p-OXYPROPIOPHENONE IN TREATMENT OF MENOPAUSAL DISORDERS

A STUDY FROM GENERAL PRACTICE

BY

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No reliable agent for provoking the secretion of anterior pituitary follicle-stimulating hormone (F.S.H.) has yet been discovered. To inhibit its secretion, however, we can use oestrogens and androgens; these substances will act as a brake on the anterior pituitary, but they have unwanted and even dangerous effects on the genital organs. For a long time, therefore, a search has been made for a substance which would inhibit pituitary activity without exerting a peripheral stimulating action. Buu-Hoï *et al.* (1950) and Lacassagne *et al.* (1950) succeeded in modifying the chemical structure of synthetic oestrogens in such a way that they lose their peripheral oestrogenic action. The new compound, which they have called 4-hydroxy-propio-phénone, represents chemically one-half of the diethylstilboestrol molecule:

Perrault (1950) introduced this substance into therapy. Several authors (Perrault and Vignalou, 1949; Perrault *et al.*, 1949; Gennes *et al.*, 1950; Husslein, 1951) have reported that, in men, *p*-oxypropiofenone ("popp") tends to inhibit the gonadotrophic secretion of the anterior pituitary, although its oestrogenic activity is less than 1/10,000 to 1/1,000 of that of stilboestrol (Hohlweg, 1949). The potential value of the compound was quickly recognized. Perrault, de Gennes *et al.*, and Husslein used it clinically in conditions in which they suspected excessive anterior pituitary activity, especially where this was associated with hyperfolliculinaemia. They claimed that symptoms could be controlled without undesirable side-effects.

Clinical Trial

It seemed of interest, therefore, to try the compound in cases in which peripheral oestrogenic activity could be readily assessed, control of anterior lobe function seemed

Some Details About the 34 Patients Treated

Age Groups:	45-50	51-55
Last period 2 years ago	10	4
" " 3 or more years ago	12	8
Flashes up to 15 or more daily	16	8
" " " 5 a day maximum	6	4
Vaginal smears, cornification present	20	7
" " " semi-atrophic condition	4	3
Weight normal	11	5
" above normal	7	4
" under "	4	3
" after treatment normal	15 (+4)	6 (+1)
" " above normal	5 (-2)	3 (-1)
" " " under "	3 (-1)	2 (-1)

desirable, and the symptoms could not be ascribed entirely or primarily to deficiency of oestrogens. The substance was therefore submitted to clinical test in 34 women complaining of post-menopausal disturbances, in particular of flushes (see Table). Most of these women had previously received treatment with oestrogens for periods of at least six months without improvement, and they could therefore be regarded as refractory. Before treatment with "popp" (four weeks or more after the last administration of oestrogens) vaginal smears were examined. In 27 cases vaginal cornification was still in evidence, whereas in the remaining seven cases the epithelium showed the typical semi-atrophic appearance with prominent basal and transitional cells. Eleven of these women were overweight, seven were somewhat below normal weight, and none of them showed any complicating systemic disorder. The group as a whole was thus highly selective, being composed of women with varying oestrogen levels but with the common characteristics of frequent flushes refractory to oestrogen medication.

After the initial vaginal smear, treatment was begun. Following Husslein's procedure 0.5 g. of "popp" was given twice daily by mouth and this dosage was maintained until the frequency of flushes was significantly reduced; the dose was then gradually lowered to a maintenance dose of 0.1 g. twice daily for two to three months, after which treatment was stopped. In the cases which did not respond the maintenance dose of 0.1 g. twice daily was also stopped after three months. During treatment vaginal smears were examined periodically.

Results

Effect upon Flushes.—In 31 out of the 34 patients the symptoms were readily controlled by treatment. For instance, in a woman aged 55 who had had no period for two years and had experienced up to 15 flushes daily the attacks were reduced after 11 days' treatment to one or two flushes daily. Continuation of the treatment at the reduced dosage level resulted in reducing their occurrence to one every third or fourth day, and ultimately to one weekly, and this only in the presence of some exciting factor such as agitation. The symptoms did not recur after stopping treatment, and the patient has remained free of symptoms (duration of observation one year). Similar striking results were observed in 30 other patients. In three there was no definite effect. They were sophisticated women who had already seen many physicians and had demanded hormones for their rejuvenating effect (which effect I failed to observe in them).

Effect upon Vaginal Smears.—Cornification persisted throughout treatment in 19 of the 27 women in whom it was present before treatment, nor did cornification appear to be reduced after treatment (six weeks after its termination). In the seven women in whom the smears had shown a more or less atrophic condition of the epithelium, cornification was not restored with the doses used; however, it must be stressed that the smears were taken after the dose had been reduced to 0.1 g. twice daily (equivalent to less than 1/1,000 to 1/100 mg. of stilboestrol).

Toxic Effects.—No toxic effects were observed, and the only side-effect was slight indigestion, which responded rapidly to sodium bicarbonate. Three overweight patients lost some weight. There was no vaginal bleeding either during treatment or after its termination, and no other pelvic changes were noted.

Discussion

The results indicate that in a high proportion of women with menopausal flushes refractory to oestrogens control may be achieved by "popp." (I have lately used "popp" indiscriminately in all cases of menopausal flushes with satisfactory results.) The response can safely be ascribed to medication rather than to any psychological reaction to treatment, since all the women had received treatment "with tablets" before the present course without reporting any response.

It is unlikely that the drug acted by virtue of its peripheral oestrogenic action, not only because animal tests have shown this to be low but also because the doses used failed to evoke vaginal cornification. The drug's apparent efficacy is of particular interest as its use may obviate two dangers which occur in oestrogen therapy. Oestrogens may advance pre-carcinomatous conditions; in addition, they may give rise to an "unphysiological state." In the natural climacteric oestrogens are gradually eliminated from the endocrine concert, and any artificial increase in their level, besides placing an additional burden upon the mechanism of sterol inactivation, tends to aggravate the state of disbalance now recognized to be present in many menopausal disorders (*British Medical Journal*).

In the present series absence of irregular vaginal bleeding was particularly noticeable, as bleeding is a common occurrence in patients receiving oestrogens and is worrying to both patient and physician alike.

While it is clear that the clinical effect of "popp" can hardly be ascribed to its minute oestrogenic action, it is difficult to provide a satisfactory alternative explanation. The control of anterior pituitary secretion which Lacassagne and others claimed for "popp" has not been observed by other authors experimenting on animals (Guillemin, 1951; Money *et al.*, 1951; Paulsen *et al.*, 1951; Schaffenburg *et al.*, 1951). It is of course possible that the substance is sufficiently potent to regulate anterior lobe function during the labile menopausal state. Further clinical experiments, involving the study of the gonadotrophic titre of the urine, are now being planned.

Summary

Thirty-four women with post-menopausal flushes uncontrolled by oestrogens were treated with *para*-oxypropiphenone ("popp"). This drug is related to stilboestrol and is claimed to inhibit pituitary gonadotrophic activity without exerting a peripheral oestrogenic effect.

Of the 34 patients, 31 were completely relieved of their symptoms. There were no toxic effects and no vaginal bleeding such as may be encountered during oestrogen therapy.

Smears taken during and after treatment showed no evidence of vaginal cornification in seven patients with semi-atrophic epithelium. This is interpreted as indicating that "popp" does not exert any appreciable oestrogenic effect.

The mode of action of the drug is discussed.

I am indebted to Messrs. Metochem, of Vienna, VI, Austria, for supplying tablets of "inphysen" (*p*-oxypropiphenone) and to Messrs. Arthur H. Cox & Co., Brighton, for making up such tablets. I am also indebted to Dr. Erica Wachtel for cytological information concerning vaginal smears.

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THE WINTER VOMITING DISEASE

A REPORT FROM GENERAL PRACTICE

BY

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About the end of January, 1953, we began to see a number of patients whose main complaint was sudden and severe vomiting. Measles and the usual feverish colds were prevalent, chickenpox was ending after a mild visitation, influenza due to virus A had just arrived from the South, and there were a surprising number of cases of true lobar pneumonia.

The typical story was of a person going to bed "as right as rain" and waking up in the early hours to vomit energetically, repeatedly, and copiously. This was preceded by brief nausea, accompanied by epigastric pain and some collapse, and followed by a few loose pale stools. The appetite was poor and nausea persisted for a day or two, after which recovery was complete and the patient was ready to accept the diagnosis of "gastric flu" from either his doctor or his friends.

This diagnosis was not confirmed by serological tests from nine patients. No change was found in complement-fixation titre to virus A or B of influenza, as between sera taken early in the disease and after recovery.

Faeces from six patients were not found to contain pathogenic organisms. E.S.R. and white-cell counts were done for four patients seen in the acute stage, and were normal.

It was decided to make a more detailed study, and it soon became apparent from patients whom we examined that friends and relatives had suffered from this disease but had not consulted a doctor. Of 46 patients 11 neither called nor consulted us for their attack of vomiting. It was obvious that the epidemic was far larger than we ever knew.

We were not impressed with the infectivity of the disease, for of our 46 patients 35 were the only sufferers in the household. Frequently there was another member of the family who had had a cold, but this was thought to be coincidental. Only five of our patients had an upper respiratory infection at the time of their attack.

The illness was brief, usually less than two days, though those patients whom we had previously treated for functional dyspepsias took longer to recover. There were six such patients, and their illness lasted six days on an average.

Only one patient had a relapse. Two patients who never vomited are included in the series. Both were seized with diarrhoea at dawn, for no obvious reason, and both lost their appetite for a day or two. One such attack was followed the next day by the typical illness in another member of the household.

It seemed to be impressive that only two patients ascribed their illness to food. Why food, which is blamed for hypertension, rheumatism, and the failing strength of old age, should escape incrimination for a gastro-intestinal upset is a mystery which was not solved. One man ascribed his attack to having just felt the first movement of his first child in his wife's abdomen.

The typical attack is easy to recognize in an epidemic; the less typical or the isolated attack has to be distinguished