Present Status and Application of Oral Contraceptive Agents

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In 1951 the Governing Council of the American Public Health Association issued a policy statement recognizing that the present increase in population ". . . threatened the health and well-being of millions of people". Statements such as these are only an echo of the feelings of many public health workers in all parts of the world. This increase in population is chiefly attributed to a decline in the death rate, a fact which should make the medical profession keenly aware of its responsibilities in this matter.

Many have felt that the obvious solution is a drop in the birth rate by massive effective contraception, something which conventional methods of contraception cannot be relied upon to do. The modern era of contraception control was ushered in by Makepeace who in 1937 demonstrated that progesterone would inhibit ovulation in rabbits, and by Pincus and Rock who demonstrated the clinical effectiveness of the 19-nor-steroid compounds in preventing conception on a mass scale. These latter preparations are at least 30 times stronger than progesterone and can be given orally. They consist of a combination of progesterone and estrogen: the progesterone blocks the proliferative (and supposedly carcinogenic) effects of the estrogenic component, and the latter decreases the breakthrough bleeding effect of progesterone given alone. Three groups of synthetic steroids are currently available: testosterone derivatives, the 19-nor-steroids, and 17-hydroxyprogesterone derivatives. The United States Food and Drug Administration has approved two progestins for oral contraceptive use. These are Enovid and Norlutin, both of which are 19-nor-steroids. Enovid has received by far the most intensive study because of its earlier introduction but in principle what applies to Enovid applies as well to the other compounds.

For contraception the patient takes the prescribed agent on the 5th day of the menstural cycle, counting the first day of the menses as day one. The patient is often instructed to take the drug with the evening meal, as this timing decreases the likelihood of nausea and spaces the doses 24 hours apart. She takes one tablet daily for 20 consecutive days and stops. Within 48 to 72 hours following the last dose, bleeding ordinarily begins. The day of the commencement of bleeding is counted as the first day of the next cycle and the 20 day course of one tablet daily is repeated beginning on the 5th day of bleeding (i.e. 5th day of the new cycle). Bleeding occasionally does not follow discontinuation of the medication. In such a situation the patient is instructed to start the next 20 day cycle one week after the preceding one has stopped. Ordinarily the patient menstruates after the second course of medication but as many as seven missed cycles have occurred in succession.

The mechanism of action of these agents represents an intriguing and unanswered problem. The functional activity of the ovary, or the reproductive tract has not been shown as yet to be altered in such a way as to produce effective contraception. The most popular theory to date concerning the mechanism of action of the oral progestins is that they inhibit ovulation. Although several studies report that in most women taking these agents the overnight urinary excretion of pregnanediol is at anovulatory level and that this, together with the virtual absence of pregnancies, is evidence that the effectiveness of these drugs is due to ovulation inhibition, other studies report that the methods of bioassay at present are not specific enough, and hence the technical problems in evaluating the gonadotrophin suppressant activity

of progesterones seems to be a formidable one. It must be kept in mind that the indirect criteria of ovulation, basal temperature changes, etc., are meaningless in this context, since the progestins alone would be expected to influence them.

The following tissue changes in the endometrium are observed with oral progestin usage. There is a very early appearance of glandular secretion, rarely progressing, however, beyond a stage comparable to day 16 of the normal cycle. The glands themselves do not increase in size nor do they change in shape. Following the appearance of intraepithelial vacuolation, the glands cease to progress and instead become small, involuted, and inactive in appearance, regressing to the picture seen on day 5 of the normal cycle. The stroma becomes markedly edematous, reaching a peak at the 24th day with various degrees of pseudodecidual reaction after about 5 days. Advanced atrophy and sometimes hyaline changes are observed. These endometria have a remarkable capacity to rebound immediately to functional and histologic normalcy once treatment is halted.

Many are concerned, and rightfully so, over the possible long-term results of pituitary suppression. Estrogens in female rats and mice cause a rapid depletion of the pituitary content of gonadotrophins accompanied or followed by an increase in number of both acidophilic and basophilic cells. The pituitary increases in size, as it does during human pregnancy, becomes hyperaemic, acidophilic and basophilic cells become degranulated, and the number of chromophobes increases. Continued administration of very high doses may cause tumor formation. The only observations on exogenous hormones in man are in cases of advanced malignancy. Here it is noted that although secretory cells become pyknotic and that long continued treatment causes increased fibrosis of rostral and peripheral parts of the anterior lobe, there is no evidence of estrogen-induced hypertrophy or adenoma formation. Interpretation of these results is difficult. In any event the findings in diseased patients can hardly be applied to healthy young women.

An indication of the clinical effectiveness of the oral progestins can be obtained by drawing collectively from the increasing number of large scale field trials being conducted on this continent and in Europe. Although the largest and most comprehensive studies were carried out in Puerto Rico, a relatively poor region in which population pressure is a major public health problem, representative samples are present in many of the other studies from all geographical, educational, sociological, and financial walks of life. In all surveys, approximately 30% of subjects dropped out. Only 15% did so because of side effects: other reasons included desire to plan a pregnancy, death or separation of husband, religious prohibition, etc.

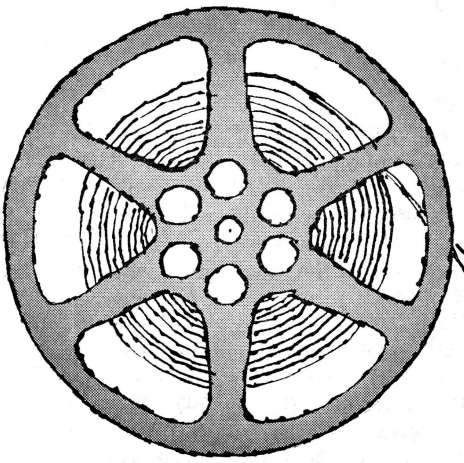
Provided that the medication was faithfully taken according to instructions and in the correct dosage, the likelihood of a women becoming pregnant while on oral progestins was virtually nil. The word "virtually" is employed because in some cases pregnancy did occur during medication. The two most common causes of an unplanned pregnancy included failure to take the drug reliably every day and, following the occurrence of amenorrhea, waiting longer than 7-10 days before beginning the next set of tablets. There was no evidence whatsoever that the future fertility of these women was in any way impoverished. If anything, the fertility of a women on oral progestin medication was enhanced for the first one or two cycles following discontinuation of the agent. The incidence of abnormal pregnancy and delivery was well within normal limits. Menstrual cycles were extremely regular and generally lasted 27-28 days. A very large number noted decreased flow. On the whole the effects on menstruation were favorably and readily accepted by the majority of women.

Side effects may be divided into short- and long-term. Most of the short-term side effects were thought to be due to the estrogenic component of the agent. They were most common during the beginning cycles of treatment and were generally controlled with simple therapy. They became less troublesome or disappeared with subsequent cycles. Some felt that the short-term side effects were in large part iatrogenic. It was found that if the physician prescribed the medication without special admonitions to the patient, she was likely to have a minimum of side effects. The most common short-term side effects were breakthrough bleeding and nausea. If he listed the symptoms she might expect, one or several were likely to be noted. The former usually took the appearance of spotting and was usually controlled by increasing the dosage temporarily. When breakthrough bleeding occurred for the second time most investigators felt obligated to rule out the possibility of a malignancy. Nausea, more frequently without vomiting, was usually decreased by antacids and taking the medication with a large meal or at bedtime. Depression, weight gain, and abdominal bloating with cramps were also reported quite frequently. Many more noted an increase in libido than a decrease and this was attributed to psychological freedom from fear of pregnancy. Lactation was found to continue in most women even though oral contraception was practiced. Most authors felt that the incidence of virilization of the female infant, reported by many, was no higher than for the general population. Mild acne was the most common skin reaction. There was no evidence that haemoglobin, blood pressure, or significant biochemical changes occurred. On two occasions when 60 mg. and 140 mg. of orthonovum were accidently ingested by a one year old girl and a three year old boy respectively, there were no ill effects noted. Apparently the drug was rapidly eliminated from the body.

The possible long-term side effects include the following. Up to December 1962, there had been 277 cases reported of thromboembolic disease in Enovid users with 31 fatalities. There were 100 non-fatal cases reported in the United States, but none reported from the Caribbean area where Enovid has been used the longest. From the evidence to date it appears that Enovid does not increase any circulatory factors which would be expected to initiate clotting. However, many authorities do not advocate the use of these agents in patients with a history of peripheral vascular disease. Because of the extreme difficulty of obtaining figures on the incidence of spontaneous thrombophlebitis in healthy, non-pregnant women 15 to 45 years of age who are not taking any drug for comparison of the incidence among a similar group who are taking or have recently taken Enovid, no statistical comparison can be made. This is where the situation rests today.

Another fear has been raised—that of carcinogenesis. In humans, although the incidence of uterine cancer is higher in women who have an increased level of endogenous estrogen production, there is no evidence of administered estrogen having this effect. The progesterone would seem to have a protective effect in humans, as well as in guinea pigs, which shields the animal from any adverse effects of the estrogen. Hence there is so far no evidence by Pap smears and endometrial biopsy that prolonged administration of oral progestins is carcinogenic.

The possibility of permanent endocrinological upset is brought to mind and this effect on the pituitary has already been mentioned. There appears to be no substantial effect on any other endocrine gland, except possibly on the adrenal cortex, in which there is an average lowering of excretion of its products which involves some alteration in the metabolism of hydrocortisone. There is a decreased urinary excretion of 17-hydroxycorticosteroids, but the plasma 17-hydroxycorticosteroid levels are above normal. Therefore there seems to be some decrease in hydrocortisone



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clearance. The fear that these agents might postpone the menopause, and hence predispose the patient among other things to the danger of pregnancy and giving birth at an older age than normal, hardly seems justified since the menopause has occurred in a few women while on medication. We can only assume that the time schedule for the menopause is determined by other factors.

The only contraindication to the oral progestins that is generally accepted is the presence of fibromyomatas. These tumours very occasionally increase in size with long-term cyclic administration or oral progestins, and regress to premedication size when the treatment is withdrawn. Hence, although these tumours are not an absolute contraindication for the use of these agents, it is necessary that such patients are under careful medical supervision.

How, then, do the oral contraceptive agents, presently being prescribed measure up to the criteria desired of an ideal contraceptive? It may be said conclusively that they are virtually completely effective when correctly used in the proper dosages. They are convenient to use, psychologically and aesthetically acceptable, and do not seem to have any interference with future fertility. They are still fairly expensive for many people, and there are hopes that these costs will decrease if and when production on a large scale becomes a real thing. Their instructions are simple to follow and studies have shown that even the most unlearned can interpret them successfully. They are not without side effects, but in the majority of women they can be easily controlled and tend to disappear spontaneously with further usage. That they are absolutely and completely safe to use for prolonged periods, perhaps a lifetime, has obviously not been ascertained. That they are safe for use continuously during at least a two-year period seems at present to be quite accepted by most authorities. For most of the users, the oral progestins are an effective, well tolerated, and acceptable contraceptive agent and preliminary experience with this technique suggests a major therapeutic triumph. The most serious question concerning these drugs arises from the fact that they have not been used over a sufficient part of the human life span (only 7 years to rule out the possibility of important injurious effects. Although the medical committee of the Planned Parenthood Federation of America, the authorative national birth control organization, has advised its affiliated clinics that steroid contraception can be considered one of the regular methods available to patients, 20 years may elapse before we can be sure about the safety of these agents. Many authorities, particularly among the British, feel that in a fortunate and well-fed country where other methods of contraception are available and to a large degree effective, it seems sensible to restrict the use of the oral progestins to those menstrual irregularities that must be corrected or to those circumstances where other methods are impossible or ineffective. In over-crowded lands however, where starvation for many is a more serious and immediate threat than uncertainity about future ill-health in a few, the advantages of oral contraception may well be judged to outweigh the risks involved.

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