METHODS OF FERTILITY REGULATION:
ADVANCES IN RESEARCH AND CLINICAL EXPERIENCE

Report of a WHO Scientific Group

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WHO SCIENTIFIC GROUP ON
METHODS OF FERTILITY REGULATION :
ADVANCES IN RESEARCH AND CLINICAL EXPERIENCE

Geneva, 14-18 December 1970

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METHODS OF FERTILITY REGULATION:
ADVANCES IN RESEARCH
AND CLINICAL EXPERIENCE

Report of a WHO Scientific Group

A WHO Scientific Group on Methods of Fertility Regulation met in Geneva from 14-18 December 1970. The meeting was opened by Dr H. Mahler, Assistant Director-General, on behalf of the Director-General.

1. INTRODUCTION

The World Health Organization has convened several scientific groups on methods of fertility control. During the past few years, meetings have been devoted to such topics as intrauterine devices,\(^1\) periodic abstinence,\(^2\) hormonal contraceptives,\(^3\) developments in fertility control,\(^4\) immunological approaches,\(^5\) and the problem of abortion.\(^6\) Other meetings, such as the one on the health aspects of family planning,\(^7\) have also touched on questions of contraception. The purpose of the present meeting was to review certain developments in approaches to fertility control that have taken place during the past 3 years, with special emphasis on advances in knowledge of mechanisms of action of different methods, clinical experience on effectiveness and side effects, and research strategies for the development of improved methods. Attention was focused on the assessment of the methods used in evaluating the problems of contraceptive effectiveness and side effects. The Group was aided in its work by the reports of several previous WHO scientific groups,\(^1,3,4,8\) and the present report will concentrate on developments that have occurred since the publication of these reports. In most instances, repetition of material already presented has been avoided and the present report should, therefore, be read in conjunction with the earlier ones, especially those on intrauterine devices\(^1\) and hormonal contraceptives.\(^9\)

2. MECHANISMS OF ACTION OF HORMONAL CONTRACEPTIVE STEROIDS AND INTRAUTERINE DEVICES

2.1 Mechanism of Action of Hormonal Contraceptives

2.1.1 Regimens and formulations

The contraceptive steroids currently in use and/or under study can be classified as follows:

(a) combined formulations (oestrogen-progestogen)
(b) sequential formulations (oestrogen-progestogen)
(c) oral progestogens given continuously
(d) slow-release injectable progestogens or oestrogen-progestogen combinations

At present most of the steroid contraceptives available for use are either low-dose oral formulations of type (a), (b), or (c), or long-acting injectable preparations. All other formulations and regimens referred to in section 6 are still under investigation in limited series of cases.

2.1.2. Mechanism of action

A WHO scientific group convened in 1968\(^\text{1}\) emphasized that the mechanism of action of contraceptive steroids was incompletely understood. This statement is still valid today. Inhibition of ovulation can explain the antifertility action of combined preparations. It is not certain, however, whether other effects of these compounds also contribute to their desired action, nor is there complete understanding of the mechanism of action of oral contraceptives that do not inhibit ovulation.

One of the difficulties in assessing the mode of action of contraceptive steroids in women is to ascertain, by the use of indirect methods, whether or not ovulation has been inhibited. Parameters used for the indirect appraisal of ovulation include urinary and plasma levels of follicle stimulating hormone (FSH) or luteinizing hormone (LH), plasma levels of progesterone and 17-\(\alpha\)-hydroxyprogesterone, urinary excretion of pregnanediol, and the plasma and urinary levels of certain oestrogens. The most significant recent developments in this field have been the wide use of immunological methods for assessing plasma and urinary levels of FSH and LH, and the extensive use of protein-binding methods to study daily variations in blood progesterone levels. Studies published so far indicate considerable variation not only among different individuals but also in the same individual in successive treatment cycles. This is particularly

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true when progestogens alone are administered orally in a continuous fashion. These data suggest that in order to reach definite conclusions concerning the hormonal parameters mentioned above, a large number of women need to be studied; such studies have not been published. Limited knowledge of processes such as sperm function and transport, fertilization, ovum and zygote transport, and implantation represent other obstacles to the understanding of the mechanisms of action of hormonal contraceptives. With these limitations in mind, the most probable mechanisms of action of the different types of contraceptive steroids may be characterized as follows:

2.1.2.1 Combined oral formulations

The balance of evidence indicates that the combined oral formulations at present in use interfere with ovulation and ovarian steroidogenesis in an overwhelming majority of cases. This result is secondary to suppression of the hypothalamo-hypophyseal system for production and release of gonadotrophins. This conclusion has been arrived at chiefly by study of various parameters indicated above. Evidence for suppression of ovulation is also provided by inspection of the ovaries at laparotomy. Combined oral contraceptives, apart from suppressing ovulation, also induce histological and biochemical changes in the endometrium, physicochemical changes in the cervical mucus, and changes in tubal physiology and uterine motility. It is not known, however, whether these changes are involved in the antifertility effect of the combined preparations.

2.1.2.2 Sequential formulations

Available evidence indicates that inhibition of ovulation and of ovarian steroid production occurs in a majority of women taking sequential formulations, and that it is due mainly to the feedback action of oestrogens during the first phase of the treatment. Sperm penetration occurs readily and has been shown not to be altered until the progestational phase of the regimen.

2.1.2.3 Oral progestogens administered continuously

Hormonal studies have been carried out in subjects taking various types of continuous oral progestogens. As had been stated by a previous WHO Scientific Group such formulations do not consistently inhibit ovulation although they offer a high degree of protection against conception. This has been further substantiated by recent long-term studies on plasma and urinary LH, plasma progesterone, and urinary pregnanediol. These studies reveal that the mid-cycle LH peak is often reduced, and

that such a reduction may or may not be associated with absence of the post-ovulatory rise in plasma progesterone and urinary pregnanediol. In other subjects, plasma progesterone levels showed a definite post-ovulatory rise, although this was somewhat lower than in the preceding or subsequent untreated cycle. It is therefore not always possible to define the exact relationship of plasma or urinary LH, plasma progesterone, or urinary pregnanediol levels to ovulatory or non-ovulatory cycles. In addition to their effect on the hypothalamo-pituitary axis, certain oral progestogens have been shown to interfere with the normal steroidogenic process in the corpus luteum.

Oral progestogens administered continuously are known to induce changes in the physico-chemical properties of the cervical mucus, but the significance of these changes is unclear as these changes are also brought about by dose levels that do not have an antifertility effect. Oral progestogens also influence both the histological and biochemical characteristics of the endometrium, and it has been suggested that the endometrium exposed to the continuous use of progestogens becomes unsuitable for implantation. Since continuous oral progestogens given only during the second part of the cycle have little if any contraceptive effect, their antifertility effect cannot be attributed only to an action on the endometrium. Whether such formulations affect other functions, such as sperm transport, capacitation, fertilization, and ovum transport, in the human remains to be investigated further.

2.1.2.4 Slow-release preparations

Injectable combined oestrogen-progestogen preparations interfere with ovulation in the majority of women studied, as evidenced by urinary and plasma gonadotrophin levels and by the inspection of ovaries at laparotomy. Injectable preparations of progestogens alone also inhibit ovulation, as indicated by the same criteria. The administration of injectable progestogen results most frequently in endometrial atrophy resulting from continuous progestogen stimulation in the absence of sufficient ovarian oestrogen production to provide adequate endometrial priming.

2.2 Mechanism of Action of Intrauterine Devices

2.2.1 Antifertility effects

Since the last report on intrauterine devices,\(^1\) relatively little information has been published on studies in man. This section, therefore, refers mainly to data published on experiments in animals.

2.2.2 Systemic effects

The previous report on this subject reviewed information available until 1968 on systemic effects associated with the presence of an IUD. In summary, the data revealed that there were no systemic responses other than those of the hypothalamo-hypophysal-ovarian axis, which included effects on the timing of LH release from the pituitary of rabbits or ewes. The significance of these findings still remains unclear. The most puzzling observation was the failure of the Indian water buffalo to form corpora lutea when fitted with an IUD. The interpretation of this finding has now been obscured by the realization that the devices used caused uterine distension. The effect could thus have been due either to the foreign body or to the distension, a phenomenon that in itself could cause neurogenic suppression of ovulation.

2.2.3 Mechanisms of action suggested

In all animal species studied, the presence of a foreign body in the uterus undoubtedly exerted an antifertility effect. Among possible explanations of this action, it has been suggested that myometrial function was altered so as to prevent fertilization or to expel the fertilized egg; that tubal transport of ova, fertilized or unfertilized, was accelerated; that biochemical changes in the endometrium made this tissue unable to deciduate and nidate a blastocyst; that endometrial sensitivity to mechanical stimuli at the time of implantation was impaired; that the response of the uterus to endogenous hormones was altered; and that the mobilization of polymorphonuclear leucocytes created a uterine environment hostile to spermatozoa or to blastocysts. Several of these theories have been abandoned in the light of subsequent data, while others have developed from observations in a single species that cannot be transferred to other species, including man. The theory implicating mobilization of polymorphonuclear leucocytes was based first on work with rats, and has since been supported by observations on mice, rabbits, the rhesus monkey, and the human female.

2.2.4 IUDs and leucocytic infiltration

In 1965 it was reported that an inflammatory reaction occurred along the entire length of rat uterine horns containing foreign bodies. A leucocytic infiltration of the endometrium was consistently observed in uteri from which embryos were missing, whereas implantations did occur when the foreign body failed to mobilize leucocytes. The antifertility effect of a localized foreign body was enhanced by treating the animals with phenylbutazone, a compound that increased the production
of leucocytes by bone marrow. In such animals, an enhancement of the leucocytic invasion of the endometrium was observed. On the other hand, the use of an inert foreign body — stainless steel instead of silk — reduced both the inflammatory response and the antifertility effect.

That the association of inflammation with the antifertility activity of an IUD is not specific to the rat is evident from observations in cattle, sheep, rhesus monkeys, and women. In each of these species, microscopic evidence of inflammation associated with IUDs has been reported. The term "inflammation", although generally accepted, may be too broad to characterize the observed leucocytic infiltration of the endometrium, since it is unaccompanied by increased capillary permeability, and any suggestion that it resembles inflammation due to infection should be avoided. Furthermore, although phagocytic activity by macrophages is characteristic of the inflammatory process, investigators working with fixed material have not singled out phagocytosis as a histological characteristic of uteri containing foreign bodies. The reaction to such foreign bodies in the human female has been reported to consist of infiltration with polymorphonuclear leucocytes, plasma cells and lymphocytes in the stroma and the lumen of the uterus. The incidence of this reaction has been reported to be highest in the first few months after insertion of an IUD. One investigator has also reported leucocytic infiltration in the fallopian tube. Smear preparations made from IUDs freshly removed from human uteri have shown macrophages in large numbers surrounding the device. Endometrial aspiration smears from control patients have shown few if any macrophages.

2.2.5 Leucocytic infiltration and antifertility action of IUDs

Several investigators have shown that the segment of the uterus rendered infertile by the presence of an IUD is usually the same as the segment infiltrated by polymorphonuclear leucocytes. In the rat, which has a uterus divided into two by a cervical septum, leucocytes and antifertility effects have been observed as early as two days in the horn containing the foreign body, fertility remaining unaffected in the contralateral horn.

In the mouse, which has an incomplete cervical septum, a unilateral foreign body causes bilateral infertility although normal fertilization and ovum transport take place on both sides. Leucocytic infiltration occurs in the endometrium and lumen of both horns, in contrast to the findings in the rat. Surgically separated uterine horns in the mouse respond identically to those of the rat with respect to both fertility and leucocytic infiltration. These experiments can be viewed, therefore, as further confirmatory evidence that a direct relationship exists between the region of infertility created by an intrauterine foreign body and the region of leucocytic infiltration. In man, the incidence of ovarian pregnancies
in the presence of an IUD has been reported to be higher than expected. The presence of leucocytes in the uterus and fallopian tube indicate indirectly the relationship of leucocyte infiltration to the antifertility effect of the IUD. Further studies in man are, however, needed to clarify this relationship.

2.2.6 Quantitative measures of uterine leucocytes and fertility

The mild response to an IUD in the rabbit has been used to establish the correlation between the number of leucocytes per mm³ in uterine flushings and several quantitative measures of fertility—leucocytes in these washings being primarily polymorphonuclear leucocytes. Experiments have indicated that as the leucocyte count increases the fertility ratio decreases progressively, the fertility of each horn being measured in terms of implantation sites per number of corpora lutea in the corresponding ovary. Using the normal development of a rabbit implantation site as the measure of fertility, the concentration of leucocytes elicited by the foreign body has been shown to correlate directly with the intensity of the antifertility effect. In the rabbit, a linear relationship has been reported between the leucocyte concentration and the distance between two implantation sites, as an expression of the antifertility effect of an IUD. Data published on the rabbit are thus strong evidence that the action of the foreign body can be closely correlated with the leucocyte stimulation evoked by the foreign body.

2.2.7 Consequences of leucocyte mobilization

The uterine fluid of a uterus with a foreign body resembles an inflammatory exudate, containing polymorphonuclear leucocytes and the products released from leucocytes. For example, measurable quantities of lysozyme are found in the IUD-containing uterine horns of rats or rabbits, but not in the control horns of the same animals. Other lytic enzymes are undoubtedly released as leucocytic degradation occurs.

Calcium levels are higher in endometrial tissue extracts taken from women with IUDs than in controls and the total protein concentration of the uterine fluid is elevated. Both these phenomena may be related to the inflammatory process.

Whether the uterine environment in such circumstances is primarily blastotoxic, spermotoxic or antagonistic to the functions of the endometrium has not yet been established. That the blastocysts do not survive long in this environment has been shown by ova recovery experiments. However, the deterioration and disappearance of ova could be secondary to their failure to nidate on schedule.
Methods of Fertility Regulation

Studies on ovum transfer undertaken to analyse the antifertility effect of metallic copper when placed in the rat uterus have further substantiated these views. The contraceptive action of intrauterine copper was shown to be due to an influence on the uterus, and not on the blastocysts. Normal blastocysts transplanted into rat uteri that had contained a copper device failed to implant. Conversely, when copper-influenced blastocysts were transferred to normal uteri, the percentage of successful implantations was similar to the control value. The effect of copper, therefore, appears to be primarily on the uterus, but whether this is mediated through a leucocytic stimulation remains to be investigated.

2.2.8 Conclusion

The relationship between the antifertility action of intrauterine foreign bodies and leucocyte stimulation seems to be a close one. From the aggregate of evidence the principal mechanism of action of intrauterine foreign bodies appears to be that they stimulate leucocyte mobilization in the uterus and, in most species, the concentration of leucocytes is inadequate to create a spermotoxic environment but sufficient to prevent nidation of normal blastocysts arriving, on schedule, from the oviducts. It will be of great interest to pursue the question at a more fundamental level, in the hope of extending understanding to intracellular events. Meanwhile, a practical conclusion to be drawn from present knowledge is that the size and shape of an IUD probably has less bearing on its effectiveness in preventing pregnancy than does the nature of the material and the leucocytic response it elicits.

3. Effectiveness and Continuation of Use of Steroidal Contraceptives and IUDs

Any discussion of the effectiveness of contraceptive methods must distinguish between theoretical effectiveness and use-effectiveness. Theoretical effectiveness refers to the antifertility action of the compound, device, or procedure under ideal conditions, without omissions or errors in technique. Use-effectiveness reflects the level of protection achieved by a population using the method, in a given place, at a given time under given circumstances. To a considerable extent, use-effectiveness is determined by continuation of use and consistent practice of whatever method has been adopted by the couple. In turn, continuation and regularity of use reflect, among many other factors, the frequency of side effects experienced with the method.
3.1 Theoretical Effectiveness

3.1.1 Combined oral contraceptives

Assessment of theoretical effectiveness continues as experience accumulates. It remains true that, taken according to the prescribed regimen, oral contraceptives of the combined type are almost 100% effective in preventing pregnancy. Large-scale clinical studies cover a total of about 325,000 cycles of medication. Only 17 pregnancies during this period of use were considered by the authors to be failures of the method, because they were not associated with the omission of one or more tablets, according to the statements of the users. The occurrence of one pregnancy in almost 20,000 cycles of consistent use suggests a level of theoretical effectiveness corresponding to a rate of 0.07 pregnancies per 100 women per year, with lower and upper 95% confidence limits of 0.03 and 0.10 per 100 women-years. The significance of these statistics should not be exaggerated. The classification of a pregnancy as a method failure depends on the user’s response to questioning by the investigator, which may be more persistent in some instances than in others. It may be significant that 9 of the 17 method failures were reported in the original study of norethynodrel with mestranol in Puerto Rico, covering about 36,000 cycles without omission of tablets. It is not unlikely that later investigators, expecting a 100% level of effectiveness, probed more intensively. All that can be said with certainty is that “true” method failures appear to be extremely rare.

3.1.2 Sequential oral contraceptives

Sequential medication appears to be less effective than combined medication. Published clinical studies, in which method failures are separated from patient failures, cover approximately 116,000 cycles of medication with 30 pregnancies not associated with the omission of one or more tablets, corresponding to a failure rate of 0.34 per 100 women per year, with 95% confidence limits of 0.20 and 0.56 per 100 women-years. As with combined medication, about one-half of all pregnancies classified as method failures among users of sequential oral contraceptives originated in a single study covering about 27,000 cycles, with 15 method failures and 29 patient failures. The greater frequency of method failures with the sequential regimen, as compared with the combined regimen, may reflect the absence during the major portion of the cycle of the subsidiary effects of the progesterogen component which, under the combined regimen, neutralize the occasional failures of the oestrogen component to suppress ovulation.
3.1.3 Continuous progestational contraceptives

Published clinical experience with continuous (noncyclical) ingestion of small doses of progestogen alone (without oestrogen) is now available for many different preparations. Large-scale experience is limited to chlormadinone acetate in the 0.5 mg dosage, a product that has recently been withdrawn from sale or investigation in several countries following reports of the development of breast nodules in beagle dogs treated with the substance (see section 4.3.2.2). Five studies of chlormadinone acetate, each based on more than 1200 cycles have been published, totaling 23,000 cycles in all. Forty-two pregnancies were attributed to method failure, corresponding to a rate of 2.3 pregnancies per 100 women per year, with lower and upper 95% confidence limits of 1.6 and 3.0 respectively. Thus, theoretical effectiveness appears to be substantially lower for the continuous low-dose preparation than for oral contraceptives of either the combined or the sequential type.

3.1.4 Injectable progestational contraceptives

Among the hormonal type contraceptives still in the testing stage, injectable progestational agents appear to be highly effective, although not 100% reliable. A few pregnancies have been reported even among women who received their injections according to the prescribed schedule.

3.1.5 Intrauterine devices

Information on effectiveness is most complete for intrauterine devices, since theoretical effectiveness and use-effectiveness are almost identical with this method. According to the experience of the Cooperative Statistical Program in the United States of America, which reflects mainly clinic practice, failure rates based on all pregnancies with the most widely used IUDs—i.e., the large sizes of the loop (C and D), the large spiral, and the double coil—ranged from 1.5 to 3.0 per 100 women during the first year of use and declined during later years. Failure rates based on pregnancies with the IUD verified as in situ averaged about one-fourth less than the corresponding rates based on all pregnancies. Since some conceptions after an IUD has been expelled could have been avoided by careful self-examination, the theoretical effectiveness of the loop may be placed somewhere between the rate based on all pregnancies and the rate based on pregnancies with IUDs in situ.
3.2 Use-Effectiveness and Continuation of Use

In the evaluation of use-effectiveness and continuation of use of intrauterine and oral contraceptives, a number of important developments have taken place over the past 3 years, i.e., since the most recent meetings of WHO scientific groups on these subjects in late 1967.

During this period, follow-up studies of women fitted with IUDs, based on samples of acceptors in national programmes, have been made in a number of countries. The life table method of analysis has been employed in most of these studies, but the level of statistical sophistication achieved varies widely, as does the success of the investigators in implementing adequate follow-up procedures. In some instances it cannot even be determined whether published cumulative termination rates are gross rates or net rates, or whether continuation rates are based on first segments or on all segments of use (see definitions of these terms below). It is important to keep these distinctions in mind.

Gross cumulative rates, derived from a single-decrement life table, are based on independent probabilities of experiencing a particular type of termination during successive months. Net rates, on the other hand, are derived from a multiple-decrement life table and are based, for each type of termination, on monthly probabilities of termination, which are dependent on the incidence of different types of termination. Net rates are always lower than the corresponding gross rates.

Gross rates are more suitable than net rates for evaluating the relative incidence of a specific type of termination for different types of device and among different groups of users, characterized by demographic, socio-economic, or cultural attributes. Net rates, on the other hand, have the advantage that they can be summated to arrive at a total termination rate from all causes, of which the continuation rate is the complement. This procedure is not applicable to gross rates.

A “segment” of IUD use is defined as the period beginning with the insertion of a device; it may be still continuing at the time of the study or may have been terminated by pregnancy, expulsion, or removal of the IUD. “First segments” are those starting with the first insertion of an IUD; “all segments” means the total of all segments initiated by the insertion or re-insertion of a device. Continuation rates based on first segments are always lower than continuation rates based on all segments. The latter reflect more completely the level of protection against unwanted pregnancy enjoyed by the population; they also reflect the willingness of users to seek or accept re-insertion and the willingness of doctors or other health personnel to re-insert IUDs.

In general, continuation rates have been lower in national programmes than had been expected on the basis of experience in those clinics in the same country where the IUD was originally evaluated. When it
became manifest that IUDs were not accepted by a substantial portion of the population, several countries began to include oral contraceptives in their family planning programmes, and, consequently, to evaluate experience with this method. However, the application of the life table to the analysis of the continuation of use and use-effectiveness of oral contraceptives has lagged substantially behind the evaluation of the IUDs, partly because of uncertainty among researchers as to how to cope with "missed cycles" and the problem of incomplete follow-up.

In most localities where continuation rates for oral contraceptives have been computed for clinic populations, they were found to be lower—at times substantially lower—than comparable rates for IUDs.

In the United States, where use of oral contraceptives has become the leading method of contraception, the 1965 National Fertility Survey (NFS) showed that the continuation rate prior to 1965 was 73% 1 year after starting use and 62% 2 years after starting. These rates do not take into account suspension of contraception in order to plan pregnancy. In this survey, the 2-year continuation rate was only 56% for women over 30 years of age and for those with 3 or more children. No later national data are available from the United States, and none for any other country.

To date studies suggest that pregnancy usually occurs promptly following discontinuation of use of hormonal contraceptives or IUDs (see however section 4.3.3). A useful concept is that of "extended use-effectiveness", whereby any period of non-use, other than non-use to achieve pregnancy or non-use without exposure to the risk of pregnancy, is assimilated to the preceding period of use. In this way it is possible to compute cumulative pregnancy rates that include all unplanned conceptions following acceptance of the first method, i.e., conceptions occurring during use of the first method, those with other methods, and those after discontinuation of contraception. Where both oral contraceptives and IUDs have been offered to and adopted by considerable numbers of women attending the same family planning clinic, cumulative pregnancy rates have been found consistently and significantly higher for those using the former.

Detailed epidemiological analysis of these findings is needed, as well as additional studies to determine their general applicability.

SIDE EFFECTS OF STEROIDAL CONTRACEPTIVES AND IUDs

4.1 Methods of Evaluating Side Effects of Steroidal Contraceptives

At the outset, it should be stressed that, although it has become commonplace to refer to "the oral contraceptives" or to "the pill" as if all the various formulations are equivalent, they do in fact differ
in the nature of the constituent steroids, steroid dosages, or both. It
is obvious that hormone dosage is likely to be an important factor in
determining the effects of any preparation, but it should also be noted
that the individual constituent steroids, especially the progestogens, are
known to vary in certain respects and that oestrogens may modify the
actions of progestogens and vice versa. It follows that a comprehensive
evaluation of the side effects and safety of each individual oral contra-
ceptive formulation should be undertaken. To some extent this is, of
course, carried out during the development of a new preparation but,
as will be shown, there are formidable problems in attempting to assess
possible differences between formulations with respect to rare adverse
reactions that may affect less than one in every 1000 users.

4.1.1 Common side effects

By definition, common side effects, such as nausea, headache and
breast tenderness, occur with sufficient frequency to be assessed during
the course of normal clinical investigation. Unfortunately, however, a
great deal of confusion still exists as to the frequency with which such
side effects occur, largely because they are difficult to define and mostly
subjective. The results obtained in an investigation therefore depend
closely on such factors as the phrasing of questions and the personal
biases of the investigator. Adequate assessment requires double-blind,
randomized trials in which different contraceptive formulations can be
compared according to a standardized protocol. Although they present
no special difficulties, remarkably few such trials have been reported.
The inclusion of a placebo group in double blind trials would, of course,
be extremely difficult; all participants in the trial would have to agree
to avoid or accept any risk of pregnancy or to use some other contra-
ceptive method. Since, however, the absolute levels of the common
side effects are of less interest than the comparative levels between different
contraceptive preparations, placebo comparisons are unlikely to be required.

In planning such trials, attention should be paid to ensuring an
adequate sample size and, in reporting rates of occurrence, a clear dis-
tinction should be made between rates per 100 cycles and rates per
100 women. Little attention has been paid to these principles in much
past work.

4.1.2 Rare side effects

4.1.2.1 Animal studies

As with all other drugs, the development and initial evaluation of
oestrogens, progestogens and oral contraceptives depends largely on
animal experiments. Unfortunately, however, many of the infrequently
occurring adverse effects of drugs in man cannot be predicted from currently used toxicological investigations in animals. This may be due not only to intrinsic differences between species, but also to the difficulty usually experienced in making an adequate assessment of the comparability of dosage levels and durations of treatment between man and other species.

Despite these problems, animal studies undoubtedly do have some role to play in the study of rare adverse effects of contraceptive steroids. Thus, on occasion, they may direct attention to areas of potential pathology in man, and sometimes they help to elucidate the mechanisms whereby adverse effects first observed in man are produced.

4.1.2.2 Human studies

Laboratory investigations

Investigations on relatively few human subjects have provided useful data concerning the effects of oral contraceptives on biochemical functions, metabolic processes and tissue morphology. Many studies of this type have been undertaken. For example, the effects of a variety of oral contraceptives on liver function tests, blood coagulation mechanisms, serum lipids, glucose tolerance, and endometrial histology, have all been investigated.

While studies of this type have, in general, been unable to show whether the changes observed will eventually result in overt disease, they have greatly increased understanding of the mechanisms whereby harmful effects might be produced.

Clinical investigations

In some circumstances it is possible to investigate the relationship between a drug and a suspected adverse reaction by alternately administering and withdrawing the drug and seeing whether there is any corresponding variation in the intensity of the reaction. This method can, of course, be used only when the reaction is reversible. It may be noted, however, that some of the most compelling evidence that steroidal contraceptives are a cause of jaundice and of hypertension has been obtained from investigations of this type.

Morbidity and mortality studies

From the preceding discussion it is clear that the investigation of the safety of oral contraceptives depends ultimately on the study of patterns of morbidity and mortality among women using the preparations. There are 4 principal sources of such information, namely, (a) clinical trials, (b) case reports in the medical literature and to official bodies responsible for drug safety, (c) official vital statistics, and (d) ad hoc epidemiological studies. These sources will now be considered individually.
(a) Clinical trials. The major clinical trials of efficacy and acceptability of oral contraceptives have provided useful data concerning the common side effects of medication but, for the following reasons, have made a very limited contribution to knowledge of the rarer major hazards: (1) the numbers of women studied have been too small to reveal infrequent effects, and follow-up has been continued for only a limited period of time; (2) an appropriate control series of women using non-hormonal methods of contraception has seldom been included; (3) follow-up coverage has usually been unsatisfactory. Attempts to make good these deficiencies should be made in future work.

(b) Case reports. Many hundreds of case reports concerning women who have suffered a fatal or major illness while using oral contraceptives have been published in the medical journals. The majority of these reports relate to thromboembolic disease or jaundice, but many other disorders have been observed as well. All the illnesses described are also known to occur in women who do not use oral contraceptives and so, in general, case reports do not provide valid evidence that oral contraceptives are a cause of the conditions in question. They do, however, serve as pointers towards areas where closer study might be useful.

(c) Vital statistics. Many countries publish detailed mortality statistics arranged according to the International Statistical Classification of Diseases. Examination of the trends in mortality from disorders suspected of being adverse reactions to oral contraceptives may throw some light on the existence or otherwise of an association. Clearly, evidence of this type is very indirect, but any major effect of oral contraceptives on mortality from a disorder that is otherwise uncommon should be reflected in the vital statistics when young male and young female death-rates are compared.

(d) Epidemiological studies. The need for intensive epidemiological investigation as the definitive method of evaluating the safety of oral contraceptives emerges clearly from all that has so far been discussed. Various groups of experts have suggested that large-scale prospective studies designed to provide data on the full possible range of adverse reactions to oral contraceptives should be undertaken, but surveys of this type present such formidable difficulties that many investigators have been reluctant to start them. The most important of these difficulties are as follows: (1) the number of women who would have to be studied is very large (see Table 1); (2) in a study starting now, a period of follow-up of about 10 years would have to be envisaged; (3) information concern-
TABLE I.  MINIMUM SAMPLE SIZES REQUIRED TO DETECT DIFFERENCES IN ANNUAL DISEASE RATES BETWEEN USERS OF ORAL CONTRACEPTIVES AND CONTROLS IN A PROSPECTIVE STUDY*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year of study</th>
<th>Average annual incidence rate in controls (per 10,000)</th>
<th>No. of persons required in each group:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>To detect a two- fold increase in incidence in oral contraceptive users</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1st</td>
<td>3.2</td>
<td>85,000</td>
</tr>
<tr>
<td>Corpus cancer</td>
<td>1st</td>
<td>0.3</td>
<td>60,000</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1st</td>
<td>3.1</td>
<td>60,000</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10th</td>
<td>7.5</td>
<td>25,000</td>
</tr>
<tr>
<td>Corpus cancer</td>
<td>10th</td>
<td>1.3</td>
<td>140,000</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>10th</td>
<td>5.6</td>
<td>35,000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1st</td>
<td>20</td>
<td>9,000</td>
</tr>
<tr>
<td>All malformations</td>
<td>1st</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>1st</td>
<td>20</td>
<td>9,000</td>
</tr>
</tbody>
</table>


It is assumed that the study group in each case consists of women who have at some time used the preparations, that the control group is of equal size, and that both groups are composed of women entering a prospective study at ages between 20 and 45 years. Incidence rates are lower than would normally be seen in women aged 20-45 years since they are calculated on the assumption that a representative sample of those who have at some time used oral contraceptives (in the USA) would contain a disproportionately large number of younger women. Rates are those that would be expected in the control group in the first year of follow-up and ten years later. Sample sizes given for malformations relate to the number of births. The table is computed for one-tailed significance tests at the 0.05 level with power equal to 0.8.

...ing morbidity as well as mortality would certainly be required; (4) it is impossible to predict which women will continue to take oral contraceptives for many years, which will never take them, and which will take them only for a short time; (5) the contraceptives now in use may not be the same as those to be used in the future; (6) there would be many opportunities for the intrusion of bias. Despite these difficulties, a number of comprehensive major prospective epidemiological studies have been started. It is too early to know whether or not valuable results are likely to be obtained.

In addition to comprehensive studies of the type referred to above, it is also possible, of course, to set up prospective epidemiological investigations in which a particular suspected adverse reaction to oral contraceptives is extensively studied. The requirements for such studies depend closely on the nature of the adverse effect under investigation. Examples of such investigations that are in progress include the prospective evaluation of blood pressure changes, and studies in which the transition from cervical dysplasia to carcinoma in situ is being assessed.

From the foregoing it is evident that little progress would have been made in evaluating the safety of oral contraceptives if prospective epidemiological studies were the only method of investigation available. There is, however, also the retrospective or case-control method. For the investigation of very small risks, such as that of death from pulmonary...
embolism, the retrospective approach may be the only practicable one. Such studies, however, are liable to distortion from bias in the selection of both the subjects with the disease under investigation and the controls, and they usually provide only very limited information about the magnitude of any risk that they demonstrate. Furthermore, they are designed to test specific hypotheses and cannot be expected to detect a completely unknown hazard. To compensate for these disadvantages, case control studies can provide results within a relatively short period of time and often require only small numbers of subjects to give statistically valid results (see Table 2).

<table>
<thead>
<tr>
<th>Percentage of women in population who at same time use oral contraceptives</th>
<th>Number of cases and controls required to detect a twofold increase in the risk of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>130</td>
</tr>
<tr>
<td>50</td>
<td>310</td>
</tr>
<tr>
<td>90</td>
<td>340</td>
</tr>
</tbody>
</table>


The method of computation is such that the same results obtain for all the disorders shown in Table 1 and for any others in the same low incidence range. The sample size does, however, depend on the prevalence of oral contraceptive use and requirements are shown for three different levels of use. The numbers given are those needed to detect a doubling of the risk of disease; even smaller samples are needed if the increase in risk is greater. The table is computed for one-tailed significance at the 0.05 level with power equal to 0.8.

4.2 Metabolic Effects of Steroidal Contraception

The combined oestrogen-progestogen oral contraceptives have been studied much more extensively since the last report. New data are available concerning metabolic effects that were recognized at the time the last report was written and some previously unidentified metabolic effects have been discovered.

Although the metabolic effects of progestogens alone, both orally and parenterally administered, are beginning to be studied, there is very little published information on this topic. Those studies that have been reported suggest that progestogens used alone in the doses employed
for oral contraception have few metabolic effects. The following account is therefore concerned with oestrogen-progestogen oral contraceptives, except where otherwise stated.

It needs to be emphasized that contraceptive steroids have wide-ranging metabolic activities that extend to tissues outside the generally recognized targets such as the genital tract, the pituitary gland, and the hypothalamus. The liver is especially involved in such effects. The metabolic changes induced by oral contraceptives are likely to be responsible for most, if not all, of the unwanted effects of oral contraceptives, such as thrombosis, weight gain, hypertension, and mood changes. An appreciation of these metabolic changes is necessary for an understanding of the clinical symptomatology induced by oral contraceptives, but it must be remembered that the significance of many of the metabolic effects remains unclear.

Attention should be drawn to the fact that metabolic studies with oral contraceptives have been confined predominantly to populations of European and American women. There is a regrettable absence of similar studies in women from other regions; differences in factors such as nutrition, climate, socio-economic status, and race may all be important. Likewise, general health as well as the prevalence in some regions of systemic diseases, such as malaria, bilharziasis and gastrointestinal disorders, must be considered. The conclusions drawn about the metabolic effects of oral contraceptives may, therefore, not necessarily be applicable to women outside Europe and the United States.

4.2.1 Effects on cortisol metabolism

Plasma cortisol levels are elevated in women taking oral contraceptives, but there is no interference with the diurnal pattern of cortisol secretion. The elevated levels are due mainly to an increase in the protein-bound fraction, but there is also a modest but definite increase in the free (non-protein-bound) plasma cortisol level. The oestrogen in oral contraceptives is responsible for this effect, which is mediated by an increased hepatic synthesis of the cortisol-binding globulin (transcortin); although the effect is dose dependent, it is still distinct with the preparations containing only 50 μg of mestranol or ethinyl oestradiol. Stimulation of transcortin production occurs within the first few days of oral contraceptive administration and persists throughout the period of use. A similar elevation of plasma cortisol levels occurs during the last trimester of pregnancy, but free plasma cortisol levels are higher in pregnant women than in oral contraceptive users.

In addition to the increase in plasma-bound and free cortisol that occurs in women using oral contraceptives, there is a considerable reduc-
tion in the rate at which cortisol is inactivated in the liver. This effect is also dose dependent and attributable to the oestrogen.

These various changes in cortisol metabolism may account for, or contribute to, a number of unwanted effects of oral contraceptives, such as weight gain, fluid retention, headache, hypertension, neuropsychiatric disturbances, and changes in carbohydrate and lipid metabolism. They also potentiate effects of glucocorticoids and ACTH when these substances are used therapeutically.

4.2.2 Carbohydrate metabolism

In previous reports reference was made to the impairment of glucose tolerance induced by oral contraceptives. This aspect has been more intensively investigated since then. It would appear that many women using oral contraceptives show detectable impairment of oral glucose tolerance and that in about 15% the impairment constitutes “chemical diabetes” as judged by conventional criteria, such as those advocated by the British Diabetic Association. It must be stressed that this abnormality is symptomless and as yet of uncertain significance.

The mean plasma insulin levels have been found to be elevated during the glucose tolerance test when the same women were tested before and after taking oral contraceptives. Some women, however, have a subnormal insulin response.

The mean blood levels of pyruvate and lactate, both fasting and during the glucose tolerance test, are elevated by the use of oral contraceptives.

The separate effects of obesity and oral contraceptives on carbohydrate metabolism have been identified and have been shown to be similar and to summate. Furthermore, the changes induced by small doses of glucocorticoids are comparable to those found in obesity and in women using oral contraceptives. The suggestion has been made that the mechanism for all these changes is an excess of glucocorticoid activity.

It is not yet clear whether these changes in carbohydrate metabolism vary with the type of preparation and the duration of use. It is generally believed that the changes are reversible, but one recent report suggests that this may not always be so. Some workers have found that the changes in carbohydrate metabolism are most distinct in older women and in those with a history suggesting a prediabetic state, such as gestational diabetes, large or congenitally malformed babies, or a strong family history of diabetes.

4.2.3 Effects on lipid metabolism

The most striking change in serum lipids induced by oral contraceptives is an increase in triglyceride levels. Almost all women show some elevation, and in about one-third the values are above the highest levels found in control subjects. There is a small but significant increase in serum cholesterol levels, and, in the only study reported, there was an increase in the low density and very low density lipoproteins. Some, but not all, reports show an increasing hyperlipidaemic effect with duration of therapy, and there is some evidence that the lipid changes are related to the steroid dosage, but this aspect needs further examination.

Various theories have been advanced to explain the influence of the oral contraceptives on serum lipids. Hyperinsulinism, depression of postheparin lipoprotein lipase activity, and stimulation of apoprotein synthesis have all been postulated as possible causes of these lipid changes.

4.2.4 Effects on the renin-angiotensin-aldosterone system

The occurrence of hypertension, usually reversible, in a proportion of women taking oral contraceptives has focused attention upon the changes induced by these compounds in the renin-angiotensin systems. The most prominent change is a 2–3-fold increase in the level of renin substrate, which is an $\alpha_2$-globulin synthesized in the liver. These changes occur within a few days of commencing the oral contraceptive. In the majority of women plasma renin levels are low, as would be expected with a normally functioning feedback mechanism, and the circulating angiotensin and aldosterone levels are normal. In some women who become hypertensive while taking oral contraceptives, the plasma renin levels are inappropriately high and in consequence the plasma angiotensin and aldosterone levels are also raised. These abnormal levels of angiotensin and aldosterone may explain the hypertensive effect of oral contraceptives, but other mechanisms may be involved, for example enhanced glucocorticoid activity.

4.2.5 Effects on tryptophan metabolism

Consistent changes induced by oral contraceptives have been demonstrated in the metabolism of tryptophan. These changes are of theoretical and practical importance because they may help to explain some of the neuropsychiatric symptoms experienced by some women while taking oral contraceptives. Tryptophan is normally metabolized by two pathways. The major pathway is the nicotinic acid-ribonucleotide sequence occurring predominantly in the liver, and the minor pathway the serotonin sequence occurring mainly in the brain. Serotonin levels
are thought to be important in determining mood and affect, low levels being associated with depression and sleep disturbances, and high levels with over-excitement and activity. Serotonin, a primary amine, is however only one of a number of such compounds which are thought to play a part in brain function. Within a few weeks of taking oral contraceptives containing a high oestrogen dose (100 µg or more of mestranol or ethinyl oestradiol), or within a few months of taking preparations containing a lower dose (50 µg), changes can be found in the urinary metabolites of tryptophan, especially after the challenge of a tryptophan load, which may be as little as 2 g. There is an abnormally high excretion of the end-product metabolite N-methyl nicotinamide and of the intermediate metabolites, kynurenine, 3-hydroxy kynurenine, xanthurenic acid, and 3-hydroxy anthranilic acid.

These changes can be brought about by cortisol alone and are due to the induction in the liver of the critical rate-limiting enzyme tryptophan oxygenase. Oestrogen given alone produces similar changes, but in the adrenalectomized rat the effect of oestrogen is abolished, showing its dependence upon endogenous cortisol, the activity of which is increased by oestrogens in the manner already alluded to above. The greater metabolism of tryptophan via the nicotinic acid-ribonucleotide path diverts tryptophan from the minor pathway and thus reduces its availability for the formation of serotonin (5-OH tryptamine) in the brain.

Certain of these metabolic abnormalities, namely the abnormal excretions of xanthurenic acid, kynurenine, and 3-hydroxy kynurenine, are also found in pyridoxine (vitamin B₆) deficiency. It is thought that some women taking oral contraceptives develop a relative pyridoxal deficiency. Similar changes are found in the latter part of pregnancy. Administration of vitamin B₆ in doses of 30-40 mg a day will correct certain of the abnormalities of tryptophan metabolism. The primary change, however, the induction of the rate-limiting enzyme tryptophan oxygenase, is unaffected. It remains to be seen whether the administration of vitamin B₆ to women taking oral contraceptives will offer any therapeutic benefit.

4.2.6 Effects on the blood clotting system

There is no longer any doubt that oral contraceptives increase the incidence of venous and arterial thrombosis in otherwise healthy women in Europe and the United States of America (see section 4.3.1). This state of hypercoagulability might be due to changes in the levels of various clotting factors, in platelet function, and in the physical state of the vessels themselves. In arteries, clotting appears to be initiated by platelet adhesion to damaged endothelium or foreign surfaces with formation of a fibrin thrombus. In veins it is the clotting process per se that is involved.
Oral contraceptives may increase the platelet count, their adhesiveness, and their response to aggregating agents. According to one report, so far not independently confirmed, the increased response to the aggregating agent adenosine diphosphate (ADP) shown by the platelets in women taking oral contraceptives and in patients with manifest occlusive vascular disease is due to an abnormality in the phospholipids in the low-density lipoproteins seen in both groups. This effect is produced by the synthetic oestrogens; progestogens alone are without effect upon platelet function.

Other significant changes that may occur in oral contraceptive users include a decrease in clotting time, a reduction in prothrombin time, a rise in fibrinogen levels, and an increase in factors VII, VIII, IX, X and XII. Increased fibrinolysis, as measured in the euglobulin lysistine, occurs in about one half of the oral contraceptive users, and appears to be an effect of the progestin.

4.2.7 Effects on the liver

Considerable research has gone into the study of the effects of oral contraceptives on liver function and structure. References have been made to much of this work in previous reports. Bile excretory function is reduced, and changes in the levels of numerous hepatic enzymes have been found; electron microscopy shows changes in hepatic cell ultrastructure, including dilatation of the canaliculi, shortening or disappearance of microvilli, intracytoplasmic dense bodies, myelin figures, and dilatation of the smooth endoplasmic reticulum. Although these studies are valuable in helping to explain changes in the overall metabolic function of the liver, as exemplified by the precipitation of an attack of acute intermittent porphyria in a predisposed subject through the induction of the mitochondrial enzyme 5-aminolaevulinic (ALA) synthetase, no new disease process has been revealed that would make it necessary to modify existing practice in the use of oral contraceptives.

4.2.8 Other metabolic effects

Changes in many additional metabolic functions have been described but they are for the most part symptomless and of uncertain clinical significance. They include increased fasting plasma levels of growth hormone and protein-bound thyroxine, raised serum iron and copper, decreased serum and urine magnesium, low folate levels in red cells and serum, and abnormal urine FIGLU excretion after histidine loading. The level of several plasma amino acids is altered by oral contraceptives, and the concentration and pattern of various serum proteins is also altered.
4.3 Clinical Aspects of Side Effects of Steroidal Contraceptives

4.3.1 Thromboembolic phenomena

4.3.1.1 Venous thrombosis and pulmonary embolism

Since the publication of the last report on hormonal contraceptives, a great deal of new evidence has become available concerning the relationship between oestrogen-progesterone oral contraceptives and venous thromboembolism. This new evidence may be summarized as follows:

(a) The detailed results of 4 case-control studies, 3 carried out in the United Kingdom and one in the United States of America, have been published. All these studies indicate that, in healthy women without predisposing conditions, the risk of developing deep-vein thrombosis or pulmonary embolism is increased 3–8 times by the use of oral contraceptives, the best estimate from the pooled data being 5 times. Absolute figures for the risk of thromboembolic disease are shown in Table 3.

<table>
<thead>
<tr>
<th>Morbidity [a] — general practice consultations</th>
<th>Age (years)</th>
<th>Annual rates per 100 000 healthy women without predisposing conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity [b] — hospital admissions</td>
<td>15–49</td>
<td>450</td>
</tr>
<tr>
<td>Morbidity [b] — hospital admissions</td>
<td>16–40</td>
<td>50</td>
</tr>
<tr>
<td>Mortality [b] — hospital admissions</td>
<td>20–34</td>
<td>1.5</td>
</tr>
<tr>
<td>Mortality [b] — hospital admissions</td>
<td>35–44</td>
<td>3.9</td>
</tr>
<tr>
<td>Mortality [b] — hospital admissions</td>
<td>45–64</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\[a] Venous thromboembolism (predominantly superficial thrombophlebitis).
\[b] Venous thromboembolism (deep-vein thrombosis and pulmonary embolism) and cerebral thrombosis.

(b) A further case-control study, carried out in the United Kingdom, has suggested that the use of oral contraceptives during the month preceding a surgical operation increases the risk of postoperative deep-vein thrombosis or pulmonary embolism 3–4 times.

(c) All these case-control studies have suggested that the increase in the risk of venous thromboembolism occurring in women using oral contraceptives is independent of the duration of use of the preparations.

(d) An analysis of reports of venous thromboembolic disease received by the national bodies responsible for drug safety in Britain, Sweden, and Denmark has shown that the thromboembolic risk is approximately proportional to the dose of oestrogen contained in the oral contraceptive preparations. No evidence was found in this study that the risks associated with products containing ethinyloestradiol differ from those associated with products containing the same amount of mestranol. In several countries, a recommendation has been made by the drug regulatory agencies that oral contraceptives containing more than 50 µg of oestrogen should not normally be prescribed.

(e) One study has indicated that genetic factors are involved in the risk of venous thromboembolism. The risk of developing deep-vein thrombosis or pulmonary embolism while using oral contraceptives appears to be 3 times as great in women of blood groups A, B, and AB as in women of blood group O.

(f) In addition to the epidemiological evidence of a relationship between the use of oral contraceptives and venous thromboembolism, there are other data that are relevant to the problem. Firstly, it has been shown that the use of large doses of oestrogens to suppress lactation increases the risk of puerperal thromboembolism. Secondly, oestrogens used in the treatment of arterial disease and cancer of the prostate in elderly men have also been found to increase the risk of both arterial and venous thrombosis. Thirdly, it is clear that oral contraceptives may increase the circulating levels of certain coagulation factors, may alter platelet behaviour (see section 4.2.6), and may increase venous distensibility and reduce venous blood flow. Finally, histological changes in the intima of the blood vessels of women dying from venous thromboembolism after using oral contraceptives have been described in a single study.

It should be noted that all the above studies have been carried out in Europe or the United States of America. It is commonly believed, although not clearly substantiated, that in some countries venous thromboembolic disease is rare. Whether the findings described above have any relevance for such countries is unknown.

4.3.1.2 Cerebral thrombosis

The 4 case-control studies referred to in the previous section (4.3.1.1) have also provided data concerning cerebral thrombosis. Although the numbers of cases are small, the findings have been consistent and, taken together, provide strong evidence that, in healthy women free from predisposing conditions, the risk of cerebral thrombosis is increased about 6 times by using oral contraceptives.
Additional evidence for this association has been provided by 6 out of 8 clinical series in which physicians reviewed their total experience of cerebral thrombosis in young women over a period of time.

There are not yet sufficient data available to determine whether the risk of cerebral thrombosis is dependent in any way on the duration of use of the preparations. It has been established, however, that the risk is approximately proportional to the dose of oestrogen, as is the case with venous thromboembolism.

4.3.1.3 Coronary thrombosis

While the epidemiological data relating oral contraceptives to venous thromboembolism and cerebral thrombosis seem to be clear-cut, those concerning coronary thrombosis are contradictory. The 4 case-control studies referred to in earlier sections did not provide any conclusive evidence of an association, but two recent findings suggest that a relationship may, in fact, exist. Firstly, among 22 women of fertile age treated for coronary thrombosis in recent years by one physician in Edinburgh, Scotland, 50% had been using contraceptive steroids, a much greater proportion than that corresponding to the general level of use of the preparations in the population. Secondly, the study referred to earlier that showed a relationship between the oestrogen content of oral contraceptives and the risks of both venous thromboembolism and cerebral thrombosis also showed a similar relationship for coronary thrombosis.

The changes in carbohydrate and lipid metabolism that have been described in earlier sections are of a type known to occur in some subjects predisposed to coronary thrombosis. There is thus some reason to suspect that oral contraceptives may eventually be shown to increase the risk of this disease. Further epidemiological studies are urgently required. These studies should take into account the recently demonstrated fact that women who use oral contraceptives tend to smoke more heavily than other women. Cigarette smoking is known to be an important risk factor in coronary thrombosis in young adults.

4.3.2 Malignant disease

4.3.2.1 Carcinoma of the cervix

In the 1968 report, it was noted that some observers have reported an association between the use of oral contraceptives and the occurrence of focal hyperplasia of the cervical glandular epithelium in a few women, a finding that has been supported by more recent studies. No evidence was presented that the preparations might also increase the risk of cervical cancer. Since that time, however, a survey of women attending family planning clinics in New York City has revealed that the prevalence of
epithelial abnormalities of the cervix, diagnosed after biopsy as carcinoma in situ, was higher among women using oral contraceptives than among those using the diaphragm.

In this study, women who had used oral contraceptives for one year or more were individually matched against diaphragm users with regard to 5 variables — age, parity, age at first pregnancy, ethnic group, and family income. Because more women had used oral contraceptives (6331) than the diaphragm (3874) and because the distributions of the two groups of women were quite different in terms of the 5 variables, 3 matchings were performed: (1) 1 woman who had used the diaphragm against 1 who had used oral contraceptives; (2) 1 diaphragm user against 2 oral contraceptive users; and (3) 1 diaphragm user against 3 oral contraceptive users. In each matching, the prevalence of carcinoma in situ was about twice as high among those who used oral contraceptives as among those who used the diaphragm, and the difference between the groups was statistically significant at the 5% level in each instance.

These results may be interpreted in at least 3 ways. Either the steroid contraceptives caused the development of carcinoma in situ, or the diaphragm protected against it, or the women who chose to use oral contraceptives were more likely, for reasons not taken into account in the matching process, to develop the pathological lesion. While it is impossible to be sure which of these possibilities was responsible for the results of the New York study, it may be relevant that in another recent report, women choosing oral contraceptives were found to have cervical dysplasia more often than those choosing other methods and that this difference could not be attributed to age, race, or family income. The need for further work is clear.

What sort of investigations should be undertaken? Retrospective studies are unlikely to be of much value as there are too many complicating factors that might interfere with their interpretation. Prevalence studies will give reliable results only if the population under study was previously unscreened or had a precisely known screening history (a requirement that was not met by the New York study). Prospective incidence studies, while feasible, are likely to be extremely difficult. An adequate study would have to incorporate a detailed sexual history from each participant — no mean undertaking when thousands of subjects are involved. The maintenance of a uniform cytological and histological technique would also present serious problems. Studies of the transition time for the conversion of cervical dysplasia to carcinoma in situ provide an attractive alternative approach, since the number of women required would be much smaller and the duration of the study would be much shorter. However, such studies require highly developed diagnostic and clinical facilities and continuous follow-up of all (or nearly all) participants.
Finally, a recent study has suggested that sexual activity may be increased by the use of oral contraceptives. If confirmed, this observation will further complicate the study of the relationship, if any, between contraceptive steroids and carcinoma of the cervix.

4.3.2.2 *Breast cancer*

Since the 1968 report was written, several progestogens, including chlormadinone acetate and medroxyprogesterone acetate, have been withdrawn from sale following reports of the development of nodules in the breasts of beagle bitches to which the steroids were administered. Full details of these animal studies are not yet available.

Little progress has been made in the last 3 years in evaluating the relationship, if any, between oral contraceptives and breast cancer in human beings. It may be noted, however, that at least 4 case-control studies and 3 large-scale prospective studies are in progress with the primary objective of elucidating this problem.

Finally, it should be noted that the most recently available vital statistics relating to the incidence of, and the mortality from, breast cancer in the United Kingdom and the United States of America do not show any changes in trend in the childbearing age group that could be attributed to the increasingly widespread use of oral contraceptives.

4.3.2.3 *Endometrial cancer*

No new data have been published concerning the possible relationship between oral contraceptives and endometrial cancer since the last report was prepared. This disease is extremely rare in women of childbearing age, and case-control studies are likely to provide the only approach to the problem.

4.3.3 *Subsequent fertility*

In the 1968 report, it was stated that previous levels of fertility are usually quickly restored after withdrawal of oral contraceptives, but that in a few women prolonged amenorrhoea and anovulation occur. Newer data support these conclusions, but controlled studies of adequate size remain to be done.

Amenorrhoea frequently occurs during the use of injectable progestogens and persists after discontinuation of the method. Restoration of ovulation after discontinuation of the method frequently takes many months and it is unknown whether all women regain their normal fertility.
4.3.4 Subsequent offspring

Concern about the possible effects of steroid contraception on subsequent offspring involves 3 groups of individuals: (1) children conceived while the mothers are taking oral contraceptives and therefore subject to the effects of the medication for several weeks of early intrauterine existence; (2) children conceived after discontinuation of contraception; and (3) future generations descended from those in groups (1) and (2).

While no systematic investigations of large numbers of children in groups (1) and (2) have been reported, the absence of case reports concerning group (1) and limited observations on several hundred children in group (2) have to some extent allayed earlier anxieties. A definitive assessment of the effect on future generations cannot be undertaken before the late 1980's, if at all.

One study has been reported in which 54 abortuses from women who conceived within 6 months of discontinuing oral contraceptives were subjected to chromosomal analysis. A highly significant excess of polyplloid abortuses was found in comparison with a control series. Trisomy and X-monosomy were not increased.

Even if these results are confirmed in other studies, it should be remembered that polyplloid is incompatible with live birth, so that an increase in chromosomally abnormal offspring would not be expected.

4.3.5 Lactation

Evidence suggests that combined oral contraceptive preparations decrease milk secretion in a way that is dose related. Studies have also indicated that contraceptive steroids and their metabolites are to some extent excreted in the milk, although their effect on the child is far from clear. In view of the importance of lactation in some developing countries and the possible adverse effects of steroids excreted in the milk, it is recommended that during the period of lactation other methods of contraception should be used if possible.

Continuous low doses of progestogens do not appear to affect the duration of lactation quantitatively. Injectable progestogen preparations have also been shown to have no adverse effect on lactation; indeed, it has been suggested that milk production may be increased by their use. Investigations on the immuno-electrophoretic pattern of breast milk have not shown significant changes, although increases in IgG and IgM have been reported in some cases.

4.3.6 Psychiatric effects

A number of controlled studies in which the possible psychiatric effects of oral contraceptives have been assessed by the use of standard
questionnaires have been published in the last 3 years. These studies have, in general, provided further evidence that oral contraceptives may cause depressive symptoms in some women. Women with previous attacks of depression and those who suffer from premenstrual depression may be at greater risk.

A possible mechanism whereby oral contraceptives might produce disturbances of mood has been discussed in section 4.2.5.

4.3.7 Hypertension

That oral contraceptives may cause hypertension in some women has now been established beyond reasonable doubt. The most convincing evidence of the effect has been obtained in women in whom the alternate administration and withdrawal of the steroids has been associated with corresponding changes in blood pressure. The frequency with which a blood pressure rise occurs in women after starting oral contraceptives remains to be shown.

A possible mechanism for this effect has been described in section 4.2.4.

4.3.8 Eye changes

Cases of papilloedema and other adverse ophthalmological phenomena have been ascribed to oral contraceptives. However, in the only well-controlled study that has been reported, in which 184 women using either combined, sequential, or low-dose progestogen preparations were compared with 361 non-users, no significant differences in eye abnormalities were found between the groups.

4.3.9 Venereal disease

The incidence of venereal diseases is rising in many countries, and attempts have been made to correlate this trend with the increasing use of oral contraceptives.

No conclusive evidence of this association has been provided, although it seems likely that the ready availability of oral contraceptives might encourage sexual contact without the protection afforded by the condom.

4.4 Side Effects of IUDs

No important new side effects of IUDs have been reported since the meeting of the WHO Scientific Group on the subject in 1967. However, greater experience with the IUD in the family planning programmes of a number of countries has brought about some changes in interest and encouraged research on specific aspects.
Sections 4.4.1 to 4.4.6 below concentrate on developments during the past few years and do not present a complete picture; they should therefore be read in conjunction with the previous report.¹

4.4.1 Bleeding

Abnormal vaginal bleeding is still the most frequent complaint of women fitted with the types of IUD in common use. In addition to the bleeding that occurs for a few days immediately following insertion, menorrhagia and metrorrhagia are frequently encountered. These menstrual irregularities are very common during the first few months, after which they tend to disappear. If they do not, the IUD is usually removed. Bleeding abnormalities also arise after satisfactory use for a few years. It is unknown whether the incidence of such bleeding episodes is higher than that of menstrual irregularities in a comparable group of women in the general population, without IUDs, followed up over similar periods of time. With the types of IUD most widely used, moderate bleeding during the first few months is a rule rather than an exception. In later months, bleeding, where it is a problem, tends to take the form of protracted or profuse menstruation, although intermenstrual bleeding is also observed. Menorrhagia rarely reaches haemorrhagic proportions, but even a moderate increase in blood loss may require medical attention, especially in the presence of pre-existing anaemia in malnourished populations. Removal of the IUD is indicated if the bleeding is profuse or persistent.

Most of the menstrual difficulties occurring soon after IUD insertion are thought to be related to the initial trauma and to physical and biochemical reactions of the uterus to the presence of the IUD. Recent studies with a very slender device in the form of a “T” have shown a decreased incidence of bleeding indicative of a direct relationship between the bulk, size, and configuration of an IUD with bleeding. No additional treatment has been described that is demonstrably superior to non-specific measures, such as rest and cold or hot compresses.

4.4.2 Pelvic infection

Pelvic inflammatory disease must not be confused with the sterile leucocytic infiltration that appears to be the basis of the mode of action of IUDs (see section 2.2). Pelvic inflammatory disease is a collective term that includes acute, subacute, and chronic conditions of the ovaries, tubes, connective tissue, and pelvic peritoneum and is usually the result of gonococcal infection, septic abortion, or poor care during delivery.

Although much remains to be learned about the epidemiology of pelvic inflammatory disease in the presence of an IUD, at least one carefully designed and executed study has been carried out. This showed that in an economically and culturally deprived population in the United States of America the incidence of pelvic inflammatory disease among women fitted with an IUD was significantly higher than among women using other contraceptives or no contraceptive.

The incidence of pelvic inflammatory disease is markedly higher during the first two weeks after insertion of an IUD than later. It is believed that in many cases the acute episode represents the reactivation of a pre-existing subchronic or chronic condition. Whether the insertion of an IUD can produce pelvic inflammatory disease in a healthy woman is not known.

Ten deaths attributed to pelvic inflammatory disease in the presence of an IUD have been reported in North America; 4 of these deaths occurred shortly after the insertion of an IUD and were attributed to the procedure. Since the number of IUDs inserted prior to the above-mentioned report is not known, it is not possible to compute a reliable rate of mortality.

4.4.3 Uterine perforation

Reports of uterine perforation following the insertion of an IUD continue to appear in the literature. However, there is no agreement among research workers as to the timing of this event. Some believe that most perforations occur at the time of insertion, whereas others maintain that an IUD properly placed in the uterus can translocate from the uterine cavity to the abdomen over a protracted period of time. The difference between these two views may be more apparent than real, since partial perforation of the myometrium at the time of insertion may be followed later by complete translocation of the IUD.

It needs to be emphasized that the body of the IUD may be partly or even wholly outside the uterus, while the appendage or tail is still visible at the external os. Early surgical removal of an IUD from the abdominal cavity following uterine perforation is mandatory for closed devices but may be optional for open devices.

4.4.4 Effect on pregnancy

In one study of 722 pregnancies, abortion was substantially more frequent (54%) if pregnancy occurred with an IUD in situ than if it occurred after the device had been expelled without the knowledge of the user (33%). It cannot be determined with certainty, however, what proportion of the pregnancies in either category were terminated by induced abortion. In the case of devices with appendages, removal of
the device during early pregnancy does not significantly affect the outcome of the pregnancy. Removal of the device by the introduction of a hook or other instrument into the uterine cavity increases the chances of abortion.

Ectopic pregnancies are relatively more frequent (1 in 20) among the few pregnancies occurring with an IUD in situ. This high ratio is caused by the fact that the IUD, by some mechanism, prevents uterine pregnancy more effectively than ectopic pregnancy; there is no evidence that the IUD can cause the conceptus to implant ectopically. Symptoms of pregnancy in a woman fitted with an IUD should alert the physician to the possibility of an ectopic gestation.

4.4.5 Expulsions

Efforts at reducing expulsion rates have been more successful in recent years than efforts to reduce the incidence of side effects leading to the removal of an IUD. It should be noted, however, that most devices shaped in such a way as to ensure a low expulsion rate are also more difficult to remove, so that the risks of haemorrhage or perforation during removal are increased. This difficulty does not arise with devices that have a low expulsion rate because of the incorporation of materials such as copper into their composition, rather than because of their shape.

4.4.6 Carcinoma

Carcinoma is not a known side effect of the IUD, although in view of the long latent period for the development of cancer in the human, no definite statement can yet be made.

The scanty data available relate to cervical cancer and not cancer of the endometrium and do not point to an increased incidence of the disease among women fitted with an IUD. Very carefully controlled studies have not provided any evidence that progress from dysplasia to carcinoma in situ is accelerated in IUD users compared to women using no contraceptives.

4.4.7 Deterioration of IUDs

In general, the plastic IUDs in common use are manufactured and distributed in batches of uniform quality and are not subject to deterioration either in storage or in utero. Instances of breakage of the device and/or of avulsion of the cervical appendage have, however, been reported to have occurred in association with attempts at removal or even spontaneously. These accidents point to the necessity of maintaining adequate quality control in the production process and/or at the point of procurement.
5. INDICATIONS AND CONTRAINDICATIONS

5.1 Oral Contraceptives

Advances in research and clinical experience during the past three years have increased understanding of hormonal contraception; at the same time, knowledge of both immediate and long-range effects remains rather limited.

Hormonal contraceptives have their place in contraceptive management; nevertheless, in view of their wide range of effects they should be prescribed with caution and their users kept under observation. It is necessary to assess the risks of steroid contraception in comparison with those of other methods and with those of not using any method whatsoever. Such an assessment will have to be made within the context of prevailing morbidity and mortality; the level and pattern of the health and educational services; and the availability of alternative methods of birth control. The social and cultural milieu may well affect the degree to which the various types of hormonal contraceptive and other methods of fertility control may be used effectively by different individuals and population groups.

The decision as to whether to use an oral contraceptive will be based on knowledge of the health and life situation of the individual. All women using contraceptive steroids should be made aware of potential risks and advised which symptoms or side effects should cause them to seek medical attention.

For healthy women, matters will be relatively straightforward, but for a woman with established illness, or with a known or suspected predisposition to a particular disease that may be aggravated by oral contraceptives, the decision is not so straightforward. In such a case, the known or presumed effect of oral contraceptives upon the disease in question must be balanced against the risks to the woman of an unwanted pregnancy should a less effective contraceptive method be used.

The following discussion refers primarily to oestrogen-progestogen oral contraceptives. Certain diseases, whether actually present or previously experienced, probably constitute an absolute contraindication to the use of oral contraceptives. These include cholestatic jaundice of pregnancy, benign familial recurrent cholestasis, chronic familial jaundice (Dubin-Johnson syndrome), acute intermittent porphyria, pruritus of pregnancy, herpes gestationalis, and cancer of the breast in a premenopausal woman. There are several other conditions in which oral contraceptives should be prescribed with considerable reluctance, if at all. They include past or current venous or arterial thromboembolism, congestive cardiac failure, pulmonary hypertension, active parenchymal liver disease,
and blood dyscrasias that carry an increased risk of thrombosis, such as polycythaemia or leukaemia.

Caution should be exercised in essential or malignant hypertension, and hypertension of renal origin, since oral contraceptives may aggravate the disease. In these conditions, therefore, the drug should be withdrawn if its use is associated either with further elevation of the blood pressure or the need to use larger doses of hypotensive agents than would otherwise be the case.

In diabetes mellitus requiring insulin, oral contraception should not be considered the method of choice, especially if the use of oral contraceptives leads to a substantial increase in insulin requirements, less satisfactory control of the diabetes, or a weight gain of more than 2–3 kg.

Oral contraceptives often cause patients with diabetes not requiring insulin to gain more weight, and glucose tolerance may be further compromised. Oral contraceptives may therefore be hazardous in such patients. Indeed, in symptomless chemical diabetes, oral contraceptives may provoke the overt manifestation of the disease.

A question to which there is no ready answer is whether to prescribe oral contraceptives for a patient with a strong family history of diabetes or other indication of a diabetic trait, such as the development of gestational diabetes or a suggestive obstetric history. Oral contraceptives should be prescribed with extra caution in such patients and, if possible, oral glucose tolerance tests should be carried out before treatment is started and after 3 months of treatment. Thereafter, yearly checks of glucose tolerance are a wise precaution.

Obesity is not, per se, a contraindication to the use of oral contraceptives, but it should be recognized that many obese patients have abnormal glucose tolerance and the incidence of diabetes, hypertension, and occlusive vascular disease is higher in obese subjects than in subjects of normal weight. Oral contraceptives may cause undue weight gain in non-obese subjects, and may aggravate the weight problem in obese women. The mechanism of the weight gain induced by oral contraceptives is related to changes in carbohydrate and lipid metabolism, especially the hyperinsulinism and the hypertriglyceridaemia.

Some fluid retention is a common finding in women in the first few cycles after starting oral contraceptive administration. It usually corrects itself spontaneously but may persist and produce frank oedema. Idiopathic cyclical oedema may be made worse by oral contraceptives, and this also applies to oedema seen in other conditions, such as hepatic insufficiency, cardiac failure, nephrotic syndrome, and renal failure. In conditions in which fluid retention is caused or aggravated by oral contraceptives, withdrawal of medication may have to be considered, since the alternative of a low-salt diet with or without diuretics is better avoided if possible.
Oral contraceptives may cause depression in otherwise healthy subjects or aggravate it in the predisposed woman, although in some depressed patients oral contraceptives have no apparent effect on the mood. Caution is therefore needed in prescribing these preparations in women with a history of depression, or who are depressed or become depressed while taking the medication. A possible mechanism for these effects has been described in section 4.2.5.

Persistent headache or migraine associated with the use of oral contraceptives is a relative contraindication to their continued use, and migraine associated with neurological symptoms, such as paraesthesia, or paresis, is a strong indication for stopping the drug. Epilepsy (grand mal or petit mal) may occur for the first time when oral contraceptives are used and continued use of the drug is then unwise. Similarly, if seizures are made more frequent, or are of greater severity, the oral contraceptive should be discontinued.

Choreiform disorders may be precipitated by oral contraceptive administration. Varicose veins, unless severe, or associated with thrombosis, are not a contraindication, but the rapid development of varicose veins during medication is generally recognized as a good reason for stopping the oral contraceptive.

A number of gynaecological conditions cause concern when oral contraceptives are used; these include preceding amenorrhoea or pronounced menstrual irregularity, especially in nulliparae, persistent amenorrhoeic cycles unresponsive to alterations in the oestrogen-progestogen combination, the occurrence of uterine fibroids, and non-malignant breast tumours.

There is a regrettable lack of information about the effect of oral contraceptive medication in the presence of malnutrition or systemic disease, such as bilharziasis. Likewise, the effects of such medication on adolescents whose growth has not ceased are still unknown. This should be borne in mind when prescribing oral contraceptives for adolescent girls.

5.2 Intrauterine Devices

The observations made in the 1968 report of a WHO Scientific Group concerning indications for and contraindications to the use of IUDs are still valid. Experience so far suggests that the “T”-shaped IUD with an element of metallic copper is likely to be better tolerated by the uteri of nulligravida women than the smaller devices previously prescribed for these women.

6. RECENT DEVELOPMENTS IN CLINICAL INVESTIGATIONS

Spurred by the success of hormonally induced suppression of ovulation as a method of contraception, but conscious of its limitations, scientists in several countries are searching for ways of interfering with other critical links in the reproductive chain of events. A variety of pharmacological agents and mechanical devices for use in the female and in the male are under clinical investigation. In the female, these are intended to influence sperm passage through the cervical mucus, the normal pattern of activity of the myometrium and/or the tubal musculature, the preparation of the endometrium for nidation, the function of the corpus luteum, tubal patency, and early embryonic development; in the male, the aim is to influence sperm motility or transport.

6.1 Modifications of Existing Methods

6.1.1 Intrauterine contraceptive devices

Preliminary observations on a new type of IUD were presented in a previous report. This device is made of polyethylene, shaped in the form of a slender T, with a thin copper wire around the vertical member of the T. It has been tested with several different lengths of copper wire and the contraceptive effectiveness has been found to be directly proportional to the surface area of the copper. According to preliminary studies, with a surface area of 200 mm² the effectiveness of the device approaches to, and may equal, the theoretical effectiveness of oral ovulation suppressants. Expulsion rates are very low, as is the incidence of complaints that may require removal of the IUD, such as abnormal bleeding. The available data justify the expectation that the continuation rate 12 months after insertion will be at least 90% and perhaps as high as 95%.

The daily loss of metallic copper through ionization in the uterine cavity is reported to be 30 µg, an amount considerably below the physiological daily requirements of that metal, which are normally met by ingestion of food and drink. Biopsies of human uteri over a period of 4 years have not revealed endometrial changes that would suggest a carcinogenic action of the copper, nor has a study of the world’s scientific literature revealed evidence of such an action.

6.1.2 Hormonal suppression of ovulation

6.1.2.1 Oral steroid combination taken monthly

Steroids that are stored in adipose tissue after absorption from the gastrointestinal tract are being investigated as possible one-pill-a-month contraceptives. The investigation is aimed at calibrating the oral dose of the combination so that it will result in a month-long release of steroid from the adipose tissue at a level sufficient to suppress ovulation while maintaining an acceptable endometrial bleeding pattern. Until now, the problems of uniformity of response and unpredictable endometrial bleeding have not been resolved.

6.1.2.2 Monthly injectable combinations

Intramuscular injections of steroids can give a depot effect, adjusted to last a single month. A widely tested monthly injection regimen has been based on the use of an injectable oestrogen-progestogen combination, the effect of which will “wear off” approximately 30 days after administration. For clinical situations in which the physician does not want control of drug therapy to be left to the patient’s responsibility, this procedure has distinct advantages, but more studies are required to establish the total pattern of safety, efficacy, side effects, and reversibility.

6.1.2.3 Long-term injectable progestogens

The most widely studied compound for injectable hormonal contraception is medroxy-progesterone acetate (6α-methyl-17α-hydroxy-progesterone acetate); several thousands of women have been included in studies in many countries. The regimen investigated most completely is 150 mg injected every 90 days, although studies are also in progress with semiannual injections of larger doses. With this procedure ovulation is generally suppressed. Nevertheless, ovarian follicle development appears to proceed, so that endogenous oestrogen production may not be completely obliterated. The endometrial pattern, however, reveals that the established oestrogen-progestogen balance is far from normal. As a result, uterine bleeding is totally unpredictable in women on this regimen. There is considerable patient variation but by the end of a year the majority of women have atrophic endometria and are amenorrhoeic. An extremely low pregnancy rate has been obtained with this procedure. There is, however, considerable delay in the restoration of ovulatory cycles when administration is stopped. Long delays in ovulation are not uncommon and the time required for the establishment of a regular ovulatory pattern after cessation of treatment is still not certain.
order to regularize the pattern of endometrial bleeding, some clinicians have employed the periodic administration of oestrogen either orally or by injection as an adjunct to injected progestogen. Since this requires monthly return visits, or self-administered monthly courses of oral oestrogen, it detracts considerably from the method’s simplicity. It should be stressed, however, that injectable preparations have a high degree of acceptability in certain parts of the world.

6.1.2.4 Silastic vaginal ring

The same compound has been tested for anti-ovulatory activity following absorption through the vaginal mucosa. A novel mode of administration, in the form of a vaginal ring, has been designed for this purpose. The compound is homogenized with a non-vulcanized form of a silicone polymer, and the mixture is moulded in the form of a ring, similar to the rim of a diaphragm. The physicochemical properties of the polymer are such that the hormonal steroid diffuses from the ring at a relatively constant rate, and can be absorbed through the vaginal mucosa. The daily release rate is sufficiently high to provide systemic levels of the hormone that cause pituitary suppression and the inhibition of ovulation. The vaginal ring can be positioned by the woman and left in place for three weeks. After removal of the ring, endometrial sloughing and bleeding occur. Subsequently, a new ring can be used for the next month. Thus, a simulated anovulatory menstrual cycle can be induced, similar to that achieved with anti-ovulatory therapy using oral hormones.

6.1.3 Hormonal contraception without suppressing ovulation

6.1.3.1 Low-dose continuous progestogens orally

Most of the data available on the mechanism of action, effectiveness, and side effects of low-dose oral progestogens (see sections 2.1, 3 and 4), relate to chlormadinone acetate, a preparation that has been withdrawn from use in most countries. Several other progestogens (norethisterone acetate, lynoestrenol, megestrol acetate, norgestrel, ethynodiol diacetate) continue to be evaluated, however, and have been found to be effective by low-dose continuous oral administration. With one of these compounds, norgestrel, low pregnancy rates have been reported, even with daily oral doses of 30–40 μg. At this dose level, the compound does not influence carbohydrate and lipid metabolism in the way that combinations of oral contraceptives do. However, approximately one-third of cycles are irregular. Until now, problems with cycle control have occurred with all progestogens used in continuous low-dose therapy.
6.1.3.2 Progestogen-containing subdermal capsules

Steroid hormones may be released at relatively steady rates from capsules made of various silicone polymers. One such material, polydimethylsiloxane, which is used in surgery, has been found acceptable for subdermal implantations in human subjects. Capsules made of this material and containing the synthetic progestogen 6-methyl-6-dehydro-17-a-acetoxy progesterone (megestrol acetate) are being tested as a method of providing, with a single administration, long-term, reversible control of fertility, while maintaining ovarian function and menstrual cycles. Studies are being conducted in several countries on a total of more than two hundred women and have now extended over 2 years. A cluster of 4 implants, which release approximately 80 μg of the steroid daily, provides highly effective contraception for a period of one year. With this procedure, cycle control is better than that achieved with oral administration of the same compound. Tests with modifications of the implants, with respect to both size and steroid content, are in progress.

6.1.3.3 Progestogen-containing intrauterine device

An intrauterine device of conventional size and shape has been modified by removing a small segment of the plastic and substituting a small silastic capsule containing progesterone. This modified device has been used in a small number of women. The method is based on the assumption that the local action of the released progesterone aids in reducing the removal and expulsion rates that would be expected with a conventional device.

6.1.3.4 Other experimental forms of hormonal contraception

Results obtained with the methods described above have already been published in the literature. Several other experimental forms of hormonal contraception are at present undergoing clinical trial; they include:

(a) Luteolytic, anti-progestational, or menses-inducing preparations. There are several synthetic steroids that appear to interfere with luteal function as measured by plasma progestogen determinations. They are being tested to induce menses in women with suspected early pregnancy or on a regular monthly schedule, at the time of the expected menses. A vaginal preparation of prostaglandin is being prepared for test on a similar basis.

(b) Immediate postcoital steroidal or non-steroidal contraception. This method aims at achieving contraception during the few days following coitus. For this purpose, conventional oestrogens are given in very
high doses, which give rise to considerable side effects. There are no reports yet to suggest that they are effective; indeed in one investigation they were found to be unsatisfactory. Several synthetic non-steroidal compounds are also under investigation.

(c) One-pill-a-week hormonal contraception. A compound reported to be anti-progestational in laboratory animals is being tested in several countries for antifertility activity based on a one-pill-a-week regimen. The mechanism of action of this contraceptive remains to be established.

6.1.4 Early abortifacients

At least two prostaglandins (PGF<sub>2α</sub> and PGE<sub>2</sub>) have been shown to interrupt gestation by causing myometrial contractions following intravenous administration. Thus far, best results have been achieved during the first 2 months of gestation. At later stages of gestation, however, incomplete evacuation of the uterus occurs frequently. This problem requires further study as do other safety considerations. Studies involving intrauterine and intravaginal administration are in progress.

6.1.5 Transvaginal chemical sterilization

In this method, sterilization is achieved without surgical intervention and hospitalization. An aqueous solution of mepacrine or another sclerosing chemical is administered through a catheter inserted into the uterine cavity. Over one hundred women who have been treated with mepacrine are now in the second year of observation. So far, spontaneous recanalization of the tubes has not occurred.

6.1.6 Temporary occlusion of the vas deferens

Procedures are being tested to replace vasectomy by vasal ligation in a manner that would improve the prospects for reversibility. One study involves the use of removable plugs made of silastic. Another approach consists of the use of removable clips applied through a small scrotal incision.

7. RESEARCH STRATEGIES AND GUIDELINES FOR THE DEVELOPMENT OF NEW METHODS OF FERTILITY CONTROL

There are three aspects to fertility control research and development: research on the biology, sociology, and health service implications of reproduction; clinical trials and related toxicological investigations; and the development of new products or techniques. Any overall strategy
for the development of new agents or methods for fertility control must take into proper consideration these three interlocking aspects.

7.1 Biology, Sociology, and Health Service Implications of Reproduction

Lack of knowledge about the biology, sociology, and health service implications of reproduction, is a major obstacle to the rapid development of new approaches and methods of fertility regulation. In order to discover additional steps in the reproductive processes that are susceptible to regulation and to provide ways and means for a more rational development of fertility controlling agents, there is a need for intensified research along the following lines:

The physiological regulation of the normal reproductive processes should be investigated in a wide range of animal species in general and in the human species in particular. The pharmacology of fertility regulating agents, including their metabolism and their metabolic effects, must be studied. Such research should be carried out in a large number of species in order to identify suitable animal models that have relevance to human pharmacological and toxicological problems. There is also a great need for the development of newer methods employing a variety of parameters—hormonal, cytological, metabolic, genetic, etc.—to determine both the desired and the unwanted effects of potential fertility-regulating agents.

A great deal of epidemiological work is required to define the range of variations of such reproductive phenomena as puberty, reproductive senescence, menstruation, gestation, and lactation, as well as the underlying physiological processes. Such studies should be carried out in a wide range of populations throughout the world.

The social and cultural aspects of reproduction, including its control, and the health service implications of different methods offer another important field of study. In particular, it is necessary (a) to examine folk practices of fertility control, especially where these appear to have a definite impact on natality; (b) to study the socio-cultural “profiles” of different populations in order to formulate approaches to fertility control best suited to their specific needs; and (c) to define the health service implications of individual methods in terms of such factors as personnel requirements, training, follow-up, and logistics.

7.2 Clinical Trials and Related Toxicological Investigations

General guidelines for clinical trials and related toxicological investigations in the field of fertility control methods are given in the report of a previous Scientific Group.¹ That report points out that because

of the fear of unwanted pregnancies, clinical studies of fertility controlling agents in the past were more often than not characterized by a failure to utilize generally accepted pharmacological principles to establish the dose-response relationship. A more liberal legislation on the interruption of gestation may improve this situation in several countries.

In order to permit any promising leads for new methods of fertility control to be followed up in clinical trials, it would be very desirable to establish co-ordinated programmes for the systematic assessment, in different parts of the world, of the mechanism of action, effectiveness, and side effects of potential methods. The use of a series of internationally accepted, technically sound protocols would be of great value in helping to determine the proper time for the initiation of large-scale clinical trials and related toxicological studies.

There is a need to establish a variety of administrative arrangements to ensure that decisions on drug development are based primarily on scientific considerations and social needs. In this respect, careful attention should be paid to the proper relationship between the public and private sectors.

The important role of national drug regulatory agencies in monitoring applied pharmacological investigations can best be fulfilled through closer collaboration among different national bodies, and between these bodies and the scientific community.

7.3 Development of New Products and Techniques

The Group recognized that even when agents and methods have undergone full toxicological and clinical investigation, many problems — e.g., patent rights, legal aspects, quality control, formulations, packaging and labelling — remain to be settled before they can be converted into final products for general use.

8. RESEARCH NEEDS

The Group reviewed the research needs listed in the previous reports on intrauterine devices\(^1\) and hormonal contraceptives\(^2\) and considered that the majority of them were still in need of attention.

In addition, the Group recommended that the following problems should be studied:

1. The metabolic effects of hormonal steroids in different geographical areas of the world.

(2) The natural frequency of thromboembolic disease in different geographical areas and the frequency of thromboembolic disease as a complication of oral contraception in those areas.

(3) The immediate and late metabolic changes induced by combined contraceptive steroids and by progestogens alone, the reversibility of these changes, and their relationship to overt disease.

(4) The metabolism of contraceptive steroids in different animal species used as pharmacological and toxicological models.

(5) The relationship between contraceptive steroids and hypertension (prospective studies).

(6) The relationship between contraceptive steroids and coronary thrombosis.

(7) The mechanism of pigmentation changes induced by contraceptive steroids.

(8) The effect of contraceptive steroids on immunological responses.

(9) The frequency distribution of the weight changes in women taking contraceptive steroids as compared with women using other fertility controlling methods.

(10) The effect of contraceptive steroids on enzyme induction.

(11) Incidence, mechanism, and treatment of galactorrhea and breast atrophy in women taking oral contraceptives, and in those who have discontinued taking such preparations.

(12) Induction of chromosomal changes by various fertility regulating agents.

(13) The relative effectiveness of various ovulation-inducing agents in re-establishing ovulatory cycles following the use of contraceptive steroids.

(14) The mechanism of actions of contraceptive steroids when ovulation is not inhibited.

(15) The effectiveness of post-coital oestrogens for fertility control.

(16) The improvement of methods for the study of changes in cervical mucus and endometrium, and the possible effect of different drugs on the secretion and induced spermatoxicity of cervical mucus.

(17) The influence of trace metals on the endometrium.

(18) The recovery of sperm from the fallopian tubes of women using different types of IUDs, especially those containing copper.

(19) The use of serial sections of uterine strips, instead of tissue samples from endometrial biopsy, to ascertain histological changes caused by different types of IUD.
(20) The occurrence of uterine leucocytic infiltration in women using different types of IUD.

(21) Establishment of standards for assessing the quality of IUDs, with special reference to deterioration and breakage.

(22) The effect of contraceptive steroids on subsequent pregnancy, outcome of pregnancy, and the subsequent child.