

The Future of Steroids in Contraception

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Any prediction about the future role of steroids in human contraception is bound to be subjective. Therefore, readers should be aware that my own perspective is based on a mixture of faint optimism and profound pessimism, flavored with a heavy dose of "I told you so."

My pessimism may seem paradoxical. In 1951, two weeks before my twenty-eighth birthday, we had completed the first synthesis¹ of a steroid -- norethindrone (1) -- which, 35 years later, is still the active ingredient of nearly half the oral contraceptives used world-wide. In the 1950's, nobody predicted the rapidity with which oral contraceptives would eventually be accepted by millions of women or that 35 years later, the steroid discovered in 1951 would still be used so widely in medicine. I still recall a woman asking me sometime around 1958 what the long-term biological consequences might be if she took such an oral contraceptive for ten or twenty years. I replied that I thought it unlikely that this question would ever be answered -- not because it is unanswerable, but because I was convinced that twenty years later such oral contraceptives would only be a historical curiosity. Given the then flourishing interest in human fertility control and the rapidity with which laboratory discoveries were converted into practical drugs, I was certain

that fundamentally new contraceptive approaches would be developed, which would still retain the Pill's enormous advantages of unsurpassed efficacy and being unrelated time-wise to coitus, but no longer be based on a long term use of a progestagen and estrogen combination. The woman who posed this question in the late 1950's now holds what is undoubtedly the world record for continuous use of an oral contraceptive, since in 1986 she is still taking a norethindrone-estrogen combination pill!

Some ten years later, I was the first person to warn in print^{2,3} that unless major changes in public policy are instituted, human birth control in the mid-1980's would not differ significantly from that existing in 1970. In fact, the situation is even worse than predicted then, since one of the major options for women -- the IUD -- has for all practical purposes been removed as a viable choice for American women. What then is the prognosis for the future, say for the turn of the century?

If we concern ourselves solely with the continued use of steroids in human contraception, an optimistic outlook is justified: there is no doubt in my mind that in the year 2000, steroids will still represent a crucial and probably even increasing component of female contraception. This opinion is not necessarily based on spectacular advances in steroid chemistry and medicine, but rather on the pessimistic component of my prediction: the dearth of new advances in practical steroid and non-steroid contraception alike. In other words, in the year

2000 we may be even more dependent on agents and methods developed decades earlier. Much more guarded optimism would be required in prognosticating about male contraception, but even in this area, advances based on steroid entities stand one of the best chances of scientific success. Whether this can be converted into a practical method is very much open to question.

(1) Steroid Ovulation Inhibitors

At present, the Pill and condoms represent the two most widely used forms of reversible contraception. If easy reversibility is not a criterion, sterilization must now be added to that list, although this method is restricted primarily to parents. In many developing countries, notably in Latin America and certain Moslem areas (e.g. Egypt, Pakistan, Indonesia), the Pill is the premier method of contraception and its popularity continues to increase. In my opinion, nothing on the horizon will change this state of affairs through the turn of this century. In fact, new delivery methods (vide infra) of "old" steroids may increase still further their popularity in the Third World.

In developed countries, such predictions have to be accompanied by several qualifications, but even here I feel that during the next fifteen years the incidence of oral contraceptive use will increase substantially. I shall cite the U.S.A. as my first example. This is the country which at one time boasted of nearly ten million women on the Pill; it is also the one which has responded most dramatically to uncritical and even sensational media presentations and litigious practices, thus

contracting to the current level of ca. eight million users. In spite of this drop, the Pill has remained⁴ the most prevalent method of reversible fertility control in the U.S.A.; among never married women, it exceeds all other methods combined. Several recent developments support my prediction that the popularity of the Pill will again increase in the U.S.A.

(a) As a result of numerous epidemiological studies designed for the discovery of potential deleterious side effects of the Pill, notably in terms of cancer and cardiovascular disease, several non-contraceptive beneficial side effects have been uncovered⁵ which are receiving increased publicity. It is now generally accepted that many more lives are saved through these non-contraceptive benefits than are lost due to lethal side effects of the Pill. Gradually, this message will become obvious to new users.

(b) Product litigation has increased dramatically in the U.S.A.⁶ and while this has led to the withdrawal by the manufacturers of virtually all IUDs and has discouraged many pharmaceutical companies from entering the contraceptive field, it has not affected those companies who already have an important stake in the oral contraceptive market. Even though patent coverage of several older steroid drugs, such as norethindrone, has expired long ago, no cheap generic equivalents have been introduced into the American market -- primarily because of the fear and cost of litigation. Consequently, prices have increased, rather than diminished, and companies with a significant share of the oral contraceptive market can afford to

handle any litigation exposure, especially since new unexpected issues subject to litigation are unlikely to arise. We see here another example of mixed optimism and pessimism: of negative factors that tend to stabilize and even increase the use of currently available steroids, but which are likely to restrict the introduction of new alternatives.

(c) The most important positive development favoring a gradually increasing use of oral contraceptives is the marked reduction which has occurred during the past few years in the daily dosage of the progestational and estrogenic components of the Pill. Consequently, many of the earlier long-term studies relating to side effects of the Pill will have to be repeated since they had been conducted with much higher dosage regimens. It is very likely that such new studies will provide more assurance to prospective users, who increasingly are represented by women below the age of 35 -- a group that intrinsically is at lower risk.

(d) The present administration in Washington is strongly opposed to abortion. If an equally conservative successor is elected in 1988, it is conceivable that abortion in America may become so restrictive that greater emphasis will be placed on the use of a contraceptive method -- i.e. the Pill -- with the lowest failure rate.

Admittedly, several of the factors enumerated above are peculiar to the American social and political setting. However, in the absence of new contraceptive advances it is likely that other developed countries will also exhibit an increased

acceptance of oral contraceptives, because fear of untoward health effects has been shown to be the most serious constraint to wider use of the Pill by women in all countries. The single largest untapped population is represented by Japan -- a country which in terms of drug consumption is only surpassed by the U.S.A. Nevertheless, Japan is the only advanced country in the world where the contraceptive use of the Pill cannot be promoted. The reasons for this prohibition are multiple,⁷ but one is specific to Japan: the vociferous objection of gynecologists, who are the main providers in Japan of abortion services and fear the loss of significant income. Officially, it is claimed in Japan that the Pill's prohibition is associated with insufficient knowledge of side effects, but this claim can clearly not be maintained until the turn of this century.

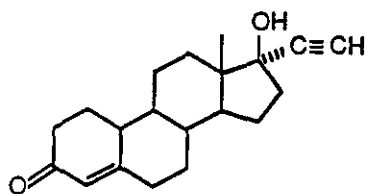
Certain sections of Western Europe are also likely to show a gradual increase in the use of oral contraceptives -- the leading candidates being Italy and Spain, and to a lesser extent France. Whereas 38 % and 33 %, respectively, of sexually active fertile women in Great Britain and West Germany use the Pill, only 6 % do so in Italy and 19 % in Spain.⁸ Furthermore, while only 10 % of British women do not rely on some contraceptive method, 30 % of Italian, 26 % of Spanish and 24 % of French women consistently practice unprotected intercourse. In the absence of new contraceptive alternatives and the likelihood of improved sexual education in these countries, an increasingly larger proportion of their young women can be expected to become Pill users.

In summary, by the turn of this century I expect that for young women throughout the developed world, and for fertile women

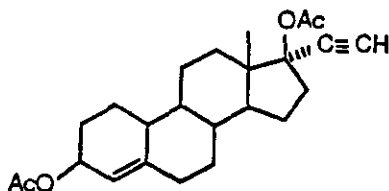
of all ages in many developing countries, the Pill will again be the most popular choice for reversible contraception. Chemically speaking, what will be the constituents of that Pill? The estrogenic component is likely to remain 17 α -ethinylestradiol, which has now displaced its methyl ether, mestranol, in most contraceptive formulations throughout the world. More diversity can be expected among progestagens, simply because a greater variety is used currently and at least one more is likely to reach the market during the next few years.

At present probably 80 - 90 % of all oral contraceptives throughout the world contain either norethindrone (1) or levonorgestrel (2) as the active ingredient, the remainder being shared by ethynodiol diacetate (3), lynestrenol (4) and desogestrel (5). Norgestimate (6), the oxime derivative of levonorgestrel (2) may be added to this list in the next few years. From a metabolic viewpoint, this array can be reduced to three active ingredients: norethindrone (1), the major active metabolite of 3 and 4; levonorgestrel (2); and the 3-keto analog (7) of desogestrel. What the actual mix of these agents will be among the Pills of the year 2000 is difficult to predict. The older steroids (1 and 2) have the advantage of long-term use and consequent knowledge of long-term exposure. Newer agents, such as 5 have the advantage that they were developed during a period of newer bioassays for measuring various biochemical parameters (e.g. lipid and carbohydrate metabolism, receptor binding) and to that extent can be considered to be more "tailored" to today's clinical requirements. An additional important factor is the

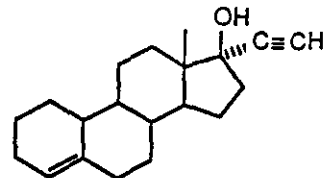
actual delivery vehicle since any advances in this area are bound to contribute to an increased use of steroids in contraception.



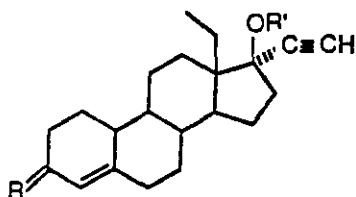
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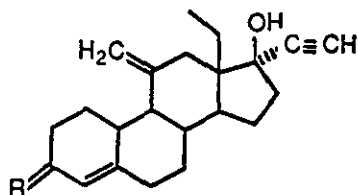


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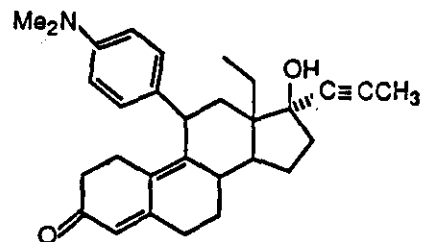
2 R = O; R' = H

6 R = NOH; R' = Ac



5 R = H₂

7 R = O



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(2) Advances in Drug Delivery.

The most widely publicized modification has been the phasic approach to oral contraception. Virtually all manufacturers have introduced triphasic pills⁹, which supposedly reflect more accurately the quantitative changes in hormonal balance of the normal menstrual cycle. Some question has been raised¹⁰ whether this modification is indeed beneficial in terms of endometrial morphology, but there is no doubt that it accomplishes one aim desired by everybody: to lower the overall hormonal

administration to the woman. Other formulations, such as incorporation of a progestagen into a vaginal ring -- especially in the presence of an estrogen to minimize menstrual disorders -- may also accomplish the same goal. Whether such a formulation will actually be introduced into medical practice remains to be seen; its utility would be primarily in developed countries.

By contrast, subdermal Silastic implants of progestagen-containing devices that retain their contraceptive efficacy for up to five years, are likely to find general acceptance only in certain Third World regions. NORPLANT, which contains levonorgestrel as the active ingredient, has been under development for many years¹¹ and is now being approved for marketing in several countries. Its main drawbacks -- menstrual irregularities and the relatively cumbersome procedure of removing the implant if a woman wishes to become pregnant -- are unlikely to make it an attractive option for many women in the affluent countries. It is questionable whether any multi-national pharmaceutical company will undertake the major marketing effort required to reach a significant proportion of the female population of the U.S.A. or Western Europe, and assume the increased legal liability associated with such a sustained-release formulation. Most potential users in those countries will probably opt for sterilization instead of a long-term implant. However, if distribution is assumed by government agencies in highly populated countries such as China, it is conceivable that such an implant (or preferably a biodegradable one) could contribute to a wider use of contraceptive steroids in

the Third World.

Steroid-medicated IUDs may also be considered a form of drug delivery. In fact, the only IUD still remaining on the U.S. market is Alza's PROGESTASERT -- an IUD containing progesterone that is efficacious for one year. If this IUD survives in the present American climate and perhaps grows in acceptability, then it is possible that developments of other medicated IUDs may be resumed in the U.S.A. The best alternative is for other countries not to follow the American example but to continue using existing ones while working on improvements. China is likely to be the test case: currently, it is estimated that up to 35 million Chinese women may be wearing IUDs (conventional metal type). This may be the country where a steroid-medicated IUD of improved efficacy and fairly long duration may stand a sporting chance of success.

(3) Postcoital Steroid Contraception

All the steroid contraceptive methods discussed so far in this paper are variations on an old theme: precoital ovulation inhibition. With one exception, the chances of coming up with something fundamentally new in practical human fertility control for the rest of this century are very low.¹² That exception is based on our increasing knowledge of sex hormone-binding protein receptors, which opened a way to screen for competitive progesterone inhibitors.¹³ It is this area of postcoital contraception -- popularly defined as a once-a-month menses inducing pill -- to which I drew attention in 1970³ by pointing

out that it would take on the order of 15 years to develop such an agent. Its utility¹⁴ in ameliorating the American teenage pregnancy problem is only one example of its enormous potential. A 19-nor steroid of structure 8 and bearing the code number RU-486 has been shown in preliminary clinical studies¹⁵ to be effective as a postcoital agent in terminating very early pregnancies shortly after a missed menses. Combination with an orally effective prostaglandin greatly increased the clinical reliability of such a postcoital contraceptive (or interceptive) regimen.¹⁶ Monthly administration of RU-486 as a menses inducer appears to suffer from some serious potential difficulties;¹⁷ however, as an abortifacient agent shortly after a missed period, it offers great promise. The wide use of such a postcoital approach is highly unlikely to occur before the middle 1990's. Nevertheless, it is the only fundamentally new development in human contraception that stands any chance of making it into the medicine cabinets of the average bathroom before the turn of the century. The fact that it is based on a steroid is the only reason why my paper ends on the same note of cautious optimism with which it started.

Bibliography

1. For review see (a) Djerassi, C.: Steroid Oral Contraceptives. *Science* 151, 1055-1061 (1966);
(b) Djerassi, C.: *The Politics of Contraception*. W.H. Freeman, New York, 1981, pp. 227-256.
2. Djerassi, C.: Prognosis for the Development of New Chemical Birth Control Agents. *Science* 166, 468-473 (1969).
3. Djerassi, C.: Birth Control after 1984. *Science* 169, 941-951 (1970).
4. Bachrach, C.A.: Contraceptive Practice Among American Women, 1973-1982. *Family Plann. Perspect.* 16, 253-259 (1984).
5. Mishell, D.R.: Noncontraceptive Health Benefits of Oral Steroidal Contraceptives. *Am. J. Obstet. Gynecol.* 142, 809-816 (1982).
6. (a) Huber, P.W.: The Bhopalization of U.S. Tort Law. *Issues in Science and Technology* 2, 73-82 (1985);
(b) *World Population and Fertility Planning Technologies*, Office of Technology Assessment, Washington, DC, 1982, pp. 117-119.
7. Coleman, S.: *Family Planning in Japanese Society*. Princeton Univ. Press, Princeton, NJ, 1983, pp. 35-38.
8. Riphagen, F.E.: *Epidemiology of Contraception in Western*

Europe. International Health Foundation, Brussels, 1986.

9. Upton, G.V.: The Phasic Approach to Oral Contraception: The Triphasic Concept and its Clinical Application. *Int. J. Fertil.* 28, 121-140 (1983).
10. Wynants, P., and Ide, P.: Endometrial Morphology During a Normophasic and a Triphasic Regimen: A Comparison. *Contraception* 33, 149-157 (1986).
11. Segal, S. J. : The Development of NORPLANT Implants. *Studies in Family Planning*, 14, 161-163 (1983).
12. Djerassi, C.: What Contraceptive Revolution? *Family Planning Perspectives*, 18, 100 (1986).
13. Reel, J.R.; Humphrey, M.S.; Shih, Y-H.; Windsor, B.L.; Sakowski, R.; Creger, P.L. and Edgren, R.A.: Competitive Progesterone Antagonists: Receptor Binding and Biologic Activity of Testosterone and 19-Nortestosterone Derivatives. *Fertility and Sterility*, 31, 552-561 (1979).
14. Djerassi, C.: Searching for Ideal Contraceptives. *Society* 23,41-43 (1985).
15. (a) Herrmann, W.; Wyss, R.; Riodel, A.; Philibert, D.; Teutsch, G.; Sakiz, E. and Baulieu, E-E.: Effet d'un Steroide Anti-Progesterone Chez la Femme: Interruption du Cycle Menstruel et de la Grossesse au Debut. *C. R. Acad. Sc. Paris, Serie III*, 933-938 (1982).

- (b) Kovacs, L.; Sas, M., Resch, B.A.; Ugocsai, G.; Swahn, M.L.; Bygdeman, M. and Rowe, P.J.: Termination of Very Early Pregnancy by RU-486 - An Antiprogestational Compound. *Contraception*, 29, 399-410 (1984).
16. Bygdeman, M., and Swahn, M-L.: Progesterone Receptor Blockage. *Contraception* 32, 45-51 (1985).
17. Healy, D.L.: The Antiprogestones Are Coming: Menses Induction, Abortion, and Labour? *Brit. Med. J.* 290, 580-581 (1985).