PARFR

SERIES ON FERTILITY REGULATION

Research Frontiers in Fertility Regulation

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The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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FOREWORD

On February 11 to 14, 1980, some 155 scientists and clinicians representing 25 countries met in Mexico City, Mexico, to attend the International Workshop on Research Frontiers in Fertility Regulation. The workshop was organized and developed by the staff of the Program for Applied Research on Fertility Regulation (PARFR), with the support of the United States Agency for International Development and the United Nations Fund for Population Activities. This volume presents the proceedings of that workshop.

During the two and one-half days of the conference, the participants discussed the development of new methods of fertility regulation and the improvement of present methods, giving special attention to making these methods more readily available, acceptable, and applicable to the needs of developing countries. Consideration was given to the evaluation of new contraceptives, to contraceptive research issues related to family planning program needs, to pharmacologic and hormonal methods in male fertility regulation, to new developments in fertility regulation devices, and to the important field of luteal phase contraception.

In addition to the formal presentations, a significant amount of time was reserved for the open discussion of issues in areas of controversy, rapid change, and expansion, as well as to the exchange of ideas relative to the research reports presented by the participants. These discussions were recorded and have been summarized; relevant material is included at the conclusion of each major section.

This conference is the eighth in a series of PARFR workshops bringing together scientists, physicians, and international family planning experts to consider significant and timely issues in the field of fertility regulation. Earlier conferences focused on the following topics: Hysteroscopic Sterilization; Control of Male Fertility; Advances in Female Sterilization Techniques; Risks, Benefits, and Controversies in Fertility Control; Reversal of Sterilization; Pregnancy Termination: Procedures, Safety, and New Developments; and Vaginal Contraception: New Developments. PARFR also supported a workshop sponsored by the National Academy of Sciences/Institute of Laboratory Animal Resources, on Animal Models for Research on Contraception and Fertility. Proceedings of these workshops have been published as the PARFR Series on Fertility Regulation.

Sponsorship of international workshops is only one component of PARFR, which was established in 1972. In association with the United States Agency for International Development, PARFR provides scientific and technical assistance and funding support to investigators in the United States and in foreign institutions who are working on applied research in the field of contraceptive development. Priority is given to proposals that involve foreign-based projects and that are concerned with the development of new or improved methods of fertility regulation which would be appropriate for use in developing countries.

Of major interest to PARFR are research projects concerned with fertility regulation methods that do not require physician services, frequent administration, or high levels of motivation. Also of interest are methods that can be self-administered, that may be effective on a postcoital or hindsight basis, and that minimize supply and distribution problems.

The research projects which have received PARFR support or are presently being funded by PARFR include biodegradable contraceptive drug-release systems, intravaginal barrier methods, intrauterine delivery systems, male pharmacologic methods, postcoital contraceptive methods, and luteolytic contraceptive agents. Research projects involving male or female sterilization by pharmacologic, mechanical, or surgical methods have also received substantial attention from PARFR, and projects involving reversible occlusive sterilization devices in the male and the female are presently under investigation.

Traditional methods of contraception have tended to be most popular in those countries with well-developed health care delivery systems, that is, the countries that have been most successful in regulating their fertility. It is the hope of the editors of this volume, and of the scientists and clinicians participating in the workshop on Research Frontiers in Fertility Regulation, that new contraceptives under investigation, and improvements in present methods, will extend the capability for successful fertility regulation to all countries and all peoples of the world.

Gerald I. Zatuchni, M.D.

PREFACE

In 1979, the estimates of moneys spent worldwide for contraceptive development and safety studies by all organizations (private or governmental agencies, foundations, pharmaceutical companies, and allied industries) came to approximately $28 million. In these days of inflation, that amount decreases to $16 million, when measured in 1970 dollars.

It is painfully obvious to each of us involved in some aspect of the field of fertility regulation that the amount of money available is insignificant in helping to solve the world's most important problem, the problem of excess population growth. One of the major reasons for these token expenditures is that researchers, clinicians, public health experts, and administrators involved in programs of fertility regulation have not been sufficiently vocal in expressing the needs of the field to those politicians who are in charge of spending our tax dollars. Some politicians have suggested that the presently available methods of fertility control are entirely adequate, and that what we need instead are more programs to reach men and women not using birth control methods.

As has been documented time and time again, the methods available today are adequate, but for only a very small segment of the world's population. There are no methods of fertility regulation available today that are fully effective and fully safe, nor that fully appeal to all groups and societies around the world.

The single most significant factor in the failure of research to provide new and highly acceptable methods of fertility regulation is severe lack of funds. Yet, despite this lack of funds, an astounding amount of knowledge of the physiology of reproduction has been acquired in recent years. Along with that knowledge we see reflected in the proceedings of this workshop the early and middle stages of research and development that will result in improved methods of fertility regulation for both men and women.

This volume provides the evidence that new methods of fertility regulation soon will be available. Just how soon they will be available will depend mostly upon the willingness of those persons controlling the purse strings to recognize this field of research and development as a top priority. Surely, if we can spend $100 billion to send half a dozen earthlings to the moon to collect rocks, we should be able to spend $1 billion to provide for a better quality of life on earth.

Gerald I. Zatuchni, M.D.

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CONTENTS

EVALUATION OF NEW CONTRACEPTIVES

1

Evaluation of New Contraceptives: A Study Design

SAMUEL A. PASQUALE

This chapter provides a brief overview of the development of a new systemic contraceptive agent, beginning with its synthesis as a compound at the chemist's bench and progressing through the animal testing, the filing of the Investigational New Drug (IND) forms, the various phases of clinical testing, and finally, the filing of a new drug application for approval to market. Much of this review relates to requirements in the United States. Although there may be variations in specific requirements in some countries, the basic development process is the same from one country to another.

The discovery and development of new drugs does not lie within the purview of any one scientific discipline, but requires the cooperation of many different scientists working toward a common goal, that is, the ultimate availability of a new effective agent which has an acceptable risk-to-benefit ratio. The essential disciplines which must be coordinated include chemistry, pharmacology, pharmaceutical development, drug safety, and medicine. Only through cooperative interaction of these groups can a new systemic contraceptive be successfully developed. Today it is estimated that the length of time from the chemist's bench to the introduction of a new drug to the public is 10 to 15 years. The cost, including loss of interest on investment, has been estimated to be more than 50 million dollars.[14]

Before describing the process involved in the development of a systemic contraceptive, some differences between the development of systemic contraceptives and most other "ethical" drugs should be noted. Systemic contraceptives are often perceived as drugs of convenience rather than drugs that are necessary for the treatment of disease; therefore, the degree of safety required of systemic contraceptives is often greater than that required for many other pharmaceutical agents.

Systemic contraceptives must be viewed from the standpoint of long-term therapy, with special concern about possible long-term toxicity. Since systemic contraceptives are taken by young, healthy individuals, any medical condition occurring in a user is suspected to have been "caused" by the contraceptive agent. Experience with the oral contraceptive has conditioned us to expect practically 100% effectiveness, a capability not usually achievable with other therapeutic agents.

CHEMICAL DISCOVERY

The development of any drug, including a systemic contraceptive, begins at the chemist's bench, with the production of the chemical compound *de novo* or by modification of known molecular structures. The reproductive biologist takes small amounts of the chemicals produced by the chemist, runs screening tests for reproductive effects in animals, and relays this information back to the chemist. If a desired activity is discovered, the chemist modifies the structure of the compound in an attempt to increase certain activities of the compound or decrease other activities. Numerous analogues may be produced to establish a structure-activity relationship.

Once the desired activity is achieved with one or perhaps several compounds of similar structure, additional screening tests for reproductive activity are carried out. Additionally, other pharmacologic screens must be performed to evaluate, at least grossly, any possible effects of the compounds on body systems other than the reproductive system. These screening tests might include:

1. cardiovascular, *i.e.*, spontaneous hypertension rats (SHR),[25,29] dog hind limb perfusion[32]
2. central nervous system, *i.e.*, CNS Test[2,3,4,10,12,17,31]
3. gastrointestinal, *i.e.*, charcoal meal (motility),[21] pylorus ligation for studies of gastric secretion in the rat[30]
4. endocrine profile, *i.e.*, estrogenicity-uterine weight method,[9,19] estrogenicity-vaginal cornification method (Allen-Doisy[1]), progestational test,[24] antiprogestational test,[24] androgenic-anabolic test,[16] antiandrogenic-anabolic test,[27] antiestrogenicity-uterine weight method,[8] antiestrogenicity-vaginal cornification method (Allen-Doisy[7]), antigonadotropin test,[26] progestin receptor,[23] estrogen receptor,[13] corpus luteum progesterone production,[15,18] McGinty test.[22]

SELECTION OF THE COMPOUND

Following this screening process, the most promising compound is selected for further study. Among the criteria used for selection are:

1. **potency.** The degree of desired activity in the test system. Generally, the greater the potency, the more interesting the compound, assuming that other parameters are equal. Unfortunately, increased potency is often associated with increased toxicity.
2. **specificity or selectivity.** Additional pharmacologic effects or lack of other pharmacologic effects. Ideally, the compound selected would have no other pharmacologic effects.
3. **onset and duration of action and anticipated route of administration.** These factors are extremely important, especially as they relate to formulation and bioavailability. Consideration must be given to the anticipated frequency of administration, whether the drug requires administration by

a health professional or can be self-administered and, of course, the anticipated overall acceptability to the patient.

4. **stability of the raw chemical.** Chemical compounds are more or less stable, depending on their molecular structure. Stability must be viewed in relation to production on a manufacturing scale. For example, a highly potent compound of high specificity which is unstable may become unattractive because special facilities may be required for production and storage, markedly increasing the cost of the chemical.
5. **anticipated difficulty of production on a manufacturing scale, and possible cost of production.** Cost and difficulty of production must be evaluated at the earliest possible stage and reevaluated throughout the process of development of the product. Synthesis in the laboratory does not ensure that synthesis can be accomplished on a production scale. New synthetic routes may be required. The yield from a laboratory procedure may be satisfactory for the scientist to conduct animal and even clinical trials but quite unacceptable from a production standpoint.
6. **anticipated future formulation problems or ease of formulation.** The ability to formulate the compound into an acceptable dosage form must be evaluated early in the selection process. Desirability of the tablet rather than the capsule or even liquid form must be considered. Past experience with chemicals of similar molecular structures becomes invaluable.
7. **anticipated toxicity.** Expectations regarding toxicity are based on past experience with compounds of similar structure.

DEVELOPMENT PROCEDURE

PHARMACOLOGIC STUDIES:

Following selection of the compound for future development, reproductive pharmacology studies in nonprimate and primate species are conducted in order to:

1. **elucidate possible mechanisms of action.** Typically, gonadotropin suppression studies are conducted in several species. These usually include at least one rodent species and a nonhuman primate such as the monkey or baboon. The effect of the compound on the reproductive organs is evaluated histologically. Receptor binding assays for LH would be done at this stage.
2. **estimate further the degree of activity.** Fertility studies in nonhuman primates such as the baboon are ideally conducted at this point in time. Dose response studies would be performed to assist in the choice of a future human dose.
3. **anticipate possible side-effects.** During all testing, the scientist must be cognizant of the importance of potential toxic effects. The evaluation of toxicity is not limited to the toxicologist. The reproductive biologist has the opportunity to uncover potential toxicity problems during the course of his reproductive studies.

PHARMACEUTICAL DEVELOPMENT

The chemist, in cooperation with both the reproductive biologist and the pharmaceutical chemist, must work toward the development of a production process for the raw material which will be: (1) simple, (2) reproducible on a large scale, and (3) cost-efficient.

Pharmaceutical development begins with the consideration of various formulations which allow the production of a suitable dosage form capable of being produced on a commercial scale. Numerous aspects must be considered, such as:

1. optimum formulation: (1) oral solution, emulsion, suspension, tablet, capsules; (2) aerosol; (3) injectable; and (4) other
2. stability of the formulation under usual and stress conditions. The final formulation in use by the patient may be exposed to many different environmental stress conditions, *e.g.*, high humidity, very high or freezing temperatures, intense light. The formulation is placed under controlled stress conditions in the laboratory (accelerated stability) to study the possible effects of various environmental factors. Additionally, stability testing is conducted under nonstress conditions where environmental conditions are controlled. This stability testing requires careful design and sampling during a time period extending for a number of years.
3. absorption and pharmacokinetic characteristics
4. cost
5. packaging, including the size of the package, and the compatibility of the dosage form with the packaging material. Various polymers used for packaging material, and other packaging materials that come into intimate contact with the formulation, may affect the drug chemically, resulting in loss of activity due to degradation; this may even lead to the production of a toxic degradation product. These factors must be studied and evaluated by the pharmaceutical development chemist.

The color of tablets involves special problems. Although colors may seem to be useful only for aesthetic purposes, different colors are tremendously helpful in preventing mix-ups of tablets during the production process. In recent years, many dyes have been banned because of possible carcinogenicity. This severely limits the pharmaceutical development chemist. He must choose appropriate dyes which are judged to be safe, which provide a colored tablet distinct from other tablets being produced at the same facility, and which will not interfere with the active components of the tablet.

DRUG SAFETY EVALUATION

Toxicology studies in animals must be conducted in a number of species. These studies include: acute studies, subacute studies, and chronic toxicity studies, *i.e.*, 2-year toxicology studies, in rats, dogs, and monkeys. In conducting toxicology studies, some factors must be considered in addition to the obvious selection process, housing, and environmental control. These are:

1. route of administration, *i.e.*, by gavage or mouth feeding
2. availability of the compound in food or various vehicles (the animal will not be taking the final human formulation)
3. pharmacokinetics in various species

Prior to initiation of any clinical trials in the United States, the following toxicology studies must be completed[5]:

1. acute toxicity. These studies are conducted in at least two species to evaluate the ED_{50}, which is the value representing that dose which would exert a particular effect in one-half the population of a certain species under specified conditions. The LD_{50} (acute toxicity, acute lethality) should be compared among the species studied. Additional information is derived from these studies, beyond a simple mortality statistic. Observations should include motor activity, tremors, convulsions, loss of righting reflex, ataxia, sedation, ptosis, lacrimation, salivation, diarrhea, writhing, effects on respiration, depression, stimulation, blanching, cyanosis, vasodilatation, and others.[5]
2. subacute toxicity (90 days). At least two species are usually studied, with observations including body weights, food consumption, behavior, hemograms, coagulation tests, hepatic and renal function tests, fasting blood sugar, ophthalmologic examinations, metabolic studies, and gross and microscopic examinations. For parenterally administered drugs, irritation studies would be conducted with histologic evaluation of the injection sites.[5]

Before clinical trials can be expanded to more than 50 subjects or for periods longer than 3 months, 2-year toxicology studies in rats, dogs, and monkeys must be completed.[11] Therefore, from a practical standpoint, information concerning the degree of effectiveness is extremely limited prior to completion of the 2-year animal studies. These studies are conducted with doses approximately 1 to 3 times, 10 times, and 50 times the expected human dose.[11] They usually involve approximately 150 to 200 rats, 60 to 80 dogs, and 60 to 80 monkeys.

During these studies, the animals are observed daily for clinical signs. Periodic physical examinations are conducted, as are periodic laboratory examinations, and those observations previously listed under subacute toxicity. Upon completion of these studies, as many as 10,000 to 15,000 microscopic slides may have been generated, and these require histologic evaluation.

The effects of the drug on general reproductive performance is evaluated by the reproductive biologist during the course of his evaluation of the agent for effectiveness. The results of these studies serve as a guideline for the toxicologist in his subsequent studies of possible teratologic effects and possible effects on late fetal development, labor and delivery, lactation, neonatal viability, and growth of the newborn (perinatal and postnatal studies).[6]

In the teratologic studies, at least two species are used, usually the mouse and the rabbit or rat. The drug is administered during the period of organogenesis. Delivery is by cesarean section, and the number of fetuses, their placement in the uterine horn, correlation with the number of corpora lutea, live and dead fetuses, and early and late resorptions are determined. The