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CLINICAL ASPECTS OF ORAL GESTOGENS

Report of a WHO Scientific Group

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WORLD HEALTH ORGANIZATION

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WHO SCIENTIFIC GROUP ON THE CLINICAL ASPECTS
OF ORAL GESTOGENS

Geneva, 30 November - 6 December 1965

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CLINICAL ASPECTS OF ORAL GESTOGENS

Report of a WHO Scientific Group

A Scientific Group was convened between 30 November and 6 December 1965 in Geneva to advise the Director-General on the clinical aspects of oral gestogens. This was done, in part, as a response to the resolution¹ adopted by the Eighteenth World Health Assembly on 21 May 1965, a portion of which stated "requests the Director-General to develop further the programme proposed : (a) in the fields of reference services, studies on medical aspects of sterility and fertility control methods and health aspects of population dynamics". Further, the use of oral agents as well as other methods, for fertility control has increased at such a rapid pace in certain areas of the world that the time seemed propitious to make an evaluation of work accomplished. This evaluation should prove a unifying source of reference for further studies as well as serve as a standard of procedure for national, regional and community groups which might wish to institute or expand a programme of oral agents for fertility control. It should be noted that it is planned that WHO should keep information concerning oral gestogens current by periodical review of the subject. The reader should be aware that several controversial subjects were discussed in detail, and Group agreement was not always unanimous. Concurrent with the rapid increase in the use of oral gestogens for fertility control, there has been an equally—perhaps more—rapid increase in the alarm reaction of lay publicity as to possible deleterious effects from the use of these compounds.

This report considers all aspects of the action of oral gestogens on the system and on individual organs, and recognizes both the benefits and possible hazards involved in their use. Often it has been possible to point to conditions in the human female where the hazards, if any, involved in the use of these oral agents may be considered to be less than the hazards of pregnancy.

No attempt is made to equilibrate the benefits, hazards and effectiveness of the orally active steroids with those of other methods of contraception. Many specific points are recognized as needing more research and are so listed. No attempt has been made to cite references which would have proved to be very lengthy, and perhaps incomplete because of the great number of publications which are appearing so rapidly.

¹ World Health Organization (1965) *Handbook of resolutions and decisions...*, Geneva, pp. 76-77 (Resolution WHA18.49).

1. INTRODUCTION

1.1 Whereas there is no doubt as to the superior effectiveness of current oral oestrogen-progestogen preparations over that of previous methods of fertility control, and whereas this method has proved acceptable to women in all continents and at all social levels, the increasingly widespread use of these compounds has raised questions of hazard in the minds both of clinicians and of the public. This is true in respect not only of short-term use but still more so of long-term use, since continuing use for periods of twenty years and more could become commonplace.

1.2 For the purposes of this report the term "gestogen" is regarded as comprising oestrogens and progestogens, the latter being taken to include all substances which produce secretory changes in the oestrogen-primed endometrium, whether directly or indirectly after passage through another tissue.¹

1.3 It would be a mistake to suppose that the therapeutic use of this class of compounds is of only recent introduction; on the contrary, synthetic oestrogens and the progestogen 17 α -ethynyltestosterone (ethindrone, ethisterone) have been in clinical use since 1938, although the 19-nor-steroids and other, newer progestogens have been used only since the early 1950s. For the oestrogens, controversy in relation to clinical use in women has existed hitherto only over the possibility of carcinogenesis, and on this the most informed opinion is that evidence for such an effect from administered oestrogens in the woman is lacking. Nevertheless, it may rightly be argued that, until the advent of steroidal oral contraception, the continuous, albeit cyclic, administration of these compounds for clinical purposes over long periods of time has not been common in women of reproductive age. Studies on small numbers of women who have been so treated, in some cases for 15 years or more, do not appear to have revealed harmful effects. However, as the WHO Scientific Group on Mechanism of Action of Sex Hormones and Analogous Substances¹ has emphasized, the long-term administration of exogenous steroids can lead to a wide variety of effects. Thus there is a need for the critical evaluation of these compounds as possible sources of risk to the individuals undergoing treatment.

1.4 The estimated annual average numbers of users of oral contraceptives in the United States of America have been reported by the Food and Drug Administration as follows :

1961	408 000	1964	3 950 000
1962	1 187 000	1965	5 000 000
1963	2 235 000		

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1965, 303.

In other countries an estimated two million women were taking these compounds in late 1965. In view of this widespread use it is to be expected that many diseases, common as well as rare, to which women in general are subject, will also be encountered among oral contraceptive users. When, in a woman using oral contraceptives, such disease becomes manifest, there is naturally a tendency to assume that this is a consequence of the treatment. Unless the biological mechanism of a side-effect has been established, it is essential in evaluating the possible harmfulness of oral contraceptives to take into account the incidence of the disease in comparable women who do not use these agents. Thus a cause-and-effect relationship should only be accepted when the disease is encountered significantly more frequently among oral contraceptive users than among non-users or when adequate experimental data confirm such a relationship. Failure to do this by either method has been all too conspicuous in many isolated reports of various diseases occurring among women using oral gestogens, although the possible "early warning" value of such reports is not denied. The importance of individual idiosyncrasies must not be overlooked and deserves further exploration.

1.5 Oral contraceptives have been used in two forms—combined and sequential. In the former each tablet consists of a highly potent, orally active, synthetic oestrogen—either ethinyloestradiol or mestrenol—combined with an orally active progestogen. Among the latter, compounds of widely varying potency are in use. The tablets are taken daily, beginning on the fifth day of a menstrual cycle, for 20-22 days and then resumed on the fifth day of the subsequent cycle or after seven days. In the usual sequential regimen, oestrogen alone is taken for 15 or 16 days, beginning on the fifth day of a menstrual cycle, and is followed by oestrogen plus progestogen for five days. An 11/10-day and a 14/7-day regimen have also been studied experimentally. Currently marketed oral contraceptives known to be effective are shown in the accompanying table; additional formulations with the same and other progestogens have been used in clinical trials. Experimental studies are in progress on, *inter alia*, the continuous use of certain progestogens alone in low dosage and of long-acting injectable progestogens with or without oestrogens. Acceptable forms of male oral contraception have not yet been developed; therefore, no further reference will be made to the subject in this report, though the need for the development of safe, readily reversible, and acceptable agents for male fertility control is recognized.

2. GENERAL MEDICAL CONSIDERATIONS

2.1 Oestrogens and progestogens have been employed extensively in gynaecology, particularly in treating disturbances of the menstrual cycle, dysmenorrhoea and the multifarious manifestations of the premenstrual

REGIMENS IN USE WITH CURRENTLY MARKETED ORAL CONTRACEPTIVES

Combined therapy	
Progestogen (mg)	Oestrogen (mg)
Ethinodiol diacetate (17 α -ethynloestrene-3 β , 17 β -diol-diacetate) 1	Mestrenol (17 α -ethynloestradiol-3-methyl ether) 0.1
Lynoestrenol (17 α -ethynyl-17 β -hydroxy-oestrene) 5 2.5	Mestrenol 0.15 0.075
Medroxyprogesterone acetate (6 α -methyl-17 α -hydroxyprogesterone acetate) 10 5	Ethinloestradiol 0.05 0.075
Megestrol acetate (6-methyl-6-dehydro-17 α -hydroxyprogesterone acetate) 5 4	Ethinloestradiol 0.1 0.05
Megestrol acetate 5	Mestrenol 0.1
Norethindrone (17 α -ethynyl-19-nor-testosterone) 10 5 2 2 2 1	Mestrenol 0.06 0.075 0.1 0.09 0.08 0.05
Norethindrone acetate 4 3 2.5	Ethinloestradiol 0.05 0.05 0.05
Norethynodrel (17 α -ethynyl-5(10)-oestrenolone) 10 5 2.5	Mestrenol 0.15 0.075 0.1
Sequential therapy	
Preparation	Days
Chlormadinone acetate (6-chloro-6-dehydro-17 α -hydroxyprogesterone acetate) and mestrenol : Mestrenol 0.08 mg Mestrenol 0.08 mg + chlormadinone 2 mg	15 5
Dimethisterone (6 α ,16 α -dimethyl-17 α -ethynyl testosterone) and ethynloestradiol : Ethinloestradiol 0.1 mg Ethinloestradiol 0.1 mg + dimethisterone 2.5 mg	16 5
Megestrol acetate and ethynloestradiol : Ethinloestradiol 0.1 mg Ethinloestradiol 0.1 mg + megestrol acetate 5 mg Inert tablets	16 5 7
Norethindrone and mestrenol : Mestrenol 0.08 mg Mestrenol 0.08 mg + norethindrone 2 mg	14 6
Norethynodrel and mestrenol : Mestrenol 0.1 mg Mestrenol 0.075 mg + norethynodrel 5 mg	15 5

syndrome. Oestrogen/progestogen formulations appear to be of value for the symptomatic treatment of menorrhagia, especially that which occurs soon after puberty or preceding the menopause. Oestrogens, and in some instances oestrogen/progestogen combinations, in dosages well above those used for most therapeutic purposes, have been employed for the suppression of lactation. Another application is in the treatment of certain forms of acne. Oestrogen is used for the palliative treatment of mammary carcinoma in post-menopausal women and, in low dosage, for the climacteric syndrome. Progestogens are used for the treatment of progestational insufficiency in some women complaining of infertility and in the treatment of threatened and repeated abortion believed to be due to progesterone deficiency. In recent years progestogens, either alone or in combination with oestrogen, have been given continuously and in dosage much higher than is used for oral contraception, for periods of six to twelve months or even more for the treatment of endometriosis. While there is no unanimity as to the rationale or effectiveness of these various gynaecological uses, it is notable that they are not attended by any substantiated therapeutic hazards.

3. EFFECTS ON ENDOCRINE FUNCTION

3.1 Pituitary gland

Experimental studies on the human indicate that oral contraceptives have little effect on the urinary output of "total gonadotrophin" as determined by immature mouse uterine weight assay but they appear to suppress the mid-cycle peak of luteinizing hormone (LH). By appropriate experimental methods, effects on the secretion of other pituitary trophic hormones may be demonstrated; whether these are of clinical significance is debatable. It is possible that the effects on pituitary function are mediated by the hypothalamus but how the functions of this brain centre are affected in detail by oral gestogens is unknown. There is at present no evidence that permanent structural changes in the pituitary or hypothalamus result from the use of oral contraceptives by women, but data are necessarily very limited and further studies are required.

3.2 Thyroid gland

The protein-bound iodine (PBI) in the blood may be increased in users of oral contraceptives. This is known to occur in pregnancy but perhaps for other reasons. The effect in the oral contraceptive users is attributed to the oestrogen component of the treatment which causes

an increase in thyroxine-binding globulin (TBG). The increase in TBG is not progressive and returns to premedication values soon after treatment is stopped. There is no evidence for the development of either clinical hyperthyroidism or hypothyroidism in oral contraceptive users, but the effects of these agents on women suffering from thyroid dysfunction require further study.

3.3 Adrenal cortex

The oestrogen component of oral gestogens causes an increase in the level of corticosteroid-binding globulin (transcortin) in the plasma and this in turn leads to an increase in the total plasma cortisol (hydrocortisone) level. This is not known to be progressive. However, after equilibrium is established, it is likely that the amount of free corticoid is not markedly altered. Although there is some evidence for a small increase in the function of the pituitary-adrenal axis, clinical cortical hyperfunction has not been demonstrated. On the other hand, certain progestational substances having the 17 α -hydroxy group have been shown to be converted *in vivo* to substances with corticoid activity. These indirectly suppress the adrenal but there is no evidence for clinical cortical insufficiency. When both oestrogen and progestogens are applied together, the physiological response is too complex to be analysed here. For practical purposes, no clinical problems need be anticipated on the basis of present clinical evidence, which fails to show conclusively any lack of adrenal responsiveness under stress. There are limited laboratory data, based on reduced responses to metyrapone, pointing to the contrary, though the validity of these data is uncertain.

3.4 Carbohydrate metabolism

Some clinical investigators suggest that carbohydrate tolerance may be impaired in women using oral contraceptives, but other observers have not encountered unexpectedly high frequencies of abnormal glucose tolerance. The renal threshold for glucose may be decreased in the absence of an effect on glucose tolerance. Oral gestogens do not appear to alter the severity of diabetes, as measured by insulin requirements, but no data are available on their vascular effects in these patients. The development of diabetes has not been observed in large clinical studies of oral contraceptive users extending to more than seven years. From this, it may be inferred that the risk of their hastening the onset of frank diabetes in pre-diabetic women is probably less than such an effect from pregnancy. There is a need for further and more extensive investigation of carbohydrate metabolism in users of oral contraceptives.

3.5 Ovaries

Direct examination of the ovaries reveals a prompt alteration in their general appearance, even after only one 20-day course of treatment. The size of the ovary is decreased; it looks inactive and resembles a post-menopausal ovary. However, in the limited number of cases studied, the appearance has returned to normal promptly (within one to three cycles) on cessation of treatment. Studies of the output of urinary metabolites of ovarian steroids ordinarily show a correspondingly prompt return to normal function. However, in a small proportion of cases such return may be delayed for some months, though the explanation of this is not clear. The ovaries of women using orally active oestrogen/progestogen combinations are consistently reported as showing no functioning corpora lutea. Though based on only one study, histological evidence suggests an increase in the density of follicles per unit volume in the ovaries of norethynodrel/mestrenol users as compared with untreated controls. No difference was detected in the percentage of atretic follicles. There was a decrease in follicle density in women treated for 58 or more cycles, as compared with the findings in those treated for a shorter period, but no corresponding alteration in the percentage of atretic follicles. The explanation for this may be the older age of the long-term users, who had a significantly lower follicle density than those in the control group. No pathological changes in ovaries have been reported. The hypothesis has been suggested that orally active steroids might cause genetic damage to the oocytes, but no evidence has been presented that they have such an effect.

4. EFFECTS ON GENERATIVE ORGANS AND BREASTS

4.1 Endometrium—combined therapy

Characteristic effects on the endometrium are produced by combined oestrogen/progestogen contraceptives. They vary in only minor degree with differing formulations. Briefly, they consist of the rapid transformation of the endometrial glands through the early stages of the secretory phase into one resembling secretory exhaustion. At the same time the stroma assumes, to a varying degree, a predecidual appearance. Especially after several cycles of treatment, the endometrium becomes thin and hypoplastic, in which condition it continues during at least five years of treatment. On discontinuation of medication there is prompt return, in most cases within one to three months, to the normal appearance. Reports are in agreement that the incidence of endometrial pathology among oral contraceptive users is significantly lower than in non-users.

4.2 Endometrium—sequential therapy

The effects on the endometrium of sequential contraceptives depend on the compounds and on the regimen used. During the early phase of the artificial cycle, when oestrogen alone is given, proliferative changes, sometimes including appearances suggestive of hyperoestrogenic stimulation, are seen. In the latter part of the cycle, under the influence of the combined therapy, incomplete secretory transformation occurs, without evidence of predecidual change. There is no tendency to endometrial hypoplasia with long-continued use.

4.3 Menstrual cycle

The variability of cycle length is significantly less in oral contraceptive users than in controls. In general, the duration of menstrual flow is reduced and the amount of menstrual loss is decreased, particularly with the combined regimen. This pattern remains constant during at least five years of continuous use. Breakthrough bleeding or spotting, which may be associated with failure to take the tablets regularly and daily, is commonest during the early cycles and rare thereafter. Its frequency is not uniformly related to dosage levels and differs with different products, as well as in different populations. It may be related to the average body-weight of oral contraceptive users in a given community as well as to their nutritional state. The occurrence of irregular uterine bleeding in a woman who has been using oral contraceptives with regular menstrual cycles for a long time is unlikely to be an effect of the treatment and requires the same gynaecological investigation as it would in a non-user.

4.4 Endometrial carcinoma

There are differences of opinion among gynaecologists on the role of large amounts of oestrogen or prolonged oestrogenic stimulation on the induction of endometrial cancer, though most are agreed that cystic and adenomatous glandular hyperplasia is often seen in patients who are eventually diagnosed as having endometrial carcinoma. Most gynaecologists also agree that cystic and adenomatous glandular hyperplasia can be ameliorated by treatment with progestogens. However, agreement does not extend to the possible beneficial role of oral contraceptives in preventing malignancy. Obviously, this requires additional investigation. There is agreement that oral contraceptives do not cause endometrial carcinoma, but, because carcinogenic action may involve a long latent interval, the possibility of ultimate long-term effects cannot yet be excluded,

since experience with oral contraceptives does not extend beyond ten years. These considerations also apply to possible carcinogenic effects of oral gestogens at other sites.

4.5 Fibromyomata

An increase in the size of pre-existing fibromyomata during oral contraceptive use has been reported. The frequency of this finding is low and its significance unknown in the absence of suitably controlled studies, especially as the natural history of fibromyomata involves continuing growth until the menopause.

4.6 Cervix uteri

An increased frequency of erosion of the cervix uteri has been reported by some observers, but it is doubtful if this has any pathological significance. There is no evidence of an increase in the frequency of cytological smears suspicious for carcinoma; on the other hand, there is some evidence for a lower frequency of such suspicious smears, at least in a part of the world where carcinoma of the cervix has a high endemic rate. There has been no increase in the frequency of diagnosis, by biopsy, of cervical carcinoma in oral contraceptive users. There are no data to support the concept that carcinoma of the cervix is hormonally determined, and there is no theoretical background for suspecting a carcinogenic effect on the cervix from oral gestogens.

4.7 Vaginitis

Vaginitis, specific and non-specific, has been reported in oral contraceptive users, but studies providing evidence for an increased frequency in comparison with non-users are lacking.

4.8 Breasts

Changes in the size of the breast in women using oral contraceptives are infrequent. About equal numbers (roughly 10%) report increases and decreases except with 10 mg norethynodrel/mestrenol tablets, on which about 20% of patients allege an increase in size. The subjective evaluation of breast size is notoriously liable to error and reported breast enlargement may, in some cases, represent increased turgor. Complaints of breast discomfort are commonest in the first cycle of use, a frequency varying between 0 and 27% being reported with different compounds and by different investigators. It has been suggested that breast discomfort

is related to the oestrogen component since progestogens alone may decrease it. The relationship of hormones to mammary cancer is complex and still largely obscure. Claims for the remission of established breast cancer have been made for many steroids, including some of those used in oral contraceptives. There is no evidence for an increase in the frequency of breast cancer in oral contraceptive users, in spite of evidence that breast cancer in the general population is increasing, at least in some countries.

4.9 Lactation

The effect of oral contraceptives on lactation has been inadequately studied, because in all reports the basis for comparison has been the woman's own recollection of her previous performance. Higher dosages appear to decrease lactation, though at lower dosage there is probably little effect. In one study, for example, 2.5 mg of norethynodrel/mestrenol had no effect on lactation in 70% of women, caused an alleged decrease in 15% and an increase in 15%; control data are not available. The possibility of excretion of oral gestogens or their metabolites into maternal milk and consequent effects on the baby requires further study.

4.10 Menopause

There is no basis for the belief that the reproductive span could be extended by long-continued ovulation inhibition, neither is there any reason to suppose that the onset of the menopause, with its associated permanent sterility, would be hastened by it. While not directly relevant to oral contraception, the possibility that in post-menopausal women oestrogen/progestogen combinations might be hepatotoxic requires further elucidation; so does the possibility that they might retard aging processes.

5. SYSTEMIC EFFECTS

5.1 Liver

The storage in the liver of bromsulphthalein sodium (BSP) may be increased, and its transfer maximum decreased, during the last trimester of normal pregnancy, and during the administration of oestrogens, of certain C₁₇-alkylated steroids and of oral contraceptives, although not necessarily for the same reasons. In the same situations, cholestatic jaundice may occur, though rarely. These findings are also seen in certain hereditary disorders of hepatic excretory function, such as the Dubin-Johnson and Rotor syndromes. However, the drug-induced abnormality in BSP metabolism is reversible, transient, and frequently disappears even

with continued medication. While studies of hepatic excretory function on substantial numbers of long-term oral contraceptive users have revealed an increase in the number of abnormal results, the limited pathological significance of these tests should be borne in mind. Following the administration of large doses of oral contraceptives to rats and a few humans, alterations in liver structure, as observed by light and electron microscopy, have been reported, including cholestasis, altered cell membrane staining reactions, changes in lysosomes and dilatation of canaliculi with blunting of microvilli; the significance of these findings is uncertain and of unknown relevance to the practical use of oral contraceptives. The available data suggest that oral contraceptives should not be given to patients with hereditary defects in hepatic excretory function; cirrhosis and viral hepatitis do not appear to be aggravated by these agents, according to limited observations.

5.2 Malnutrition

Anxieties have been expressed that women suffering from malnutrition might be more likely than well-nourished women to experience adverse hepatic (and other) effects from the use of oral contraceptives. However, a substantial proportion of the subjects studied in some of the large-scale trials are clinically undernourished but nevertheless do not show evidence of impaired hepatic function. There is a definite need for studies of liver function in relation to the various components of nutritional deficiency, and of other metabolic parameters in these deficiencies.

5.3 Blood coagulation

Oral contraceptives appear to produce changes in the blood-clotting mechanism, but there are wide differences in the reports of different observers. The relationship of thrombo-embolic disease to alterations in blood-clotting factors is uncertain, and haematologists agree that although deficiencies in blood coagulation can be correlated with deficiencies of clotting factors, states of hypercoagulability cannot be defined on the basis of excesses of any of these factors. Alterations in blood circulation, the state of the vessel wall, and in platelet stickiness are possibly of more fundamental importance in intravascular thrombosis.

5.4 Venous thrombo-embolic disease

Thrombo-embolic disease has been encountered among women using oral contraceptives, just as it is among non-users. It has often been stated that thrombophlebitis has an increased incidence during pregnancy, a relationship to the augmented sex hormone levels being assumed. This

in fact is not true; it is during the puerperium, at a time when oestrogen and progesterone levels are at their lowest, that the increased incidence is seen. There can be no doubt that the high incidence of puerperal thrombosis, like post-operative thrombosis, is primarily due to trauma and local alterations in blood circulation. The incidence of thrombophlebitis in non-pregnant women between the ages of 15 and 45 years is not known with certainty, but the best available estimates suggest that it is between 1 and 3 per thousand women per annum. The incidence in women using oral contraceptives is also uncertain because of incompleteness of reporting and bias in the selection of patients but in no reported series has it exceeded the above range. Attempts to determine the mortality from "idiopathic" pulmonary embolism among oral contraceptive users and to compare it with that of other non-pregnant and non-puerperal women of reproductive age have so far been unsuccessful. This is primarily because the number of deaths cannot be determined with comparable accuracy in the two groups. Because of this difficulty, the Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions¹ was not able to establish a statistically valid relationship between thrombophlebitic-embolic death and the use of oral contraceptives. Further, the vital statistics from the United States of America show that while the age-specific death-rates attributed to this condition in females have risen during the period from 1950 to 1964 inclusive, a similar rise has occurred in the male. Finally, the trend shows no change during the 1960s, when oral contraceptives came increasingly into use in the USA. Age-specific death-rates recorded for this condition in the United Kingdom show no change during the past ten years for either sex under the age of 45 years. Experience with high-dosage oral gestogen therapy for endometriosis is also relevant; in a series of 678 patients (USA) treated for this condition with norethynodrel/mestrenol in doses ranging from 30 mg to 120 mg per day for 3-10 months, some of whom were also subjected to pelvic surgery, no thrombo-embolic phenomena were observed. In a smaller series, treatment at 70 mg per day was continued for up to three years, again without vascular complications.

5.5 Arterial thrombo-embolic disease

With regard to arterial thrombotic lesions causing death, the Committee on Safety of Drugs² in the United Kingdom was not able to establish a statistically valid relationship between such thrombo-embolic deaths and the use of oral contraceptives. Indeed, in the USA the death-

¹ Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions (1963) *J. Amer. med. Ass.*, **185**, 776.

² Cahal, D. A. [Committee on Safety of Drugs] (1965) *Brit. med. J.*, **2**, 1180.

rate among women of child-bearing age from cerebrovascular accidents has not significantly changed during the period from 1950 to 1964 inclusive. This fact is of considerable significance, since it has been estimated that one-tenth of the 40 million women of child-bearing age in that country were using oral contraceptives during 1964. Furthermore, cerebrovascular lesions are a not uncommon cause of death in the untreated female of child-bearing age. For instance, United States vital statistical data for 1959—that is, well before oral contraceptives came into relatively common use in that country—reveal that, as a cause of death, such cerebrovascular lesions ranked fourth among females from 25 to 39 years of age, behind malignant neoplasms, heart disease, and accidents. The desirability of continued accurate recording of data is obvious, but it must be realized that many physicians have come to avoid the prescription of these agents for women with a history of thrombo-embolic disease. Unless this selective practice (which applies to other alleged contra-indications as well) is discontinued, it will necessarily impair the validity of any conclusions which may be drawn in the future from statistical evidence.

5.6 Skin and its appendages

The development of chloasma has been reported in Puerto Rican, Haitian and Mexican women using oral contraceptives. This condition appears to occur more frequently in darker-complexioned women, whether or not they use oral contraceptives. It may also occur under treatment with oestrogens. It may be related to dietary and other environmental factors since it is less often seen in women of the same ethnic groups residing in the USA. The production of sebum may be decreased by oral gestogens, more particularly by those which are more oestrogenic. As a consequence, acne generally improves. The infrequent occurrence of hair loss in women using oral contraceptives is probably fortuitous, and there is no evidence that they cause hirsutism. Skin disorders of an allergic nature—for example, eczema and urticaria—have occasionally been observed to appear among women using oral contraceptives; in others with the disorder pre-existing, improvement and exacerbation have both been reported.

5.7 Change in weight

Gain in weight of 3 pounds (1.5 kg) or more has been reported in from 4% to 50% of subjects by different observers. This has been more apparent with higher dosage preparations and with those progestogens that have a greater nitrogen anabolic activity. Weight loss has been reported in from 5% to 16% of users. The proportion of users who have gained weight is maximal between six and twelve months and declines thereafter. The cause of weight change is undoubtedly complex and may

be related to psychological factors affecting appetite as well as to possible anabolic and water-and salt-retaining effects of the administered steroids. Further studies are needed to elucidate the mechanism of weight gain.

5.8 Skeletal growth

Many endocrinologists believe that oestrogens may accelerate epiphyseal closure. Their administration in the immature female, it is thought, might result in a shorter stature than would otherwise be attained. However, in the menstruating female, endogenous oestrogen production is already significant and the likelihood of detectable effects on growth from the administration of oral gestogens is remote.

5.9 Subjective side-effects

Although the use of oral contraceptives is generally not associated with a change in the sense of well-being, the attention that has been paid to complaints of various subjective side-effects, experienced by a minority of patients, has perhaps been disproportionate, especially since controlled studies have not been made. Of these side-effects, nausea, sometimes with vomiting, is perhaps the most common, although decidedly less so, even with the same compounds and at the same dosage, than it used to be during previous years; evidently it is partly psychologically determined. Nausea is, of course, less likely with low than with high dosage. It is rarely encountered after the first two cycles. Headache is most commonly experienced by migraine sufferers and is then apt to occur between successive courses of tablets. It does not appear to decrease with continuing use. Cramps of the abdomen and legs, paraesthesiae, and a number of other minor symptoms may be experienced.

5.10 Women who discontinue medication

There are women who, after various periods of treatment with oral gestogens, choose to discontinue the medication because of side-effects unacceptable to them. The percentage of such individuals varies and decreases rapidly after the first few cycles. These "drop-outs" are not to be confused with the smaller number of individuals who discontinue a specific regimen on medical advice.

5.11 Psychological effects

Adequately controlled studies of the effects of oral contraceptives on central nervous activity, emotional reactions, sexual behaviour and other psychological aspects are almost totally lacking; therefore it is impossible

with conviction to ascribe psychological changes to a pharmacological action of these substances.

6. EFFECTS ON THE FOETUS AND SUBSEQUENT FERTILITY

6.1 Virilization of female foetuses, consisting mostly of no more than enlargement of the clitoris but rarely associated with varying degrees of labial fusion, is occasionally encountered in the population at large. Such babies have been born to mothers who have received no medication during pregnancy but it has been claimed that the occurrence is somewhat greater among those who have received various "sex hormones" during pregnancy. Available statistics do not support this contention. The relationship between hormone administration during pregnancy and effects on the foetus is incompletely established but it is doubtful if, at the dosage level currently used in oral contraceptives, foetal virilization could ever be the consequence of their unwitting use at some time during pregnancy.

6.2 There is no evidence that the fertility of women is impaired after the long-term use of oral contraceptives (five or more years). It is well established that resumption of normal pituitary-ovarian relationships, with ovulation, the normal output of ovarian steroids and the normal endometrial response, is generally prompt on cessation of treatment, though prolonged amenorrhoea, of uncertain origin, has been reported. There is no substantial evidence that babies subsequently conceived have an increased incidence of congenital defects or that foetal wastage and perinatal mortality are increased.

6.3 Opinions have been expressed that, after withdrawal of medication, fertility is actually increased. Reports of pregnancy rates after stopping oral contraception range from 40% to 65% in the first cycle (compared with 35% after stopping traditional contraception), 50% - 80% within two cycles and 90% within six months of stopping treatment. However, since the initial fertility of many of the women concerned may have been above average, the apparent increase in fertility after stopping medication may not be significant. The view that the "rebound effect" following withdrawal of oral gestogens might increase the fertility of previously infertile women is not well supported.

7. RELATIONSHIP OF COMPOUNDS AND LEVEL OF DOSAGE TO EFFECTIVENESS AND SIDE-EFFECTS

7.1 The effectiveness of currently used combined oestrogen/progestogen oral contraceptives is reflected in a pregnancy rate of not more than 0.1 per 100 women-years of use if the contraceptives are taken according to

instructions. This is as true for the lower as for the higher dosages listed in the table on page 6. The effectiveness of the currently available sequential regimens appears to be somewhat less. Omission of one tablet or more increases the risk of conception under either regimen, but the risk remains substantially less than with comparable irregularities in the use of traditional contraceptives, such as the diaphragm or the condom.

7.2 It is not known whether the frequency and importance of side-effects in users of sequential treatment are significantly different from those encountered with combined formulations, although certain studies suggest this. It has been claimed that the administration of oestrogen unopposed during part of the cycle might carry additional risks, but no evidence is known which substantiates this. Some women appear to derive advantages from the alterations in hormonal stimulation which obtain with the sequential regimen but not with the combined regimen. In the absence of appropriately controlled studies the significance of these observations is doubtful.

7.3 There appear to be differences in the effects that varying dosages of different preparations may have on bleeding phenomena. For example, combined with oestrogen, 2 mg of one progestogen may produce less breakthrough bleeding than 10 mg of the same compound, whereas with other progestogens the reverse situation may hold. It is impossible to generalize, particularly since the ratio of progestogen to oestrogen varies among available preparations, and statistics from different studies are not always comparable. Except for generally higher rates of gastrointestinal side-effects and of vaginal mucorrhoea with higher oestrogen dosage, the relationship of dosage to side-effects is not clear.

7.4 It would be desirable to evaluate the biological action of synthetic steroids used in oral contraceptive formulations in terms of the production of endogenous hormones during the natural menstrual cycle. However, reliable information is not available since quantitative data are very difficult to obtain. There is no adequate basis for the belief that the changes produced by oral contraceptives result in a state of hormonal flooding which could be described as "pseudopregnancy", although this term has injudiciously been employed to explain such side-effects as nausea, breast enlargement and elevated protein-bound iodine levels.

7.5 It is now clear that the dosage of the originally introduced oral contraceptives was substantially higher than is necessary for ovulation inhibition. It has also become clear that, with reduction of dosage of certain combined preparations, the absolute amount of oestrogen is critical. In the lower dosage range of combined preparations, it is the oestrogen which is more important as an ovulation inhibitor, while in the sequential regimen, oestrogen is all important for that purpose.

7.6 The two oestrogens, ethinyloestradiol and mestrenol, have been used somewhat arbitrarily in oral contraceptive formulations. We have inadequate knowledge about their relative potencies in the human, especially in their capacity as ovulation inhibitors. Further studies are required of these and other oestrogens.

8. CONTRA-INDICATIONS TO THE USE OF ORAL CONTRACEPTIVES

8.1 Little is known with certainty about contra-indications to the use of oral contraceptives. It can be stated as a general principle that the prescribing physician should, in each individual case, weigh possible effects of the treatment against the effectiveness, acceptability and safety of available alternative contraceptive methods and against the known hazards of pregnancy.

8.2 A few rare conditions are known to be aggravated by oral contraceptive administration. These are certain acquired or hereditary defects of hepatic excretory function, including the Dubin-Johnson and Rotor syndromes (see 5.1). Women who have experienced idiopathic recurrent jaundice of pregnancy redevelop jaundice if given oral gestogens.

8.3 There are other conditions in which there is no substantial evidence of adverse reaction to oral contraceptives but where *a priori* considerations of pathology counsel caution in their use. These include a history or suspicion of carcinoma of the generative organs and the breasts, as well as past or present liver disease without evidence of impaired excretory function. In the presence of cardiovascular-renal disease the possible adverse consequences of sodium and fluid retention have to be considered.

8.4 From time to time yet other conditions have been suggested as contra-indications to oral contraceptive use in the absence of convincing evidence of a cause-and-effect relationship but without *a priori* reasons for assuming one. These include thrombo-embolic disease, varicose veins, cerebrovascular accidents, certain ophthalmological manifestations (e.g., papilloedema, retinal artery thrombosis, retrobulbar neuritis, visual diminution and peripheral field restriction) and psychic depressive states. There appears to be no justification for regarding these several conditions as contra-indications. However, it must be emphasized that, as with any therapeutic agent, the possibility of rare, individual idiosyncrasy cannot be overlooked.

8.5 A number of conditions, especially some with a supposedly allergic basis—for example, asthma, eczema, vasomotor rhinitis and migraine—and others such as alopecia, epilepsy, multiple sclerosis, and rheumatoid

arthritis, may be made worse in some women by the use of oral contraceptives. In other women, however, they may be improved.

8.6 During lactation, the administration of high-dosage oral contraceptives should be avoided where continued breast-feeding is desired.

8.7 There is need for further study of the use of oral contraceptives in women suffering from a variety of common diseases, for example, diabetes, tuberculosis, cardiovascular-renal disorders, various parasitic and neoplastic diseases, and, particularly, malnutrition.

9. MANAGEMENT OF ORAL CONTRACEPTIVE USERS

9.1 Reasonable standards of medical practice require that any woman, before being started on oral contraception, should have her medical history taken with due regard to the several aspects covered in previous sections of this report; and she should be subjected to a general physical examination, including breasts and pelvis with cervical exfoliative cytology. It is implicit in this statement that the physical examination should be carried out by a qualified medical practitioner.

9.2 Oral contraceptive users should undergo medical review at intervals of approximately six months, although during the early cycles more frequent supervision may be required in individual circumstances. Exfoliative cytology should be repeated annually in all women, whether or not they use oral contraceptives.

9.3 It is recognized that rigid insistence on these standards would seriously diminish possibilities of the use of oral contraceptives by women of many countries. Consequently, it is suggested that the modifications which may have to be made in order to permit the inclusion of oral contraception within the fertility control programmes of interested Member Governments of WHO be decided by those Governments in the light of national, regional and local circumstances. Considerations should include the possibility of the utilization of paramedical personnel, realizing that where such persons are employed they should be properly instructed and supervised.

10. RESEARCH NEEDS

Throughout this report attention has been drawn to areas of uncertainty requiring additional investigation. For convenience, these research needs are here listed, not necessarily in order of importance. The references in parentheses indicate the relevant passages in the body of the report.

(1) Investigations into the part played by individual idiosyncrasies in the occurrence of adverse reactions (1.4).

- (2) Study of the central nervous control of pituitary function and the action of oral gestogens on higher nerve centres (3.1).
- (3) Elucidation of the effects of oral contraceptives on thyroid function and in women suffering from thyroid dysfunction; and the effects on adrenocortical function (3.2; 3.3).
- (4) Further and more detailed studies of carbohydrate metabolism in oral contraceptive users, especially diabetic women (3.4).
- (5) Morphological studies of ovaries, where opportunity presents, of users of oral contraceptives for various periods of time, especially at various intervals after treatment is stopped (3.5).
- (6) Elucidation of the occasional failure of return of ovarian function after long-term oral contraceptive use (3.5; 6.2).
- (7) Inquiry into the possibility of genetic effects of oral gestogens (3.5; 6.2).
- (8) Inquiry into the possibility of long-term carcinogenic effects of oral contraceptives on the generative organs, and of prophylaxis against the development of cancer (4.4; 4.6; 4.8).
- (9) Study of the effects of oral contraceptives on fibromyomata, and on the occurrence of vaginitis (4.5; 4.7).
- (10) Study of the effects on lactation and its products, and of effects, if any, on breast-fed babies (4.9).
- (11) Investigation into the effects of oestrogens and progestogens, alone and in combination, on hepatic structure and function, in normal and post-menopausal women, and in patients suffering from cirrhosis, viral hepatitis, amoebic hepatitis and other forms of liver disease, and malnutrition (4.10; 5.1; 5.2).
- (12) Study of the effects of oral gestogens on the blood coagulation mechanism, including the mechanism of thrombosis and of the factors responsible for its occurrence (5.3).
- (13) The continued accurate recording of statistical data on thrombo-embolic disease, in oral contraceptive users and non-users, with special care to avoid bias through selection of users (5.4; 5.5).
- (14) Metabolic studies of the effects of oral gestogens on weight gain (5.7).
- (15) Controlled studies of psychological aspects of oral contraceptive use (5.11).
- (16) Study of the effects of oral gestogens on the frequency of congenital malformations and on the perinatal mortality of infants born subsequent to their use (6.2).

(17) Well-designed studies to compare the frequency of side-effects and the contraceptive effectiveness of the combined and sequential regimens (7.2; 10.2).

(18) More extensive studies to determine the relative biological potencies of the two oestrogens used so far; and to investigate the suitability of other, possibly preferable, alternative compounds (7.6).

(19) More extensive clinical studies of the use of oral gestogens by women suffering from a variety of common diseases, including diabetes, tuberculosis, cardiovascular-renal, parasitic and neoplastic diseases, and malnutrition (8.7).

(20) The development of safe, readily reversible, acceptable and effective agents for male fertility control (1.5).

11. GENERAL CONCLUSIONS

11.1 Since the introduction of steroidal oral contraceptives ten years ago, vast numbers of clinical observations and laboratory data have been accumulated.

11.2 Combined oestrogen-progestogen preparations, used as oral contraceptives according to instruction, are virtually 100% effective in preventing pregnancy. On the basis of data now available, sequential medication appears to be somewhat less effective; continued study in this area is needed, and the Scientific Group notes that plans have been made for periodical reviews by WHO Scientific Groups.

11.3 Laboratory studies of users of oral contraceptives have revealed a number of deviations from established norms, but few, if any, of these appear to have pathological significance.

11.4 Serious adverse experiences of various kinds, such as thromboembolic phenomena, have been reported in users of oral contraceptives, but no cause-and-effect relationship has been established either by available statistics or by experimental evidence.

12. RECOMMENDATIONS AND SUGGESTIONS

12.1 Since it is apparent from this report that more basic and applied knowledge pertaining to the use of oral agents for fertility control is needed, the Scientific Group recommends that WHO continue to encourage research at all levels in this field and all other aspects of human reproduction. In particular, investigations involving humans and other primates, as opposed

to subprimate species, should be greatly multiplied. Comparison of the different compounds, dosages and regimens in rigidly controlled clinical studies of appropriate experimental design are much needed. Knowledge of the long-term effects will accumulate only if adequate support is forthcoming for those investigators who are endeavouring to maintain substantial numbers of women on oral contraceptive treatment for an indefinite number of years. Attention is invited to the problems requiring further research (listed on pages 20-22).

12.2 It should also be noted that, despite the obvious merits of the currently available oral agents, they should be considered merely as a first major step towards even more generally useful methods of fertility control. Therefore it is recommended that WHO encourage research leading to the development of such methods.

12.3 It is recommended that WHO convene a Scientific Group to consider and advise on the collection, evaluation and presentation of statistical data pertaining to fertility control, including the use of oral agents.

12.4 The Scientific Group recognizes the fact that the usefulness of a method of fertility control, such as oral agents, depends on its acceptability as well as on its effectiveness and safety. The Group also recognizes that not only medical but also psychological and sociological factors are involved and that it would not have been within its province to discuss these latter. It is suggested, therefore, that WHO convene at an early date a Scientific Group to consider and advise on these matters.

12.5 The Scientific Group notes with favour that plans have been made to convene periodically a WHO Scientific Group on the Clinical Aspects of Oral Gestogens, and expresses the belief that many problems listed in this report as unsolved, or needing more data and study, will be resolved within the next few years. Further, it was favourably noted that WHO will soon convene a WHO Scientific Group on the Basic and Clinical Aspects of Intra-Uterine Devices. Accordingly, no attempt has been made to compare these two methods of fertility control.

12.6 The Scientific Group suggests that WHO consider recommending that Member Governments interested in utilizing oral agents in programmes of fertility control should :

- (a) organize existing governmental agencies or, where necessary, establish new agencies, presumably under their Ministries of Health, for evaluation and approval of the formulations to be used, and for the selection and training of medical and paramedical personnel;
- (b) provide for co-ordination through WHO headquarters, in order that the experience gained in their national programmes may be of

benefit to other Member Governments. To this end, it is further suggested that Member Governments furnish annual reports to WHO.

12.7 The Scientific Group suggests that WHO should remain in constant readiness to institute and aid training and educational programmes for key personnel in any country which desires to undertake new, or to extend existing, programmes of fertility control.