Drug Treatment of Disease

PROGESTOGENS AND THEIR CLINICAL USES: PART I

BY

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PROGESTOGENS

Until recently, progesterone itself and ethisterone (ethynyltestosterone, anhydrohydroxy progesterone, pregneninolone) were the only available progestational agents. Now a whole range of new steroids possessing some, though not necessarily all, of the properties of progesterone, have been produced by the steroid chemists. Some of these substances are considerably more potent than progesterone itself, while others appear to possess special properties of their own. In consequence, a great deal of interest in progestational agents has been reawakened and much research has been carried out, though regrettably little of it in Great Britain. This paper will discuss the more important progestogens from the standpoint of therapeutics.

Progesterone

The intramuscular route is most commonly used for the administration of progesterone, in oily solution, because it is only feebly active by mouth. It has also been administered as vaginal pessaries, but this, too, is an uneconomical method.

Since the average daily output of progesterone during the luteal phase of the menstrual cycle is about 20 mg., it is unlikely that a lower daily dose can have much therapeutic effect. In pregnancy, the daily output is probably 100 to 400 mg., so then daily doses must be of at least 100 or 200 mg. to have much value. These doses are substantially higher than those commonly used in the past, and they are not always well tolerated. Indeed, there have been reports (e.g., Wilkins *et al.*, 1958) of the birth of female pseudohermaphrodites of non-adrenal origin to mothers receiving intensive progesterone therapy during pregnancy, though of course this is a rarity. Progesterone has also been administered in the form of micro-crystals, to produce a depot effect, and as implants.

Progesterone Microcrystals.—Administered by intramuscular injection, they are considered to exert an effect lasting three or four weeks. Some patients experience quite severe pain at the site of injection—which obviously limits their usefulness.

Progesterone Implants.—Progesterone in the form of cylindrical fused pellets has been implanted, mainly in cases of habitual abortion. The pellets must be placed deeply, in muscle, beneath the deep fascia by means of a trocar and cannula, as otherwise they are very likely to extrude. Pellets of 25 and 50 mg. are mostly used; 100-mg. pellets are seldom retained.

17 α -Hydroxyprogesterone Capronate.—Because of the fleeting effects of intramuscular injections of oily solutions of progesterone, usually necessitating frequent, repeated injections, 17 α -hydroxyprogesterone capronate ("primolut-depot") was introduced as a long-acting ester (Junkmann, 1954). This is available in strengths of 65, 125, and 250 mg. per ml. of oily solution, is well

tolerated, and exerts an effect lasting for about seven days. Two intramuscular injections, each of 125 mg., seven days apart can produce a full secretory endometrial response in oestrogen-primed castrate women.

Ethisterone.—Though this has been widely used as an orally-active progestogen for many years, there is no doubt that it is of very low potency, at any rate as judged by the amount required to produce a full secretory endometrial response in oestrogen-primed castrate women. Thus, whereas a daily intramuscular injection of 20 mg. of progesterone for 14 days can produce a late secretory endometrium, the daily oral dose of ethisterone required to produce an equivalent response was found to be 250–300 mg. (Wied and Davis, 1958)—i.e., 12–15 times as much. It is doubtful if progesterone orally (or sublingually) is any less potent than ethisterone by the same route (Bickers, 1949).

The daily doses of ethisterone usually administered (5–100 mg.) can seldom produce anything approaching a full therapeutic effect.

Newer Progestational Steroids

A large number of synthetic steroids, some derivatives of progesterone, others nortestosterone derivatives, have, in recent years, been tested for progestational activity. Much information on these is collected in the report of a Symposium on New Steroid Compounds with Progestational Activity held in 1957 in New York (Rakoff, 1958). From the clinical point of view, interest centres mainly on some of the nortestosterone derivatives, which alone will be considered further here.

Several of the nortestosterone derivatives have considerable progestational activity. In some—for example, 19-nortestosterone, 17 α -methyl-19-nortestosterone (methyloestrenolone), and 17 α -ethyl-19-nortestosterone (norethandrolone)—nitrogen anabolic activity is prominent, and indeed overshadows progestational potency. Androgenic properties are also possessed by these steroids; their potencies are probably very similar, and indeed differ little, if any, from that of methyltestosterone itself (Saunders and Drill, 1956; Overbeck and de Visser, 1956). On the other hand, 17 α -ethynyl-19-nortestosterone (norethisterone, norethindrone ("primolut N")) and norethynodrel ("enavid"), in addition to their progestational activities, also have oestrogenic but not androgenic action; for clinical use as progestogens, therefore, these substances would appear to be preferable. All these nor-steroids appear to be powerful pituitary inhibitors.

Norethisterone Acetate.—This is the latest and most potent oral progestogen developed by Junkmann. Potts (1958) found that a total dose of 10–40 mg. given over ten days to oestrogen-primed castrate women produced a full secretory endometrial response. In women with secondary amenorrhoea, Swyer (1959) found a rather higher dosage necessary (40–80 mg.). Both authors

agree that norethisterone acetate is about three times more potent than norethisterone and that it is well tolerated—even in high doses, up to 18 mg. a day.

Norethynodrel.—This steroid differs chemically from norethisterone only in the presence in the first ring of a double bond in the 5–10 position instead of the 4–5 position. In addition to its marked progestational activity (about equivalent to that of norethisterone), it has inherent weak oestrogenic properties. These are further enhanced by the presence of ethinyloestradiol-3-methyl ether, which occurred in the original preparations as a contaminant. It was found that, when pure norethynodrel was administered, break-through

bleeding was more common than with the contaminated preparation, and therefore in enavid the proportion of ethinyloestradiol-3-methyl ether is deliberately increased so that each tablet contains 0.15 mg. with 9.85 mg. of norethynodrel.

Very extensive investigations have been carried out with enavid, mainly in the United States, and its properties are well known (see Rakoff, 1958; Conference on Enavid, 1958).

Briefly, when administered to normal women in a dose of 10–20 mg. daily, from the fifth day of the cycle, it causes a rapid secretory transformation of the endometrium—within about 5 days—but instead of the glands passing into a typical late secretory appearance they soon undergo what has been termed “exhaustion atrophy.” At the same time the stroma is stimulated and a predecidual appearance is commonly found in biopsies taken on the nineteenth or twentieth day of the cycle. More prolonged treatment produces endometrial appearances similar to those found in mid- and late pregnancy. By means of continuous treatment, at a sufficiently high dose, menstruation can be postponed, apparently indefinitely. On cessation of treatment the usual withdrawal bleeding occurs. In some patients break-through bleeding occurs before treatment is stopped, but doubling the dose usually leads to prompt arrest of bleeding. If two or three successive cycles of treatment have been given, it is usual for ovulation to be somewhat delayed in the next cycle, so that the first spontaneous period may be a week or 10 days late.

Some patients show intolerance to enavid; the proportion so affected has varied with different observers, but on the whole it is probably not less than 20%. Nausea, vomiting, general malaise, dizziness, breast discomfort, and headaches are the symptoms most commonly experienced. In some patients they are mild and soon wear off, especially if the treatment is taken at night; but in others they are sufficiently severe to make continued treatment impossible.

Like the other nor-steroids, enavid appears to have potent pituitary-inhibiting effects. As a consequence, it prevents ovulation, by virtue of which it has proved to be a highly effective oral contraceptive (Pincus *et al.*, 1958). In animal experiments it has not shown pregnancy-maintaining properties (Saunders and Drill, 1958).

(Part II, with list of references, will appear next week.)

A report has recently been issued describing the results of a pilot survey undertaken on 120 people over the age of 65 living mainly in and around London. The work was undertaken as a preliminary aid to planning wider surveys of old age; and, along with other projected studies, it has arisen from several years' discussion between social scientists in many countries. “By an organized attempt,” say the authors, “to investigate the problem of the aged in different Western countries, using identical methods, we hope to rouse interest in a problem common to many nations. We also hope to arouse interest in the variations to be found in different countries. Finally, we hope to prepare the way for more frequent international collaboration, both in carrying out social research and in providing practical help with social problems.” (*The Personal, Family, and Social Circumstances of Old People*, International Association of Gerontology, Social Science Research Committee, European Section, by Peter Townsend and Brian Rees, Department of Social Science, London University.)