EFFECTS OF ORAL CONTRACEPTIVES[1]

By Sumner M. Kalman
Department of Pharmacology,
Stanford University School of Medicine,
Stanford, California

This review is limited to certain topics of current concern with respect to the use of orally-active steroid contraceptives. The clinical use and the side actions of these drugs were reviewed by Tyler (1). New trends in contraceptive research and development were discussed in a recent review (2). The possible mechanisms of action of the various steroids, combination, by which conception is prevented have been discussed in a penetrating survey by Diczfalusy (3). The preparations of oral contraceptives in current use in this country are listed in Table I. A comprehensive review of the chemistry, pharmacology, and clinical uses of progestins, including anti-conception therapy, has appeared (4).

Thromboembolism

In May of 1967 the British Medical Journal published a preliminary report of the Medical Research Council which established an association between the use of oral contraceptives and thromboembolic disease (5). This report was remarkable for several reasons. It was a very carefully designed study which produced clear-cut results from a relatively small sample. A system of matching was used so that age, parity, and other factors were controlled for persons on oral contraceptives as compared to those not taking these drugs. Finally, the British report contrasted sharply with an earlier study carried out in the United States whereby no association was demonstrated. An *ad hoc* committee established by the Food and Drug Administration had reported in 1963 that there was no significant increase in the risk of death from thromboembolic disease on the basis of available data. They did call attention to the inadequacies of the data and to the need for careful, prospective studies. In their report, the committee found highly significant increases in the incidence of death from thromboembolism among women in the older age groups taking Enovid, as compared to a comparable, non-pregnant age group (6). But then there followed a discussion about the possibility that the number of users of Enovid had not been estimated properly. The authors asserted that a ten per cent "decrease" (sic) in the number of users would not yield a death rate among Enovid users significantly different from that of the general population, either for the

[1] The survey of literature pertaining to this review was concluded in June 1968.

TABLE I[a]

ORAL CONTRACEPTIVES

Combination Drugs Trade Name	Progestogen	Estrogen	Ratio Progestogen: Estrogen
Enovid 10 mg	norethynodrel 9.85 mg	mestranol 0.15 mg	66:1
Enovid 5 mg	norethynodrel 5 mg	mestranol 0.075 mg	67:1
Enovid-E 2.5 mg	norethynodrel 2.5 mg	mestranol 0.1 mg	25:1
Norinyl 2 mg	norethindrone 2 mg	mestranol 0.1 mg	20:1
Norinyl 1 mg	norethindrone 1 mg	mestranol 0.05 mg	20:1
Noriday	norethindrone 1 mg	mestranol 0.05 mg	20:1
Norlestrin 2.5 mg	norethindrone acetate 2.5 mg	ethinyl estradiol 0.05 mg	50:1
Norlestrin 1 mg	norethindrone acetate 1 mg	ethinyl estradiol 0.05 mg	20:1
Ortho-Novum 10 mg	norethindrone 10 mg	mestranol 0.06 mg	167:1
Ortho-Novum 2 mg	norethindrone 2 mg	mestranol 0.1 mg	20:1
Ortho-Novum 1 mg	norethindrone 1 mg	mestranol 0.05 mg	20:1
Ovral	norgestrel 0.5 mg	ethinyl estradiol 0.05 mg	10:1
Ovulen	ethynodiol diacetate 1 mg	mestranol 0.1 mg	10:1
Ovulen-21	ethynodiol diacetate 1 mg	mestranol 0.1 mg	10:1
Provest 10 mg	medroxyprogesterone acetate 10 mg	ethinyl estradiol 0.05 mg	200:1

Sequential Drugs	Progestogen	Estrogen	Schedule
C-Quens	chlormadinone acetate 2 mg	mestranol 0.08 mg	mestranol 15 days; chlormadinone acetate plus mestranol 5 days
Norquen	norethindrone 2 mg	mestranol 0.08 mg	mestranol 14 days; norethindrone plus mestranol 6 days.
Oracon	dimethisterone 25 mg	ethinyl estradiol 0.1 mg	ethinyl estradiol 16 days; dimethisterone plus ethinyl estradiol 5 days.
Ortho-Novum SQ	norethindrone 2 mg	mestranol 0.08 mg	mestranol 14 days; norethindrone plus mestranol 6 days.

[a] Approved by U.S. Food and Drug Administration as of June, 1968.
(Table courtesy Ben Z. Taber)

total group or for the different groups. Finally, the assertion was made that the data were not indicative of a causal relationship between Enovid use and death due to thromboembolism. One could summarize the report by saying that the value of a fraction cannot be determined if the numerator and denominator are not known.

In a report presented by the Food and Drug Administration in August of 1966 (7) this comment was made: "The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause, they do so very infrequently relative to the number of users." The committee responsible for this report then suggested that an epidemiological study (not based on "haphazard" reporting of adverse effects or causes of mortality) be initiated to answer the question. The Council on Drugs of the American Medical Association published an evaluation of oral contraceptives in February of 1967. This report included the following statement:

> Existing experimental and statistical evidence provides no proof of a causal relationship. Nevertheless, until there is adequate evidence that such a relationship is improbable, the possibility that vascular complications sometimes may be caused by oral contraceptives should be borne in mind, particularly when these preparations are considered for use in patients with a history of thromboembolic or other vascular disease. (8)

Two reports in April of 1968 summarized the most recent conclusions of the Medical Research Council. The first of these deals with the risk of death due to thromboembolic disease (9), and the second considers the incidence of disease due to thromboembolism (10). The risk of thromboembolic disease among women taking oral contraceptives appears to be greater than that estimated from the preliminary report. Thus, 26 out of 58 hospitalized patients with deep vein thrombosis or pulmonary embolism had been taking oral contraceptives. Only ten out of a matched control group of 116 women admitted to hospitals for other illnesses were taking oral contraceptives. An increase in cerebral thrombosis appears to be related also to therapy with oral contraceptives. There was no proof of an association between myocardial infarction and the use of oral contraceptives. The risk of death due to pulmonary embolism or cerebral thrombosis among users of oral contraceptives amounts to 1.5 per 100,000 women aged 20 to 34 years as against 0.2 for a comparable group not using the drugs; for users of oral contraceptives 35 to 44 years old the risk rises to 3.9 per 100,000 compared to a death rate of 0.5 for nonusers. It was not possible to make a direct comparison to the risk of fatalities from thromboembolic phenomena in pregnancy because of the way deaths due to maternity (including the puerperium) were coded. However, the authors conclude that the risks appear to be

about the same within each age group. This contrasts with the early report (5) in which the risk due to pregnancy was estimated to be about four times as great as the risk associated with taking oral contraceptives.

To place these data in perspective it should be pointed out that the death rates due to all causes during pregnancy for England and Wales in 1966 were 22.8 and 57.6 per 100,000 women, aged 20 to 34 and 35 to 44 respectively. The annual death rates per 100,000 total female population due to all causes, including accidents, were 60.1 and 170.5 for age groups 20 to 34 and 35 to 44 years, respectively. Thus, the use of oral contraceptives adds an increased risk of death amounting to about two per cent for each age group (1.3/60.1, 3.4/170.5).

On the basis of the British studies, the U.S. Food and Drug Administration has recently sent to physicians and hospital administrators in the United States a warning letter about the association between oral contraceptive use and the incidence of blood clotting disease. As of July 1, 1968, additional cautionary labeling reflecting the association alluded to above was required of manufacturers.

It is interesting to re-examine some of the earlier reports from this country. I. C. Winter reviewed the data of the Wright Committee and extended it to include some vital statistics for the years 1958–1962, which were not available in time for the Final Enovid Report (11). It is remarkable that reports of thromboembolic episodes among women taking oral contraceptives actually fell below the estimated incidence of these diseases for the population at large; in certain years it was lower by an order of magnitude. This curious finding was dismissed as being due to underreporting. But any study where underreporting is suspected is also suspect. The basic flaw in the design appears to be dependence upon voluntary reporting, which is notoriously casual and which has since been condemned in the later U.S. report (7). In fact the British investigators (9) noted that only 15 per cent of the thromboembolic episodes they studied had been reported by attending physicians to the Committee on Safety of Drugs. The message is clear: There is an urgent need for more careful control of reporting of adverse drug effects and, in particular, for a method whereby the true incidence of adverse effects can be detected early. It is noteworthy that a recent inquiry concerning serious complications associated with another contraceptive, the intrauterine device (IUD), makes use of voluntary replies to a questionnaire. This study does in fact provide some useful information, but it does not provide useful data about the incidence of complications. In addition, there was apparently no attempt to compare the incidence of serious pelvic inflammatory disease attributed to the IUD with that found among matched nonusers (12).

No differences could be found among the various preparations of oral contraceptives available in Great Britain with regard to the risk of thromboembolic phenomena. Since it is suspected that the estrogenic component is largely responsible for abnormal clotting tendencies it will be of interest to

see if this is dose-related. Evidence for the implication of estrogens comes from several sources. For example, in a small series of male patients treated with ethinyl estradiol following myocardial infarction there was a higher incidence of thrombophlebitis, pulmonary infarction, and cerebrovascular accidents than in a control group receiving placebos. The figures for a 5-year period of treatment were as follows; seven cases of thrombophlebitis or pulmonary infarction among estrogen users against four for nonusers, five cerebrovascular accidents for estrogen-treated patients against one for the nonestrogen-treated. There were 50 patients in each group at the start of this trial (13).

In a study of patients treated for prostatic carcinoma in U.S. Veterans Hospitals there were more deaths due to "heart disease" and to cerebrovascular accidents among those treated with estrogens than among the patients who did not receive estrogens. All patients were randomized. Curiously, the death rate from all causes was lower among those who did not receive estrogens, even though more of these patients died from the presence of the tumor. An incidental finding was that either estrogen therapy or orchiectomy provided some clinical improvement in selected cases. This improvement was not enhanced if both treatments were given (14, 15). These data indicate that mortality from cardiovascular disease, probably from myocardial infarction and cardiac failure, appears to be increased in this population of older veterans when they are treated with estrogens.

There is evidence that the use of estrogens to suppress lactation increases the incidence of thromboembolism. Forty-four cases of thromboembolism that occurred among women of Cardiff during the puerperium in the years 1965 and 1966 were investigated. Thromboembolism was defined as deep vein thrombosis or pulmonary embolism. The increased risk associated with suppression of lactation by administration of diethylstilbestrol was most striking among women over 25 years of age; in this group the risk was tenfold greater than that of lactating mothers. Rather high doses of estrogens were used in this group of patients. The usual regimen was 30 to 60 mg for 3 days, 20 to 30 mg for the next 3 days, and 20 mg daily for a final 3 days (16).

The possibility of pulmonary embolism must be borne in mind by physicians prescribing oral contraceptives, because diagnosis of this disease is difficult. In a study of consecutive autopsies at the University of Michigan Hospital, 606 cases of pulmonary arterial embolism were found for the 10-year period 1945 through 1954, an incidence among total autopsies of 13.8 per cent. Of these cases a "definitive diagnosis" prior to death had been made in only 7 per cent (17). It seems probable that many cases of thromboembolism among women receiving contraceptive steroids have gone unrecognized. The diagnosis is not always easy to make. For example, in a group of eight elderly patients who suffered pulmonary emboli, four were diagnosed as having cerebrovascular disease, two were thought to have gastrointestinal disease, and two were diagnosed as having a disease resem-

bling bacterial endocarditis. In several of these patients an accompanying sign was jaundice, due to the blood pigments coming from infarcts in the lung (18). Because jaundice may also be due to another side effect, cholestasis, associated with administration of oral contraceptives, it behooves the physician to make this important differential diagnosis.

There is also the possibility that thromboembolism might occur in unusual sites. In 1963 Reed & Coon (19) reported four cases of thromboembolism. Two of these patients had thrombophlebitis, one had pulmonary embolism, and the other had a probable pulmonary embolism. A third patient had thrombosis of the superior mesenteric vein, and a fourth had thrombosis of the left axillary artery. All women were receiving orally-active progestins. Vascular occlusion of the colon was diagnosed in two women taking oral contraceptives (Norlestrin (2.5 mg) and Enovid (9.85 mg) respectively). The signs and the symptoms of vascular obstruction cleared up in each case when the administration of the oral contraceptive was stopped (20).

Until more is known, the potential hazard of thromboembolism must be carefully weighed before estrogens are used for treatment of nonlethal conditions. These include disorders of menstruation, symptoms of the menopause, vaginitis, and the suppression of lactation. An experimental method for the control of fertility should be carefully appraised. This technique entails the post-coital administration of large doses of estrogen, for example, up to 50 mg per day of diethylstilbestrol or 5 mg per day of ethinyl estradiol, for a 5-day period to prevent implantation (21).

Blood platelets behave differently in women taking oral contraceptives compared to a similar group of women not taking these drugs. The adhesiveness of platelets to glass, under standardized conditions, is increased among women on the drugs (22). The drugs used were norethynodrel, 5 mg, plus the 3-methyl ether of ethinyl estradiol, 0.075 mg; and norethisterone acetate, 4 mg, plus ethinyl estradiol, 0.05 mg. A similar tendency has been noted in cases of cirrhosis and in a man receiving diethylstilbestrol for treatment of prostatic carcinoma.

A comprehensive study of blood clotting was carried out on three groups of women; ten were "normal nulliparae," ten were in the fifth to seventh month of pregnancy, and ten had received treatment with a contraceptive combination containing 5 mg megestrol acetate plus 0.1 mg of mestranol. No significant differences were found between groups with respect to tests of platelet adhesiveness, platelet morphology, platelet aggregation, or capillary fragility. But factors II and VII were increased in the pregnant women and in the women taking steroids. The thromboplastin screening test showed differences between the nulliparae and the other two groups which were indicative of accelerated thromboplastin formation. The plasminogen concentration was higher in the steroid-treated group than for the control women; this value for the pregnant women was intermediate between, but not significantly different from, the other two groups. Euglobulin

activity on fibrin plates was lower among pregnant women than for the other groups. Reduced fibrinolytic activity was also observed for the pregnant women. The steroid-treated group, in contrast to the pregnant women, showed increased fibrinolysis. The authors conclude that differences between groups can be detected by currently available laboratory tests with regard to coagulation *in vitro,* but they do not claim prognostic value for any of the tests with regard to the risk of thromboembolic disease (23). Similar results have been obtained in other trials, although details of technique and results differ somewhat (24–26). There is no agreement about the clinical implications of these studies.

Cerebral vascular occlusions also occur in women taking oral steroids (27). This paper also lists many of the other side actions of these drugs. Another paper compiles case reports and discusses the problem (28).

One report contains tabular data for a 13-year period that shows an increase in the occurrence of cerebral vascular insufficiency, that begins in 1964, and is apparently related to the use of oral contraceptives (29). From the years 1964 through 1966, 18 of 25 women under the age of 45 years who experienced signs and symptoms of cerebrovascular insufficiency were taking various kinds of combined oral contraceptive tablets. Most of the cases associated with steroid drugs cleared up readily when the drug was stopped.

There is a suggestive report (30) about untoward effects of oral contraceptives in three women with congenital heart disease (septal defects). The cardiovascular condition of each patient deteriorated rapidly during the use of steroid contraceptives. The common finding was an increased pulmonary vascular resistance, not obviously from embolism. One patient died; autopsy showed vessel changes characteristic of chronic increased pulmonary blood flow. Another patient went into failure, and was maintained on digitalis and diuretics. A third patient noticed reduced capability for physical activity. Her downhill course was arrested when the contraceptive was stopped. The authors state that they have not observed heretofore this type of rapid deterioration in the status of young adults with congenital septal defects. This report suggests that women with pulmonary hypertension due to congenital heart disease should probably not receive steroid contraceptives. And it raises the question as to whether women with pulmonary hypertension due to any cause should get these drugs.

Contraindications to the use of steroid contraceptives must now include any history of thromboembolic disease or disorders of the blood-clotting mechanism. Certainly caution is also warranted in cases where there already exists a predilection to thromboembolism, for example, certain types of cardiovascular disease and polycythemia. It is obviously an issue of high priority to determine whether the estrogenic component or the progestogen, or the combination, is the offending agent. It may in fact be a more subtle relationship, the ratio, or the dosage, or the time of exposure to a certain dosage. In any case the answers to questions of this type will determine the proper future course of development for this group of drugs.

Liver Injury

Many case reports and several surveys indicate a causal relationship between the use of oral contraceptives and liver injury. Abnormalities in liver function tests and occasional cases of jaundice, reversible upon stopping the medication, have been noted. It has been known for some time that 17-α-alkyl-substituted steroids can cause cholestasis, but this structural requirement is not absolute; methylandrostenolone, a steroid with no substitution in the 17-position, is also cholestatic (31). In a discussion of steroids shown to be "cholestatic" it has been suggested that oral activity is a prerequisite (32).

Liver function tests.—In a series of 22 young Swedish women treated with combination oral contraceptives, an increase in bromsulfalein (BSP) retention (2-hr test) was detected in 16 of the subjects. This increased retention reached a maximum by 3 months of treatment and remained elevated during 1 year of treatment. Among 12 subjects studied about 1 month after treatment was stopped, two of the six women who had had elevated BSP retention (greater than 2 per cent) still showed increased retention. Serum glutamic oxaloacetic transaminase (SGOT) became elevated in six patients during treatment and serum glutamic pyruvic transaminase (SGPT) became elevated in 11 patients. During therapy these tests of liver function reverted to normal values, except in one case where SGPT was elevated after 12 cycles. Drugs used were Conluten (norethindrone, 2 mg, plus the 3-methyl ether of ethinyl estradiol, 0.1 mg), Volidan (megestrol acetate, 4 mg, plus ethinyl estradiol, 0.05 mg), Aconcen (chlormadinone acetate, 3 mg, plus the 3-methyl ether of ethinyl estradiol, 0.1 mg), and Lyndiol (lynestrenol, 2.5 mg, plus the 3-methyl ether of ethinyl estradiol, 0.075 mg) (33). Because most of the reports of jaundice and impairment of liver function tests have come from Scandinavia, it is important to consider reviews carried out in this country. Tyler (1) has suggested that abnormalities of BSP retention do not necessarily reflect liver injury, and also that a high incidence of hepatotoxicity noted in Finland may represent a peculiarity in diet or in racial composition. In support of Tyler's position there are reports from Holland that indicate a very low incidence of liver injury or abnormalities in liver function tests (34–36). In most reports there has been decreased BSP excretion and there has been an increase in serum transaminase levels; both changes tend to return to normal values if medication is continued. In some cases increased serum bilirubin and increased serum alkaline phosphatase levels have been observed. The cephalin flocculation test, the thymol turbidity test, and the galactose tolerance test are usually normal.

Morphological study of liver biopsy specimens from six women taking oral contraceptives showed intrahepatic cholestasis and slight hepatocellular damage by light microscopy as well as by electron microscopy. In these cases liver function tests were abnormal. In another set of six women tak-

ing oral contraceptives, whose liver function tests were essentially normal, the same investigators found morphological changes in some of the biopsy specimens studied by electron microscopy (37). In two patients who had jaundice while receiving oral contraceptives, the same authors detected intrahepatic cholestasis and hepatocellular damage by light microscopy and electron microscopy. In both of these women BSP retention, SGOT, and alkaline phosphatase levels were elevated (38).

Clinical manifestations.—The signs and symptoms of the jaundice associated with taking oral contraceptives appear to be similar for all types of preparations and independent of the locale. Ockner & Davidson (39) summarized case histories from 40 reports of jaundice due to oral contraceptives. In the usual report the patient first experienced malaise, anorexia, nausea, and pruritus. The onset of signs and symptoms generally occurred by 4 weeks of treatment. Cases included women in South America, Canada, the United States, Scandinavia, and England.

Relation to jaundice of pregnancy.—There appears to be a predisposing factor among women who develop jaundice while taking oral contraceptives. A remarkable number of such subjects have had idiopathic jaundice of pregnancy. For example, 23 women who developed jaundice while receiving oral contraceptives had been pregnant and histories of their gestations were available. Five of these had had pruritus gravidarum and 12 had had intrahepatic cholestasis. The six remaining pregnancies were described as normal. Estrogens have been known to influence bile flow. In late pregnancy, when most cases of jaundice occur, estriol production is increased about 1000-fold (40). Observations of this type suggest a genetic predisposition for this particular side effect. Among six subjects studied by Haemmerli & Wyss (41) jaundice or pruritus, or both, were observed in both pregnancies for each of two women, for four pregnancies in each of two women, for five pregnancies of one woman, and for the last three of four pregnancies in another woman. From their review these authors conclude that women who have had intrahepatic cholestasis during pregnancy are about 2000 to 8000 times more susceptible to jaundice with the oral contraceptive pill than women selected at random from the general population. The similarity of the liver injury that occurs in late pregnancy to that seen among users of the oral contraceptives makes it probable that large amounts of normally occurring estrogens or progesterone, or both, can produce cholestatic jaundice in susceptible individuals. This would argue against the suggestion of Sherlock that oral activity is a prerequisite (32).

Hormones responsible for liver injury.—Case reports show that a wide variety of contraceptives may cause liver injury. Most of these contain both a progestin and an estrogenic component. It is known that both natural and synthetic estrogens interfere with the biliary excretion of BSP. Structural alterations in ring A of the steroid hormones markedly affect activity in this regard. Diethylstilbestrol also interfered with BSP excretion (42). Nor-

ethynodrel combined with mestranol was shown to reduce transport of BSP in women when it was given in doses equivalent to those used in the oral contraceptive (43). Administration of estradiol alone did not affect BSP transport in the study cited. However, there is a great deal of evidence that estrogens can induce liver injury or affect BSP transport, or both. For example, a patient who experienced jaundice while receiving a combined preparation (Enovid), was subsequently challenged with mestranol, 0.16 mg daily, and with norethynodrel, 10 mg daily, on separate occasions. On combined medication she experienced pruritus, her serum alkaline phosphatase was elevated, BSP retention was enhanced and plasma bilirubin increased. Norethynodrel for the same period of time caused no symptoms and only a transient rise in BSP retention to 10 per cent on day 4, with return to normal on day 8. Estradiol at a dose of 5 mg per day caused a transient rise in SGOT and an elevation of BSP retention (43a). In one study, 2 of 26 patients receiving progestin alone (lynoestranol, 5 mg) had slightly elevated SGPT and "only a few" cases showed increased BSP retention. But four of ten women receiving combined therapy (lynoestranol, 5 mg, plus mestranol, 0.15 mg) had extremely high SGPT values (44). Kappas (40) has suggested that estrogens are responsible for the liver function abnormalities noted with use of the oral contraceptives, and some progestins, alkylated in the 17-position, may contribute to the effect on the liver.

It is difficult to detect a clear message from the many studies and reviews of hormone-induced liver malfunction. There seems to be little evidence for permanent liver damage, but very definite evidence for bile stasis and transient morphological changes. A conservative position would be to withhold oral contraceptives from women with a history of jaundice of pregnancy, or with demonstrable prior liver damage. The difficulty in assessing the relationship between liver injury and drug medication has been discussed by Levi (45) with particular mention of oral contraceptives.

Fertility and Infertility

It has been asserted that women who take oral contraceptives exhibit enhanced fertility when they stop taking the drug. For example, in one discussion the evidence for "superfertility" is said to appear "unequivocal" (46). The kind of evidence used for this assertion appears to be comparison between small groups of patients on oral contraceptives and groups who stopped using some other type of contraception. For example, Goldzieher and his colleagues (47) cite experience with 41 women in their clinic who stopped taking oral contraceptives in order to become pregnant, and compared them with 2677 women described by Tietze (48) who had stopped using various other kinds of contraceptives in order to achieve conception. However, increased fertility following use of oral contraceptives is not an established fact (3) and treatment of infertility with norethynodrel showed no advantage over conventional therapy or no treatment (49).

Reduction of fertility has been attributed to long-term therapy with oral

contraceptives. For example, four cases are described in which various menstrual irregularities followed cessation of oral steroid contraception (50). Many patients who have amenorrhea after long-term therapy with the oral contraceptives, appear to respond to treatment with clomiphene; it has been asserted that the ovarian changes disclosed by biopsy of these patients reflect a potential, irreversible change towards infertility (51). Steptoe suggests (51) that young women not be given these drugs until their fertility is demonstrated. Much more work needs to be done before any adverse effect on fertility is established. For example, in cases where fertility reduction is suspected it must be demonstrable that fertility prior to the use of steroid contraceptives was unimpaired.

Miscellaneous Adverse Effects

A causal association between oral contraceptives and migraine has been suggested. Three cases were reported for patients taking sequential tablets (52). In another case report the patient was taking combined medication. In this report the migraine took the form of scintillating scotomata in a 31-year old woman with no previous history of migraine (53). A study was carried out on women who had had a history of migraine and on women who had not. Various combined preparations were used, none of which could be singled out as having a different effect. Among 20 patients who had had migraine, the attacks became more intense and their frequency increased for 15 members of this group. This group was compared to 21 subjects who developed headaches while on the drugs, but who had not had migraine before. Hemicranial headaches occurred in seven patients of this group. There were other features such as nausea and photophobia that suggested a migrainous character to these *de novo* headaches. The author of this report suggests that many of the side effects previously classified as "headache" in the earlier studies of the oral contraceptives may have been migraine (54). Two cases of migraine, one a recurrence, were reported for women receiving diethylstilbestrol therapy for symptoms of the menopause (55).

The psychological effects of oral steroid therapy have not received much attention. In the paper by Phillips (54), four of his subjects who reported that they had headaches also complained of severe depressions. The psychological effects and marital adjustments entailed in the use of "ovulation suppressors" have been studied in a group of 39 couples living in southern California (56). A study of side effects with emphasis upon psychological manifestations was conducted by the Departments of Psychiatry and of Obstetrics and Gynecology at Lund in another population treated with oral contraceptives (57). A review in the form of a discussion has also appeared (58).

Information about metabolic effects of oral contraceptives continues to accumulate. Thus, papers have appeared about carbohydrate metabolism (59, 60), lipid metabolism (61, 62), and effects upon thyroid function tests

(63). Orally-active steroids, including those used in contraceptives, have effects upon microsomal enzyme systems in the liver that are responsible for drug metabolism. Most of the effects described are stimulatory, although estradiol has been reported to decrease the activity of some enzymes (64, 65).

Certain lessons emerge from the discussions about toxicities or suggested toxicities of the orally-active contraceptive drugs. The promotional quality of the early literature helped to delay the recognition of potential and real hazards. And the methods at hand for the reporting of adverse reactions are still primitive. The appraisal of new drugs has been discussed elsewhere (66).

One problem in particular that related to the oral contraceptives concerns the question of dosage. A glance at Table I shows that several doses are available for individual brands. For many years the progestational component of the combined oral contraceptive was about 10 mg. Later it was reduced to 5 mg or to 2 mg, then 1 mg, and, recently, it is apparent that some of these agents are effective at 0.5 mg. Certainly many toxicities are dose-related, and it seems likely that there would have been fewer withdrawals from the method if the lower doses had been used earlier. It should be borne in mind that the mechanism of action of these drugs was asserted to be blockade of ovulation. This is still the commonly-held view, although there is reason to believe that there are other relevant effects (3). It is remarkable that experiments were not devised much earlier to test for the required dosage schedule. It is not too late to set up criteria for proper dosage scheduling of drugs not yet introduced.

Acceptance

When the orally-active steroid contraceptives were first introduced, much hope was expressed that they would be an important aid to population control, especially in the underdeveloped parts of the world. It is quite obvious that they have had acceptance only in the highly-developed nations. And even in these countries the complex nature of population growth and its control makes it very difficult to assess the impact of contraceptive techniques. It is likely that attitudes toward family size are much more critical than particular methods of contraception. But we may inquire about the acceptibility of a method. It is important to know not only about efficacy but also about whether the subject will adhere to a regimen, and for how long.

It was estimated a few years ago that about one quarter of the married females below 45 years of age in the U.S. who exhibited a desire for contraceptives and who had access to contraceptives had elected to use the oral steroids or to try them (67). A report from the Central Marriage Guidance Clinic in Helsinki concerned the administration of Lyndiol (5 mg lynestrenol and 0.15 mg 3-methoxy-ethinyl estradiol) to 120 women between the ages of 19 and 35 for a period of 3 to 15 months (mean 7.3 months). During this time there was an overall dropout rate of 23 per cent. Nausea and

vomiting was cited most frequently, nine cases; disorders of "menstruation," 12 cases; and miscellaneous complaints consisting of headache, breast discomfort, weight gain, etc. These patients were said to have come from different social groups, "many from the lowest social stratum" (67 a).

Another report described experience over a 9-year period with 126 patients from a middle income group. Average time for treatment was about 23 months, and the medication consisted of different formulations of Enovid and Ovulen. The medications were given without cost. Careful follow-up was carried out to try to assess efficacy and side effects. Forty women (32 per cent) discontinued medication. Among these, 12 complained directly about side actions, three wanted the intrauterine device, and one was tired of taking the pill. Eight gave no reason, the remaining 20 stopped for nonrelevant reasons (68). The same group compared this experience with a 2-year study of American Indians, ". . . to a great extent an illiterate, non-English speaking, indigent group of people." The locale for the study was a Navajo reservation in the Southwest. This group has apparently had an extraordinarily high birth rate in recent years with very little fertility control and incomplete medical and economic assistance to judge from the description; ". . . many surviving at less than subsistence levels." In this study Enovid was given for 21 days followed by saccharin (placebo) for seven days. The patients returned to the clinic for medication and appraisal at 28-day intervals. Most of the patients were Navajos, but there were a few Hopis and others. There were 459 women in the group, and the trial lasted 2828 cycles; thus, the mean length of observation was about 6.6 months. During this time 190 women dropped out of the study, or 41 per cent. In this study the side effects did not constitute a major reason for dropout. Pregnancies constituted a number of cases (15) who discontinued use of the drug. Distance from the hospital was a definite but not major deterrant. It was noteworthy that three-fourths of those who dropped out did so by the end of the second cycle (69).

A report from the city of Bombay concerns couples in the "low socioeconomic group." When wives alone were asked to select a method of contraception 60 out of 168 selected the oral pill as against 52, condom; 37, IUD; 17, jelly; 2, diaphragm and jelly. Husbands alone (10 of 16) expressed a preference for the condom (70).

Preferences for contraceptive techniques change rapidly. Clinic studies in a section of Puerto Rico where women were offered free choice of contraceptives showed that the intrauterine device was the most popular method in the period from December, 1964, to July 1965. In this time about 2800 new admissions to family planning centers chose this technique compared to about 1350 who selected "orals" and about 400 who desired conventional techniques. A comparison was also made between the IUD and the oral method with regard to persistence, i.e., the number who remained "active" on the method selected. For this purpose two groups were followed

for up to 3.5 years after their first visit for IUD or pill. Twenty-two per cent of the pill users remained "active" compared to 50 per cent on the IUD. This is rather a high figure for the IUD, and it may reflect a trend in "fashion," as suggested by the author, for the time period 1962 to 1965 (71).

Reports about the activities of family planning groups were collected from 43 countries by the International Planned Parenthood Federation (I.P.P.F.) and published recently (72). In one part of this report comments about experience with oral contraceptives were listed. The most frequent disadvantage cited by respondents was expense. This is rather startling because it is seldom mentioned in studies reported in conventional, medical journals. Other disadvantages reported included side effects, "unspecified" and "specified," and difficulties in dosage scheduling. Two rather important groups of objections were "propaganda against . . ." and "contraindications," six and four respondents, respectively. One interesting comparison is that between the number of favorable versus the number of unfavorable comments about oral contraceptives. This technique received the highest number of each kind of comment, 40 favorable and 41 unfavorable. By comparison the IUD received 37 favorable versus 28 unfavorable replies. Evidently, the IUD is being used more extensively in under-developed countries.

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