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Oral Contraceptives: Therapeutics *versus* Adverse Reactions, with an Outlook for the Future II*

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ADVERSE REACTIONS: OTHER EFFECTS

Cancer and Hyperplasia—The historical developments that led to the theory that steroid hormones might play a role in the etiology and pathogenesis of cancer were reviewed in 1967 by Hertz (163). He discussed the pertinent animal and human studies prior to that time. It was evident from this review that the steroid hormones were able to induce cancer in various tissues of some nonhuman species. However, at that time, data from clinical observations were inadequate to determine whether or not similar effects were produced in humans. The inadequacy of the data resulted from several factors: (*a*) most of the studies had been uncontrolled, (*b*) the populations involved were lacking in sufficient numbers to provide statistically adequate samples, and (*c*) the periods of observation had been too short to allow for the usually long latent period for carcinogenesis in humans. Subsequent studies (*vide infra*), including those reviewed by Goldzieher (80) in 1970, have served to demonstrate further that no simple relationship exists between estrogens, with or without a progestagen, and breast or genital cancer in the human.

Hyperplasia of the uterine cervix was reported in a total of 35 oral contraceptive users (164–166) and in five pregnant patients (166). The distinctive lesion, characterized by atypical polypoid endocervical hyperplasia, had not been recognized previously (164). Of importance was the fact that this lesion resembled adenocarcinoma (164), and an erroneous diagnosis of the latter had been made initially in some instances (165).

The incidence of general atypical cytology of the genital tract has been reported. Kline *et al.* (167) compared cytological smears from the genital tracts of 2296 oral contraceptive users with smears from the genital tracts of a comparable group of 17,724 nonusers. The duration of oral contraceptive use ranged from 2 months to 7 years. A 2.0% incidence of atypical cells was found in the oral contraceptive group and a 1.0% incidence was found in the controls. A significant difference ($p < 0.01$) between the two groups was found for patients less than 30 years of age. The possibility that these atypical manifestations might be precancerous was discussed; observations that their course is unpredictable argues in favor of continuous followup of patients exhibiting them.

Dougherty (168) reported the results of a study of 1983 women who had used sequential oral contraceptives for 0–92 menstrual cycles. He found that the occurrence of atypical cytology in treated patients was twice as high as expected but that the length of time of exposure to the oral contraceptives did not affect the incidence rate of atypical cytology. No patients developed adenocarcinoma during the study.

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Melamed *et al.* (169) compared the prevalence rate of carcinoma *in situ* between two groups of patients: 27,508 women using oral contraceptives and 6809 using the diaphragm. A small difference was found between the two groups, which suggested a higher rate in oral contraceptive users. This difference, however, could have been due to a decreased prevalence rate for women using the diaphragm (a possible protective barrier effect) and/or to an increased rate in oral contraceptive users. The initial observations had shown this apparent difference also, but prior contraceptive use was not reported.

Interestingly, Stern *et al.* (170) found a significant association of cervical dysplasia with contraceptive choice. The prevalence of dysplasia among women from an apparently homogeneous population, who chose oral contraceptives, was 82/1000; among choosers of intrauterine devices, it was 51/1000; and among choosers of other methods, it was 36/1000. These observations emphasize the importance of making genital tract examinations prior to starting women on oral contraceptives, particularly if an association between the latter and cervical cancer is to be proven or disproven.

The data from a 5-year family planning clinic study of cervical epithelial changes during oral contraceptive use were reported by Chai *et al.* (171). Smears from 14 of 4164 women who had been using various oral contraceptives for 0–3 years were found to be positive, *i.e.*, suggestive of severe dysplasia or carcinoma *in situ*. Of the 14, followup was lacking in four. Of the other 10, there were six cases of carcinoma *in situ*, one of moderate dysplasia, one of severe dysplasia, and two of chronic cervicitis. The incidence rate in the oral contraceptive users was compared with that in a group of 30,834 women who were attending other clinics in the same medical center. The incidence rates of positive findings per 1000 were calculated to be 3.36 for the oral contraceptive users and 6.32 for the other group; the corresponding rates for carcinoma *in situ* were 0.96/1000 and 1.68/1000, respectively. No information was given concerning the health status or drug usage of the women attending the other clinics, but at least cervical abnormalities did not appear to be greater in the family planning clinic oral contraceptive users.

Nichols and Fidler (172) examined 128 consecutive cone biopsies that had been taken from patients because of suspicious or positive cytologic findings. Microglandular hyperplasia was found in 24% of the entire series, and the greater proportion of the patients with this condition had been oral contraceptive users. On the other hand, there was no significant difference between users and nonusers with respect to the degree or duration of cytologic squamous dyskaryosis or malignant change.

In 1972 the results were reported of an 8-year prospective study (173) involving the largest group of oral contraceptive users observed thus far for abnormal cervical cytology. The 9634 women were assigned either to an oral group (4846) or a nonoral group (4788) according to a predetermined random procedure. Those in the oral group took norethynodrel with mestranol; those in the nonoral group used other contraceptive methods, excluding intrauterine devices. Requirements for admission into the study included the following: (*a*) age between 21 and 39 years, (*b*) at least one normal pregnancy prior to admission, and (*c*) no previous use of oral contraceptives or intrauterine devices. Excluded were individuals who had a history of serious illness including neoplastic disease, those who were bedridden, and those who had a life expectancy of less than 5 years. At the initial interview the women were given a general physical and a gynecological examination; thereafter, the women returned every 2 months for interviews and annually for a physical examination.

Changes in cervical cytology, *i.e.*, progression to a higher Papanicolaou classification or regression to a lower Papanicolaou classification, were recorded. During the 8-year period, 43.9% of the oral group and 44.3% of the nonoral experienced one or more changes. The data given for the first three changes suggested that there was no difference between the two groups either with respect to the numbers of women undergoing progressive changes or with respect to the numbers undergoing regressive changes.

Various hormones, particularly estrogens, are known to influence the physiology of the breasts, producing cyclic engorgement, for example. Such changes, which can be accentuated by exogenous estrogens, may appear pathologic in some women, but upon scrutiny they often are found merely to be the result of aberrations in breast physiology (174).

Wiegenstein *et al.* (175), however, reported observing multiple fibroadenomas in 12 patients between 1967 and 1971; 11 of the patients were known to be oral contraceptive users. The condition had not been observed during the prior 7 years in that laboratory and was believed to be relatively uncommon. Unfortunately, no figure was given for the normal incidence of this condition.

Arthes *et al.* (176) described three studies involving a total of 283 cases of breast cancer and 585 controls. The results offered no evidence to indicate that administration of female hormones might be associated with the development of breast cancer; no significant excess of estrogen or oral contraceptive users was found among the cancer patients. In one of the studies, however, the number of oral contraceptive users was small, most of the diagnoses having been made prior to 1963 and the majority of women having been over 45 years of age at the time. In the second study, only 30 cases of breast cancer in patients under 35 years of age were found in a diagnostic index of hospitals in four of five study areas. The third study, however, involved 119 patients with breast carcinoma who had been treated at the Johns Hopkins Hospital from June 1969 to December 1970; these cases were matched with an equal number of controls. Analysis of data concerning prior hormone treatment indicated that neither in the total series nor in only those patients under 50 years of age was there any evidence of greater use of estrogens or oral contraceptives in the cases as opposed to the controls.

Vessey *et al.* (177) similarly reported that in a case-control study of 220 women and 216 matched controls, no evidence was found to associate oral contraceptives with either an increased risk of breast neoplasia or an increased development of benign breast lesions.

Leis (178) reviewed a number of studies involving various estrogens and estrogen–progestagen combinations. He concluded that there was no statistically significant evidence to indicate an increased incidence of breast cancer since the advent of widespread use of such compounds. He pointed out studies that had shown no difference between the degree of papillomatosis, hyperplasia, or other types of fibrocystic disease in the breasts of users and in those of nonusers of oral contraceptives. Other studies had shown no difference between the incidence of fibroadenomas, fibrocystic disease, or breast cancer in otherwise comparable groups of users and nonusers.

Taylor (179) reviewed several studies that had shown: (*a*) no histological differences between normal mammary tissue from oral contraceptive users and that taken from nonusers, and (*b*) no histological differences between fibroadenomas, other fibrocystic diseased mammary tissue, and breast carcinomas taken from users as opposed to nonusers.

Leis (178) further commented on the fallacy of drawing generalizations from isolated reports of abnormal breast findings in patients using oral contraceptives. He added, however, that it would be reasonable to stop use of such medication were abnormal breast lesions to develop while using it; altering the hormonal milieu in which breast cancers develop, for example, can lead to retardation of the cancer growth. Finally, in 1971, Lewison (180) observed that the data available were still insufficient for one to draw definite conclusions concerning the association, or lack thereof, between estrogens and/or contraceptives and breast malignancies. Nevertheless, he recommended caution in prescribing such preparations for high-risk patients. He included in this group patients with: (*a*) a strong family history of cancer, (*b*) a history of cancer of one breast (especially lobular cancer), (*c*) recurrent chronic cystic mastitis, (*d*) lobular carcinoma *in situ* of the breast, and (*e*) abnormal mammograms. He concluded, moreover, that prolonged use of these hormones was contraindicated in these predisposed patients.

Hypertension—In their 1970 review, Russell and Sullivan (181) pointed out that prior to 1967 only two isolated case reports concerning the development of hypertension in oral contraceptive users had appeared in the literature; hypertension, furthermore, was reported to be strikingly similar to that which occurred in toxemia of pregnancy. In 1967, reports began to appear of studies of small groups of women in whom the development or enhancement of hypertension was thought to be related to the use of oral contraceptives. In addition, it was suggested that the hypertensive action might be mediated through the renin–angiotensin–aldosterone system (*vide infra*).

The authors quoted three subsequent studies of oral contraceptive users in which it was reported that seven of 45, 51 of 129, and 40 of 141 women, respectively, had shown an elevation in blood pressure. The degree of elevation and definition of hypertension varied among the studies, however, as did the type of drug administered and the population of women receiving treatment. Moreover, in the one study that employed a control group of intrauterine device users, no significant difference was found between the latter group's blood pressure changes and those of the oral contraceptive users. A large-scale study, however, involving 1575 women did indicate a higher and statistically significant adjusted mean systolic and diastolic blood pressure in users as opposed to nonusers of oral contraceptives. The investigator reported that a blood pressure elevation does occur in oral contraceptive users but that it is not marked and requires sophisticated analysis, such as covariance analysis, to reveal statistically significant differences.

Russell and Sullivan (181) also reported data concerning 411 women who had had their blood pressure measured either prior to or during contraceptive therapy. Twenty-three percent of 34 patients and 22% of 26 were classified as hypertensive (b.p. $\geq$ 140/90 mm. Hg) prior to and during, respectively, their use of an intrauterine device or diaphragm. Nine percent of 225 patients and 16% of 126 were classified as hypertensive prior to and during, respectively, their use of various oral contraceptives. These observations might be of interest if it were known that the "before" and "during" users of the nonoral and oral contraceptives, respectively, had been comparable prior to treatment.

During 1970 and 1971, a number of other reports appeared that also associated the use of oral contraceptives with induced or aggravated hypertension. Lansing (182), for example, presented four case reports of oral contraceptive users with hypertension (b.p. $\geq$ 160/100 mm. Hg). In each instance the pressure returned to normal levels ($\leq$ 130/70) when the medication was discontinued.

Within a 10-month period, Clezy (183) observed 11 patients who had developed hypertension while taking oral contraceptives. Guanethidine appeared to produce an unsatisfactory response in the presence of oral contraceptives while blood pressure appeared to decrease when the oral contraceptives were withdrawn. An accurate evaluation is difficult, however, since other drugs, including amobarbital, bendroflumethiazide, chlorothiazide, phenobarbital, and/or methyldopa, had been used concurrently in some patients.

Spellacy and Birk (184) reported a study of 57 women whose blood pressure was measured during pregnancy (45 women only), during labor, at 4 weeks or more postpartum (prior to contraceptive treatment), and during the sixth cycle of oral contraceptive therapy. The women randomly were given a combined (100 mcg. mestranol plus 1 mg. ethynodiol diacetate, 24 women) or sequential (100 mcg. mestranol, 100 mcg. mestranol plus 1.5 mg. chlormadinone acetate, 33 women) preparation. Eight of the combined preparation users demonstrated hypertension (systolic pressure $\geq$ 140 mm. Hg and/or diastolic pressure $\geq$ 90 mm. Hg) while only one of the sequential preparation users did. However, four of the eight in the former group previously had had high blood pressure reading(s) during pregnancy; a prenatal value for the sequential product user was not given.

Chidell (185) reported the results of a study in which 99 of 9000 oral contraceptive users were found to be hypertensive (b.p. > 140°/90 mm. Hg). Approximately one-third previously had been normotensive. One-third

previously had had a higher than average starting blood pressure; 50% of the latter patients showed a further rise while using oral contraceptives. The remaining third already were taking oral contraceptives when their first blood pressure measurements showed them to be hypertensive. Withdrawal of the medication was followed by a reduction in pressure in 27 of 32 women, by no change in four, and by a rise in one. Continuing the medication in 34 other women was accompanied by a continued elevation of pressure in 29, a fall in three, and a further rise in two.

Similar observations were made by Saruta *et al.* (186). Fifty-six of 62 postpartum patients were classified initially as normotensive, and the remaining six were classified as hypertensive; the dividing line was a blood pressure of 140/90 mm. Hg. The initially normotensive patients were classified as becoming hypertensive if their diastolic pressure increased by at least 10 mm. Hg to a level of 90 or more. For those initially hypertensive, a rise of the diastolic pressure by at least 10 mm. Hg was interpreted as their having developed increased hypertension. During the use of 50 mcg. mestranol plus 1 mg. norethindrone, 10 of the 56 became hypertensive under these criteria while of the other six, blood pressure became normal in one, remained unchanged in four, and increased further in the sixth. Among those who became hypertensive, there had been a higher incidence of hypertension during pregnancy.

These workers also found that blood pressure returned to normal in three women in whom oral contraceptive therapy had been discontinued for 6 weeks. Finally, they commented on 18 additional patients, four of whom also became hypertensive during oral contraceptive treatment. The total incidence of hypertension development or enhancement in their series, therefore, became 19%.

Wallace (187) observed retrospectively that 15 of 26 (58%) 20–45-year-old women who had been admitted to one hospital over a 22-month period had been using oral contraceptives for an average of 5.5 years (range 18 months–9 years) at the time of being diagnosed hypertensive (mean diastolic blood pressure for the group: 133 mm. Hg, range 120–170 mm. Hg). He compared this figure (58%) with that of an estimated 32% usage of oral contraceptives in the general population. However, it cannot be assumed that these 26 patients necessarily were a representative sample of New Zealand women. Furthermore, precontraceptive blood pressure values were not known for eight of the 15 and were known to have been high in two others.

A much smaller proportion (17%) of a much larger group (325) of hypertensive women referred to a California medical center was reported by Crane *et al.* (188) to have been taking oral contraceptives or conjugated estrogen. For their study, these workers defined hypertension as a persistent blood pressure $\geq$ 160 mm. Hg systolic or $\geq$ 100 mm. Hg diastolic, and they defined normotensive as a blood pressure $\leq$ 145/95 mm. Hg. Twenty-two of the 36 oral contraceptive users observed by them and five of 20 users of conjugated estrogen had been normotensive prior to therapy. Withdrawal of the medication resulted in a return of the blood pressure in most of the women to normotensive levels.

Weir *et al.* (189), in their 1-year prospective study, found a significant increase in mean systolic pressure in 50 of 66 oral contraceptive users, but in no case did the blood pressure rise as high as 140/90. No change in mean systolic pressure occurred in a control group of 21 women using diaphragms or intrauterine devices; neither did mean diastolic pressure change in either group. Of the two women who had a history of hypertension during pregnancy (preeclampsia), systolic pressure rose in one and decreased in the other after 1 year of oral contraceptive use.

Investigations also have been carried out in an effort to determine the mechanism by which blood pressure may be increased in some women during the use of oral contraceptives. Walters and Lim (190), for example, studied a number of hemodynamic parameters including cardiac output, stroke volume, blood pressure, and heart rate in a group of 30 healthy young women using oral contraceptives of the combined type. Although the absolute numerical value of the mean obtained for the group showed a slight increase for most variables and a slight decrease for a few during therapy, in contrast to before or following therapy, the values of the standard deviations overlapped to a large extent.

Most investigations, however, have been concerned with changes in the renin–angiotensin–aldosterone system. As a result of such studies, it has been postulated that the pressor effects of estrogen and/or progestagen preparations may be mediated by derangements in this system and by associated induced changes in sodium and water balance (191, 192). Indeed, a significant correlation between diastolic pressure and blood angiotensin-II concentration has been found in three forms of hypertension (severe essential, renal, and malignant) while prominent increases in blood levels of this substance have been observed also during oral contraceptive therapy (193, 194).

Actually, a number of parameters have been studied including: (*a*) aldosterone excretion rate (188), (*b*) renin activity (the ability of the plasma to form angiotensin on incubation) (181, 186, 188), (*c*) blood angiotensin concentration (determined by radioimmunoassay) (193, 194), (*d*) renin concentration (renin activity at a constant substrate concentration) (181, 186, 194), and (*e*) renin substrate (angiotensin released by excess renin) (181, 186, 188, 194). A review of the works cited reveals some inconsistencies among the results. Increases usually were reported for blood levels of angiotensin-II, plasma renin activity, renin substrate, and aldosterone excretion, while reports concerning plasma renin concentration tend to be conflicting. Russell and Sullivan (181), for example, quoted a study which had shown that renin concentration tended to fall while renin substrate increased, resulting in no change in the rate of angiotensin formation. Cain *et al.* (194) also found a decrease in renin concentration. However, this decrease was inversely correlated with a marked rise in blood angiotensin-II. Saruta *et al.* (186), on the other hand, found essentially no change in renin concentration in their oral contraceptive users whose blood pressure had remained unchanged; they did find a slight increase in the former parameter in those whose blood pressure had increased. The latter workers suggested that such data

support the hypothesis that hypertension induced by oral contraceptives may be related to a diminished suppression of renin release.

Further complicating an attempt to explain these observations, however, is the fact that derangements in the renin–angiotensin–aldosterone system were found by other workers in oral contraceptive users who had not developed hypertension (181, 191). Nevertheless, it does appear that the oral contraceptives may aggravate preexisting hypertension or precipitate its onset in some patients and that the effect may be mediated by changes in the renin–angiotensin–aldosterone system. However, as Stokes (191) pointed out, it is necessary to postulate the possible presence of other determinants of hypertension, such as an hereditary predisposition, or a previous history of toxemia of pregnancy or renal disease in those patients in whom the blood pressure rises. In conclusion, caution in prescribing oral contraceptives to patients suspected of being at risk is certainly warranted (191), and regular blood pressure determinations in all oral contraceptive users obviously are advisable (181, 186).

Effects on Carbohydrate Metabolism—In 1969, Spellacy (195) reviewed the literature concerning the effects of oral contraceptives on carbohydrate metabolism. Abnormalities that had appeared in some women using these preparations included: (*a*) abnormal response to the oral or cortisone-stimulated oral glucose tolerance test; (*b*) abnormal response to the intravenous glucose tolerance test; (*c*) elevated levels of growth hormone; and (*d*) elevated levels of circulating insulin. Greater numbers of abnormal responses had been associated with oral glucose tolerance tests than with intravenous tests. Greater numbers of abnormal responses also had been associated with the use of combination-type preparations than with the sequential type. Fewer reports were available concerning the sequential type, however, and the duration of use of the latter tended to be shorter. Spellacy suggested a number of factors that might be related to the production of such abnormalities in women using oral contraceptives: (*a*) type(s) of steroid in the preparations, (*b*) duration of treatment, (*c*) age, (*d*) family history of diabetes mellitus, and (*e*) body weight, weight gain while taking the medication, and birth weight of previous infants. He also speculated on the possible mechanisms by which the oral contraceptives might alter carbohydrate metabolism by: (*a*) production of excess cortisol and/or excess growth hormone, (*b*) alteration of liver function, (*c*) alteration of the GI tract (absorption and/or gut-insulin release factors), and/or (*d*) alteration of peripheral tissue glucose utilization. Finally, Spellacy concluded that the presence of diabetes mellitus need not be considered a contraindication to the use of oral contraceptives, but that close supervision of such patients using these drugs was advisable. Subsequent studies (*vide infra*) have provided additional information concerning many of the above points.

A number of studies (196–200), in which a variety of oral contraceptives were employed for varying periods of time, have shown no difference between fasting blood glucose levels in normal women prior to and during therapy with these drugs. In contrast, fasting blood glucose was increased during oral contraceptive use in women with subclinical diabetes (201). Furthermore, 33 of 37 women using an injectable contraceptive, medroxyprogesterone acetate, developed increased fasting blood glucose levels after 1 year of use. Although the remaining four showed a decrease in fasting levels, the increase for the group as a whole was statistically significant (202). Fasting insulin levels, on the other hand, usually have been reported as increased during steroid contraceptive therapy (197, 199, 200, 202), although evidence to the contrary has been reported (196, 198). In general, it would appear that normal glucose levels may be maintained in oral contraceptive users at the expense of increased insulin levels (197). Such observations suggest an increased peripheral resistance to the actions of insulin during oral contraceptive therapy (196).

Oral (196, 199, 200, 202, 203), prednisone-stimulated oral (204), and intravenous (196, 197, 205–207) glucose tolerance tests, as well as intravenous arginine-stimulation tests (198) have been performed in steroid contraceptive users prior to and during therapy. The arginine-stimulation test in 26 women revealed no abnormalities in blood glucose and insulin responses after 3 months of therapy with daily doses of 0.35 mg. ethynodiol diacetate.

The different types of glucose tolerance tests have shown some variation in the results produced, apparently at least partly due to the different contraceptive preparations used as well as to variations in duration of use. Also, more insulin has been reported to be released in the oral test than in the intravenous, probably because gut factors may be stimulated to act at the β-cells, in addition to the glucose (200), in the oral test.

Wynn and Doar (196) reported a deterioration of oral glucose tolerance, as measured by the area under the plasma glucose curve, in 78% of 91 women after they had been treated for 6 months (range 3–42) with a variety of combination and sequential oral contraceptives. Intravenous glucose tolerance similarly was impaired in 70% of these women. Plasma insulin levels also rose significantly. Thirty-nine other women were tested after oral contraceptive therapy was discontinued; 90% of these showed improved oral glucose tolerance and 85% showed improved intravenous glucose tolerance.

One study (197) employed intravenous glucose tolerance tests in users of combined (50 mcg. ethinyl estradiol plus 4.0 mg. megestrol acetate), sequential (100 mcg. mestranol, 100 mcg. mestranol plus 2.0 mg. anagestone acetate), and progestagen-only (0.5 mg. chlormadinone acetate) oral contraceptives. Insulin levels increased during the test after 12–16 months of therapy, but no changes from pretreatment values were observed in the glucose tolerance curves. In a second study (207), no absolute glucose values were given. However, the investigator concluded that one of the three oral contraceptives tested (100 mcg. mestranol plus 1.0 mg. ethynodiol diacetate, but not 50 mcg. ethinyl estradiol plus 4.0 mg. norethindrone acetate or 50 mcg. ethinyl estradiol plus 4.0 mg. megestrol acetate) had a transient diabetogenic effect, as indicated by a slower rate of glucose disappearance from the blood following intra-

venous administration. The effect was statistically significant after 6 months of therapy with this oral contraceptive but almost negligible after 1 year. The results of a study (204) in which patients were given prednisone-stimulated oral glucose tolerance tests also suggested that mestranol (80 mcg.) might have a transient diabetogenic effect; the percentage of abnormal tests increased during the 1st and 3rd months of therapy but had decreased by the 9th month. These investigators had concluded previously that progestagens had no effect on glucose tolerance. Consequently, they presented combined data for women using preparations containing two different progestagens: 2.0 mg. chlormadinone acetate in a sequential preparation and 5.0 mg. norethindrone acetate in a combination product. Moreover, not all women were tested at each time period.

Clinch *et al.* (205) suggested that there might be an improved intravenous glucose tolerance in patients using 50 mcg. mestranol with 1.0 mg. norethindrone, as indicated by a faster decrease in blood glucose levels. The absolute mean values attained during testing were higher, however, after 4 months of therapy in comparison with pretreatment levels.

Spellacy (206) compared the results of intravenous glucose tolerance tests in patients using a combined oral contraceptive (80 mcg. mestranol plus 5.0 mg. norethynodrel) or a sequential product (80 mcg. mestranol, 80 mcg. mestranol plus 2.0 mg. chlormadinone acetate). All women were tested prior to therapy, but only some were tested after 6 months and others after 12 months. During the 6-month test, plasma insulin values, but not glucose values, were elevated significantly in both groups; at the 12-month test, both insulin and glucose values increased above pretreatment test levels in the combination drug-treated group but not in the other. Since the mestranol doses were the same, an influence of the progestagens was suggested. However, the group results tended to return to normal after 2–3 years of oral contraceptive therapy, although some individuals developed abnormal glucose tolerance curves.

Somewhat different responses to oral glucose tolerance tests were reported (199, 200) for patients using a sequential preparation containing 100 mcg. mestranol followed by 100 mcg. mestranol plus 1.5 mg. chlormadinone acetate. In these studies, blood glucose levels during testing were significantly elevated after 6 months of treatment, while plasma insulin levels were increased above pretreatment test values at both 6 and 12 months. Oral glucose tolerance tests in patients using injectable medroxyprogesterone acetate for 12 months produced higher mean blood glucose levels and higher mean plasma insulin levels as compared with pretreatment values of these substances (202).

In the studies just described, levels of blood constituents were measured before and following a period of oral contraceptive use (usually 1 year or less). In other studies (208, 209), these same constituents were measured in women following long-term (5 or more years) use of oral contraceptives. These studies have the disadvantage that no information prior to drug use is available. Abnormal glucose curves were obtained in response to standard oral glucose tolerance tests in 36.8% of 19 women who had used a combination-type (100 mcg. mestranol plus 1.0 mg. ethynodiol diacetate) oral contraceptive for 72–85 cycles. Abnormal responses occurred in 24.5% of 45 women who had used a sequential preparation (80 mcg. mestranol, 80 mcg. mestranol plus 2.0 mg. chlormadinone acetate) for 65–97 cycles. The difference between the two groups was not significant (208). However, a significant difference between the incidence of abnormal oral glucose tolerance curves was observed in the other study (209); the incidence of abnormal responses in this case was 77.4 and 25.8% among 59 combination product users and 43 sequential-type users, respectively. The sequential preparation used in both studies was the same and the duration of use was similar. The parameters differed, however, for the combination product users. The latter in this study (209) had used a preparation containing 60 mcg. mestranol and 10.0 mg. norethindrone for 6 years (approximately 72 cycles), followed by a preparation containing 100 mcg. mestranol and 2.0 mg. norethindrone, which provided this group with a total minimum of 100 cycles of oral contraceptive use. In both studies (208, 209), women who exhibited abnormal glucose curves also had delayed insulin peaks. Moreover, the insulin levels reached at the peaks were higher than normal.

No significant relationship was found in one of these retrospective studies (208) between the occurrence of an abnormal glucose tolerance test and: (*a*) family history of diabetes mellitus; (*b*) the delivery of an excessively large, anomalous, or stillborn infant; or (*c*) the subject's age, parity, or weight. A similar lack of correlation between abnormal glucose tolerance and the patient's: (*a*) age, (*b*) degree of obesity or change of weight during therapy, (*c*) parity, or (*d*) family history of diabetes also was found by Wynn and Doar (196). On the other hand, Spellacy (206) and Spellacy *et al.* (200), in reporting their short-term prospective-type studies, suggested that glucose and insulin changes might be related to age, parity, weight changes, delivery of excessively large infants, and family history of diabetes. Duration of treatment, if sufficiently long, may obscure any influence these other factors might have had initially.

Some patients indeed may be at risk (203). Fifteen patients showed abnormal oral glucose tolerance in their third trimester but normal tolerance following delivery. Five of five who subsequently received a combination-type oral contraceptive (50 mcg. mestranol plus 1.0 mg. norethindrone) had a recurrence of abnormal glucose tolerance during therapy. The other 10 practiced other methods of birth control, and three of them showed a deterioration of glucose tolerance. Although tolbutamide has been shown to correct oral contraceptive-induced glucose tolerance disturbances (201), some investigators have advised against the use of hormonal contraception in women exhibiting definite carbohydrate metabolic derangement (201, 204) or in those with latent diabetes (203, 204) or a family history of diabetes (204). On the other hand, one investigator (207) suggested that such women merely should receive special study. The available evidence, at the very least, seems to argue for close monitoring of carbohydrate metabolism in oral contraceptive users (206, 209).

The mechanism(s) by which oral contraceptives may alter carbohydrate metabolism in some women is(are) still unclear. Growth hormone has been reported to be diabetogenic (195, 204, 208). However, most recent studies of this hormone during contraceptive therapy have not provided evidence to support its having an etiologic effect. For example, growth hormone levels have remained normal in spite of the development of impaired glucose tolerance (196, 202). Furthermore, the normal suppressibility of growth hormone by increased glucose levels has been reported to be intact in oral contraceptive users (208, 209). A second suggested mechanism, involving impaired liver function, still seems tenable (*vide infra*). That the effect may be mediated at least partly by cortisol also seems plausible. Indeed, plasma cortisol levels have been shown to increase in some patients during oral contraceptive therapy with ethinyl estradiol and dimethisterone (210). More importantly perhaps, it has been pointed out (196) that several metabolic patterns are shared by nonobese women using oral contraceptives, nonobese women receiving glucocorticoid therapy, and obese, nondiabetic women. For example, fasting blood pyruvate levels, as well as the increment of the latter following a glucose load, have been reported to be elevated in these three conditions. It has been suggested that these changes might result from glucocorticoid excess in all three classes of women. Finally, although Seng *et al.* (211) did find significant elevations of plasma levels of a number of metabolites, including pyruvate, in women using 75 mcg. mestranol with 2.5 mg. lynestrenol, all of the values found were within their respective normal ranges.

Effects on Lipid Metabolism—Plasma triglyceride levels have been found to be elevated in women using a number of different oral contraceptives (211–218). Although statistically significant, the average elevation usually did not exceed the normal upper limit of 150 mg./100 ml. (215). Evidence does suggest that severe endogenous hypertriglyceridemia might develop in response to the use of contraceptive steroids in individuals who already have high triglyceride levels and in whom an excessive insulin response occurs following a glucose load (219). The increased triglyceride levels have been reported by most workers (212, 213, 215, 217) to be associated with concomitant increases in plasma levels of very low density, low density, and/or high density lipoproteins. Seng *et al.* (211), however, found increased triglyceride levels in the absence of increased lipoprotein levels.

Slight, but significant, increases in cholesterol levels also have been reported in some oral contraceptive users (212, 215–217), although not for eight of nine women using a quinestrol–quingestanol acetate preparation (218). The increases were associated with increases in low (215) and very low (212, 215) density lipoproteins, and no consistent changes occurred in high density lipoprotein cholesterol (215). One study reported a significant decrease in cholesterol esterification (213).

Fewer data are available concerning other parameters of lipid metabolism in oral contraceptive users. Phospholipids have been reported to be significantly elevated in association with a rise in high density lipoproteins (215, 218), although Rössner *et al.* (212) found an increase in phospholipids associated with very low density lipoproteins. Free fatty acids were reported to be significantly increased in one study (213) and unchanged in another (212).

Changes in lipid metabolism parameters can be seen within a few weeks after initiation of oral contraceptive therapy (214, 215). They increase progressively in magnitude for several weeks; within 2–3 months the values may reach a plateau which then is maintained throughout therapy (215). Levels of these metabolites may continue to rise during treatment with some preparations, although they can be expected to return almost to pretreatment values within 6 months after cessation of therapy (216). Virtually no reversal of effects was observed, however, within 1 month after withdrawal (214).

Although the evidence is not conclusive, it has been suggested that the estrogenic component of the oral contraceptives may be responsible for the lipid metabolism alterations. Increases in serum cholesterol and triglycerides were seen in women using combination-type preparations (100 mcg. mestranol plus 2.0 mg. norethindrone and 50 mcg. mestranol plus 1.0 mg. norethindrone) but not in those using a progestagen-only preparation (216). However, since the latter contained 0.5 mg. chlormadinone acetate, these data merely indicate that one particular progestagen, but not necessarily any other, appears to have no effect on lipid metabolism. Triglyceride levels, which had been elevated markedly in patients using 100 mcg. mestranol with 3.0 mg. chlormadinone acetate, did indeed decrease, although not to pretreatment levels, when the medication was changed to 3.0 mg. chlormadinone acetate alone (212). Dosage also might be of some importance. Barton *et al.* (216) pointed out that mean serum cholesterol and triglyceride levels were higher in those patients using the higher dose combined preparation. However, no information was given to indicate the degree of variability among patients.

Studies designed to elucidate the mechanism(s) by which oral contraceptives may alter lipid metabolism have focused primarily on the changes produced in triglyceride levels. That impaired removal of triglycerides might be involved was suggested by studies (212, 220–223) in which a decrease in postheparin lipoprotein lipase activity during oral contraceptive use was found. However, neither oral (223) nor intravenous (212) fat tolerance was shown to be impaired in oral contraceptive users, suggesting that increased triglyceride levels in these patients might not be the result of impaired removal of these metabolites.

An alternative explanation for the increased triglyceride levels found during oral contraceptive use is an increase in triglyceride production rate (turnover) (212, 214) due to increased secretion of these compounds by the liver (212). A study (214) of the transport kinetics of plasma triglycerides showed that triglyceride production rate was almost twice as high in a group of oral contraceptive users as in a control group. Furthermore, there actually was a simultaneous increase in the efficiency of triglyceride removal in the experimental

group which, however, only partly compensated for the large increase in triglyceride production.

Oral contraceptive use, therefore, has been associated with both increased insulin levels (223) (*vide supra*) and increased triglyceride levels. Consequently, the hypothesis has been suggested (206, 223) that the increase in triglyceride levels may be secondary to the hyperinsulinemia; that is, the elevated insulin levels might stimulate increased hepatic lipogenesis. What relationship, if any, might exist between such changes in lipid (and carbohydrate) metabolism and the occurrence of vascular lesions in oral contraceptive users (*vide supra*) remains to be determined (15).

Effects on Protein Metabolism—The plasma levels of a number of proteins have been reported to be increased, and for others decreased, in users of a variety of oral contraceptives. However, the relevance, if any, of such changes to the overall health status of the patients is unknown in most cases. Furthermore, protocols of the various studies discussed below have differed markedly, and in some cases the reports concerning specific proteins have been conflicting.

Plasma levels of transferrin, the β-globulin responsible for iron transport, have been shown to increase in oral contraceptive users (224–227). The total iron-binding capacity of the serum, a measure of transferrin levels, also was shown to increase in women given 1.0- or 3.0-mg. doses of norethindrone acetate with 50-mcg. doses of ethinyl estradiol (228); it did not increase, however, when doses of 10–75 mcg. of ethinyl estradiol alone were given.

Plasma levels of copper (229, 230) and ceruloplasm, a copper-binding globulin (224, 225, 229), also have been shown to increase during oral contraceptive therapy. Norethindrone acetate (0.3 mg.) did not have these effects when given alone (229). However, Schenker *et al.* (230) showed that a different progestagen, chlormadinone acetate (2.0 mg.), did cause an increase in serum copper.

Studies of α_2-macroglobulin levels during oral contraceptive use have revealed either insignificant changes (225, 226) or significant increases (224, 231). Since this substance has antiplasmin activity *in vitro*, it has been speculated (226, 231) that increases in its plasma levels might lead to an increased clotting tendency and, hence, play a role in the production of thromboembolism (*vide supra*).

C-Reactive protein, a complex glycoprotein synthesized in the liver, is an abnormal, nonspecific, acute-phase protein seen in pregnancy and with tissue injury and necrosis. This protein also was found in the serums of greater numbers of oral contraceptive (combined and sequential types) users and of women who had been using an intrauterine device for longer than 3 years than of control women (232).

Transcortin (cortisol-binding globulin) is increased during oral contraceptive therapy (233), with the result that increased plasma levels of cortisol can be found in women using these drugs (210, 224, 233) (*vide supra*). Some progestagen-only preparations do not appear to have this effect (210). Furthermore, it appears that the free (active) fraction of cortisol may be increased as well as the bound (inactive) fraction (233).

Thyroxine-binding globulin also is increased during oral contraceptive therapy (224, 234). As a result, the serum protein-bound iodine (PBI) is increased and the triiodothyronine (T_3) resin uptake is decreased (234, 235). Therefore, although the functional status of the thyroid is believed to remain normal during oral contraceptive therapy (234), thyroid function tests in patients using these drugs are likely to yield abnormal results (235). These effects are believed to be due primarily to estrogenic components of the oral contraceptives; except for norethynodrel, administration of oral progestagens did not alter PBI levels or T_3 uptake (234).

Plasma levels of a number of other proteins in oral contraceptive users have been studied less extensively. Haptoglobulins (224, 225, 228), orosomucoid (224, 228), and α_1-acid glycoprotein (225) have been shown to decrease during oral contraceptive therapy, whereas α_1-antitrypsin (224, 225) and β_{1A}-globulin (225) have been found to increase. Albumin levels have been unchanged (225, 226) or decreased (224, 228). Some investigators (224, 225) found no change in immunoglobulin levels in women using oral contraceptives, while others (226, 231) found increases in serum levels of γG-globulin.

Many of the proteins mentioned here are synthesized in the liver. Consequently, it has been suggested (225) that changes in plasma levels of these proteins occurring during oral contraceptive therapy might be the result of actions of the estrogens and/or progestagens on the liver.

Liver Dysfunction and Jaundice—A 1967 review (236) of the hepatic effects of oral contraceptives revealed that a total of 40 cases of jaundice, in patients from five different countries, had been attributed to five different oral contraceptives. This side effect was considered to be rare (236, 237), and an incidence rate of 1/10,000 or lower was estimated (238).

The 40 case histories reviewed (236) displayed a marked similarity. The early symptoms of pruritus, malaise, anorexia, and nausea usually appeared within the first 4 weeks of oral contraceptive therapy. Subsequently, the urine darkened and jaundice appeared. Bilirubin and transaminase levels were elevated, with marked increases in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) being found occasionally. Histological examination of liver biopsy revealed: (*a*) canalicular and hepatocellular bile stasis; (*b*) generally slight, but variable, degrees of hepatocellular degeneration and necrosis; and (*c*) minimal or absent inflammatory reaction. Electron microscopy revealed dilatation of the canaliculi, shortening or disappearance of the microvilli, intracytoplasmic dense bodies, myelin figures, and dilation of the smooth endoplasmic reticulum. Cessation of oral contraceptive treatment usually was associated with complete clinical and chemical remission within a few weeks or months. Jaundice recurred, however, in two patients following readministration of oral contraceptives. Of significance is the fact that 13 of these women previously had experienced recurrent jaundice or severe pruritus of pregnancy.

It appeared to the reviewer (236) that, in a small number of women, oral contraceptives could produce jaundice associated with reversible, noninflammatory intrahepatic cholestasis. The finding of other abnormalities of liver function tests in oral contraceptive users was more common, however. Sulfobromophthalein retention, for example, was mildly increased in 21% of the women in a Los Angeles study who had been using norethindrone (2.0 mg.) with mestranol. The same product was associated with mildly increased sulfobromophthalein retention in 42% of the women in a Swedish study. Other oral contraceptive products were reported to have produced an increase in sulfobromophthalein retention in 19–48% of users in Finland and in 7–29% of users in the United States. Various studies demonstrated elevations in transaminase levels in 0–18% of oral contraceptive users and slight elevations in alkaline phosphatase in 2%, or fewer, of the subjects. Minimal elevations of serum bilirubin occurred only rarely or not at all.

Observations that greater numbers of oral contraceptive users in Scandinavia and in Chile than in other parts of the world appear to develop jaundice (234) and/or show abnormalities in liver function tests (234) have suggested to a number of workers (234, 237, 239, 240) that some type of predisposition, possibly genetic, might be involved.

Results of studies reported since Ockner and Davidson's review (236) have tended to support earlier findings. There have been isolated case reports (241, 242) of women developing jaundice and pruritus during use of norethindrone (2.0 mg.) with mestranol. One woman (241) had a history of jaundice during pregnancy. Neither woman developed symptoms when treated subsequently with 0.5 mg. chlormadinone acetate (241) or 80 mcg. mestranol followed by 80 mcg. mestranol plus 2.0 mg. chlormadinone acetate (242).

Liver biopsies from six jaundiced and/or pruritic and six nonjaundiced, nonpruritic oral contraceptive users were compared histologically and found to be similar (243); no samples from untreated patients were studied. The authors did point out, however, that the type of mitochondria-like organelles found were similar to those found in livers of patients with hyperbilirubinemia induced by anabolic steroids. Except for one case of elevated serum glutamic pyruvic transaminase, liver function tests were normal in the asymptomatic patients. Bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase, but not thymol turbidity, were elevated in most cases in the symptomatic group. Four of the five parous, symptomatic patients, but none of the five parous women in the asymptomatic group, had a history of pruritus during pregnancy.

Two other studies (244, 245) also attempted to correlate liver function test results with liver biopsy findings. In one study (244), data were compared from women with gallbladder disease who were either users or nonusers of oral contraceptives. Histological appearance of the livers from the two groups was similar, but again no healthy, untreated control livers were examined. Levels of bilirubin, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase, but not of thymol turbidity or alkaline phosphatase, were elevated in the users as compared with the nonusers. The second study (245) found filamentous mitochondrial inclusions in a small group of oral contraceptive users. However, they were present both in jaundiced and nonjaundiced patients, and in those with extremely or only moderately elevated levels of serum glutamic oxaloacetic transaminase and/or serum glutamic pyruvic transaminase. Although these workers did not find such inclusions in liver biopsies from their one normal female and three normal male patients, they pointed out that others had reported such observations. They suggested that individuals with such inclusions could be the ones more likely to develop toxic hepatitis when using oral contraceptives.

Liver function tests have been performed on other asymptomatic oral contraceptive users. The results of one study (246) suggested that oral contraceptive use was associated with increased numbers of abnormal sulfobromophthalein tests, that the increase was dose dependent, and that the proportion of women with abnormal sulfobromophthalein tests might decrease as the duration of steroid administration increased. Somewhat different observations were made in another study (247). In the latter study, the percentage of abnormal sulfobromophthalein tests increased during the first 3 months of oral contraceptive therapy and then maintained a plateau throughout the remaining nine cycles of observation; however, the criteria for abnormal sulfobromophthalein retention differed between the two studies. Larsson-Cohn (247) also studied serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels in his patients; the frequency of elevated transaminases was found to be maximum after 1 month of oral contraceptive use and then was observed to decrease.

It appears that morphological and at least temporary functional changes may take place in the livers of some oral contraceptive users. Such findings lend support to the hypothesis (*vide supra*) that at least some of the changes seen in carbohydrate, fat, and protein metabolism in oral contraceptive users might be mediated by an effect(s) of the medication on the liver. Whether the estrogenic and/or progestagenic component(s) of the oral contraceptives may be responsible for the liver changes has not been resolved. It has been shown, for example, that 17α-alkyl-substituted derivatives of testosterone (anabolic steroids) may interfere with bile excretion at the biliary canalicular level and cause cholestatic jaundice (234), as well as reduce the biliary transport maximum for sulfobromophthalein (239). Moreover, most progestagens in the commercially available contraceptive preparations are chemically very closely related to the former (*vide supra*). However, the estrogenic components, ethinyl estradiol and mestranol, also have unsaturated hydrocarbon groups in the 17α-position (234) and have been shown (241) to impair liver function tests when given to women with a history of jaundice of pregnancy. Although the 19-nortestosterone-derived progestagens and the commercially available synthetic estrogens all may have the potential of affecting the liver, the former are administered in doses of 1.0 mg. or greater while the latter are used in

doses of 100 mcg. or less (247). The details of one case report (242) described previously serve to emphasize this point. The woman became jaundiced while using 2.0 mg. norethindrone with 100 mcg. mestranol but remained asymptomatic while using 80 mcg. mestranol followed by 80 mcg. mestranol plus 2.0 mg. chlormadinone acetate. This latter progestagen, furthermore, is a 17α-hydroxyprogesterone derivative (*vide supra*).

Amenorrhea and Galactorrhea—It was noted that use of injectable progestagen-only contraceptives often results in prolonged amenorrhea (26). However, this phenomenon also has been reported to occur following termination of the use of oral contraceptive preparations of both the combined and sequential types (248–251). Its occurrence obviously would be of concern to women who were using these compounds merely to delay the start of their families or to space their children.

The actual incidence of this phenomenon, variously termed "post-pill amenorrhea" (251) and the "oversuppression syndrome" (252, 253), appears to be low. Arrata and de Alvarez (253), for example, pointed out that various workers estimated the postcontraceptive incidence to be 1–10%. On the other hand, little is known about the incidence of spontaneous secondary amenorrhea in the general population, making it difficult to determine the significance of its incidence in women who have discontinued the use of oral contraceptives. As a possible comparison, it can be stated that reports indicated a 2–7% (15) and 6–22% (254) incidence of secondary amenorrhea in young women exposed to minor life-stresses such as leaving home to live in a new environment. Postcontraceptive amenorrhea has occurred in women who had regular menstrual cycles prior to treatment as well as in those who previously exhibited irregular cycles (250–253, 255). Consequently, inquiries into the true incidence of oral contraceptive-induced temporary amenorrhea following termination of use of the latter should take into consideration the patient's menstrual history prior to its use.

The phenomenon of postpill amenorrhea, providing other causative factors such as a pituitary tumor can be ruled out, represents an extension of the therapeutic effect of the oral contraceptives (*vide supra*). In some patients, apparently, the hypothalamic blockade continues, to varying degrees (253), following cessation of medication. For example, the first posttreatment cycle merely may be prolonged, 36–80 days in length (248). On the other hand, the spontaneous return of menstruation did not occur in one woman until she had been amenorrheic for 6 years (250), while a second woman was still amenorrheic after 8 years.

That some degree of hypothalamic dysfunction probably is responsible tends to be supported by the results of treatment (*vide infra*) and by laboratory determinations. Specifically, although Arrata and Howard (255) did find that total urinary gonadotropins were within normal limits by bioassay criteria, they pointed out that the bioassay method yields grossly inaccurate and nonspecific results. Subsequent measurements of serum LH by radioimmunoassay revealed normal tonic levels but the absence of an ovulatory surge (253). Gambrell *et al.* (251), furthermore, found low to normal serum FSH and LH levels in their amenorrheic patients. Estrogen levels tended to be low in a number of the patients as well (251, 253, 255).

Galactorrhea accompanies the amenorrhea in some women (250–253, 255). The former may begin while the patient is still taking the contraceptive tablets (251, 255) or, alternatively, it may not become manifest until after cessation of therapy. Presumably, this phenomenon also is the result of excessive hypothalamic blockade. In this case, however, the blockade is thought to release the pituitary from hypothalamic inhibition (253). Specifically, secretion of the pituitary hormone, prolactin, is thought normally to be suppressed by a hypothalamic inhibitory factor, PIF. Furthermore, although the exact function of prolactin in the human is poorly understood (256), its concentration is known to be elevated in lactating women.

A comparison of the works cited revealed no relationship between the duration of contraceptive therapy and the occurrence of prolonged amenorrhea and/or galactorrhea. It may be of significance, however, that of the 105 amenorrheic patients reported (248, 250–253, 255), none had taken the medication for less than three cycles.

It should be emphasized that: (*a*) the incidence of postpill amenorrhea is low (251); (*b*) menstruation was reported in one study (248) to recur within 48 days (somewhat sooner for sequential-type users than for users of the combined type) following cessation of therapy in the vast majority of women and that ovulation did occur in a large number of these women during their first three posttreatment cycles; and (*c*) that among the patients in another study (253), normal menses tended to resume within the first 6 months following cessation of oral contraceptive therapy.

Assuming they wish to become pregnant, at least some of the women with secondary amenorrhea following the use of oral contraceptives may be treated successfully. The true success is difficult to evaluate, however, because the number of women reported in the various studies (250–253, 255) is small. It would appear that about half the women may respond to treatment with clomiphene citrate, again supporting the idea that the phenomenon represents hypothalamic dysfunction and/or a desynchronization of normal cyclic events. For clomiphene to be effective, the woman's pituitary must be capable of secreting gonadotropins and her ovaries must contain follicles capable of maturing and rupturing (257). In addition, there should be adequate estrogen secretion (255). Women not responding to clomiphene may respond to gonadotropins [human pituitary (250), human menopausal (251), FSH (252), and/or human chorionic (251, 252)] administered instead of, or in addition to, clomiphene. Despite spontaneous or induced ovulation in these women, however, pregnancy is not always achieved. One possible explanation was suggested by Maqueo *et al.* (258); these workers found histological evidence indicative of postcontraceptive endometrial refractoriness (inactivity) in some patients, a phenomenon which, theoretically, could impair fertility.

Miscellaneous Reactions and Complaints—Numerous reports concerning a variety of reactions and complaints

that might possibly be associated with the concurrent use of oral contraceptives have been cited in the literature (15, 23, 26, 84, 234, 240, 259–262). It has been pointed out (84), however, that many such reports involve observations made on only one or two patients. Consequently, the use of statistical analysis to determine the probability of a cause-and-effect relationship in such cases is an impossibility. On the other hand, the appearance of unusual symptoms during oral contraceptive therapy (in the absence of other drug use or predisposing conditions), their disappearance following drug withdrawal, and their reappearance upon readministration of the oral contraceptives would seem to suggest that unusual reactions may develop in rare cases as a result of oral contraceptive use. Nevertheless, the lack of placebo trials (*vide infra*) in these isolated cases prevents one from concluding positively that these reactions actually were due to the medication and were not merely coincidental occurrences (26).

Jelinek (260), for example, reviewed the available data concerning a number of cutaneous reactions reported to be associated with oral contraceptive use. These reactions include photosensitivity, herpes gestationis (in women who had previous attacks during pregnancy), and the induction or exacerbation (260, 261) of lupus erythematosus. Melasma, brown facial pigmentation, may be the most common cutaneous complication of oral contraceptive use; its incidence in users in the United States has been estimated at 5–8% (260). After cessation of oral contraceptive therapy, melasma appears to fade more slowly than does that which accompanies pregnancy, and it actually may be permanent. In addition, women who have had melasma during pregnancy appear to be more likely to develop the condition during subsequent oral contraceptive use.

Various neurological manifestations similarly have been associated with oral contraceptive use. In some cases, however, the events cited may have had a vascular etiology. Reported symptoms include chorea (262), migraine (15, 26, 259), and decreased visual acuity (259), as well as other ocular disorders (15, 259).

Goldzieher *et al.* (263) recently pointed out that although numerous reports exist in the literature that suggest an association between subjective complaints, such as nervousness and depression, and the use of oral contraceptives, the frequency of such symptoms actually attributable to these drugs is still unknown. Previous studies lacked an experimental design that incorporated: (*a*) randomization of drug and placebo assignment, (*b*) double-blind administration, and (*c*) appropriate crossover of drugs and placebo. Using such a design, these workers showed that: (*a*) the incidence, during a pretreatment cycle, of complaints including nausea, vomiting, abdominal discomfort, mastalgia, headache, and depression could not be used as a baseline, and all of these symptoms, except for nausea and vomiting, diminished markedly upon initiation of placebo treatment; (*b*) significant increases in nausea, vomiting, headache, and nervousness could be demonstrated statistically only in the first treatment cycle with high estrogen agents; and (*c*) although a weight gain of 2.3 kg. (5 lb.) or more occurred in a substantial number of women over a period of four cycles, the weight gain was the same in the placebo group as in the other four groups which had been using, respectively, two different combination-type preparations, a sequential preparation, and a progestagen-only preparation.

The authors pointed out that the results of their study should not be construed as indicating that these various phenomena were not associated with oral contraceptive use, but rather that the true incidence of drug-related complaints was probably much lower than previously had been assumed. In support of this conclusion, Goldzieher *et al.* (263, 264) cited a study in which changes in the color of contraceptive medication had elicited changes in nausea and headache, as well as a decrease in libido. On the other hand, Goldzieher *et al.* (263) indicated that some degree of weight gain, for example, theoretically could be induced by the oral contraceptives since metabolic studies had shown an anabolic effect of progestagenic steroids when they were given to estrogen-primed women. Kudzma *et al.* (265), however, showed that in four women on a constant caloric intake, metabolic balance changes occurring during oral contraceptive-treated cycles were similar in magnitude to those occurring during normal, untreated menstrual cycles. Nevertheless, the results of a study (266) of adolescent users of oral contraceptives suggested that other factors, nutritional or psychological, for example, might play a role in weight gain during oral contraceptive use. The risk of significant weight gain in this study was found to be related directly to the patient's initial weight percentile at the start of contraceptive treatment.

In spite of the drawbacks of non-double-blind studies, a number of such investigations have been carried out in an effort to determine the incidence of various subjective and semisubjective complaints, particularly depression, in users and nonusers of oral contraceptives. Goldzieher (85), for example, compared the answers given by oral contraceptive users and intrauterine device users to nonleading questions regarding their health. Except during the first three cycles of oral contraceptive use, when the incidence of nausea was found to be high, the incidence of various symptoms including nausea, vomiting, diarrhea, malaise, tiredness, weakness, headache, dizziness, nervousness, depression, and decreased libido was found to be similar in oral contraceptive and intrauterine device users. The results of other studies, however, indicated: (*a*) less depression in oral contraceptive users than in intrauterine device users (267) or (*b*) greater depression in oral contraceptive users than in nonusers, the majority of the latter having been diaphragm users (268). Several explanations for the discrepancies have been suggested. With respect to the diaphragm users, it is Hart's (269) opinion that such a group would be highly selected (nonrandom), *i.e.*, that individuals using the diaphragm were likely to be of a more stable temperament than would be oral contraceptive users. With respect to the other study (267), the intrauterine device users had been significantly more depressed than the oral contraceptive users prior to the start of contraception by these groups. Other studies, furthermore, have shown that women with histories of depression (270–272) and other emotional disorders (272, 273) were the ones most likely to

complain of depression (270–272), to have psychotic reactions (273), and/or to experience tension, nausea, dizziness, forgetfulness, and anger (272) while using oral contraceptives.

Other factors also are likely to have an influence on whether or not side effects such as depression may develop in oral contraceptive users. Reactions such as depression, headache, and loss of libido were conspicuously absent from O'Dwyer's (274) patients. These women were strongly motivated to remain well and nonpregnant; the majority already had three or more children and had experienced unhealthy, unpleasant, and dangerous episodes during their pregnancies. Main (275) also emphasized the psychogenic aspect of oral contraceptive-induced depression. He outlined a number of problems that use of such medication produced in certain women: (*a*) sadness that there would be no chance of a slip-up and pregnancy; (*b*) sadness at removal of an "essential" ingredient for sexual pleasure—the risk; and (*c*) a number of other points, all of which suggested that the women studied had a poor adjustment to their sexuality. In conclusion, it is tempting to speculate that similar psychological factors contribute to the discrepancies found between the theoretical effectiveness and the use effectiveness of the various oral contraceptives (*vide supra*), as well as of various other methods of birth control.

OUTLOOK FOR THE FUTURE

The commercially available oral contraceptives are highly effective agents, although patient failures and even method failures can occur. They are also agents whose use has been associated with serious adverse reactions in some women. Consequently, the contraindication of their use in thromboembolic disorders, markedly impaired liver function, and estrogen-dependent neoplasia seems justified. Nevertheless, there is some evidence to suggest that both their effectiveness and the occurrence of severe adverse reactions in patients using them may be partly related to factors such as size of the individual and ethnic group (67) or genetic predisposition (142–146, 234, 237, 239). Furthermore, in the case of women with thromboembolic disorders, care must be taken to provide equivalently effective alternative method(s) of birth control, since the incidence of postpartum thrombosis has been shown to be higher than that occurring with the use of oral contraceptives (104, 119). With respect to women with liver disease, cautious advice (236) has been to avoid oral contraceptives in the presence of any type of acute or chronic disturbance of liver function; others (240), however, have indicated that the only absolute contraindication need be in patients with any type of acute or chronic cholestatic hepatobiliary illness "since the hepatic abnormalities induced by the pill are basically in the bile-secreting function."

Attempts to develop steroid contraceptives that might have less potential for producing serious adverse reactions, the low dose, progestagen-only preparations, for example, unfortunately have resulted in compounds that also are somewhat less effective than the conventional agents. On the other hand, greater effectiveness from the point of view of eliminating patient failures may be achieved by more extensive use of depot preparations, although method effectiveness in comparison with that of the conventional oral contraceptives does not seem to be altered. Furthermore, irregular bleeding seems to be more common with dosage forms and dosage regimens other than those of the commercially available combined and sequential oral preparations. Perhaps it is for this reason that it has been suggested that the injectable preparations may be abandoned as contraceptives for future use (75).

The intrauterine device, of which many types are available (276), seems to offer a good alternative to steroid contraception in that patient failure due to forgetting to take one's medication obviously is eliminated. Effectiveness varies, however, due to a number of factors, although the addition of a chemical, such as copper, to the intrauterine device may increase its effectiveness (277). Nevertheless, the long-term effects of the presence of an intrauterine device, not to mention the presence of a chemical in addition, cannot be anticipated at this time, particularly since the mechanism of action of the intrauterine device is thought to involve a foreign body-induced low grade inflammation in the endometrium (278).

Perhaps the most promising contraceptive means for the future may prove to be the use of agents with abortifacient, luteolytic, and/or menses-inducing properties. Such agents would be used once a month (15) and perhaps only in the event that menstruation was delayed due to fertilization and implantation having taken place. Menstruation has indeed been induced in women by the intravaginal administration of PGE_2 and $PGF_{2\alpha}$ (279). Bleeding was induced in 24 hr. or less in 11 of 12 women in whom menstruation had been delayed for 2–7 days. Eight of the 11 had a positive test for pregnancy. The 12th woman also was found to be pregnant and was aborted with a 5-mcg./min. PGE_2 infusion.

Prostaglandins are thought to be involved in the natural process of menstruation (279). Nevertheless, the mechanism by which intravaginally administered prostaglandins induce menstruation is not clear. It has been suggested that it may be the result of the increased uterine contractility that is produced, although an inhibitory effect on the corpus luteum has not been ruled out. The ease with which prostaglandins could be self-administered intravaginally within a few days of a missed menstrual period [or, alternatively, just prior to the expected time of menstruation every month, regardless of whether or not fertilization might have occurred (280)] gives these compounds a potentially important place in the future of contraception.

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RESEARCH ARTICLES

Pharmacokinetics of the β-Adrenergic Blocker Sotalol in Dogs

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Abstract □ The time course of absorption, distribution, and excretion of the β-blocker sotalol was studied in three unanesthetized dogs at three dosage levels of 1, 2, and 4 mg./kg. i.v. and 2, 4, and 8 mg./kg. p.o. The drug was assayed in body fluids and excreta by a spectrophotofluorometric method and by counting of tritiated drug. Unchanged sotalol is excreted up to 90% (±12%) in the urine. There was no protein binding, and the partition coefficient between plasma and red blood cells was unity. The data obtained in the studies were fitted graphically and by analog computer techniques and demonstrated no dose dependence. The graphical fit of the plasma levels following intravenous administration in accordance with a two-compartment open body model revealed a rapid distribution phase with a $t_{1/2}$ of 3.2 ± 1.1 min., which was followed by a disposition phase with a $t_{1/2}$ of 4.8 ± 1.03 hr. The analog computer fittings of the plasma and urine data according to the two-compartment model gave constants similar to those obtained from the graphical fits. The addition of a third tissue compartment that was in slow equilibrium with the central compartment proved necessary for a better fit of the data obtained at the high dosage level and in the ^{3}H-sotalol assays. The 75–90% absorption of sotalol in solution following oral administration was rapid ($t_{1/2}$ = 11–17 min.).

Keyphrases □ Sotalol pharmacokinetics—absorption, distribution, and excretion after intravenous and oral administration to dogs, protein binding and plasma/red blood cell partition studies □ Pharmacokinetics, sotalol—absorption, distribution, and excretion following intravenous and oral administration, dogs □ Absorption, sotalol—following intravenous and oral administration, dogs

Sotalol hydrochloride[1], 4′-[1-hydroxy-2-(isopropylamino)ethyl]methanesulfonanilide monohydrochloride, is a specific and potent β-adrenergic blocking drug. Several studies in both animals and man have demonstrated that the compound reverses isoproterenol- and epinephrine-induced tachycardia (1–3) and reverses the increase in blood levels of free fatty acids, lactic acid, and glucose that follows isoproterenol and epinephrine infusion (4, 5). Since the drug possesses less "quinidine-like" activity, it has been suggested that sotalol therapy may be preferred over other β-blockers with pronounced negative inotropic side effects (6).

It has been indicated that the plasma levels of tritium-labeled drug are related to the drug's pharmacological

[1] MJ 1999.