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Oral Contraceptives: Nature, Use and Physiological Effects

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"Within a few years 80 million women on this continent alone will be taking 'the pill'!"

John Gillies, *Medical World*

Approximately 5,000,000 American women are now using oral contraceptives. "Never have so many people taken such potent drugs voluntarily over such a protracted period for an objective other than the control of disease."[1] So spoke a special advisory committee of the U. S. Food and Drug Administration.

But is "the pill" safe to take? To this question came the answer: "The committee finds no adequate scientific data, at this time, proving these compounds unsafe for human use."[2] The tone of reservation implicit in the double negative of the statement is not surprising. Even without reading the *Time* magazine report, a non-professional layman knows that medicines "cannot be certified as completely safe until after years of detailed study on tens of thousands of patients."[3] And even then certification can be valid only if large scale, careful reporting is adhered to.

As "the pill" moves into its second decade of consumption, however, interest in it grows apace. numb- ber of aspects, particul the moral and socio-economic, re in- triguing. But this paper ls ex- clusively with the natu use, and physiological effects oral contraceptives.

NATURE

All oral contraceptives consist basically of two synthetic eroids, an estrogen and a progesto n. Se- lection of one of two nthetic estrogens and one of ten ogesto- gens accounts for the trad names. If the two steroids are adm istered together for twenty days, e ther- apy is called *combinatio* If an estrogen is given for fifte n days, then a progestogen for the ast five, the therapy is called *sequen l.*[4] The combined steroids are old as Enovid (the original "pill" Ortho- Novum, Norinyl, Prov t, and Norlestin. The estrogen-pr estogen composite goes by the mes of Oracon and C-Quens, b h more recently developed drugs. T e differ- ence? Theoretically, the s quential therapy resembles the sec tion se- quence as it occurs in the body. Practically, however, neith type of therapy replicates the natural proc- ess of secretion of the sex hormones, nor are all the synthetic steroids chemically identical with the natural steroid hormones of either class. In efficacy and general side effects, none the less, the combined and sequential forms are similar.

USES

"The pill," composed of synthetic steroids, has several uses. Paradoxically, it is employed for both conceptive and contraceptive purposes. As a contraceptive agent, it is unquestionably effective. In fact, its 99+% efficiency rate is becoming a dictum. Over and above their efficacy as contraceptives, "the pills" have proved remedial for gynecological orders. Irregular menses, amenorrhea, dysmenorrhea, endometriosis, and menopausal complaints are some of these. Obviously, it will be some time before the overall therapeutic value of "the pills" is established. Even so, oral contraceptives to date have been an important medical tool.

PHYSIOLOGICAL EFFECTS

Ironically, despite their 99+% effectiveness when taken as directed, the mode of action of oral contraceptives is little understood. Authorities are certain of only the obvious: that administered daily from the fifth through the twenty-fourth day of the menstrual cycle, "the pill" will prevent conception and produce an artificial menstrual period resembling the natural one in both duration and quantity of flow.

Many authorities believe that ovulation is prevented. In support of this view, Edwin DeCosta, writing in *J.A.M.A.*, postulates that the two hormones in "the pill" suppress ovulation by acting on the pituitary gland.[5] "The pill" inhibits the pituitary from secreting the gonadotrophic hormones, FSH and LH. Since these two hormones are not secreted, the egg is not "prepared" for ovulation, and the process does not occur. R. L. Holmes in the journal *Lancet*, states a different opinion, namely, that LH release is not blocked, and that suppression of FSH has neither been proved nor disproved.[6] Experiments with animals do indicate that ovulation is suppressed, but since ovulation in animals is not identical with that of women, what may be true of animals is not necessarily true of humans, in this regard. Other investigators have suggested other mechanisms by which oral contraceptives may produce functional sterility (There is some evidence of permanent sterility, incidentally, which may work a hardship for those women who plan to have children after a year or two on "the pill"). These mechanisms may be either a direct influence on the ovary, or a deleterious action on the germ cells themselves.[7,8]

Whatever the uncertainty regarding the mode of action of "the pills," their influence on the body's natural hormone balance is well known. The estrogen-progestogen combinations taken daily lead also to alterations of the harmonics of several other systems including the neurological, which are concerned in reproductive and behavioral physiology.[9] Experiments with estrogen-progestogen in animals also demonstrate that pituitary tumors are frequently found after prolonged treatment.

The most obvious effects of these contraceptive agents, however, is a local one, i.e., the radical change produced in the endometrium. In contrast to a normal endometrium, characterized by vascular tissue

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supplied with many glands, the progestogen-treated endometrium exhibits only a few involuted glands, poor vascularity, and stromal edema.[10] Collectively, these changes produce the appearance of aging of the endometrium.[11] Although neoplastic relationships as such will be dealt with later on in this paper, attention should be called here to the observation that "in predisposed individuals, the unopposed action of estrogenic substances — and all oral contraceptives are estrogenic — for considerable periods of time will result in endometrial adenomatous hyperplasia, carcinoma *in situ*, and eventually in carcinoma."[12]

Over and above the influence of oral contraceptives on the endocrine and other systems in general, and the uterine lining in particular, their action is associated with liver damage. The estrogen component of "the pill" is known to impair the excretory function of the liver; it may damage liver cells directly.[13] Tests generally employed in medical practice to detect hepatic impairment are 1) serum transaminase level, 2) bromsulphthalein retention, 3) serum alkaline phosphatase levels. Abnormally high serum transaminase levels and bromsulphthalein retention appear in almost every tested user of "the pill."[14,15,16,17] Stroll noted an increase in serum transaminase from the normal 10-40 units to 200 units, and in serum isocitric dehydrogenase levels from the normal 3-10 units to 77-165 units.[18] Bromsulphthalein retention has been known to increase to pathological levels within two weeks during "pill" use. Hepatic malfunction may develop in as few as 28 days, or one cycle of treatment.

In 1963, Enovid was brought under criticism for its suspected relationship with thromboembolism. This is not astonishing, for thromboembolism has been associated with pregnancy, during which time high concentrations of estrogens and progestins appear in the blood. What brought "the pill" to more idity headlines, however, was the report that more than 350 cases of thromboembolism had occurred in Enovid users in little over a twelve month period. At this point, the FDA appointed the Wright Committee to investigate these cases; the committee reported its findings later in 1963. Wright and his workers tallied a 12.1% incidence of fatal thromboemboli among Enovid users, as compared with the 8.4% rate in the general population.[19] The figures became statistically more significant when age groups were considered. In women users who were over thirty-five, there was a disproportionately greater incidence of thromboembolism. Using the same statistics as Wright, Kassouf calculated fatality rates on a different basis. He used "woman-years" (twelve women taking the drug for one month each) as the unit of exposure. This was the basis on which most of the favorable statistics on Enovid had been calculated. According to Kassouf's calculations, the death rate from thromboembolism was 22.3 per million per year, nearly three times as high as that in the population at large.[20] Notwithstanding, the Wright Committee concluded that a definite cause-effect relationship between "the pill" and thromboemboli is yet to be statistically demonstrated. Still to be demonstrated, however, is the absence of cause and effect correlation between "pill" and clot. In the interim, though, it is not irrelevant to note that oral progestins are being used in the treatment of *hemorrhagic* disorders.[21]

A second circulatory phenomenon observed in "the pill" users is an increased venous distensibility similar to that observed in pregnancy. Over a period of time, the valves which prevent the backflow of blood become incompetent, and allow the blood to stagnate in the vessels, thereby providing opportune environment for thrombophlebitis and/or thromboemboli. As Eugene F. Diamond points out, even those who disagree on the association between "the pill" and thromboemboli, "fairly uniformly admit the association between oral progestins and thrombophlebitis."[22] And how many cardiovascular specialists would deny that thrombophlebitis at least predisposes vessels to the formation of clots?

Finally, estrogenic agents, even naturally occurring ones, have been known since the turn of the century to be associated with malignancies. To what extent malignant neoplasms are effected or affected by estrogens depends in part upon the *type* of neoplasm[23,24] and the *amount* of estrogen administered.[25] In certain predisposed humans and research animals, estrogen has been known to "cause" cancer. This is usually a gradual process, which begins with the alteration of the hormone balance, which in turn produces cellular changes in the ovary or other parts of the body, and eventually ends with tumors.[26] A much more common concomitant of estrogen therapy, however, is a pronounced growth of already existing tumors. Very small breast carcinomas have developed with great rapidity during oral contraceptive use, according to Shipman.[27] Moreover, the progestogen component of "the pill" may increase metastasis of an initially localized malignancy.[28]

Above and beyond the major ill-effects so far mentioned, oral contraceptives may induce so-called minor side-effects:[29,30,31,32] 1) break-through bleeding or "spotting," 2) nausea, 3) weight-gain — up to ten pounds, 4) breast soreness and enlargement, 5) acne, 6) headache, 7) dizziness, 8) depression and fatigue, 9) irritability, 10) edema, 11) augmented pre-menstrual tension, 12) stoppage of lactation, 13) insomnia, 14) increased facial pigmentation, 15) leg cramping, 16) rash/itching, 17) amenorrhea, 18) loss or growth of body hair, 19) growth of uterine fibroids, 20) virilization of the female infant. Many of these are, admittedly, more disagreeable than dangerous. A few, however, carry a subtle threat. Two of these only will be treated here.

First, break-through or intermenstrual bleeding. Under *ordinary* conditions, unusual bleeding may be symptomatic of malignancy. Since, however, spotting is to be expected during oral contraceptive use, both patient and doctor may dismiss such bleeding as unimportant. G. H. Green highlights the danger latent

in such a dismissal: a young woman of thirty had complained of spotting while taking "the pill." The attending physician had attached no significance to the event, because the woman had had a cervical smear within the year. That six months later she was found to have a far advanced malignancy[33] would seem to be somewhat alarming.

The second side-effect deserving special comment is virilization of the female infant. Not always, but frequently enough, oral contraceptives taken during the early months of pregnancy affect the female foetus. The masculinizing effect is usually in the form of an enlarged clitoris, of which the implications for the child's future may be more than incidental.

Having come this far, let us take a backward glance at these data on "the pills." They are effective as contraceptives to the extent of almost 100%. They are useful as gynecological tools. Such is medical consensus about their efficacy. About their safety, however, there is not such unanimity. Even so, suppose that all the side-effects, major and minor, are later obviated. What will be the results of long term — a possible thirty years[34] — alteration of human female metabolic rhythms? Of the disruption of the delicate and dynamic body equilibrium which physiologists have so long sought to understand and to preserve? Perhaps not even time will tell.

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