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VAGINAL OESTRIOL: EFFECTIVE MENOPAUSAL THERAPY NOT ASSOCIATED WITH ENDOMETRIAL HYPERPLASIA

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Summary: The Authors have studied the oestriol activity in vaginal conditions in postmenopausal period.

This therapy needs a very careful choice of the subjects. The important findings in their study were that oestriol administered vaginally in a daily dose of 0.5 mg. alleviated vasomotor as well as urogenital symptoms associated with the menopause and that there was neither endometrial hyperplasia, hyperlipidaemia nor hypertension after three months continuous therapy.

Oestriol has hitherto been considered a weak oestrogen. And «weak» effects were in indeed observed on the endometrium in their study but « strong » effects were apparent on the vaginal wall epithelium and urogenital symptoms and also on menopausal flushing. These effects of vaginal oestriol administration suggest that it might be suitable for use without progestogens and that further study of its action on a long term basis is indicated.

Although oestrogens relieve vasomotor, urogenital and other symptoms experienced at the menopause, the preparations most commonly used – oestradiol, oestrone or conjugated equine oestrogens – may induce endometrial hyperplasia. Furthermore long term unopposed oestrogen treatment has been reported to increase the incidence of endometrial carcinoma ([1]).

However, oestriol, hitherto considered a "weak" oestrogen, exerts trophic effects on the cervical and vaginal epithelia in doses which do not apparently cause endometrial hyperplasia ([2]). This raises the possibility that menopausal women with urogenital symptoms might benefit from local, i.e., vaginal oestriol therapy, in the absence of adverse stimulatory effects on the endometrium. Since oestrogens are readily absorbed from the skin and mucus membranes, we thought it possible that vaginal administration of oestriol could exert beneficial systemic effects in women with vasomotor or other symptoms at the menopause.

We have therefore investigated clinical and biochemical effects of oestriol given per vaginam daily for at least three months to women with urogenital and other symptoms referrable to the menopause. Our study included assessment of acute effects of oestriol and electron microscopical examination of the endometrium after at least three months' continuous therapy.

DESIGN OF STUDY AND SUBJECTS

The study comprised two separate investigations: (i) acute biochemical effects of a single vaginal application of oestriol and (ii) biochemical, clinical and electron microscopical effects of at least three months' therapy with daily vaginal oestriol.

i) The acute study was conducted in 12 healthy menopausal volunteers who had not received any drugs for at least three months previously.

Venous blood for estimation of oestriol, oestradiol and oestrone was taken at regular intervals (quarter hourly for two hours, half hourly for the third hour and then hourly) for six hours after vaginal insertion of a pessary containing 0.5 mg oestriol. Nine subjects were studied at rest and recumbent after insertion of the vaginal pessary so as to simulate nocturnal administration in patiens; the remainder (three women) were erect and ambulant after inserting the pessary as would

be the case if patients had done so on rising in the morning.

ii) The "chronic" study – clinical, biochemcial and cytological effects of daily oestriol administration per vaginam – was conducted in 30 women selected from among those referred to our Endocrine Outpatients for treatment of menopausal symptoms.

Selection and Exclusion Criteria

All patients studied complained of urogenital symptoms such as dyspareunia or urethral syndrome; some women also complained of hot flushes, sleep loss or joint pain. In some subjects oral oestrogen therapy had failed in the past to control genito-urinary symptoms or had induced unacceptable side effects. In no instance, however, had any ostrogen been taken for at least two months prior to starting treatment with vaginal oestriol.

Patients with known or suspected breast or genital tract malignancy, severe psychiatric or systemic disease, were excluded from the trial but 11 patients receiving replacement therapy for hypothyroidism – all of whom were clinically and biochemically euthyroid – were included.

A total of 36 women were initially incorporated into the study. Six women – for reasons detailed under "Results" – either failed to take medication as prescribed or did not attend for the first monthly check and five women failed to complete at least three months' continuous treatment. Their mean age was 52 (range 31 to 62) and the mean duration of their symptoms five years (range one to 12). The menopause had occurred spontaneous in the majority (24 women) and as the result of surgery performed for benign conditions in the remaining six. Hysterectomy had also been performed several years before the menopause for menorrhagia or fibroids in seven women. Thus, the uterus was *in situ* in only 17 of the 25 patients treated continuously for at least three months.

TREATMENT

Treatment consisted of one 0.5 mg oestriol pessary inserted vaginally daily after rising and washing, for at least three consecutive months. Patients were seen monthly for assessment of symptoms according to a standardized questionnaire and for clinical examination.

Blood was taken for measurement of oestrogens, gonadotrophins and lipids before starting treatment and at each monthly visit, two-and-a-half to three hours after vaginal administration of a pessary containing 0.5 mg oestriol. Vaginal and cervical smears were taken at the conclusion of three months' treatment and examined by conventional light microscopy. Endometrial biopsy specimens from 10 women who had completed at least three months' daily vaginal oestriol therapy were also examined by scanning electron microscopy.

METHODS

a) *Hormone levels*

The concentration of each hormone was determined by radioimmunoassay.

The total amounts of unconjugated oestriol, oestrone and oestradiol were measured by the method of Emment *et al.*. ([3]), using specific antisera to the 6-carboxymethyl oxime-BSA derivatives of each compound. The total concentration of conjugated oestriol (in the form of glucuronides and sulphates) was measured after hydrolysis with beta-glucuronidase and solvolysis. Five hundred (500) µl of extracted plasma was added to 20 µl of beta-glucuronidase (350 units). The mixture was incubated for one hour at 37 °C and the liberated oestriol extracted with 2 ml of diethyl ether and dried under nitrogen at 30 °C. One ml of a 2 per cent solution of sulphuric acid in ethanol was added to the aqueous phase and the mixture incubated at 37 °C for 24 hours. The tubes were centrifuged at 2000 g for 10 minutes; 50 µl aliquots (in duplicate) of the supernatants were removed and dried under vacuum at 37 °C. All extracts were redissolved in 100 µl of buffer and the concentraiton of oestriol deter-

mined by radioimmunoassay. The results were expressed as pmol per litre.

The levels of LH and FSH were determined with reagents and a protocol supplied by the WHO Match Reagent Programme; the respective reference preparations of human pituitary gonadotrophin were Code Number 68/40 containing 77 i.u. LH per ampoule and Code Number 69/104 containing 10 i.u. FSH per ampoule.

coated with platinum and viewed in a Philips 501 scanning electron microscope.

d) *Assessment of Symptoms*

The different symptoms of which the women complained were grouped under three headings – urogenital (dysuria, frequency, vaginal dryness etc. – five symptoms), vasomotor (hot flushes, sweating etc. – four symptoms) and psychological

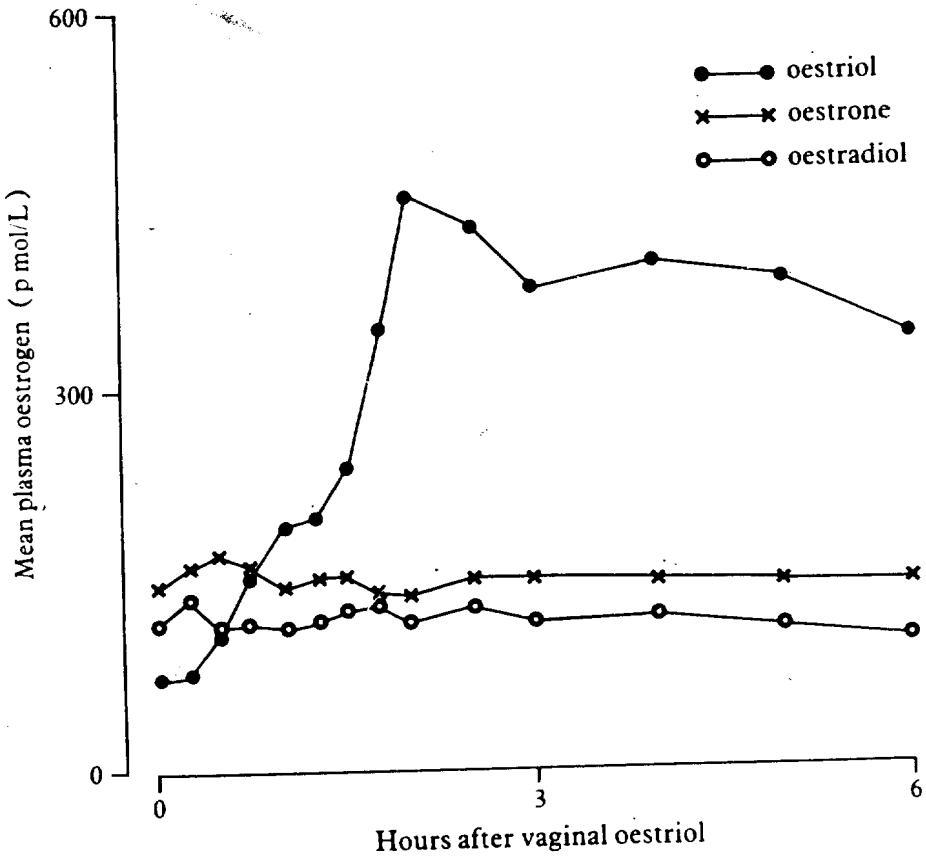

Fig. 1. — Mean plasma oestriol (solid circles), oestrone (crosses) and oestradiol (open circles) after vaginal insertion of pessary containing 0.5 mg oestriol in six menopausal women who remained recumbent for six hours.

b) *Blood Lipids*

Total cholesterol was measured enzymatically ([4]) and the HDL-cholesterol fraction by selective precipitation of LDL ([5]) using a magnesium-phosphotungstate reagent. Triglyceride was measured by an enzymatic method ([6]).

c) *Electron Microscopy*

Endometrial tissue for scanning electron microscopy was fixed in cacodylate buffered (0.2 M) 3% glutaraldehyde and dehydrated through graded acetone/water mixtures. The specimens were critical point dried in a Polaron E 3000 CPD,

(headache, fatigue etc. – four symptoms). In each instance the symptoms were assigned a numerical score of 0 to 3 according to their severity, i.e., "none", "mild", "moderate" or "severe". Thus, the maximum score possible, assuming that the patient rated each symptom as "severe" was 39. At each monthly attendance, one of two physicians (RF/JG) recorded the patient's symptom score according to the standard questionnaire.

e) *Statistical Evaluation*

Statistical significance was evaluated by Students T test or the Wilcoxon Ranking test as appropriate.

RESULTS

1. ACUTE HORMONAL EFFECTS OF 0.5 mg VAGINAL OESTRIOL

a) *Oestriol, oestradiol and oestrone*

The oestrogen values for the 9 subjects who remained recumbent for six hours are shown in fig. 1. Plasma oestriol increased significantly ($P < 0.05$) within half an hour of inserting 0.5 mg oestriol per vaginam, peak plasma levels of 450 (± 113) * p mol per L being reached within two hours. Four hours later, i.e., six hours after insertion of the pessary, plasma oestriol concentration was still significantly ($P < 0.01$) elevated at 336 ($\pm$ 85) p mol per L. There was however no significant change in oestrone or oestradiol concentration during this period.

In the three women who were active for six hours after vaginal insertion of the passary, plasma oestriol similarly increased within half an hour but peak values were reached somewhat earlier (at one-and-a-half hours) than in the recumbent women, and fell two hours later to reach basal values four hours after insertion of the pessary (fig. 2).

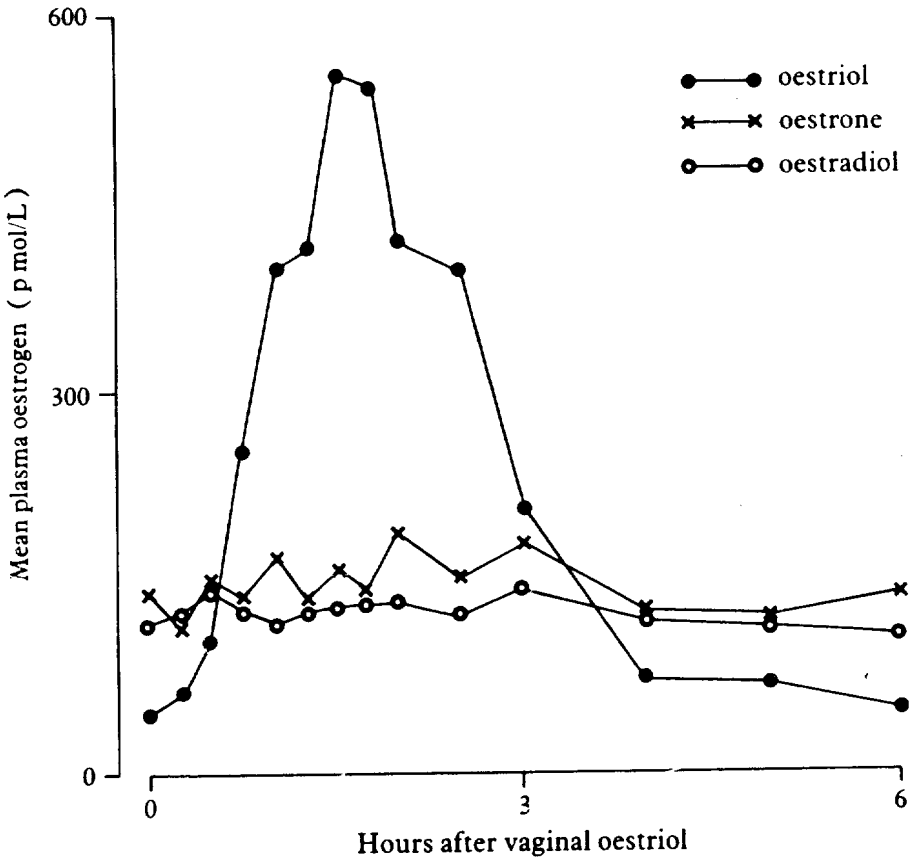

Fig. 2. — Mean plasma oestriol (solid circles), oestrone (crosses) and oestradiol (open circles) after vaginal insertion of pessary containing 0.5 mg oestriol in three menopausal women who were active for six hours.

b) *Conjugated oestriol and gonadotrophins* (fig. 3).

The oestriol glucuronide and sulphate fractions were measured in three of the nine patients who remained supine after

* Figures in parentheses are the standard error of the mean.

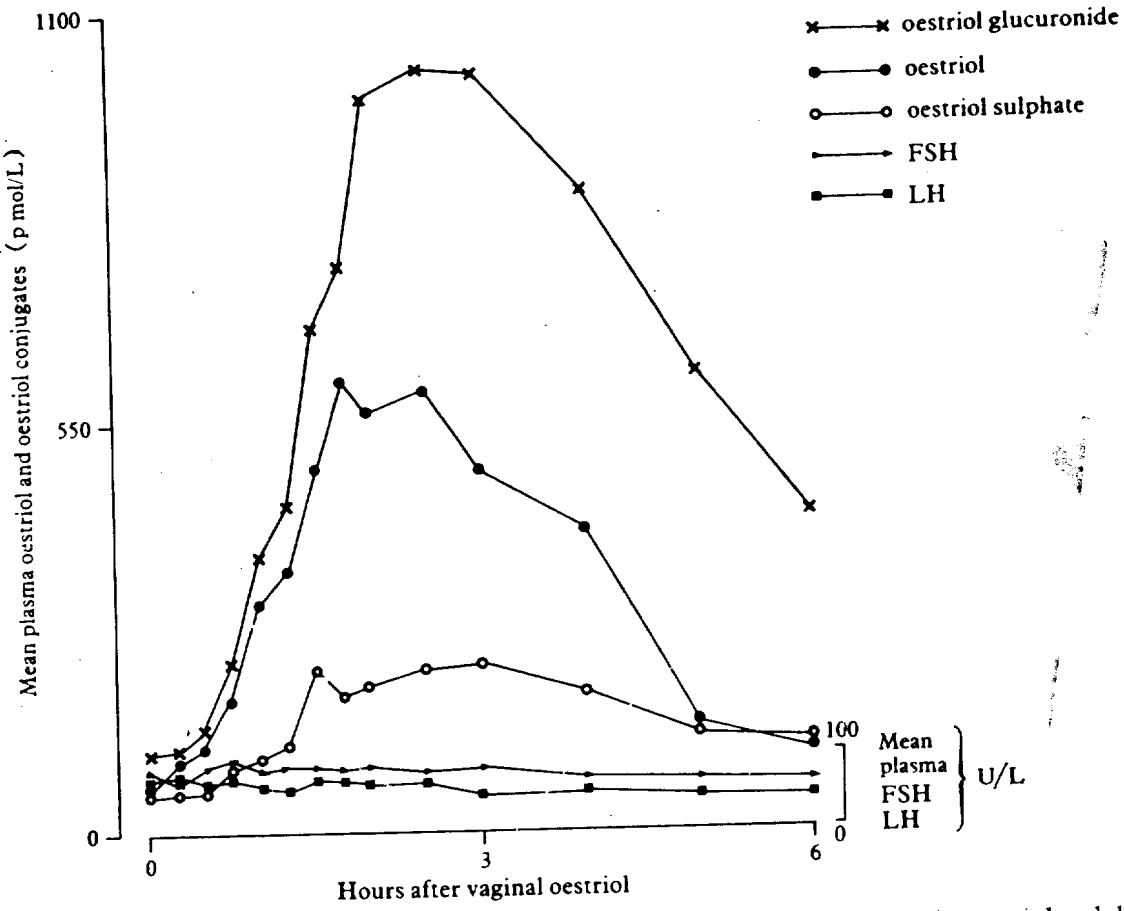

Fig. 3. — Mean plasma oestriol (solid circles), oestriol glucuronide (crosses), oestriol sulphate (open circles), FSH (solid triangles) and LH (solid squares) after vaginal insertion of pessary containing 0.5 mg oestriol in three menopausal women who remained recumbent for six hours.

the vaginal oestriol. In each case the glucuronide fraction increased progressively after insertion of the pessary, to reach a peak one-and-a-half to two hours later. Glucuronide concentration then fell slightly but levels were still elevated above the basal value at the end of six hours.

There was a slower rise in the sulphate fraction after vaginal oestriol. Whereas with the glucuronide, an increase was noted within half-an-hour of inserting the pessary and a marked rise was apparent by three-quarters-of-an-hour, there was no change in the sulphate fraction over the first half hour. Thereafter, however, there was a progressive rise in oestriol sulphate to a maximum at about two-and-a-half hours, after which the levels fell but remained elevated above baseline six hours after insertion of the pessary.

LH concentration was unchanged for the first two-and-a-half hours and then fell progressively, but the mean level at six hours did not differ significantly from the control mean. There was no significant change in FSH concentration during this period.

2. "CHRONIC" STUDY: EFFECTS OF DAILY VAGINAL OESTRIOL

i) Biochemical

a) *Oestriol, oestrone, oestradiol* (fig. 4)

Circulating oestriol increased some four-fold at the end of the first month of daily application of 0.5 mg oestriol vaginally -

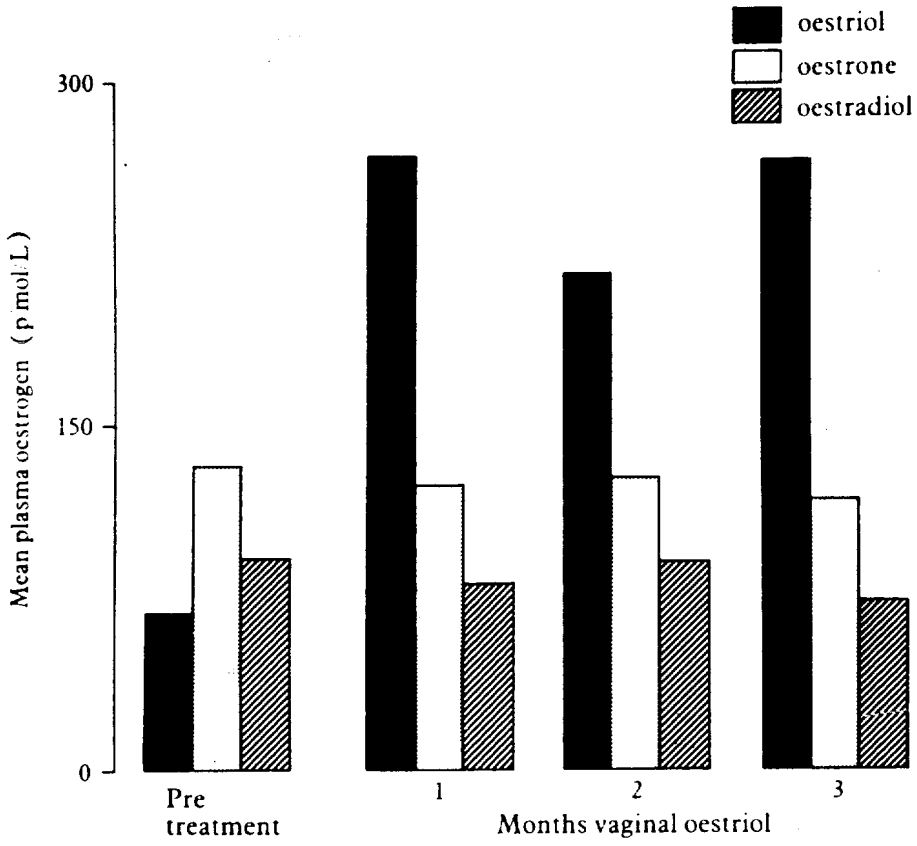

Fig. 4. — Mean plasma oestriol (solid histograms), oestrone (stippled histograms), oestradiol (diagonally hatched histograms) at monthly intervals in 25 menopausal women treated with daily vaginal oestriol (0.5 mg) for three months).

from 67.3 (±9.5) p mol per litre initially to 266.1 (±39.4) p mol per litre. The difference between these two means is highly significant - $P<0.001$. A significant ($P<0.001$) rise in blood oestriol was maintained in subsequent months, the mean oestriol level after three months being 264.8 (±45.7) p mol per litre.

There was, however, no significant change in either oestradiol or oestrone during the three months of treatment. Thus basal oestradiol concentration 90.7 (±17.8) and those recorded after one and three months continous treatment – 79.5 (±10.9) and 71.1 (±4.2) p mol per litre respectively – were simliar. Likewise, the corresponding oestrone values – 130.3 (±10.9), 121.3 (±0.8) and 116.3 (±9.8) p mol per litre respectively – were comparable.

b) *Oestriol conjugates and gonadotrophins* (table 1)

Plasma concentrations of oestriol glucuronide and sulphate and also of gonadotrophins were measured in four patients receiving daily oestriol.

Initially, total plasma oestriol concentration – unconjugated oestriol, glucuronide and sulphate – was 193.2 p mol per litre in these four patients. After three months' treatment, mean total oestriol concentration had increased to 3158.6 p mol per litre.

Before treatment, mean unconjugated oestriol concentration (71 p mol per litre) represented 37 per cent of the total oestriol measured (193.2 p mol per litre). After three months' treatment, unconjugated oestriol concentration (344.4 p mol

Table 1. — *Effect of daily vaginal oestriol (0.5 mg) on plasma levels of oestriol, conjugates and gonadotrophins in four wowen.*

	0	1	2	3	months' treatment
Oestriol	70.8 (5.6)*	344.4 (106.2)	276.1 (50.5)	344.1 (107.1)	p mol per L
Oestriol glucuronide	64.3 (5.1)	1421.3 (145.1)	1665.6 (149.4)	2127.2 (409.4)	
Oestriol sulphate	58.1 (1.0)	369.5 (47.3)	490.2 (119.1)	687.3 (176.1)	
LH	52.6 (12.0)	59.1 (13.8)	58.2 (15.9)	66.8 (23.4)	U per L
FSH	70.2 (12.6)	59.5 (13.2)	56.5 (9.3)	60.6 (11.5)	

* Standard error of mean in parentheses.

per litre) represented only 11 per cent of the total (3158.6 p mol per litre).

The respective change for the glucuronide fraction was from 33 per cent (64.3 p mol per litre initially, before treatment, to 67 per cent (2127.2 p mol per litre) after three months' daily oestriol. Thus the proportion of glucuronide increased after oestriol administration both relatively and absolutely. However, with the sulphate, although the absolute amount increased from 58.1 p mol per litre before treatment to 687.3 p mol per litre after three months' oestriol the relative proportion fell as the result of treatment, being 30 per cent initially but only 22 per cent after treatment.

LH and FSH values showed no significant change over the three months of treatment.

c) *Plasma lipids*

Mean fasting plasma triglyceride levels were 1.1 (±0.2) m mol per litre initially and 1.2 (±0.2) m mol per litre after three months' treatment. These values are not significantly different.

Fasting plasma cholesterol averaged 6.2 (±0.2) m mol per litre before treatment. After three months' treatment, mean plasma cholesterol was 6.3 (±0.2) m mol per litre, a value not significantly different from the pretreatment value. A slight but insignificant rise in HDL cholesterol occurred after oestriol therapy, the mean value being 1.2 (±0.1) m mol per litre at the end of three months' continuous treatment compared with 1.0 (±0.1) m mol per litre initially.

ii) CLINICAL

a) *Drop outs*

Six women discontinued treatment within the first month – one because of cancerphobia, one because she disliked vaginal administration and one because of lassitude, a symptom present at the start of treatment and which was not alleviated by discontinuing the oestriol. Vertigo occurred after three weeks' treatment in one woman and migraine in another; in both cases the symptoms cleared after stopping treatment. The sixth was lost to follow-up.

Five women failed to complete three months' treatment – two because of depression after two months' (and which persisted after the withdrawal of oestriol) and two because they preferred conjugated equine oestrogens which they had received previously. One woman left the United Kingdom because of her husband's work but expressed a desire to resume oestriol therapy should they return to London.

There was thus no consistent reason for ceasing treatment with vaginal oestriol.

b) *Symptomatic responses*

The 25 women who completed three months' treatment all reported considerable symptomatic benefit from vaginal oestriol treatment. However, in the majority there was a latent period of some ten to 14 days between the start of treat-

ment and significant clinical improvement. In many instances, the first sign of improvement was the sensation of a hot flush "coming on" but with no subsequent materialisation of the "full-blown" hot flush. The sweating which generally accompanied the hot flush likewise failed to occur. These abortive flushes continued for a further three to five days, after which they disappeared or occurred only occasionally, less intense than before oestriol treatment.

Most women reported improvement in the quality and length of sleep. This they attributed to the disappearance of their drenching night sweats. The restoration of sleep was a clinical turning point, which in turn led to a feeling of greater well being, reduced fatigue and increased energy.

Alleviation of dyspareunia was generally apparent within two to three weeks' and relief from the urethral syndrome within six weeks' of starting treatment.

At the end of the three monts' trial period, all but one of the 25 women requested continuance of the vaginal oestriol treatment; to date 18 women have used this preparation for well over a year, and some for over two years.

c) *Symptom questionnaires* (table 2)

Symptomatic responses based on the symptom questionnaire, showed a marked overall improvement after the first month of treatment and which was sustained during the three month trial period. Improvement occurred in each major symptom category, with a significant fall in the calculated score for each group – from a mean of 4.5 to 1.2 ($P<0.001$) for genito-urinary symptoms after one months' treatment and from 7.2 to 3.6 ($P<0.001$) and 5.8 to 3.9 ($P<0.01$) for vasomotor and psychological complaints respectively.

Table 2. — *Effect of daily vaginal oestriol (0.5 mg) on menopausal symptoms.*

	0	1	2	3 months' treatment
Genito-urinary	4.5 (0.6)*	1.2 (0.3)	0.8 (0.3)	0.3 (0.2)
Vasomotor	7.2 (0.6)	3.6 (0.7)	2.6 (0.6)	2.1 (0.7)
Psychological	5.8 (0.4)	3.9 (0.6)	2.4 (0.5)	2.5 (0.8)
Overall	17.8 (1.0)	8.7 (1.2)	5.8 (1.2)	4.9 (1.4)

* Standard error of mean in parentheses.

d) *Blood pressure*

Before treatment blood pressure expressed as the mean of systolic and diastolic values averaged 109 (± 2.7) mmHg. After three months' treatment blood pressure had fallen slightly to 100 (± 2.6) mmHg; these values are significantly ($P<0.01$) different.

iii) Cytology and Histological Studies

Routine vaginal and cervical smears taken after three months' treatment showed normal oestrogenised cells; no malignant or atypical cells were observed.

Initially attempts were made to obtain endometrial specimens by Vabra curettage from women who had completed three months' continuous treatment with oestriol. However, it proved impossible to obtain a significant amount of endometrial tissue after Vabra curettage in these patients. Examination by conventional light microscopy showed that the specimens we had obtained by this means were essentially composed of red blood cells; a few endometrial cells only were identified and these appeared to be in the quiescent phase. This was confirmed on further study by scanning electron microscopy.

The opportunity subsequently arose in 10 patients, all of whom had completed at least three months' vaginal oestriol treatment (and some a year) to obtain endometrial biopsy specimens at dilatation and curettage performed under general

anaesthesia. These specimens were then studied by scanning electron microscopy. In the majority (eight women) there was only a minimal endometrial response to vaginal oestriol, the histological features being characteristic of inactive endometrium. Thus the endometrial surface was composed of flattened dome-like cells with prominent intercellular ridges (fig. 5), covered by abundant microvilli which varied from short and stubby to moderately well-developed. The occurrence of ciliated cells, even around gland mouths, was rare.

The endometrial surface in biopsies from the remaining two patients showed features similar to those observed in normal mid-proliferative endometrium ([7]). There was a mixture of ciliated and non-ciliated cells (fig. 5) and in the interglandular zone 30 to 40 per cent of the surface cells were covered by cilia, most of which were long and of equal length though a few cells had short cilia which were still developing. Among these were groups of non-ciliated cells most of which were covered by numerous microvilli to a variable extent. These changes represent the maximal endometrial response observed after vaginal oestriol. The underlying histology substantiated the aforementioned electron microscopy findings.

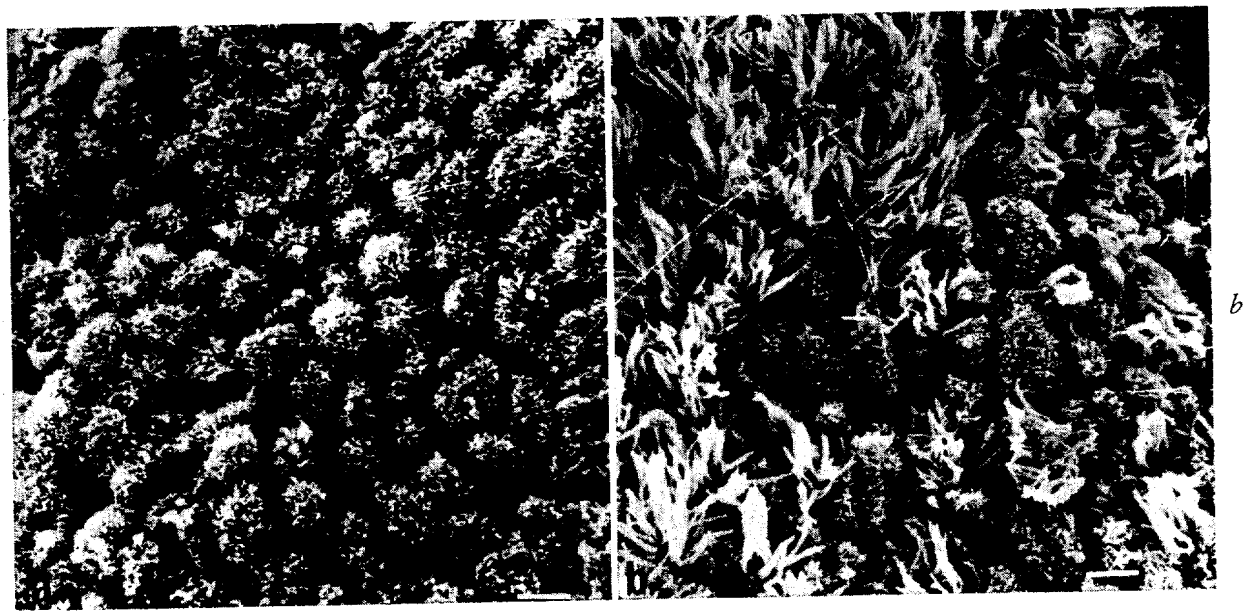

Fig. 5. — Scanning electron micrographs of the endometrial surface of biopsies from two patients after three months vaginal oestriol. In a) The cells have a cobble-stone appearance and are covered by numerous microvilli. b) About 40 per cent of the cells show the development of cilia (bar = 2 mu).

DISCUSSION

The important findings in our study were that oestriol administered vaginally in a daily dose of 0.5 mg alleviated vasomotor as well as urogenital symptoms associated with the menopause and that there was neither endometrial hyperplasia, hyperlipidaemia nor hypertension after three months continuous therapy. A similar trend was apparent in those patients who continued using vaginal oestriol after the three months' trial period for up to and over a year.

The decision to administer oestriol vaginally rather than orally was made for two main reasons – to ensure a high local

concentration for relief of urgenital symptoms and because post absorption profiles differ according to the route of administration. Thus after oral ingestion, when oestriol is first subjected to metabolic change in the gut and then undergoes biotransformation in the liver, only three per cent is present in the circulation as unconjugated oestrogen, the remaining 97 per cent consisting of hepatic conjugates of oestriol ([8]). However, after vaginal administration, which avoids the initial effects of intestinal action and hepatic metabolism, around 11 per cent is in the unconjugated form and 80 per cent circulates as conjugated oestriol metabolites ([8]). The possibility that the reduced level of conjugated oestriol after vaginal compared with oral administration may relate to the absence of endometrial stimulation thus requires investigation. The different relative proportion of oestriol metabolites after vaginal and oral administration may also be relevant. With oral oestriol the concentration of the glucuronide fraction is higher than that of oestriol sulphate ([8]) whereas in our study the relative proportion of the sulphate fell after vaginal oestriol. Sulphatase and beta glucuronidase enzymes are widely distributed in tissues. Unconjugated oestriol could thus readily be released and made available to different tissues but the extent to which this occurs after vaginal oestriol administration would in turn relate to many other factors, as for example, the relative half life of the different metabolites.

The absorptive capacity of the post menopausal vaginal wall is remarkably efficient. In the acute study, plasma oestriol was increased some sixfold over baseline only two hours after vaginal insertion of 0.5 mg. Absorption after daily treatment for one month was of a similar order to that observed after acute administration and plasma oestriol concentrations after three months' treatment were similar to those found after one month. The trophic effect of oestriol on vaginal wall epithelium had thus apparently not impaired its absorptive function. This contrasts with previous reports of the effects of conjugated equine oestrogens ([9, 10]) in which there was loss of local effect with prolonged vaginal treatment and apparent refractoriness of responsive tissues with impaired steroid absorption when oestrogen stimulation lasted more than 14 days. No such "fall off" occurred over three months' either biochemically or clincally. And even after more prolonged treatment as in those patients who continued with vaginal application on completion of the three months' trial, symptomatic improvement was maintained and raised oestriol levels recorded after a year.

The absence of endometrial hyperplasia after several months' vaginal oestriol is in accordance with previous observasions of the effects of oral oestriol. No endometrial stimulation was observed after oestriol had been taken orally for up to six months in single doses of two to eight mg daily ([11-14]) – i.e. 16 times the amount given vaginally in the present study. And when 6 mg per day was given in divided doses of 2 mg t.d.s., slight endometrial proliferation was noted in only one woman so treated ([15]).

The affinity of oestriol for the endometrial oestrogen receptors differs from that of E_1 and E_2. In rats the duration of endometrial binding of oestriol is brief and unless repeated doses are given, endometrial proliferation is not seen ([16]). This parallels our findings in women and contrasts with the abnormal ultrastructural appearance of the endometrium reported after other oestrogens ([17]).

Current therapy for menopausal symptoms results in a disproportionate rise in circulating oestrone irrelevantly of whether oestrone (E_1), oestradiol (E_2) or conjugated equine oestrogens are taken ([18]). The normal ratio of E_2 to E_1 is thus disturbed and this may influence morbidity, for increased E_1 and E_2 are thought

to enhance hypertriglyceridemia ([19]), vascular disease and endometrial neoplasia ([20]). That no significant change occurred in E_1 or in the E_2: E_1 ratio after vaginal oestriol is thus of considerable importance and indicates a potential advantage of oestriol over other oestrogens for treatment of menopausal symptoms. The absence of endometrial hyperplasia may also relate to the fact that E_2 and E_1 do not rise after vaginal E_3. Hence there is no intracellular oestrogen stimulus to the endometrium as occurs with conventional types of oestrogen therapy.

Vaginal oestriol administration over three months caused surprisingly little disturbance in hormonal and biochemical profiles. Aside the unchanged oestradiol and oestrone concentrations discussed above, gonadotrophin levels remained elevated (although hot flushes were alleviated) and lipid patterns did not vary. Furthermore, the level of oestriol we recorded in our study – although somewhat higher than that found in the normal menstrual cycle – was not grossly nor continuously elevated. There was thus no "pharmacological" rise in circulating oestrogen after oestriol.

Oestriol has hitherto been considered a "weak" oestrogen. And "weak" effects were indeed observed on the endometrium in our study but "strong" effects were apparent on the vaginal wall epithelium and urogenital symptoms and also on menopausal flushing. These effects of vaginal oestriol administration suggest that it might be suitable for use without progestogens and that further study of its action on a long term basis is indicated.

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