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THE ELEVENTH OLIVER BIRD LECTURE

CURRENT RESEARCH IN STEROID CONTRACEPTION*

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INTRODUCTION

I did not select the title of this particular presentation, but I must compliment those who did because, fortunately, it allows a considerable amount of latitude insofar as the subject matter is concerned. While the current researches I plan to discuss are rather diversified, they essentially have been built upon our early studies. Therefore, perhaps by way of introduction, it would be appropriate to discuss briefly the history of our clinical research programme in general.

Our Family Planning Centres in Los Angeles embarked on a programme of evaluation of simpler forms of contraception in the early 1950s. At that time, we were looked upon as 'radicals' because we had the temerity to suggest that perhaps the diaphragm and jelly did not have to be the only effective medically-prescribed method of contraception. We went so far as to suggest, and then demonstrate, that certain specially prepared creams and jellies and, later, foams might have a reasonably good degree of effectiveness on their own and that the diaphragm could be eliminated (Behne, Clark, Jennings, Pallais, Olson, Wolf & Tyler, 1956; Wolf, Olson & Tyler, 1957). With these efforts which gained us a reputation for being renegades, we, naturally, were easy prey for anyone who approached us with a reasonable contraceptive idea that merited investigation.

It was with this clinical research background, therefore, that, in 1956, a few months after the original study of steroid oral contraceptives was begun in Puerto Rico, our clinics began the initial investigation of these agents in the United States. Since that time, we have tested virtually every preparation made available to investigators in our country as well as a few from overseas. Much of our work has already been published and, perhaps, has come to the attention of some of you, particularly those who may read 'American'—a language obviously quite different from English! I will not take time today to review the past, but if you scan the table it will illustrate a diversified programme (Table 1). But, I would like to discuss a few points in connexion with some of our past efforts just to set the record straight where there is current confusion.

For example, there is still talk in many circles about a male oral contraceptive and I don't know how this keeps getting revived. To my knowledge (and I have looked into this rather carefully), there have been only two specific compounds (other than the androgens or progestagens) investigated to any extent in recent

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years as male contraceptives. Both of these are in the category of bis-diamines, and we studied them some time ago and found that one of the two (known from the investigational standpoint as Win-18446) was quite effective in suppressing spermatogenesis, but we discovered it had an unusual effect. When one of our first volunteers, a truck driver, stopped for lunch, had a beer and took his pill, it produced the same effect as if he had downed about a fifth of well-mellowed Scotch within about 2 minutes. This created an interesting situation when he shortly caromed off the crowded freeway in his truck, producing what we may scientifically term a scattergram! Fortunately, or perhaps unfortunately, the

TABLE 1

CHRONOLOGICAL COURSE OF INVESTIGATIONS AT FAMILY PLANNING CENTRES OF LOS ANGELES

Early 1950s	Creams and jellies 'alone'
Mid-1950s	Suppositories, vaginal 'films'
Later 1950s	Aerosol foams, foaming and non-foaming tablets
1956	Initiation of first U.S. study of oral contraception, 2 months after Pincus–Rock study in Puerto Rico. Los Angeles study is second longest continuing study existing
1958	First studies of low-dosage forms of oral contraception initiated
1959	Studies of immunological factors in fertility started
Early 1960s	Studies of 'sequential' forms of oral contraception
1961	Clinical pharmacology of oestrogen–progestagen injection method
1962	Initiation of IUD programme
1962	Clinical trials of oestrogen–progestagen 28-day injection method
1962	Clinical trials of oral male contraceptives
1962	Intensive toxicology studies of long-term oral contraceptive users. Detailed blood coagulation studies, etc.
1963	Routine biopsy IUD programme
1964	Induction of ovulation for more effective use of rhythm, employing clomiphene
1964	Detailed ophthalmological studies of oral contraceptive users
1965	Micro-dose progestagen method initiated, using continuous daily oral doses
1965	Trials of improved contraceptive IUDs
1965	Medroxy-progesterone acetate 90-day injection trials started
1966	Very low dose oestrogen–progestagen combinations successfully employed
1967	Medroxy-progesterone acetate 180-day injection trials started
1967	'Mini-micro-dose' progestagens in clinical trial
1964 to 1968	New types of 'sequential' oral contraceptives, with varied sequences
1968	Histo-chemical studies of endometria in IUD patients

beer industry didn't have to worry about it because shortly afterwards it was determined that these compounds possessed marked liver toxicity; hence, a crisis was averted and the preparations were dropped as potentially useful drugs.

Another one of our past studies that I will mention, simply to have you discard it, is the attempt we made to improve the use of rhythm for Catholic patients who could use no other method. Following our original report that anti-oestrogens such as clomiphene could produce ovulation (Tyler & Olson, 1959),

we wondered whether clomiphene could be used to produce ovulation on schedule in the hope that this would limit the number of fertile days in the cycle and permit more accurate timing of relations so that conception would not occur. Our studies of this contraceptive method failed for several reasons: (1) It was almost impossible to project exactly when ovulation would occur following a given dose of clomiphene in a substantial number of women; (2) It was obvious to us that, while perhaps the length of time in which the ovum may be fertilized is only 24 hours after ovulation, the time of viability of the spermatozoa is undoubtedly several days, for under certain circumstances we have seen active spermatozoa in the cervix as long as 7 days after intercourse (this may be considered an extension of the so-called 'double-standard') and (3) Catholic women, who would use medication, wanted 'the' pill and not an unproved substitute.

A third item requiring some initial negative comment, is the so-called 'morning after' pill. This might better be termed the 'hangover' pill because, facetiously, anyone who believes there currently *is* such a pill is probably suffering from a hangover. While there has been some significant experimentation in monkeys with one of these compounds, there has not as yet been any reasonable experiment or group of experiments on a post-coital or anti-nidation pill in humans. That holds for the 'Swedish' pill, the 'German' pill and the 'U.S.A.' pill, which at the present stage must all be considered identical with the pill from Samoa. (If you use these pills to prevent children, you'll definitely have Samoa!)

Current research

The major topic of this presentation is, of course, current research in steroid contraception at our clinics, and I would like to include the following topics in varying degrees of detail: (1) the use of injectable contraceptives; (2) micro- and mini-micro-dose progestagen contraceptives; (3) newer low-dose oestrogen–progestagen combinations; (4) 'graduated sequential' contraception; (5) coagulation studies during steroid contraception; and (6) some general long-term toxicity observations.

INJECTABLE CONTRACEPTIVES

Recognizing that one of the defects in any oral contraceptive programme is the failure of patients to remember to take their pills daily, we embarked upon studies over 6 years ago to determine whether similar hormonal preparations, given by injection, could produce equally effective and practical contraception while, at the same time, removing the factor of human error—the inability to remember to take medication daily. Two major forms of injectable contraceptives have been investigated during the past few years. One of these is a once-a-month injection, which is intended to maintain the normal bleeding pattern, while also providing contraception. These injections, therefore, contain both oestrogen and progestagen, and are given approximately once-every-28-days, as described below, in an attempt to produce 'periods' (actually, withdrawal bleeding) that are approximately 4 weeks apart. Obviously, in order to main-

tain cycles of about 4 weeks' duration, it is necessary that a relatively constant stimulation of the endometrium be maintained so that the latter does not shed prematurely. The second type of injection contains progestagen alone, and is given at intervals of either 90 or 180 days, depending on the dose.

'ONCE-A-MONTH' OESTROGEN–PROGESTAGEN INJECTION

Method

The development of a once-a-month injection required the preparation and availability of hormonal agents, each with injectable durations of action approximating to 3 weeks, thus simulating the normal ovarian endocrine support to the endometrium during the cycle. Two particular agents were found to be potentially suitable for this purpose; (1) a modified progesterone, known as dihydroxyprogesterone acetophenide, and (2) oestradiol enanthate.

After a considerable time, it was independently established by a majority of separate investigators that a combination of 150 mg of the progestagen with 10 mg of the oestrogen provided the most satisfactory combination to ensure regular cyclic bleeding (Reifenstein, Pratt, Hartzell & Shafer, 1965). This combination was then prepared for clinical use in 1-cc disposable syringes. The syringe is so designed that the guard used to protect the needle is removed to provide a plunger for the syringe. The advantage of such a syringe, including the fact that the entire unit is completely disposable, is that it assures an accurately measured dose of the hormones. The protocol for this study provided for administration of 1 ml of the oestrogen–progestagen combination, injected intramuscularly in the buttocks, on the 8th day of the menstrual cycle, and thereafter at 28-day intervals, or on the 8th day of all subsequent cycles, depending on which came first. If the 8th day occurred at a weekend, the medication could be given (according to the protocol) on either Day 7 or 9 with subsequent injections reverting to the 8-day schedule as soon as possible. Those patients who failed to obtain the injection on any of these days were dropped from the study, but could be readmitted, following temporary use of an alternative non-hormonal method of conception control. This procedure, therefore, requires uninterrupted and consecutive injections for all study patients, and the day for injection is easily remembered by the patient, since she is instructed to call the Clinic on the day that bleeding starts, requesting an appointment for her next injection exactly 1 week later.

Summary of clinical results

The details of results obtained in a series of 806 admissions to this study are published elsewhere. In brief, it has been ascertained that approximately 75% of patients have satisfactory cycles with acceptable bleeding patterns, while many of the remainder have cycles during treatment that are too short, too long, or are associated with profuse and irregular bleeding. In 4385 cycles of use, there were no pregnancies among those women who followed the protocol described above. This is, therefore, a very effective and useful contraceptive technique, within the limitations of bleeding problems, required visits for injections and associated questions of economic factors.

'ONCE-EVERY-THREE-MONTHS' PROGESTAGEN INJECTION

The once-every-three-months injection is also administered intramuscularly by means of the disposable syringe. The medication used is medroxy-progesterone acetate (MPA), given in doses of 150 mg every 90 days. In the United States at present, this long-acting progestagen is commercially available, but is only approved for limited therapeutic purposes. In a few countries, it is being employed for contraceptive purposes, but this use is not widespread. We have employed medroxyprogesterone acetate experimentally for about 3 years for contraceptive purposes, and have recently published a preliminary report of our findings (Tyler, 1968).

It should be noted at this point that, with this programme, we are dealing with a new concept in hormonal contraception. In all of the other types of hormonal contraceptives that have been used systemically, including the once-a-month injection, there has been a theoretical design to maintain the normal menstrual pattern. Even with the low daily doses, or 'micro-dose', of chlormadinone and other progestagens, there is at least the hope that the normal pattern can be maintained. With MPA injectable contraception, there is no real initial effort to maintain what might be normal cycles, and it is accepted, to begin with, that there are going to be menstrual alterations. The patients, therefore, are told in advance that they are not going to be 'regular' from the standpoint of having 28- to 30-day cycles, during their use of this contraceptive technique. A very important question, then, is how do women accept this particular type of contraception? Since, in our clinics, we use the so-called 'cafeteria' system, patients are able to choose any method they like, unless there is a medical contra-indication. Thus, women who decide they want the once-every-three-months injection, have already rejected the once-a-month injection because they prefer a less frequent injection, and they have either tried or do not care for the various pills, intra-uterine devices and vaginal methods. Consequently, they probably have some kind of empathy for this type of therapy. They also, undoubtedly, have quite a good deal of motivation and it is, therefore, very important to note that, with all the difficulties in bleeding, only about 5½% of patients discontinued this particular programme because of bleeding problems.

Eliminating those who moved away and those who could not get to the clinic, the total possible medicine-related 'drop outs' were found to be less than 20% which is considered rather good in any clinic series. Of major importance is effectiveness, and up to date, there have been 2150 woman-months of use with no pregnancies.

With the once-every-three months injection, the grossly irregular bleeding pattern was accepted quite well by our group of forewarned subjects, but how the average woman will accept this remains to be established. Also, since one hope for this type of infrequent injection is that it may be useful in countries less developed than the United States, it is important to determine whether such considerable alteration of the menstrual cycle will provoke great concern. A clue to the fact that this may be a significant problem is that in one study, in Latin America, an attempt is being made to produce regular intervals.

One point that both these injection studies obviously demonstrate is the fact that virtually any effective and relatively safe method of contraception will meet with acceptance among certain groups in the population. A technique that may be highly acceptable for one couple may be completely useless for another. Furthermore, the development of new methods does not necessarily mean the discarding of older ones, as witness the continuing large-scale use of diaphragms, creams, jellies, foams and condoms, despite the availability and promotion of hormonal agents.

The extent of usefulness of these new injectable methods remains to be seen, and it is likely that considerable proof of safety will be required in the United States by the F.D.A. before either method becomes generally available. Efforts to obtain these data are under way in our clinics and elsewhere and, presumably, in the foreseeable future, the practising physician or health officer will be in a position to determine whether either of these methods will be useful in his own particular programme.

CONTINUOUS LOW-DOSE PROGESTAGEN CONTRACEPTION

In recent years, as I am sure most of you know, there have been investigations of the potential of progestational agents used alone in very small doses on a continuous daily basis. I believe the idea for this type of therapy started with Rudel and Martinez-Manataou and their co-workers (Martinez-Manatou, Cortez, Giner, Aznar, Casasola & Rudel, 1965). The first agent to be used in this connexion was a 17-acetoxyprogesterone, chlormadinone acetate, a progestagen used in a sequential contraceptive which has had considerable use (Goldzieher, 1968).

The documentation for continuous micro-dose chlormadinone acetate effectiveness is quite substantial at this time; there was a Symposium on the subject in London not very long ago. The same compound, chlormadinone acetate, given in a daily dose of 0·5 mg, has provided rather effective contraception in a relatively small series of cases, numbering less than 200. As is well recognized, one of the major problems in continuous low-dosage progestagen contraception is the disruption of the normal cycle. This, together with the occurrence of a higher pregnancy rate than that obtained with the combined or sequential agents, has cast at least some doubt on the potential usefulness of the micro-dose method. Attempts are going ahead in the United States to market the product and it is said to be already available to physicians in England.

Since clinical trials of this agent have been reported, I would like simply to refer briefly to some ancillary studies in which we are involved, with a view to obtaining more data on the aetiology of the irregular bleeding pattern, as well as a possible mechanism of action related to certain endometrial changes. In this work we have been associated with Dr Milan R. Henzl and Dr Gary Boost, and our group is taking endometrial biopsies on patients using chlormadinone therapy and on suitable controls during various times of the cycle. These are being examined by histochemical techniques, as well as electron microscopy and, while the numbers involved so far do not justify a report, I would simply like to refer to the fact that this work is going on and that the major charac-

teristics we are seeking to observe are tissue changes which might give a clue as to how micro-dose progestagens work and why irregular bleeding is such a common problem.

A more notable aspect of our micro-dose work, I believe, refers to our efforts in utilizing the so-called 'mini-micro-dose' progestational agents. I refer to the fact that the chlormadinone acetate dose is generally 0·5 mg daily, or in some cases 0·3 mg, and in a number of investigations even 0·2 mg, but we are using norgestrel, another progestagen, in much smaller amounts.

When norgestrel combined with ethinyl oestradiol was apparently very effective in doses of 0·5 mg norgestrel and 0·05 mg ethinyl oestradiol (Tyler, Matsner, Gotlib, Levin, Daniels, Shimabukuro, Dolman & Elliott, 1968), it appeared that this particular agent might be useful at even a lower continuous daily dosage level than chlormadinone. With suitable indications for this, we initiated a study of a series of subjects, giving each a daily dose of 0·075 mg norgestrel, alone, on a continuous basis. At the same time, we also started a group using norgestrel at 0·05 mg daily. The reason for using the term 'mini-micro-dose' obviously is that 0·05 mg norgestrel is only a tenth of the micro-dose of chlormadinone that has been employed. If we carry this analysis further, it is evident that this dose of the new progestagen is only 1/200th of the amount that was then considered an extremely potent progestagen, norethynodrel, employed in the original nor-steroid contraceptives. It should, obviously, be mentioned parenthetically that, of course, we are referring to milligram doses, and it is certainly likely that the physiological or metabolic and constitutional effects produced by a small dose of one agent may be comparable to a larger dose of another and, therefore, these milligram comparisons are not necessarily valid. At any rate, it is of importance to note that this extremely low milligram dosage of a steroid is being employed and apparently with some potential usefulness.

We began these studies about 2 years ago with a group of patients who were willing to volunteer to take a very low-dose unproved agent, recognizing the risk of a pregnancy but also recognizing that, if the serious side-effects publicized concerning the standard contraceptives actually do relate to either dosage or the oestrogen component, there might be some increased safety in using an extremely low dose of just one of the agents. In our original small pilot group, it appeared that both doses were quite effective—at least in the chlormadinone effectiveness range, but that the higher dose seemed to be associated with somewhat increased bleeding problems (Tyler, 1969). At about that time, reports from elsewhere suggested simultaneously that perhaps failures were occurring with greater frequency in the 0·05-mg dose; it was therefore decided then to concentrate on the 75-gamma preparation. The original patients who were started on the 50-gamma dose are continuing to use this dose as long as there are no major problems, but the major portion of our effort has involved the 75-gamma dose in a series which now numbers about 500 admissions.

The incidence of bleeding irregularities on both the 0·05-mg and 0·075-mg norgestrel preparations was considerable, but most of the other usual complaints relative to oral contraception were minimal. The reasons why patients were dropped from the study usually were either 'break-through bleeding' or 'moved

from the area'. Many young college women, who were concerned about contraceptive side-effects, wanted to try the mini-dose, but their reliability as far as return visits was concerned was quite unpredictable. There is a tendency for this group of patients to change from one campus to another; but perhaps some of those listed as 'moved away' might correctly be characterized as having had bleeding problems. In addition, although this could also be considered to affect our pregnancy rate, we have the impression in our clinic that one major reason subjects will return is to report the occurrence of a pregnancy.

One question relative to all these micro-dose preparations, as previously indicated, is the question of mode of action. There have been various theories, but the one that is most commonly suggested is that the cervical mucus is altered to the extent that sperm penetration is not adequate for conception. For this reason, we have been studying cervical mucus at various times in the cycle, particularly near the theoretical mid-cycle when ovulation would be expected to occur. The results of a number of post-coital studies to determine whether a persistent cervical hostility was present, showed that, while a great majority of the tests were poor, there were at least some that could be considered in the category of normal post-coital findings. Considering, also, that many of these patients, on a spot-check basis, were found to be ovulating according to the usual criteria, it is likely that we are dealing with a combination of protective measures. At least a few of these are as yet undefined, but search is continuing for them. Perhaps the relation of anti-trypsin, in cervical mucus, may be a clue, since trypsin is now said to affect sperm penetration of the zona pellucida (Tyler, 1969).

One of the more commonly suggested mechanisms is that the endometrium quickly becomes 'out of phase' with use of these agents, and, therefore, normal implantation does not occur. While there may be some merit to this, we must also recognize that thousands of women over the years have achieved pregnancies when progestational medication is given during the luteal phase, and this, therefore, could not be considered a barrier to pregnancy. An opposing view to this is the fact that these patients are given a progestational agent, early in the cycle, in an unphysiological way.

Regardless of mechanism, it is interesting to reflect on the effectiveness of this mini-micro-dose preparation, as indicated by our experience to date. In a total of approximately 150 woman-years of use of the 0·075 mg dose, and approximately 30 woman-years use of the 0·05-mg dose, we have had very few unplanned pregnancies.

Since there is a tendency for fewer bleeding problems, with lower doses of these agents, although effectiveness seems to be diminished, we are 'splitting hairs' now and employing a dose of 0·062 mg in the hope that this may produce a more optimal level with both effectiveness and control of bleeding.

THE USE OF LOWERED DOSAGES OF ESTABLISHED PROGESTAGEN–OESTROGEN COMBINATIONS

Many years ago, we began our norethindrone–mestranol studies with a tablet containing 10 mg of norethindrone with 0·06 mg of mestranol. Since that time, as everyone is aware, the dosage of this combination has been steadily

dropping and about a year ago, in the United States, a tablet containing 1 mg norethindrone with 0·05 mg mestranol was marketed as being as effective as the original 10-mg dose. In fact, in our experiences with a fairly substantial series on the 1-mg tablet, we were quite impressed with it in comparison with higher doses of the same progestagen. One feature that seemed to reduce the general usefulness of the 1-mg tablet was the fact that its clinical application seemed to be associated with a greater degree of irregular bleeding (and occasionally amenorrhoea) than had been noted with the 2-mg preparation. Therefore, we attempted to compensate for this deficiency by increasing the amount of oestrogen to 0·08 mg from the 0·05 mg present in the 1-mg tablet. Recently, we have analysed the records of our series of patients who received the 1-mg plus 0·08-mg dosage, since this has been one of our studies of a product that has just become available.

This clinical study began in February 1967, and is still in progress. All patients admitted were given an initial supply of tablets, but a few did not return at all after the initial visit and some made only one return visit thereafter. These are not included in this report.

There were 753 patients in our 1/80 programme representing 3573 cycles of therapy (Tyler, Levin & Matsner, 1969). The average number of completed cycles per patient for the entire group was 4·7. The maximum number of cycles for a patient up to June 1968 was fourteen. Forty-one per cent had completed six cycles of therapy, 106 patients, (14·1%) had completed nine cycles and nineteen patients (2·5%) had completed twelve cycles. The patients in this group were of an age range of relative maximal fertility with 545 (72·4%) being between 16 and 27 years of age. Only twenty (2·7%) were over 40 years. The average age of those reported was 24·9 years. The fertile nature of this group is illustrated by the fact that 71% of these 753 patients had had at least one full term delivery before entering the study. Several of the remainder also had pregnancies which did not go to term. The average number of pregnancies of this group before treatment was 2·4; the average number of deliveries was 2·2.

In this group, the average pre-therapy cycle length was 27·9 days. While on therapy, 70·4% of the cycles were in the range of 27 to 29 days. It is evident then that there was a tendency to somewhat shorter cycles. Average cycle length on therapy was 27·1 days.

Questioning patients about their reliability in taking tablets revealed that a fair percentage of those showing cycle lengths of less than 25 days had in fact taken tablets incorrectly, especially twenty-four of fifty-nine patients (40·7%) with cycles of less than 25 days.

A comparison of days of flow, pre-therapy and during therapy is, of course, also important. Pre-therapy was 4·6 days and during therapy the average was 4·0 days. Categorizing the amount of flow subjectively as 'not stated', 'none', 'light', 'moderate' and 'heavy', and assigning these values of 0 to 3, our data indicates that average pre-therapy amount of flow was 2·0, while average amount of flow during therapy was 1·9. Thus, the figures for both duration and amount of flow would suggest a slight diminution in bleeding while on this therapy. This would ordinarily be considered a positive side-effect.

One pregnancy occurred in this year. Since the patient denied missing pills, it must be considered a method failure, but with 298 years of woman-use, this would provide a pregnancy rate of 0·3, a figure comparable to those reported for other extremely effective oral contraceptives.

GRADUATED SEQUENTIAL CONTRACEPTION

The graduated sequential-type of oral contraceptive is a new programme with which we have been involved, wherein at least some amount of hormonal medication is given each day of the cycle. The sequence of tablet taking is as follows: on Day 1, the patient starts with four tablets of 0·025 mg ethinyl-oestradiol and then on Day 5 takes 0·1 mg ethinyl oestradiol for 14 days. Following this, 0·125 mg ethinyl oestradiol + 10 mg medroxyprogesterone acetate is taken daily for 7 days. For the last 3 days before bleeding, the patient will be taking the remaining three tablets of 0·025 mg ethinyl oestradiol which are in the package. It had been felt by the proponents of this method that a more effective type of sequential programme would result and that the incidence of side-effects would be quite low.

We have been studying several hundred subjects using the graduated sequential programme for a few years. Over a 2-year period there were 4250 cycles of use among 675 patients, with an incidence of breakthrough bleeding of 3%, and an incidence of nausea of 10% of all cycles. Breast problems and headaches also occurred in about 10% of the total number of cycles, which is somewhat high. With only two pregnancies reported among patients who insist they took the pills, this method provides a pregnancy rate of approximately 0·7/100 woman years. While this is considered a very effective rate for the sequential preparations, informal reports related to me, suggest that the actual pregnancy rate among all patients involved nationally in this particular programme is only 0·125/100 woman years. The present medroxyprogesterone acetate preparation, therefore, in sequential form seems to offer decided advantages over the previously combined ethinyl oestradiol–medroxyprogesterone acetate 10-mg preparation, with which clinical experiences have been quite discouraging.

EVALUATION OF CONTINUOUS LONG-TERM USE OF COMBINED OESTROGEN–PROGESTAGEN ORAL CONTRACEPTION

As noted earlier, we have been employing the oestrogen–progestagen combinations since 1956. The preparation which we have used for the longest period of time is the norethindrone–mestranol combination and the second longest in our studies has been the norethynodrel group. A few years ago we decided to perform a number of laboratory tests and detailed physical examinations on all patients continuing in this latter series. At that time, with research support by the pharmaceutical manufacturer, we called in 176 women for these special long-term examinations. Only women who had taken a norethynodrel–mestranol preparation continuously for forty-eight or more cycles were included in this evaluation.

Because of the retrospective nature of this long-term investigation, matching control groups were not available and, of course, we could not take into account

all norethynodrel–mestranol users who had been dropped from the programme. This specific study, in short, cannot, therefore, be applied to the population group as a whole, but it describes the physical condition of a series of women after taking norethynodrel–mestranol cyclically for extended periods of time.

The following laboratory tests were done for all these long-term patients: White blood count, differential white blood count, haemoglobin, haematocrit, fasting blood sugar, serum alkaline phosphatase and serum glutamic pyruvic acid transaminase. The data for the women in each group show no apparent deviations from normal values. In addition, the data for women receiving the lower dosage 2·5-mg tablets showed no apparent difference from women who took higher dosages.

Comparison of weight data show that women with normal initial weight, in all dosage groups, tended to gain weight.

Similarly, women classed as underweight before starting norethynodrel–mestranol showed a tendency to gain weight. In the initially overweight group, weight changes were more evenly distributed between gain and loss.

Fundoscopic examination was also done on all the women in this series. Four of the women had narrowing of the retinal arterioles and each of these women had hypertension, two of them having had hypertension before beginning oral contraception.

Each woman was questioned as to her health while taking the progestagen–oestrogen preparation and the majority of each group reported their health as being unchanged. In addition, women were questioned as to the status of their marital life while taking oral contraceptives and the answers show that 130 reported this as unchanged, thirty-six better, eight worse.

When asked how much longer they wished to remain on oral contraceptives, 157 of 176 indicated that they desired to continue norethynodrel–mestranol as long as they remained fertile.

From this portion of our presentation today, it may be concluded that the general health and physical condition of a selected group of women taking norethynodrel–mestranol in combination for oral contraception continuously for a minimum of 4 years to as long as over 9 years showed no apparent difference from that to be expected in the general population (Tyler, Cole, Levin & Elliott, 1969). While the numbers of patients in this long-term series is relatively small, it does represent a group of women in whom apparently no acute major problem developed as a result of the use of the contraceptive pill.

CONCLUSIONS

It has been a pleasure to summarize some of our various contraceptive studies, and while, in certain projects, only sketchy results have been reported here, the detailed reports are due for publication shortly. I want again to thank the Committee for its invitation and this fine audience for its interest and attention.

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