Drug Treatment of Disease

PROGESTOGENS AND THEIR CLINICAL USES: PART II

BY

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CLINICAL USES OF PROGESTOGENS

Threatened and Habitual Abortion

Progestogens have been used mainly in the treatment of threatened and habitual abortion, and of various menstrual disorders. So far as abortion is concerned, it is now pretty clear that the doses commonly administered are unlikely to have had much therapeutic effect, and it is therefore not surprising that widespread doubts have been entertained that progesterone is of any real value in these conditions. Now that the need for far higher doses (in order to simulate physiological conditions) has been recognized, and potent new progestogens have become available, the whole problem needs critical and controlled re-evaluation.

Even so, it is as well to remember that in many cases abortion is undoubtedly due to defect of the ovum and not to insufficiency of progesterone, while in not a few cases of habitual abortion anatomical uterine defects are the responsible factors. Clearly, progestogens, no matter how potent, cannot help these cases. Therefore, though a number of observers have reported encouraging results from the treatment of threatened and habitual abortion with 17- α -hydroxyprogesterone capronate, norethisterone, and enavid, these claims should, it is felt, be received with caution. Much the same kind of results have previously been reported with oestrogens, vitamins, and so forth. The situation is admirably summed up by Goldzieher's (1958) remark that, "Bevis (1951), for example, achieved results on a psychotherapeutic basis which do not differ statistically from those obtained by Javert (1954), who used a most complex and restrictive regime, all of which he claims to be essential."

Progestational Insufficiency

This is a relatively uncommon but quite real cause of infertility, and progestogens are logically indicated in its treatment. Ethisterone, in a dose of 60–80 mg. daily for ten days from the fifteenth day of the cycle, will often produce a full secretory response where previously the premenstrual endometrial biopsy has shown inadequate development. The same result may be obtained with a daily dose of 10–15 mg. of norethisterone.

It has often been supposed that continued treatment with progestogen is necessary, should conception occur in these patients, in order to prevent abortion. In the writer's experience, this has not been the case.

Control of Dysfunctional Uterine Bleeding

Progesterone injections have been used for the treatment of metropathia haemorrhagica (e.g., Scowen, 1944). By means of these, secretory transformation followed by shedding of the hyperplastic endometrium is obtained, and, by regular treatment, regular normal menstrual bleedings can be substituted for the previous prolonged and irregular bleedings.

Greenblatt (1947) proposed the use of combined injections of progesterone and testosterone propionate for the control of prolonged bleeding. The precise dosage is unimportant: 25 mg. of each, given daily for four days, usually arrests the bleeding and is followed, a few days later, by progesterone-withdrawal bleeding, simulating a normal period.

There is now a good deal of evidence that the nortestosterone derivatives are very useful in the treatment of menorrhagia. Bleeding is usually promptly controlled by enavid or norethisterone 10–20 mg. a day, and a few days after treatment is stopped a withdrawal bleeding occurs. Cyclic treatment, for twenty days from the fifth day of the cycle, given for a few months, is often followed by regular spontaneous menstruation when treatment is stopped.

In some cases of regular menorrhagia without organic cause, norethisterone 10 mg. daily, given from the fifteenth day of the cycle for ten days, has appreciably reduced the extent and duration of bleeding. Norethisterone acetate, 3 mg. daily, has been equally effective.

Premenstrual Syndrome

It is commonly supposed that a relative deficiency of progesterone, or excess of oestrogen, is responsible for the premenstrual psychic disturbances, breast discomfort, migraine, water retention, etc., which some women experience. Direct evidence for this view is lacking, but the use of progesterone in treatment has its enthusiastic advocates (e.g., Greene and Dalton, 1953).

Intramuscular injections of 25–100 mg. thrice weekly during the premenstrual fortnight are effective in some but by no means all cases, and implants of up to 500 mg. of progesterone have also been used. Ethisterone has, in general, been disappointing. Good results have been obtained with norethisterone 10–15 mg. daily for ten days from the fifteenth day of the cycle. Enavid has also been used successfully, but in some patients it aggravates rather than relieves the breast discomfort. Furthermore, in some patients treated in this way water retention is increased in spite of a decrease in the subjective symptoms. The addition of chlorothiazide 0.5 g. daily for four or five days at a time usually prevents the water retention.

Dysmenorrhoea

In primary or essential dysmenorrhoea progesterone appears to play a key role, since, if its secretion is prevented by administration of oestrogen so as to inhibit ovulation, painless withdrawal bleedings are obtained. On the other hand progesterone or ethisterone given in the premenstrual phase to those patients usually makes the dysmenorrhoea worse. Nevertheless, it is reported that nor-steroids, given from the fifth day of the cycle for 20 days so as to inhibit ovulation, also abolish dysmenorrhoea (Rock *et al.*,

1957; Savi and Cigada, 1958). Weinberg (1958) reported a 78% successful response using enavid 10 mg. daily from the fifth day of the cycle for twenty days in cases of primary dysmenorrhoea. In secondary dysmenorrhoea the results were appreciably less satisfactory, and when endometriosis was present this regime generally made the dysmenorrhoea worse—so much so that Weinberg feels such a response to be suggestive of endometriosis where previously it had been unsuspected.

Endometriosis

Though progesterone therapy has been tried in the past, the results have been unimpressive, and it has generally been considered to be of little value. We have to bear in mind that the dosages used may well have been insufficient to produce any pharmacological effect. Using enavid, Kistner (Conference on Enavid, 1958) has reported successful results in the treatment of endometriosis in a series of patients. His regime is to start with 10 mg. nightly for two weeks, increasing to 20 mg. for the next two weeks, 30 mg. for the next two weeks, and thereafter 40 mg. nightly for six to nine months. It will be noted that the treatment is continuous. Nausea at the start of therapy was present in 90% of the patients, but it usually disappeared later. In 15% it was severe—to the extent that in some cases treatment had to be discontinued.

It should be emphasized that this regime must be regarded as experimental, but it does seem to offer appreciable hope for some patients who otherwise are doomed to persistent pain and discomfort from this distressing disease.

Oral Contraception

The strikingly successful results of the use of enavid as an oral contraceptive in the Puerto Rico experiment conducted by Pincus and his colleagues (Pincus *et al.*, 1958) are now well known. It is perhaps doubtful if in its ultimately perfected form the contraceptive pill will be a progestogen, but certainly the reported results are so encouraging that renewed interest in the problem has been aroused and further advances are now inevitable. Comment beyond this need not be made here.

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MEDICAL NEW YEAR HONOURS

The names of the following members of the medical profession were included in the New Year Honours List published in the *London Gazette* on January 1.

Baronetcy

Sir JAMES PATERSON ROSS, K.C.V.O., M.S., Hon. LL.D., Hon.F.R.A.C.S., Hon.F.A.C.S. Surgeon to H.M. the Queen. President of the Royal College of Surgeons of England. Professor of Surgery in the University of London.

K.C.M.G.

Sir CHARLES BICKERTON BLACKBURN, O.B.E., M.D., F.R.C.P. Lieutenant-Colonel, R.A.A.M.C. (retired). Chancellor of the University of Sydney. For services to education and medicine.

K.C.V.O.

IVAN WHITESIDE MAGILL, C.V.O., Hon.D.Sc., M.B., B.Ch., F.R.C.S., F.F.A.R.C.S. Honorary Consultant Anaesthetist to Westminster Hospital.

K.B.E. (Civil Division)

JOHN PATRICK WALSH, D.D.Sc., M.D.S., M.B., B.S. Professor in and Dean of the University of Otago Dental School, Dunedin, New Zealand.

Knighthood

ANDREW MOYNIHAN CLAYE, M.D., F.R.C.S. President of the Royal College of Obstetricians and Gynaecologists. Professor of Obstetrics and Gynaecology in the University of Leeds.

DERRICK MELVILLE DUNLOP, M.D., F.R.C.P., F.R.C.P.Ed. Professor of Therapeutics and Clinical Medicine in the University of Edinburgh. Chairman of the British Pharmacopoeia Commission, 1948–58.

EDWARD FORD, O.B.E., M.D., F.R.C.P. Director of the School of Public Health and Tropical Medicine, Commonwealth Department of Health, University of Sydney, New South Wales, Australia.

WILLIAM WALLACE STEWART JOHNSTON, C.B.E., D.S.O., M.C., E.D., M.D., F.R.A.C.P. Consulting Physician to the Royal Melbourne Hospital, Melbourne, Victoria, Australia. In recognition of his work for postgraduate education in medicine.

C.B. (Military Division)

DOUGLAS MURDO BEATON, O.B.E., L.R.C.P.&S.Ed., Surgeon Rear-Admiral. Honorary Physician to the Queen.

FRANK McLEAN RICHARDSON, D.S.O., O.B.E., M.D. Major-General, late R.A.M.C. Honorary Surgeon to the Queen.

THOMAS FREDERICK MACKIE WOODS, O.B.E., M.D., M.R.C.P.I. Major-General, late R.A.M.C. Honorary Physician to the Queen.

C.M.G.

JOHN CAIRNEY, M.D., F.R.A.C.S. Director-General of Health and Inspector-General of Hospitals, New Zealand.

C.B.E. (Military Division)

WILLIAM PERCIVALE STAMM, M.B., B.S., F.R.C.P., D.C.P., D.T.M.&H. Air Commodore, R.A.F. Honorary Surgeon to the Queen.

C.B.E. (Civil Division)

STANLEY ALSTEAD, M.D., F.R.C.P., F.R.C.P.Ed., F.R.F.P.S. Regius Professor of Materia Medica and Therapeutics in the University of Glasgow. Past President, Royal Faculty of Physicians and Surgeons of Glasgow.

LOUIS ABEL CELESTIN, M.C., M.D., D.T.M. For public services in Mauritius.

THOMAS FRANK DAVEY, O.B.E., M.D., M.Sc. Senior Specialist (Leprologist), Eastern Region, Nigeria.

GEORGE LIGHTBODY MONTGOMERY, T.D., M.D., Ph.D., F.R.C.P.Ed., F.R.F.P.S. Professor of Pathology in the University of Edinburgh. For services as chairman of the Scottish Health Services Council.

TIMOTHY JOSEPH O'LEARY, M.B., B.Ch. Senior Flying Doctor in the State of Queensland of the Royal Flying Doctor Service of Australia.