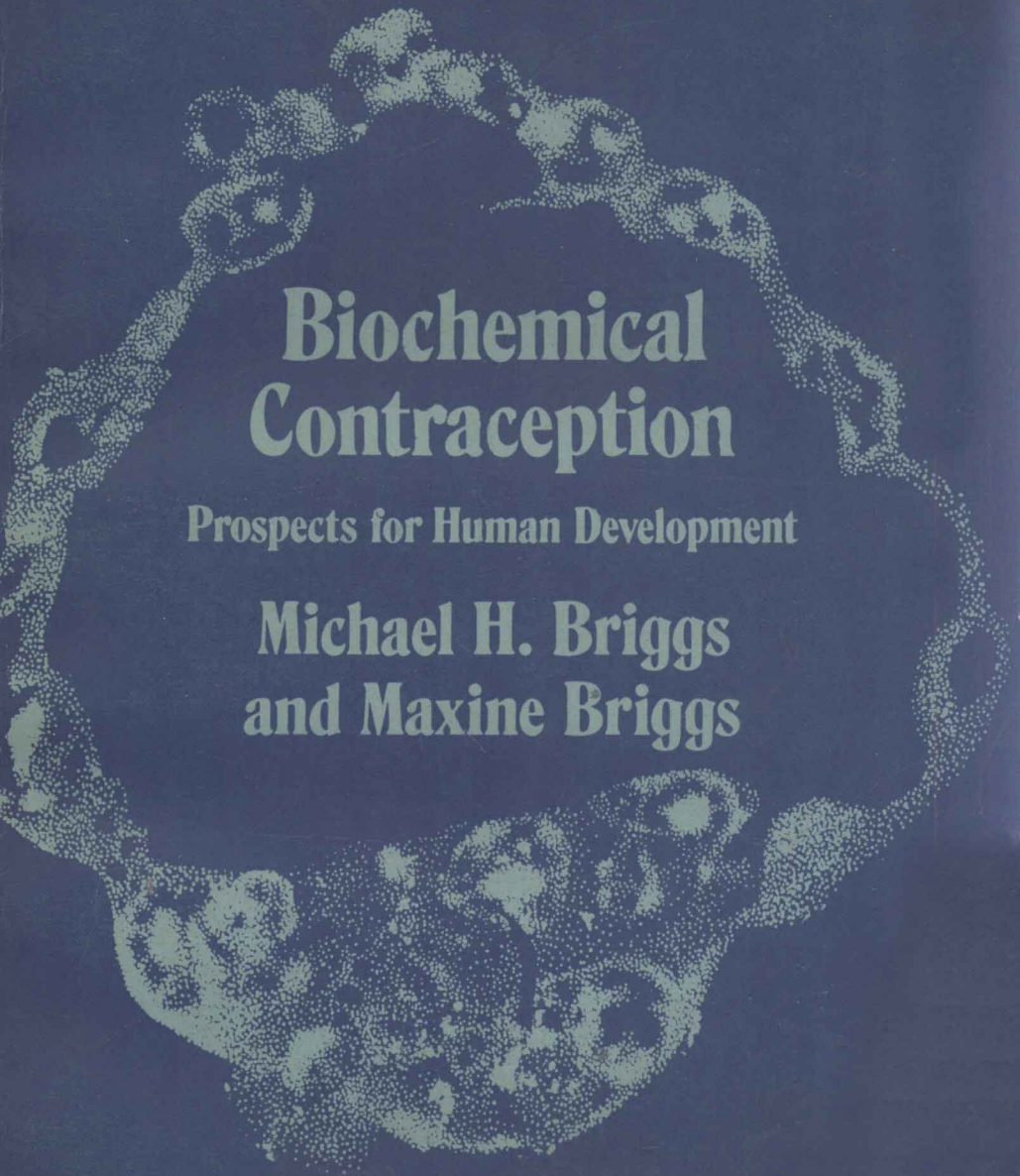

Biochemical Contraception

Prospects for Human Development

Michael H. Briggs
and Maxine Briggs

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PREFACE

The manuscript that follows is *not* a comprehensive, impartial review of the medical and scientific literature on biochemical contraception. It is a personal, highly slanted perspective. Some of the views expressed are unorthodox. They are meant to be. The literature cited is carefully selected to support particular approaches; other interpretations are entirely possible. The aim has been to supply a series of research approaches to contraceptive development, many of which can be *immediately* investigated in humans. Long-term prospects have been largely ignored.

No attempt has been made to present our data in traditional "text-book" fashion. To lessen the chances of misleading unwary readers we have included many cross-references, both internally within the book, and to authoritative outside sources.

Few people now doubt the urgency of dealing with the world population explosion, and the impact of existing contraceptive methods has been small. In our view, the problem is largely one of finding acceptable methods for particular groups of people. We believe, therefore, that the more ways human contraception can be attained, the greater will be the restraint on population increase.

Michael H. Briggs
Maxine Briggs
Geneva

CONTENTS

I INTRODUCTION

I.1 Existing Steroid Contraceptives

Contraceptives containing synthetic steroid hormones have been marketed for women in most countries of the world over the past decade. The original products were oral medications containing a synthetic estrogen and a synthetic progestogen (mestranol and norethynodrel) and were taken for 20 or 21 days, beginning on day five of a menstrual cycle. This was followed by a seven- or eight-day medication-free interval, then the next course of tablets was started. Uterine bleeding, similar to a normal menstruation, occurs for the last few of the tablet-free days, due to estrogen-withdrawal.

Improvements on the original products were achieved by the following modifications to formulation.

1. Reducing the dose of progestogen.
2. Reducing the dose of estrogen.
3. Using a chemically different progestogen.
4. Using a chemically different estrogen.

It takes a long time to test new drugs clinically, but it soon became clear that the doses of steroids contained in the original products could be considerably reduced, without affecting efficacy, but improving acceptability and lessening side-effects. Numerous synthetic progestogens were discovered, differing not only in progestational potency, but in secondary hormone properties (androgenicity, anti-androgenicity, estrogenicity, anti-estrogenicity, glucorticoid properties etc.). This allowed considerable latitude for clinicians to match products to their estimates of individual patients' hormonal milieu, so that changes induced by an oral contraceptive were not so marked, and side-effects were less. The only modification of estrogen was replacement in some products of mestranol by the somewhat more potent ethinylestradiol.

Table I.1 provides a list of oral contraceptive preparations, marketed or on clinical trial. While 36 different hormone combinations are listed, the table is certainly incomplete, for every pharmaceutical company with interests in this field has tested numerous modifications and many unsuccessful products are not reported in the medical and scientific literature.

It is interesting to see that daily estrogen dosage has been reduced from 100 or 150 to 50 μg in most products, while trials are under way at even lower doses. Similarly, progestogens have been reduced several fold in most cases, without any significant change in contraceptive efficacy of the products.

It must also be mentioned that clever packaging has been designed for many products to lessen chances of missed doses.

A new type of oral contraceptive was introduced a few years after the "combined-type". It was variously known as a "sequential" or "serial" product. It was developed as an attempt to provide a series of hormone changes in women

Table I.1 *Combined-type oral contraceptives*[a]

Norethisterone acetate 4.0 mg + ethinylestradiol 50 μg
Norethisterone acetate 3.0 mg + ethinylestradiol 50 μg
Norethisterone acetate 2.5 mg + ethinylestradiol 50 μg
Norethisterone acetate 1.0 mg + ethinylestradiol 50 μg

Norethisterone 10.0 mg + mestranol 60 μg
Norethisterone 2.0 mg + mestranol 100 μg
Norethisterone 2.0 mg + mestranol 80 μg
Norethisterone 2.0 mg + mestranol 50 μg
Norethisterone 1.0 mg + mestranol 100 μg
Norethisterone 1.0 mg + mestranol 80 μg
Norethisterone 1.0 mg + mestranol 50 μg

Ethynodiol diacetate 1.0 mg + mestranol 100 μg
Ethynodiol diacetate 1.0 mg + mestranol 60 μg
Ethynodiol diacetate 1.0 mg + ethinylestradiol 50 μg
Ethynodiol diacetate 0.5 mg + mestranol 100 μg
Ethynodiol diacetate 0.5 mg + ethinylestradiol 50 μg
Ethynodiol diacetate 0.1 mg + mestranol 100 μg
(then ethynodiol diacetate 0.5 mg + mestranol 100 μg)

Lynestranol 5.0 mg + mestranol 150 μg
Lynestranol 2.5 mg + mestranol 75 μg
Lynestranol 3.5 mg + ethinylestradiol 50 μg

Chlormadinone acetate 3.0 mg + mestranol 100 μg

Medroxyprogesterone acetate 10.0 mg + ethinylestradiol 50 μg
Medroxyprogesterone acetate 5.0 mg + ethinylestradiol 50 μg
Medroxyprogesterone acetate 2.0 mg + ethinylestradiol 20 μg

Norethynodrel 10.0 mg + mestranol 150 μg
Norethynodrel 5.0 mg + mestranol 75 μg
Norethynodrel 3.0 mg + mestranol 75 μg
Norethynodrel 2.5 mg + mestranol 100 μg
Megestrol acetate 5.0 mg + mestranol 100 μg
Megestrol acetate 4.0 mg + ethinylestradiol 50 μg
Megestrol acetate 2.0 mg + ethinylestradiol 100 μg

dl-Norgestrel 0.5 mg + ethinylestradiol 50 μg
d(−)-Norgestrel 0.75 mg + ethinylestradiol 30 μg (Bodin *et al.*, 1972)
d(−)-Norgestrel 0.50 mg + ethinylestradiol 30 μg (Bodin *et al.*, 1972)
d(−)-Norgestrel 0.25 mg + ethinylestradiol 50 μg
d(−)-Norgestrel 0.15 mg + ethinylestradiol 30 μg (Bodin *et al.*, 1972; Rozenbaum, 1972)

[a] Unless otherwise indicated, details of regimes, trade-names etc. may be found in Briggs *et al.* (1970).

that more closely matched the endogenous ebb and flow of estrogen and progestogen during a normal menstrual cycle. In these products, the first course of tablets, beginning on day five, contained only estrogen and were taken for 14, 15 or 16 days, depending on the particular product. At the end of these tablets, the woman switched immediately to tablets containing both estrogen (at the same dose as before) *and progestogen*. These second tablets were taken for five, six or 17 days according to product, then followed by a seven- or eight-day tablet-free period, during which time a withdrawal-bleeding occurred. By reducing exposure to progestogen, it was hoped that certain side-effects, such as depression, thought to be caused by progestogens, would be reduced.

A list of sequential oral contraceptive formulations is given in Table I.2.

Table I.2 *Sequential-type oral contraceptives*

Mestranol 100 μg (14 days) + chlormadinone acetate 1.5 mg and mestranol 100 μg	(7 days)
Mestranol 80 μg (15 days) + chlormadinone acetate 2.0 mg and mestranol 80 μg	(5 days)
Mestranol 100 μg (15 days) + norethynodrel 5.0 mg and mestranol 100 μg	(5 days)
Mestranol 100 μg (14 days) + norethisterone 2.0 mg and mestranol 100 μg	(7 days)
Mestranol 80 μg (14 days) + norethisterone 2.0 mg and mestranol 80 μg	(6 days)
Mestranol 100 μg (14 days) + anagesterone acetate 2.0 mg and mestranol 100 μg	(7 days)
Ethinylestradiol 100 μg (16 days) + megestrol acetate 1.0 mg and ethinylestradiol 100 μg	(5 days)
Ethinylestradiol 100 μg (16 days) + dimethisterone 25 mg and ethinylestradiol 100 μg	(5 days)

Again, the list is incomplete for the same reason as before.

Products of this type have not been so widely used as combined oral contraceptives. Moreover they are significantly less effective (see, for example, Haller, 1969). Most combined oral contraceptives have failure rates of 0.1 pregnancies per 100 woman-years (or less), while sequential-type products usually show failure rates as high as two or three pregnancies per 100 women-years. Even so, these rates compare favourably with failure rates of other contraceptive methods (spermicides, rhythm method and coitus interruptus all show failures of about 25 pregnancies per 100 woman-years, condoms or diaphragms about 15, and most types of IUD about two or three).

A major setback to the use of sequential oral contraceptives came with reports that combined-type products containing more than 50 μg daily estrogen are associated with a significantly higher incidence of thrombo-embolic diseases (Inman *et al.*, 1970). The report specifically excluded sequential products, all of which contain more than 50 μg daily estrogen, because there was insufficient evidence, due to the relatively few women using them, to allow proper statistical evaluation of their association with thrombo-embolic disease. Nevertheless, most clinicians stopped prescribing sequential contraceptives and changed their patients to combined products containing less estrogen. Some pharmaceutical companies even stopped manufacturing sequential contraceptives. Whether these

actions were justified is debatable, for more recent surveys have found no association between sequential products and thrombo-embolism (Wait *et al.*, 1972). It seems unlikely, however, that they will ever gain much support again, though they are still available and are recommended by their manufacturers mainly for use in women requiring higher than normal estrogen, or who show progestogen-linked side-effects.

A hybrid of combined and sequential oral contraceptives has been marked, but also has failed to gain much acceptance. It provides a course of 16 daily 100 μg doses of mestranol with a very low dose of progestogen (ethynodiol diacetate 0.1 mg), then a final seven days of estrogen (at the same dose as before), but with a much larger amount of progestogen (0.5 mg).

A more recent development in oral contraception has been the use of progestogen-only products, which have to be taken continuously, without the medication-free interval of combined or sequential products. It has been found that, given alone, progestogens have contraceptive efficacy at much lower doses than when used in combination with estrogens. The most widely tested of these "mini-pills" is 0.5 mg daily chlormadinone acetate, though numerous other compounds are on clinical trial (see Table I.3). For some of the newer progestogens, doses as low as 30 μg daily appear to give reasonable protection.

Two major difficulties have arisen from clinical trials of these products. Initial studies, which were conducted mainly in Central and South America, indicated a failure-rate similar to that of sequential oral contraceptives (i.e. about one or

Table I.3 *Continuous-dose, progestogen-only, "mini-pills"*

Chlormadinone acetate 0.5 mg (Christie and Moore-Robinson, 1969)
Chlormadinone acetate 0.4 mg (Martinez-Manautou, 1971)
Chlormadinone acetate 0.3 mg (Martinez-Manautou, 1971)
Norethisterone 0.35 mg (Board, 1971)
Norethisterone 0.3 mg (Martinez-Manautou, 1971)
Norethisterone 0.25 mg (Martinez-Manautou, 1971)
Norethisterone acetate 0.3 mg (Briggs and Briggs, 1972; Jacobs *et al.*, 1972)
Megestrol acetate 0.5 mg (Balin and Wan, 1970)
Megestrol acetate 0.35 mg (Balin and Wan, 1970)
dl-Norgestrel 0.075 mg (Foss, 1969; Roland, 1972)
dl-Norgestrel 0.05 mg (Roland, 1972)
d(−)-Norgestrel 0.03 mg (Laurie and Korba, 1972; Roland, 1972)
Quingestanol acetate 0.3 mg (Rubio *et al.*, 1972; Moggia *et al.*, 1972; Kesseru *et al.* 1972)
Cigestol 0.5 mg (Papanikandros, 1972)
16 α-ethylthio-retroprogesterone 20 mg (Beck and Hoffmann, 1972; Rindt, 1972)
Medroxy-retroprogesterone acetate (Phillips-Duphar, unpublished)
R 2323 (13-ethyl-17 α-ethinyl-17 β-hydroxy-4,9,11-gonatrien-3-one) 5mg weekly (Sakiz and Azadian-Boulanger, 1971)

two per 100 woman-years), but this has not been confirmed in many more recent studies from Europe and North America, where rates as high as six to 12 pregnancies per 100 women-years have been reported. A second problem has been the very high incidence of irregular cycles and inter-menstrual bleeding.

At least one "mini-pill' was commercially available, but on-going chronic toxicity tests of its progestogen (chlormadinone acetate) at higher than human-doses in beagle bitches showed the development of mammary gland tumors, so the product was withdrawn from sale. A considerable dispute followed, based mainly on the suitability of beagles as a test-animal in toxicity studies of progestogens (Hill, 1972). This, and other, mini-pills have now been re-marketed, but their use on a wide scale seems unlikely; firstly, because of the cloud of uncertainty that surrounds their long-term toxicity, and secondly, their high failure-rates and undesirable effects on cycle length.

All types of oral contraceptive mentioned above are eminently suitable for use by women in developed countries, but their use by women of under-developed lands causes considerable difficulties. Such products demand a certain

Table I.4 *Long-acting depot-contraceptives*

Progestogens only (i.m.)

Medroxyprogesterone acetate (1000 mg/6 months) (Zanartu, 1968)
Medroxyprogesterone acetate (500 mg/6 months) (Zanartu, 1968)
Medroxyprogesterone acetate (400 mg/6 months) (Ringrose, 1972)
Medroxyprogesterone acetate (300 mg/6 months) (Karstadt, 1970)
Medroxyprogesterone acetate (150 mg/3 months) (Bloch, 1971)
Norethisterone enanthate (200 mg/3 months) (Zanartu and Navarro, 1968; El-Mahgoub and Karim, 1972)
Dihydroxyprogesterone acetophenide (150 mg/month) (Taymor *et al.*, 1964)
Chlormadinone acetate (100 mg/3 months) (Zanartu, 1968)
Hydroxyprogesterone caproate (500 mg/month) (Siegel, 1963)
Lynestrenol-cypionate (50 mg/month) (Papanikandros, 1972)

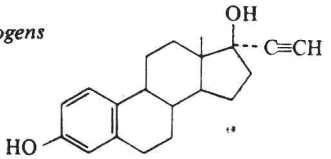
Progestogen-estrogen combinations

Medroxyprogesterone acetate (i.m. 150 mg/3 months) + diethylstilbestrol (p.o. 0.5 mg/day for 10 days each month) (McDaniel and Zelenik, 1970)
Medroxyprogesterone acetate (i.m. 150 mg/3 months) + ethinylestradiol (p.o. 40 μg/day for 10 days each month) (McDaniel and Pardthaisong, 1972)
Medroxyprogesterone acetate (i.m. 50 mg/5 weeks) + estradiol cypionate (i.m. 10 mg/5 weeks) (Scommegna *et al.*, 1970)
Dihydroxyprogesterone acetophenide (i.m. 150 mg/month) + estradiol enanthate (i.m. 10 mg/month) (Wallach and Garcia, 1970; Sammour *et al.*, 1971)
Hydroxyprogesterone caproate (i.m. 500 mg/month) + estradiol valerate (i.m. 10 mg/month) (Siegel, 1963)
Hydroxyprogesterone caproate (i.m. 250 mg/month) + estradiol valerate (i.m. 50 mg/month) (Faundes and Luukkainen, 1972)
Norgestrel (i.m. 25 mg/month) + estradiol hexahydrobenzoate (i.m. 5 mg/month) (Souza and Coutinho, 1972).

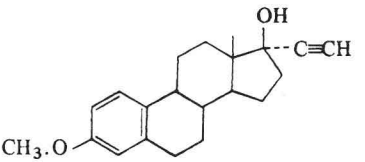
Estrogens only (i.m.)

Estradiol undecylate (30 mg/month) (El-Mahgoub and Karim, 1972)

Estrogens

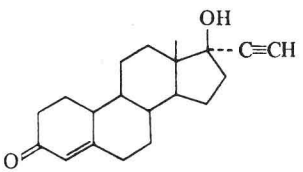


ethinylestradiol

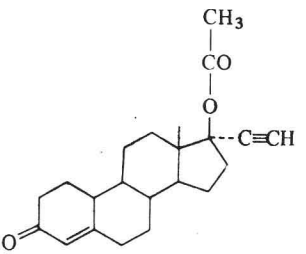


mestranol

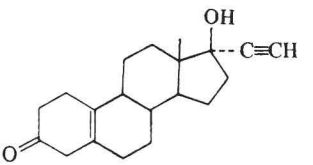
Progestogens



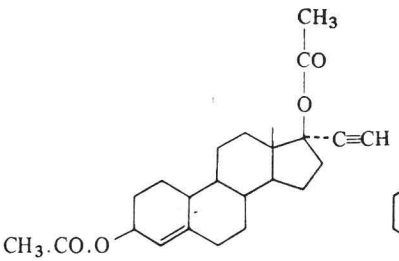
norethisterone



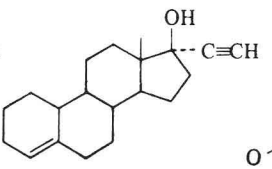
norethisterone acetate



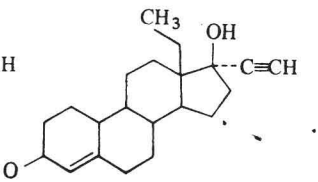
norethynodrel



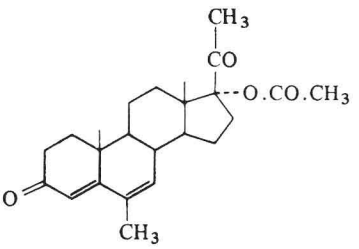
ethynodial diacetate



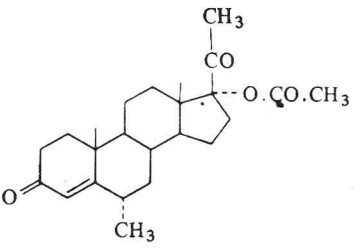
lynestrenol



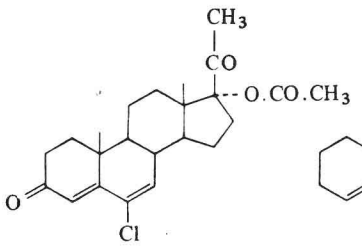
norgestrel



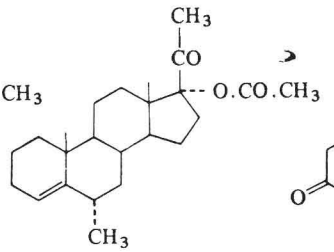
megestrol acetate



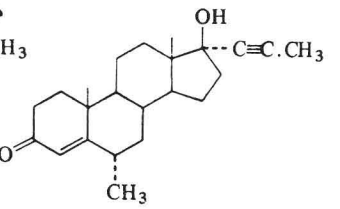
medroxyprogesterone acetate



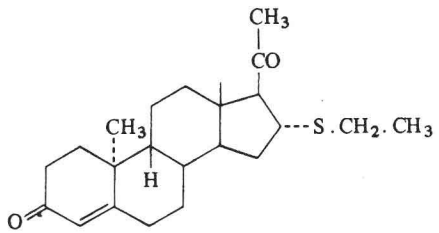
chlormadinone acetate



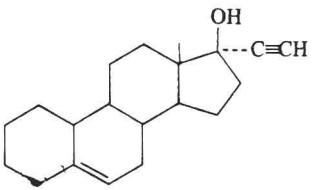
anagesterone acetate



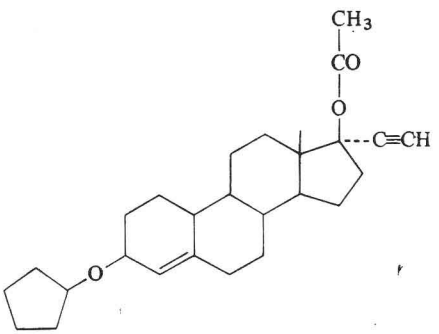
dimethisterone



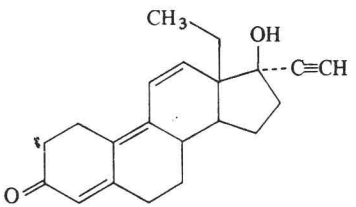
16 α-ethylthio-retroprogesterone



cingestol



quingestanol acetate



R 2323
(ethylnorgestriene)

Fig. I.2 Chemical structures of some newer steroid hormones used in "mini-pills".

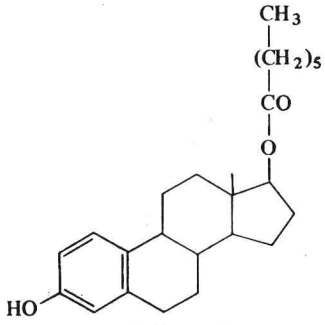
minimum understanding of human reproductive physiology, together with a location in the household where a packet of oral contraceptive tablets can be stored away from children and domestic animals. It also presumes a familiarity with oral medicines of other types, together with a desire for effective contraception without the use of devices or chemicals at the time of intercourse. Most of these criteria are not met by many women from parts of Africa, Asia and South America. Moreover, many cannot afford oral contraceptives.

Largely to supply the needs for contraception in women of underdeveloped countries, studies have been undertaken to find depot products that can be injected at infrequent intervals (a month or more), yet are as effective and safe as oral contraceptives. A list of products available, or under trial, is given in Table I.4.

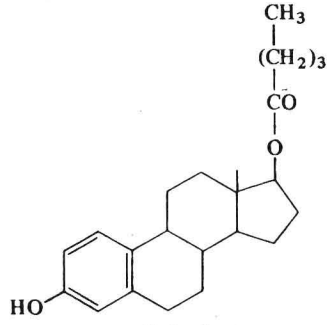
Some depot contraceptives contain only progestogens, but others are used in combination with estrogens. The latter may be either incorporated into the oily vehicle with the progestogen, or given separately as i.m. injections, or as orally active compounds.

Fig. I.1 Chemical structures

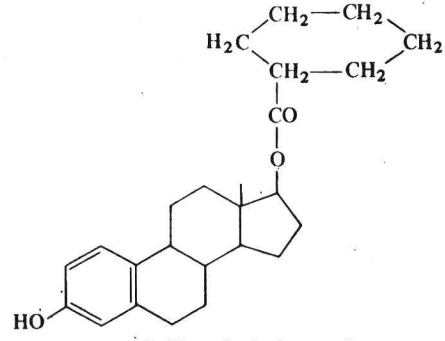
CH3
(CH2)5
CO
O
C≡CH
O
norethisterone enanthate
(n-heptanoate)
CH3
CO
O
O
CH.CH2
O
dihydroxyprogesterone
acetophenide
CH3
CO
O.CO(CH2)4.CH3
O
hydroxyprogesterone caproate
(n-hexanoate)
H2C—CH2
H2C H CH2
C
CH2
CH2
O
C≡CH
lynestrenol cypionate
(cyclopentylpropionate)
OH
CH3
H2C
C
C
CH2
CH3
HO
diethylstilbestrol
(trans-isomer)
H2C—CH2
H2C H CH2
C
CH2
CH2
O
HO
estradiol cypionate
(cyclopentyl-propionate)



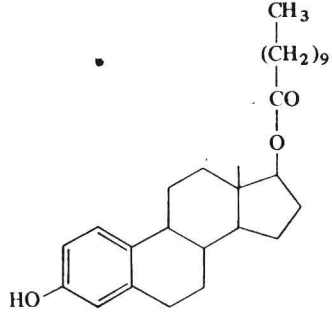
estradiol enanthate
(*n*-heptanoate)



estradiol valerate
(*n*-pentanoate)



estradiol hexahydrobenzoate
(cyclohexanoate)



estradiol undecclate

Fig. I.3 Structures of steroid hormones used in depot-contraceptives. (Structures are not given of compounds also found in oral contraceptives.)

As with "mini-pills", depot progestogens tend to produce irregular cycles, with intra-menstrual bleeding, while blood loss can be considerable at times. They are also sometimes followed by prolonged anovulatory periods, even though no further injections are given. Addition of estrogen to the depot is said to improve cycle control for the shorter acting preparations (i.e. once a month preparations), though not for products intended to last for three months or more. Short courses of oral estrogen help to regularise cycles for the latter products, but this is a return to the disadvantages of oral products for underdeveloped countries. Reliability of most depot contraceptives is about 0.5 to two pregnancies per 100 woman-years.

Estrogens alone have a contraceptive effect, though there is a tendency for "escape" ovulations to occur after a few courses of treatment. Estrogens are also more associated with undesirable side-effects than progestogens. Nevertheless, use of depot estrogen alone has been reported (El-Mahgoub and Karim, 1972) to be a successful long-acting contraceptive in young women with mild uterine hypoplasia.

Chemical structures of steroid hormones used in combined or sequential oral contraceptive products are given in Fig. I.1, while those of some fairly new steroids, so far used only as "mini-pills", are given in Fig. I.2. Finally, structures of steroids used in depot contraceptive products (not already mentioned in Fig. I.1) are shown in Fig. I.3.

I.2 Mode of Action of Oral and Depot Contraceptives

A great deal is now known of the mechanisms by which steroid hormone administration induces temporary infertility in women, and has been the subject of many reviews (see, for example, Diczfalusy, 1968, 1971; Haller, 1969). Only the major features will be mentioned here.

Oral contraceptives of the combined or sequential type are most effective inhibitors of ovulation. It is difficult to estimate the number of "escape" ovulations that occur, but it is probably not more than 15 or 20 per 100,000 monthly cycles for combined products, though it may be as high as 150 to 200 per 100,000 for sequentials. The mechanism whereby ovulation is inhibited is less clear. Secretion of both LH and FSH by the pituitary is reduced in women taking almost any oral contraceptive product. The characteristic mid-cycle "surge" (Fig. I.4) is eliminated, while even basal secretion of gonadotrophins at other times of the cycle is depressed.

There is no conclusive evidence as to whether this gonadotrophin inhibition occurs at hypothalamic or pituitary levels or both. Administration of synthetic LH-releasing factor (LRF) to women under treatment with combined-type oral contraceptives produces a rise in plasma LH, suggesting that secretion of LRF is blocked by contraceptive steroids. However, it is not known what amounts of

LRF are secreted naturally, so it is still possible that some effect also occurs in the pituitary.

While ovulation-inhibition may be the primary mode of action for combined and sequential oral contraceptives, effects at other sites undoubtedly occur. These presumably contribute to overall contraceptive efficacy of the products. A list of these "secondary" sites is given below:

1. *ovary*: ovarian sensitivity to gonadotrophins is reduced by oral contraceptives, while steroidogenesis is abnormal;
2. *fallopian tubes*: motility, secretion and metabolism are altered by contraceptive steroid hormones;
3. *uterus*: motility, secretion and metabolism of the uterus are markedly altered by oral contraceptives, while the uterine endometrium has altered vasculature and becomes unsuitable for ovum implantation;
4. *cervix*: secretion of mucus is reduced by steroid contraceptives and is unsuited to sperm migration;
5. *sperm*: it is possible, though not definitely established, that capacitation of sperm is inhibited in women treated by oral contraceptives.

It is less clear on which effect the primary contraceptive action of "mini-pills" is based. Some products definitely induce inhibition of ovulation in some women (10 to 60% depending on progestogen and dose), but "mini-pills" do not inhibit ovulation in most women. It is likely that these products also act at the five sites mentioned above, but little is known of their effects on these tissues. It

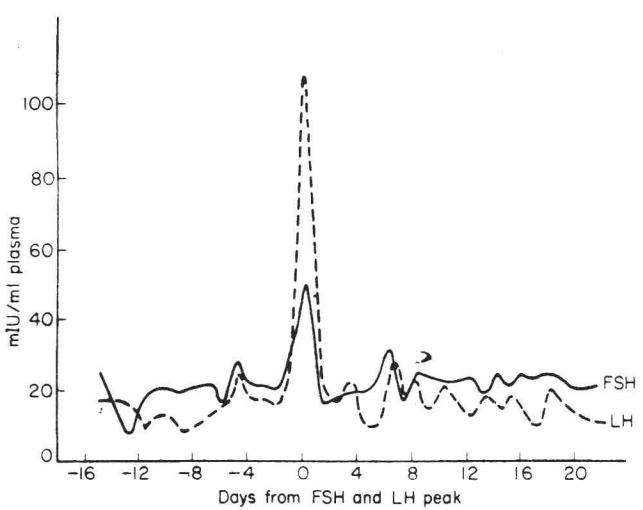


Fig. I.4 Normal mid-cycle surge of gonadotrophins.