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CLINICAL INVESTIGATIONS OF A LONG-ACTING OESTRIOL (POLYOESTRIOL PHOSPHATE)

By

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Puck 1957

ABSTRACT

A description is given of experimental investigations and preliminary clinical experience with the long-acting oestriol compound polyoestriol phosphate - a water-soluble polymere of oestriol and phosphoric acid. The compound seems to exert all the physiologically important effects of oestriol. Even with high doses the hormone causes no proliferation of the endometrium and no withdrawal bleeding. It has no untoward effect on metabolism. It decreases slightly the cholesterol concentration (to the extent of $\frac{1}{3}$ - $\frac{1}{5}$ of the effect produced by long-acting oestradiol esters). The compound has a wide therapeutic range. No side-effects have been observed. Doses of 10 mg or more have a prolonged duration. Additional prolongation of the effect is largely dependent on dosage. To ensure an effect lasting for 4 weeks 40 mg polyoestriol phosphate (corresponding with 80 mg oestriol) is required - an amount which roughly corresponds with physiological quantitative data.

The compound, which involves an interesting new principle of prolongation, was most effectively used in the treatment of menopausal symptoms and genital organic disorders. For these indications it can be recommended without reservation.

triol (oestra-1,3,5(10)-triene-3,16 α ,17 β -triol), both as a hormone and as a therapeutic agent has received considerable attention in publications over the few years (Puck 1957; Puck et al. 1957; Borglin 1959; Unger 1959). Our understanding of the biological characteristics of this steroid has consequently improved in many respects. The almost complete absence of a proliferative effect on the uterine endometrium is doubtless an important positive argument for

hormonal treatment. The absence of untoward effects on the metabolism, associated with the maintenance of other typical oestrogenic actions, must be regarded as equally valuable. The majority of investigators have reported very favourably on the efficacy of oestriol, particularly in cases with menopausal symptoms, and have stressed the surprisingly small doses which are effective in some of the cases (*Puck 1957; Borglin 1959*).

The well-known disadvantages of oral medication or daily injections are avoided in present day pharmacotherapy by treatment with depot drugs. It is undoubtedly desirable that oestriol, with its many clinical indications should also be available in the form of a long-acting substance for parenteral administration; this would ensure effective and well-controlled administration of the hormone over a longer period.

This paper reports on experimental trials and clinical experience with such a long-acting oestriol. As far as we know, this is the first report made so far on such an investigation. The oestriol concerned is the polyoestriol phosphate produced by Leo A. B. in Hälsingborg, Sweden, which was made available to us for experimental purposes in »dry« ampoules. The substance is water-soluble (lyophilized) and can be injected intramuscularly as well as intravenously. In practice the intramuscular route of administration is preferred. In animal experiments it was found to have a prolonged effect and a low toxicity. It contains no oestriol epimeres.

Mechanism of action. – With this high-molecular water-soluble polymere of oestriol and phosphoric acid, an interesting mechanism is concerned in prolonging its effects. After absorption from the site of injection, the compound is presumably broken down slowly in the organism by phosphatases, during the course of which the biologically effective steroid oestriol is liberated (*Diczfalussy et al. 1956*). Since this polymer (like polyoestradiol phosphate) is also a phosphatase-inhibitor, the breakdown reaction is even further delayed (*Fernö et al. 1958*). It may also be assumed that a negatively charged colloid electrolyte such as polyoestriol phosphate is present in its highest concentration in the liver and spleen, from which sites it slowly becomes effective (*Beling & Diczfalussy 1959*).

MATERIAL

A total of 79 women were treated with various doses of polyoestriol phosphate. Of these patients, 56 were aged between 48 and 65, the menopause having occurred spontaneously at least 2 years previously. The investigation also included 7 surgical castrates (female), 14 patients with a history of ovarian irradiation, one patient in whom radioactive gold had been implanted into the pituitary gland for mammary carcinoma, and one chromosomally female subject with ovarian aplasia but with an intact uterus. Eleven patients of the first group have so far received up to 8 injections of polyoestriol phosphate over a 5-month period.

RESULTS

Tolerance. — Deep intramuscular injections of polyoestriol phosphate at the dosage used (10–50 mg, and 100 mg in one case) were tolerated without any local pain or any reactions. No redness, infiltration or allergic symptoms were seen. Slow intravenous administration of 10–30 mg polyoestriol phosphate within about one minute was similarly tolerated without any reaction. No general side-effects were observed.

Start and duration of action. — As evaluated on the basis of proliferation of the vaginal epithelium, the oestrogenic effect of polyoestriol phosphate begins on the 2nd–3rd day after intramuscular or intravenous injection, *i. e.* it then becomes visible in vaginal smears obtained from the treated women. Within the ranges investigated, the start of action would seem to be practically independent of the dose. The maximal effect occurs after 5–10 days, according to the dose administered (see Fig. 1). The duration of the effect, too, is largely dependent on the dosage.

The following averages as evidenced by vaginal smears were obtained for the duration of action of polyoestriol phosphate:

- 10 mg polyoestriol phosphate (corresp. to 7.5 mg oestriol)
about 7 (6–8) days.
- 20 mg polyoestriol phosphate (corresp. to 15 mg oestriol)
about 12 (10–15) days.
- 30 mg polyoestriol phosphate (corresp. to 22.5 mg oestriol)
about 21 (17–24) days.
- 40 mg polyoestriol phosphate (corresp. to 30 mg oestriol)
about 28 (24–35) days.
- 50 mg polyoestriol phosphate (corresp. to 37.5 mg oestriol)
about 35 (27–42) days.

These values suggest, that about 1 mg/d of oestriol can be set free and become effective in the body. In consequence one would expect to find about 800 μ g of oestriol in the 24 hours urine, a quantity which would roughly correspond to the excretion of oestriol in the 3rd–4th month of pregnancy. This is corroborated by determinations of urinary oestriol in a patient treated with 50 mg of polyoestriol phosphate (Fig. 2).

These findings, obtained by using vaginal smears and chemical determination of oestriol in urine, are corroborated by the subjective reports of menopausal patients on the control and recurrence of their symptoms of functional loss (Fig. 3). In some cases the improvement of symptoms continued for slightly longer than did the proliferative effect on the vaginal epithelium.

An unmistakable improvement of symptoms started as a rule at least some 48 hours after an intramuscular injection, and about 18–24 hours after intra-

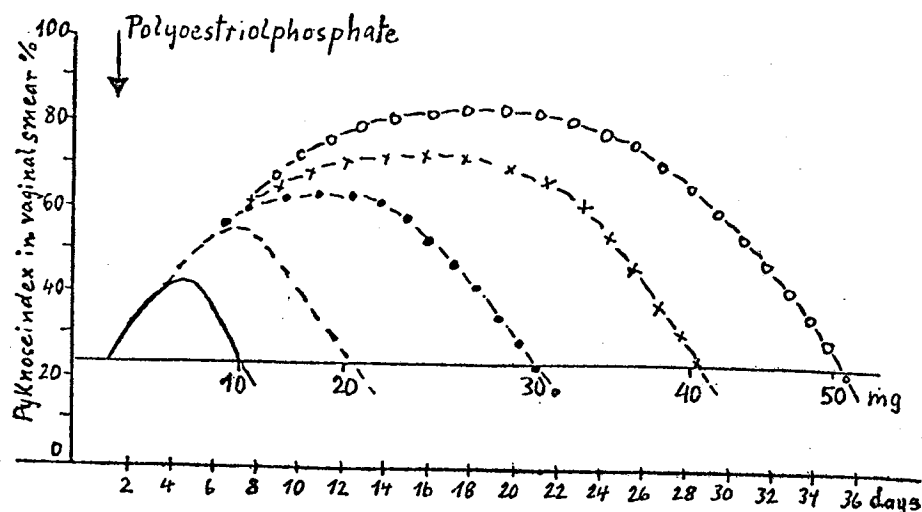


Fig. 1.

Schematic drawing showing the average duration of action of polyoestriol phosphate given intramuscularly in doses of 10, 20, 30, 40 and 50 mg (corresponding to 7.5, 15.0, 22.5, 30 and 37.5 mg oestriol), measured on the basis of the pyknosis index of the vaginal smear and of the disappearance and recurrence of menopausal symptoms (indicated in the horizontal line); 54 women.

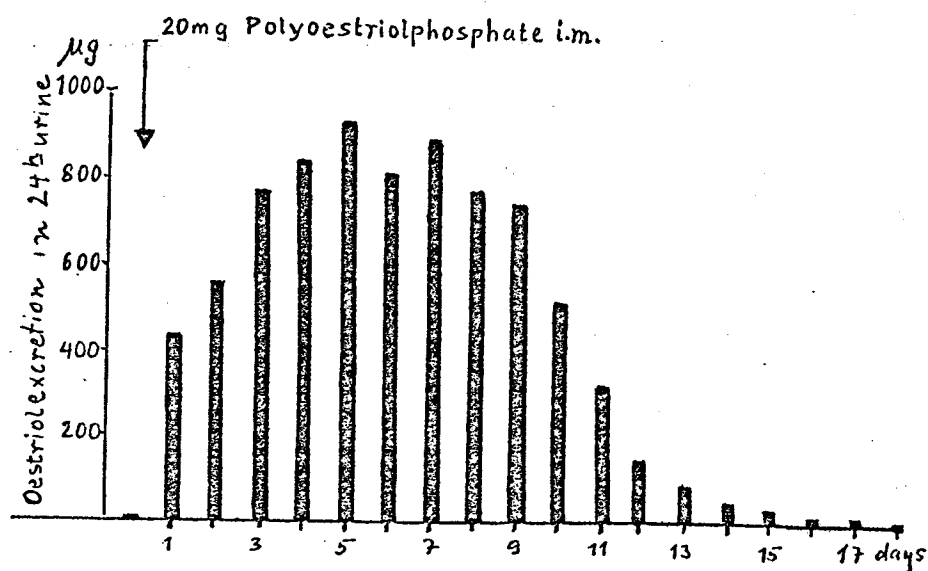


Fig. 2.

Excretion of oestriol in the urine of a 47 years old healthy surgically castrated woman after administration of 20 mg polyoestriol phosphate i.m. Method of *Ittrich* (1958). Control values between 3-9 μg/24 hours urine.

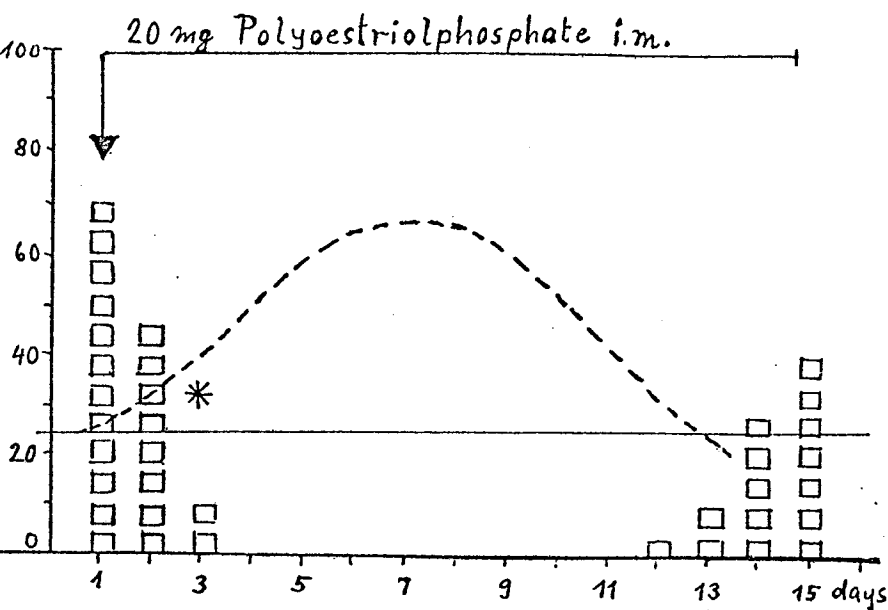


Fig. 3.

Effect of polyoestriol phosphate (20 mg i. m.) on menopausal symptoms, measured on the basis of the number of flushes per 24 hours. □

* Occurrence of palm-leaf reactions in the cervical mucosa.

--- Cytological pyknosis index.

52-year-old patient 3 years after natural menopause.

ous administration. The optimal effect was attained after 3-5 days. The duration of action was almost the same after both methods of administration, though it seemed sometimes slightly shorter after an intravenous injection. With a further increase of the dosage, the duration of action could be further prolonged without any risk of side effects. An intramuscular injection of 100 mg polyoestriol phosphate was the largest single dose administered. As estimated on the basis of the above criteria, its effect lasted almost 3 months.

The therapeutic value of the substance was then tested on the basis of its effect on the typical symptoms of the menopause. The results obtained are presented in Table 1.

The table shows that polyoestriol phosphate is a highly effective aid in controlling the most frequent menopausal symptoms. Similarly favourable results were seen in the treatment of withdrawal effects following surgical (7 cases) and radiological castration (14 cases). Definite failure of treatment was rarely observed. Symptoms unchanged in spite of treatment were not definitely identified as purely menopausal in nature, but were rather more in the nature of marginal symptoms, based on other, underlying disorders or of primary

Table 1.
Results of treatment of menopausal symptoms with long-acting oestriol (polyoestriol phosphate) in 56 women, at least 2 years after menopause. Dose: 10-60 mg i. m.

Symptoms	Number of patients	Controlled	Improved	Unchanged
Hot flushes	49	42	7	—
Nervous irritability, depressions	34	28	5	1
Tachycardia	7	5	1	1
Insomnia	22	16	3	3
Nocturnal sweating	20	19	1	—
Dizziness	4	3	—	1
Circulatory disorders, paraesthesias	7	5	1	1
Menopausal labile hypertension	5	4	1	—
Migraine	2	—	1	1

psychogenic origin. Twelve patients had previously been treated with other hormonal substances — as a rule combinations of oestrogen-androgen or of stilbenes. All were highly satisfied with the therapeutic result obtained with polyoestriol phosphate. Five of the patients found oestriol treatment definitely better than previous hormonal therapy, although positive suggestions were carefully avoided. Only after preceding treatment by implantation of large doses of stilboestrol were the results obtained with oestriol initially less satisfactory. Failure in such cases can be overcome by the administration of an initial higher dose of the preparation. Polyoestriol phosphate had no appreciable psychological effect or effect on libido.

As a rule, flushes were first reduced in duration, and then in frequency, until they completely disappeared after 3-5 days. The influence on the nervous symptoms can readily be explained on the basis of the mild parasympathicotonic effect of oestriol. The stabilizing effect of oestriol on the autonomic nervous system could be evaluated objectively on the basis of the results of vegetative tests carried out before and after treatment with polyoestriol phosphate (Figs. 4 and 5).

The favourable influence on dizziness, circulatory disturbances, paraesthesia, hypertension and migraine in a number of cases drew attention to a possible *circulatory action* of oestriol. An attempt was made to verify this by determinations of skin temperature and re-warming time at the periphery. Administration of polyoestriol phosphate was not followed by a demonstrable significant change in skin temperature in 4 normal subjects and one woman with severe peripheral circulatory disturbances. The body temperature too was not markedly influenced.

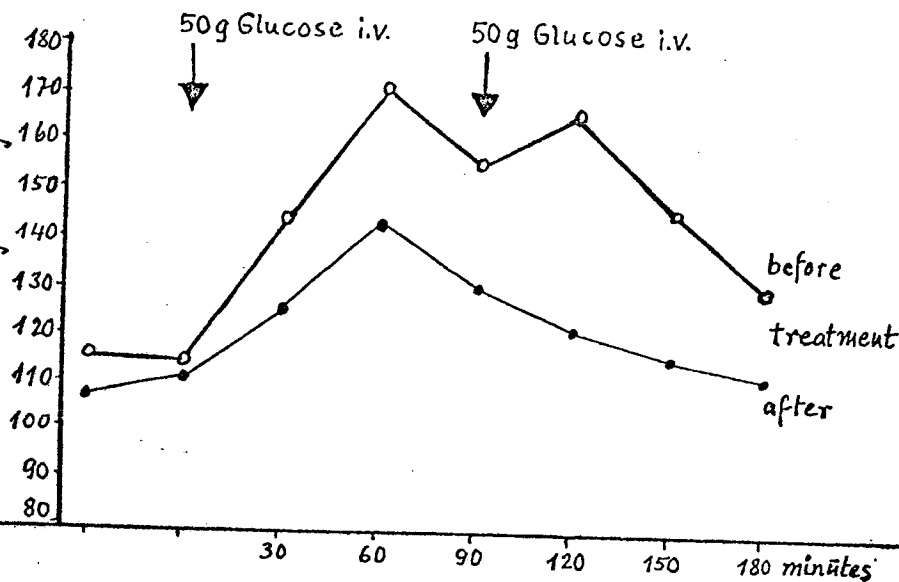


Fig. 4.

...dextrose tolerance test according to Staub-Traugott, before and 14 days after treatment with 50 mg polyoestriol phosphate. Before treatment, hyperregulatory tolerance curve: excessive increase in blood sugar with recurrence of peak after second administration of glucose (negative Staub effect).

...fourteen days after 50 mg polyoestriol phosphate i.m., normal reaction, with flat, monophasic curve; 52-year-old otherwise healthy woman with menopausal symptoms, 4 years after menopause.

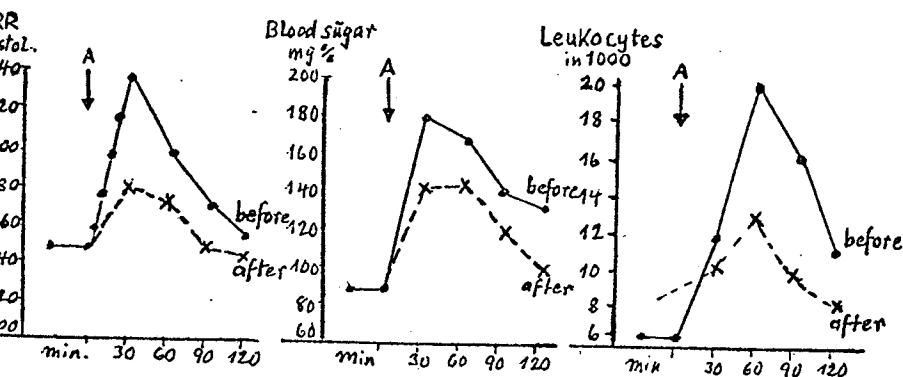


Fig. 5.

...renaline tolerance test (1 mg s.c.), before and 14 days after administration of 50 mg polyoestriol phosphate i.m. Before treatment, hyperreactive reaction, with excessive increase in blood pressure, blood sugar and leucocyte count. After treatment, normal reaction; 57-year-old woman with menopausal symptoms 8 years after the menopause - otherwise healthy.

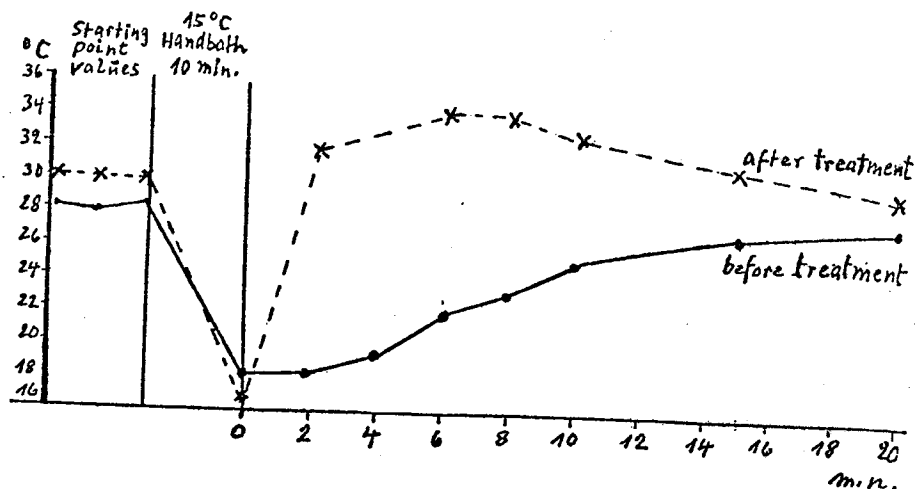


Fig. 6.

Before treatment, abnormally long re-warming time. After i.m. injection of 50 mg polyoestriol phosphate, unmistakable shortening of the re-warming time (normalized): 55-year-old woman with bilateral paraesthesia of the hand 5 years after the menopause — otherwise normal.

The acral re-warming test, however, revealed an unmistakable shortening of the re-warming time after polyoestriol phosphate treatment in 3 patients with paraesthesia of the fingers as a result of circulatory disturbances (Fig. 6). This seems to indicate a beneficial effect of oestriol on the functional reactivity of the small blood-vessels.

Menopausal hypertension is generally characterized by labile blood pressure values. Paroxysmal increases in blood pressure in such cases occur several times a day, usually associated with flushes and attacks of hyperhidrosis. In 2 patients such sympathicotonic attacks were controlled by polyoestriol phosphate administration (Fig. 7). The substance did of course not influence established hypertension.

Gonadotrophin excretion. — In the 3 menopausal patients examined, administration of 50 mg polyoestriol phosphate did not markedly influence the urinary excretion of total gonadotrophins (method of Loraine and Brown) (Fig. 8). No distinction was made, however, between FSH and LH activity. The absence of influence on gonadotrophins is also manifested by the fact that 50 mg polyoestriol phosphate i.m. failed to cause an appreciable shift in the cycle in the 11 normally menstruating women examined so far.

Metabolic effects. — The known metabolic effects of oestrogens were investigated in 18 women, who received 50 mg polyoestriol phosphate.

Total serum cholesterol value. — In a 62-year-old woman on a constant diet, the total serum cholesterol value decreased from an initial 480 mg/100 ml to

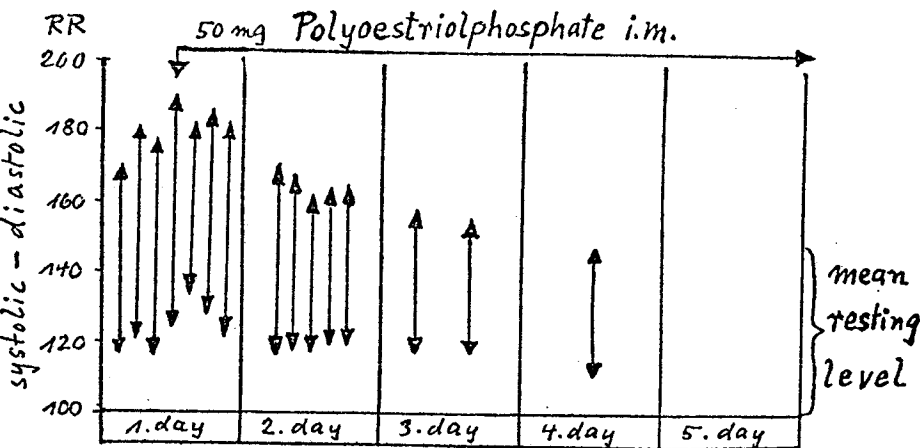


Fig. 7.

Control of paroxysmal menopausal hypertension after i.m. injection of 50 mg polyoestriol phosphate; 52-year-old woman 5 years after the menopause. Initial value after bed rest for 7 days.

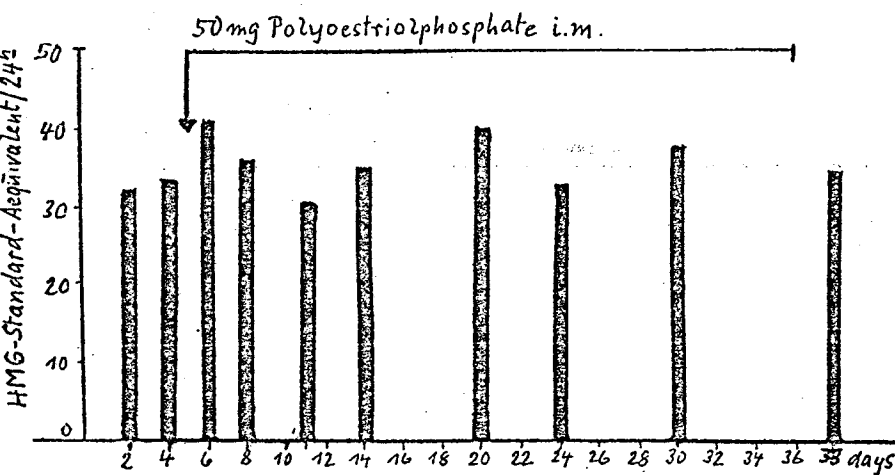


Fig. 8.

No marked influence on total gonadotrophin excretion in 24-hour urine after a single i.m. injection of 50 mg polyoestriol phosphate in a 56-year-old woman with moderately marked menopausal functional symptoms, 7 years after the menopause. Method: uterine weight test in infantile mice; 4-point test, with 5 animals per group. Preparation of urine according to Loraine and Brown.

26 mg/100 ml in the course of 3 weeks. In a 67-year-old woman there was a decrease from 456 mg/100 ml to 421 and then to 398 mg/100 ml in the 4th week; a 72-year-old woman showed a crease from 493 to 432 mg/100 ml. Although the number of patients examined is small and the decrease of chole-

sterol values not established beyond doubt, a uniform trend in the depression of total serum cholesterol seems to be indicated.

Nitrogen excretion. – This remained uninfluenced after 50 mg polyoestriol phosphate in 2 menopausal women with moderate osteoporosis. Continual weight determinations showed that no increase in weight occurred even after prolonged treatment with up to 5 injections of 50 mg each.

Creatine and creatinine excretion. – Polyoestriol phosphate was found to have no demonstrable effect on creatine and creatinine excretion in 2 patients with increased excretions resulting from hyperthyroidism and chronic glomerulonephritis, respectively.

Serum phosphatase. – An injection of 50 mg polyoestriol phosphate in 4 healthy subjects failed to influence significantly the normal acid and alkaline phosphatase values in the serum. In 2 patients with distinctly increased levels of acid phosphatase associated with pelvic metastases in cancer of the cervix a moderate decrease towards a normal range was seen.

Electrolyte balance. – No influence was demonstrated on the serum calcium and the urinary calcium excretion; potassium, sodium and chlorine values likewise remained unaffected (4 patients).

Water metabolism. – No oedema occurred even after large doses of polyoestriol phosphate (250 mg within 4 weeks). Body weight, urine output and specific gravity remained unchanged in all patients. The Kaufmann diuresis test yielded the same result before and after treatment (2 patients). In one woman with untreated diabetes insipidus after implantation of radioactive gold into the pituitary gland for mammary carcinoma, the urinary output remained unaffected after the administration of 100 mg polyoestriol phosphate during a control period of 3 weeks.

Blood sugar. – Whereas the hyperregulatory dextrose tolerance curve and the excessive blood sugar increase after adrenaline injection in menopausal women could be decreased by intramuscular injection of polyoestriol phosphate (Figs. 4 and 5), the hormone ester was (as expected) incapable of decreasing a pathologically high blood sugar level in diabetes mellitus or of normalizing a pathological result of the dextrose double tolerance test in diabetes according to Staub-Traugott. This was established in a 58-year-old and a 65-year-old woman with recently discovered moderately severe senile diabetes, both of whom showed blood sugar values between 180 and 230 mg/100 ml.

Blood picture. – Polyoestriol phosphate prevented an abnormally high increase of leucocyte values following adrenaline injection (see Fig. 5). Differential blood counts made in 7 women during treatment showed no anomalies before, during and after treatment. The reticulocyte count was determined in 2 women, and showed no marked change. The platelet count remained unchanged, regardless of whether the values were low or normal (3 patients)

Organic symptoms following the loss of gonadal activity are most significant-

ly manifested by the condition of the oestrogen target organs, viz: uterus, vagina, vulva and mammae, and urethra and trigonum vesicae as derived from the urogenital sinus. Whereas atrophy of the uterus and the mammae hardly ever give rise to complaints, atrophy of the vaginal epithelium is not uncommonly accompanied by kraurotic shrinking of the posterior third of the vagina and the vaginal vault. The vulva also often shows atrophic processes which are manifested as kraurosis of the vulva with vulvitis, leucoplakia or pruritus vulvae. Difficulties in coitus too are not uncommon.

Polyoestriol phosphate was therefore used in the treatment of senile colpitis, vaginal kraurosis, kraurosis of the vulva, pruritus vulvae and menopausal urethrocystitis. The influence of polyoestriol phosphate on the vagina was objectively demonstrated by the increase in the pyknotic and acidophile index (Figs. 1 and 3) with disappearance of leucocytes, by the normalization of the vaginal flora and the vaginal pH, and the occurrence of cervical mucus secretion with increased »spinnbarkeit« and typical palm leaf crystals (Fig. 3). It was thus found that all these biological actions of polyoestriol phosphate are apparently identical with those of pure oestriol.

Although treatment with oestriol compounds alone is not always sufficient to control completely senile colpitis or vulvitis, it has nevertheless been shown to be a valuable basic therapeutic or adjuvant in addition to antibacterial and symptomatic medication; apart from this, it also seems to be of prophylactic value. Thirty of our patients had vaginitis vetularum and were therefore treated with 50 mg polyoestriol phosphate. Additional local application of sulphonamide was given in 12 cases. Healing occurred in all cases after 2-3 weeks. Polyoestriol phosphate was also found to be suitable for the treatment of vaginal

Table 2.

Therapeutic results with polyoestriol phosphate in menopausal genital organic disorders.
Dose: 10-50 mg i. m. in some cases repeated administration.

Diagnosis	Number of patients	Controlled	Improved	Unchanged
Atrophic senile colpitis	31	25	2	4
Vaginal decubital ulcer	2	2	—	—
Vaginal kraurosis and dyspareunia	4	—	4	—
Kraurosis vulvae	6	3	3	—
Pruritus vulvae (4 with vulvitis)	7	5*	1	1
Leucoplakia	2	2	—	—
Urethrocystitis	18	14	3	1

* Relapse after discontinuation of treatment in 3 cases.

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ulcers caused by pessary pressure (2 cases), the healing of which it clearly accelerated, and for the treatment of vaginal kraurosis impeding coitus (4 cases). A very good proliferative and hyperaemic effect was also seen in pretreatment for operation of vaginal fistula due to radiation. Among 7 patients with pruritus vulvae and vulvitis treated for a long time without effect, there were 5 who became asymptomatic for the duration of treatment after administration of 50 mg polyoestriol phosphate. Two patients showed a permanent cure. In the remaining 3 the symptoms recurred as the hormonal effect receded. One woman with haematometra was given polyoestriol phosphate in the hope that the oestrogen would dilate the cervix and thus prevent another occlusion of the cervical canal. No relapse occurred. Nine patients with menopausal urethrocystitis were treated with 20-50 mg polyoestriol phosphate; subjective changes disappeared without any other therapy. The result was signified by cystoscopy, bacteriological examination, sediment findings and determination of the pyknosis-index of the epithelium in the urinary sediment. In another woman, who showed no improvement in her cystitis, a mixed infection with proteus and trichomonas was present which only responded to additional intense chemotherapy.

Effect on the uterine endometrium. - In none of the 79 patients treated did a withdrawal or break-through bleeding occur after polyoestriol phosphate treatment; not even after the administration of up to 250 mg per week. This fact should be ascribed not only to the mild endometrial effect of oestriol, but also to its very prolonged effect.

In a woman with ovarian aplasia but intact uterus, a curettage of the endometrium was performed before and 14 days after administration of 50 mg polyoestriol phosphate. On both occasions the endometrium was completely atrophic. That it could respond to oestrogenic stimulation was shown by the fact that this patient, after administration of 25 mg stilboestrol (crystal implantation), developed a very marked lasting haemorrhage which necessitated a full curettage. Histological examination revealed glandular-cystic hyperplasia. The same patient subsequently also had a haemorrhage after the administration of an androgen-oestrogen depot compound.

It should be pointed out, however, that in some women shortly after the menopause oestriol is apparently capable of causing reactivation of ovarian activity and the recurrence of cyclic haemorrhages. This would seem to indicate a direct influence on the ovaries; probably by stimulating follicle growth to the stage of gonadotrophin dependence.

Effect on the mammary glands. - In the doses used, polyoestriol phosphate seems to exert no or only a very slight proliferative influence on the human mammary gland tissue. None of the patients mentioned changes or complaints in the breast which could be interpreted as a sequel of hormonal medication.

A single injection of 50 mg polyoestriol phosphate in a normal 68-year-old

man caused no subjective changes in the mammary gland tissue or in the mamillae.

Polyoestriol phosphate was also used to interrupt breast-feeding in the case of 5 puerperal women. The results were hardly convincing, but seemed subjectively comparable with those obtained with other oestrogens when the substance was not given later than on the first day of the puerperium.

DISCUSSION

Polyoestriol phosphate was found to be a highly effective oestrogen in the treatment of functional menopausal changes and organic disorders. It possesses apparently all or at least all the essential known biological characteristics of natural oestriol. Its reliable and prolonged action renders it particularly suitable for prolonged specific oestrogen substitution treatment in all forms and for all indications in which an influence on the endometrium, the gonadotrophin secretion and the metabolism is unnecessary or undesirable. On the basis of these characteristics this compound overrules all the objections so far used as arguments against the use of oestrogens after the menopause. In particular, this new hormone ester makes it possible to institute definitely causal and pragmatic therapy in the case of menopausal disorders. It should be emphasized that additional psychotherapy or vegetative sedative medication is seldom necessary during treatment with polyoestriol phosphate. The unusually wide therapeutic range of this compound is worthy of note. A reliable prolonged effect is obtained with doses of 10 mg or more, and the substance is tolerated without side-effects up to a dose of 250 mg/week. The impression was gained that the transition to an undisturbed postmenopausal condition and the final withdrawal of exogenous hormone supply is facilitated and accelerated more markedly by polyoestriol phosphate than by other substances.

Our therapeutic results warrant certain fundamental conclusions: There would seem to be general significance in the fact that no endometrial proliferation occurred after large doses of polyoestriol phosphate, *i.e.* in the presence of a prolonged and relatively high constant oestriol concentration. This fact, in our opinion, definitely refutes the argument that the failure of oestriol to influence the uterine mucosa is chiefly due to a relatively rapid inactivation or excretion of exogenous oestriol, as a result of which tissues with a complex structure and greater differentiation (*e.g.* the endometrium) show no appreciable morphological response to oestriol because of an insufficiently prolonged action.

Consequently, oestriol, even when continually administered over a prolonged period and adapted to physiological conditions, is an oestrogen which, in the human, almost exclusively influences the cervix, vagina and vulva while having

no important effect on the endometrium or on metabolism. Within the limited range of its action, moreover, it is certainly not a poor but indeed a very effective oestrogen. All the findings obtained suggest that its more limited range of action is based on the absence of influence or on a quantitatively less marked influence on certain enzyme systems.

The fact that polyoestriol phosphate, even in large doses, does not reduce the total urinary gonadotrophin secretion although it can completely control all menopausal symptoms, affords further definite proof against the hypothesis of a direct correlation between the extent of the gonadotrophin excretion and the severity of menopausal symptoms. Accepting the current theory that the vegetative symptoms of the menopause are based on a secondary disturbance in the equilibrium of regulatory processes in the diencephalon, we must assume that the quantities of hormone required to ensure diencephalic equilibrium are considerably smaller than the quantities required to influence the gonadotrophin excretion, and that even an oestrogen metabolite (oestriol) suffices for this purpose. Apart from this it is possible that certain of the menopausal symptoms are based on peripheral withdrawal symptoms or disturbances of the hormonal homeostasis in the tissue (and their sequelae), rather than on any other factors, so that the current theories about central regulation must not necessarily be an explanation.

A few remarks should be made, finally, on the treatment of menopausal symptoms with oestrogen-androgen combinations. Like many other authors, we have had favourable experiences with such combinations. The combination of oestradiol with testosterone esters in suitable proportions reduces the side-effects both of oestradiol and of testosterone. Owing to a synergism between the two substances as regards the control of menopausal symptoms, moreover, it is possible to reduce the total dose administered. Nevertheless, breakdown haemorrhage, virilization, increased weight, water retention and untoward psychological effects are sometimes seen. The ratio between oestrogen and androgen in these compounds is generally about 1:20 or higher. Such hormonal mixtures have been described as «physiological» by several authors, because androgens are also found in the female. Since this point of view crops up again and again, however, it should be pointed out that testosterone has hitherto never been demonstrated *in vivo* in females, and that such a high oestrogen-androgen ratio is in no way commensurate with the usually very low or absent increase of androgen excretion after the menopause.

As regards the androgens secreted from the adrenal glands and perhaps also from the ovaries in postmenopausal women, we are chiefly concerned with biologically weaker androgens. The above-mentioned oestrogen-androgen preparations, therefore, cannot be described as physiological, but rather as pharmacologically well-balanced and useful hormone combinations which, as such, nevertheless constitute a compromise. The therapeutic application of such hor-

mones seems best indicated in cases requiring an anabolic effect, an influence on the calcium metabolism (e. g. in osteoporosis) and the gonadotrophin excretion, or a psycho-sexual effect. In such cases this therapy can certainly claim a place among the various specific treatments.

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