CLINICAL EXPERIENCE WITH NORETHISTERONE AND NORETHISTERONE ACETATE

BY

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The discovery of the 19-nortestosterone steroids had made available oral substances for clinical use with a more potent progestational effect than the natural hormone progesterone by injection. Previously, for many years the only oral progestogen was ethisterone—ethinyltestosterone, pregnenolone, or anhydrohydroxy progesterone—which was of low potency and about 12 to 15 times less effective than a daily injection of 20 mg. of progesterone for 14 days in producing a full secretory phase in the endometrium (Wied and Davis, 1958).

The relationship of these norsteroid progestogens to the naturally occurring hormone in the corpus luteum, and their uses, are discussed by Swyer (1959a).

During the last two and a half years experience has been gained with the use of norethisterone ("primolut-N") and more recently with norethisterone acetate.

Norethisterone, when given orally in a total dose of 150–200 mg. over 10 days to oestrogen-primed castrated women, or women with secondary amenorrhoea, has been shown to produce a good secretory response in the endometrium (Hertz, Waite and Thomas, 1956; Ober, 1957; Kaiser, 1957; Pots, 1957; Swyer, 1959b). It is, in fact, more potent by this route than progesterone by daily intramuscular injection.

Norethisterone acetate was developed by Junkmann (1959), and a dose of 10–40 mg. over 10 days given to oestrogen-primed castrated women likewise produced a full secretory-phase endometrium (Pots, 1958). Although Swyer (1959b), found a dose of 40–80 mg. more certain in this respect, both authors agreed that it was about three more times potent than norethisterone in its effect on the secretory transformation of the endometrium. However, both steroids are of equivalent potency in decreasing oestrogen and pregnanediol excretion (Brown, Fotherby, and Loraine, 1960), and when used to suppress or postpone menstruation Swyer, Sebok, and Barns (1960) found that a larger dose of norethisterone acetate was required.

When the present trial started, although the progestational dose of norethisterone was reasonably settled and its value established clinically, it was necessary to determine the smallest doses for the effective control of dysfunctional bleeding, when given over many cycles, in order to reduce the cost of long-term treatment. Little was known of the clinical use and value of norethisterone acetate.

The objectives of the trial were: (1) to confirm the dose of norethisterone acetate which would develop an oestrogen-primed endometrium into a secretory phase; (2) to observe and compare the clinical effects of both steroids in the treatment of primary and secondary amenorrhoea, the control of dysfunctional menstrual bleeding, and, in a smaller group, the control of oligomenorrhoea and dysmenorrhoea; (3) to observe the effect of norethisterone acetate on the postponement of menstruation.

Material and Method

The 90 patients in this series were attending the hospital out-patient department or were seen in private practice, and had mostly been referred from gynaecologists. Thirty-four were given only norethisterone, 21 were given only norethisterone acetate, and the remaining 35 had been treated with both steroids at different times. Norethisterone was available in tablets of 5 mg., and norethisterone acetate in tablets of 2 mg.

A series of patients with long-standing amenorrhoea were given oestrogens for 18 days, using tablets of ethinylloestradiol, 0.1 mg. daily, "premarin," 1.25 mg. t.d.s., or intramuscular injections of oestradiol monobenzoate, 10 mg. every four days, according to their individual tolerance. After this, norethisterone acetate was given in doses of 2, 4, or 6 mg. daily for 10 days. In a smaller number of similar cases norethisterone was given in doses of 10–15 mg. daily for 6–10 days after oestrogen priming.

Endometrial biopsies were then carried out with the use of a Sharman curette, and one or two small strips were taken from the upper portion of the anterior wall of the uterus. These biopsies were taken between the 25th and 32nd days of the cycle as near as possible to the last day of progestogen treatment.

Most of the biopsy material was fixed in Bouin's solution at once, except for some which was put into absolute alcohol as suggested by Pots (1959, personal communication). However, this method was abandoned owing to the degree of desiccation with distortion of the endometrium. Sections were stained with haematoxylin and eosin.

Interpretation of the degrees of secretory activity of the endometrium was based on descriptions by Rock and Bartlett (1937) and Swyer (1959c), taking into account study of the glands, nuclei, secretory activity, and also the state of the stroma, the tortuosity of the arterioles, and presence of venous lakes.

Most of the married patients with dysfunctional menstruation, with irregular or regular heavy or prolonged loss, had been previously curetted, but in some of the younger patients biopsies were not conducted to confirm a presumptive diagnosis of metropathia from the typical history. Some cases with menorrhagia were found to have cervical erosions or polyps or thought to have small fibroids, and were treated as a temporary measure before operation.

In a number of cases of menometrorrhagia with proved metropathia biopsies were made usually after 10 days' treatment with norethisterone acetate in different doses, and in some cases two or three biopsies were done in the same patient at intervals after various doses.

As a method of treatment it was usual to give norethisterone for 3 to 10 days from the 24th or the 18th day after the onset of a previous period; but with norethisterone acetate the dose was given as a rule for the last 10 days of the cycle.

Another scheme adopted in some cases of menorrhagia and dysmenorrhoea was that described by Swyer (1960) from the 5th to the 25th day, although this is more expensive. In a few cases norethisterone acetate has been given for 20 to 30 days after the 11th to the 23rd day to observe the effect on postponement of menstruation (Greenblatt, 1958).

In patients with primary amenorrhoea norethisterone was given cyclically in conjunction with oral oestrogens or implanted oestradiol tablets.

Both steroids were used in cases of secondary amenorrhoea, usually after oestrogen priming in the first half of the cycle, or were given together for 6 to 14 days cyclically. The number of patients, the cycles treated, and the indications are shown for both norethisterone and norethisterone acetate (Table I).

TABLE I.—Number of Patients Treated

Norethisterone			Norethisterone Acetate		
	No. of Patients	No. of Cycles		No. of Patients	No. of Cycles
Menorrhagia ..	26	101	Menorrhagia ..	38	205
Primary amenorrhoea ..	7	76	Secondary amenorrhoea ..	10	22
Secondary amenorrhoea ..	25	320	Others ..	8	20
Oligomenorrhoea ..	5	23			
Dysmenorrhoea ..	6	15			
Total ..	69	535	Total ..	56	247

Results

Amenorrhoea

Norethisterone was given to 25 patients in 320 cycles for secondary amenorrhoea, and to 7 patients in 76 cycles for primary amenorrhoea, with satisfactory regular cyclical rhythm. After an oestradiol implant cyclical norethisterone treatment ensured a regular shedding of the endometrium.

Three of the cases of secondary amenorrhoea were shown to have a slow-growing intrasellar tumour without any evidence of pressure on the optic chiasma, and with no other evidence of endocrine dysfunction except the failure of pituitary ovarian rhythm. In these, vaginal smears showed some oestrogenic activity, and cyclical bleeding occurred after the administration of norethisterone alone without any oestrogens.

Norethisterone acetate was given to only 10 patients with secondary amenorrhoea for 22 cycles. Various doses were used after the initial oestrogen priming, and biopsies were conducted in 12 of these cycles. Some of these cases were also given norethisterone to compare their secretory effect on the endometrium.

In these 12 biopsies after norethisterone acetate a secretory phase was observed in the endometrium in all of them except one. This varied in degree from minimal or early after doses of 20 mg. in 10 days (Figs. 1, 2, and 3) to moderate or full after total doses of 60 mg. The one exception was found in a patient who was unable

to take ethinylloestradiol 0.1 mg. daily, and was given only two injections of oestradiol monobenzoate 10 mg. followed by 40 mg. of norethisterone acetate (Table II).

FIG. 1.—Case 9 (T). Secondary amenorrhoea. Norethisterone acetate 20 mg. in 10 days. Biopsy 28th day. ($\times 94$.) Early secretory phase.

FIG. 2.—Case 1 (Ar). Secondary amenorrhoea. Norethisterone acetate 40 mg. in 10 days. Biopsy 28th day. ($\times 94$.) Early secretory activity with nuclear migration and zona pellucida.

FIG. 3.—Case 7 (Lo). Secondary amenorrhoea. Norethisterone acetate 60 mg. in 10 days. Biopsy 28th day. ($\times 94$.) Secretory phase.

TABLE II.—Cases of Secondary Amenorrhoea

Case No.	Dose (mg.)	Biopsy Day	Result
<i>Norethisterone Acetate</i>			
1. Ar	40	28	Early secretory; nuclear migration; zona pellucida
2. Au	60	30	Secretory
3. H	60	28	
4. H	40	32	No secretory phase. Inadequate priming with oestradiol benzoate
5. H	20	31	Slight secretory with active stromal reaction
6. Lo	40	30	Moderate secretory
7. Lo	60	28	Secretory
8. P	32	25	Early secretory with nuclear migration
9. T	20	28	Early secretory
10. T	40	28	Secretory with active stromal reaction
11. W	60	27	Moderate secretory
12. W	20	28	Minimal secretory; nuclear migration; stromal reaction
<i>Norethisterone</i>			
13. Ar	50	28	No secretory activity
14. Lo	100	28	Secretory
15. P	100	28	Early secretory
16. S	120	30	Moderate ..

Only four patients were biopsied after norethisterone (Table II). Some degree of secretory activity was seen with 100 mg. In one woman, aged 29, a comparable secretory-phase endometrium was seen after 100 mg. of norethisterone and 40 mg. of norethisterone acetate. Previous treatment had been given before both of these cycles when the biopsy was taken.

Menometrorrhagia

There were 18 cases of metropathia treated with norethisterone acetate: of these, six were not proved by biopsy but had a typical history. Nine of the proved cases were given various doses over a 10-day period, and then had biopsies on the last day of treatment. The results are shown in Table III. It will be seen that in 18 out of the 20 cycles investigated treatment was given for 10 days prior to the biopsy as near as possible to the 28th day of the cycle, and with doses varying from 20 to 180 mg. a secretory change was found in all, although it was early or minimal in a few (Figs. 4, 5, and 6). Two biopsies were preceded by treatment with 2 and 6 mg. daily for 20 days from the 5th to the 25th day, and in both these endometria the glands were small and undeveloped, suggesting that ovulation had been suppressed (Fig. 7).

Bleeding immediately after this series of biopsies was normal except in three patients who had a heavy loss from a secretory-phase endometrium.

TABLE III.—Cases of Metropathia Treated with Norethisterone Acetate

Name	Dose (mg.)	Cycle Days	Biopsy Day	Result	Cycle Length	Loss
Ab	60	Last 10	26	Secretory; oedema; pseudodecidua	29	N
	40	" "	31	Secretory with bleeding	32	N
Co	40	" "	28	Secretory	28	N
	60	" "	23	"	24	Heavy
El	180	" "	25	"	27	N
	40	" "	25	"	25	N
Fo	20	" "	25	Early secretory	25	N
	120	" "	29	Secretory	30	Heavy
Ha	40	" "	32	Early secretory	33	N
	60	" "	30	"	32	N
Sm	40	" "	28	"	29	N
	120	5-25	25	Small undeveloped glands	26	N
Wa	60	Last 10	26	Secretory; oedema; pseudodecidua	26	Scanty
Je	60	" "	36	Secretory	38	N
	60	" "	30	Early secretory	32	N
Kr	40	" "	26	"	28	N
	20	" "	25	Minimal secretory	26	N
No	60	" "	34	Early secretory; oedema	36	Scanty
	40	5-25	32	Small undeveloped glands	33	Spots
Pi	60	Last 10	40	Early secretory	41	Heavy

FIG. 4.—Case El. Metropathia. Norethisterone acetate 20 mg. in 10 days. Biopsy on 25th day. ($\times 94$.) Early secretory activity.

FIG. 6.—Case Ab. Metropathia. Norethisterone acetate 60 mg. in 10 days. Biopsy on 26th day. ($\times 94$.) Full secretory change with arterial tortuosity.

FIG. 5.—Case Sm. Metropathia. Norethisterone acetate 60 mg. in 10 days. Biopsy on 30th day. ($\times 94$.) Secretory activity with prominent arterioles.

FIG. 7.—Case Sm. Metropathia. Norethisterone acetate 120 mg. from 5 to 25 days. Biopsy on 25th day. ($\times 94$.) Small inactive glands.

In the whole group of 38 cases of menometrorrhagia treated with norethisterone acetate, control of menstrual loss was obtained in 75% of 205 cycles, but the dose necessary to gain control varied from 20 to 320 mg. per cycle. The generally adopted dose was 60 mg. in the last 10 days. Fig. 8 shows the relationship of controlled to uncontrolled cycles for each dose level used. Fig. 9 shows the onset of bleeding relative to the end of treatment expressed as a percentage of treated cycles.

With norethisterone 26 patients were treated for 101 cycles with satisfactory control of menstrual loss in 83%. An average dose used was 90–150 mg., but control was sometimes achieved with as little as 10 mg. for four days or 15 mg. for three days after several cycles had been treated. Fig. 10 shows the relationship of controlled to uncontrolled cycles at each dose level.

FIG. 8.—Treatment of menometrorrhagia with norethisterone acetate. White columns=controlled cycles; black columns=uncontrolled cycles.

FIG. 9.—Onset of bleeding relative to completion of course of norethisterone acetate in cases of menometrorrhagia. Showing percentage of treated cycles.

FIG. 10.—Treatment of menometrorrhagia with norethisterone. White columns=controlled cycles; black columns=uncontrolled cycles.

Haemostasis.—Some patients were first treated for very heavy and prolonged flooding, and in six such cases bleeding stopped after about 24–48 hours, and a normal withdrawal bleed occurred after finishing treatment. Cyclical treatment with either steroid was then continued.

Two patients with regular menorrhagia and one with metrorrhagia due to metropathia became pregnant during cyclical treatment with norethisterone acetate, and two of these, one in each group, gave birth to normal babies. The patient with metropathia had been trying to have a child for five years before treatment started.

The rest of the cases treated in this trial were made up of dysmenorrhoea, oligomenorrhoea, endometriosis, premenstrual tension, or premenstrual asthma, but the numbers in each group and the cycles treated are too few for a satisfactory clinical assessment of the value of the treatment. In several cases in this series treated during the last 10 days of the cycle painful menstruation was noted where it was normally unusual.

On 11 occasions treatment with norethisterone acetate was given from the 10th to the 23rd day of the cycle for 20 to 30 days, to determine whether menstruation could be postponed. This was successful only five times, when the cycle was longer than normal. In all except two a scanty breakthrough bleeding occurred before completion of the course (Table IV).

TABLE IV.—Attempt to Postpone Menses by Norethisterone Acetate

Patient	Starting	Dose	Result
		mg. days	
Mo	19th day.	4 × 30	Failed. Scanty bleed 31st day
Ma	21st "	6 × 28	" Bled 29th day
"	18th "	12 × 28	Postponed. Bled 34th day
Da	17th "	6 × 30	" to 49th day
Wi	18th "	6 × 20	Scanty bleed on 29th day
"	10th "	4 × 20	" loss on 24th "
Kr	21st "	4 × 20	Postponed to 42nd day
Wa	21st "	6 × 20	Scanty bleed 30th day
Wi	18th "	16 × 20	Dribbling bleed 30th day
Bu	21st "	8 × 30	Postponed to 37 days
El	23rd "	4 × 30	" " 50 "

Discussion

The results of these trials of norethisterone acetate on the oestrogen-primed endometria of cases of secondary amenorrhoea tend to confirm Swyer's (1959b) findings that an adequate secretory dose is slightly higher than that reported by Pots (1958). Although some evidence of secretory changes were seen with 20 mg., even 60 mg. in 10 days did not always produce a full secretory phase. Whereas in the few patients who had biopsies after treatment with norethisterone 100 mg. seemed to be a satisfactory transformation dose, which agrees with Pots's (1958) findings, a similar degree of transformation would appear to be 40–60 mg. of the acetate: so that the ratio is just about 2½–2:1. The difference in potency is probably too small to justify its introduction as an additional progestogen for clinical use, as norethisterone is already being successfully employed, with all its advantages over intramuscular progestogenic treatment. In the routine treatment of amenorrhoeas, both primary and secondary, or for long or irregular cycles with normal loss, both steroids are equally effective.

In dysfunctional heavy or prolonged menstruation, particularly when this is due to metropathia, both substances are again equally useful for controlling menstrual loss in about 75–83% of cases, which agrees well with the findings of Bishop and de Almeida (1960) for norethisterone.

Both steroids will regularize the cycles if an adequate dose has been given, and in the majority of cycles treated bleeding started within four days of finishing a course of treatment.

The endometrium of proved cases of metropathia was shown to have some secretory transformation even with 20 mg. of norethisterone acetate in 10 days, and subsequent bleeding was normal after biopsy in the majority, although occasionally a heavy menstrual loss followed a proved secretory transformation. A cyclical dose of 40–60 mg. of norethisterone acetate in 10 days or 90–120 mg. of norethisterone in the last phase of the cycle is generally satisfactory in producing regular normal bleeding, and is preferable, particularly in women who desire pregnancy. It also requires less steroid than if given from the 5th to the 25th day, and with the latter regime sometimes a breakthrough bleeding occurs before the patient has finished the 20 days' treatment, thus altering the cyclical rhythm.

A number of these patients treated for menorrhagia with cyclical progestogens at the end of the cycle complained of dysmenorrhoea, but, as Bishop and de Almeida (1960) found in their series, this was not severe enough to make them unwilling to continue treatment if the loss was successfully controlled.

Swyer's (1960) method of giving treatment for 20 days from the 5th to the 25th day of the cycle is more expensive, but has the advantage of inhibiting ovulation and so preventing dysmenorrhoea and acting as an oral contraceptive.

The number of cycles in this series when norethisterone acetate was given deliberately to attempt to postpone menstruation is small, partly because the quantity of this steroid available was not unlimited; but doses of up to 16 mg. daily for 20 to 30 days cannot be relied upon for this purpose. In this respect Swyer, Sebok, and Barns (1960) have shown that norethisterone acetate is less potent than norethisterone, of which 20–30 mg. daily will delay a normal menstrual period and induce a pseudo-pregnancy of as much as seven months (Greenblatt and Jungck, 1958).

Summary

During the last two and a half years norethisterone and more recently norethisterone acetate have been used in a total series of 90 women. Some were given either the one or the other, and some were treated with both steroids at different times. The conditions treated were primary and secondary amenorrhoea, oligomenorrhoea, some dysmenorrhoea, and a larger series of cases of menometrorrhagia.

For secondary amenorrhoea both steroids were equally effective when used with oestrogens to induce menstruation.

An assessment of the secretory transitional dose of norethisterone acetate in oestrogen-primed married women with secondary amenorrhoea was made, and the effect of similar doses on the endometrium of women suffering from metropathia was investigated.

The control of prolonged excessive regular or irregular menstruation was about equally effective with norethisterone and norethisterone acetate (83:75%), but, weight for weight, the latter was about twice as potent.

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TREATMENT OF URINARY INFECTIONS WITH CYCLOSERINE

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Infections of the urinary tract constitute one of the most difficult groups of infection encountered in a general hospital at the present time. Many are complicated by some underlying anatomical abnormality or neurological condition, and while infections with sensitive organisms, such as the coliforms, tend to respond readily to routine therapy, an increasing number are being caused by organisms resistant to the usual chemotherapeutic agents. The causative organism is often a *Proteus*, *Ps. pyocyanea*, or paracolon which tend to be resistant to the sulphonamides, nitrofurantoin, chloramphenicol, and tetracycline. These cases have consequently become a major problem, and the introduction of a new effective antibiotic would be an important development.

Cycloserine, an antibiotic prepared from *Str. orchidaceus*, was originally used for the treatment of tuberculosis. It has, however, a wide antibacterial spectrum, and, though it has a relatively low grade of *in vitro* activity, it has been found to produce concentrations in the urine which may be effective against some resistant organisms responsible for urinary infections (Welch *et al.*, 1955). Although toxic manifestations were a serious problem when cycloserine was used for the treatment of tuberculosis, only minimal side-effects were observed with the smaller doses required for urinary infections. Moreover, encouraging results were given in some patients with chronic resistant infections (Herrold *et al.*, 1955).

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