intermittently, so as to allow endometrial regression from time to time, but there is not infrequently a problem with the recrudescence of symptoms during the intervals. Some workers give oestrogens continuously in conjunction with periodic courses of a progestogen. Everyone is agreed that some kind of regular screening is required for all patients receiving oestrogens, but what kind of examinations and how often they should be done are not agreed. The occurrence and regularity of uterine bleeding have been shown by Whitehead *et al.* (1977) not to be reliable guides to endometrial histology. These findings have relevance to the question of when curettage should be used.

Controversy has largely shifted away from the treatment of the climacteric syndrome to long-term prophylactic treatment. Both its indications and its safety are debated. Evidence that there are degenerative processes specifically attributable to the loss of oestrogens, and that oestrogen treatment can retard or even reverse some of these processes, is too well known to need repetition here, but there is uncertainty about the percentage of women who would benefit from prophylactic oestrogens after the menopause. At present, estimates vary widely.

The chief controversy about long-term use at present concerns a possible risk of cancer. The W.H.O.'s international agency for research on cancer in its 1974 volume on the evaluation of the carcinogenic risk of sex hormones to man, after reviewing several follow-up studies of women receiving long-term treatment with oestrogens, concluded, despite some reservations about methodological weaknesses: 'it cannot be denied that the incidence of cancer of the breast and of the reproductive system in the studies detailed . . . appears to be low. Certainly they do not provide any evidence of a carcinogenic risk'. The long-term study with the best follow-up record – 100% – that of Burch, Byrd and Vaughan (1976), showed no increase in the mortality of any disease. However, all Burch's patients had been hysterectomized. Some recent retrospective studies have suggested the possibility of an increased incidence of endometrial carcinoma.

The result has been to focus attention on combinations of an oestrogen with a progestogen. It appears that at present only about 10% of oestrogens are given in combinations with progestogens, but it is likely that the use of progestogens will rapidly grow far beyond this figure, and may well become the norm. The purpose of this workshop is to assess the significance of the progestogen component in terms of the endometrium, and also to consider what other roles it may play.

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The physiological action of progesterone and the pharmacological effects of progestogens – a short review

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Summary

Substances described as progestogens differ greatly in their additional properties, which determine the limitations of their clinical use. The extrapolation of animal assays to human use requires caution, since synergism with oestrogens, which is usually necessary, shows widely-differing species-specific ratios. In other ratios, progestogens are often antagonistic to oestrogens.

STEROIDS called 'progestogens' have at least one property in common – they are all able to cause secretory transformation of an endometrium that has been proliferated by oestrogens. Although 'progestogen' is derived from the Latin word 'gestatio' – pregnancy, not all progestogens are able to maintain pregnancy in animals after castration.

It is difficult to define progesterone and synthetic progestogens concisely in terms of their respective physiological and pharmacological effects, since virtually none of the effects is exclusive to progesterone or progestogens (for review see Junkmann, 1968, 1969; Tausk, 1971, 1972). Progesterone becomes effective only after oestrogen-priming has occurred. Oestrogens have mainly growth-stimulating effects, while the action of progestogens is directed more towards modification and differentiation. However, some stimulation of growth must be present before progesterone can become effective. This is true for organs such as the uterus, the vagina and the mammary gland.

Practically all processes of female reproduction are regulated by progesterone and oestrogens acting together. It is important to know that progesterone-oestrogen synergism occurs only when the ratio of oestrogen to progesterone and the time-sequence of their interaction are optimal (Neumann & Elger, 1972). Since this is a particularly important aspect, it will be considered again below.

TABLE 1. Some specific activities of progesterone

Organ/function	Influence of progesterone
Endometrium	Transformation, growth of the uterine glands, induction of decidual reaction under certain conditions
Myometrium	Reduced contractility
Cervical mucus	Increase in consistence, spinnbarkeit, amount reduced
Vagina	Lowering of the karyopyknotic index
Pregnancy	Maintenance of pregnancy
Mammary gland	Stimulation of tubulo-alveolar growth in most mammals (synergism with oestrogens and prolactin)
Pituitary/hypothalamic system	Inhibition of gonadotrophin secretion, under certain conditions positive feedback on LH-secretion
Sperm capacitation	Inhibition
Metabolism of sperm in the uterus	Lowering effect
Egg transport	Inconsistent effect (species differences)
Tubular secretion	Decrease
Libido	Decrease of libido in most species
Body temperature	Increase

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A number of physiological effects of progesterone is listed in Table 1. It is by no means complete. In addition to its specific effects on sexual organs, progesterone has a number of extragenital effects. It is, for example, possible to keep adrenalectomized animals alive with progesterone. There is, after all, a certain structural similarity to corticoids, which likewise belong to the group of steroids with 21 carbon atoms. At extremely high doses, progesterone also has an anaesthetic effect.

Pharmacology of progestogens

The synthetic progestogens are derived from testosterone, 19-nor-testosterone or hydroxyprogesterone. Figure 1 shows the structural formulae of some 19-nor-testosterone derivatives, while the hydroxyprogesterone derivatives are shown in Fig. 2. The 19-nor-testosterone derivatives are distinguished by an alkyl group at carbon atom 17. This alkyl group prevents rapid metabolism in the liver and is essential for strong oral activity. The alkyl or halogen substitutions at carbon atom 6 have a similar function in the case of the hydroxyprogesterone derivatives.

The term 'progestogen' is sometimes no more than a convenient partial description, since there are some synthetic progestogens which, at least on the basis of their properties and effects in many animal species, could just as easily be classed as androgens or oestrogens. The individual synthetic progestogens have varying spectra of effects, none of which corresponds exactly with that of progesterone (Hammerstein, 1971).

TABLE 2. Possible activities of progestogens

Progestational	e.g.	Transformation of the endometrium
Oestrogenic	e.g.	Positive Allen-Doisy assay
Androgenic	e.g.	Stimulation of prostate and seminal vesicle growth in castrated rodents
Antioestrogenic	e.g.	Inhibition of oestrogen-induced uterine growth
Antiandrogenic	e.g.	Inhibition of androgen-induced growth of prostate and seminal vesicle in castrated rodents
Antigonadotrophic	e.g.	Inhibition of ovulation
Glucocorticoid-like activity	e.g.	Inhibition of ACTH secretion and adrenal atrophy
ACTH stimulation	e.g.	Increased glucocorticoid secretion, increase of transcortin
Virilization of ♀ fetuses		(Androgenic)
Feminization of ♂ fetuses		(Antiandrogenic)

A number of possible effects of progestogens are listed in Table 2. Figure 3 presents the effects of a number of synthetic progestogens and of progesterone. This very simplified figure ignores the relative potencies of these individual effects.

As regards the chemical structure, there are three different groups, and it can be seen at a glance that

Chemistry of progestogens

I Testosterone derivatives

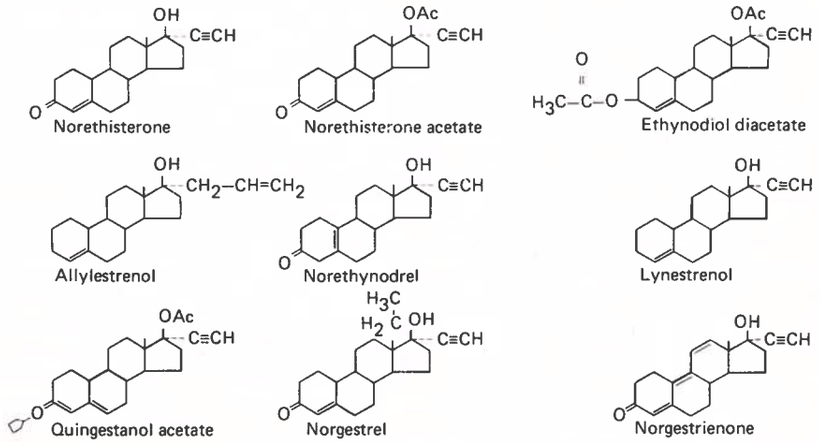


FIG. 1. Structure of progestogens – 19-nor-testosterone derivatives.

FIG. 3. Activity spectrum of some progestogens

Compound	Endometrial transformation	Oestrogenic	Androgenic	Anti-oestrogenic	Anti-androgenic	Antigona-dotrophic	Glucocorticoid-like activity	ACTH-stimulation	Virilization	Feminization	Chemical classification
Progesterone	+	–	–	+	±	+	+	–	–	–	
Norethisterone	+	+	+	+	–	+	–	+	+	–	19-nortestosterone derivatives
Lynestrenol	+	+	+	+	–	+	–	+	+	–	
Levonorgestrel	+	–	+	+	–	+	–	–	+	±	
Norethynodrel	±	+	±	–	–	+	–	+	±	+	
Medroxyprogesterone ac.	+	–	–	+	±	+	+	–	–	+	Alkylated and halogenated acetoxyprogesterone derivatives
Chlormadinone acetate	+	–	–	+	+	+	+	–	–	+	
Cyproterone acetate	+	–	–	+	+	+	+	–	–	+	
Megestrol acetate	+	–	–	+	+	+	+	–	–	+	
Hydroxyprogesterone caproate*	+	–	–	+	–	+	–	–	–	–	"Pure" progestogens (no androgenic and oestrogenic activity)
Gestonorone caproate*	+	–	–	+	–	+	–	–	–	–	

* = depot progestogens

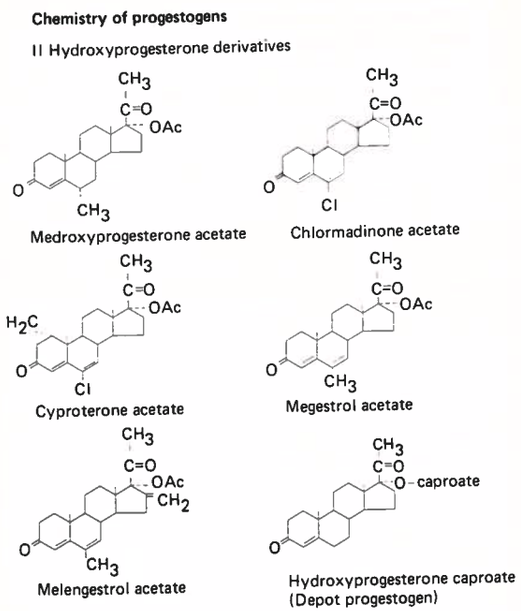


FIG. 2. Structure of progestogens – 11-hydroxyprogesterone derivatives.

particular effects are dependent on certain structures, although there are exceptions to these 'rules'. For instance, all 19-nor-testosterone derivatives have androgenic properties – with the exception of norethynodrel – and oestrogenic activities – with the exception of levonorgestrel. None of these progestogens has any glucocorticoid-like properties. The progestogens with oestrogenic activity lead rather to ACTH-stimulation – again with the exception of levonorgestrel. In the case of norethynodrel, the oestrogenic properties are so pronounced that this compound could almost be classed as an oestrogen. This oestrogenic activity is seen in the human, e.g. by an increase of transcortin (Schwartz and Hammerstein, 1974).

The alkylated or halogenated acetoxyprogesterone derivatives are distinguished by the absence of androgenic and oestrogenic effects. Megestrol acetate, chlormadinone acetate and cyproterone acetate have antiandrogenic properties, which are most pronounced in the case of cyproterone acetate (Neumann and Steinbeck, 1974).

All the progestogens of this group listed here also have certain glucocorticoid-like effects, which can become manifest clinically at extremely high dosage, e.g. in the therapy of precocious puberty with cyproterone acetate at doses of more than 100 mg/m² (Girard and Baumann, 1975; von Muhlendahl, 1977; Camanni, Massara and Molinatti, 1963; Mathews, Abrams and Morishima, 1970; Sadeghi-Nejad, Kaplan and Grumbach, 1971). Because of their antiandrogenic effects, chloramdinone acetate, megestrol acetate and cyproterone acetate all have the potential of feminizing male foetuses (Neumann and Steinbeck, 1974; Neumann *et al.*, 1970).

Medroxyprogesterone acetate, on the other hand, has virilizing properties, although it is not androgenic in the classical tests (Neumann, Gräf and Elger, 1974).

The last two progestogens listed in Fig. 3 are hydroxyprogesterone esters with a depot effect. They must be classed as so-called 'pure' progestogens, since they have neither androgenic nor oestrogenic properties. These progestogens also have no apparent influence on foetal development (Neumann, Kramer and Raspé, 1968).

As already mentioned, clinical use is determined largely by the spectrum of effects of the individual progestogens. A substance with strong antigonadotrophic and strong antioestrogenic effects is to be preferred as the progestogen component for a hormonal contraceptive. Such a compound is said to contribute to the inhibition of ovulation and to induce the known changes in the cervical mucus that render sperm ascent difficult (minipill effect).

An oral contraceptive containing cyproterone acetate or chlormadinone acetate is to be preferred for women predisposed to acne, seborrhoea or mild hirsutism, since the antiandrogenic effect represents an advantage in such cases. Such a preparation can be classed as a therapeutic formulation, in which case the contraceptive effect can be regarded as a side effect. In a double-blind study, treatment with a combined preparation consisting of 2 mg cyproterone acetate plus 50 μg ethinyl oestradiol led to an improvement and healing of the condition in 60% to 90% of the cases, depending on the symptoms. In this study, the contraceptive formulation containing cyproterone acetate was far superior to a classical contraceptive (Neogynon®) with respect to its therapeutic effect on the acne and seborrhoea (Lachnit and Kaufmann, 1977).

Only so-called 'pure' progestogens, which have no androgenic or oestrogenic effects, can be considered for use in disturbances of pregnancy. Clinical experience indicates that progestogens with androgenic effects – in combination with an oestrogen – achieve particularly favourable results in the therapy of the female climacteric. Women with depression are said to respond especially well to such progestogens.

These few examples are sufficient to show that the indication is dependent on the spectrum of activities and that selective use of progestogens is not always simple for the physician.

TABLE 3. Potency of some progestogens in the Clauberg assay in rabbits and in the Kaufmann assay (endometrial transformation in castrated women or in climacteric patients).

Progestogen	Clauberg assay, threshold dose in mg/animal p.o.	subc. (i.m.)	Kaufmann assay effective dose/cycle in mg
Progesterone	>10	~0·5	~200 (i.m.)
Norethisterone	0·1–0·3	≤0·1	100–150 (p.o.)
Norethisterone acetate	0·03–0·1	0·03–0·1	30–60 (p.o.)
Norethisterone acetate (micronized)	—	—	12–14 (p.o.)
Norgestrel	0·03–0·1	0·03	~12 (p.o.)
Levonorgestrel	0·03	0·03–0·01	~6 (p.o.)
Levonorgestrel (micronized)	—	—	~2·5 (p.o.)
Norethynodrel	>0·3	0·3	150–200 (p.o.)
Lynoestrenol	0·1–0·3	0·1–0·3	35–70 (p.o.)
Chlormadinone acetate	~0·01	0·01	20–30 (p.o.)
Cyproterone acetate	~0·003	0·003–0·01	≤20 (p.o.)
Medroxyprogesterone acetate	0·01–0·03	0·01–0·03	40–70 (p.o.)
Megestrol acetate	0·03	0·01–0·03	35–50 (p.o.)

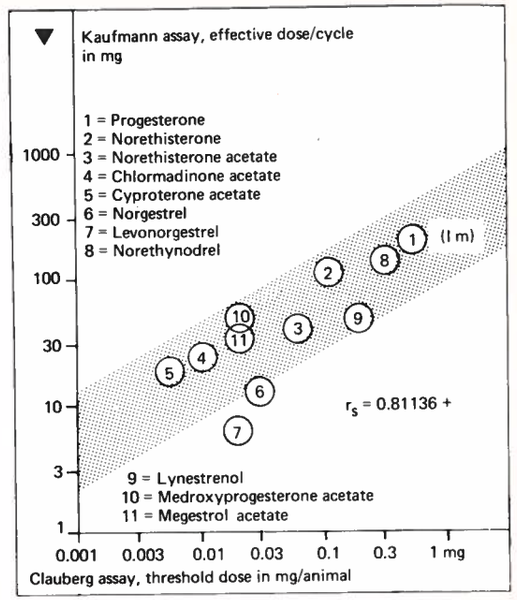


FIG. 4. Potency of some progestogens in the subcutaneous Clauberg assay in rabbits and in the oral Kaufmann assay.

Potency of synthetic progestogens (Neumann *et al.*, 1977)

Table 3 shows the potency of some progestogens in the Kaufmann test (endometrial transformation in oestrogen-primed castrated or climacteric women) and in the highly comparable Clauberg test in the rabbit. Figures 4 and 5 show very nicely that good correlations exist between the two test models. In women, the most effective progestogens are DL-norgestrel and levonorgestrel. They are somewhat more effective than one would expect on the basis of their potency in the Clauberg assay.

In a test in mice, we use an increase in the sialic acid content of the vagina of oestrogen-primed animals as the parameter for an anti-oestrogenic effect (Nishino and Neumann, 1974). Comparable with this parameter is the effect of progestogens on the amount, consistency and composition of cervical secretion in women – that is, the so-called 'minipill effect'.

Table 4 and Fig. 6 show that this test model correlates well with both the minipill doses and the effective dose in the Kaufmann assay. A striking phenomenon is that the 19-nor-testosterone derivatives are more effective than hydroxyprogesterone, although levonorgestrel is most effective of all.

The antiovulatory potency, a parameter of the antigonadotrophic effect, is also most pronounced in the case of norgestrel and levonorgestrel, as Table 5 and Fig. 7 show.

Potencies established in receptor assays do not correlate with clinical potency, even when human tissue is used (Smith *et al.*, 1974). This can be seen

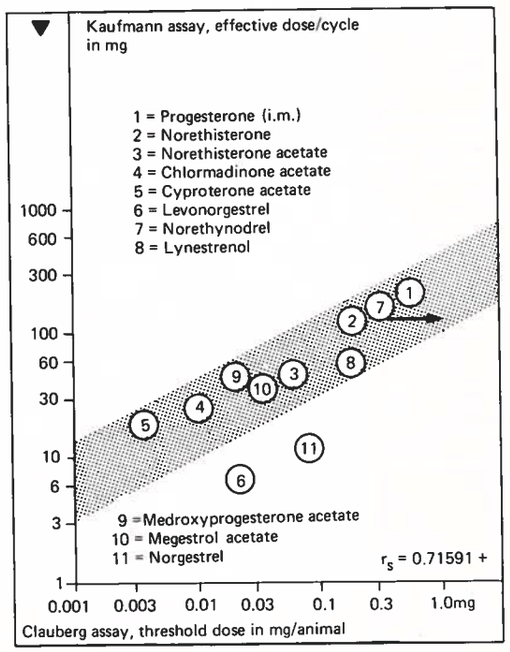


FIG. 5. Potency of some progestogens in the oral Clauberg assay in rabbits and in the oral Kaufmann assay.

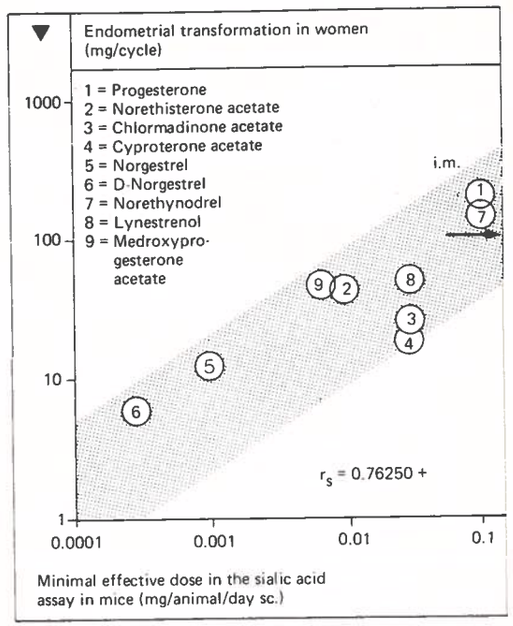


FIG. 6. Comparison of the oral transformation dose in women with the antioestrogenic effective dose in the mouse.

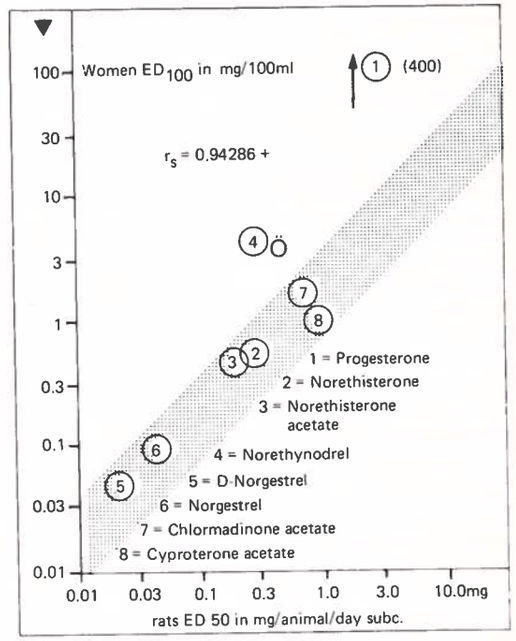


FIG. 7. Antiovulatory potency of some progestogens in rats (subc.) and human (p.o.)

TABLE 4. Comparison of the anti-oestrogenic efficacy of various gestogens in the subcutaneous sialic acid test in the mouse with the oral 'mini-pill' dose in women

Progestogen	Sialic acid assay in mice. Effective dose range (μg/animal/day)	Relative potency (Chlormadinone acetate = 1*)	'Minipill' dose/women (mg/day)	Relative potency (Chlormadinone acetate = 1*)
Norethisterone acetate	10–100	8	0·6	1·7
D-Norgestrel	0·3–10	83	0·03	33
Chlormadinone acetate	30–1000	1	~1	1
Cyproterone acetate	30–300	1	<1	≥1

*Analysis of covariance

TABLE 5. Antiovulatory potency of some progestogens in rats and humans

Progestogen	ED_{50} rat (mg/animal/day) p.o.	subc. (i.m.)	Effective antiovulatory dose in women (mg/day)
Progesterone	>10·0	≤3·0	300–500
Norethisterone	2–4	≤0·3	≥0·5
Norethisterone acetate	1–3	~0·3	≥0·5
Norgestrel	≥10·0	~0·04	~0·1
Levonorgestrel	10·0	0·01–0·03	~0·05
Norethynodrel	~ 1·0	~0·3	(2·5–10)
Chlormadinone acetate	~ 3·0	0·5–1·0	1·5–2
Cyproterone acetate	~ 3·0	~1·0	≤1·0

TABLE 6. Potency of some progestogens in the Kaufmann assay and an *in vitro* receptor assay, using human uterine preparations

Compound	Kaufmann assay (mg/cycle p.o.)	Receptor affinity Progesterone = 100
Progesterone	200 (i.m.)	100 (per def.)
Norethisterone	100–150	150
Levonorgestrel	6	180
Chlormadinone acetate*	20–30	50
Medroxyprogesterone acetate*	40–70	90

*Hydroxyprogesterone derivatives

clearly in Table 6. For example the receptor affinity of levonorgestrel is only 80% higher than that of progesterone, but it is 30 to 50 times more effective clinically. Chlormadinone acetate and medroxyprogesterone acetate have less affinity for the progesterone receptor than progesterone itself.

The menstruation-postponement test is also not very suitable for establishing the potencies of different progestogens, as Table 7 shows (Mears, 1965; Swyer, 1968). When administered alone, some progestogens are completely incapable of postponing menstruation.

TABLE 7. Potency of some progestogens in the Clauberg assay and in the menstruation delay test

Compound	Clauberg assay, threshold dose in mg/animal s.c.	Delay of menstruation (ED_{50} mg/day p.o.) without oestrogen	with oestrogen
Medroxyprogesterone acetate	0·01–0·03	>10	22·4
Megestrol acetate	0·01–0·03	>10	1·8
Norethisterone	≤0·1	4·25	—
Norgestrel	0·03	5	0·125
Norethynodrel	0·3	20	5·3
Ethynodiol diacetate	0·1	> 4	1·5

*Mears 1965 and Swyer 1968

These few examples are intended to show that not all tests are suitable for determining the potencies of different progestogens and that the order of efficacy of the individual progestogens can be different depending on the method of assay employed. This is just as valid for experimental pharmacology as it is in the clinical situation. An exact knowledge of the potential efficacy is, however, essential if an optimal oestrogen/progestogen combination is to be determined. This is relevant both for hormonal contraceptives and for preparations for the treatment of climacteric symptoms. As already mentioned, the desired synergistic and antagonistic effects of oestrogen/progestogen combinations can only be achieved at a particular ratio.

Interaction of progestogens and oestrogens

A few examples will show that whether oestrogens and progestogens will behave synergistically and antagonistically in the desired manner depends mainly on the oestrogen/progestogen ratio. It must be emphasized here that there are considerable differences between different species.

Table 8 shows the optimal oestrogen/progesterone ratio in respect of the decidual reaction. The optimum for the rat is an oestrogen/progestogen ratio of about 1:10,000 to 1:20,000. In the rabbit, the ratio is 1:1000. In the rhesus monkey, it is 1:50. In the woman, too, the optimal oestrogen/progesterone ratio lies between about 1:50 and 1:100. If the ratio is changed in favour of either the progestogen or the oestrogen, no decidual reaction can be induced.

Another example of progestogen and oestrogen interaction is shown in Table 9, demonstrating the induction of an endometrial reaction by various

TABLE 9. Effect of varying amounts of oestrogen in combination with progesterone on the endometrial reaction of ovariectomized rabbits (7 days of pretreatment with a total of 0·07 mg of oestrone or 0·00588 mg of oestradiol benzoate, then progesterone + oestrone twice a day for 4 days). (After Gillman and Stein, 1942)

Dosage, mg Oestrone	Progesterone	Endometrial reaction	Progesterone/ oestrone ratio
0·2	0·75	0	3·75:1
0·01	0·75	0	75 :1
0·08	1·5	0	18·5 :1
0·04	1·5	0	37·5 :1
0·02	1·5	+	75 :1
0·0025	1·5	+ + +	600 :1

TABLE 8. Optimum oestrogen/progesterone ratio and absolute doses (animal/day, given subcutaneously) for producing the decidual reaction in various species.

Species	Oestradiol-17β	Progesterone	E/P ratio	Reference
Hamster	not essential	2000 μg	1:∞	Dubois *et al.*, 1964
Rat	0·1 μg	2000 μg	~1:20,000	Yochim and de Feo, 1962
Rabbit	1·0–1·3 μg	1000 μg	~1: 1000	Chambon, 1949
Rhesus monkey	20–40 μg	1000–2000 μg	~1: 50	Good and Moyer, 1968

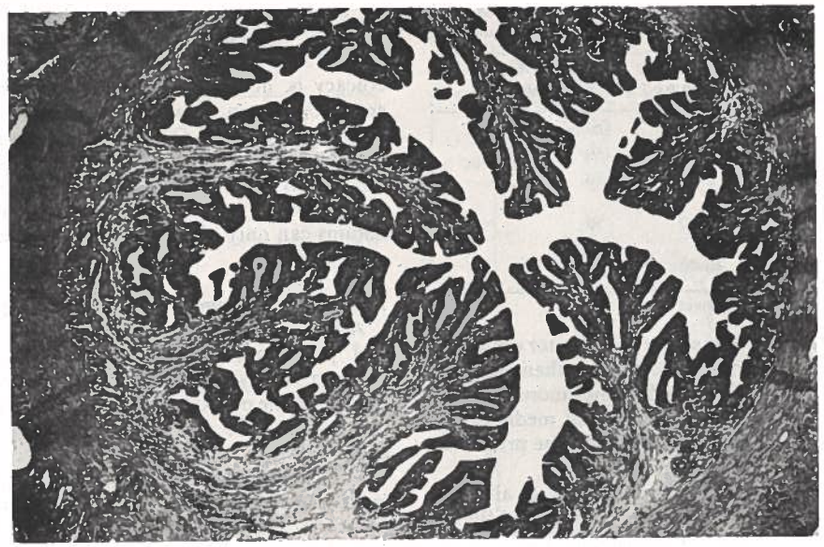
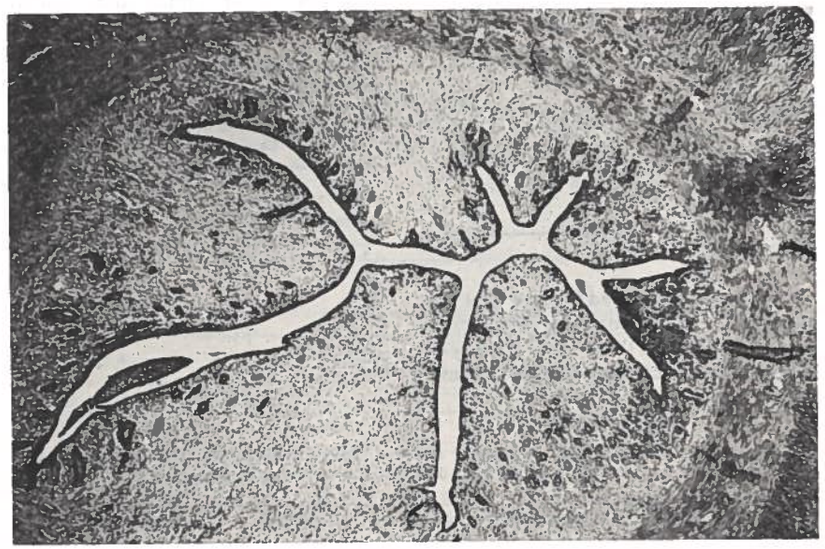


FIG. 8. Progestogen/oestrogen synergism and antagonism in the uterus. The usual Clauberg-McPhail test in immature rabbits. Pretreatment for 6 days with 0·5 μg oestradiol per day s.c. From the 7th to the 11th day the animals received an oestradiol/progesterone combination: (a) a total of 1·0 mg progesterone + 5·0 μg oestradiol s.c. The endometrium is quite transformed; (b) a total of 1·0 mg progesterone + 40·0 μg oestradiol s.c. Although the uteri are large and the muscularis is strongly developed, no transformation of the endometrium has taken place. Magnification: about 35. Staining: Hematoxylin-Eosin.



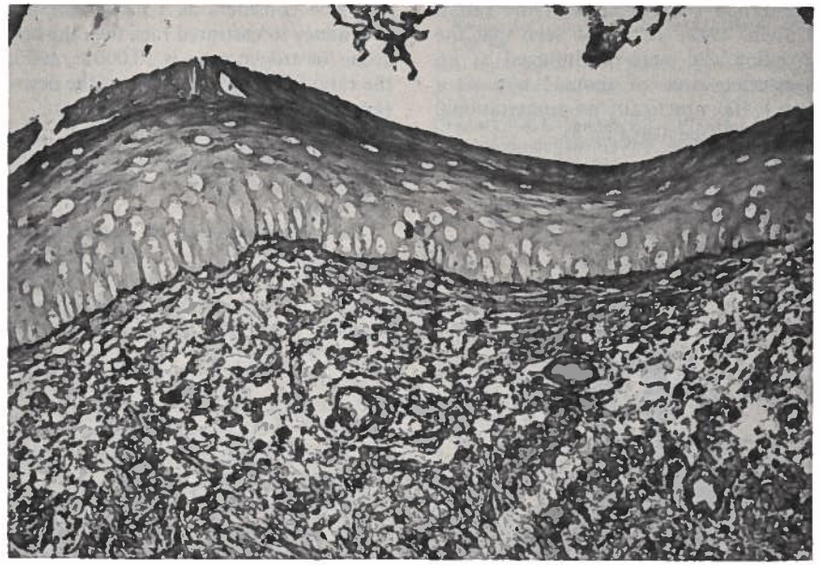


FIG. 10. (a) Section of the cervix from a castrated mouse treated with 0·1 μg oestradiol s.c. for 3 days. Note the vigorous stratification and cornification of the epithelium.

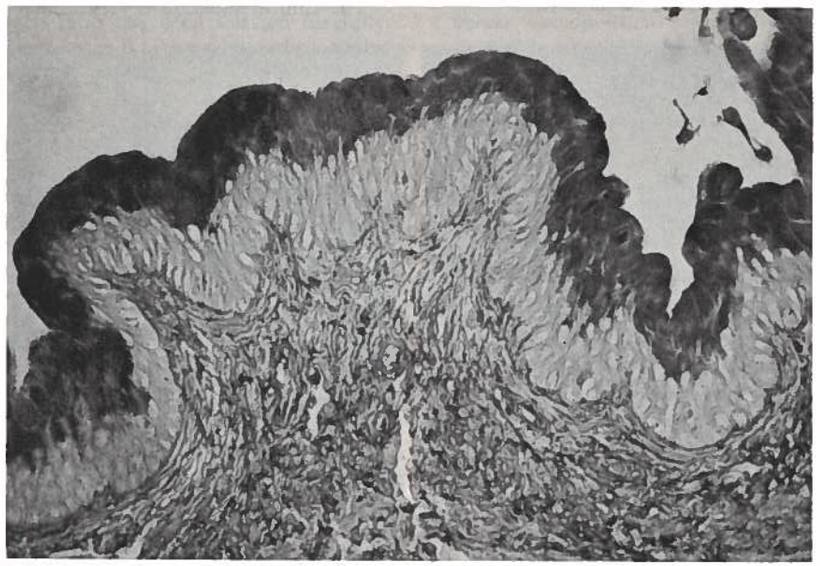


FIG. 10. (b) Same as before but in addition treatment with 1 mg progesterone/animal s.c. Note the great secretory activity of mucous cells of the epithelium.

oestrogen/progesterone combinations in the rabbit (Gillman and Stein, 1942). It can be seen that the endometrial reaction can only be induced at an oestrogen/progesterone ratio of about 1:600. At a ratio of less than 1:100, practically no progestational effect can be observed (see also Fig. 8).

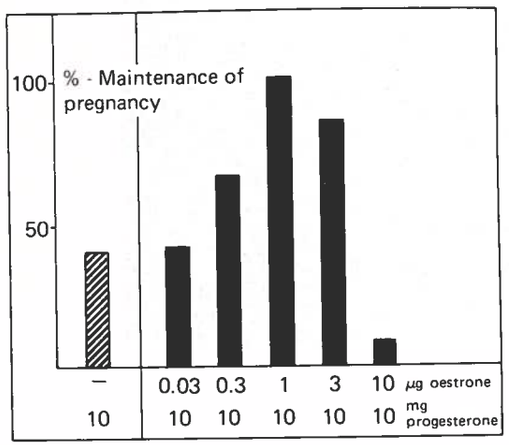


FIG. 9. Maintenance of pregnancy in castrated rats. Synergistic and antagonistic effects of oestrone and progesterone.

If one considers as a model the maintenance of pregnancy in castrated rats, then the optimal progesterone/oestrogen ratio is 10,000:1, as Fig. 9 shows. If the ratio is shifted in favour of the oestrogen then the pregnancy-maintaining effect is lost.

Finally, it can be shown how progestogens can modify oestrogen effects and how the effects partly antagonize each other at a sensible oestrogen/progestogen ratio.

The administration of oestrogens to castrated rodents is known to lead to cornification of the vaginal epithelium. The additional administration of a progestogen at the appropriate dosage induces mucification. The epithelium of the cervix behaves similarly, as is shown in Fig. 10.

Oestrogens stimulate uterine growth, and both the endometrium and the myometrium are involved. This proliferative effect of oestrogens can be counteracted by the administration of a progestogen at the appropriate dosage (see Fig. 11).

If the oestrogen dominates, the endometrial epithelium in rats and mice is tall columnar, while it is cubical to flat under the concurrent influence of an effective progestogen dose (see Fig. 12). When the oestrogen dominates, the mitosis rate is high in the epithelium and low in the endometrium. After administration of a progestogen the mitosis rate decreases in the epithelium and increases in the endometrium.

The clinical situation is very similar if the oestrogen/progestogen ratio has been selected carefully. This is important, since it offers a kind of protective mechanism against excessive proliferation due to oestrogens.

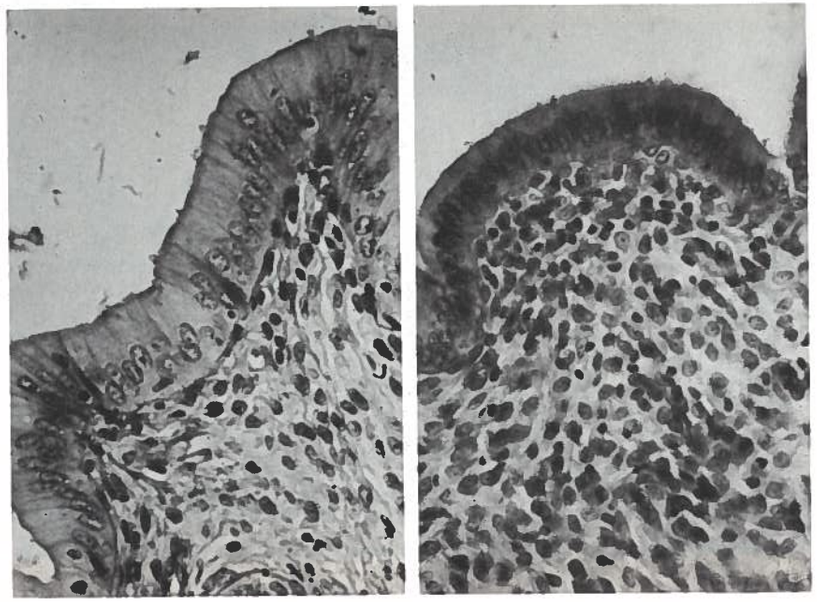


FIG. 12. Influence of oestradiol undecylate or oestradiol undecylate and progesterone on the uterine epithelium of castrated rats. (a) Oestradiol undecylate 1 × 25 µg subcutaneous, autopsy 1 week after treatment. (b) Same as before, but in addition daily treatment with 10 mg progesterone/animal s.c.

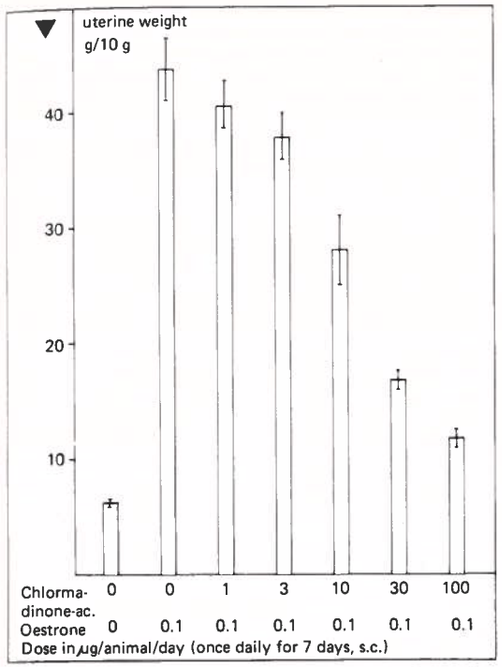


FIG. 11. Antioestrogenic effect of chlormadinone acetate in castrated mice (uterine growth test).

It is by no means true that we now have suitable progestogens for every purpose and every indication, which is why the search for new progestogens with special spectra of activities continues. All the progestogens currently used in commercially-available oral contraceptives still have androgenic activity. A large number of potentially interesting progestogens, some of which have also proved their value in clinical use, have fallen by the wayside during toxicity studies e.g. producing mammary-gland nodules in beagle dogs Although this subject cannot be discussed here, it is relevant that we now have good evidence that these findings (development of mammary-gland nodules) cannot be extrapolated to man (Gräf, El Etreby and Neumann, 1977).

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Discussion

MR BEARD: When a pharmacological preparation is being formulated is it on purely clinical findings that the ratio of progestogen to oestrogen is decided?

PROFESSOR NEUMANN: We have to use quite different ratios in animal and human experiments; for instance, the appropriate ratio of oestrogen to progesterone may be 1:10,000 in the rat, but 1:100 in the human. However, there is some correlation in relative potencies as measured in some animal species. Having compared the potency of a progestogen with that of progesterone in animal experiments, we multiply the progesterone dose by the appropriate factor to arrive at the correct ratio when using that progestogen either in animals or in humans.

DR HERRMANN: Among the physiological actions of progesterone you mentioned a decrease in libido in all animals. Do you think this is a general statement or only true for higher doses?

PROFESSOR NEUMANN: You may have in mind doses high enough to inhibit pituitary function, but this is not the only way in which libido may be diminished. It has been shown in primates that sexual activity decreases during the luteal phase and in veterinary medicine progestogens are used to inhibit 'heat' in dogs and cats. Some studies have been done in humans, I think in the USA, which have shown some decrease in the libido in the secretory phase of the menstrual cycle.

DR BYE: There is evidence from Vermeulen that testosterone shows the same cyclical behaviour as LH, with a substantial increase at mid-cycle. This could be a very important element in determining changes in libido; much more important than the change in progesterone.

DR. HERRMANN: There is really no study proving that progestogens decrease libido in humans. It may be that libido is increased around the ovulatory phase and then returns to normal in the progestational phase.

PROFESSOR NEUMANN: It is well known that oestrogens have a stimulatory effect on libido, and there is some correlation, at least in lower mammalian species, including some monkeys, between libido and the levels of both oestrogen and progesterone. Oestrogens have a positive effect, progestogens rather a negative effect, but I do not know whether or not this is true for the human.

MR STUDD: Dr Bye, there may be many reasons why you and others are unhappy about implants, but I wonder what biological system you have in mind which has to be switched off for seven days each month for safety?

DR BYE: I did not say I was unhappy about implants. I said it was conceivable that a complete interruption of the oestrogen on a short cyclical basis might become regarded as essential, although personally I doubt that it will. What we do not know is whether or not the production of shedding of the endometrium is sufficient in itself to overcome the effects of the oestrogen stimulus. But I think it is premature to discuss this aspect.

DR COOPE: Dr Bye's figure of 6% for the use of progestogen seems appallingly low in view of the fact that the pioneers of hormone replacement therapy such as Robert Wilson, Greenblatt and Sir John Peel, have always advocated it and its importance is increasingly recognized. Are your data based simply on packs which include a progestogen, such as Cyclo-Progynova or Menophase (Syntex) or do they include ordinary GP prescribing?

DR BYE: They include both. They were taken from prescriptions, and therefore reflect the total picture for the country, rather than the somewhat misleading picture that you get from looking at the specialist clinics. It seems clear that GPs are using oestrogens alone, unlike most of the people currently running the clinics. If the prescription also included a progestogen, this was recorded, so I do know whenever an oestrogen was prescribed with a progestogen, as well as when a combined product was prescribed.

PROFESSOR ELSTEIN: Could Dr Bye or Professor Neumann define a 'natural' as compared to a 'synthetic' oestrogen?

DR BYE: Oestradiol, oestrone and oestriol are present in the human and therefore are obviously, and unquestionably, 'natural' oestrogens. Whether or not any modification of the molecule before it is introduced into the body entitles us to go on referring to it as a natural oestrogen is debatable, and it will take a lot of work to determine the final answer. I think the longer the molecule remains unchanged in the body the more entitled we are to be cautious about attaching the name 'natural oestrogen' to such a product. When the breakdown is extremely rapid, then I think it is a not unreasonable and convenient portmanteau term to cover a number of somewhat similar products.

PROFESSOR CAMPBELL: It is said that the E1/E2 ratio is similar whether oestrogens are taken as an oestradiol complex or an oestrone complex. Is there any information as to where this takes place, because Dr Bye suggested that with an oestradiol complex, oestradiol receptors may be flooded initially. However, present indications seem to point to the conversion taking place in the gut, in which case this would not be the case. Could you explain this a little further?

DR BYE: It seems logical that at the time of absorption the plasma concentration of the administered hormone, wherever the conversion is taking place, will be higher than it becomes at a steady state. That is, unless the whole of the

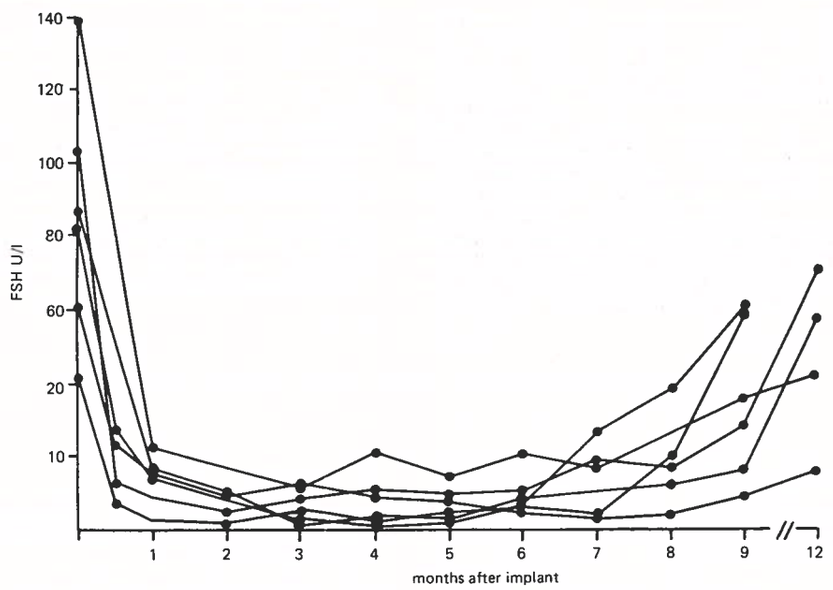

FIG. 1. Oestradiol 100 mg implant.

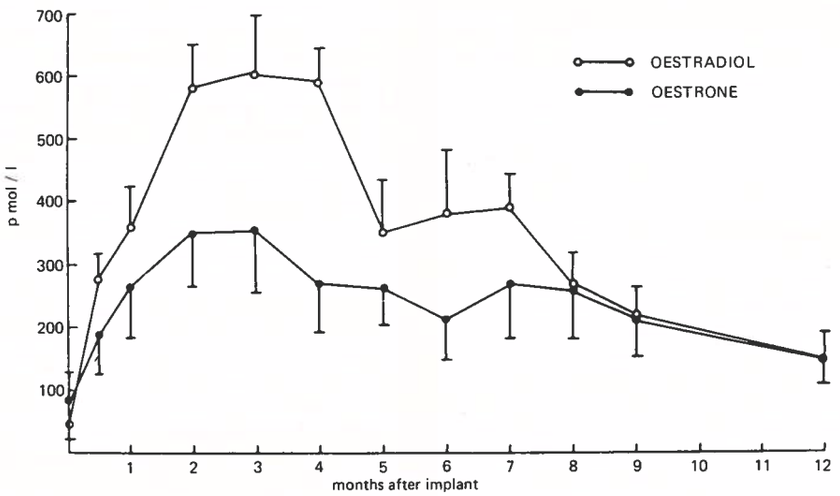

FIG. 2. Oestradiol 100 mg implant.

conversion takes place in the intestinal wall, which, I believe, is not the case.

MR STUDD: We have some data on this. We investigated six patients who had had bilateral oophorectomy and hysterectomy and were given an implant of 100 mg oestradiol. A full profile of plasma hormones was taken every month; FSH fell from the initial high level and within one month reached normal values, which was sustained for 8–9 months, as is shown in Fig. 1. It has been reported that if patients are given oestrone or oestradiol therapy orally, then high levels of oestrone and low levels of oestradiol result. However, if the gut is by-passed by means of an implant, then the reverse is found, with high oestradiol and low oestrone levels, as is shown in Fig. 2. These results suggest that the route of administration may be a determining factor in the metabolism of oestrogens, and certainly may be helpful in the investigation of where conversion occurs. Perhaps the use of implants, although carrying some disadvantages, deserves further exploration.

PROFESSOR VAN HALL: Professor Neumann, you mentioned that some progestogens had oestrogenic activity. Is this because of conversion to oestrogens *in vivo*, or do they have intrinsic oestrogenic activity? We have sometimes successfully used such compounds in women for whom oestrogens would be contra-indicated.

PROFESSOR NEUMANN: In the case of norethisterone and norethisterone acetate it may be an intrinsic property; they are converted to oestrogens only to a minor extent. Lynestrenol is similar, as it is converted to norethisterone *in vivo*, but there may be some difference with norethynodrel as it is much more strongly oestrogenic.

Postgraduate Medical Journal, 1978, **54** (Suppl. 2), 25–30.

SESSION II

Biochemistry

Chairman: PROFESSOR K. GRIFFITHS

Plasma hormone profiles after the menopause and bilateral oöphorectomy

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Summary

A study of 60 women, one to thirty years after the normal menopause, revealed that androstenedione, oestrone and oestradiol concentrations were reduced to about 20% of the values recorded during the early proliferative stage of the menstrual cycle. Mean concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) reached peaks of 18·4 times, and 3·4 times their respective mean proliferative-stage values at two to three years after the menopause, and then gradually declined in the next three decades to values that were 40 to 50% of these maximal levels. The plasma testosterone concentrations remained in the range normal for premenopausal women. Investigation of 100 women up to twenty years after bilateral oöphorectomy revealed that maximal values of FSH and LH after oöphorectomy were reached during the first year, and there was no decrease in the concentrations of these hormones with increasing age. Plasma oestradiol levels were about 80% below the mean values of days one to ten of the menstrual cycle, being the same as are found at comparable years after a normal menopause. Plasma testosterone, however, was at most intervals after oöphorectomy somewhat lower than after a natural menopause.

There was no correlation between plasma hormone levels and the presence of vasomotor symptoms or depression. In pre-menopausal women, a correlation was found between the incidence of flushes and high mean FSH and LH levels.

Introduction

During the latter stage of reproductive life, ovarian activity gradually declines and menstruation stops. Profound changes in the gonadal secretion and plasma levels of steroidal hormones occur, and may be associated with symptoms of varying intensity and duration. Ovarian stimulation and suppression tests have confirmed the inability of the post-menopausal ovary to produce oestrogens, although androstenedione and testosterone are still produced by the ovarian stroma for many years after apparent ovarian failure.

This study was designed to compare the plasma hormone profiles after a normal menopause and after surgical castration, and to determine what correlation, if any, exists between plasma hormone levels and the symptoms of the climacteric.

Methods

(a) *Normal Menopause.* Sixty post-menopausal but otherwise healthy women were selected from hospital staff, geriatric inpatients, and new patients attending the Menopause Clinic at Dulwich Hospital. Their ages ranged from 49–91 years and represented six groups of ten patients, 1, 3, 5, 10, 20 and 30 years from the menopause. No person had ever received oestrogen replacement therapy and all were free from current medical or surgical conditions.

(b) *Surgical Menopause.* A total of 100 patients were studied; eighty-six women were traced from 104 consecutive cases of total hysterectomy and bilateral salpingo-oöphorectomy in pre-menopausal women performed at Dulwich Hospital during 1965 to 1975; fourteen others, representing different intervals after surgery, were enlisted from the Menopause Clinic. The total range of the study was 1–31 years following oöphorectomy. A review of the histology revealed that fifty-eight patients had had healthy ovaries removed.

Two samples of peripheral venous plasma (20 ml) were taken, a week apart, between 10 a.m. and 2 p.m. They were analysed in random order. All were by

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