# ANTIFERTILITY AGENTS[1]

By Edward T. Tyler
*University of California School of Medicine and The Tyler Clinic, Los Angeles, California*



While the years 1963–66 provided some completely new developments in research on antifertility agents, much of the published material relates to further documentation of the effectiveness and expanded clinical use of the presently available progestogen-estrogen oral contraceptives. These reports include references to studies of established or suspected ancillary effects of the clinical use of these agents. It would be impossible to cover, in adequate detail to permit formulation of conclusions, the many controversial aspects of oral contraception in this review, but, fortunately, there were two important documents published in 1966 which will serve those who require comprehensive surveys of the current status of these antifertility agents. One is the report of the World Health Organization's Special Group on Oral Gestogens, which provides the conclusions of a week's deliberations by experienced investigators in this field, during a Geneva meeting in December 1965 (1). The second, representing a prolonged and exhaustive analysis of available data by a special obstetrics-gynecology advisory committee to the U. S. Food and Drug Administration provides the recommendations of the committee to the FDA (2). The considerable attention given to these hormonal contraceptive agents is undoubtedly deserved as suggested by the recent report of Ryder & Westoff on the numbers of women using this form of conception control (3). These authors quote U. S. Bureau of Census figures which indicate that by 1965, 6.4 million women had used oral contraceptives and that another 4.7 million indicated likely future use, based on interviews, with appropriate sampling. The conclusions of this National Fertility Study are of significance, and the authors state:

> The prospects for increased use of oral contraception seem very good at present, but they may be limited by further developments in the technology of fertility regulation. Meanwhile the birth rate has declined substantially. Although much sophisticated analysis of other data from the survey will be required to determine the extent of the contribution of oral contraception to this decline, the findings presented here suggest that the contribution is substantial for young married couples. The major effect on the couple's eventual number of children may be less than the effect on the time pattern of childbearing; in any event, both lower eventual parity and delayed fertility contribute to a decline in the numbers of births from year to year. Whatever the intent may be, it is apparent that young American couples have adopted a new means for achieving their reproductive goals.

The authors may also have added an additional qualification relative to possible expanding use of the present oral contraceptives, namely, the results

[1] The survey of the literature pertaining to this review was concluded in July 1966.

of ongoing studies of suspected toxicity. During the past few years, much attention has been directed toward the question of adverse effects of these agents in several specific areas. For example, possible liver toxicity has been repeatedly suggested and investigated (4–11). Reporting on a small group of seven users of a norethindrone acetate preparation, Thulin details findings in six of these women on whom liver biopsies were done (12). The biopsies showed a picture of intrahepatic stasis with slight hepatocellular damage, as in drug-induced damage of the chlorpromazine type. Clinical laboratory tests, however, differed from the pattern that is considered characteristic of chlorpromazine damage, in that alkaline phosphatase levels were normal or only slightly raised in all seven patients, and in four cases SGPT exceeded 400 international units. This divergence in laboratory findings from those seen in chlorpromazine-induced jaundice may indicate another type of liver damage, if it actually is damage. All of these patients recovered, having almost normal liver function tests within one to two months after the onset of jaundice.

In a rather extended study of liver function tests among users of almost all generally available (in the United States) oral contraceptives, Allan & Tyler found significant changes in the Bromsulphalein (BSP) retention levels that were apparently related to several factors, particularly hormone dosage, but they noted that these changes were reversible on discontinuance of medication (13). In similar studies, Eisalo et al. also found that abnormal liver function tests returned to normal within a short time after withdrawal of the drug, but they recommended that discontinuance of medication be considered in patients demonstrating abnormal serum transaminase levels and BSP retention (14). Commenting on this latter study, Swyer & Little offered the following possible reasons for the abnormal tests observed: (*a*) Eisalo et al. studied postmenopausal women 52 to 80 years of age. (*b*) Their tests were carried out in the first cycle of treatment. It is possible that the abnormal values do not actually reflect liver damage and will revert to normal as the liver becomes adjusted to the altered hormonal milieu as it does in pregnancy. (*c*) The majority of evidence suggesting a hepatotoxic effect of oral contraceptives has come from Finland; perhaps a racial difference or a peculiarity of diet is significant (15).

Additional new areas which were suggested as possibly related to side effects produced by oral contraceptives included, among others, neurological syndromes (16), impaired subsequent fertility following discontinuance of use (17), cerebral arterial occlusion (18), erythema nodosum (19), and vulvovaginal candidiasis (20, 21). Considerably more interest centered on possible ophthalmologic complications as a result of the editorial offer of Walsh and associates to collect and report instances of eye symptomatology among oral contraceptive users (22). Subsequently, these authors accumulated and summarized data for 69 cases (23). Most of the patients tabulated were in their twenties and thirties, and had been taking contraceptive drugs cyclically; in some cases the specific drug was not reported, and in some the dosages used

suggested treatment of menstrual disorders rather than contraception. The drugs known to have been used were norethindrone with ethinyl estradiol, norethynodrel with mestranol, norethindrone with mestranol, norethindrone acetate with ethinyl estradiol, norethindrone, dimethisterone with ethinyl estradiol, and ethynodiol diacetate with mestranol. The tabulated cases were categorized as pseudotumor cerebri syndrome, 4 cases; stroke syndromes, 17; ocular involvement, 22; migraine, 14; cranial nerve palsy, 1; vertigo, 2; and sensory changes, 1. In some cases the past history almost certainly eliminated the oral contraceptive as being primarily responsible for the symptomatology, while in other instances the relationship of past history of the problem may or may not have been significant. As a result of their tabulations, the authors suggested that the relationship between oral contraceptives and migraine has not received the consideration it deserves. The course of ocular symptomatology, per se, varied. Of eight patients with optic neuritis, three recovered completely, one of these after prednisone therapy and one after therapy with methylprednisolone. The retinal artery or branches were occluded in five other cases and the central retinal vein in three. Faust & Tyler subsequently provided detailed eye examination of 212 women using various oral contraceptives for one to three years and found no eye pathology that could not be expected in a random sample of the population using no long-term medication (24).

Further reports appeared in connection with such previously suspected side effects as blood coagulation changes, alterations in cervical smears, as well as the generally accepted minor side effects. In an extensive vaginal cytologic smear investigation, Wied, Davis & Frank compared findings in 1628 patients who had been taking medroxyprogesterone acetate plus ethinyl estradiol or norethynodrel plus mestranol for more than one year with those in 19,352 controls (25). Those taking a contraceptive drug showed no increase in even slight atypia. The only significant differences between control and treatment groups were in the microbiological content of the genital tract, and whether or not these changes were actually caused by the medication was conjectural. Data for the two groups, including information on the pattern of squamous cells, glandular cells, hormonal pattern, presence of infection, and microbiologic classification, were retrieved electronically and compared. The observations were age-adjusted, the age groups ranging from 15–19 to 45 plus. Findings in the 1628 women on hormonal contraceptive therapy were summarized as follows: (*a*) negative (Papanicolaou class 1): 1038 (63.8 per cent) observed as compared to 1042.9161 (64.7 per cent) expected; (*b*) negative (Papanicolaou class 2): 573 (35.2 per cent) observed as compared to 558.813 (33.9 per cent) expected; (*c*) suspicious or positive (Papanicolaou classes 3, 4, 5): 7 (0.45 per cent) observed as compared to 10.028 (0.5 per cent) expected; (*d*) unsatisfactory for diagnosis: 10 (0.6 per cent) observed as compared to 16.198 (1 per cent) expected. Case reports were presented for the seven patients with cytological findings classified as suspicious who were

receiving hormonal contraceptives. Four had evidence of carcinoma *in situ*. Pretherapy smears were available for five. In no case was there a histologically verified atypical lesion that could not have existed before therapy.

In general, the evidence accumulated in most surveys of Papanicolaou smear studies are inconclusive as yet, and several more years of study in the various major series will be required for statistical significance (26). This conclusion represents opinion of the study groups referred to earlier in this review.

## Toxicity of Oral Contraceptives

Attempts to determine whether or not a relationship exists between the use of oral contraceptives and thromboembolic disease have continued. For example, in a relatively small group of patients, as compared to controls, no increase in platelet stickiness was observed (27). Hougie and associates studied prothrombin, factor X, and prothrombin and proconvertin levels (28). They found these were significantly higher in 41 women taking 2 mg norethindrone and 100 $\mu$g mestranol cyclically for contraception than in controls (married women using vaginal contraceptives and young unmarried women). The authors were not able to say whether increases in clotting factors such as found in this study might tip the hemostatic balance in the direction of thrombosis in an otherwise predisposed individual. No patient in the series had any clinical or subclinical evidence of thromboembolic significance.

In another study of blood clotting factors, Donayre & Pincus evaluated 64 women comprising three groups. Forty were on cyclic (2.5, 5, or 10 mg norethynodrel with mestranol) for one year or less, 14 on norethynodrel for more than one year, and 8 patients off medication for an average of 45.7 cycles after short-term or long-term therapy (29). In the women receiving therapy, there were significant increases in some of the blood clotting factors that are also elevated during normal pregnancy (factors VII–X "complex," VII "specific," and fibrinogen) and in factors not increased during pregnancy (prothrombin and fibrinolysin). The authors concluded that the enhanced fibrinolytic activity in treated patients places them in a better condition than pregnant women, in whom fibrinolytic activity is decreased.

Thomson studied 40 women taking oral contraceptives and performed various tests of blood coagulability on 111 occasions (30). These revealed a significant change only in factor VII levels, which increased after the third month of contraceptive therapy. The marked changes revealed by the tests in normal women after exercise and in ten patients with deep-vein thrombosis indicated that all the tests were sensitive. Further study was deemed necessary to determine whether all the oral contraceptive preparations available are equally liable to produce raised factor VII levels, which the authors considered to be an undesirable side effect.

The oral contraceptive preparations used were norethynodrel with

mestranol in 17; norethindrone with ethinyl estradiol in 7; ethynodiol diacetate with mestranol in 9; norethindrone acetate with ethinyl estradiol in 3; and megestrol acetate with ethinyl estradiol in 4. Patients were tested every month for three months, then every three months, using the following tests: Quick test of prothrombin activity, heparin plasma clotting time, factor VII assay, thromboplastin generation test, and either cephalin time (in first 56 tests) or factor VIII (antihemophilic globulin) assay. Some patients started the oral contraceptive during this study, while others had been taking the drugs for some time. By the end of the study the longest duration of oral contraceptive therapy was two and a half years. When coagulation test results in the contraceptive-treated group and a parallel group of normal female controls were compared, there were no significant differences in prothrombin activity, thromboplastin generation test, heparin plasma clotting times, cephalin times, or factor VIII assay. Overall changes in factor VII levels were not significant, but the levels were significantly increased in those who had taken contraceptive drugs for more than three months. The change, though slight, was progressive with continuation of treatment.

The authors also tested nine women and one man, with an average age of 46 years, within 24 hours of clinical onset of deep-vein thrombosis. Factor VII levels were elevated in this group, the mean being slightly higher than that in patients treated with contraceptives for six to twelve months. Heparin clotting time was dramatically shortened in the patients with thrombosis, confirming the authors' previous studies. It was emphasized that this change was not present in the contraceptive-treated group.

Exercise undertaken by normal women in an age group similar to that of the patients using oral contraceptives did not alter factor VII levels. Moderate exercise (ten minutes' physical training) in six and more violent exercise (ten minutes' energetic netball followed by a halfmile road race) in six both resulted in significant shortening of cephalin times and rise in factor VIII levels. Estimation of hemoglobin and packed cell volume showed that these changes were not caused simply by hemoconcentration. Additional studies relative to blood coagulation involved determinations of blood viscosity (31), the effects of contraceptives on pelvic congestion (32), and relatively complete batteries of blood coagulation factors (33).

Investigations of less serious side effects related to further evaluation of such considerations as skin alterations, changing menstrual periods, weight changes, alteration in breast size and emotional responses. Ringrose studied the effects of cyclic contraceptive therapy with 2 mg norethindrone and mestranol on weight gain, change in breast size, and chloasma in a series of 100 women (34). An overall weight increase was observed in 58, no change in 27, and a decrease in 15. Of 33 who were above average weight for their age and height before therapy, 30 persisted above average. Eight who were below average weight before therapy gained an average of five pounds and attained an above average weight. Thirty-four gained without going above average

for their age and height. Thirteen who were overweight at the start of therapy gained an average of nine pounds; the average gain in 41 patients who had been underweight was seven pounds. Weight gain was a problem in 21 subjects, including 13 who had been overweight before starting therapy. There was no predictable or repetitive correlation of weight gain with age, parity, years of marriage, or duration of contraceptive therapy.

Twenty-seven women noted an increase in breast size; 20 of these also gained weight. The assessment of change in breast size was subjective; most women experienced a two-inch increase in brassiere size. The 27 subjects included 37 per cent of the 35 nulliparas and 22 per cent of the 65 parous women. Five women who had started therapy two weeks post partum noted a decrease in breast size, attributed to a continuation of natural involution. Two women developed chloasma, but elected to continue the tablets.

Kahn, Novic & Diamond suggested that, although irregular bleeding during therapy may be common, severe uterine bleeding following prolonged contraception may occur more frequently than has been reported (35). They reviewed two cases of severe uterine bleeding, following norethynodrel with mestranol, which occurred some time after discontinuance of use. The severe bleeding occurred 11 to 14 days after a normal menstrual period and microscopic findings at curettage in both cases indicated stromal hyperplasia of the endometrium consistent with norethynodrel-mestranol therapy. Subsequent menstrual cycles were normal. Ringrose reported on the emotional responses of married women receiving oral contraceptives, on the basis of questionnaires distributed to 100 married women who were taking norethindrone 2 mg with mestranol 0.1 mg (36). The group, which is described with regard to age, parity, years of marriage, religious faith, and educational attainments, provided replies concerning the effects of oral contraception as follows: (*a*) libido—increased in 22, decreased in 13, no change in 55, no opinion in 10; (*b*) coital satisfaction—improved in 53, worsened in 4, not altered in 35, uncertain in 8. Deterioration in sexual morals was predicted by 22 whose religious faith, education level, and length of marriage are reported, of whom six attributed this possibility to abolition of fear of pregnancy; six others felt morals would decline if the tablets were available to single women or juveniles, or without prescription.

Effects of oral contraceptives on radioiodine thyroid uptake were described by Irizarry, Paniagua & Pincus (60), and Aurell and associates described elevations which occur in serum lipids, particularly in low-density lipoproteins occurring one year after administration of a norethindrone-mestranol preparation (61). The low-density lipoprotein fraction reached levels typical for postmenopausal women.

In view of the introduction of oral contraceptives as long ago as 1956, reports have begun to appear on long-term use, confirming clinical safety over a significant period of years. Among the initial investigators describing effects of continued use were Pincus (39, 40, 41), Garcia (42, 43), Rock (44), and Tyler (45–48).

## "Sequential" Oral Contraceptives

Evaluation of the effectiveness of sequential type of oral contraception continued to engender considerable activity. Among the several reports appearing during the year were those relating to norethindrone-mestranol and also chlormadinone-mestranol sequential contraception, as well as dimethisterone-ethinyl estradiol (49–53). A new progestogen was also employed in a sequential program with mestranol. Board & Borland reported the use of mestranol and 3-deoxy-6$\alpha$-methyl-17$\alpha$-acetoxy progesterone (DMAP) in an oral sequential contraceptive regimen (54). The structural formula of DMAP is very similar to that of 6$\alpha$-methyl-17$\alpha$-acetoxy progesterone (medroxyprogesterone acetate). DMAP has been shown to inhibit ovulation in rats and rabbits when given in adequate doses. Much lower doses produce secretory changes in rabbit endometrium. In a preliminary study of the sequential regimen through 343 cycles in 84 women, 1 mg DMAP given for six days beginning on cycle day 19 was inadequate to induce secretory changes consistently. In the present study in 139 women through 633 cycles, 2 mg DMAP added to 0.08 mg mestranol on cycle days 19 through 24, after 14 days of therapy with 0.08 mg/day mestranol alone, regularly induced secretory changes in the endometrium. In 68 women who had been on sequential therapy using the 1 mg DMAP dosage, the incidence of breakthrough bleeding and intermenstrual spotting was lower during the first cycle of therapy with 2 mg DMAP than it was in the 71 who had not used an oral contraceptive before. The total incidence of breakthrough bleeding in 633 cycles was 3 per cent and of intermenstrual spotting 2.4 per cent. Premenstrual spotting, considered an insignificant symptom, occurred in 3 per cent of the cycles, and nausea or vomiting in 9.5 per cent. Symptoms were more frequent in the early cycles. Of 167 women originally given this medication, 30 are no longer in the study, but only three stopped because of symptoms they attributed to the medication: one "felt pregnant," another "felt faint and dizzy," and the third developed a skin rash.

A comprehensive survey of effectiveness of several studies of mestranol-chlormadinone sequential contraception was provided by Maas and associates (55). Goldzieher reported statistics claiming at least equal effectiveness for sequential mestranol-chlormadinone compared to the longer established progestogen-estrogen "combined" preparations (56).

## Mechanism of Action

Among studies of hormonal changes during administration of oral contraceptives, Vorys & Stevens studied FSH and LH excretion and concluded that the contraceptives now being used have different mechanisms of action in preventing conception (57). The majority prevent ovulation by suppression of gonadotropins, but not all by the same mechanism, according to the authors. Loraine, Bell & Harkness also evaluated the hormone excretion patterns during and after the long-term administration of oral contracep-

tives, and found that long-term administration of oral contraceptives to six women did not produce pituitary inhibition, and cycles reverted to an ovulatory pattern after medication was withdrawn (58). The pattern of urinary steroid was atypical in two women during the first cycle after treatment. Since detailed hormone excretion studies were not common, the following observations were reported and merit inclusion in this review: subjects A, B, and C received 4 mg norethindrone acetate plus 0.05 mg ethinyl estradiol for 22 to 30 cycles, subject D received 5 mg lynestrenol plus 0.15 mg mestranol for 24 cycles, subject E, 2.5 mg norethynodrel plus 0.1 mg mestranol for 38 cycles, and subject F received norethindrone acetate alone, 2 mg/day, for 67 cycles. Subject C complained of breast swelling and tenderness in many of the treatment cycles, and subject E had increased appetite and gained weight. Otherwise, there were no marked side effects, but subject F did not menstruate in 10 treatment periods on withdrawal of norethindrone. Complete 24-hour urine samples were collected throughout the investigation periods, which consisted of the last one or two treatment cycles (except in subject C) plus the first two cycles off treatment. Measurements were made of the urinary levels of estriol, estrone, estradiol, pregnanediol, and human pituitary gonadotropins in all but subject F, in whom estrogen estimations were not made. The patterns of steroid excretion indicated that the first cycle after withdrawal of contraceptive medication was anovulatory in subject B and had an atypical pattern of estrogen excretion in subject C. In subject F, ovulation occurred during the last cycle on norethindrone acetate, and yet she did not become pregnant in spite of intercourse during this cycle. In all subjects, follicular phase levels of estrogen and pregnanediol were higher in the second post-treatment cycle than in the first.

In an important theoretical paper on probable mode of action of oral contraceptives Diczfalusy proposed several theories (62). He stated that it is suggested that the "classical" progestogen-estrogen combinations inhibit ovulation by suppressing the formation and release of pituitary luteinizing hormone. Apparently they also render the cervical mucus hostile to sperm penetration. Information about possible endometrial changes induced by oral contraceptives is scanty, the author stated, and it is not yet known whether such changes are of significance in preventing implantation of the blastocyst. There is as yet no evidence of a direct effect on the secretion or motility of the fallopian tubes. The author does not believe that suppression of ovarian response to endogenous gonadotropic stimulation plays a major role. He stated that the mode of action of sequential contraceptive therapy appears to be somewhat different. If a high enough dose of estrogen is given, it by itself will be sufficient to inhibit ovulation by suppressing both luteinizing hormone and follicle stimulating hormone excretion, and the gestagen component is needed only to ensure a better shedding of the endometrium. "Escape" ovulations without pregnancy have been reported with this regimen, however, and sequential therapy may have another action, according to Diczfalusy.

### Acceptability of Oral Contraceptives

Rice-Wray and associates reported on general acceptability of contraception in Latin America and presented evidence that oral contraceptives are more acceptable than any other method of contraception to women in Puerto Rico and Mexico, particularly since the introduction of smaller doses (37, 38). They also stated that women from the underprivileged group take the contraceptive tablets as faithfully as do upper-class women, fertility is not impaired after medication is discontinued, future offspring are normal, and regular menstruation continues in women on cyclic oral medication for three, four, and five years. Endometrial biopsies taken after 30 to 67 cycles on the 10 mg dose of norethindrone are indistinguishable from those taken in cycle three.

Frank & Tietze reported on acceptance of an oral contraceptive program in the city of Chicago (59). Of 14,157 patients for whom norethynodrel-mestranol was prescribed between December 1960 and December 31, 1963, in the Chicago Planned Parenthood Centers, 70 to 83 per cent (minimum and maximum estimations) continued medication for at least 30 months, indicating excellent patient acceptance. A total of 1314 were known to have discontinued medication for reasons relevant to acceptability of oral contraception, including the following: unintended pregnancy, 39; nausea, 231; breakthrough bleeding, 111; weight gain, 61; miscellaneous physical complaints, 400; fear of thrombophlebitis or long-term effects, 169; economic reasons, 133; difficulty in following schedule or "lack of motivation," 126; and religious scruples, 6. A total of 537 were known to have discontinued medication for nonrelevant reasons, and 1523 became lost to follow-up. Maximum estimates of those continuing therapy were based on the assumption that some of those lost to follow-up, as well as those transferred to the care of a private physician (189), were still taking the tablets, but purchasing them privately. There were only seven patients known to have suffered an attack of thrombophlebitis while taking norethynodrel-mestranol. The percentage of thrombophlebitis in this series was lower than the rate expected in similar groups of women not treated with oral contraceptives.

### Lowered Dosage Forms

Progress was made in reduction of the effect of doses of the progestogens in oral contraceptives and several studies were reported indicating that low dosage medication was equally effective with higher doses of several progestogens and in some instances side effects were reduced (63–66).

Of considerable interest was the documentation that the norethindrone-mestranol combination, originally thought to require 10 mg norethindrone, was found equally effective using only 1 mg norethindrone (67).

Clinical use of low dosage progestogens alone for contraception took place in 1965 and 1966 based on the theories of Rudel. In a report on the role of progestogens in fertility control, Rudel, Martinez-Manautou & Maqueo-

Topete drew the following conclusions: (*a*) Sufficient doses of progestogens or estrogens are able to inhibit ovulation, but ovulation may occur on a random basis with estrogens, progestogens, and estrogen-progestogen combinations. (*b*) In addition to their antiovulatory action, progestogens may confer other antifertility effects including production of a state of maturation of the endogenous or exogenous estrogen-stimulated endometrium that is out of phase with ovulation should it occur, and changes in the cervical mucus incompatible with vital and motile spermatozoa. (*c*) The effects of the progestogen may be lost when a suboptimal ovulation-inhibiting dose of a progestogen is combined with a fully effective dose of estrogen, resulting in failure to convert the endometrium into an irregular pattern (68).

Martinez-Manautou et al. described this clinical usage (69). Comparing their findings, using progestogens alone in a cyclic as compared to continuous fashion, the authors found that there were two pregnancies among 124 patients on cyclic therapy and two among 320 on continuous medication when chlormadinone acetate 0.5 mg/day was given orally. One pregnancy in each group was a result of patient failure. The authors indicated that ovulation probably occurred in about 60 per cent of the patients, and that lack of pituitary-hypothalamic suppression was also evidenced by the fact that the majority of patients on continuous therapy had 24- to 34-day menstrual cycles. The drug apparently increased spermatozoal hostility of the cervical mucus. There were no side effects, except spotting and breakthrough bleeding. The patients were of proven fertility and were aged 36 or less. Some were selected at random for endometrial biopsy during the latter part of the cycle, measurement of urinary pregnanediol levels to detect ovulation, endocervical mucus studies on cycle days 9 to 16, ovarian visualization by culdoscopy, and in a few instances ovarian biopsy. Chlormadinone was given on days 5 to 25 through 416 cycles. Fourteen patients dropped out of the study. The pregnancy not due to patient failure occurred during the fourth cycle. Normal secretory endometrium was seen in 80 (73.4 per cent) of 109 biopsy specimens; there was inhibition of glandular development with irregular secretory or inactive endometrium in 11 per cent. Proliferative endometrium was found in 15.6 per cent; in some, there was an apparent inhibition of mitotic activity both in the glands and stroma of a proliferative endometrium. In 33 (27 per cent) of 122 urinary pregnanediol determinations, concentrations were at ovulatory levels (1 mg/24 hr or more). The authors suggested that more accurate urine collections would probably have yielded more evidence of ovulation. Culdoscopic findings indicated follicular activity or corpora lutea in 18 of 19 patients studied. Postcoital cervical mucus examinations showed definite spermatozoal hostility in 93 of 100 patients. Spotting occurred in 25 cycles and breakthrough bleeding in 62, usually in the first three cycles.

Chlormadinone was given continuously through 1214 cycles, and the pregnancy not attributed to patient failure occurred during the fourth cycle in this group. Sixteen patients dropped out of the study. There was less evi-

dence of normal endometrial secretory activity than during cyclic therapy, perhaps partly because some patients had previously received cyclic therapy with progestogen-estrogen combinations. Biopsy in 84 showed the endometrium to be secretory in 14, proliferative in 17, irregularly secretory in 33, and inactive in 20. Of five ovarian biopsy specimens, three showed recent corpora lutea, one a corpus luteum with involutional changes, and one atretic follicles with cystic degeneration; the authors indicated that ovulation apparently also occurs during continuous therapy. In the first seven cycles, 57.7 per cent to 70.1 per cent of the patients had cycles 24 to 34 days in length, and cycles of $>34$ days were more common than cycles of $<24$ days; 79 to 96 per cent of the women had seven days or less of bleeding or spotting per cycle. The authors made the suggestion that a parenterally administered controlled-release material with antifertility properties similar to those of chlormadinone would be an answer to the population problem. Rudel further suggests that the effectiveness of microdose progestogen alone for contraception offers opportunities to control fertility by such techniques as annual or longer-interval injections, one pill per month or blood additives.



## Injectable Contraceptives

Two major types of injectable hormone preparations have been used to produce contraception. One involves the use of a potent long-acting progestogen with a long-acting estrogen given on a "once-a-month" basis, and the other relates to the use of a progestogen alone, having "depot" activity. Describing the development of the "once-a-month" injection, Reifenstein and his associates reported data on the length and characteristics of the menstrual cycles induced by a single 1 ml injection of 150 mg of dihydroxyprogesterone acetophenide with 10 mg of estradiol enanthate given once a month to regularly ovulating women (70). On the basis of these findings, monthly injections were given to patients and evaluated for conception control, preferably with 1 ml administered as a deep intramuscular injection on day eight after onset of desquamation bleeding, whether or not the flow had stopped. The authors' data support the concept that an injection given on day eight will fully protect the woman against conception for 30 to 60 days. The dose may be given on day seven or nine if day eight is inconvenient. Reifenstein and his colleagues reported that 60 women with regular monthly cycles were treated in a total of 198 treatment cycles with 1 ml of the progestogen-estrogen on day seven, eight, nine, or ten after the onset of bleeding of the previous menstrual cycle Each woman was treated for a maximum of six consecutive cycles.

The injections induced consecutive monthly cycles of desquamation averaging 24.4 days (in the sixth cycle) to 27.4 days (in the fifth cycle). The length of cycle was reasonably consistent from patient to patient; it varied six days or less from cycle to cycle in the same individual in 88 per cent of those injected on day eight and in 82 per cent of those injected on day seven, nine, or ten. Monthly desquamation was adequate and considered to be sim-

ilar to the usual bleeding patterns in quantity; duration of bleeding averaged six days (range four to eight days in 88 per cent), and the quantity of bleeding ranged from moderately decreased to moderately increased in 93 per cent. Pregnanediol levels indicated that ovulation was inhibited in the treatment cycles of all the women, and none became pregnant while receiving the injections. Among the minority of patients who discontinued injections, two to four months were required for spontaneous monthly ovulatory cycles to be resumed.

Rizkallah & Taymor similarly studied the same injectable estrogen-progestogen combination but reported on a variety of different ratios (71). They found that 150 mg of the progestogen with 10 mg of the estrogen produced less variability in cycle length than did other combinations and there was also a good return of ovulation. Side effects in 31 subjects under observation were weight gain in five, five had increased appetite, fluid retention occurred in two, premenstrual bloating in two, and breast tenderness in three. Symptoms often associated with oral contraceptives did not occur. Patient acceptance was excellent.

Tyler reported excellent effectiveness using the same 150 mg progestogen with 10 mg estrogen preparation in over 500 women but almost 30 per cent experienced troublesome bleeding irregularities. The majority maintained good, cyclic patterns. (83).

Documentation of the results of the progestogen-alone long-acting contraceptive injection has been more limited, but effectiveness has been reported for medroxyprogesterone acetate given in doses of 150 mg per injection approximately every 90 days (72, 73, 83).

## Intrauterine Devices

Continued support of the usefulness of the intrauterine contraceptive devices is noted by reviewing the results of published reports in the past few years. For example, Nash, describing experiences with four types of intrauterine contraceptive devices at a New York City hospital, evaluated 4240 woman-months of use in a series of 260 women (74). There were four pregnancies following unnoticed expulsion of one type of device no longer used, and one pregnancy with another device *in situ*; the location of this same type of device in another patient was not known during pregnancy, but after delivery, which was normal, X ray showed that it had migrated through the uterus into the abdominal cavity. The only device used since mid-1963 by the author was the polyethylene Lippes loop. In 130 insertions of this type of device, there were no pregnancies and only one expulsion. The patients were aged 18 to 45. The total number of insertions was 278; 38 women had a device in place for 1 to 3 months, 86 for 3 to 12 months, and 136 for 12 to 36 months. In 65 insertions of an involuted loop of polyethylene there were 15 expulsions. In 34 insertions of an incomplete circle of polyethylene and 13 insertions of a stainless steel ring there were no expulsions.

The devices were removed for the following reasons: pregnancy desired, 4; excessive cramps, 1; staining or bleeding, 7; and suspected (but unproved) infection, 1. All four who wished to become pregnant succeeded immediately in conceiving and all returned following delivery to the same method of contraception. The endometrium of the seven patients with staining or bleeding was biopsied; the endometrium appeared normal in six, while one had formed a decidua-like endometrial lining. The endometrium in this case became normal after the device was removed. Yearly Papanicolaou smears have shown no evidence of cancer.

Brooks & Horne also report on intrauterine devices, having inserted such contraceptives in 188 patients with parity of two or more (75). There were four unplanned pregnancies (average 3.1 per 100 patient-years exposure) but only one occurred in the presence of the newer and larger devices.

During the first year of the study, the Lippes loop and Margulies spiral were used about equally often. The Margulies device was discontinued because of a greater frequency of leukorrhea, intermenstrual spotting, and irritation to the husband during intercourse. There was no significant discomfort or difficulty with insertion of either device when it was done in the early postmenstrual phase of the cycle. The authors believe that a thorough one-hour orientation session prior to insertion and a strong recommendation for self-examination after every menstruation are the most important factors in improving the acceptance rates. A knot in the end of the suture on tailed intrauterine devices makes identification easier.

Patients were examined one month after insertion and every six months thereafter. The intrauterine device could not be tolerated because of side effects in 23 (12.2 per cent), including those with unplanned pregnancies. It was removed because of bleeding in 21; 10 of 15 who consented to reinsertion of another size or type remained asymptomatic. The device was expelled by 17; only one of twelve who consented to reinsertion expelled each type tried.

Willson and his colleagues reported on their continuing extensive experience with the intrauterine Margulies spiral in a series of 623 clinic patients (76). The devices proved to be an acceptable method for contraception control in 88 per cent, i.e., they were removed because of a definite contraindication in only 12 per cent. The pregnancy rate for those in whom the spiral remained in the uterus was 1.5 pregnancies per 100 years of use. Complications included intermenstrual bleeding in 399, increase in menstrual flow in 39, and infection in 48.

Almost all of the patients were Negroes living in densely populated slum areas with a minimum of sanitary facilities, and many had made no prior attempt to control fertility. Each one selected the intrauterine device when the various contraceptive methods were explained. They ranged in age from 15 to 45, and all but two were parous, having had from one to sixteen children. Usually the device was introduced into postpartum patients at the first clinic visit, six to eight weeks after delivery. The Margulies tailed spiral

No. 5 was used in 293 cases, followed 1 to 30 months, for a total of 3625 months of use; the Margulies tailless spiral was used in 300 cases, followed for 1 to 28 months, for a total of 1981 months of use.

The device was expelled one or more times by 94 women, but in 58 it was replaced and eventually retained, so that the final expulsion rate for the entire series was 5.7 per cent. The tailed spirals were removed in 11 cases because of intermenstrual bleeding and in four because of increased menstrual bleeding; the tailless spirals were removed in 10 cases because of intermenstrual bleeding and in 3 because of increased menstrual bleeding. In most cases intrauterine bleeding consisted of only spotting during the first cycle or two. Of those developing genital infections, 22 of those using tailed spirals developed acute upper genital tract infection and three lower tract infection, while 21 using tailless spirals developed acute upper tract infection and two lower tract infection. It was noted that the incidence of genital infection (7.7 per cent), which would be considered high in private patients, is not unusual in the population studied. The authors stated that they did not have cases of genital infections in their private patients fitted with the intrauterine devices. In this series, all the infections subsided after antibiotic therapy, whether the coil was left in place or removed. In three patients the beaded polyethylene tail of the spiral became imbedded in the wall of the cervix, and in three others it penetrated the posterior vaginal wall. Three reported that the protruding tail produced injury during coitus. All these complications were corrected by shortening the tail. Abortions occured in two patients in whom the spirals were inserted when they were pregnant. In another patient the uterus was apparently perforated by the introducer, and the coil was placed in the peritoneal cavity where it remained throughout a pregnancy; it was removed from the anterior cul-de-sac at the time of tubal ligation following an uneventful delivery. Eleven intrauterine pregnancies occurred after the spiral was expelled; three intrauterine and three ectopic pregnancies occurred with the spiral in place. The number of tubal pregnancies is considerably less than would be expected in this segment of the population.

Tyler, Gottlieb, & Matsner reported on a comparative study of several different intrauterine devices among approximately 1500 family planning clinic patients in Los Angeles and found the Lippes loop and the nylon-tailed, distally-tied spiral most effective and associated with low expulsion rates of about eight per hundred insertions. Pregnancy rates among those retaining the devices were between 1 and 2 (77).

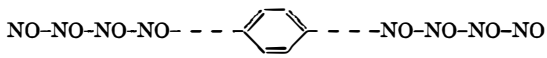
For several years, major investigators of intrauterine devices in various countries have provided data for one central compilation under auspices of the Population Council. The data are processed and analyzed by Tietze of the National Committee of Maternal Health, and reports have appeared at regular intervals. Tietze's most recent summary, encompassing about 22,000 intrauterine device insertions and over 22,000 woman-years of use, suggests a pregnancy rate of about two to four for the spiral or the loop (78).

Reports have also appeared concerning possible mechanism of action of the device (79, 80). Data have also appeared relative to endometrial changes, associated with the use of intrauterine devices (81).

## Miscellaneous Antifertility Agents

Suggestions were made of possible antinidation compounds, popularly termed "morning-after" pills, although new compounds have not been tried in humans (82). Antigonadotropic agents were unsuccessfully employed (83), as were antispermatogenic compounds (84), despite early encouraging reports (85, 86). The use of a long-acting progestogen in the male has been suggested (87). Despite theoretically useful approaches to fertility control with antibodies, comprehensive reviews have failed to indicate any practical development of the long-sought contraceptive vaccine, although this area is being increasingly explored by A. Tyler and others (88, 89). Also during the past few years, possibilities of improving the effectiveness of the rhythm method of contraception were investigated as a result of the discovery by E. Tyler in 1958 that ovulation could be induced using simple oral agents of the clomiphene type (90, 91). Despite
tion has had very limited success, and the status of periodic abstinence was recently reviewed by a World Health Organization Study Group (92).

One interesting recent development related to a new preparation described by Greenstein, who reported on a new contraceptive drug, Armpitin, which when applied to the axillary regions of the female causes a temporary and reversible sterilization in the male partner upon inhalation (93). Easily applied, like any commercial deodorant, Armpitin is said to have the sole side effect of increasing female libido. The author reported that the active portion of the molecule has the following configuration:




Armpitin was synthesized in the search for a deodorant to solve an odor problem in animal research facilities. After the drug was installed in the dispenser, it was soon apparent that (*a*) all the animal species had greatly increased their copulatory frequency and vigor; (*b*) married employees working in the animal rooms no longer brought their lunches but went home at the noon hour; (*c*) a ban on mixing of attendants of the two sexes in the same animal room was required; and (*d*) absolutely none of the females of any species was becoming pregnant. A total of 345 human volunteers used Armpitin for 2415 cycles and there were no pregnancies. The incidence of side effects such as nausea, vaginal spotting, and weight gain was nil, but increased female libido was frequently noted. Two subjects discontinued Armpitin at their husbands' request. One suburban housewife ceased to cooperate because of guilt feelings associated with improved marital relations. Questioning regarding libido distribution in the normal menstrual cycle of 300 of the volunteers showed that before Armpitin no particular

part of the menstrual cycle was optimum for intercourse, 16.66 per cent favoring the time just prior to menstruation, 16.66 per cent just after menstruation, 16.66 anytime, etc. After Armpitin, however, anytime was optimum for 298 (99.33 per cent), the difference being significant at an absurd level of confidence. There was no evidence that Armpitin directly affected libido in the male partners, but a significant sexual hyperexcitability was common among these males as a natural response to the behavior of their mates. The publication of this report has stimulated search for a number of related compounds, which may not be associated with similar side effects.

In summary, no major new pharmacological developments in the past few years have occurred to suggest an imminent completely unique, clinically effective, new antifertility agent. The volume of reports attests to the great current interest in this area of research, and there is considerable possibility that the current methods, the microdose progestogens, and the new injection methods of administration of the present hormonal agents, or other potential "break-throughs" may significantly alter our disastrous population trends—provided they can be put to wide use. But this is more of a socio-economic-theologic-political problem than a pharmacological one!



## LITERATURE CITED


1. Clinical Use of Oral Gestogens, *World Health Organ,. Tech. Rept. Ser., No.326*, (1966)
2. *Report of Obstetrics-Gynecology Advisory Committee to F.D.A.* (U.S. Govt. Printing Office, Washington, D.C., July 1966)
3. Ryder, N., and Westoff, C. F., *Science*, **153**, 37 (1966)
4. Lovgren, O., *Brit. Med. J.*, **I**, 250 (1965)
5. Baines, G. F., *Lancet*, **I**, 108–9 (1965)
6. Elliott, A. J., and Hendry, J., *Can. Med. Assoc. J.*, **92**, 344–45 (1965)
7. Cullberg, G., Lundstrom, R., and Stenram, U., *Brit. Med. J.*, **I**, 695–97 (1965)
8. Larsson-Cohn, U., and Stenram, U., *J. Am. Med. Assoc.*, **193**, 422–26 (1965)
9. von Olderhausen, H.-F., Dold, U., and Knorr, K., *Ger. Med. Monthly*, **11**, 24–28 (1966)
10. Larsson-Cohn, U., *Brit. Med. J.*, **I**, 1414–15 (1965)
11. Editorial, Oral Contraceptives and Liver Injury, *Brit. Med. J.*, **I**, 1391 (1965)
12. Thulin, K. E., and Nermark, J., *Brit. Med. J.*, **I**, 584–86 (1966)
13. Allan, J., and Tyler, E. T., *Fertility Sterility* (In press)
14. Eisalo, A., Jarvinen, P. A., and Luukkainen, T., *Brit. Med. J.*, **I**, 1416–17 (1965)
15. Swyer, G. I. M., and Little, V., *Brit. Med. J.*, **I**, 1412–14 (1965)
16. Shafey, S., and Scheinberg, P., *Neurology*, **16**, 205–11 (1966)
17. Whitelaw, M. J., Nola, V. F., and Kalman, C. F., *J. Am. Med. Assoc.*, **195**, 780–82 (1966)
18. Illis, L., Kocen, R. S., McDonald, W. I., and Mondkar, V. P., *Brit. Med. J.*, **II**, 1164–66 (1966)
19. Holcomb, F. D., *Obstet. Gynecol.*, **25**, 156–57 (1965)
20. Porter, P. S., Lyle, J. S., *Arch. Dermatol.*, **93**, 402–3 (1966)
21. Walsh, H., Hildebrandt, R., J., and Prystowsky, H., *Am. J. Obstet. Gynecol.*, **93**, 904–5 (1965)
22. Walsh, F. B., *Arch. Ophthalmol.*, **73**, 461 (1965)
23. Walsh, F. B., Clark, D. B., Thompson, R. S., and Nicholson, D. H., *Arch. Ophthalmol.*, **74**, 628–40 (1965)
24. Faust, J. M., and Tyler, E. T., *Fertility Sterility*, **17**, 1–6 (1966)
25. Wied, G. L., Davis, M. E., Frank, R., Segal, P. B., Meier, P., and Rosenthal, E., *Obstet. Gynecol.*, **27**, 327–43 (1966)
26. Tyler, E. T., *J. Am. Med. Assoc.*, **187**, 562–65 (1964)
27. Caspary, E. A., and Peberdy, M., *Lancet*, **I**, 1142–43 (1965)
28. Hougie, C., Rutherford, R. N., Banks, A. L., and Coburn, W., *Metabolism*, **14**, 414–17 (1965)

29. Donayre, J., and Pincus, G., *Metabolism*, **14**, 418–21 (1965)
30. Thomson, J. M., and Poller, L., *Brit. Med. J.*, **II**, 270–73 (1965)
31. Dintenfass, L., Julian, D. G., and Miller, G., *Lancet*, **I**, 234–35 (1966)
32. Feste, J. R., and Kaufman, R. H., *Southern Med. J.*, **58**, 945–48 (1965)
33. Samuels, A., Lepowsky, F., Tyler, E. T., and Samuels, A., *Intern J. Fertility*, **8**, 665–68 (1963)
34. Ringrose, C. A., *Appl. Therap.*, **7**, 629–30 (1965)
35. Kahn, S., Novic, O., and Diamond, S., *Obstet. Gynecol.*, **25**, 298–301 (1965)
36. Ringrose, C. A., *Can. Med. Assoc. J.*, **92**, 1207–9 (1965)
37. Rice-Wray, E., Cervantes, A., Gutierrez, J., Aranda-Rosell, A., and Goldzieher, J. W., *Metabolism*, **14**, 451–56 (1965)
38. Rice-Wray, E., Gonzalez, O., Ferrer, S., Aranda-Rosell, A., Maqueo, M., and Mungina, H., *Am. J. Obstet. Gynecol.*, **93**, 115–21 (1965)
39. Pincus, G., and Garcia, C. R., *Metabolism*, 14, 344–47 (1965)
40. Pincus, G., *Science*, **153**, 493–500 (1966)
41. Pincus, G., *The Control of Fertility* (Academic Press, Inc., New York, 1965)
42. Garcia, C. R., Pendleton-Satterthwaite, A., and Pincus, G., *Excerpta Med.*, **72**, 3–7 (1964)
43. Garcia, C. R., Rocamora, H., and Pincus, G., *Long Term Effects of Oral Contraception* (Presented at the Brit. Med. Assoc. Clin. Congr., Dundee, Scotland, April 2, 1965)
44. Rock, J., *J. Am. Med. Assoc.*, **192**, 401–2 (1965)
45. Tyler, E. T. *Advances in the Treatment of Menstrual Dysfunction* (Goldfarb, A. L., Ed., Lea and Febiger, Philadelphia, Pa., 1964)
46. Tyler, E. T., *Brit. Med. J.*, **III**, 843 (1964)
47. Tyler, E. T., *Public Health and Population Change* (Sheps, M. C., and Ridley, J. C., Eds., Univ. of Pittsburgh Press, Pittsburgh, Pa., 1965)
48. Tyler, E. T., *The Population Dilemma* (Tyler, E.T., Ed., Charles C Thomas, Publ., Springfield, Ill., in press)
49. Loewenberg, L. S., *Penn. Med. J.*, **69** 37–39 (1966)
50. Young, C. C., Jr., Mammen, E. F., and Spain, W. T., *Pacific Med. Surg.*, **73**, 35–40 (1965)
51. Jungck, E. C., *Am. J. Obstet. Gynecol.*, **94**, 165–69 (1966)
52. Board, J. A., *Obstet. Gynecol.*, **27**, 217–21 (1966)
53. Tyler, E. T., *Obstet. Gynecol.* (In press)
54. Board, J. A., and Borland, D. S., *Fertility Sterility*, **17**, 234–44 (1966)
55. Maas, J. M., *Summary of Studies of Mestranol-Chlormadinone Oral Contraception* (Presented at Ann. Meeting Pacific Coast Fertility Soc., Las Vegas, Nev., Oct. 1965).
56. Goldzieher, J. W., *Effectiveness of Sequential Oral Contraception*, (Presented Am. Fertility Soc. Ann. Meeting, Chicago, Ill., April 1966)
57. Vorys, N., Ullery, J. C., and Stevens, V., *Am. J. Obstet. Gynecol.*, **93**, 641–58 (1965)
58. Loraine, J. A., Bell, E. T., Harkness, R. A., Mears, E., and Jackson, M. C. N., *Acta Endocrinol.*, **50**, 15–24 (1965)
59. Frank, R., and Tietze, C., *Am. J. Obstet. Gynecol.*, **93**, 122–27 (1965)
60. Irizarry, S., Paniagua, M., Pincus, G., Janer, J. L., and Frias, Z., *J. Clin. Endocrinol. Metab.*, **26**, 6–10 (1966)
61. Aurell, M., Cramer, K., and Rybo, G., *Lancet*, **I**, 291–93 (1966)
62. Diczfalusy, E., *Brit. Med. J.*, **II**, 1394–99 (1965)
63. Roland, M., Clyman, M. J., Decker, A., and Ober, W. B., *Obstet. Gynecol.*, **27**, 222–31 (1966)
64. Hutcherson, W. P., Schwartz, H. A., and Weathers, W., Jr., *Fertility Sterility*, **17**, 59–67 (1966)
65. Puebla, R. A., Zarate, A., and Greenblatt, R. B., *Fertility Sterility*, **16**, 805–12 (1965)
66. Statzer, D. E., Cohn, S. L., and Floyd, W. S., *Fertility Sterility*, **17**, 250–60 (1966)
67. Tyler, E. T., Advances in Fertility Control, *Excerpta Med.* **1**, No. 1 (1966)
68. Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M., *Fertility Sterility*, 16, 158–69 (1965)
69. Martinez-Manautou, J., Cortez, V., Giner, J., Aznar, R., Casasola, J., and Rudel, H. W., *Fertility Sterility*, **17**, 49–57 (1966)
70. Reifenstein, E. C., Jr., Pratt, T. E., Hartzell, K. A., and Shafer, W. B., *Fertility Sterility*, **16**, 562–64 (1965)
71. Rizkallah, T. H., and Taymor, M. L., *Am. J. Obstet. Gynecol.*, **94**, 161–64 (1966)
72. Rice-Wray, E., Becerra, C., de la Pena, F., Maqueo, M., and Salas, J., *Ovulation Inhibition with Long-Acting Injectable Steroids: A Preliminary Re-*

*port* (Presented at Sixth Pan-Am. Congr. Endocrinol., June 1966)
73. Continio, E. M., De Sanza, J. C., and Csapo, A. J., *Fertility Sterility*, **17**, 261–66 (1966)
74. Nash, W., *N. Y. J. Med.*, **65**, 1872–75 (1965)
75. Brooks, P. G., and Horne, H. W., Jr., *Fertility Sterility*, **17**, 267–72 (1966)
76. Willson, J. R., Ledger, W. J., Bollinger, C. C., and Andros, G. J., *Am. J. Obstet. Gynecol.*, **92**, 62–70 (1965)
77. Tyler, E. T., Gottlieb, M., and Matsner, E., *Comparative Study of Intrauterine Contraceptive Devices* (Presented at Am. Acad. Osteopath. Obstet. Gynecol. Ann. Meeting, Miami, Fla., Feb. 1966)
78. Tietze, C., *Cooperative Statistical Program for the Evaluation of Intrauterine Devices* (Natl. Committee Maternal Health, Progr. Rept., 6th, Part I, New York, Dec. 1965)
79. Bengtsson, L., and Moawad, A. H., *Lancet*, **I**, 146 (1966)
80. Mastroianni, L., Proceedings of the Second Conference of Intrauterine Contraceptive Devices, *Excerpta Med.*, Ser. No. 86 (Intern. Cong. New York, 1964)
81. Southam, A. L., *Clin. Obstet. Gynecol.*, **7**, (3), 814 (1964)
82. Morris, J. M., *Use of Anti-Nidation Agents for Contraception* (Presented at Am. Fertility Soc. Ann. Meeting, Chicago, Ill., April 1966)
83. Tyler, E. T., The experimental use of a new anti-gonadotrophic agent, AY 61122 *Am. Chem. Soc., Ann. Meeting, Los Angeles, Calif., April 1963*
84. Tyler, E. T. *Oral and Injectable Contraception* (Presented at Contraception Seminar Am. Med. Assoc., Ann. Meeting, Chicago, Ill., June 1966)
85. Heller, C. G., Flageolle, B. Y., and Matson, L. J., *Exptl. Mol. Pathol. Suppl.*, **2**, 107 (1963)
86. Heller, C. G., and Clermont, Y., *Recent Progr. Hormone Res.*, **20**, 545 (1964)
87. Laron, Z., Rumney, G., and Rat, L., *Acta Endocrinol.*, **44**, 75 (1963)
88. Tyler, A. *Am. Naturalist*, 99, 309–34 (1965)
89. Tyler, A., *Clin. Obstet. Gynecol.*, **7**, 829–43 (1964)
90. Tyler, E. T., and Olson, H. J., Proc. World Congr. Fertility Sterility, 3rd, *Excerpta Med.*, No. 33, 822–23 (1959)
91. Tyler, E. T., Olson, H. J., and Gottlieb, M., *Intern. J. Fertility*, **5**, 429–32 (1960)
92. Fertility Control by Periodic Abstinence, *World Health Organ. Tech. Rept. Ser.* (1966)
93. Greenstein, J. S., *Can. Med. Assoc. J.*, **93**, 1351–55 (1965)

# CONTENTS