Injectable Contraceptive Synthesis: An Example of International Cooperation

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Summary. Since many contraceptives appropriate for use in developing countries are not of major interest to the pharmaceutical companies in developed countries, the World Health Organization has sponsored a program whereby contraceptives are developed outside the traditional pharmaceutical industry channels. This program might serve as a model for the development of other drugs or even pesticides.

Until now pharmaceutical companies have played the dominant role in the field of chemical contraception because of the availability, within one organization, of the wide array of disciplines needed to bring such an agent to the general public (*1*). During the past decade, however, the pharmaceutical industry has reduced, on an absolute and relative basis, its research efforts in the contraceptive field (*2*). This is particularly true with regard to contraceptive methods that would be appropriate in developing countries but of relatively little interest in highly developed ones. For example, there is a great demand for long-lasting, injectable steroid contraceptives in many lesser developed nations, but the only two widely available agents (Depo-Provera and norethisterone enanthate) suffer from several disadvantages, one of these being that, although they were developed in the 1960's, they have still not been approved for general use as contraceptives by the U.S. Food and Drug Administration.

Initiation of Program

The development of new injectable contraceptives requires that a concerted effort be made to synthesize novel steroid compounds and subject them to thorough biological evaluation. Since such an effort was not being made by international pharmaceutical companies, the World Health Organization (WHO), as part of its Special Programme of Research, Development and Research Training in Human Reproduction, established a task force to determine whether such a development program could be launched outside the pharmaceutical industry. At a meeting at the WHO headquarters in Geneva in January 1975 (*3*), it was concluded that the development of a new, long-acting contraceptive agent would be worth combining with an effort at institution building in lesser developed countries. In this article we outline the initiation and organization of this program. The results obtained to date suggest that this program might serve as a model for other drug development programs outside the traditional pharmaceutical industry mechanism. For example, the development of drugs for such parasitic diseases as leishmaniasis, schistosomiasis, and onchocerciasis has been neglected by the pharmaceutical industry; a similar approach could also be envisaged for the creation of new pesticides.

In July 1975, a group of internationally recognized steroid chemists (*4*) with past or current experience in the pharmaceutical industry attended a meeting held under WHO auspices at Stanford University. These chemists compiled a list of approximately 150 hypothetical steroid compounds that they considered could be synthesized and should be subjected to biological screening in a program designed to uncover new and effective sustained-release injectable contraceptives. They also proposed 15 laboratories as candidates for participating in the program to synthesize new steroids. These laboratories, most of which are located in developing countries, were contacted by WHO headquarters staff to determine whether they would be receptive to the idea of participating in the program. The arrangement proposed was that WHO, in addition to supplying literature, material, and chemicals, would fund each laboratory to the extent of $10,000 to $15,000, the sole requirement being that 5-gram quantities of pure steroid would have to be delivered to WHO headquarters. Patent rights would remain with WHO.

Chemical Objectives

The objective of the chemical synthesis program was to modify chemically an active contraceptive steroid drug into a "prodrug" that would either be inactive or less active than the parent steroid. A simple and efficient way to achieve this goal is to protect the free 17-hydroxyl group of an active steroid by inserting an appropriate acid chain, thus producing the corresponding 17-ester (prodrug). When administered to humans, such a prodrug is converted into an active contraceptive agent by enzymatic hydrolysis in vivo (*5*). The rate at which the hydrolysis occurs determines whether the prodrug might be suitable for use as a long-acting, injectable contraceptive. The main goal of the program initiated in 1976 was to design novel steroid esters that could serve to enlarge the number of long-acting injectable contraceptives available to women. The strategy was typical of that used frequently in industrial organizations in that it involved the initial preparation of a number of esters of the known contraceptive agents 17α-hydroxyprogesterone, norethisterone [norethinyltestosterone (NET)], and levo-norgestrel. The list of steroid esters to be investigated has now been expanded to well over 250 compounds.

The natural male sex hormone, testosterone, was also included in the program, since esterification of its free hydroxyl group might afford potential candidates for an injectable male contraceptive. NET was selected as a potential progestogen, since laboratory and clinical experience has shown that it is one of the safest progestogens available and is no longer protected by patents. Levo-norgestrel, although still covered by patents, was chosen because of its high progestational potency. It is thus a good candidate for conversion into long-acting derivatives by esterification.

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Organizational Aspects

Eventually, 12 laboratories agreed to participate in the program. The laboratories are located in Australia, Brazil, Bulgaria, German Democratic Republic, Iran, Mexico, Nigeria, Poland, Singapore, Spain, and Sri Lanka (*6*). The participants each received a list of 16 to 20 ester structures, and were invited to submit a research proposal outlining how they intended to synthesize the acid chain to be introduced into the steroid molecule. They were also asked to submit a budget. Both items were reviewed by the WHO Secretariat with the aid of at least one outside referee and the coordinator of the program (*7*). Once the proposals were approved, a CTS agreement (*8*) was drafted which permitted funding to be instituted.

During the first 3 years of the program the coordinator visited most laboratories at least once. The purpose of the site visits was to brief the investigators about the precise objectives of the program and operating details, to offer appropriate scientific information and advice, to become familiar with the local research facilities, and to solve a number of administrative problems. Each center had different difficulties, for example, inexperienced personnel, lack of sophisticated equipment and instruments, inclement weather conditions, or frequent power failures. Most centers faced one common problem, namely, that of complying with the cumbersome and time-consuming regulations that many of the countries impose on importers of chemical reagents and small equipment items. It soon became evident that many of the developing countries would do well to overhaul their customs regulations if they wish to upgrade and expedite scientific research. The only feasible solution for the chemical synthesis program proved to be for WHO to keep in Geneva part of the money allocated to each center. The WHO Secretariat ordered directly the chemicals for the principal investigators in accordance with their requests and budgets, and arrangements were made to ship the chemicals through the auspices of WHO international channels. The organization of such a network is difficult, but in the long range it proved to be crucial because it saved a great deal of time and unnecessary delays and frustrations.

In addition to providing background information and technical literature to all principal investigators, the coordinator was in charge of examining and labeling the samples (a code number was used for every compound submitted by the centers) and checking the data sheets (each sample sent to WHO headquarters was accompanied by a data sheet giving a full description of the substance including its physical, spectroscopic, and analytical properties). The coordinator acted as a general troubleshooter and was easily available to the various principal investigators; together with the WHO Secretariat he reviewed all the manuscripts originating in the various centers because of their possible impact on the filing of patents on behalf of WHO for the most promising compounds.

The preparation of the long-acting esters presented several difficulties. First, the acid chains—encompassing over 100 different chemical structures—had to be synthesized, since most of them had not been described in the chemical literature. Their synthesis invariably involved a number of steps, frequently with a variety of stereochemical problems. Another problem was the esterification reaction, which is difficult to perform on tertiary alcohols of the type present in NET and levo-norgestrel. In several instances, sophisticated techniques were used and with certain acids a new esterification method had to be developed. A third problem, both time- and material-consuming, was that of reaching the requested high purity (about 99 percent).

Formulation and Bioassay

After they were synthesized, all compounds were shipped to the Department of Chemistry of the City University, London, for quality control and further purification, when necessary. The compounds were then forwarded to the School of Pharmacy of the University of London for formulation. Once satisfactory stability was established, the microcrystalline suspensions were sent for bioassay to the National Institute of Child Health and Human Development (NICHHD) of the U.S. Department of Health, Education, and Welfare in Bethesda. This NIH unit under G. Bialy handled both the funding and operational details of the biological evaluation in rodents (and currently in primates). Esters not suitable for the preparation of aqueous suspensions were bioassayed as oily solutions. After leaving WHO headquarters for quality control at the City University, London, every sample was followed by the WHO Secretariat and by the coordinator (appropriate forms were used at every stage of the program) until the biological results were returned.

The bioassay chosen for the determination of the duration of action of long-acting progestogens was the suppression of estrus in female rats, with depot-medroxyprogesterone acetate and norethisterone enanthate—the only two currently available long-acting injectable contraceptives—being used as comparison standards. Tests for prolonged androgenic activity were carried out in castrated male rats, with the weight increase of the ventral prostate being used as the measure of biological activity and testosterone enanthate being used as a standard. The biological results were supplied to the various principal investigators, who frequently undertook the synthesis of additional esters based on particularly promising biological leads.

Present Status

The synthesis and screening programs were reviewed in depth during consultations held in November 1977 (Geneva), January 1979 (Geneva), and January 1980 (Jena, German Democratic Republic) with participation of most principal investigators, expert chemists, biologists, the coordinator, and WHO staff members. Approximately 220 steroids had been synthesized in the 12 participating laboratories, many of which had had no previous steroid experience but which are now able and willing to extend such work. The biological evaluation of potential male contraceptives is being discontinued for financial reasons (*9*), but six compounds of possible use in female contraception have now been selected for further development. The next phase of research—testing in primates and preparation of larger amounts for toxicology and for eventual phase I clinical studies in one of the WHO Clinical Centers—has already been initiated. Until now all of this work has been performed outside the regular pharmaceutical industrial channels. If a promising drug should emerge from such phase I clinical studies, then it is anticipated that the large-scale synthesis would be commissioned with some chemical firm before long-term toxicology and phase II and III clinical studies are conducted.

Excluding efforts by military establishments (*10*), this is probably the first instance in which an international public sector agency has launched successfully a program of this nature, and it is reasonable to ask how economical the program is. In terms of time, the chemical synthesis has taken longer than it would have in the steroid synthesis laboratory

of a large pharmaceutical firm in the United States, Western Europe, or Japan. However, part of that extra time was consumed in institution building and in creating technical capability in developing countries—two features that will be of long-lasting benefit. In terms of direct funding from the WHO (and indirectly from the NIH through its support of the biological screening) this program has proved to be much cheaper than would have been the case in a pharmaceutical industrial laboratory. This is because all of the indirect costs and a substantial portion of the personnel charges were absorbed by the participating university and government laboratories, thus making this a truly cooperative economic project. However, if these indirect costs were combined, then it is unlikely that the present program is much cheaper than the usual industrial effort. What is important is that societal goals rather than pure economics have become the driving force.

Conclusion

Even if no practical new contraceptive agent is eventually developed as a result of this research effort, the WHO program illustrates how a multinational cooperative project in drug chemical synthesis can be established outside the traditional pharmaceutical channels—a model that is of particular relevance to lesser developed nations. The program is an impressive example of an interdisciplinary and fruitful cooperation between an international organization, such as WHO, university or government laboratories from countries all over the world, and a prominent national public institution, such as the National Institutes of Health in the United States. The mechanisms utilized by the WHO chemical synthesis program could serve as a model for international collaboration in other areas.

References and Notes

1. The disciplines needed to bring a chemical contraceptive to the public include the following: organic chemistry, pharmacology, pharmaceutical formulation, biochemistry, physiology, toxicology, and clinical medicine. The skills of people trained in regulatory affairs and market research are also required.
2. C. Djerassi, *The Politics of Contraception* (Norton, New York, 1980).
3. This meeting was attended by Egon Diczfalusy (Karolinska Institute, Stockholm), Carl Djerassi (Stanford University), and Josef Fried (University of Chicago).
4. The attendees of this meeting were: Sydney Archer (Rensselaer Polytechnic Institute, Troy, New York), Giuseppe Benagiano (WHO Headquarters, Geneva), Pierre Crabbé, Egon Diczfalusy, Carl Djerassi, Josef Fried, Takeru Higuchi (University of Kansas), and Waturu Nagata (Shionogi Laboratories, Osaka, Japan).
5. World Health Organization, *Seventh Annual Report, Special Programme of Research, Development and Research Training in Human Reproduction* (WHO, Geneva, 1978).
6. The principal investigators are the following: Australia: T. Watson, Deakin University; Brazil: E. Ruveda, Universidad de Campinas (São Paulo); Bulgaria: R. Vlahov, Bulgarian Academy of Sciences, Sofia; German Democratic Republic: K. Schubert, ZIMET, Jena; Iran: A. Shafiee, University of Teheran; Mexico, two centers: G. Garcia, Universidad Nacional Autónoma de México, and J. Herz, Centro de Estudios Avanzados del Instituto Politécnico Nacional, México; Nigeria: E. K. Adesogan, University of Ibadan; Poland: M. Kielczewski, University of Poznan; Singapore: the late P. N. Natarajan and, more recently, Ngiam Tong Lan, University of Singapore; Spain: A. Gonzalez, Universidad La Laguna, Tenerife; Sri Lanka: S. Sotheeswaran, University of Sri Lanka, Peradeniya. Early in 1980, a Chinese group (Huang Liang, Institute of Materia Medica, Beijing) also joined the project.
7. P. Crabbé has acted in a part-time capacity as coordinator of the WHO chemical synthesis program since its inception.
8. A Contractual Technical Services Agreement is the official agreement document between WHO and a specific institution.
9. The background to this deplorable situation is little known and illustrates the importance of political considerations: As pointed out elsewhere (*2*, pp. 224–225), the U.S. government has never contributed financially to the WHO Special Programme of Research, Development and Research Training in Human Reproduction, even though the United States has been a major recipient of WHO funds because much research had to be contracted with American investigators or firms. In spite of strong congressional and White House support for U.S. financial aid to the WHO, all appropriations (most recently, the sum of $2 million) have always been vetoed by Senator Daniel Inouye of Hawaii, the chairman of the relevant Senate appropriations subcommittee. As a result, some reduction in the WHO research programs is being instituted; male contraceptive research is one of these areas.
10. For example, the antimalarial program during World War II was organized by the military.