

Further Doubts about Oral Contraceptives

The two firms which market the only pure progestational oral contraceptive available in Britain have suspended their products from sale (see letter p. 303). This decision follows the news that in long-term toxicity trials non-carcinomatous nodules had developed in the mammary glands of bitches. The compound in question is chlormadinone acetate (6-chloro-6-dehydro-17 α -acetoxyprogesterone). Being a derivative of 17 α -hydroxyprogesterone, it is much closer in structure to the physiological hormone, progesterone, than the nortestosterone derivatives which form the basis of most oral contraceptives. Women on continuous treatment with small doses (0.5 mg. daily) of chlormadinone acetate do not, as a rule, show an inhibition of ovulation. The contraceptive effect of the hormone is due mainly to its action on the cervical mucus, which becomes thick and resistant to penetration by sperm.

Growing disenchantment with the established oestrogen-progesterone combinations had put a great deal of weight on the low-dose pure progestogen method. Though clinical trials on several other pure progestogens are going on, chlormadinone acetate was the only one available in Britain. There is good evidence that many of the untoward effects, particularly thromboembolic phenomena, of the combination pills are due to the oestrogen component, and pharmaceutical firms were quick to take the hint from the Scowen Committee and to withdraw all combination pills containing more than 50 μ g. of oestrogen. This has only partly met the case. Though it is probable that thromboembolism is dose-related, there is no evidence that it stops altogether below 50 μ g. of ethinyloestradiol or mestranol per day, and most of the nortestosterones are themselves oestrogenic.

In the matter of toxicity there are strong arguments in favour of chlormadinone acetate. It does not affect blood clotting factors¹ and is less hepatotoxic.² The evidence which has now brought it under suspicion is slender. There is a great gap between the effects of long-term treatment with high doses in bitches and the effect of much smaller doses in women. Furthermore, the lesions in the bitches were fibroadenomatous, not carcinomatous, and progesterone itself, under physiological conditions causes proliferation of alveolar tissue in the human.

Chlormadinone acetate is by no means an entirely satisfactory alternative to the oestrogen-nortestosterone combinations. Recent clinical trials³⁻⁵ have brought out two major disadvantages. Firstly, its use is accompanied by a high incidence of menstrual irregularity, and between a quarter and a half of the patients can be expected to withdraw in the first few months. Secondly, chlormadinone acetate is not as reliable a contraceptive as the combined preparations. Various authors give failure rates ranging from 2 to 12 per 100 women years, which is much higher than for the oestrogen containing pills. Chlormadinone acetate is therefore contraindicated in cases in which prevention of pregnancy is a prime consideration.

Where do we go from here? The one way we cannot go is backward. Steroidal contraception, like the motor car, is an aspect of contemporary civilization. In a recent review⁶ it was calculated that the net deaths attributable to steroid contraceptives amounted to 5 women per year in every 800,000. In the same period 35 women in every 800,000

die in road accidents. But nobody suggests that motor cars should be banned. The Food and Drug Administration in the States and the Committee on Safety of Drugs in Britain were consulted before chlormadinone acetate was withdrawn, but neither body has actively banned it; and in view of the tenuous evidence against it it is to be hoped that they will not do so. Other purely progestational compounds may be made available soon, and at the present time the case against chlormadinone acetate is no more damning than that against its alternatives. A review in last month's issue of the *British Medical Bulletin*⁷ points the way clearly. Compared to the risks of pregnancy the existing steroidal contraceptives offer a favourable bargain. That should not deter us from seeking improvements more far-reaching than those likely to result from manipulations of dosage or method of administration or from modest quantitative changes in biological activity by structural rearrangement of traditional molecules.

¹ Poller, L., Thomson, J. M., Tabiowa, A., and Priest, C. M., *British Medical Journal*, 1969, **1**, 554.

² Thompson, R. P. H., and Williams, R., *British Medical Journal*, 1970, **1**, 152.

³ Howard, G., Elstein, M., Blair, M., and Morris, N. F., *Lancet*, 1969, **2**, 24.

⁴ Mears, E., Vessey, M. P., Andolšek, L., and Oven, A., *British Medical Journal*, 1969, **2**, 730.

⁵ Butler C., and Hill, H., *Lancet*, 1969, **1**, 1116.

⁶ Jeffery, J., and Klopper, A. I., *Journal of Reproduction and Fertility*, 1968, *Supplement* **4**, 81.

⁷ Klopper, A., *British Medical Bulletin*, 1970, **26**, 39.

Annual Meeting at Harrogate

As every kind of occupation and technique demands increasingly specialized skill, so communication becomes ever more puzzling. Appropriately, therefore, the B.M.A.'s Annual Scientific Meeting at Harrogate this year begins by devoting two plenary sessions to this problem. Sir John Richardson, who is President-Elect, will open them in his presidential address on "The Problems at Higher Levels of the Health Service." A variety of topics will be discussed in this and the following session next day, including communication between doctor and patient and between doctor and the public. No doubt the lower levels of the Health Service will receive some notice too. And the title of one address, "Non-Verbal Communication," is a reminder that doctors must occasionally stifle the unworthy impulse to try the palm of the hand instead of the power of speech.

The B.M.A.'s Annual Scientific Meetings are in themselves one of the profession's most lively attempts at communication between practitioners in different branches and specialties. At Harrogate experts will speak on many themes of clinical importance today, some particularly topical ones being renal dialysis, pesticides, health of immigrants, subfertility, and drug addiction, while others have been at the forefront of medical practice for generations—depression, rheumatism, varicose veins, and diuretics.

Opportunities for learning something about the latest ideas and discussing them informally, together with the warm welcome awaiting everyone who attends the Annual Meetings, make these occasions enjoyable as well as instructive. From the provisional programme in the *Supplement* this week it will be seen that entertainments, excursions, and dinners will offer enjoyable relaxation. Details about recognition of the scientific sessions for the postgraduate training allowance and seniority payments in the N.H.S. for general practitioners will be published later.