders a relationship a little less mystical.

Reports on the success of this treatment have not been unanimous but are inclined to be in its favour. Steinberg (1946) produced the first paper on this subject and described the effects of massive doses of vitamin E on seven cases of Dupuytren's contracture. In six of these cases the contracture disappeared and the sclerodermatous condition of the skin changed to a normal state. One case failed to respond, and this was attributed to the fact that the patient suffered from early portal cirrhosis. In such cases the blood vitamin E level has been shown to be low and large doses of vitamin E are not absorbed. All these cases were treated with a daily dose of 300 mg. of vitamin E orally over a period of 7 to 53 days. Scott and Scardino (1948) discussed six cases treated with 300 mg. of mixed tocopherols or 200 mg. of "ephynal" daily. One case showed marked improvement, three moderate improvement, and two no change. Wrigley (personal communication, 1949) treated three cases with 400 mg. of "ephynal" a day; there was a definite response in two cases and none in the third.

On the other hand, Langston and Badre (1948) treated five cases with the large doses of vitamin E recommended by Steinberg without any demonstrable result. Parsons (1948) treated one case with 300 mg. a day for over 100 days and reported no objective change, although the patient thought he could open one of his fingers a little more freely. Recently, King (1949) described 13 cases treated with 300 mg. of ephynal a day without result. Four of the cases developed hitherto unreported toxic

manifestations, which made further treatment impossible. Four other patients were sure they had gained improvement, but none was seen. The longest period of treatment lasted eight weeks.

Present Series

In this series of 13 cases of Dupuytren's contracture involving 22 hands all cases except one were treated with ephynal, four 50-mg. tablets being the daily dose. The minimum length of time that any case has been under treatment is 12 weeks; the majority have been under treatment for 20 weeks. It was notable that the excepted case above and the one previously reported (Thomson, 1949) were treated with wheat germ oil in a weekly dose of 30 mg. and responded dramatically in two weeks, whereas in the cases treated with ephynal a response was unusual within six weeks and common at about eight weeks.

The initial response was usually subjective in character and the patients variably stated that "the bands feel softer," that "there seems to be a little more movement in the fingers," or that "the pain in the palm has gone." Thereafter improvement clinically started to take place, and progress was steady, with end-results as described below.

The hands were divided into three groups, according to the type and severity of the contracture.

Group A: Early Cases.—In these the disease was of short duration, the palmar bands and nodules were present to a moderate degree, and the fingers were not contracted closer than 90 degrees towards the palm. Ten such hands

FIG. 1.—Case 1 (a) before vitamin E; (b) after vitamin E.

FIG. 2.—Case 3 (a) before vitamin E; (b) after vitamin E.

FIG. 3.—Case 6 (a) before vitamin E; (b) after vitamin E.