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Vaginal Contraception:
NEW DEVELOPMENTS

edited by

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Foreword

In April 1979, some two hundred physicians, family-planning administrators, researchers, and social scientists from 42 countries met in Guatemala City, Guatemala, to attend the International Workshop on New Developments in Vaginal Contraception. The objectives of the three-day workshop were to review the worldwide use of vaginal contraceptive methods and determine the factors influencing their use; to describe research and development of new methods of vaginal contraception; and to consider new methodologies for the evaluation and testing of vaginal contraceptives.

This volume presents the proceedings of that conference, which is the seventh in a series of workshops focusing on significant and timely issues in the field of fertility regulation, sponsored by the Program for Applied Research on Fertility Regulation (PARFR) of Northwestern University, in cooperation with the United States Agency for International Development (USAID). At these workshops, leading national and international scientists and clinicians representing a broad variety of disciplines have presented their experiences and exchanged ideas 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; and Pregnancy Termination: Procedures, Safety and 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.

The Program for Applied Research on Fertility Regulation was established in 1972 at the University of Minnesota, and moved in 1975 to its present location at Northwestern University. In association with the USAID, PARFR provides scientific and technical assistance and funding support to foreign and U.S. institutions for applied research in the field of contraceptive development. Priority is given to proposals for new or improved methods of fertility control appropriate for use in developing countries. Foreign-based research projects or collaborative efforts between United States and foreign institutions are encouraged.

Of major interest to PARFR are fertility control methods which do not require physician services; do not require frequent administration; do not require high levels of motivation; can be self-administered; may be effective on a postcoital or hindsight basis; and are able to minimize supply and distribution problems.

Research projects which have received PARFR support, or are presently being funded by PARFR, include biodegradable contraceptive drug release systems, intravaginal barrier methods, immunologic approaches, intrauterine delivery systems, contragestational intervention methods, sperm enzyme inhibitors, male pharmacologic methods, postcoital contraceptive methods, ovum transport manipulation, and luteolytic contraceptive agents.

Research projects involving male or female sterilization by pharmacologic, mechanical, and surgical methods have also received PARFR funding, as have projects involving reversible occlusive sterilization devices in the male and female.

Several PARFR-supported research projects involving new approaches to vaginal contraception are described in this volume. The recent resurgence of interest in this important contraceptive modality has prompted the present assessment of vaginal contraceptives and will hopefully provide some indications of their potential for further development, increased effectiveness, and greater applicability.

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Introduction

Vaginal contraception is the oldest means by which women and men have attempted to control their fertility. The ancient Egyptians, Hebrews, Romans, Greeks, Indians, Chinese, and Japanese knew of, and used, an extensive array of vaginal methods of fertility control. In light of modern scientific inquiry, many of the ingredients described in ancient texts have been shown to possess spermicidal properties.

From earliest times until 1960, couples controlled their fertility by sexual abstinence, coitus interruptus, abortion, and vaginal contraception. In many countries, especially in Europe, Japan, and the United States, the demographic transition from a high-fertility society to one characterized by low fertility was accomplished by couples using combinations of these four measures. In the 1960s, scientific technology created a revolution in fertility regulation—namely, the development of oral contraceptives and the reemergence of intrauterine contraception. Because of these technological developments, methods of vaginal contraception became far less attractive and their use declined significantly, even in developed societies.

Within five years of becoming generally available to the public in 1960, the pill and the IUD had gained acceptance in family-planning programs worldwide. In the U.S. by 1965, 16% of married couples were relying on these methods and their use doubled during the next eight years. By the early 1970s, surgical sterilization was becoming the most commonly used method of fertility control, having been selected by twice as many married U.S. couples in 1973 as in 1965. With these occurrences, the use of vaginal contraception decreased further.

Interesting shifts in the reliance on various methods of contraception have been revealed by epidemiologic studies, especially in the United States. Several such studies, begun in the 1950s and 1960s, seem to indicate that a trend toward greater acceptance and use of the vaginal methods may be beginning. The most significant change in contraceptive practice between 1973 and 1976 was the decline for the first time in the proportion of U.S. couples using oral contraceptives and intrauterine devices. Concomitantly, the traditional methods, while still constituting a relatively minor proportion, were no longer declining in use at the same rapid rate they had been used previously and, among certain groups, even showed an increase in use. While these increases were not dramatic, the patterns of change are nonetheless worthy of comment for the potential directions, relating to the use of vaginal contraception, which they suggest.

Although none of the presently available methods of fertility control is completely effective, completely safe, and completely reversible, vaginal contraceptives offer considerable advantages with regard to safety and reversibility. They fall short in terms of use-effectiveness, however. Contraceptive failure rates during the first 12 months of use by married women 15–44 years of age are calculated to be 2:100 for women using oral contraceptives

and 5:100 for those using IUDs, as compared with 13:100 for those using the diaphragm in combination with a spermicidal jelly, 15:100 for couples using the condom alone, and 20:100 for women relying on contraceptive foam or jelly alone. Yet when these latter methods are used consistently and correctly by highly motivated couples, the failure rates are significantly reduced.

In recent years, anthropologists, sociologists, and psychologists have shed some light on cultural and personal factors affecting the acceptability of vaginal contraceptives. These factors include attitudes associated with pregnancy and childbearing; religious or moral beliefs that govern the use of certain methods; the openness with which matters of sexuality and contraception may be discussed and dealt with; the traditional relationship between men and women, as well as the way individual partners interact; the cultural expectations as to which partner will assume responsibility for contraception; the role of the physician in providing contraceptive information and services; and the attitudes and expectations associated with specific methods of contraception.

Contraceptive methods are viewed by many users as having clusters of attributes, with cultural meanings which influence the overall acceptability of the method. The role of such cultural influences is as yet poorly understood. In the past, more emphasis has been placed upon safety and effectiveness than upon why methods are acceptable, upon knowledge and use of specific contraceptives than upon attitudes toward them. As indicated by this workshop, however, there is increasing scientific interest in the development of vaginal methods of contraception that are socially and culturally acceptable, and that can be made available without health professionals. Basic to the development of the technology is a better understanding of vaginal and cervical anatomy, physiology, and biologic function.

Much is being learned about vaginal physiology during sexual intercourse. An understanding of the functions of the vagina is necessary to improve the effectiveness of vaginal methods of contraception, because the inherent characteristics of the vagina tend to thwart any attempt to prevent pregnancy. As Flowers and associates indicate that the lubrication of the vagina encourages impregnation when withdrawal is used for contraception, or when the ejaculate is spread over the labia and not deposited in the vagina. Secretions within the vagina also reduce the effectiveness of contraceptive agents placed in it; copious vaginal and cervical secretions produced during intercourse reduce the effectiveness of vaginal foams and foaming tablets by diluting them. In addition, tenacious cervical secretions protect the sperm from spermicidal agents, while simultaneously facilitating sperm migration. The effectiveness of the diaphragm is reduced by anatomic changes within the vagina during sexual excitement; some diaphragm failures are due to the elongation and ballooning of the upper third of the vagina and elevation of the cervix during orgasm, which allow penile thrusting to displace the diaphragm from the cervix.

Development of improved and more effective contraceptives depends also upon a better understanding of sperm migration in the human female. Only by understanding the physiologic processes involved can fertility be regu-

lated without significantly altering other bodily functions. According to Meghissi, sperm migration through the cervix involves the ability of sperm to penetrate the mucus. Despite the assistance the sperm may derive from uterine contractions during their ascent in the female reproductive tract, their own motility is essential for reproductive performance. The fibrillar structure of cervical mucin, enabling it to participate actively in the process of sperm transport, is another important factor requiring greater understanding, as is the morphologic configuration of cervical crypts which contribute to the storage and preservation of sperm in the cervical canal, and their sustained and prolonged release into the upper tract.

Improving methods for evaluating vaginal contraceptives is a matter of considerable concern. A major effort of the U.S. Food and Drug Administration (FDA) involves a panel of physicians and other specialists in the field of family planning, charged with the task of determining the safety, effectiveness, and proper labeling of vaginal contraceptives that are presently available over the counter, and establishing guidelines for future evaluative studies. Approximately 50 products, including more than 30 active ingredients used in other vaginal drug products, have so far been reviewed by the panel. The members have recommended that testing for contraceptive effectiveness of vaginal products be standardized. With presently used testing procedures, wide ranges of method and use-effectiveness, with failure rates as low as 3% or as high as 40%, are reported for the same product in different studies.

The effectiveness of any vaginal contraceptive is related directly to the accuracy and consistency with which it is used. Because most vaginal contraceptives are sold without prescription and are used without professional guidance, the labeling and packaging inserts are extremely important, warranting closer attention and more careful preparation than has been the case in the past. Instructions for use should be simply and concisely stated, so that the consumer has a clear understanding of the results to be anticipated; ingredients should be listed, in case users have allergies; and effectiveness claims should be more carefully stated, so as not to cause unrealistic expectations of performance. Better package inserts and patient education could improve the use-effectiveness of vaginal contraceptives.

Some investigators are attempting to evaluate and improve spermicidal agents and vaginal contraceptive formulations by critically reappraising the methodologies for *in vitro* testing. Efforts are being made to establish standards for the variables affecting spermicidal activity—such factors as pH of vaginal contraceptive formulations, semen age, temperature, and semen donor variations.

In vitro studies have certain recognized limitations; for example, concentrations of a contraceptive agent to which spermatozoa are exposed are not always equivalent to concentrations of the agent within the vagina; assessment of interactions between the microbiologic or biochemical environment of the vagina and the contraceptive agent is difficult; and unique anatomic and mechanical aspects of *in vivo* contraceptive use that may modify efficacy cannot be adequately evaluated by *in vitro* methods. The latter cannot account for such factors as the different time intervals after insertion of the contraceptive agent into the vagina, alterations in intravaginal distribution due to

changes in coital positioning or penile thrusting patterns, variations in vaginal vault expansion and lubrication with different levels of sexual excitation, or changes in effect when seminal fluid is introduced intravaginally two or more times within a specified time interval. Controlled human postcoital *in vivo* evaluation methods have been developed by scientists at the Masters and Johnson Institute to overcome these limitations. The studies are intended to be used only after *in vitro* testing of an intravaginal contraceptive product has been completed, and before the product has been released for testing in clinical settings.

The need for *in vivo* testing procedures is well recognized. A contraceptive product may have good *in vitro* spermicidal activity, but this may not be the case in the vagina. Therefore, testing the spermicidal activity of a vaginal formulation *in vivo* is advisable before fertility experiments are initiated. Opinions vary as to the most appropriate animal models for this type of testing. Until recently, a good animal model for the evaluation of the effectiveness of vaginal contraceptives was not available. A concern, when using the rabbit, dog, or any other nonprimate for this type of work, is that significant differences may exist in the reproductive processes between these species and the human. The only species that has a reproductive tract similar to that of the woman, and cycles in the same fashion, is the nonhuman primate. Zaneveld, B. Zatuchni, and Hahn have found that the stumptailed macaque is useful for the evaluation of contraceptive activity and effectiveness of vaginal formulations.

In the past, evaluations have been limited to vaginal irritation studies, in rabbits and monkeys, which assess the potential for local tissue irritation without reference to systemic toxicity. Recent studies have shown that the vagina has the ability to absorb substances placed within it and transport them to the systemic circulation. Therefore, in addition to studying possible effects of a new vaginal contraceptive on the vaginal mucosa, investigators are studying the effects on the nonpregnant woman or on the woman in early pregnancy; the effects on the embryo; the effects on the fetus during the period up to birth; and the effects on the neonate, in case an ingredient is secreted in milk.

The new spermicide-releasing sponges and spermicidal condoms presently being developed have created a need for special assay procedures that indicate how much and at what rate a spermicide is released; whether the amount released is sufficient to immobilize sperm; whether or not the sponges absorb semen, and if so, what the rate and capacity for absorption is in relation to the mass of these sponges; and whether these characteristics change in the presence of cervical mucus.

Answers are sought to certain fundamental questions pertaining to preclinical efficacy studies, such as whether a direct correlation can be shown between preclinical efficacy, as judged by *in vitro* and *in vivo* test procedures, and clinical efficacy, as judged by valid clinical trials; and to what extent the barrier provided by the vehicle contributes to the overall clinical efficacy of the product.

The final measure of clinical effectiveness must be obtained through clinical trials in which many couples use the method over a period of time.

While there is no substitute for such studies, they are time-consuming, costly, and sometimes unreliable. Contraceptors may become pregnant because they do not use a method, because they use it incorrectly, or because the method fails, even though it is used exactly according to instructions. Additional factors, such as age of persons in the study population, individual and couple fertility, motivation, and experience with a given method, childbearing history, plans for future pregnancies, attitude toward a product, instructions in use of the method, amount of follow-up provided, and attitudes of the investigational staff, must be considered. Sorting out these factors is especially significant in the evaluation of vaginal contraceptives, whose successful use depends heavily on the compliance and motivation of the subjects involved. Clinical study models are being developed, and are described in this volume by Bernstein and Nakamura, Stolley *et al*, and Derman.

As newer and more efficacious vaginal contraceptives are developed, they must be monitored for side effects, with surveillance continuing after the contraceptives have been marketed. Difficult effects to determine are those that occur only after long-term or chronic use, those that are delayed in appearance, and those that occur at low frequencies. These effects are best determined by epidemiologic surveillance systems. Several types of studies, such as the controlled clinical trial, cohort studies, case-control studies, and congenital malformation and cancer registries, are useful depending upon the type of information sought.

Major emphasis of past research focused on dosage form development for vaginal contraceptives, so as to make products containing surfactants more effective by enhancing consumer compliance. However, research emphasis is shifting to the development of longer-acting delivery systems, such as sustained release vaginal inserts and spermicide-releasing sponges, condoms, and diaphragms, which would make these methods temporarily independent of intercourse. Although investigators are taking different approaches in their research, the goal is the same: new products which are long-acting and independent of coitus, which have maximum convenience and greater acceptability, and which are inexpensive.

Approaches to lowering the failure rate of present spermicides all aim at improving the spermicidal activity of the agents or their method of delivery. However, because of the nature of the reproductive process, spermicidal activity alone may never be sufficient to provide a high degree of contraceptive effectiveness. It may be that agents will be incorporated into spermicidal preparations that work on an entirely different principle. For example, agents might prevent liquefaction of the seminal coagulum, thereby trapping the spermatozoa and preventing penetration of the spermatozoa into the cervix, allowing more time for the spermicides to affect them. Or an agent that alters the physical properties of the cervical mucus could be incorporated into a vaginal suppository, thus delaying or preventing sperm penetration. These possibilities are strictly theoretical at the present time. Research is underway on another type of agent that binds to the spermatozoan and prevents its union with the egg. In order to pass through the zona pellucida of the egg, spermatozoa require the activity of acrosin, a proteinase located in the sperm acrosome. Synthetic acrosin inhibitors have prevented fertiliza-

tion in nonhuman primate species and show good contraceptive activity when applied vaginally.

Several types of contraceptive sponges are presently being investigated. A sponge made of collagen fibrous protein, being evaluated at the University of Arizona and other places, appears to have the necessary resilience, fluid-binding capacity, easy insertion and removal, and possibility of incorporating medications, such as spermicidal agents, into the sponge matrix, that are required for successful contraception. Preliminary testing in volunteers indicates that the sponge is nonirritating, noncarcinogenic, and stable in contact with the vaginal tissue. It continuously covers the cervix as a mechanical barrier against sperm and is of a size which minimizes dislodgement during intercourse. Postcoital efficacy tests have been most favorable, although the contraceptive efficacy increases substantially when the sponge is used in combination with a spermicide. Together they provide a potentially promising intravaginal barrier method.

Another sponge, made of polyurethane and containing nonoxynol 9, is being tested in several countries, with moderate success. A third type of sponge is made of polyester and nonoxynol. When this sponge is compressed by coital thrusts, the nonoxynol is released from foam and provides spermicidal action for two hours or longer. Hydrophilic properties enable the sponge to absorb seminal and vaginal fluids much in excess of its own weight and hold them until the sponge is removed. The active ingredient is mostly released from the sponge during the coital act, and replacement of spermicide is unnecessary for multiple acts of coitus occurring within a 72-hr period.

Several contraceptive vaginal suppositories are under evaluation. An effervescent intravaginal suppository containing the spermicide menfegol is being tested in Guatemala and Bogotá. The tablet is inserted a few minutes prior to coitus to allow time for it to dissolve, a prerequisite of contraceptive action. If more than 15 min elapse between insertion and intercourse, another tablet must be inserted. Users complain that this activity interferes with enjoyment. Other disadvantages are postcoital discharge, a hot or burning sensation in the vagina, and vaginal or penile irritation. Advantages are simplicity and relative inexpensiveness.

Some 70% of all vaginal contraceptive users in West Germany use a foaming contraceptive suppository called Patentex Oval. Although the manufacturer claims that it is as efficacious as the pill, investigators suspect that Patentex Oval has a fairly high rate of failure, based on interviews with women going to the Netherlands for induced abortion. This is a serious matter, because the suppositories are widely available without a prescription, and intensive advertising campaigns are directed to teenagers. In a multicenter study, with data from 30 different Pro Familia abortion centers in West Germany, pregnancy rates with Patentex Oval accounted for 12% to 19% of all pregnancies, whereas the rate of pregnancy among oral contraceptive users was just over 3%. Clinicians have reported that in some women the suppository does not foam at all, resulting in uneven and partial distribution of the spermicide and inadequate covering of the cervix.

Another area of concern is the pharmacokinetics of nonoxynol 9. Chvapil and his colleagues, at the University of Arizona, report that when large

doses of nonoxynol 9 were administered intraperitoneally to rats for five consecutive days, the livers showed a marked increase in the density of rough endoplasmic reticulum. Lung tissue, however, remained unchanged. Changes in liver chemistry occurred after intravaginal administration of large doses of the spermicide; collagen content in the liver was significantly increased at 15 days. Five or more intravaginal administrations of nonoxynol 9 to rats also increased serum glutamic-oxaloacetic transaminase (SGOT).

The implication is that nonoxynol 9 is rapidly transported from the vagina to the blood: almost 100% of the nonoxynol is resorbed from the sponge within 9 days, and is efficiently cleared from the blood by the kidneys or the liver. The liver retains 20–50 times more nonoxynol 9 than other organs six days later, suggesting that the liver would be the organ most affected by this chemical. Studies of the chronic effects of nonoxynol 9 in humans have just begun.

Modern condoms have had widespread use in their present form since the 1930s and, in developing countries, since the 1940s. Present interest focuses on increased marketing effectiveness and quality control, as well as refinements and new developments. Regarding condom quality, primary considerations are whether the standard tests now in use actually measure condom quality, thus assuring effectiveness; how well the condoms meeting these standards can withstand local climate and other conditions; and whether standard quality criteria unnecessarily rule out reasonably effective condoms which would be more acceptable to users.

Appropriate packaging (foil or plastic film) for various climatic conditions is being debated, as are quality standards regarding thickness. Advocates of the thin Japanese condoms say U.S. condoms are unacceptably thick, while U.S. condom advocates say Japanese condoms are associated with high failure rates.

Most family-planning programs have been inhospitable to condom distribution because of their tight structure, female and clinical orientation, and distribution of prescriptions by medical and trained auxiliary personnel. In the 1970s, the trend shifted toward less formal, more liberal clinical services, and expansion of nonclinical distribution, which favors the condom and has significantly increased its use. Surveys of contraceptive use, however, generally mention the pill, IUD, sterilization, and "other methods," thus statistics on condom use are incomplete. Virtually no efforts have been made to study condom use in-depth in various countries.

New research developments involve water-soluble condoms made of biocompatible films and plasticizers, which dissolve rapidly and are easily inserted on the penis. A number of resins and plasticizers are being investigated as possible penile caps or wrap-around sheaths that would act as a spermicidal barrier. The films have good potential, but studies are required to determine whether they can dissolve rapidly enough to act on the ejaculate. *In vivo* spermicidal activity, dispersion within the vagina, long-term stability and shelf life, and user acceptability remain to be seen.

Few data are available on the effects on condom quality of multiple adverse conditions of temperature, humidity, electrical storm activity, exposure to natural or artificial light, abrasion, and mechanical load. A new approach to monitoring of condom quality has been developed and is known as the

PIACT Field Testing Package for Condoms. It includes air-inflation and surface stress tests to determine volume and pressure at burst; biaxial tension and tearing; and an apparatus to test for pinholes, which comes with detailed operating procedures, sampling protocols, calibration checks, data collection forms, and ancillary equipment for handling condoms and performing standard dimension checks. The system is being used in Mexico and Bangkok and promises to be useful on a wider basis.

A major area of interest is the social marketing of contraceptives; that is, the research, development, selling, and promotion of a contraceptive product or service to fill a perceived need of the consumer and to provide a social benefit to the community, using the traditional commercial distribution system. Such commercial distribution programs are intended to be used in concert with clinical programs to provide educational services and care for lower economic individuals.

Where social marketing programs have been initiated, positive results are being reported. Presently at least seven countries are developing such programs. Eleven other countries are adding commercial divisions to their official family-planning programs, and still others are planning to increase their existing coverage.

One of the strongest commercial distribution programs is in Mexico, where contraceptives are offered through pharmacies, self-service outlets, and food stores, supplemented by a training program directed to retail store owners and employees, and an informational and educational program through the mass media. Preliminary results indicate that the campaign is effectively increasing contraceptive acceptance and use.

Commercial techniques to promote condom use are also being applied in the Philippines, where, after a year, the Condom Marketing Research Project of the Population Center Foundation has produced a significant increase in the acceptance and use of condoms. A three- to fourfold increase in condom use was achieved with an intensive campaign involving advertising and door-to-door selling activities.

A community distribution program (CDP) in Guatemala has grown rapidly since its inception in 1976. The use of barrier methods has increased notably, as a result of the CDP, and this increase is expected to continue. The relatively high cost of these methods, a major problem, exists because they are not subsidized or provided without cost by international assistance programs. Providing these methods at a nominal price would facilitate their acceptability and use.

A knowledge and practice assessment was made of condom use in two areas of rural Bangladesh. In one area, condoms and instructions were provided to all interested couples, and in the other area, no special effort at education and distribution was made. Results indicated that although knowledge and understanding of proper condom use existed in the former area, actual condom use increased by only 3.8%, suggesting that considerable educational and promotional work will be required to substantially increase condom acceptance in rural Bangladesh. Social marketing programs may help to correct this situation.

Of the estimated $30 million spent in 1978 on contraceptive development by all agencies worldwide, both private and public, it is likely that no more

than 3%, or $1 million, was spent in the area of vaginal contraception. Funding by the various research groups may increase, however. Private pharmaceutical corporations and other medical supply manufacturers are showing considerable interest in product development. Much of this interest has been generated by the apparent safety of the methods, the relative ease in marketing the products, the repeated use of the product, and the declining use of oral contraceptives and IUDs. In a commercial sense, these are true motivating forces.

Directors of family-planning programs in developing countries, whether government or privately sponsored, typically face problems of material scarcity, coupled with mismanagement of resources. For a family-planning program to achieve consumer acceptance and positively affect public health, contraceptive supplies must be delivered to the user. The procurement and use process, described in this volume by Bates, Hartman, and their associates, must be understood by family-planning administrators. Systems for the supply of contraceptive materials are being implemented in Afghanistan, Nepal, Bolivia, and other countries to provide more effective distribution of contraceptive goods. The technically perfect contraceptive does not exist; yet in many countries, fertility rates could be lowered by regular supply and appropriate use of existing contraceptive technologies and commodities.

Potts has stated that "vaginal contraceptives are to family planning what a buffalo cart is to a modern transport system; more certain ways of solving the problem may exist, but to overlook the usefulness and potential acceptability of a simple solution to a common problem, especially one that is of proven usefulness and perhaps also open to improvement, is shortsighted." Potts also notes that vaginal barrier methods are without significant side effects and probably have no long-term risks. The condom and diaphragm may reduce the risk of cancer of the cervix, and both barriers and spermicides have the potential of helping to control venereal disease. Further, in any country where abortion is legal, the combination of vaginal barrier methods of contraception and first trimester abortion presents less of health risk to the user than do IUDs or oral contraceptives.

When vaginal methods are promoted honestly, without unverifiable claims, they are well accepted. In the developing world, their marginally inferior performance in relation to effectiveness is perhaps less significant than in the West. For the many millions of persons who live out their lives in rather simple terms, the sophisticated technology of the West may not be relevant.

This volume addresses, in greater detail, the issues that have been touched upon here. It was just a century ago, in the 1880s, that the first modern vaginal contraceptive product became commercially available. Rendell's pessary, a cocoa butter vaginal suppository containing quinine sulfate, was quickly and enthusiastically accepted, first in England, and soon worldwide. Since that time, vaginal contraceptives have been sometimes widely accepted and used, and sometimes ignored.

Unquestionably, the time is right to consider vaginal contraception in light of the latest scientific thinking with regard to reproductive physiology; to the social, cultural, and personal impacts of presently available contraceptive technology; and to the development and evaluation of new approaches to vaginal contraception.

It is the hope of the editors and contributors that the present volume will provide a better understanding and appreciation of the role of vaginal contraception in fertility regulation.

Gerald I. Zatuchni, M.D.

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THE VAGINA

1

Vaginal Contraception: Historical Perspective

JOHN J. SCIARRA

The rapid progress and dramatic events in the field of fertility regulation since 1960 have prompted a reevaluation of the vaginal methods of contraception. This reevaluation includes a consideration not only of the present status of the condom, diaphragm, and spermicides, but also of their potential for further development, increased effectiveness, and greater acceptance.

Vaginal contraception is the oldest means by which women and men have attempted to control their fertility. Records extending over 4000 years catalogue pastes, gums, and gels intended to impede or destroy the movement of spermatozoa in the vagina. Pessaries, tampons, sponges, cervical caps, and penile sheaths used to block the entrance of spermatozoa into the cervical canal also have a long history (Table 1-1).

Until the 1960s, the various male and female barrier methods, as well as coitus interruptus, rhythm, and pregnancy termination, were the only forms of fertility control available to most couples. Yet historically, vaginal contraception, coupled with strong motivation, has sometimes been very effective. During the 1930s in the United States, motivation to control fertility was high, owing to the economic deprivation of the Depression. In 1933, the U.S. birth rate fell to 16.5 live births per 1000 population, representing a 20% decrease over an eight-year period—at a time when only the traditional methods of contraception were available (1). An equally low birth rate was not achieved again until 1970, when couples had a full range of contraceptives from which to choose.

The nineteenth and early twentieth centuries saw major scientific advances that were instrumental in the development of the present vaginal contraceptives. This chapter will briefly review the history and development of vaginal contraceptives and nonsteroidal intravaginal agents, and consider their present status and use worldwide.

THE CONDOM

The oldest reliable method of male contraception, the condom, was mentioned in early history as a penile sheath, probably used for decoration and later for protection against disease (4). In 1564, Fallopius, the Italian anatomist, described a sheath made of linen that provided protection against syphilis. Other early sheaths were made of animal intestines. In the eigh-

TABLE 1-1. Selected Milestones in the History of Contraception

1850 B.C.	Earliest mention of barrier contraceptives in Egyptian papyri; used for next 3500 years, along with coitus interruptus, withdrawal, rhythm, pregnancy termination
1564 A.D.	Fallopius described use of linen sheath as protection against syphilis (Italy)
1677	Spermatozoa first observed (Holland)
1700+	Penile sheaths used for contraception (England)
1840+	Process for vulcanizing rubber developed; inexpensive condoms produced (U.S.)
1882	Hasse, using pseudonym Mensinga, developed diaphragm (Germany)
1885	Rendell marketed spermicidal suppository of cocoa butter and quinine sulfate (England)
1906	First commercially produced spermicidal jelly, "Patentex" (Germany)
1920+	Holland-Rantos company began manufacture of diaphragm (U.S.)
1950+	Surfactants found to be effective spermicides (U.S.)
1960	Oral contraceptive (Enovid) first marketed (U.S.)
1960+	Development of modern laparoscope and improved female sterilization techniques
1964	Lippes loop marketed (U.S.)
1973	Abortion legislation liberalized (U.S.)

(Modified from Hatcher et al: Perinatal Care 2:38, 1978)

teenth century, these devices acquired the name condom and were used for contraception. One of the earliest mentions of this use was by Casanova, who referred to condoms as "assurance caps" ("Calottes d'assurances") or "preservatives that the English have invented to put the fair sex under shelter from all fear" (6). Their use had become fairly widespread by the eighteenth century, as indicated by the advertisement of a London condom dealer in 1776 that mentioned the receipt of several large orders ". . . from France, Spain, Portugal, Italy, and other foreign places" (4).

With the development of vulcanized rubber in the 1840s, the condom could, for the first time, be inexpensively mass-produced. Its reliability and marketability were further enhanced by the introduction of liquid latex in the 1930s (3). In recent years, the condom has undergone other refinements in design and marketing. It is available worldwide and plays a significant role in contraceptive practice in a variety of cultural settings.

THE DIAPHRAGM

The diaphragm was the first reliable method of contraception available to women. When vulcanized rubber became available in the 1840s, cervical caps were developed in Germany and, forty years later, the German physician Hasse, using the pseudonym Mensinga, developed the rubber vaginal diaphragm. This device quickly became popular in Holland and England and was introduced into the United States in the early twentieth century by Margaret Sanger. During the 1920s, diaphragms were manufactured and distributed on a mass basis (15). Today they are widely available in several different designs, depending on the type of circumferential spring reinforcing the

rim. Like condoms, diaphragms are highly effective for motivated users, although their widespread use is somewhat limited by the need for individual fitting, which requires special training.

THE SPERMICIDES

During the 1940s, safe and practical spermicidal agents also became available. Although spermatozoa had been observed by Leeuwenhoek in Holland in 1677 (11), scientists did not begin experimenting with various spermicidal agents until the nineteenth century, when the microscope had been significantly improved. The first commercial spermicidal suppository was developed by Rendell, an English pharmacist, in 1885 (4). Rendell's pessary, as it was called, consisted of soluble cocoa butter and quinine sulfate. It became so popular that, by the turn of the century, it was being sold worldwide. In 1906 in Germany, Merz developed the first commercially produced spermicidal jelly, Patentex (14), which is still used today.

During the 1920s and 1930s, numerous vaginal suppositories and foaming tablets, many containing mercury, quinine, boric acid, and other weak acids, were marketed in the United States and Europe, but tended to be irritating to the vagina. In the early 1950s, surface active agents, or surfactants, such as nonylphenoxypolyethoxyethanol (nonoxynol 9) proved to be effective spermicides and were free of the irritating effects of the earlier compounds. Like the condom, today's vaginal spermicides are available without a doctor's prescription and, when used in conjunction with the condom or diaphragm, are highly effective.

CHANGING PATTERNS OF USE

The widespread availability of oral contraceptives, IUDs, surgical sterilization, and abortion during the 1960s and 1970s was accompanied by a decline in the use of the vaginal contraceptives.

In 1960, the first oral contraceptive pill, Enovid, was marketed and, within a decade, some 70 different oral contraceptive products had become available worldwide and made up the cornerstone of most family-planning programs. Several years passed before certain disadvantages began to become apparent. By the late 1960s, epidemiologic studies in Great Britain and the United States accumulated sobering data on long-term effects. Oral contraceptives began to be viewed with suspicion by medical scientists, contraceptive users, and regulatory agencies (12).

Another important family-planning advance of the 1960s was the IUD. Margulies developed the first linear plastic IUD in 1960 and, in 1964, the Lippes loop was marketed in the United States. These were followed on a worldwide basis by two dozen types of IUDs under 250 different brand names (7). Although the IUD was hailed by some as the "ideal" contraceptive, user acceptance was disappointing, and subsequent problems involving removals for bleeding, pain, and pelvic infection soon lessened enthusiasm.

Two other developments during the 1960s had an impact on vaginal con-

traception. Technological advances increased the safety and acceptability of surgical sterilization, especially for women, providing a highly effective method of fertility regulation for couples who had completed their childbearing. The second important development was the legalization of abortion in 1973. Availability of legal abortion enabled women to turn to less effective but safer methods. Tietze and Lewit found that for women of all ages, by far the safest form of contraception was a combined regimen of vaginal contraceptives and recourse to early abortion in case of failure (16).

By 1975, professional and user interest in barrier methods of contraception was beginning to increase. Among the 16 largest affiliates of the Planned Parenthood Federation of America (PPFA), almost twice as many new patients (12.7%) chose the diaphragm during the third quarter of 1976 as in the same quarter of 1975 (6.7%) (10). While the majority of couples were still relying on oral contraception and sterilization, some had begun to feel that perhaps the traditional methods had been underrated.

PRESENT USE AND DISTRIBUTION

The Condom An accurate determination of present condom use is difficult; the latest figures from USAID (December 31, 1978) (13) place the prevalence of use at 35 million men, of which 5 million are in the People's Republic of China. Unlike the diaphragm and spermicides, the condom has had a fairly important role in developing countries. Government and private agencies, such as the USAID, the International Planned Parenthood Federation (IPPF), and the Population Council, have extensive condom distribution programs to increase availability and consumer acceptance (3). Problems of distribution involve high-import tariffs; prohibitive laws governing sales, advertising, and displaying of condoms; increased cost due to price markup by middlemen; problems of storage and effectiveness under extreme climate conditions; transportation to remote areas; and negative attitudes of family-planning policymakers and program administrators.

Mail-order marketing of condoms is common in Europe and Asia, and is increasing in the United States. In developing countries, distribution problems outweigh any other problems associated with condom use, and demand is far greater than the capacity to make them available.

The Diaphragm U.S. AID estimates suggest that the diaphragm, spermicides, or sponges are used by 30 million couples (13). Diaphragm use worldwide focuses mainly on developed countries. In the People's Republic of China, diaphragms are available but are used primarily by older women who began using them before other methods became available (15). In Africa and the Middle East, diaphragm use is negligible compared to other contraceptive methods. In Latin America, diaphragms are usually available through Family-Planning Association clinics, but distribution is relatively small. In 1974, Potts remarked that the diaphragm had "reached its peak incidence of use and seems unlikely to become a useful method in any developing country" (15).

Certainly, its use has not been encouraged in family-planning programs;

therefore, it is less available. Program administrators cite as drawbacks such factors as need for privacy for insertion and removal, ready source of water for hygiene, need for clinical services for initial fitting, need for a constant supply of spermicidal cream or jelly, problems of packaging and distribution, and high cost. Other claims may reflect certain negative attitudes of policy-makers. For example, concerns about insufficient motivation to succeed with diaphragm use by women in developing countries have not been adequately tested. It is worth noting, however, that methods based on the same principle as the diaphragm have been the primary means of contraception in most cultures for at least 4000 years. Sponges have been used for contraceptive purposes since about 1550 B.C. and are still in use in some areas of the world. An olive oil-impregnated sponge is sometimes used in this way (8). New materials that provide the barrier features of the fitted rubber diaphragm are now being combined with some of these older ideas.

Spermicidal Agents Assessing the actual use and distribution of spermicidal preparations is difficult. The worldwide use is estimated at from two to four million couples. There are about 140 spermicidal products presently on the market, all of which have two components: a relatively inert vehicle or carrier and an active spermicidal agent. They are available in four basic forms: creams, jellies, and pastes in a tube; suppositories; foams, either in tablet form or in pressurized containers; and soluble films.

In the United States prior to the 1960s, foams and other vaginal contraceptives were promoted primarily through the medical profession. In recent years, however, aerosol foam, cream products, and condoms have been advertised in popular magazines. Spermicidal products have not been promoted or marketed widely in de[illegible] Where educational and promotional programs are [illegible], however, consumer demand increases significantly (17).

Use As of 1976 in the United States, the use of oral contraceptives continued to dominate contraceptive practice among married women aged 15–44 (Table 1-2), accounting for 22.3% of users. Surgical sterilization was used by 30.2% of couples. Use of the condom declined between 1973 and 1976 (as did oral contraceptive use), but there was a slight increase in use of the diaphragm. Bruce and Schearer (2) described diaphragm acceptance among various groups served by organized family-planning services in the United States. In a public, physician–run clinic in the southern United States where diaphragm use was not stressed, only 2% of clients accepted diaphragms. In other physician–run clinics, diaphragm acceptance ranged from 6% to 20%. In three privately operated women's health services, however, where emphasis is on self-administered forms of contraception, the proportion of women selecting the di[illegible]agm was 80%.

Another study considered figures from 3112 U.S. family–planning services (Table 1-3). [illegible]een 1972 and 1976 use of the diaphragm, foam, and condom among [illegible]nic patients more than doubled. The three methods were used collectively by 15% of the 4.1 million women included in 1976, compared to 7% in 1972. It is interesting to note that condom acceptance *dropped* in both years after enrollment in the program and, in 1972, use of

TABLE 1-2. Contraceptive Use: U.S., 1973–1976; Currently Married Women Aged 15–44

Method (%)	1973*		1976†	
Using contraception	53.2		48.6	
Oral contraceptives	25.1		22.3	
IUD	6.7		6.1	
Diaphragm	2.4	= 15.3	2.9	= 13.1
Condom	9.4		7.2	
Foam	3.5		3.0	
Rhythm	2.8		3.4	
Withdrawal	1.5		2.0	
Douche	0.6		0.7	
Other	1.3		0.9	
Sterilization (Couples)	23.8		30.2	

*N = 26,646,000 †N = 27,185,000

(Advance Data: National Center for Health Statistics, August 18, 1978; Fam Plann Perspect 10:265, 1978)

TABLE 1-3. Contraceptives Used by New Patients Before and After Enrollment in Organized Programs

	(%) 1972		(%) 1976	
Method	Before	After	Before	After
Oral contraceptives	43.2	71.3	46.0	67.0
IUD	5.5	13.2	5.2	8.1
Sterilization	0.0	1.1	0.0	1.3
Diaphragm	1 3	2.0	2.5	6.7
Foam	5 9	4.6	4.9	6.5
Condom	5.7	0.8	5.9	2.0
Rhythm	1 3	0.2	1 3	0.3
Other	1.7	1.1	3.1	1.6
None	35.4	5.7	31.1	6.5

(Torres A: Organized family-planning services in the United States, 1968–1976. Fam Plann Perspect 10:83, 1978)

foam also dropped after clinic enrollment. It is apparent that these family-planning clinics are not oriented toward vaginal contraception.

EFFECTIVENESS, ADVANTAGES AND DISADVANTAGES

The higher failure rates for the vaginal contraceptives relative to oral contraceptives and IUDs are usually attributed to incorrect or inconsistent use (use-effectiveness), rather than to the potential effectiveness under ideal conditions, without omissions or errors in application (theoretical-effectiveness), such as in carefully controlled clinical studies. These two types of effectiveness rates for various contraceptive methods, expressed as the number of unwanted pregnancies per 100 women years, are shown in Table 1-4.

TABLE 1-4. Relative Effectiveness of Contraceptive Methods Expressed as Unwanted Pregnancies/100 Woman Years

Method	Theoretical Effectiveness	Use Effectiveness
Oral contraceptives	0.1	3
IUD	2	5
Condom/spermicide	1	5
Diaphragm/jelly	3	13
Condom alone	3	15
Foam, jelly alone	5	20
Coitus interruptus	3	15–23
Rhythm	14	35–40
Douche	. . .	35–40
No method	80	80
Vasectomy	0	0.15
Tubal ligation	0	0.04
Hysterectomy	0	0.0001
Abortion	0	0

(Meeker CI, Gray MJ: In Romney SL, Gray MJ, Little AB et al (eds): Gynecology and Obstetrics. The Health Care of Women. New York, McGraw-Hill, 1975, pp. 549–586)

TABLE 1-5. Condom Failure Rates/100 Woman Years of Exposure: Five U.K. Studies

Investigator/Year	Theoretical	Use
Peel (1969)	0.8	3.1
Peel (1972)	1.6	3.9
John (1973)	0.4	4.8
Glass (1974)	. . .	4.0
Potts (1975)	. . .	0.8

(Hatcher et al: Contraceptive Technology 1978–1979, 9th rev ed., New York, Irvington Publishers, Inc, 1978)

Under ideal conditions, the pregnancy rate for couples using condoms is 3:100 women years; in actual use the failure rate may be as high as 15:100. Studies from the United Kingdom, where the condom is a well-accepted form of contraception, indicate that when motivation is good, both theoretical- and use–effectiveness are extremely high (Table 1-5). When a spermicidal agent is used in conjunction with the condom, use-effectiveness approaches that of the IUD.

Advantages of the condom are that it requires no prescription, is readily available, permits the male to take responsibility in the sex act, provides protection from venereal disease, is inexpensive and easy to use, requires no sophisticated regimen, and has no medical complications. The *disadvantage* is that strong motivation is required; the condom must be used correctly with each act of intercourse and it interferes precoitally. Failures result from improper or inconsistent use and from imperfections of manufacture.

The theoretical failure rate for diaphragm use with spermicidal jelly or cream is 3:100, while use-effectiveness is 13:100. Careful instruction and good motivation can provide considerably higher use-effectiveness rates, according to findings from the Margaret Sanger Research Bureau. Staff members had positive attitudes about vaginal contraceptives and, in any given year, some 18–24% of the clients chose the diaphragm in conjunction with a spermicide. In a study by Lane, Arceo, and Sobrero (9) of 2168 new users of this method who were followed for two years, 37 accidental pregnancies resulted. This constituted an accidental pregnancy rate of 2:100 users. All but one pregnancy occurred during the first year, and 22 women admitted that they had used the method inconsistently or not at all. Among the 175 women aged 13 to 17, only two pregnancies occurred, a failure rate of 1.9:100. That use-effectiveness rates under different conditions vary widely, is indicated by Lane's finding that, among 14 clinical studies, the cumulative pregnancy rate per 100 diaphragm users after one year ranged from 1.9–28.9.

Advantages of diaphragm use are safety, high effectiveness when used with a spermicide, and female control. *Disadvantages* are that it cannot be used by some women with uterine malpositions; it causes precoital interference; it requires privacy, initial medical instruction and fitting, and subsequent development of user skill; it is cumbersome, it must be used correctly with each act of intercourse; it requires a ready supply of spermicidal foam or jelly; and the woman is required to manipulate her genitalia.

Theoretical-effectiveness of spermicidal foam is 5:100 woman years, while use-effectiveness is 20:100. Considerable confusion exists as to the actual effectiveness of contraceptive foam. Failure rates vary widely, with rates from 1.75–38.34 reported in various studies performed since 1960 (17).

Advantages of the spermicides are their localized action, their easy availability, and their accessibility for distribution and use without physician supervision. *Disadvantages* are their reported low use-effectiveness, short-term efficacy, unaesthetic qualities, and sometimes awkward delivery systems.

Table 1–6 summarizes the factors affecting the utilization of various methods of fertility control.

ATTITUDES OF HEALTH PROFESSIONALS

Hatcher (5) reports the results of an interesting study which indicates that health professionals may bias their responses in favor of oral contraceptives and IUDs, and against barrier methods. When 120 physicians, medical students, nurses, and family planners were asked how they would answer a patient who asked about the effectiveness of various contraceptive methods, respondents tended to give theoretical-effectiveness rates for diaphragms, condoms, and foam. Ninety of the respondents estimated the effectiveness of the barrier methods to be 50% or less.

It is important to recognize, however, that no one contraceptive method will always be suitable in every clinical situation. Selection will depend upon individual needs and motivation. For highly motivated couples who thoroughly understand the proper use of the method, a barrier contraceptive may be an extremely safe and effective means of fertility regulation.

TABLE 1-6 Methods of Fertility Control. Factors Affecting Their Utilization

	Foam	Condom	Oral Contraceptive	IUD	Vacuum Abortion	Diaphragm
Cost	$25/yr	$25/yr	$60/yr	$60/yr	$150 each	$60/yr
Effectiveness (Theoretical)	97%	97%	99 66%	97–99%	100%	97%
Morbidity						
Major	*	*	1%	1%	1%	*
Minor			40%	40%	8%	
Mortality (per 100,000 users/yr)	*	*	0.3–3	1.5	1.9	*
Reversibility	100%	100%	100%	100%	0	100%
Skill required†	1	1	1	2	2/3	2
Anesthesia type	0	0	0	0/local	Local	0
Time away from work	0	0	Office visit	Office visit	1/2 day	Office visit
Hospital or office time	0	0	5–15 min	5–15 min	10–15 min	15 min
Recovery time	0	0	0	0	1 hour	0
Facility	Across the counter		Office	Office	Office/outpatient	Office/across the counter

(*Continued*)

TABLE 1-6. Methods of Fertility Control: Factors Affecting Their Utilization (Cont.)

	Late Abortion	Hysterectomy	*Tubal Ligation* Laparoscopic	Minilap	Colpotomy	Vasectomy
Cost	$600 each	$2,000	$300	$1,000	$1,000	$150
Effectiveness (Theoretical)	100%	100%	99+%	99+%	99+%	99+%
Morbidity						
Major	3%	14%	0 6%	0.4%	2-4%	1%
Minor	26%	51%	1.7%	1%	3-13%	5%
Mortality (per 100,000 users/yr)	17 3	100	1-5	?	?	0
Reversibility	0	0	0-50%	0-75%	0-75%	5-90%
Skill required†	4	4	5	4	4	3
Anesthesia type	Local	General	Local/General	Local/General	Local/General	Local
Time away from work	3 days	42 days	2-7 days	2-4 weeks	2-4 weeks	1/2-5 days
Hospital or office time	12-36 hrs	6 days	1/2 day	1-2 days	1-2 days	15-20 min
Recovery time	24 hrs.	14-42 days	0-5 days	2 weeks	2 weeks	1-5 days
Facility	Hospital	Operating room	Operating room/ surgicenter	Operating room	Operating room	Office

*Pregnancy related only

† On scale of 1-5: 1 = lay; 2 = short course; 3 = medical; 4 = surgical/gyn; 5 = surgical/endoscopy (Hatcher et al: Contraceptive Technology 1978-1979, 9th rev ed., New York, Irvington Publishers, Inc., 1978, pp. 22-23)

RECOMMENDATIONS

From this review of the history and present use of the vaginal contraceptives, several considerations become apparent that might benefit the development and increase the acceptance and use of these methods:

1. Better educational programs, not only for users but for health professionals
2. New types of diaphragms that do not require individual fitting, are not directly intercourse-related, and do not require adjunctive jelly or cream
3. Development of longer-acting spermicides that can be easily and aesthetically applied
4. Better packaging, marketing, and distribution methods

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2

The Contraceptive Aspects of the Anatomy, Morphology, and Physiology of the Vagina

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Relatively few anatomists, reproductive physiologists, and obstetricians and gynecologists appreciate the complexities of the vagina's anatomy, physiology, and biologic function. It cannot be adequately characterized simply as an organ for ensheathing the penis to accomplish insemination and an anatomical birth canal.

THE ANATOMY OF THE VAGINA

The vagina is relatively devoid of nerves but its entrance is surrounded by a rich network of nervous and erectile tissues which transmit erotic stimuli. The vagina is lined with squamous epithelium, one of the body's strongest and most versatile tissues. This epithelium withstands the forces of penile thrusting by having denser epithelium at the introitus and along the posterior wall than along the anterior wall. It adapts to its role as a birth canal by having rugal folds which act as an accordion and allow the vagina to be distended without injury. The vagina is further protected from injury at childbirth by being surrounded by bands of smooth muscle and connective tissue arranged in spirals. This construction allows the vagina to distend sufficiently for delivery of a child and then return to its nonpregnant diameter by the retraction of the muscles and elastic tissue.

The epithelial layer of the vagina consists of epithelial lamina and a lamina propria. The epithelium is noncornified except when it is outside the body, as in uterine descensus. The epithelium undergoes cyclic changes but these are not nearly as pronounced as those of the endometrium. The vagina has higher squamous epithelium and greater glycogen content of its cells during the proliferative phase than during the secretory phase of the menstrual cycle, when its height is reduced by the shedding of some vaginal cells.

These cyclic changes in the vagina are particularly evident when it is studied by the scanning electron microscope. During the proliferative phase of the endometrium, the surface of the vagina appears to be a homogeneous

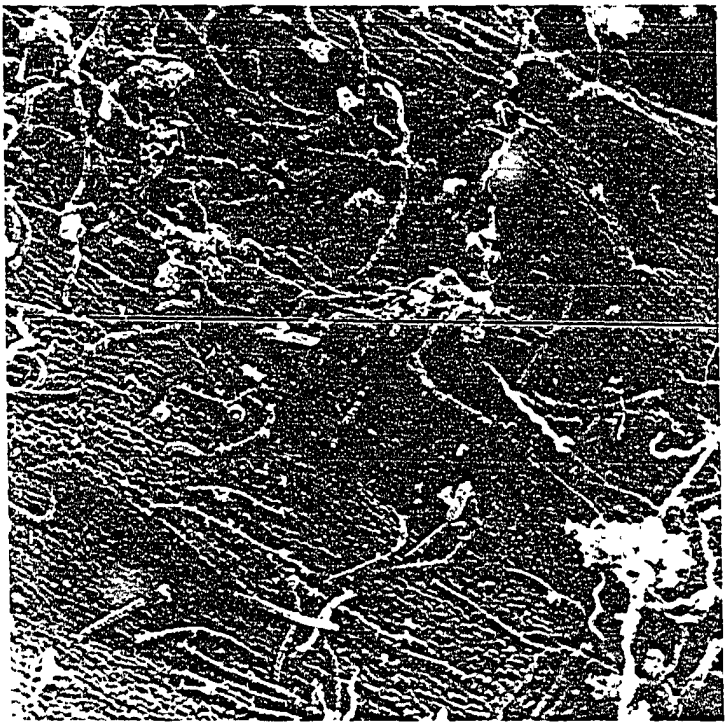

FIG. 2-1. Squamous epithelium of baboon showing anastomosing microridges and microgrooves.

group of large superficial polygonal cells. There are narrow intracellular edges and the structure is dense. However, during the luteal phase, there is desquamation of the superficial epithelial cells extending as far as the intermediate cells. This loss of vaginal cells during the luteal phase may represent the desquamation of cells which have undergone aging from the exhaustive effects of producing glycogen. The surface of the vagina is, therefore, similar to the squamous epithelium of the skin, which has a 28-day cycle from the time the basal cells are formed until they are desquamated from the cornified layer (Figure 2-1).

Pregnancy causes a tremendous increase in the circulation of the vagina and a stimulation of its estrogen receptors and glycogen content. There is a reduction in the desquamation of the cells and an increase in the cells' strength and turgor (8).

The ultrastructure of the vagina reveals a complex and functional relationship between the basal and parabasal, intermediate, transitional, and superficial cells of the squamous epithelium.

The basal and parabasal cells have not reached their functional capacity and appear immature. The endoplasmic reticulum and the mitochondria are poorly developed; there are microvilli between the interdigitating cells, but there is an absence of desmosomes. Hermidesmosomes, however, attach the

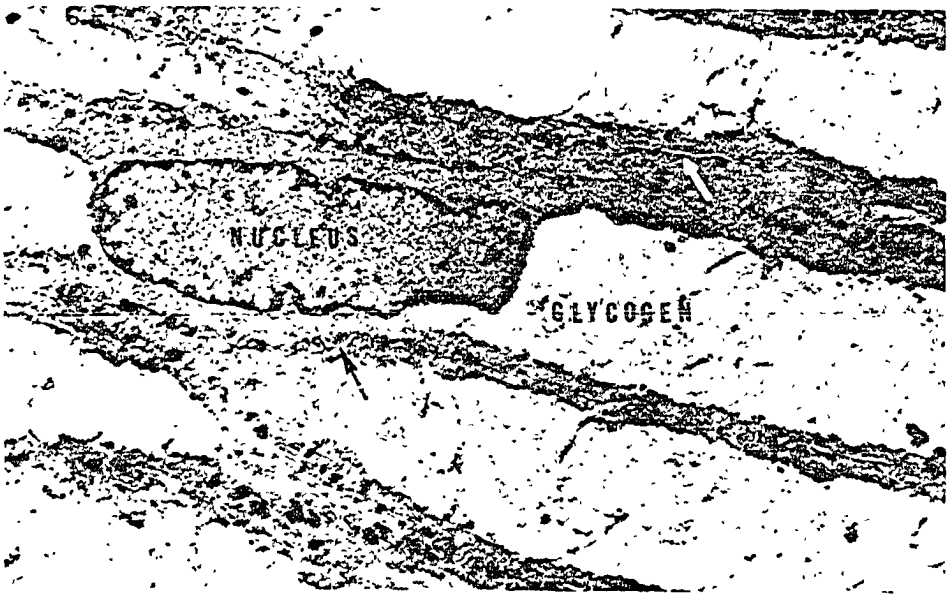

FIG. 2-2. Transitional cell of vagina showing glycogen, intercellular channels and desmosomes. (Burgos MH, Roig de Vargas-Linares CE: In Hafez ESE, Evans TN (eds): The Human Vagina. Amsterdam, Elsevier, 1978)

basal cells to the basal lamina. The intermediate cells reveal intense enzymatic activity, and protein and glycogen production. The endoplasmic reticulum is well-developed and there are glycogen granules throughout the cytoplasm. The metabolic activity and production of glycogen by the vaginal cells are related to their estrogen and progesterone receptors and respond to the level of these steroids. There is an initial binding to a cytoplasmic receptor to form an estrogen complex, with translocation to the nucleus, and synthesis of nuclear ribonucleic acid. Frequent desmosomes indicate the firm intracellular connections between the cells and attest to the resiliency and strength of the vagina.

The transitional cells, the aging cells of the vagina, indicate reduced biologic activity; they undergo a reduction in the number of microvilli and desmosomes. The superficial cells are resilient, flat, irregularly serrated, and continue to contain glycogen (3) (Figure 2-2).

The structure of the vaginal epithelium thus makes the vagina a strong and versatile organ that is relatively impervious to microorganisms and able to withstand the friction of coitus and the stretching of childbirth.

VAGINAL BACTERIA AND SECRETIONS

The natural moisture of the mucous membrane and the presence of free glycogen foster bacterial growth. The vagina contains bacteria of the bowel and

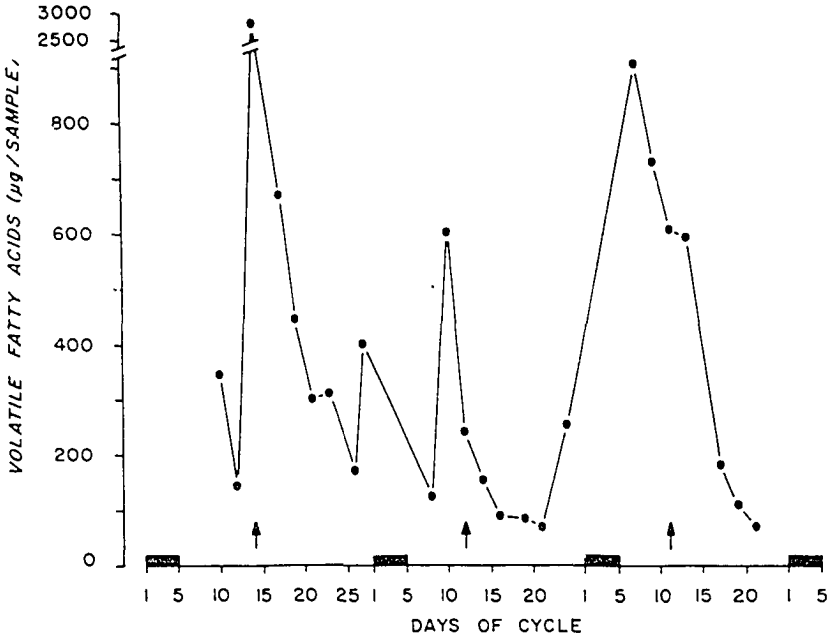

FIG. 2-3. Volatile fatty acids in samples of vaginal fluid during three menstrual cycles (28, 26, and 25 days) from woman who was one of highest "producers." There are consistent declines in the acid content during the luteal phases of each cycle. More than 42% of the total acids due to those other than acetic. Horizontal bars indicate menstruation. Arrows indicate expected day of ovulation. (Michael RP, Bonsall RW, Warner P: Science 186: 1217, 1974)

skin as well as other bacteria which at periodic intervals find the environmental conditions of the vagina favorable for their growth. These diversified bacteria are kept in balance by the dominance of the Doderlein's bacillus and other lactic acid–producing bacteria. This balance is dependent upon the virulence of bacteria, the general immunity of the host, and the adequacy of lactic acid to maintain an acid pH of 3.5–4.

The presence of these bacteria, the glycogen, and the addition of mucoprotein from the endometrium, cervix, and Bartholin and Skein glands, have allowed the vagina, through evolutionary selection, to secrete sexually stimulating odors called pheromones or copulins (5). In essentially all nonhuman mammals, including primates, these sexually stimulating odoriferous compounds play a significant role in communicating sexual receptivity.

Twenty-six different low-molecular-weight pheromones have been isolated from the human vagina. They are usually C_3 and C_5 compounds such as acetic, propionic, isobutyric, and methylvaleric acid. The amount and character of these secretions vary from woman to woman, and are influenced by the production of estrogen and progesterone (6). They are always highest at the time of ovulation. Figure 2-3 illustrates the amount and the cyclic variation of these compounds in a woman who secreted them in large amounts.

Evolutionary forces lead to appropriate adaptation of every organ. The vagina required a system of lubrication to insure optimal sexual excitement during coitus. Masters and Johnson demonstrated that individual droplets of transudation–like mucoid material appear throughout the rugal folds of the vagina. The individual droplets coalesce and form a smooth lubricant for the entire vagina. The amount of vaginal lubrication is dependent upon effective stimuli, which reflexively cause stasis and distention of the venous plexis beneath the vagina, resulting in an outpouring of the transudate from the vaginal canal and vestibule (4).

Vaginal secretions, which may be quite copious, have a pH of 7 and thus assist in raising the resting pH of the vagina from 3.5 to a more neutral level during sexual excitement. Sperm survive poorly at low pH; therefore, some adaptation for sperm survival was necessary. One adaptation is the raising of the vaginal pH by the outpouring of vaginal and cervical secretions. During sexual excitement there is an extrusion of cervical mucus in the form of elongated strings which may extend through the vagina. These cervical mucus bundles raise the pH of the vagina and may facilitate sperm transport in the vagina while protecting the sperm from the vaginal acidity. Seminal fluid, also, acts as a buffer. The sperm are maintained in gelatinous drops until conditions in the lower vagina and cervix are optimal for their transport (Figure 2-4).

THE SEXUAL FUNCTION OF THE VAGINA

The position of the vagina from the vulva to the cervix is upward and backward so that it can anatomically accommodate the upward–angulated penis. The posterior wall is longer than the anterior wall so that it can more readily accept penile thrusting and form an anatomical pool for the collection of semen.

The vagina has three compartments. The lower compartment is constricted and partially closed by the hymeneal remnants of the vestibule and the perineal muscles, which act as the orgasmic platform. The middle compartment is relatively fixed by the strong attachment of the cardinal and lateral vaginal ligaments. The upper vaginal compartment is above the levator muscles; it is relatively mobile and is capable of considerable distention. During sexual excitement a number of important changes occur in the vagina. Within ten to thirty seconds after sexual stimulation, the vagina begins to lubricate. This is precisely the time that is required for the penis to become erect.

Lubrication of the vagina is followed by an opening and retraction of the labia, elevation of the uterus, and a lengthening of the posterior vagina. A marked vasoconstriction develops which distends the bulbous erectile tissue and reduces the proximal diameter of the vagina by approximately one-third. This venous congestion allows the development of the orgasmic platform. The vagina is thus perfectly adapted for ensheathing and stimulating the penis during the orgasmic phase of sexual excitement. The orgasmic platform stimulates the penis to ejaculate by contracting 10–15 times at 0.8–second intervals (4). The cervix and uterus are elevated out of the line of

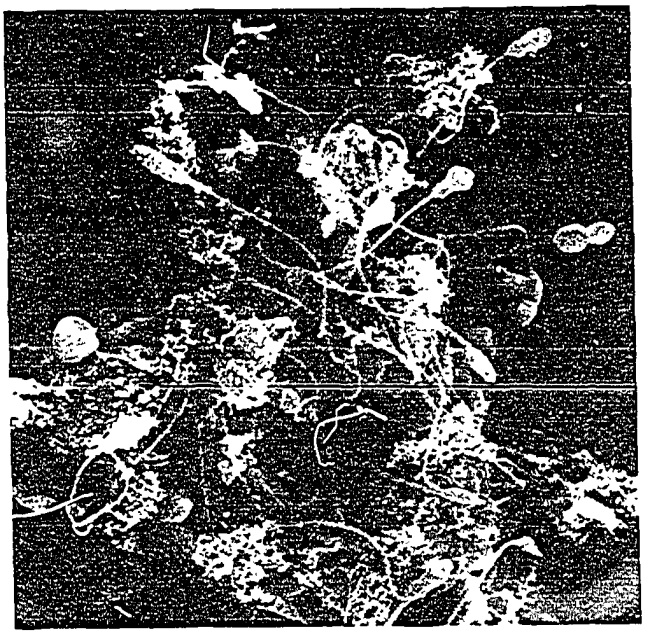

FIG. 2-4. Human sperm surrounded by seminal fluid.

penile thrusting and the upper vagina is lengthened and enlarged by 3–5 cm. The resolution phase allows the vagina to collapse and the posterior fornix to maintain the seminal fluid in contact with the cervix, where the sperm are propelled upward into the uterus and fallopian tubes by the ciliary action and contraction in the cervix and uterus.

An understanding of these anatomic, morphologic, and physiologic functions of the vagina is necessary to improve the effectiveness of vaginal methods of contraception, because the inherent characteristics of the vagina will tend to thwart any attempt to prevent a pregnancy.

An understanding of the lubrication of the vagina explains how impregnation may occur when withdrawal is used for contraception or when the ejaculate is spread over the labia and not deposited in the vagina. The labia retract during sexual excitement; thus, even if only a few sperm are deposited in or near the vestibule of the vagina, they may migrate to the cervix. It is thus important that the ineffectiveness of withdrawal and rhythm is explained to patients at every opportunity.

The vagina is a natural reservoir for contraceptive agents and it has been used as a depository for agents believed to have spermicidal or other contraceptive capabilities for more than four millennia. However, the physiologic secretions within the vagina reduce the effectiveness of agents which are placed in it, just as factors affecting sperm migration reduce the effectiveness of withdrawal. Jellies and foams which are used for contraception are diluted by the vaginal secretions. The tenacious cervical secretions protect the sperm from the spermicidal agents and simultaneously facilitate sperm migration. The ballooning of the upper one-third of the vagina increases the surface

area around the cervix and reduces the amount of contraceptive agents which may reach the cervix. Theoretically, however, the microridges of the squamous epithelium create small reservoirs where the foam and jellies may collect and be available as spermicidal agents (Fig. 2-1).

There has been no real improvement or significant research in vaginal jellies for the last two decades. However, one of the most effective spermicidal agents, phenylmercuric acetate, has been removed from the market by the Food and Drug Administration (FDA). A thicker and more tenacious jelly, in combination with more potent spermicidal agents, is needed to improve vaginal barrier methods of contraception. Increasing the contraceptive efficiency of these new agents would mean a reduction in their aesthetic aspect.

Foam and foaming vaginal tablets have provided simplicity in vaginal contraception but they have created false confidence. Birmingham clinicians found that vaginal foams and foaming tablets are responsible for 75% of the pregnancies in patients seeking terminations when some form of contraception had been used. The vagina reduces the effectiveness of these agents by the anatomical changes which occur during coitus and by the copiousness of the vaginal and cervical secretions.

The number of couples who conscientiously use barrier methods of contraception is increasing. These couples are concerned with the side effects of the pill and the intrauterine devices. They are selecting the condom in combination with a vaginal jelly or foam and the diaphragm and jelly. Not a single pregnancy has been observed in our termination clinic when these methods were used without rhythm, and when there was immediate penile withdrawal following ejaculation. These couples are rejecting Madam de Sevigne's admonishment to her daughter that "the condom is an armor against enjoyment and a spiderweb against danger." But the condom has been improved considerably since the middle of the 1600s when that statement was written.

The *diaphragm* is an excellent method of contraception, however

1. It requires careful fitting by conscientious health personnel who point out the following very specific requirements for proper diaphragm use:
   a. The diaphragm must not be used in association with rhythm.
   b. It must be used before any intromission, even during menstruation.
   c. A teaspoonful of contraceptive jelly must be placed in the cup of the diaphragm and a one-half-applicator amount of a contraceptive jelly must be placed in the vagina after the diaphragm has been seated.
   d. Proper positioning of the diaphragm must be checked by placing the fingers in the vagina, to ascertain that the diaphragm covers the cervix. This is particularly true of patients whose uterus is in third degree retroposition.
   e. If multiple coitus occurs before the diaphragm is removed, it must be checked for proper positioning and an additional one-half applicator of jelly added to the vagina.
2. The diaphragm must be cared for properly by drying and powdering after each use and inspecting for tears or defects each time it is introduced into the vagina.

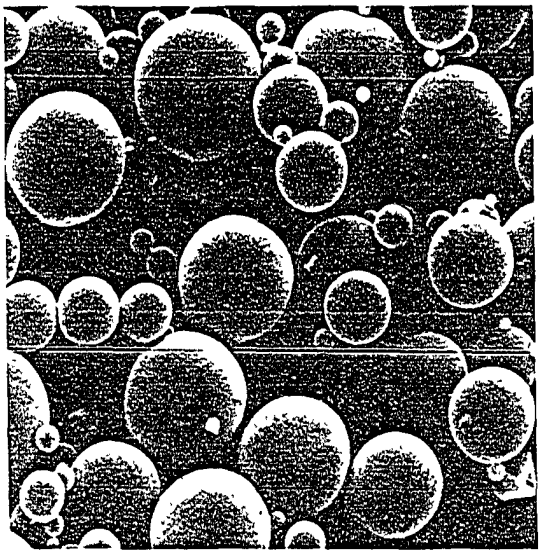

FIG. 2-5. Scanning electron micrograph of d, l–polylactic acid microcapsules containing 20% progesterone by weight. Microcapsules, when placed in vagina of baboon, release progesterone for 30 days.

Successful use of the diaphragm requires a patient who is intelligent, motivated, conscientious, and perhaps, somewhat obsessive.

Pregnancy rates for any method of contraception should be reported according to the theoretical rate of pregnancy and also the actual rate of pregnancy which occurs with use by the general population. These rates are difficult to establish for the diaphragm and are only valid when they are carefully collected and then analyzed on the basis of all the requirements for the proper use of the diaphragm, as well as such factors as age, race, religion, fertility, years of education, social class, occupation of partner, etc.

Failure rates as low as 2% have occurred when the diaphragm was consistently used, according to the criteria which have been presented. The greatest detriment to successful diaphragm use is combining it with rhythm. However, there are some diaphragm failures due to the orgasmic response of the vagina. The elongation and ballooning of the upper one–third of the vagina and the elevation of the cervix allows penile thrusting to displace the diaphragm from the cervix. It is for this reason that a contraceptive jelly should be used in front of and behind the diaphragm. Because the diaphragm is assuming a more important place as a method of contraception and because the anatomical changes within the vagina during sexual excitement reduce its effectiveness, more efficient spermicidal agents with greater surface tension between the jelly and the vagina are needed.

The vagina's rich circulation allows its rapid growth and desquamation and assists in the maintenance of its immune capacity. It facilitates the production of glycogen and provides the physiologic fluids which produce the transudation for lubrication during sexual excitement. Fortuitously, this

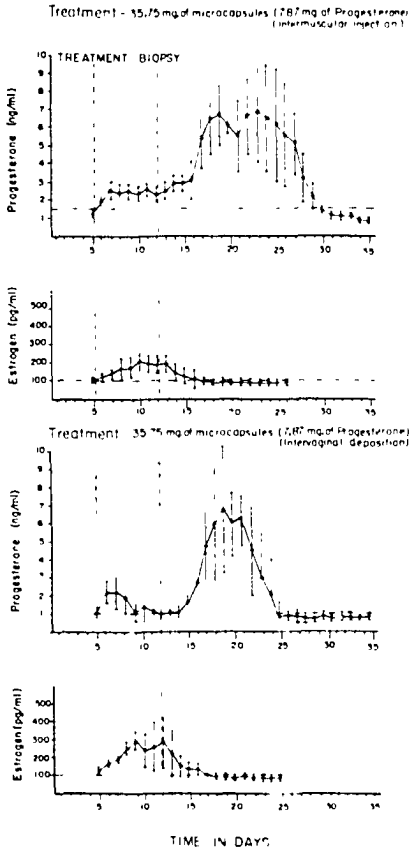

FIG. 2-6. Mean levels of immune reactive progesterone and estrogen in baboons treated by intramuscular injection (top) or intravaginal deposition (bottom) of d, l–polylactic acid microcapsules of type shown in Figure 2-1. Dose was 35 mg microcapsules containing 8 mg progesterone. Transcervical uterine biopsies performed on day 12 of menstrual cycle showed distinct progestational effect in both study groups. These preliminary studies indicate that progesterone microcapsules, when placed in vagina early in follicular phase of cycle, induce alterations in the endometrium. Further studies are planned to evaluate utility of intravaginal microcapsules for regulation of fertility.

same vaginal circulation allows venous drainage directly into the uterus, fallopian tubes, and ovary. Thus, the vagina can absorb and transport substances of low molecular weight. It can also transport antibodies, steroids, prostaglandins, prostaglandin analogues, and other pharmacologic agents. These might affect implantation, tubal, cervical, and uterine motility, as well as corpus luteum function and gonadotropin release (1). This property of the vagina may prove to be extremely advantageous because small doses of various agents, even toxic ones, might be given without traversing the gastrointestinal tract or entering the general circulation. Mishell and his associates have employed this property of the vagina by impregnating Silastic rings with progestins. The distensibility of the vagina allows the rings to remain in place without discomfort and the Silastic allows slow release of the steroids. The vaginal circulation permits absorption of the progestin directly into the general circulation where it may affect gonadotropin release or may be transmitted directly to the endometrium, fallopian tube, or ovary (7).

One of the most promising uses of the vagina as an adjunct for contraception is the employment of biodegradable microcapsules. These microcapsules are made by combining completely biodegradable nontoxic polymers

with various steroids, prostaglandins, or spermicidal agents (2). Microcapsules presently available measure from 125–200μ in diameter and contain 20% norethisterone by weight. They may be injected in combination with saline through an 18-gauge needle, and they provide six months of contraception by producing gonadotropin dysrhythmia. Studies are currently underway, however, to test the effectiveness of microcapsules that have been reduced in size to approximately 43–60μ (sperm heads measure approximately 5μ in diameter) and are adapted for intravaginal delivery using progestin or progesterone (Figure 2-5). These vaginal capsules are now ready for clinical testing. They have a one-month supply of progesterone or progestin release. The microcapsules allow medication of the endometrium by employing the villi of the cervix and endometrium to transport the microcapsules from the vagina into the endometrial cavity. It is therefore possible to deliver medication to the endometrium without the use of an intrauterine device or Silastic ring (Figure 2-6).

Because conception begins in the vagina, it is reasonable to develop methods of contraception that originate there. A basic understanding of the anatomy, morphology, and physiology of the vagina is necessary in order to improve upon present contraceptive techniques.

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3

Sperm Migration in the Female Genital Tract

KAMRAN S. MOGHISSI

Development of improved and more effective contraceptives depends largely on a better understanding of the physiologic processes involved in human reproduction. Only then can elective and specific steps be taken to inhibit or enhance fertility without significant alteration of other bodily functions. Among many unanswered questions regarding the human reproductive process, none is more important or intriguing than the mechanism of sperm migration and survival in the female reproductive tract. How do sperm reach the site of fertilization? How could their transport and survival in the female genital tract be inhibited or enhanced? Many basic concepts emerging from animal studies regarding these issues remain unconfirmed in humans.

In this report, the accumulated knowledge concerning sperm migration in the human female will be reviewed. Related human and animal studies will be considered.

I. SPERM MIGRATION THROUGH THE HUMAN CERVIX

Approximately 200 to 500 million sperm are deposited on the cervix and posterior vaginal fornix during a normal coitus. Human semen coagulates immediately after ejaculation and traps most sperm cells until seminal proteolytic enzymes bring about liquefaction. The first portion of the ejaculate contains three-fourths of the sperm, which under favorable conditions, quite promptly penetrate the cervical secretion (22). Because sperm are quickly destroyed by vaginal acidity, their entrapment in the coagulum until liquefaction takes place may be considered as a protective device to prevent their demise.

In vitro studies have shown that nonliquefying semen samples are lysed when treated with an acid buffer. It is thus possible that vaginal acidity enhances liquefaction of the seminal coagulum. Indeed, complete liquefaction of the seminal clot *in vivo* appears to occur somewhat faster after ejaculation (44).

In women, the vaginal content is usually acid, with a pH of about 3 to 5. However, cervical secretions coating the upper part of the vagina and its fornices considerably increase the alkalinity of vaginal milieu. They provide a favorable medium for sperm and appear to promote their motility and longevity.

Seminal plasma, an alkaline fluid, has a buffering effect upon the vaginal acidity and changes the vaginal pH, thus smoothing the transition of sperm from the semen into the cervical mucus. Fox *et al* (13) measured vaginal pH continuously during coitus by telemetry and observed that 8 sec after ejaculation the pH of the vagina rose from 4.3–7.2.

Sperm migration through the cervix involves three distinct but interrelated factors: the ability of sperm to penetrate the mucus by their intrinsic motility; the fibrillar structure of cervical mucin enabling it to participate actively in the process of sperm transport; and the morphologic configuration of cervical crypts which contribute to the storage and preservation of sperm in the cervical canal, and their sustained and prolonged release to the upper tract.

Sperm are highly active cells possessing the enzymes required to carry out the biochemical reactions of the Embden-Meyerhof pathway, tricarboxylic acid cycle, fatty acid oxidation, electron transport system, and, perhaps, the hexose monophosphate shunt. The metabolic and glycolytic enzymes are apparently located in the tail portion, and the respiratory enzymes are confined to the mitochondria. Despite the assistance the sperm may derive from uterine contractions during the ascent in the female reproductive tract, their own motility is essential for reproductive performance.

Sperm are capable of metabolizing a variety of exogenous and some endogenous substrates. Because they possess only a negligible reserve of endogenous glycogen, they must depend on extracellular carbohydrates for energy under anaerobic conditions and during their passage through the mucus.

Glucose is the major fuel used by human spermatozoa in the female reproductive tract. Fructose and mannose are also rapidly utilized *in vivo* by spermatozoa. Fructose is the sugar found in largest quantity in human semen (average 300 mg:100 ml). However, the affinity constant for glucose utilization by spermatozoa is nearly 30 times greater than that for fructose.

Cervical mucus contains reducing substances throughout the cycle and, at times, amounts comparable to those reported for semen. These include glycogen, glucose, mannose, and maltose. Amylase, an enzyme capable of reducing glycogen to glucose, is also found in cervical mucus.

Human seminal plasma contains a proteolytic enzyme called seminin (chymotrypsin–like enzyme). Sperm also show seminin activities similar to seminal plasma. In addition, a trypsin–like enzyme (acrosin) hyaluronidase (a corona-penetrating enzyme), and ATPase activity have been demonstrated in the sperm acrosome. Seminin is either localized in the soluble cytoplasmic portions of the sperm or, more likely, is adsorbed from the seminal plasma by the sperm cell. The involvement of these proteolytic enzymes in sperm penetration in cervical mucus will be considered.

CERVICAL SECRETION

Cervical mucus is a complex secretion produced constantly by the secretory cells of the endocervix. A small amount of endometrial, tubal, and, possibly, follicular fluid may also contribute to the cervical mucus pool. In addition to these, cellular debris from uterine and cervical epithelia and leukocytes are also present. According to Odeblad (37) there are approximately 100 mucus–

secreting, glandular-like units (crypts) in the cervical canal. Based on histologic preparations obtained from serial sections, Bernstein *et al* (3) estimated the total number of crypts per cervix to be about 10,000. In progestogen-treated women the cervix was found to contain approximately 9,000 crypts.

These secretory units produce mucus at the rate of 20–60 mg/day in normal women of reproductive age. During midcycle, the amount increases ten to 20-fold and may reach up to 700 mg/day (33, 39). Cervical mucus is a heterogeneous secretion which reveals a number of rheological properties such as viscosity, flow elasticity, spinnbarkeit, thixotropy, and tack, or stickiness.

Cervical secretion contains about 92–94% water. At ovulation, when mucus is most abundant, the water content rises to 98% (39). Inorganic salts in the mucus amount to 1%, of which the principal constituent is NaCl (0.7%). Traces of potassium, magnesium, calcium, copper, zinc, iron, phosphate, sulphate, and bicarbonate are also present (27). Low-molecular-weight organic compounds present include the free simple sugars such as glucose, maltose, and mannose, and amino acids. High molecular-weight compounds include glycogen, proteins, enzymes (such as amylase, alkaline phosphatase, esterase, aminopeptidase), certain components of fibrinolytic enzymes, and enzyme inhibitors (27).

The most important constituent of cervical mucus is a hydrogel, rich in carbohydrates and consisting of glycoproteins of the mucin type (35). Most of the physical properties of cervical mucus are due to these mucins. Biochemical and biophysical studies have demonstrated that cervical mucin is a fibrillar system consisting of a supramolecular assembly of glycoprotein subunits (4, 38). These glycoprotein fibrils have a protein backbone with oligosaccharide side chains attached to terminal sialic acids and fructose. Disulfide bonds and hydrophobic interactions are apparently involved in maintaining the association of mucin subunits among themselves and with other proteins in the gel phase.

Lee *et al* (21) have studied cervical mucin by laser light-scattering spectroscopy and believe that the mucin of human midcycle cervical mucus corresponds to an ensemble of loosely intra- and interwoven entanglements of randomly coiled macromolecules. According to this model, the viscoelastic properties of cervical mucus result mainly from entanglement of the mucin macromolecules in an arrangement closely resembling the molecular configuration of raw rubber.

Variations in the structure and viscosity of these glycoproteins are responsible for periodic receptivity and inhibition of cervical secretion to sperm penetration. Proteolytic enzymes, such as trypsin and chymotrypsin, have been found readily to hydrolyze human mucus and mucins, and to produce certain physical and chemical changes.

CYCLIC CHANGES OF CERVICAL MUCUS AND THEIR RELATION TO OVULATION AND SPERM MIGRATION

The secretion of cervical mucus is regulated by ovarian hormones. Estrogen stimulates the production of copious amounts of watery mucus, while progesterone inhibits the secretory activity of cervical epithelial cells. The physi-

cal properties and certain chemical constituents of cervical mucus show cyclic variations, and their determination may be used to evaluate indirectly the amount of circulating sex hormones, which can then be applied to detect the occurrence of ovulation. Cyclic alterations in the constituents of cervical mucus may also influence sperm penetrability, nutrition, and survival. Figure 3-1 (32) shows serial determinations of important properties of human cervical mucus, tested during a normal menstrual cycle in ten women, in relation to pituitary and ovarian hormone secretion and *in vitro* sperm penetration. These data clearly demonstrate that optimal changes of cervical mucus properties, such as greatest increase in quantity, spinnbarkeit, ferning, pH, and decrease in viscosity and cell content, occur immediately prior to ovulation, and are reversed after ovulation. Preovulatory mucus is most receptive to sperm penetration. The proportion of saline in cervical secretion directly determines the consistency of the mucus and the rate of sperm penetration.

During pregnancy, cervical secretions form a highly viscous, thick, and turbid gel which occludes the cervical canal. This mucus plug acts as an effective barrier against the invasion of the uterine cavity by both sperm and bacteria.

Sperm penetrability of human cervical mucus begins on approximately the ninth day of a normal cycle, and increases gradually to a peak at ovulation. It is usually inhibited within 1 or 2 days after ovulation, but may persist to a lesser degree for a longer period (29, 43). In some women, sperm penetrability occurs only during a limited period of the menstrual cycle. Individual variations are common. Familiarity with this process is of considerable importance since sperm migration studies timed inappropriately may lead to erroneous interpretations.

RELATIONSHIP OF CERVICAL GLANDULAR STRUCTURE TO SPERM TRANSPORT

The human uterine cervix is a thick-walled cylindrical structure which tapers off at its inferior extremity. Studies in women, in primates, and in rabbits suggest that the basic epithelial structure of the cervical mucosa is an intricate system of clefts or crypts which, grouped together, give an illusory impression of glands. These crypts may run in an oblique, transverse, or longitudinal direction, but never cross one another, although they may bifurcate or extend downward (35). Endocervical mucosa is comprised of different types of secretory and ciliated cells. The percentage of ciliated cells varies in different species and is about 5% in women. The secretory cells are responsible for mucus secretion, while the ciliated cells are concerned with the discharge of the mucus, cell debris, and exfoliated cells into the vagina.

Mattner (24, 25) was first to demonstrate that the sperm in the cervices of ruminants following mating are not uniformly distributed within the lumen, but tend to be aggregated at, or near the mucosa. According to Mattner, under natural conditions, the line of strain will originate at the mucus-secreting epithelium and pass through to the anterior portion of the vagina. On entering the mucus, sperm are constrained to follow these pathways, and pass to the mucosa of the cervix rather than penetrating directly to the uterus. Return of sperm along strain lines to the vagina is prevented by a series of intervening strain lines, each tending to reorient the sperm back toward the crypts.

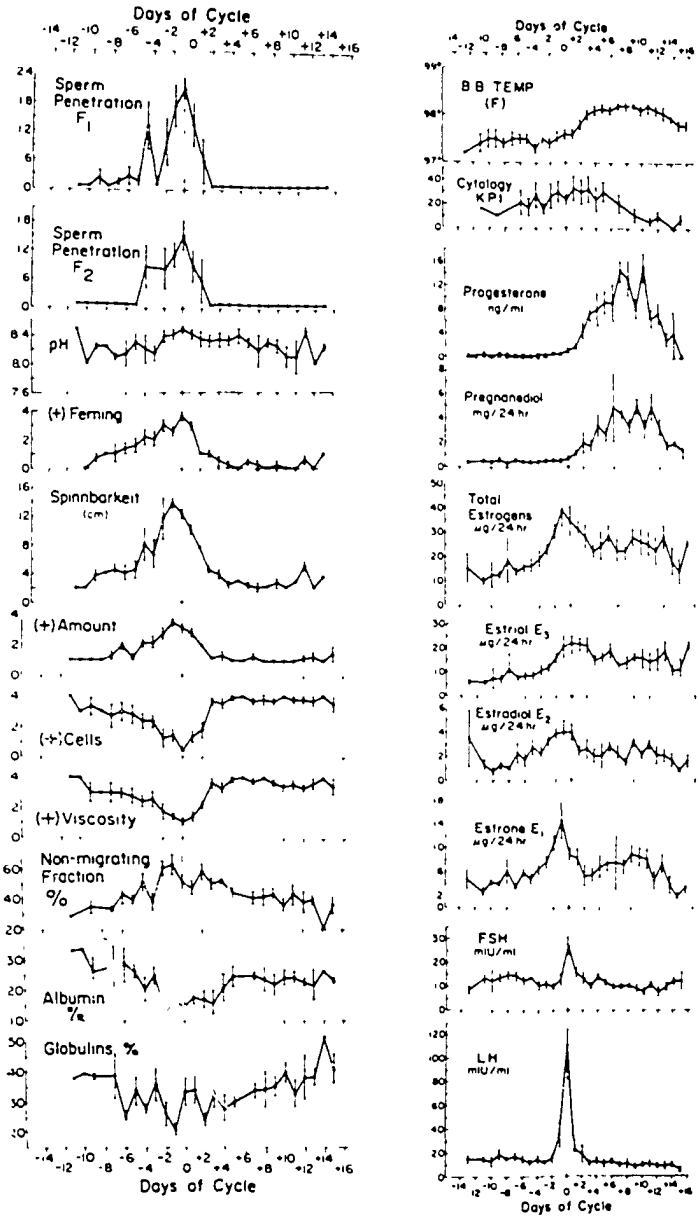

FIG. 3-1. Composite profile of serum gonadotrophin and progesterone; urinary estrogens and pregnanediol; basal body temperature (BBT); karyopyknotic index (KPI) of vaginal cytology; and cervical mucus properties throughout the menstrual cycle in 10 normal women. Day 0 = day of LH peak (dotted line). Vertical bars represent one standard error of the mean. F_1 and F_2 indicate the number of sperm in the first and second microscopic fields (200×) from interface 15 minutes after the start of the *in vitro* sperm–cervical mucus penetration test. (Moghissi KS, Syner FN, Evans TN: Am J Obstet Gynecol 114: 405, 1972)

Such a process could cause aggregation of a large number of sperm in the crypts of cervical mucosa, where they are stored and released at a constant rate into the uterus. Sperm are thus retained in the cervix despite the continued flagellation and the drainage of mucus from the cervix into the vagina. In support of this theory, Mattner (24, 25) has demonstrated that only motile sperm accumulate in the crypts of the cervical canal, where, in addition, they are protected from phagocytosis. The presence of sperm in the genital tract results in an increased number of leukocytes in the lumen of the uterus and cervix. In the cervix, the majority of leukocytes occur in the central mass of the mucus. The resulting separation of sperm and leukocytes in the cervix is, according to Mattner (25), an important factor in the survival of an adequate population of sperm in the cervix. Dead sperm cells also are confined to the central portion of the lumen, and are eliminated from the cervix. Similar observations have been made in subhuman primates in our laboratories.

The preferential accumulation of sperm in the vicinity of the mucosa and within cervical crypts in women has been demonstrated only indirectly. Certain similarities between the epithelial structure of the human cervix and cervical mucus and those of subhuman primates suggest, however, that an identical or closely related process may also be operative in women.

MECHANISM OF SPERM PENETRATION IN CERVICAL MUCUS

Sperm transport studies through the human cervix are fraught with considerable difficulties. Although cervical mucus in women can be readily sampled, the amount obtained is too small for large-scale assays. It is also difficult, if not impossible, to plan and execute experiments similar to those performed in animals, which have yielded so much valuable information on sperm transport through the cervix. By necessity, much of our knowledge of the mechanism of sperm penetration in human mucus is based on *in vitro* studies. Supporting *in vivo* data are confined to postcoital tests, uterine aspiration, and recovery of sperm from various segments of the reproductive tract during surgery or in operative specimens.

In Vitro Studies

Two different techniques have been used for *in vitro* investigation of sperm penetration of cervical mucus: the slide method and the capillary–tube system. The slide method is most useful for initial phases of sperm-migration studies. The capillary-tube system provides additional information with respect to sperm survival and depth of penetration into the mucus.

In *in vitro* studies (28) using the slide method, a sharp boundary is observed separating human cervical mucus and semen on a microscope slide. At the interface, finger–like projections, or phalanges, of seminal fluid develop within a few minutes and penetrate the mucus. Sperm usually fill these canals before entering the mucus. Most sperm cells penetrate the apex of the phalangeal canal and enter the mucus. In most instances, a single sperm cell appears to lead a column of sperm into the mucus. After the initial resistance has been overcome by the leading sperm, others follow without diffi-

culty. Once in the cervical mucus, sperm fan out and move at random. Some return to the seminal plasma layer, while most migrate deep into the cervical mucus, until they meet with resistance from cellular debris or leukocytes. They then either stop or change direction. Both phalanx and interface formation appear to be physical phenomena resulting from the contact of two biologic fluids of differing viscosities and surface tensions. They are observed more prominently in samples of mucus with relatively high viscosity, but are not seen in samples of mucus treated with proteolytic enzymes.

Phalanges increase the surface area between seminal fluid and cervical mucus and trap small pockets of semen within the mucus, which protects a number of sperm from the hostile environment of the vagina. This phenomenon may account for repeated observations of the passage of inert particles through cervical mucus. Phalanx formation, therefore, appears to facilitate sperm migration.

Cleanliness of mucus appears to be a factor favoring sperm migration. Cellular debris and leukocytes thus halt the progress of sperm in mucus. There is no resistance to sperm migration in thin mucus, but viscous mucus forms an impenetrable barrier. Viscous cervical mucus diluted artificially with normal saline or 5% dextrose is more readily penetrated by sperm than undiluted mucus (28).

Some relatively viscous samples of cervical mucus present a high degree of surface tension, and thus appear to be initially impenetrable by sperm. When these samples are mixed with semen, sperm invasion may occur in certain instances. This *in vitro* mixing test (M test) is a useful device to determine further the ability of sperm to penetrate the mucus, particularly when it is realized that during coitus such mixing of cervical mucus and semen commonly takes place.

SPERM PENETRATION IN FRACTIONATED MUCUS

Cervical mucus can be fractionated by ultracentrifugation. The supernatant contains the proteins, electrolytes, amino acids, sugars, and other organic substances. The sediments consist of the mucins. Sperm penetration has been studied in our laboratories using the cervical mucus supernatant (CMS) and mucins (CMM).

In vitro tests of sperm penetration in CMS showed no evidence of phalanx formation. Sperm movements in the CMS were jerky and abnormal, and longevity was reduced. On the contrary, CMM, reconstructed with 5% dextrose to the original dilution, behaved much like the initial mucus regarding sperm penetration. Phalanx formation similar to that of preovulatory mucus was observed, and sperm readily penetrated the reconstructed CMM, swimming in a normal and progressive manner.

EFFECT OF SPERM DILUTION

In normal saline, a decrease has been observed in the motility of bull, ram, and rabbit sperm at dilutions beyond 10^6 cells/ml. (47). In cervical mucus, however, sperm withstand indefinite dilution. In man, with a sperm sample of good motility, dilution to one million cells/ml does not affect the rate of

sperm migration in the mucus. The depression of motility at low cell concentration appears to be due to the dilution of seminal plasma and to the loss of substances from the sperm. Cervical mucus, like seminal plasma, appears to have a protective effect upon the sperm, and presumably acts by preventing the escape of intracellular constituents or surface components. Sperm are quite resistant to the effect of dilution in washed-mucus gel, freed of soluble components. However, when the rheological properties of mucus are destroyed, a marked dilution effect occurs when sperm are suspended in the medium. According to Tampion and Gibbons (47), the physical properties of glycoproteins of the mucus are the effective factors which protect sperm cells. When sperm emerge from the cervical secretion, they are susceptible to the lethal effects of dilution.

SPERM VELOCITY IN CERVICAL MUCUS AND OTHER MEDIA

It has been demonstrated that sperm from various species, including humans, readily penetrate a number of physiologic solutions and blood serum. However, with the exception of blood serum and normal saline, the progression rate of human sperm in these media is less than that in cervical mucus. Sperm cells perish instantly in distilled water.

The rate of sperm progression in cervical mucus has been determined by several investigators using the capillary–tube technique. The speed of penetration in human mucus varies during the menstrual cycle from 0.1–3 mm/min, and is greatest in preovulatory mucus (20).

The extent and depth of sperm penetration in a given sample of cervical mucus bears a direct relationship to sperm density and motility. Higher sperm density and greater motility are associated with more massive penetration into the mucus. Dead or immotile sperm do not penetrate cervical mucus. Freeze preservation of semen also reduces the ability of sperm to penetrate cervical mucus. However, when liquid nitrogen is used for storage, this reduction is limited to a degree that might still be compatible with fertility, even for storage periods approaching 3 years (12).

Broer *et al* (7) have shown that the Y-chromatin-positive spermatozoa penetrate more readily into the cervical mucus, in which their relative number is greater in samples collected postcoitally than in the ejaculate. Temperature affects the rate of sperm motility and metabolism. Higher temperatures increase the metabolic rate and correspondingly decrease the life span. *In vitro* sperm migration tests performed at 22°, 30° and 37°C have, however, yielded similar results.

In Vivo Studies

Most *in vivo* experiments in man confirm the *in vitro* findings previously cited. There is still controversy as to the significance of sperm found in cervical secretions several hours after coitus. Some investigators have suggested that they consist mainly of sperm populations of poor quality, which have failed to complete their passage of the uterus.

Grant (17) compared the results of postcoital tests and endometrial aspirations in 920 women, and found that motile sperm were present in the uteri of 10% of the subjects studied, although they could not be demonstrated in

the cervical mucus. An explanation for this finding may be that, in cases of oligospermia or when cervical mucus is relatively hostile, the more vigorous and healthier sperm penetrate the cervix and reach the uterine cavity shortly after coitus (rapid phase of sperm transport). Other sperm, which are normally stored in cervical crypts and mucus, do not survive long enough to be detected.

The postcoital test provides valuable information on sperm migration and survival and correlates well with *in vitro* tests (11). Rapid postcoital penetration of sperm in cervical mucus has been observed repeatedly. Sobrero and MacLeod (44) performed immediate postcoital tests in 47 couples and demonstrated the presence of motile sperm in samples of cervical mucus 1.5–3 min following ejaculation. In about 15 min, 1 of every 2000 sperm deposited in the vagina may be recovered from the cervix (41).

Serial postcoital tests have shown that the increased fluidity and spinnbarkeit of preovulatory cervical mucus coincides with a greater number of motile sperm in mucus samples (45). After ovulation, the mucus becomes thick, and few, if any, live sperm cells are found in the mucus. Combined postcoital tests and endometrial aspirations have demonstrated that the greatest number of sperm in the endometrial cavity are found at, or near, the time of ovulation. Very few were present in the uterus during the luteal or early follicular phases of the cycle (15).

Settlage *et al* (41) found a direct relationship between the numbers of motile sperm artificially inseminated and those recovered from the cervical mucus. The ratio of cervical mucus sperm to inseminated sperm was fairly constant from 15 min to 24 hr after insemination. By 48 hr the number of sperm in cervical mucus was negligible.

The postcoital test has also been correlated with the occurrence of pregnancy. Jette and Glass (18) found that the pregnancy rate in 555 infertile women was significantly higher in the presence of a favorable cervical mucus and when there were more than 20 sperm per high-power field (HPF = 400×) in the mucus as demonstrated in postcoital tests.

Moghissi (34) compared the results of the best postcoital tests of 57 infertile women who became pregnant to those of 143 who did not. The mean number of sperm/HPF in cervical mucus for the pregnant group was significantly higher than for those who failed to become pregnant.

FRACTIONAL POSTCOITAL TESTS

Fractional postcoital tests (*i.e.*, separate sampling of lower and upper parts of the cervical canal) in normal women have shown that, for up to 2 hr, the lower part of the cervical canal contains a larger number of sperm than the upper portion. Thereafter, the relative count in the upper part of the canal increases gradually. After 6 hr, the mucus collected from the upper half of the cervical canal usually contains a greater number of motile sperm than the lower half.

SUCTION THEORY

It has been suggested that during coitus the muscular activity, or respiratory effort, of the uterus causes a sucking-in of semen, and in this way sperm migration is aided (14).

A number of *in vitro* and *in vivo* studies have failed to confirm these observations. Noyes *et al* (36) could not demonstrate aspiration of radio-opaque oil in the reproductive tract of rabbits. Sobrero (43) was unable to observe any movement of glairy mucus from the cervix in more than 100 women during the fertile period, in the course of forcible inhalation and exhalation. In another series of experiments, he fit a group of women with a snug cervical cap containing water-soluble, opaque material or normal semen mixed with an opaque medium. Pelvic radiography, before and after masturbation and/or coitus with and without female orgasm, failed to show evidence of any radio-opaque material beyond the vagina.

Postcoital tests as early as 1.5–3 min after ejaculation have not shown any mixture of cervical mucus and semen, or the presence of male urethral epithelial cells or vaginal epithelial cells in the mucus (44). Furthermore, in these tests, the distribution of sperm in cervical mucus has been found to be uniform and in lower concentrations than in the vaginal pool, indicating an orderly and uniform sperm penetration, rather than *en bloc* insemination.

Masters (23) did not observe any displacement of the cervical plug during coitus, nor was he able to demonstrate the entry of radio-opaque fluid from a cervical cap into the uterus after coitus or clitoral stimulation. The only definitive response of the cervix to sexual stimulation appears to be a minimal dilatation of the external os. The strongest argument against the suction theory is that artificial insemination in women, with deposition of semen in the vagina or on the cervix, is followed by a high rate of pregnancy. Orgastic reaction and seminal aspiration could hardly be implicated under these conditions.

THE RELATION OF MOLECULAR STRUCTURE OF MUCUS TO SPERM TRANSPORT

Although sperm appear to move at random in the cervical secretion, they may move along strands of cervical mucus. Tampion and Gibbons (46, 47) suggested that bull sperm travel in threads of bovine mucus following the path of least resistance, and are oriented along the lines of strain, that is, parallel with the direction of elongation of the molecules. It is readily apparent that the shape of the sperm cell would favor its movement through mucus in this manner rather than by passing across the molecular network. According to Gibbons and Mattner (16), when progression of a sperm in mucus is impeded, the sperm cell usually resumes its forward course with a sudden deflection onto a parallel path, as if it had broken obliquely through the laterally restraining glycoprotein strands. *In vitro* studies using human sperm and cervical mucus confirmed this phenomenon (20).

Odeblad has suggested that, at midcycle, human cervical mucus is composed of flexible, threadlike molecules (micelles) of cross-linked glycoprotein networks. This model implies that the micelles have a diameter of about 0.5 μ. The intermicellar spaces, averaging 3μ apart, are filled with a complex cervical plasma. The micelles are looked upon as harmonic oscillators. It has been suggested that spermatozoa swim into these spaces and are assisted in their forward progression by the thermal modulations of the macromolecules, which cause the cavities with low-viscosity water to expand and contract, more or less rhythmically. The expanded regions propagate in the

mucus, conveying the swimming spermatozoa through the cervical canal with a minimum of energy expense (37, 38). It has been stated also that during the luteal phase, or in women receiving progestogens, the number of cross linkages increase, some water is lost, and the mucin assumes an arrangement of a much more dense network—a most effective barrier to sperm transport. Lee *et al* (21), on the basis of laser light scattering and cinematographic studies, have indicated that midcycle cervical mucus is composed of an ensemble of entangled, random-coiled macromolecules rather than a fibrillar system. This model suggests that the cyclic variation in the viscoelastic properties of cervical mucus is dependent on the amount of fluid in which the glycoproteins are entangled. High-speed cinematography, according to these investigators, indicates that the pioneering spermatozoa reorient local molecular arrangement and allow the other sperm which follow to move forward with much less inhibition.

THE ROLE OF PROTEOLYTIC ENZYMES IN SPERM TRANSPORT

Human seminal plasma and sperm contain several proteolytic enzymes (previously outlined). Addition of commercial pancreatic trypsin or chymotrypsin (*in vitro*) to semen or cervical mucus facilitated sperm migration (*in vitro*), when studied by the slide method. Similar studies in a capillary tube showed a slight decrease in the depth of penetration. Incubation of cervical mucus with isolated and purified seminal protease caused hydrolysis of the mucus, followed by accelerated sperm migration. The addition of seminal protease to freshly ejaculated semen also enhanced sperm migration. Ferning and spinnbarkeit decreased when cervical mucus was subjected to proteolytic digestion by adding chymotrypsin or seminal protease. Hydrolysis of cervical mucus by proteolytic enzymes was also followed by a marked reduction in its viscosity, and dissolution of gel structure. Disc gel electrophoresis of hydrolysed mucus or mucins showed a complete disappearance of nonmigrating mucin, and the appearance of a broad, intensely stained band which migrates into the gel. Sperm migration has also been studied in our laboratory in cervical mucus treated with purified human acrosin. A significant increase in sperm penetrability was observed in samples of cervical mucus incubated with acrosin when the slide test was used. In experiments where capillary test tubes were employed, a slight increase in the first centimeter was seen in acrosin-treated preparations. However, there were fewer sperm reaching the second and third centimeter levels. The impression gained from these studies is that proteolytic enzymes, including acrosin, increase the initial invasion of sperm into cervical mucus. However, because they alter the mucin structure, they may impede the depth of penetration. One may speculate that the release of acrosin from the acrosomal cap of live or dead sperm may be important during the initial phase of sperm penetration into the cervical mucus. However, the amount of acrosin released from sperm in cervical mucus may be insufficient to digest cervical mucus micelles and interfere with directional progression of sperm.

Van Bruggen and Kremer (48) have performed electron microscopy of bovine estrus and human midcycle cervical mucus. They demonstrated long, filamentous structures, often randomly aggregated in complicated networks.

Other studies (8) have confirmed the presence of long filaments and their linear orientation at midcycle. Digestion with the proteolytic enzyme, pronase, completely destroyed the filamentous structures (48). These morphological observations confirm the reported biochemical and physical changes following hydrolytic digestion of the cervical mucus. Odeblad (38), using nuclear magnetic resonance and rheological techniques, described a similar meshlike structure. The aqueous spaces between the micelles allow the passage of sperm, as well as the diffusion of soluble substances. This type of mesh is brought about by estrogen (E-type mucus). During the luteal phase, or under the influence of gestagens, the mesh size was significantly smaller and intertwined (G-type mucus).

Odeblad substantiated Tampion and Gibbons' observations (46) that sperm migration occurred within certain mucus channels. Proteolytic enzymes may hydrolyse the backbone protein and reduce the network to a less resistant mesh with more open channels for the passage of sperm. It is also possible that the escape of sperm from the cervical crypts may be opposed by filaments of glycoprotein, and that these chains are hydrolysed by protease from the sperm head.

Cervical mucus contains alpha$_1$-antitrypsin which may inhibit the activity of trypsin and acrosin. At midcycle, when the mucus is most receptive to sperm penetration, the alpha$_1$-antitrypsin content of cervical mucus is lowest.

CERVICAL MUCUS PH AND SPERM MIGRATION

Sperm are susceptible to changes in the pH of cervical mucus. Acid mucus immobilizes sperm, whereas alkaline mucus enchances their motility. Excessive alkalinity of cervical mucus (over 8.5) may also adversely affect the viability of sperm. The optimal pH for sperm migration and survival in cervical mucus is between 7 and 8.5 (28). This is the pH range of normal midcycle cervical mucus (Fig. 3-1).

THE EFFECT OF IMMUNE ANTIBODIES ON SPERM MIGRATION

Human cervical mucus contains immunoglobulins A (IgA), G (IgG), and traces of M (IgM), and secretory IgA. IgG is the most constant constituent and is found in almost all samples of cervical mucus (35). The presence of IgG, IgA, and IgM in the luminal contents of cervical crypts, basement membrane, and in the interstitium has been demonstrated by immunohistological studies. In addition, small numbers of IgG- and IgA-staining lymphoid cells have been observed in the stroma of cervical biopsy specimens. Secretory piece-staining (a component of secretory IgA) has been demonstrated in the endocervical epithelium.

Biosynthesis of IgG and IgA in the uterine, cervical, and vaginal tissues of the rabbit and the cervical tissues of women has been reported (2). A higher ratio of IgA:IgG was found in cervical tissue cultures than previously reported in cervical mucus.

Several antigenic systems are known to be present in the mammalian (including man) semen and sperm cells. They include species-specific and sperm-specific antigens and blood group, transplantation, sperm coating

and seminal plasma antigens. These antigens elicit various responses in the female reproductive tract.

In vitro studies have shown that sperm obtained from men with circulating sperm antibodies exhibit abnormal patterns when tested for penetration in cervical mucus. Low concentrations of sperm autoantibodies reduce the sperm motility in mucus, whereas high concentrations decrease both the sperm motility and the extent of sperm penetration. The antibodies responsible for this effect are agglutinating and immobilizing, and seem to be of the 7S variety. The binding sites of these antibodies on sperm are in the middle piece and tail of the cell membrane (12).

Animal experiments have demonstrated that exposure of cervical tissue to antigenic substances, such as sperm antigens, elicits a local immune response which is probably unrelated to the systemic rate of antibody production. Furthermore, these immune antibodies appear in cervical secretion and are capable of reacting with their specific antigens, thus immobilizing or agglutinating the sperm during their passage through the cervical canal. This concept is supported by several clinical observations. Cytotoxic antisperm antibodies of the IgG type have been demonstrated in the cervical mucus and serum of infertile women. Shulman *et al* (42) found an incidence of 7.5% and 40.3% respectively of sperm-agglutinating and -immobilizing antibodies in the cervical mucus of infertile women.

Our preliminary studies (34) have revealed that cervical mucus of 52% of patients with unexplained infertility contain sperm-agglutinating antibodies (24%), sperm-immobilizing antibodies (8%), or both (20%). With one exception, all of these women had negative or poor postcoital tests, even though analysis of the husband's semen in the woman's cervical mucus was associated with a normal postcoital test. Circulating sperm antibodies did not cause a deterioration of postcoital test results.

HORMONAL CONTROL OF CERVICAL SECRETIONS AND THE EFFECT OF GESTAGENS ON SPERM MIGRATION THROUGH MUCUS

Secretory activity of cervical epithelium is controlled by sex hormones. Increasing amounts of endogenous estrogen during the preovulatory phase of the cycle, or the administration of synthetic estrogens, results in the production of copious amounts of a thin, watery, alkaline, and acellular cervical secretion with intense ferning, spinnbarkeit, and sperm receptivity (Fig. 3-1). Endogenous progesterone, in the luteal phase of the cycle or in pregnancy, causes the production of scanty, viscous, and cellular mucus with low spinnbarkeit and absence of ferning. Sperm are unable to penetrate progestational cervical mucus in appreciable numbers (29, 39). Other constituents of cervical mucus such as proteins, enzymes, and electrolytes are sensitive to hormonal changes (27, 35). The surface tension and conductivity of mucus are also controlled by estrogen and progesterone.

All synthetic oral and parenteral gestagens, alone or in combination with estrogen, to some degree inhibit mucorrhea and sperm penetration through the cervical mucus (31, 51). The extent of their inhibitory activity depends on the type, dosage, and, probably, the duration of administration. Under the influence of these compounds, cervical secretion becomes scanty in amount,

highly viscous, and cellular. The ferning pattern disappears and the spinnbarkeit phenomenon is markedly reduced. The normal preovulatory decrease in albumin and sialic acid and the normal increase in mucin is altered (21). The pH, however, is not significantly changed (29). This property of gestagens is of practical importance. The contraceptive potential of microdose synthetic gestagens such as chlormadinone acetate, norgestrel, norethindrone, quingestanol, and megestrol acetate, depend largely on their ability to produce cervical mucus hostile to sperm penetration (31, 51). In very small doses, synthetic gestagens may not interfere significantly with intracervical sperm migration, but abolish intrauterine penetration. Androgens exert inhibitory effects similar to gestagens on cervical secretion (51).

SPERM SURVIVAL IN THE CERVICAL CANAL

Longevity of sperm in the female genital tract is an important factor in fertility. A distinction should be made between the duration of motility and fertilizing capacity. Sperm motility is not necessarily a criterion of fertilizing potential. Live sperm have been found in the vagina up to 12 hr following coitus (15). Kremer (20) found that the motility of human sperm which have remained in the vagina longer than 35 min is so compromised that their ability to penetrate cervical secretion is lost. Contamination with mucus at times alters the pH of the posterior fornix of the vagina, and prolongs the survival of ejaculated sperm. A clear relationship between the pH of the intravaginal seminal pool and the motility of sperm has been established. When the pool pH is higher, appreciable numbers of motile sperm are encountered in the vagina.

The viability of sperm *in vitro* is related to the glucose concentration of cervical mucus. There is normally an increase in glucose in the cervical mucus at the time of ovulation. During the fertile period cervical mucus contains 200 mg/100 ml or more of glucose. A decrease in glucose concentration in the cervical mucus has been found in many infertile patients. In postcoital tests, sperm viability was depressed in women with low glucose content of cervical mucus. Unexplained cervical hostility may then reflect a deficient glucose content in cervical mucus.

In human cervical mucus, motile sperm have been found from 2–8 days after coitus (15) and 7 days following artificial insemination. In the human uterus and oviducts, live sperm cells have been recovered up to 84 hr after sexual intercourse (1, 40).

OTHER SUBSTANCES AFFECTING SPERM MIGRATION THROUGH THE CERVIX

The effects of copper, silver, zinc, nickel, and gold on sperm penetration into the cervical mucus *in vitro* have been studied. Copper exhibited the greatest inhibition of sperm migration (19). Silver and zinc also exerted a strong spermiostatic activity, but to a lesser extent than copper. Nickel produced minimal alterations of sperm movement and gold was practically ineffective (19). Prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$) may also have some effect on sperm penetration through the cervix. Some reports have indicated that the addi-

tion of $PGF_{2\alpha}$ to sperm enhances sperm migration in cervical mucus *in vitro*. However, others have found that $PGF_{2\alpha}$ in large amounts incubated with semen caused a marked inhibition of sperm motility. The addition of kallikrein to semen brings about an acceleration of sperm penetration in cervical mucus.

II. SPERM MIGRATION THROUGH THE UTERUS AND TUBES

GENERAL CONSIDERATIONS

The rapid sperm migration through the uterotubal segment of most experimental animals cannot be attributed to intrinsic motility alone. Furthermore, nonmotile sperm cells are transported at a comparable rate (26, 29, 49). Psychosomatic influences may play a significant role in gamete transport within the human oviduct and cause infertility (6).

Transport of particulate matter and radio-opaque solutions through the reproductive tract has been described in rabbits, cows, sheep, and human females. Some investigators have been unable to confirm these findings. According to some investigators, the active swimming movements of the gametes may be generally regarded as being of little consequence in transport. In most mammalian species, the entire burden for sperm passage through the female genital tract rests upon the duct itself. Most knowledge of the mechanism of sperm migration in humans is derived from *in vitro* experiments and from studies of mammals whose reproductive behavior resembles that of humans. While similarities of reproductive functions among various mammalian species are common, differences also exist and generalizations not based on scientific evidence are fraught with hazards. Unfortunately, experiments dealing with sperm migration through the human uterus and fallopian tubes are few. Many elegant techniques used in laboratory animals are not applicable to man.

Van Demark and Hays (49, 50) demonstrated that bovine spermatozoa are transported from the cervix to the distal portion of oviducts in 2–4 min after intracervical artificial insemination and following natural mating. They also observed that various stimuli of natural mating or artificial insemination resulted in oxytocin release and an increase in uterine activity, which presumably was responsible for the rapid rate of sperm transport. Similar patterns of uterine motility were produced in the excised and perfused bovine uterus by the addition of oxytocin to the perfusate. Sperm transport was also induced by adding oxytocin to the perfusing fluid after deposition of semen in the cervix.

Rubenstein *et al* (40) detected spermatozoa at the fimbriae of human fallopian tubes within 30 min after artificial insemination. Others have found sperm in an excised human uterus 6 hr after semen was placed at the external os, and recovered spermatozoa from the end of the oviduct 68 min after they deposited semen in the cervix of human hysterectomy specimens (30). Bickers (5) simultaneously recorded uterine contractions and aspirated the fundus of the uterus after coitus in a young oophorectomized woman. He

was unable to recover sperm in the absence of uterine contractions. Estrogen administration restored uterine activity. Sperm were then recovered from the uterine cavity after coitus.

Pharmacologic studies in various animals have demonstrated that sexual stimuli lead to uterine and oviductal muscular contractions, mediated by the release of oxytocin from neurohypophysis. The possible role of this hormone in sperm migration in humans has not been fully investigated. Oxytocin does seem to sensitize the nonpregnant myometrium to various pharmacologic compounds including the prostaglandins. The extirpated human fallopian tube does not respond to oxytocin. The effect of oxytocin in animals can be modified by a variety of environmental factors that may cause release of epinephrine (50).

Sperm migration studies in excised human and bovine genital tracts were performed in our laboratories to reexamine the role of uterotubal contraction versus sperm motility. Spermatozoa migrated through the cervical canal but not beyond the internal os. None were recovered from the uterus or the oviducts in four human specimens with mucus in the cervical canal, or in two bovine estrus and two nonestrus specimens (30). These results agree with the findings of Van Demark and Hays (49) in the cow. However, they are at variance with previous observations in women. The technique of aspiration of sperm from the vaginal fornices or through the cervix for sampling of the uterine content, may result in contamination of the aspirate with vaginal contents. This may take place even after meticulous precautions and may account for the results obtained by the Van Demark and Hays.

Absence of sperm migration in the excised reproductive tract, deprived of hormonal and neurologic effects, supports the contention that sperm do not reach the oviduct solely by their intrinsic motility. Recovery of sperm from the endocervix and other *in vivo* and *in vitro* sperm–cervical mucus-penetration studies, suggest that sperm cells migrate the length of the cervical canal unaided if the cervical mucus is favorable.

An extirpated uterus is not entirely comparable to the intact genital tract where other factors may affect sperm transport. Postoperative cellular anoxia and degeneration may alter the uterine environment and affect sperm migration even when experiments are carried out promptly. The observations reviewed here suggest that the human female genital tract, like that of other mammals, is not a dynamic tube through which sperm travel independently.

THE UTEROTUBAL JUNCTION AND FALLOPIAN TUBE

The uterotubal junction is believed to have an important function in sperm transport in mammalian species. Anatomy of the uterotubal junction is complex and varies among species. In some animals, such as the pig, it provides a reservoir where spermatozoa are collected and pass continually into the oviduct to reach the site of fertilization. In primates, the cervix, uterotubal junction, and possibly endometrial glands act as sperm reservoirs that maintain graded concentrations of sperm throughout the reproductive tract.

The fallopian tube has the remarkable ability of conveying spermatozoa and ova in opposite directions. Other processes essential to reproduction which occur in the oviduct include capacitation, ovum pickup, fertilization,

cleavage, embryo transport, and nutrition. With the exception of the rabbit and a few other species, information about the function of the mammalian oviduct in general, and the human fallopian tube in particular, is scant. A better understanding of various functions of the oviduct would lead to their ultimate regulation and may provide not only newer avenues for fertility regulation, but also restore fertility to those women whose infertility is the result of tubal pathology or disturbed normal function. The pattern and rate of sperm transport through the oviduct are controlled by several mechanisms. These include contractile activities of the fallopian tube, complex contractions of the oviductal mucosal folds and mesosalpinx, fluid currents and countercurrents created by cilia, ciliary activity of endosalpingial epithelial cells, and sperm motility. The relative importance of these mechanisms in spermatozoa transport through the oviduct is unknown.

The segmental movements in the rabbit oviduct appear to propel the egg and other particles toward the uterus (6). The ciliary beat also seems to be abovarian in this animal. Size of the particles to be transported may be an important factor. Larger particles, such as ova, may be transported toward the uterus, and smaller ones, such as spermatozoa, in the direction of ovaries. Circulation of oviductal fluid in the rabbit is complex. Longitudinal folds of mucosa often form compartments which are momentarily closed. This will block abovarian currents and cause fluids to flow in the opposite direction, *i.e.*, toward the ovary through the center of the compartments. The circulation of fluids is thus abovarian along the sides of the ciliated ridges and adovarian in the central region of each compartment. Contractions of the oviduct change the configuration of the various compartments temporarily, causing fluids and spermatozoa to move from one compartment to the next. The net result of these processes is to carry the luminal content toward the ovary before ovulation. These temporary oviductal compartments provide the mechanism by which spermatozoa may be transported toward the fimbria. Current evidence indicates that the pattern of sperm transport in women is probably similar to that of experimental animals.

The number of spermatozoa flushed from the rabbit oviduct has been shown to be relatively constant regardless of whether 200 million or 20 million spermatozoa were inseminated into the vagina. In all species, the number of spermatozoa that reaches the oviduct is relatively constant and represents only a small percentage of those in the ejaculate.

The tubal isthmus may have a regulatory role in limiting the passage of spermatozoa to the ampulla and thus in preventing polyspermia. Oviductal function is regulated by estrogen and progesterone which are responsible for tubal secretion, ciliary activity and muscular contractions.

The prostaglandins, present in human seminal plasma and endometrium, have been shown to be absorbed through the vaginal mucosa and to have a marked effect on uterine and oviductal musculature. Two major groups of prostaglandins have been recognized: the PGE and the PGF types. Prostaglandins of the E series usually are present in larger quantities in the semen than are the F type and exert an inhibitory effect on the smooth muscle of the uterus and oviduct. The PGFs stimulate uterine contractions and are found predominantly in the endometrium.

Both prostaglandin $F_{2\alpha}$ and E_2 stimulate the nonpregnant human uterus *in*

vivo when given parenterally, with PGE_2 being more potent than $PGF_{2\alpha}$. *In vivo* they are almost unaffected by the endocrine status of the organ (9). Intrauterine instillation of prostaglandin $F_{2\alpha}$ also has been reported to be stimulatory whereas PGE_2 was inhibitory. The reason for the discrepancy of the effect of PGEs given IV and by instillation is not known.

The sensitivity of the human uterus to prostaglandins reaches a peak in midcycle. Postcoital administration of $PGF_{2\alpha}$ to female monkeys increased the number of spermatozoa in the uterus and to a lesser degree in the oviducts. Increased uterine contractility and enhanced passage of sperm through the cervix may be responsible for this process.

PG[illegible] stimulates, whereas PGE_2 inhibits tubal motility *in vivo*. Coutinho and Maia (9) have suggested that relaxation of the tubal isthmus induced by seminal PGE_2 is a prerequisite for sperm penetration into the tube. Thus, human seminal prostaglandins absorbed through the vaginal mucosa may play a role in the passive transport of sperm by altering uterine and tubal activity. Despite some recent data, the evidence is still inconclusive that prostaglandin-deficient semen is associated with infertility.

HUMAN STUDIES

Settlage *et al* (41) investigated sperm migration in series of women scheduled for sterilization, following artificial insemination with fresh high-quality semen. After salpingectomy, sperm were recovered from the uterine contents and various segments of the oviduct. These studies showed that the sperm were present in the oviducts 5 min after insemination. The total number of oviductal sperm found related indirectly to the number of sperm in the inseminate 15–45 min after insemination, but not at later times. From 15–45 min after insemination, the ratios remained constant, indicating no further increase in sperm numbers with increasing length of time from insemination. Indeed, sperm numbers declined dramatically by 6 hr following insemination. None were found in the one subject studied at 48 hr after insemination. This indicated that the presence of identifiable sperm in the endometrial cavity was not a feature of early sperm transport in the human. Studies in our laboratories have shown the accumulation of sperm in the endometrial gland of monkeys following normal mating. Such might be the case in the human as well.

Croxatto *et al* (10) studied the distribution of spermatozoa in the female genital tract several hours after coitus at ovulation time. The number of sperm recovered showed a wide range between 0 to 5000. From 1000 to 5000 spermatozoa were found in 38% of the endometrial cavities and in 10% of the oviducts examined. A strong correlation between the number of spermatozoa recovered and the stage of the menstrual cycle was apparent. During the follicular phase, the median for the endometrial cavity was 1397 spermatozoa, and for each oviduct, 138. During the luteal phase the corresponding values were 7 and 1 respectively.

Ahlgren *et al* (1) studied sperm transport in 3 fertile and 177 infertile women. Each subject was examined after coitus or artificial insemination for the presence of sperm in the cervical mucus, uterine cavity (transcervical aspiration), and oviducts (laparoscopy or laparotomy). He found that the num-

ber of sperm in cervical mucus and uterine cavity correlated well with that in the oviducts and pouch of Douglas. The greatest number of progressively motile sperm in all three locations was observed in the presence of a mature follicle in the ovaries. A significant decrease in motile sperm population was seen when ovaries contained corpora lutea.

However, once the sperm reached the uterine cavity, their further progression to the oviduct was not influenced by the stage of ovarian cycle. Ahlgren showed further that, although sperm penetration in cervical mucus and uterine cavity occurred more frequently before ovulation, the presence of corpora lutea did not totally prevent sperm entry into the mucus and uterine fundus. More recently, Ahlgren *et al* (1) were able to recover live sperm from the uterus, oviduct and abdominal cavity of women 63–84 hr postcoitum. They also observed that spermatozoa with normal morphology were more common in the oviduct than in the ejaculate. The presence of sperm in the uterus correlates directly with high sperm density of the cervical mucus approximately 24 hr after coitus.

CONCLUSION

The pattern of sperm migration emerging from the studies reviewed above suggests an intricate and dynamic process. These observations allow the formulation of a model which incorporates the available knowledge of the manner in which the sperm, ejaculated in the vagina, reach the distal portion of the oviducts where fertilization is believed to occur.

At least three factors seem to be responsible for the survival of sperm in the vagina, which is admittedly a hostile environment for them. These include 1) the coagulation of the ejaculate which protects spermatozoa from the acid milieu of the vagina, 2) the coating of vaginal mucosa by cervical mucus, which provides a barrier between the vaginal secretion and the ejaculate, and 3) the buffering effect of the seminal plasma which temporarily alters the pH of the vagina from acid to alkaline.

Vaginal acidity, on the other hand, favors liquefaction of sperm coagulum which occurs only 5–15 min after ejaculation, thus allowing the seminal plasma to exert its alkalinizing activity before sperm cells are freed to come into contact with the vaginal mucosa. Spermatozoa released from the seminal coagulum must, however, enter cervical mucus promptly (within 1–3 hr) or they are doomed to destruction.

From a functional point of view, the following properties may be ascribed to the cervix and its secretions: 1) receptivity to sperm penetration at or near ovulation and impedance of entry at other times, 2) sperm reservoir, 3) protection of sperm cells from the hostile environment of the vagina and from being phagocytized, 4) supplementing the energy requirements of sperm, 5) filtering effect, and 6) possible capacitation of sperm.

It is generally recognized that sperm rapidly enter normal midcycle cervical mucus. Subsequent migration through the cervical canal is accomplished principally by intrinsic motility. It may also be influenced by proteolytic activity of seminal plasma and sperm, phalanx formation due to the difference in surface tension between semen and cervical mucus, and the orientation of

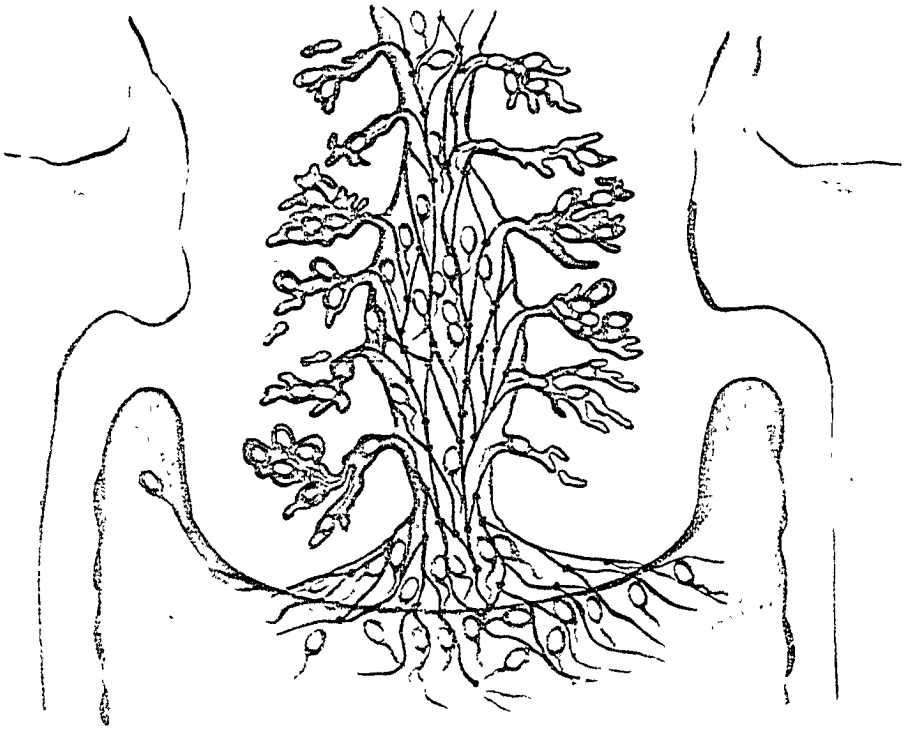

FIG. 3-2. Schematic drawing representing the current concept of sperm transport through the cervix. Observe long mucus filaments, sperm penetration along the molecular line of strains and aggregation of spermatozoa in the crypts of the cervical canal.

strands of cervical mucin. The latter phenomenon may be responsible for the storage of sperm in the cervical crypts, and their gradual release over an extended period in the uterus and oviducts. Figure 3-2 represents this process in a schematic manner. The mucus is a favorable medium for sperm survival, and probably provides sperm cells with energy substances required for their motility.

Two phases of sperm transport are recognized: a rapid phase during which the sperm reach the site of fertilization within 5 min and a slow, or delayed phase, which supplies sperm to the oviduct for at least 48 hr following a single coitus. The cervix, endometrial glands, and the uterotubal junction are reservoir sites of sperm colonization during this phase.

Retention of sperm in the mucus also protects them from the phagocytes within the female tract. Preovulatory cervical mucus contains very few, if any, leukocytes, and those which enter the mucus from the uterus and stromal phagocytes are kept physically separate from sperm. The ovum has a limited life generally believed not to exceed 6–8 hr (6). Because sperm do not

FIG. 3-3. Schematic drawing depicting sperm transport through the uterus. Relaxed state. Note colonization of the uterine glands by spermatozoa.

survive well in the uterus or oviduct and are more susceptible to phagocytosis when dead or immobilized, the protective action of cervical mucus insures a constant release of motile sperm into the upper tract following the initial rapid passage, thus increasing the chance of fertilization. *In vitro* and *in vivo* observations suggest that cervical mucus functions not only as a sperm reservoir, but also as a biologic filter where dead, abnormal, or unfit sperm are retained and prevented from reaching the uterine cavity (24, 25, 45).

Capacitation of sperm prior to fertilization in a number of mammalian species has been established. This phenomenon seems to exist also in man. The role of cervical secretion in capacitation, although not critically explored, remains a distinct possibility.

Once in the uterus, the sperm depend principally on uterine contractions for their transport. The motility of sperm is of lesser importance. Under the influence of sex steroids, the uterus contracts continuously during the menstrual cycle. Uterine contractions may be supplemented or favorably modified by prostaglandins in the seminal plasma, absorbed through the vagina. Prostaglandins, however, do not seem to be essential for sperm migration. The net result of these contractile activities is to disperse the sperm in the uterine cavity and to transport them to the oviducts, as shown schematically in Figures 3-3 and 3-4. In a relaxed state, sperm suspended in the uterine fluid (Fig. 3-3), are spread over the endometrium. Some enter the uterine glands, which may serve as a secondary storage site. When the uterus contracts (Fig. 3-4), the increase in intrauterine pressure will squeeze the sperm-containing uterine fluid out. Because the cervix is occluded by relatively vis-

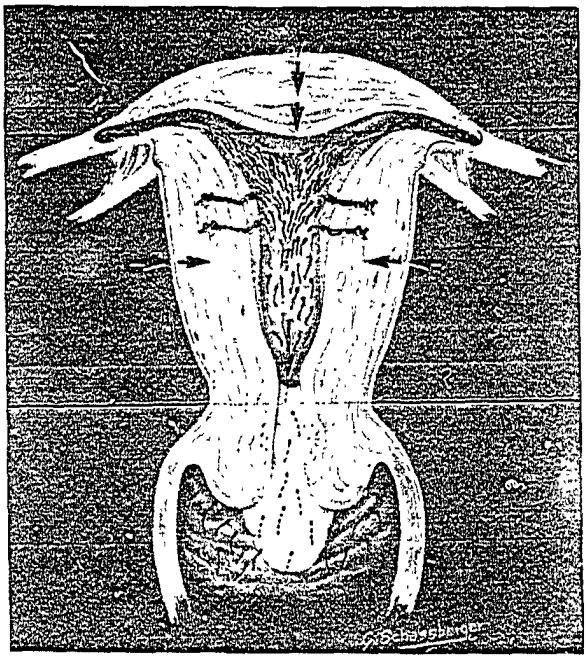

FIG. 3-4. Schematic drawing depicting sperm transport through the uterus. Contracted state. Sperm are squeezed out of the uterus through the tubal ostium into the oviducts. Egress of sperm through the cervix is blocked by cervical mucus

cous cervical mucus, the only avenue of egress for the sperm is through the tubal ostium into the oviduct.

The fallopian tube has the remarkable ability of conveying spermatozoa and ova in opposite directions. Factors responsible for sperm transport through the oviducts include 1) tubal motility, 2) motion of cilia of the cells of the endosalpinx, 3) circulation of tubal fluid, and 4) sperm motility.

The final result of these known and other unknown factors is dispersion of sperm in the fallopian tube and their progression to the site of fertilization.

The model of sperm transport proposed here admittedly leaves many questions unanswered. More human observations are required to confirm the animal studies which form the basis of the suggested hypothesis.

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CURRENT STATUS OF VAGINAL CONTRACEPTION

47

4

Spermicidal Agents: Effectiveness, Use, and Testing

AQUILES J. SOBRERO

The desire to control conception is a universal human phenomenon, and fragmentary knowledge of contraceptive means has existed in all major cultures throughout the history of social development. Although contraceptive practices are very old, knowledge of them is rather recent; in fact, the major portion of the democratizing process of contraception has occurred in Western societies since the nineteenth century (35).

Spermicidal substances have been in use since pharaonic times, and form part of the folklore of most cultures. Some, such as gum acacia, boric acid, and ricinoleic acid, have survived the test of time, and may still be found in some jellies and creams.

From the time of their discovery, spermatozoa were known to be killed by many substances. Leeuwenhoek (47) observed that dilution with rain water rendered dog spermatozoa motionless, and this was corroborated by Spallanzani (76). Almost two centuries after Leeuwenhoek's observations, Kölliker noted (45), in the first scientific study on the subject, that organic and inorganic salts were toxic to spermatozoa, and that the immobilizing effect of water could be reversed, and motility restored, by the immediate addition of salt. De Quatrefages (66, 67) described the toxic effects of lead, copper, and mercury salts, which found their way into contemporary contraception.

In more recent times, growing knowledge of cell biochemistry and of spermatozoal metabolism has provided information about substances that interfere with the functional activity of this cell. This basic approach has been paralleled by more or less empirical work aimed at finding substances with high spermicidal activity that are suitable for human use. In the latter context, the work of Baker (1-3) in the 1930s, was outstanding both for its application of scientific experimentation to chemical contraception, and for its success in determining the relative *in vitro* activity of a large number of compounds. Baker's research led to the widespread use of phenylmercuric acetate, benzoate, and nitrate as the active principles of contraceptive preparations (2).

The combination of basic and empirical research has given rise to certain general considerations. Although the spermatozoon nucleus is in a resting stage and the cell neither grows nor divides, it is metabolically active and there is a high membrane permeability to a great variety of substances. Also, spermicidal substances act in different ways; some inhibit essential enzymes,

others damage the cell membrane. Immobilization may be permanent or reversible; thus as classified by Mann (53), some substances may be spermicidal, while others are only spermiostatic—having the potential for reversal in the female genital tract as their concentration diminishes gradually—so that a spermatozoon apparently dead *in vitro* may effect fertilization *in vivo*.

SPERMICIDAL AGENTS

The large majority of spermicides fall into one of five categories with some considerable overlap: electrolytes; sulphydryl-binding substances; bactericides; surfactant agents; and enzyme inhibitors.

Electrolytes Changes in spermatozoal activity and metabolism associated with changes in tonicity have been reviewed by Blackshaw and Emmens (11). Hypertonic solutions of 5% NaCl abolish spermatozoal motility and fructolysis. This effect was used by Gamble (28) to prepare some jellies with high salt content which were highly spermicidal *in vitro*. Boric acid and tartaric acid used in effervescent vaginal contraceptives for foam production act in the same manner but in a weak way.

Sulphydryl-binding compounds These compounds exert their inhibitory action on cellular functions by several mechanisms, thus allowing their subclassification into oxidizing substances, mercaptide-forming compounds, and alkylating compounds. The activity of oxidizing compounds such as hydrogen peroxide and o-iodobenzoate probably depends on the oxidation of S–H to S–S groups. The various hydroquinones studied by Baker (1) and utilized in several spermicidal products until the late 1950s, belong to the same group. The use of hydroquinones as spermicidal agents was abandoned because of their potentially carcinogenic effect.

Mercaptide-forming compounds are heavy metals, described more than a century ago by Kölliker (45). Organic salts of copper, mercury, and lead are among the oldest known spermicides. A similar effect may be ascribed to many metallo-organic compounds (87), including phenylmercuric acetate, the most successful and durable of the group. This most recently dethroned spermicide potentially has the neurotoxic effect of chronically absorbed mercury (Minamata disease).

Alkylating agents inhibit spermatozoal motility and metabolism. Iodoacetate is an example of these. It also serves as an example of compounds that may be listed in other categories; in this case, enzyme inhibitors, illustrating that a clear delineation among spermicidal compounds is not always possible.

Bactericides From the work of Kolliker on spermatozoa and that of Erlich in bacteriology, it was reasoned that substances that were highly active microbicidals would, like all disinfectants, act effectively against spermatozoa and also protect against unwanted pregnancies and venereal diseases. A large number of creams, ointments, vaginal suppositories, douche powders, and solutions were made available by pharmaceutical entrepreneurs. Histori-

cally they played an important role. Some of these compounds may still be found in use in areas where governmental regulations are lax or nonexistent.

In modern contraceptive technology chloramine, benzethonium chloride, chinosol, and phenylmercuric acetate are used, as previously mentioned. All belong in this category and thus provide another example of the overlapping of spermicides into different categories.

Surfactant agents These are a large number of long-chain detergents and soaps possessing spermicidal activity. Their effect is the irreversible loss of motility and permanent disruption of the cell membrane. All surface-active agents—anionic, cationic, and nonionic compounds—exert a potent spermicidal effect in spite of their different membrane affinities, depending on their electric charge. Different surface-active agents—almost exclusively nonionic—are the principal ingredients of most currently available spermicidal products, worldwide. The most frequently found is nonylphenoxypolyethoxyethanol, more commonly known as nonoxynol 9. One recently incorporated in the long list is p-methanylphenylpolyoxyethylene (8.8) ether, or TS-88, which is extremely potent *in vitro* (27). Their effect depends on the interaction of the agent with the lipoproteic membrane of the cell, increasing permeability with disruption and subsequent leakage of cell components. They affect not only the spermatozoal membrane, but also any bacteria or parasite present in the vagina. This effect is also exerted upon the cells forming the vaginal mucosa. Because of the molecular structure of some of these compounds it could be reasoned that surface-active agents would not be absorbed by the vaginal mucosa. However, the vaginal mucosa is an extremely well-vascularized and active epithelium that, like the buccal mucosa, to which it is histologically similar, absorbs many substances. As epithelial disruption takes place, the vaginal epithelium becomes increasingly thin, and vaginal intolerance and irritation develop. It is possible, too, that as the epithelial structure and thickness are affected, surface-active agents may penetrate and be absorbed into the submucosa, and from there be carried by blood and/or lymphatic capillaries into the general circulation, where they might exert some systemic effects not as yet identified.

Enzyme inhibitors The effect of cyanide and carbon monoxide should be mentioned, as both inhibit respiration by combining with cytochrome oxidase. Many enzyme inhibitors are spermiostatic rather than spermicidal. Some do not have any effect on spermatozoal motility, but have proved effective *in vivo*

According to present knowledge, in order to penetrate an egg, the spermatozoon needs three acrosomal enzymes: hyaluronidase, which is responsible for dispersing the cumulus oophorus; a not-well-characterized enzyme called corona-penetrating enzyme (CPE); and acrosin, a trypsin-like neutral proteinase, which permits the spermatozoa to traverse the zona pellucida (Fig. 4-1).

Antihyaluronidase compounds have been explored as contraceptives by Beiler and Martin (4), Martin and Beiler (55), and Thompson *et al* (83). Chang and Pincus (17) reported on oral and intraperitoneal administration of phosphorylated hesperidin in the rat, with up to 80% inhibition of fertil-

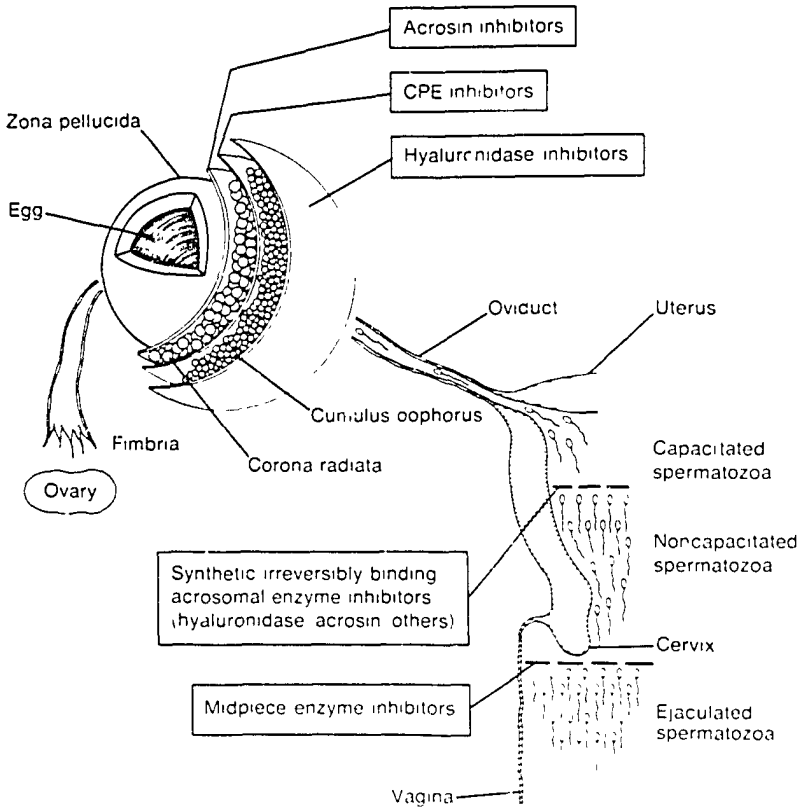

FIG. 4-1. Contraceptive action of sperm enzyme inhibitors. (Zaneveld LJD: In Hafez ESE (ed): Human Semen and Fertility Regulation in Men. St. Louis, CV Mosby, 1976)

ization. Another hyaluronidase inhibitor is a hydroquinone sulfonic acid-formaldehyde polymer, also known as 53 D/k which was originally studied by Parkes *et al* (61).

Acrosin, or acrosomal proteinase, facilitates spermatozoal penetration through the zona. Its presence in an inactive form (zymogen) in the acrosome of a large number of species, including humans, has been reported. The possible utilization of spermatozoal enzyme inhibitors as contraceptive agents has been suggested by Zaneveld *et al* (91).

More recently, Joyce, Freund, and Peterson (39) reported a series of experiments exploring the contraceptive activity of acrosin and hyaluronidase inhibitors in the rabbit. These investigators studied two acrosin inhibitors: TLCK (N-a-p-tosyl-L-lysine chloromethylketone HCl) and NPGB (p-nitrophenyl-p-guanidinobenzoate) and two hyaluronidase inhibitors, compounds 53 D/k and phosphorylated hesperidin, already mentioned. The four compounds were administered intravaginally in a contraceptive, inactive lubricat-

TABLE 4-1. Partial List of Chemicals Used as Spermicidal Compounds*

Alkylphenoxypolyethoxyethanol	p-methanylphenylpolyoxyethylene (8.8) ether(Menfegol) (TS-88)
Aluminum perlactate	Methoxypolyoxyethyleneglycol 550 laurate
Benzalkonium chloride	Methylbenzethonium chloride
Benzethonium chloride	Nicotinic acid
Boric acid	Nonylphenoxypolyethoxyethanol (Nonoxynol 9)
Cethyl alcohol	Oxyquinoline sulfate (Chinosol)
Cethylpyridynium bromide	Phenylmercuric acetate (PMA), borate, nitrate
Chloramine	Polyethyleneglycol of monoisoctylphenol ether
Cuprein lactate	Polysaccharide-polysulfuric acid ester
p-diisobutylphenoxypolyethoxyethanol (Octoxynol 9)	Ricinoleic acid
Dimethylaminoacetic acid	Sodium borate
Dioctyl sodium sulfosuccinate	Sodium dichlorosulfamidobenzoate
Dodecaethylene glycol monolaurate	Sodium lauryl sulfate
Dodecylamidochlorobenzylate	p-sulfondichloroaminobenzoic acid
Hexylresorcinol	Tartaric acid
Lactic acid	p-triisopropylphenoxypolyethoxyethanol
Laureth 10S	Zinc phenolsulfate

*The *in vitro* spermicidal potency of these compounds varies greatly. The possible chronic systemic toxicity of these chemicals as they are absorbed by the vaginal mucosa has not been established. Recommendations for the withdrawal of some of these compounds, such as the quaternary ammonium salts, phenol, boron, and mercury-releasing compounds are being considered.

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ing jelly, at concentrations not affecting spermatozoal motility and survival. Phosphorylated hesperidin inhibited fertilization in 79% of the animals; 53 D/k, 100%; NPGB, 98%; and TLCK, 100% at a dose of 200 μg/ml. The controls, using jelly alone, did not experience diminution of fertilization. The same effect of TLCK was reported by Zaneveld (89) but at a dose of 3 mg/ml.

Because some of the spermatozoal enzymes are apparently specific and not present elsewhere in the body, this group of substances should receive more attention by academic and industrial researchers interested in topical contraception. It is pertinent to note that there are species differences among these enzymes and zymogens.

A list of spermicidal compounds found in commercial vaginal contraceptives is given in Table 4-1.

Vaginal spermicides or topical contraceptives consist of two components: the active ingredient, or spermicide, and a base, usually inert, the purpose of which is to carry the spermicide and hold it in the vagina and against the cervix. The base, however, has some contraceptive action of its own as it interferes with the direct contact of the semen and the spermatozoa with the cervical mucus.

There are several pharmaceutical modalities currently available for delivering spermicidal agents into the vagina: jellies, creams, pastes, foams, suppositories (also called pessaries or vagitories), effervescent tablets and suppositories, and biodegradable or soluble films or carriers.

Vaginal spermicides offer several practical advantages and a number of disadvantages that limit their popularity. Among their disadvantages are that their dispensers or packages are bulky and conspicuous; that they require a number of immediate precoital maneuvers and handling of the genitals which, in some users, produces embarrassment; and that, together with part of the ejaculate and some female secretions, they are eliminated onto the perineum with considerable and sometimes unacceptable messiness. Possibly the most important obstacle to their diffusion and widespread utilization is that they are not a clinical or professional-oriented method; thus, until very recently, all organized family-planning programs and clinics actively discredited them, forgetting that, for many potential users, the imminence of coitus and the fear of its possible reproductive consequences are the only stimuli sufficiently intense to arouse interest in contraception. Also, family-planning clinics and centers are not available everywhere, and many women are not willing to admit their sexual activity publicly, nor are they willing to be examined genitally in the absence of a major health problem. Finally, vaginal contraceptive products are of limited popularity because they offer less contraceptive protection. Available data on the clinical effectiveness of these contraceptive products are given in Table 4-2. The following lists give the indications and contraindications for topical chemical contraception (75).

Indications

Adjuvant to mechanical method (diaphragm, condom)
Adjuvant to calendar rhythm method
Adjuvant to IUD during fertile period

(continued on p. 56)

TABLE 4-2. Clinical Effectiveness of Vaginal Chemical Contraceptives Used Alone

TYPE OF METHOD	PLACE	FAILURE RATE (PEARL INDEX)	REFERENCES
Jellies	USA	7.75	Margolis AJ, Cavanaugh AT, Ems M: Contraception with gel alone Fertil Steril 13.265, 1962
	USA	20.99	Kasabach HY: Clinical evaluation of vaginal jelly alone in the management of fertility. Clin Medic 69.894, 1962
	USA	23.1	Frank R: Clinical evaluation of a simple jelly-alone method of contraception. Fertil Steril 13:458, 1962
	Puerto Rico	36.09	Tietze C, Pai DN, Taylor CE, Gamble CJ A family planning service in rural Puerto Rico. Am J Obstet Gynecol 81:174, 1961
Creams	USA	9.06	Rovinsky JJ: Clinical effectiveness of a contraceptive cream. Obstet Gynecol 23.125, 1964
	USA	6.19	Tyler ET: Current developments in contraception. Pacif Med Surg 73.79, 1965
Foams	USA	1.75	Bushnell LF. Aerosol foam: A practical and effective method of contraception. Pacif Med Surg 73:353, 1965
	USA	3.14	Carpenter G, Martin JB: Clinical evaluation of a contraceptive foam. In Sobrero AJ, McKee C (eds). Advances in Planned Parenthood, Vol 5. New York, Excerpta Medica (ICS-207) 1970
	USA	3.98	Bernstein GS. Clinical effectiveness of an aerosol contraceptive foam. Contraception 3:37, 1971
	USA	7.53	Kleppinger RK: A vaginal contraceptive foam. Penn Med J 68:31, 1965
	England	16.6	Mears E: Chemical contraceptive trial; II. J Reprod Fertil 4.337, 1962
	USA	27.9	Sobrero AJ: Report to the Emko Company. Unpublished, 1962
	USA	28.3*	Tietze C, Lewit S: Comparison of three contraceptive methods: Diaphragm with jelly or cream, vaginal foam, and jelly/cream alone. J Sex Research 3:295, 1967
	Puerto Rico	29.25	Paniagua ME, Vaillant HW, Gamble CJ: Field trial of a contraceptive foam in Puerto Rico. JAMA 177:125, 1961

Foaming tablets	Japan	2.27	Furusawa Y, Furuya K, Iida T, Ichikawa Y, Iwakura T, Nakamura H, Hirota T, Wada Z: Clinical study of the contraceptive effervescent tablets E-136 (Neo-Sampoon Loop Tablets) wherein a new surface active agent p-methanylphenylpolyoxyethylene (8 8) ether (TS-88) is used. In: Neo Sampoon Loop Tablets Tokyo, Eisai Company Ltd, undated
	Japan	3.22	Ishihama A, Inoue T: Clinical field test of a new contraceptive vaginal foam tablet. Contraception 6:401, 1972
	USA	14.38	Tyler ET· Current developments in contraception. Pacif Med Surg 73:79, 1965
	USA	21.96	Dingle JT, Tietze C: Comparative study of three contraceptive methods: Vaginal foam tablets, jelly alone, and diaphragm with jelly or cream. Am J Obstet Gynecol 85:1012, 1963
	Puerto Rico	38.34	Tietze C, Pai DN, Taylor CE, Gamble CJ: A family planning service in rural Puerto Rico. Am J Obstet Gynecol 81.174, 1961
Suppositories	Belgium	1.79	Godts P. Etude clinique sur un contraceptif vaginal. Ars Medici 28:1055, 1973
Soluble film	Europe	5.31	Pariser G: C-film use-effectiveness studies. 1972/73
	Egypt	7.33	Paris, USV International, 1974 (unpublished)

* Calculated by the life-table method.

(Modified from Belsky R: Population Reports. Series H, No. 3, The George Washington University Medical Center, 1975)

Adjuvant to hormonal contraceptives at start of the first medication cycle or when 2 or more tablets have been missed
Temporary or transient method prescribed before sexual relations are initiated, before a systemic method can be started or IUD inserted
Low fertility or presumed infertility of woman unable or unwilling to use a mechanical method
Casual sexual encounter or infrequent intercourse

Contraindications

Absolute
Necessity for a method of high effectiveness for health, personal, or social reasons
Disruption or interruption of sexual foreplay precluding sexual interest and/or expression
Aesthetic unacceptability to either partner
Allergy to spermicidal preparations
Chronic local allergy, genital contact dermatitis, eczema genitalis, genital psoriasis, and other genital dermatoses
Relative
Interruption of sexual foreplay interfering with sexual expression
High fertility
Dyspareunia
Vaginismus
Temporary
Acute or subacute vulvovaginitis of any cause, treated or untreated
Pruritus genitalis
Herpes genitalis

Jellies and gels offer greater lubrication but, in general, are aesthetically less acceptable than others because of excess leakage after coitus. Creams are usually less lubricating and less messy, as they seem to adhere better to the mucosa of the vagina and cervix. Foams consist of a concentrate with an oil-water inert base in which the spermicidal agent is dissolved. They are packed under pressure in a container with a liquefied gas as a propellant. The concentrate is released as a foam. In foam, a colloid forms the opposite of an aerosol. The gas forms the internal phase of the colloid while the fluid forms the external phase, *i.e.*, the walls of the bubbles. Foams have good capacity for adhering to the vagina and cervix and have the advantage of remaining longer in the vagina than others. Furthermore, while the bulk of the vehicle in jellies and creams is water and other fluids and solids, the largest proportion of vehicle in foams is gas, which is eliminated inconspicuously from the vagina. Consequently, foams are less messy, have less leakage, and are aesthetically more acceptable.

Despite these theoretical advantages, in the Growth of American Families series, foam alone—the only topical contraceptive whose use was inquired about specifically—showed a very low acceptability to married white women between 1965 and 1975 (Tables 4-3, 4-4).

Most of these products have excellent shelf lives when properly stored.

TABLE 4-3. Contraceptive Methods Used by Married White Women, U.S., 1965, 1970, 1973 & 1975

METHOD	1965	1970	1973	1975
Using contraception	66.5	67.6	72.9	79.0
Not using contraception	33.5	32.4	27.1	21.0
All users	100.0	100.0	100.0	100.0
Oral contraceptives	28.4	35.4	35.5	34.3
IUD	1.1	7.5	9.5	8.7
Diaphragm	10.5	5.7	4.0	3.9
Condom	22.0	14.8	15.1	10.9
Withdrawal	4.0	2.3	2.3	2.0
Foam	3.1	6.6	5.3	3.6
Rhythm	11.5	7.1	4.0	2.8
Douche	3.4	2.3	0.5	0.4
Other	7.1	4.3	1.7	2.2
Wife sterilized	4.7	6.8	10.8	16.3
Husband sterilized	4.1	7.2	11.2	15.0

(Modified from Westoff CF, Jones EF: Fam Plann Perspect 9:153, 1977)

TABLE 4-4. Contraceptive Methods Used by White Women According to Duration of Marriage, U.S., 1975

	YEARS OF MARRIAGE				
METHOD	<5	5–9	10–14	15–19	20–24
All using contraception	71.3	76.0	85.9	85.9	79.5
Not using contraception	28.7	23.3	14.1	14.1	20.5
All users	100.0	100.0	100.0	100.0	100.0
Oral contraceptives	64.8	38.6	25.2	15.8	10.4
IUD	8.1	14.5	9.0	5.1	3.8
Diaphragm	4.3	3.3	1.7	4.0	7.5
Condom	12.0	11.7	8.8	9.5	12.6
Withdrawal	1.8	1.7	1.1	3.4	2.5
Foam	3.4	4.6	4.4	2.9	1.9
Rhythm	1.8	2.2	3.5	4.0	3.1
Douche	0.4	0.2	0.4	0.6	0.6
Other	2.0	1.5	2.6	3.2	1.9
Wife sterilized	0.8	11.7	20.6	27.8	30.2
Husband sterilized	0.7	10.0	22.7	23.8	25.5

(Modified from Westoff CF, Jones EF: Fam Plann Perspect 9:153, 1977).

They need not be refrigerated and should never be frozen. They should be kept tightly closed and stored at ordinary room temperature. At the Margaret Sanger Research Bureau, the same samples of contraceptive jellies, creams and suppositories, whose tests of spermicidal activity *in vitro* were reported by MacLeod *et al* (51), were again tested in 1970 and 1972 using the same methodology. During the 12 and 14 intervening years, the containers were kept tightly closed and stored at room temperature. No changes in spermicidal activity *in vitro* were found in any of the products tested by the three dilution tests used (14, 33, 51, 58, 60, 74). The mean spermicidal

values obtained, against ten or more semen specimens of excellent quality, were so close to the original values that tests of statistical significance were considered superfluous (Sobrero and Copeland, unpublished). The contribution of vaginal topical spermicides to the control of sexually transmissible diseases (STD) is being investigated. Laboratory studies indicate that vaginal spermicides are effective against *Neisseria gonorrhoeae, Treponema pallidum, Trichomonas vaginalis, Candida albicans* and *Herpes simplex II virus* (See Chap. 17) (12, 19–21, 46, 71, 72, 79). Should clinical studies support these findings, an important step will have been made towards controlling the spread of STD.

TESTING

The regulations governing the testing and approval of pharmaceutical preparations in the United States are very stringent. Currently, the FDA regulations for evaluation and approval of preparations for vaginal use are being revised by the FDA Advisory Committee (see Chap. 22). In general, the basic FDA requirements are that a product be harmless and effective. The harmlessness of a chemical vaginal contraceptive must be well established before any clinical testing can be undertaken.

Vaginal spermicides are tested in the laboratory for their spermicidal activity *in vitro*, and more recently, though still experimentally, for their inhibition of fertilization by the enzyme inhibitors. They are also tested in laboratory animals for toxicity and vaginal tolerance, and in humans for vaginal tolerance, aesthetic acceptability, and clinical effectiveness.

Basically, the FDA evaluation procedure starts with formula evaluation. The manufacturers are requested to submit the complete formula of the prospective product. The pharmacologic and toxicologic properties of the ingredients, as well as possible ingredient interaction are thoroughly investigated, with special attention given to possible irritating, toxic, carcinogenic or mutagenic effects. Results of acute and chronic toxicologic studies, on at least two species of laboratory animals, must also be submitted in an effort to learn of any potential undesirable effects of long-term usage.

Test for Spermicidal Action *In Vitro* Currently the accepted test for *in vitro* laboratory evaluation of spermicidal activity, for screening pure active ingredients and, equally important, for the quality control of pharmaceutical products, is the time required to stop spermatozoal motion, irreversibly, at different isotonic dilutions. Descriptions of the current techniques in use for the evaluation of spermicidal activity *in vitro, i.e.,* Brown and Gamble, Sander and Cramer, and Mende and Berliner tests, and the IPPF Agreed Test for Total Spermicidal Power, are, however, beyond the scope of this review. The main objective of *in vitro* evaluation of spermicidal capacity is to assess the rapidity and efficiency of this action (See Chap. 23) (2, 14, 33, 43, 49, 51, 58, 70, 73, 74).

In the future, however, *in vivo* experimental studies could be used to determine the antifertility effect of acrosomal enzyme inhibitors or other enzyme inhibitors on *rana pipiens* (32), *macaca arctoides* (90), or the rabbit (31,

36, 39). *In vitro* fertilization studies may also be performed to test the fertilizing ability of human spermatozoa previously subjected to these compounds (77). Eggs from hamsters or other suitable mammals can be used in the laboratory to screen and evaluate the potential effectiveness of vaginal contraceptive products containing acrosomal enzyme inhibitors, before human evaluation is attempted, and also as a means of quality control.

The physical properties of the formulation must also be evaluated because its acceptability and, to some degree, its effectiveness, depends on them, *e.g.*, spreading and adhering capacity over vaginal mucosa, persistence, etc. Control of the physical properties of jellies and creams has been a problem for both investigators and manufacturers because there is no entirely satisfactory way to measure their viscosity and adhesive capacity, although many procedures have been tried. The physical characteristics of the preparation should include the following: it should readily mix and dissolve in water or saline, it should spread and adhere readily to the vaginal mucosa, and it should produce no discoloration or staining of skin or clothing. Previously, most investigators required only that the product mixed readily in saline at room temperature.

No test has yet been devised to measure the physical properties of suppositories and nonfoaming inserts. The only criterion applied in our laboratory was that one dose unit would melt or dissolve completely, without shaking, when allowed to stand for 30 min in 10 ml of saline at body temperature.

Regarding effervescent vaginal tablets, suppositories, or inserts, a foaming vaginal spermicide in our laboratory was immersed in 10 ml of saline at body temperature. Recordings were made of the foaming time, dissolving time without shaking, volume and type of foam at 5 min, maximum foaming time and volume, uniformity of the foam, bubble size, wetness, staying time, and weight of the dry residue after the supernatant was removed. The spermicidal evaluation of the supernatant solution was carried by the standard dilution tests. The solid residue should be less than 10% of the initial weight of the tested unit.

Tests for Spermicidal Action *In Vivo* Tests for animal vaginal tolerance have also been standardized, and the rabbit has been the most suitable and universally available laboratory animal for this purpose. The vagina of this mammal is slightly more sensitive to chemicals and foreign bodies than the human vagina, which makes it very practical for use in animal screening tests (23). Zaneveld *et al* report on the suitability of the *macaca arctoides* for this type of testing (see Chap. 24).

Tests for human vaginal tolerance have been designed to assess the potential local irritation effect of a given pharmaceutical product for vaginal use and its aesthetic acceptability by human subjects. The only existing, carefully programmed evaluation for human vaginal tolerance of contraceptive products is the one established by Stone (78). The first in this series of tests is the *single dose test*. The woman's reactions are noted after 10 and 30 min, as are the physical characteristics of the preparation within the vagina. Objective observations, such as its distribution, adherence to the vaginal wall, covering of the cervix uteri, and leakage, are noted and subjective experiences, such as burning and itching, are recorded. Provided the single dose test is

satisfactory, the product is tested for a period of seven daily doses, with examinations before starting, twice during the testing period, and finally, on the 8th day, within 12 hr of the final dose. The same objective and subjective variables are recorded. This is known as the *8-day test.*

The last in this series is the *21-day test,* in which each woman is asked to apply a daily dose of the preparation for 21 consecutive days, which is the schematic nonbleeding time of a menstrual cycle. Examinations are performed before starting the test period, twice weekly during it, and finally within 48 hr after the last application. Vaginal and cervical cytology smears are taken at the first and last examinations. Again, all signs and symptoms are recorded, including any reaction by the sexual partner. If intercourse has taken place, a thorough search for spermatozoa in the cervical mucus is made.

A test of a preparation's ability to stop spermatozoa *in vivo* has also been devised and has been utilized occasionally (13, 18, 33, 38, 41, 73, 74). However, the *postcoital* evaluation, as a way to predict possible contraceptive effectiveness, has not proved valid because the available results of studies on postcoital tests and actual clinical effectiveness of the same preparation, are quite dissimilar. In our experience, 32 postcoital tests were performed under almost ideal physiologic conditions at the most suitable times in the menstrual cycles of 22 volunteer women. The women were selected because they presented several excellent postcoital tests in the absence of contraceptive vaginal preparations and were members of a stable marital relationship. In 29 instances, no spermatozoa were found in the examination of over 40 HPF; in two instances, only one motile spermatozoon was found waving its tail, but with no forward motion in over 40 HPF; and in one case, three spermatozoa were found, again with motility rated at almost zero in the endocervical mucus specimen. Yet the Pearl Index (see Effectiveness), in the actual field study of the same foam in the same clinical setting, gave a failure rate of 27.9 per hundred-women-years (HWY) (73). More recently, studies by Brehm and Albrecht (13) and Stone and Cardinale (79), evaluated a vaginal suppository using a similar methodology and the actual field performance of the same product (see Chap. 14). Their results make clear that the postcoital test, even disregarding the difficulties of finding adequate volunteer subjects, the high costs, and the cumbersome ethical and technical problems that need to be satisfied, is of no value in vaginal contraceptive evaluation.

More recently, Greenslade *et al* (31, 32), McConnell (49), Homm *et al* (36), and Zaneveld *et al* (see Chap. 24), have reported on the use of the rabbit, the *rana pipiens,* and the stumptailed macaque to evaluate the antifertility capacity of vaginal preparations *in vivo* before subjecting them to the true test of effectiveness, contraceptive performance in field trials.

EFFECTIVENESS

There are great variations in the reported rates of effectiveness of presently available contraceptives (see Table 1-4). The best rates are shown in clinical studies using careful patient selection by the investigative team, reinforcement of instructions for correct use, and countering of weakening motiva-

tion. Thus the results of most clinical studies tend to be better than the actual performance of any given method in general use, in which the method is more subject to human frailty. Currently available data for vaginal contraceptive preparations are listed in Table 4-2.

The effectiveness of a contraceptive method—its capacity to prevent unwanted pregnancies—has traditionally been expressed according to the Pearl Index (62), that is, the number of pregnancies per HWY of exposure while using the contraceptive method under study. The Pearl Index, however, is frequently misinterpreted because of the difficulty inherent in the concept of number of events per HWY. But the main problem with the Pearl Index is that the number of pregnancies which occur each month, in a given field study, is a fraction of the number of patients still active in the study until that month, so that different Pearl Index values are obtained for studies of different average length.

The failure rate per HWY does not indicate, as is frequently assumed, a percentage failure. Thus, a Pearl Index of 10 indicates 10 accidental pregnancies per HWY, which would mean 2.5 accidental pregnancies during the reproductive lifetime of an average woman.

The Pearl Index formula is stated as follows:

$$\text{Failure rate} = \frac{\text{Number of pregnancies}}{\text{Total months of exposure}} \times 1200$$

The numerator must include every known conception, regardless of outcome. The denominator (total months of exposure) is obtained by subtracting from the study period all those months during which there was no exposure. That is, during which conception was not possible because of separation, illness, etc. By convention, 10 months are deducted for a full-term pregnancy, 4 months for an abortion.

Patients in a study project of a contraceptive method may be lost to follow-up for a variety of reasons. Some reasons, such as accidental pregnancy or intolerable side effects, are directly related to the efficacy and safety of the method; but others, such as stopping for a planned pregnancy or moving out of town, are not necessarily related. The efficacy of the method under study is indicated by the rate at which women drop out because of accidental pregnancy after an interval of time in the study, and the safety of the method is indicated by the rate at which women drop out because of undesirable side effects. It is therefore important to consider all the dropouts in order to assess the value of the method. The Pearl Index has the disadvantage of not considering the monthly risk of the particular events that occur in a contraceptive clinical study. These reservations have been answered by the use of a modified "life-table" approach. *The multiple-decrement life-table method,* introduced by Potter (63–65) for contraceptive evaluation was most successfully used by Tietze (80) for the evaluation of clinical studies of intrauterine contraceptive devices. This statistical evaluation of a contraceptive clinical performance has not yet been used widely and only one clinical study of vaginal spermicides evaluated by this method has been published (81) (Table 4-2). This approach, while more statistically sophisticated than others, requires rather complex calculations, and thus has not gained the popularity it deserves. A *life-table analysis* specifically considers the size of the decreasing

population at risk, and it presents, in a tabular form, the probability that each of several recorded types of events will occur at each month of exposure; that is, the probability not only of accidental pregnancy (*failure rate*) but also of discontinuance of the method (*drop out rate*) for various side effects (*relevant reasons*) or because of *nonrelevant reasons*, such as the desire to achieve pregnancy, moving away, etc. It further provides an estimate of the percentage of women continuing in the study (*continuation rate*), and with it, an estimate of the contraceptive efficacy expressed as the cumulative percentage of women protected.

The data of the 1971 National Fertility Study (85), analyzed by the life-table procedure, show that young women in the United States had accidental unwanted pregnancies more often than older women, that 26% of couples failed in the first year to delay a pregnancy they would have preferred to have later, and that 14% failed to prevent a pregnancy that was never intended. Only 65% of those couples who did not intend to have additional children were successful in avoiding pregnancy after five years of contraceptive use; Catholics and the young showed the largest percentage of failures. These figures emphasize the need for continuing follow-up of users of contraception, reiteration of instructions, change of method if necessary, and information about the availability of male and female sterilization and about elective pregnancy interruption, as a backup method, at a medically opportune time.

In the field of fertility regulation, looked at from a worldwide perspective, an important factor is the ability to recognize, in different populations and in different cultural settings, the risk-to-benefit ratio of protecting a population from unchecked and unwanted fertility—with its multifaceted personal, medical, familial, ethical, and social ills—the potentially deleterious side effects of a given contraceptive. In this difficult process of establishing the right ratio for the local, social, and individual health realities, special care should be taken to make sure that the former (risk) is not blown out of proportion, while the latter (benefit) is not devoid of all social content.

No study has as yet been made that demonstrates a clear and positive correlation between laboratory tests results for spermicidal activity and contraceptive effectiveness in clinical use for a series of vaginal contraceptive products. Nor are results of comparative clinical studies of different formulations available that have been obtained by using identical research protocols in different cultural settings, and analyzed by the multiple-decrement life-table method.

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5

Condoms: Manufacturing Perspectives and Use

JOHN J. QUINN

Questions about the [illegible] recently raised in the international family-planning community [illegible] are primarily of concern to programs in the less-developed [illegible] the outset, it would be useful to consider briefly the history [illegible] the method.

Condoms made from [illegible] material or another have existed for centuries and have been used in spite of considerable imperfections during most of their time. There are numerous references to condoms as contraceptives in the literature of the eighteenth century. Their widespread use began in the [illegible] after the introduction of vulcanized rubber. By the 1860s and 1870s, condoms were so widely known and used in the United States that opponents were campaigning for their legal suppression. Condoms were also common in Europe at that time, particularly in England. This crepe rubber product began to be replaced in the 1930s by the early modern condoms, manufactured by dipping forms into a bath of liquid latex. This process produced a much superior product in all respects and also facilitated greater volume production. Condom use expanded rapidly thereafter.

Condoms manufactured from sheep ceca are preferred by some users, but they account for a relatively insignificant percentage of condom use, and therefore will not be discussed in this chapter. The unsuccessful experiments with plastic condoms will also be omitted, and only rubber condoms will be considered.

The extent to which condoms and other barrier methods of contraception contributed to the fertility declines of the industrialized countries is a matter of surmise, but it is known that motivation alone does not prevent pregnancy. Widespread abstinence seems unlikely, and it is doubtful that coitus interruptus, being diametrically opposed to the thrust of masculine instinct, could have been widely preferred to available contraceptives in most countries. The extent to which condoms have been used as contraceptives or as disease prophylactics is also uncertain, but they would function as contraceptives in either case.

As late as the 1940s, condom quality remained uneven, because of the varying skills or integrity of different manufacturers, and because quality control techniques were at an early stage of development. Undoubtedly, many males were introduced to the condom at that time through military issue. Like Coca-Cola, condoms followed the troops throughout the world. While condoms were not unknown in less-developed countries prior to the

1940s, exports to those countries increased significantly thereafter, and some local manufacturing began. Producers generally employed a laborious hand-dipping method, a system also common in industrialized countries at that time, where many small manufacturers existed.

Following World War II, many of the affluent, consumer-oriented societies began to expand official programs for consumer rpotection. In the United States, the FDA, having had jurisdiction over the quality of contraceptive devices since 1938, established a formal program of surveillance and testing in 1949 (2). Sweden adopted its first regulations in 1951 (7) followed by Japan in 1952 (6) and Britain in 1964 (9). The British Standard is nongovernmental and voluntary, but the mark of approval has been essential for significant sales in the United Kingdom. A number of other countries also adopted quality standards for condoms. Most of these standards have been subsequently revised and made more stringent.

The establishment of such standards has had a profound effect on the condom industry. Compliance required increasingly sophisticated techniques and elaborate controls which, in turn, required greater capital investment and larger sales volume. Many small manufacturers went out of business or merged into larger, automated facilities. Those gaining early dominance tended to be conservative with respect to product development and the opening of new distribution channels. Others relied on greater flexibility and innovation. To compete in major markets, all found it necessary to pay close attention to the control and improvement of quality, for both official and consumer acceptance reasons.

CONDOM QUALITY AND CONDOM STANDARDS

The interest in condom standards is expressed by the family-planning community in three main questions: 1) Do the standard tests now in use actually measure condom quality so as to assure a certain level of method effectiveness? 2) How well can the condoms meeting these standards withstand local climatic and other conditions? 3) Do standard quality criteria unnecessarily rule out reasonably effective condoms which would be more acceptable to users? None of these questions can be answered definitively here, but useful information and perspective might be provided.

Standards agencies test condoms for two qualities: freedom from holes and strength. The test for holes usually consists of filling the condom with 300 ml of water and inspecting it for leaks. Some standards require that it be rolled on blotting paper to reveal leaks. These standards specify an acceptable number of condoms with holes, depending upon sample size. These defect allowances vary considerably, from 1.33% under the Swedish Standard to a range of 0.2%–0.7%, depending upon sampling scheme and size, under the standard of the U.S. General Services Administration (GSA) (5). Other national standards employing this test fall between the Swedish requirement and the most stringent GSA requirement. The Japanese standard does not deal with numbers of holes. It requires an electrical test using a 1% NaCl solution inside and outside the condom, in which the condom wall must have a resistance of not less than 200,000 ohms.

Very thin holes, called pinholes, may be formed in the latex film during manufacture. To ascertain that their products will meet applicable standards, manufacturers normally test every condom on an electronic machine which automatically rejects units with holes. The Hungarian Standard (4) and the GSA Standard *require* 100% electronic testing by manufacturers. This requirement might tend to inhibit technological progress. Rather than simply establishing a minimum acceptable quality level, it prescribes how that level is to be achieved or assured by the manufacturer.

Freedom from pinholes has long been questioned as a factor in assuring contraceptive efficacy. A body of opinion holds that this requirement was intended to prevent the passage of disease organisms, and that sperm could not pass through these holes in sufficient numbers for a significant probability of conception. If this is the case, the relevant question is whether pinholes are a cause of condom rupture, and under what conditions. To establish that pinholes cause condoms to burst under the standard tests for strength would not necessarily settle this issue.

The validity of the strength tests for predicting condom performance is also questioned. Condom strength is tested by the various standards agencies in one of two ways, before and after artificially accelerated aging: by determining whether the condom will break when inflated with a specified volume of air, or by stretching a specimen cut from the condom to measure tensile strength and elongation at break. The air-inflation test is used in the Scandinavian countries, while tensile strength and elongation are tested under the British, Hungarian, Japanese, and GSA standards. An intense controversy continues between the advocates of these two testing methods, particularly in the deliberations of the Technical Committee (TC 157) of the International Standards Organization, which is attempting to draft an international condom standard.

The advocates of air inflation argue that this method tests the whole condom, rather than only the small section that is cut from the condom for the tensile and elongation test. Those advocating the latter, point to a number of variables which they claim make the results of the air-inflation test unreliable. For example, they argue that test results are significantly affected by a slight change in the shape of a condom, wall thickness, rate of inflation, and other factors. The tensile and elongation test uses a standard specimen cut from all tested condoms, wall thickness is factored into the calculation of results, and the tests are performed with precise uniformity on a very accurate machine. The air inflation advocates nevertheless object that it does not test the integrity of the entire condom.

This controversy, which is necessarily oversimplified here, tends to obscure a more important question concerning the practical relevance of either of these tests. Their purpose is to test the quality of the rubber film, but it may be questioned whether stretchability is the only or main attribute of strength in use. All other factors remaining constant, could the thickness of a rubber film be reduced to a point where it would withstand the required air inflation or stretch, but be too fragile for effective use as a contraceptive? Can the shape or texture of a condom improve or diminish its serviceability?

Theoretically, it should be possible to verify test results in actual product use. Estimates of method effectiveness of the condom, based on studies of

varying scope and sophistication, report some percentage of method failure. One difficulty is exclusion of any damage that might have occurred to the product from causes other than normal use. Such difficulties could never be eliminated in survey research, and perfectly controlled research employing or simulating actual use could be difficult to design. Nevertheless, even if method failure could be clearly isolated and shown to occur in some approximate percentage of cases, it would not necessarily be possible to say that the standard test and required performance level predicted this. It might be found that two groups of condoms of different types or manufacture, samples of which had performed comparably in standard tests, performed quite differently in actual use.

It is simply this gap in our current ability to identify and measure method effectiveness and its causes that has raised questions about the existing standards. Condoms produced to these standards have been found to be highly efficacious and to compare favorably, all things considered, with any other method. They are used with success and satisfaction by millions of consumers. Of course, expectations of condom performance may differ in different cultures.

Beyond original quality assurance, concern has been expressed about the shelf life of condoms under local climatic conditions. Family-planning program administrators have asked for a determination of condom shelf life so that an expiration date could be used. Condom shelf life is determined by a number of variable factors, however, according to specific conditions of handling and storage. Even in areas with identical climatic conditions, storage facilities and other factors may differ greatly.

In countries with a temperate range of climate, conservative estimates of condom shelf life are generally three to five years, assuming favorable storage conditions. However, condoms as old as nine or ten years have met standard requirements when tested. Deterioration of vulcanized rubber is accelerated at higher temperatures and by exposure to humidity, light, oxygen, ozone, and certain deleterious substances. Deformation also contributes to deterioration, and rubber articles should be stored in a relaxed condition, without pressure or tension. Detailed guidelines for the storage of vulcanized rubber articles are published by the International Standards Organization (11) and other agencies.

It might be asked why extensive research has not been conducted to measure the rate of condom deterioration under varied actual storage conditions, including all known variables, as opposed to accelerated aging tests in laboratories using temperature alone. The answer is that in the commercial distribution of condoms, shelf life is rarely a practical problem. Any competent businessman maintains the smallest possible inventory in relation to sales volume, provides as favorable storage conditions as he can, and carefully rotates his stock. If goods do not move steadily through the system, this business will be abandoned as unprofitable, long before shelf life becomes a cause for concern.

Commercial distributors of condoms have functioned successfully for decades in countries with the most inhospitable climatic conditions. The initiation of very large mass-distribution programs in many countries has presented an entirely new set of circumstances. The commercial distributor

normally handles condoms in consumer packaging, which is relatively sturdy and protective in other ways. Programs in the public sector are generally supplied with condoms in plastic or foil strips, which may then be out of their shelf cartons for a time during hand packaging into boxes, or may be displayed and distributed as strips without the protection of boxes.

Since commercial distribution has been limited by local purchasing power, supply lines have been much less extensive, perhaps limited to urban areas. The high, and sometimes questionable, priority given to rural distribution in public or semi-public programs, often requires distribution centers at two or more levels, with less satisfactory facilities at each lower level. The mass introduction of the condom as a new product is certain to result in some miscalculation of inventory requirements.

The commercial distributor develops his business gradually, in direct response to the market and in direct communication with the manufacturer. He orders quantities and types of goods he judges to be appropriate and consults with the manufacturer on any problems he encounters, product modifications he wishes, etc. This communication is absent or very limited for practical purposes where supplies flow through an international donor to a public program. The latter system lacks both the integration and the discipline of commercial distribution. As a result, mammoth inventories have sometimes been created in countries where corresponding consumer distribution systems did not yet exist. It is in these abnormal conditions that shelf life becomes a reasonable concern, particularly because goods are often stored under extremely unfavorable conditions.

Extraordinary situations of this kind can only be dealt with on an *ad hoc* basis. Fortunately, they are not numerous, and they are less likely to occur in the future. The current supply trend, at least in the practice of the U.S. Agency for International Development (AID), is toward a continuous flow of smaller shipments, better related to the rate of program consumption. This is obviously the first requirement for assuring the high quality of the product through to end use. The second is the provision of technical and management training to those responsible for the handling of commodities at all stages. The third is the provision, as far as possible, of suitable storage facilities. Once these steps are taken, there should seldom, if ever, be cause for concern about the condition of condoms which were of good quality to begin with. Should any abnormal circumstances give rise to concern, properly trained personnel would know how to take samples from inventories and return these goods to the donor agency or manufacturer for testing. Through experience and experimentation, each program can establish reasonably accurate estimates of shelf life under its local conditions. This concern can be rendered largely academic, however, by maintaining and rotating the smallest inventories that will assure continuity of supply.

Condoms sealed in metallic foil are sometimes thought to be better preserved under tropical conditions than those in plastic film. The present writer is not aware of any systematic tests supporting this hypothesis, and casual observations in the field have suggested the opposite conclusion. Metallic foil conducts and stores heat better than does plastic film. Also, the torn edge of a foil pouch is more likely to damage the condom upon removal than is a plastic edge. Foils, foil-paper, foil-plastic laminates, and plastic

film vary in thickness and quality, and workmanship also varies in quality. Even if foil were shown to be theoretically superior for this purpose, it would not be at all satisfactory in practice if it were poorly sealed or easily punctured, as is sometimes the case. The question of materials awaits systematic study under various conditions. Meanwhile, the quality of claims in favor of foil is best illustrated by those administrators who specify transparent cellophane on one side of the strip, so that the colored condoms will be visible, and metallic foil on the other side, because it is a better barrier to tropical elements.

The third question about condom quality and standards concerns the proposition that the pinhole restriction excludes the very thin condoms produced in Japan, that these condoms are effective contraceptives, and that they would be greatly preferred by consumers everywhere. It is true that the condoms in question are rejected because of the pinhole requirement. As for effectiveness, their failure rate is generally conceded to be somewhat higher than that of condoms in the more conventional range of thickness. It is claimed, however, that their wider use would more than offset their lower efficacy for demographic purposes.

Advocates of the superthin condom invariably single out U.S. condoms as being incredibly and uniquely thick. Actually, this is not at all true. The range of condom thickness is roughly the same in the United States and Western Europe, and condoms produced in some countries without pinhole restrictions are significantly thicker. The wall thickness of condoms in the United States varies from about 0.04 mm to more than double or, in the case of some textured products, triple that thickness. Yet there has been no surge of consumers toward the thinner brands, in spite of the fact that brand names and advertising have drawn attention to the difference.

Recently, AID took samples of Japanese and U.S. condoms from a program in Asia for independent testing. There was found to be no significant difference in thickness (1). Since the Japanese condoms were not required to meet U.S. standards, one must assume that the Japanese manufacturers supplied what they thought would meet with consumer acceptance in the recipient country.

In 1976, a consumer organization in Singapore bought samples of five condom brands in the consumer market and sent them to the Consumers' Association of the Netherlands for testing. The mean wall thickness of each brand was determined as follows: *Erotim* (West Germany) 0.076 mm, *Jellia Skin* (Korea) 0.074 mm, *Durex Gossamer* (England) 0.073 mm, *Fulex-Rony Wrinkle* (Taiwan) 0.070 mm, *Leonie* (Malaysia) 0.065 mm (10). Although several of these were manufactured by Japanese companies, the thickness range is roughly typical of what would be found in Europe or the United States, where much thinner condoms than any of these are available. Singapore had no condom standard whatever. There was intense competition among many brands. We must assume, therefore, that the superthin condoms were absent because of a market judgement on the part of the manufacturers that consumers would reject them.

What consumers find preferable or acceptable has a great deal to do with what they are accustomed to, not only concerning the product itself, but the entire framework within which the product is used. Matsumoto, Koizumi,

and Nohara (8) point out that induced abortion was widespread in Japan following World War II, and that it was the primary means of family planning. Oral contraceptives and IUDs were not available. It was against this background that the Japanese family-planning associations promoted condom use in the 1950s and 1960s. By 1965, the ratio of contraception to abortion was still only 100:104, although contraception was rapidly gaining the lead. Abortion was an easily available and well-accepted method of birth control. It is reasonable to expect that a user would accept a lower level of efficacy if the goal were to reduce the need for abortion than if the goal were to avoid pregnancy altogether. Where motivation is strong, one finds much greater skepticism about the efficacy of available condoms than is evident in other countries. The authors say

> An outstanding pattern of contraceptive practice in Japan is the tendency among married couples to utilize more than one method. The most favored combination appears to be the condom plus the safe period. The 1969 Mainichi Survey shows that approximately 44 percent combine the use of these two methods. Combination of three or four methods, and even five varying methods reported by some respondents, indicate the strong motivation for limitation of family size.

We are clearly not dealing with something typical here. There are no compelling reasons to expect that the superthin condoms produced in Japan would revolutionize acceptance of this method elsewhere. None of the foregoing necessarily reflects adversely on Japanese manufacturers. It may be said that they respond appropriately to different markets.

One condom characteristic having no relation to quality, but clear importance for acceptability, is size. The conventional size in the West is 52±3 mm in width (half circumference) and 180±10 mm in length. When these condoms were shipped to Southeast Asia by AID in 1972, they met with amusement and rejection. Since that time, Bangladesh and countries eastward have been supplied with condoms measuring 49±2 mm in width and 160±10 mm in length, and these have been found satisfactory. There is no information on size variations within that area, but a family-planning handbook (3) published in China says that condoms are generally available in three sizes. This may have been based on worldwide information, although the handbook seemed to be intended for local use in Kwangtung Province.

Although condoms in the standard Western size range are used fairly widely among some black populations, there is increasing evidence from Africa, the Caribbean, and some black communities in the United States, that availability of a larger size would lead to wider acceptance.

The topics covered in the preceding pages suggest directions for future research. An enormous amount of research has been devoted to the medical methods of contraception, in an effort to improve both the efficacy and safety of those methods. This has not been the case with the condom and other mechanical barriers, for obvious reasons: the medical methods directly involve health concerns considerably more complex than any associated with the condom (*e.g.*, the need for a nontoxic lubricant). Also, medical researchers, with some prominent exceptions, have tended to regard the condom with disdain.

CONDOM USE

In the late 1960s, population program administrators with demographic concerns began to show interest in the condom because of its significant advantages over medical methods with respect to mass distribution, use, and secondary requirements. Given a finite budget, the population program administrator must decide whether funds would be best spent in search of perfect efficacy or in an effort to get highly effective and available contraceptives into general use. The arithmetic of his problem is likely to draw him toward the latter. The medical practitioner, on the other hand, is frequently inclined to stress sophisticated technologies to optimize individual health care in preference to reaching the greatest numbers.

There is an essential incongruity between these concerns, but they were locked together in organized programs by the early decision to make clinic systems the sole or primary vehicle for contraceptive distribution. It would be a gross oversimplification to describe these concerns respectively as quantitative and qualitative. The lines of separation are by no means drawn that clearly, and each has gradually absorbed something of the other. Nevertheless, health professionals have tended to favor the use of resources to improve efficacy and safety, and to focus their attention on what they regard as most effective at present. Population professionals have tended to favor the use of resources to increase motivation and availability, and to welcome any method that lends itself to mass distribution and use.

Use of the condom has tended to increase where contraceptive distribution is pushed beyond health agencies and clinic systems, particularly those of government. For the purposes of population programs, the optimum form of contraceptive promotion and distribution is that of the commercial consumer-goods market. As population programs were being initiated in many countries, commercial distribution of condoms and other contraceptives existed in all or most of them. Nearly all of these contraceptives were imported, and their sale was often severely limited by high cost, as well as by official and social restrictions. A great part of the cost was usually added by the government in the form of heavy import duty and other taxes. Beyond the markets thus served, the existence of an unknown but very substantial demand for condoms was always evidenced by the insatiable requirements of pilferers, smugglers, and itinerant distributors. (By this index, the most successful contraceptive distribution programs anywhere do not seem to have yet exhausted current demand for condoms.) In contrast to the clinic system, this was a mobile, loose, liberal, mass-oriented, sexless, responsive, and active system of distribution.

Numerous observers and participants in population affairs favored liberating and facilitating this local entrepreneurship by simply finding a way to close the gap between cost and purchasing power. Some attempts were made to do this, but all were flawed in one way or another, by insufficient incentive, insufficient or no competition, and/or too much government direction. In all cases, however, a very large active and latent demand for condoms was discovered.

Most programs in their early stages consist of clinic services provided by

medical and trained auxiliary personnel. These systems tend to be limited, tightly structured, prescriptive, individual and female-oriented, and essentially passive with respect to the general population. They are not naturally hospitable to the condom.

In the 1970s, the trends have been toward less formal and more liberal clinic services, and toward the expansion of various forms of nonclinic distribution. These trends have favored the condom and significantly increased its use. However, only gross measurements and analyses of the effects of these trends on condom use are possible, using incomplete figures on the international movement of commodities and spotty information from country programs. Supply of condoms by the leading international donors in the past four years is shown in Tables 5-1, 5-2, 5-3, and 5-4 (12). Supply to some country programs in 1974–1976 was abnormal. This still causes some distortion of these figures as an indication of program use levels. Also, figures on supply by some smaller donors and through direct purchase are not included in the table, nor are figures on supply through the commercial sector. There is a lamentable lack of information with which to analyze condom use.

Even where large-scale, nonclinic distribution is developed, statistics are usually fed back through a system where all but medical information tends to be filtered out. Thus, surveys of contraceptive use generally report on the pill, the IUD, sterilization, and "other methods". Virtually no efforts have been made to study condom use in depth in various countries.

It would be necessary for such studies to take into account the commercial sector. After opting initially for the public health approach, population programs have been drawn back toward the commercial model in their search for effective mass distribution. Some of the resulting subsidized marketing programs and forms of community-based supply have made very dynamic beginnings in expanding distribution, particularly of condoms.

These programs might lose momentum at some point, particularly those directly supported by government as an element of the national program. Subsidy might eliminate competition, and with it the diversity of products and appeals found in a competitive market. A too-dominant program with secure government support might be less responsive and innovative than is necessary to win new users after the early gains. It would be prudent to foster some competition and diversity to satisfy the diverse tastes of consumers and create pressure for product and service improvement.

There is good reason to hope that these programs will grow. Recent trends suggest that condom distribution through programs of this kind might have to assume a much greater role in some countries. Family-planning services provided through conventional service agencies are increasingly burdened with technical criteria and social tasks which may hinder a strategy for demographic effect. Some countries could achieve their demographic targets by reaching feasible levels of contraceptive practice only in areas of concentrated population, where promotion and supply are easiest and most economical. However, universal theory now dictates that these services (and resources) be extended on a priority basis to rural areas.

Most ominous, however, is the legacy of Bucharest, where, in 1974, the opponents of population policy asserted that family-planning programs are

TABLE 5-1. Condoms Supplied by International Donors,* CY 1975 in Gross (144)

	AID	AID	IPPF	PATH	SIDA	UNFPA	TOTAL
Algeria						1,910	1,910
Aruba			200				200
Bangladesh	433,580	1,214	15,000	4,500			454,294
Barbados			7,500				7,500
Benin			1,000				1,000
Bolivia			500	200			700
Botswana			3,500				3,500
Cameroun				25			25
Chile				2,910			2,910
Colombia			43,800	300			44,100
Costa Rica	3,000		4,000				7,000
Curacao			20				20
Dominica			400	100			500
Dominican Rep	7,500	5,000	1,500	30,500			44,500
Ecuador		3,020	100	2,000			5,120
Egypt		1,012	1,000			38,000	40,012
El Salvador	22,000		5,000	10			27,010
Ethiopia			40				40
Fiji			200				200
Gambia			2,000				2,000
Ghana	25,000		700				25,700
Grenada			1,500				1,500
Guatemala		52,000	1,000				53,000
Haiti		8,005					8,005
Honduras	200		200	200			600
Hong Kong			50				50
India		1,610					1,610
Indonesia	180,200		32,040				212,540
Iran			3,600				3,600
Iraq			1,500				1,500
Jamaica	27,020		500				27,520
Jordan		6					6
Kenya	5,690						5,690
Liberia	8,320		210	380			8,910
Malaysia			800				800
Mauritius			1,700			7,000	8,700
Montserrat			100				100
Morocco	1,120		1,000				2,120
Nepal	80,000		2,000				82,000
Nicaragua			100	600			700
Nigeria		45	830	218			1,093
Pacific Islands						620	620
Pakistan	1,055,505	7,512	10,600				1,073,617
Panama	960		50				1,010
Paraguay	1,000		800				1,800
Peru		4,000					4,000
Philippines	269,200			150			269,350
St. Kitts			50				50
St. Lucia			200	800			1,000

(continued)

TABLE 5-1. Condoms Supplied by International Donors,* CY 1975 in Gross (144) (Cont.)

	AID	AID	IPPF	PATH	SIDA	UNFPA	TOTAL
St. Vincent			1,100				1,100
Senegal				200			200
Seychelles			530				530
Sierra Leone			8,000				8,000
Sri Lanka		2,800	40,500		30,000		73,300
Surinam			500				500
Taiwan		5,000					5,000
Tanzania			1,500				1,500
Thailand	35,000		95,000				130,000
Tonga						1,000	1,000
Trinidad & Tobago			20,000				20,000
Tunisia	30,000						30,000
Turkey		51 000					51,000
Uganda			200				200
Uruguay			115				115
Venezuela			200				200
Yemen Arab Rep		1					1
Zaire				195			195
Zambia		2	1,500				1,502
	2,058,595	142,227	314,435	43,288	30,000	48,530	2,764,075

*All figures obtained directly by the author from the donor agencies listed

TABLE 5-2. Condoms Supplied by International Donors,* CY 1976 in Gross (144)

	AID	FPIA	IPPF	PATH	SIDA	UNFPA	TOTAL
Afghanistan	1,520						1,520
Anguilla			200				200
Antigua			200				200
Aruba			100				100
Bangladesh	97,000	113,730	34,736				245,466
Benin	2,600						2,600
Bolivia				455			455
Botswana		10	1,500				1,510
Burma		860					860
Cameroun		316					316
Chile			2,000	20			2,020
Colombia		960					960
Costa Rica		3,500	15,000	20,000			38,500
Curacao			60				60
Dominica			400				400
Dominican Rep.				20,200			20,200
Ecuador				16,000			16,000
Egypt				85,000			85,000
El Salvador	36 060						36,060
Ethiopia		513	300				813
Fiji			3,500				3,500

(*continued*)

TABLE 5-2. Condoms Supplied by International Donors,* CY 1976 in Gross (144) (Cont.)

	AID	FPIA	IPPF	PATH	SIDA	UNFPA	TOTAL
Ghana	14,450	5,000	1,550				21,000
Grenada			3,500				3,500
Haiti	30,000	5,000					35,000
Honduras	6,760		400				7,160
India		1,400					1,400
Indonesia		260				200,000	200,260
Iran			7,000				7,000
Iraq			1,000				1,000
Ivory Coast		15					15
Jamaica	35,000	5,000	3,000				43,000
Jordan		18	100				118
Kenya			900		1,600		2,500
Lebanon			3,000				3,000
Lesotho			35				35
Liberia		31		520			551
Malaysia			2,600				2,600
Mauritius		280	1,500				1,780
Mexico		1					1
Montserrat			200				200
Morocco	6,760		200				6,960
Nepal	93,500		5,500				99,000
New Hebrides		6					6
Nicaragua	2,000	1,000	6,000				9,000
Nigeria		514	1,000				1,514
Pakistan	1,474,100	50	50,900			294,208	1,819,258
Panama	16,900	500	350				17,750
Papua New Guinea		80					80
Paraguay	2,360	20	1,000	200		300	3,880
Peru		40					40
Philippines	200,000	192,160	70,000	63,500			525,660
St. Kitts			700				700
St. Lucia			400				400
Senegal				19,150			19,150
Seychelles			540				540
Solomon Isls.		120	200				320
Sri Lanka			38,000				38,000
Syria			11,000				11,000
Taiwan		1,200					1,200
Tanzania		240	200				440
Tunisia	33,000		15,000				48,000
Turkey		47,857					47,857
Uganda		21	100				121
Uruguay			100				100
Venezuela			3,600				3,600
Vietnam					30,000		30,000
Yemen Arab Rep.						30	30
Zaire	15,000	1,880		550			17,430
Zambia		10					10
	2,067,010	382,592	287,571	225,595	31,600	494,538	3,488,906

*All figures obtained directly by the author from the donor agencies listed.

TABLE 5-3. Condoms Supplied by International Donors,* CY 1977 in Gross (144)

	AID	FPIA	IPPF	PATH	SIDA	UNFPA	TOTAL
Afghanistan	3,500						3,500
Algeria						400	400
Antigua			130				130
Bangladesh	901,576	484,891				44,588	1,431,055
Benin		500					500
Bolivia			200	200			400
Botswana			1,000				1,000
Burundi		40					40
Cameroun		217					217
Chile				25			25
Colombia		40	65,000				65,040
Costa Rica			5,000				5,000
Curacao			170				170
Cyprus			40				40
Ecuador			400				400
Egypt		40	4,150	245,000			249,190
El Salvador	60,000						60,000
Ethiopia		120	800				920
Faulkland Isls.			100				100
Fiji						3,000	3,000
Gambia		500					500
Ghana		20	1,050				1,070
Gilbert Isls.						40	40
Grenada			1,500				1,500
Haiti	58,825						58,825
Hong Kong			15,000				15,000
India		100					100
Indonesia		90					90
Iran			1,000				1,000
Jamaica	58,715		500				59,215
Jerusalem			200				200
Jordan			40			360	400
Kenya		500	950	8,040	1,000		10,490
Lebanon			1,000				1,000
Lesotho			110				110
Liberia				6,000			6,000
Madagascar			40				40
Malaysia			4,186				4,186
Mali						100	100
Mauritius		5,000	1,700			2,000	8,700
Mexico		27,778		10,000		20,000	57,778
Montserrat			200				200
Nepal			3,000				3,000
New Hebrides			200				200
Nicaragua	18,230			1,380			19,610
Nigeria		564		137			701
Pakistan		47,220					47,220
Papua New Guinea			500				500
Paraguay	2,647		1,000				3,647

(*continued*)

TABLE 5-3. Condoms Supplied by International Donors,* CY 1977 in Gross (144) (Cont.)

	AID	FPIA	IPPF	PATH	SIDA	UNFPA	TOTAL
Philippines	173,611	173,611	50,000				397,222
Rwanda		50					50
St. Kitts			400				400
St. Lucia			600				600
St. Vincent		7,000					7,000
Sierra Leone		80					80
Solomon Isls.		20	320				340
Sri Lanka			70,000				70,000
Sudan		10	120				130
Swaziland		500	500			1,250	2,250
Taiwan	13,750						13,750
Tanzania	1,000	160	1,500				2,660
Thailand		51,609	11,000			10,000	72,609
Trinidad & Tobago			10,000				10,000
Tunisia	65,000						65,000
Turkey						25,000	25,000
Uruguay			575				575
Yemen Arab Rep.		40				20	60
Zambia				1,000			1,000
	1,356,854	800,700	254,181	271,782	1,000	106,758	2,791,275

*All figures obtained directly by the author from the donor agencies listed.

TABLE 5-4. Condoms Supplied by International Donors,* CY 1978 in Gross (144)

	AID	FPIA	IPPF	PATH	UNFPA	TOTAL
Afghanistan	2,222					2,222
Argentina			50			50
Bangladesh	348,283	201,393				549,676
Benin			3,000			3,000
Bolivia		40				40
Botswana			2,500			2,500
Brazil				20		20
Cameroun		3,224				3,224
Chile			1,000			1,000
Colombia			40,000	3,480		43,480
Costa Rica	13,917	680				14,597
Curacao			42			42
Dominica			690			690
Dominican Rep.		13,889				13,889
Ecuador			400			400
Egypt	200,000	1,396	11,000			212,396
El Salvador	6,111					6,111
Fiji		1	1,000			1,001
Gambia				100		100
Ghana	14,458	60				14,518
Grenada			1,500			1,500
Haiti	64,250		2,500			66,750

(*continued*)

TABLE 5-4. Condoms Supplied by International Donors,* CY 1978 in Gross (144) (Cont.)

	AID	FPIA	IPPF	PATH	UNFPA	TOTAL
Honduras	319	128				447
Hong Kong			16,000			16,000
India		1,700				1,700
Iraq			300			300
Jamaica	4,819					4,819
Jordan		1,000	40			1,040
Kenya	1,597	7,710	600	12		9,919
Lesotho				1,000		1,000
Liberia				5,000		5,000
Malaysia			5,200			5,200
Mauritius			2,375			2,375
Mexico		122,889		10,000		132,889
Nepal	20,833		1,000			21,833
Nicaragua	5,555					5,555
Nigeria		610		200		810
Pakistan		20,847				20,847
Panama		5				5
Papua New Guinea		500				500
Paraguay	5,000	7				5,007
Peru	125	1,504		3,662		5,291
Philippines		173,611				173,611
St. Kitts			300			300
St. Vincent		2,625				2,625
Senegal				20		20
Seychelles			2,000			2,000
Sierra Leone		214				214
Sri Lanka		5,569	65,000			70,569
Sudan		32	40			72
Tanzania	1,042	20				1,062
Thailand		139,444	6,000		30,000	175,444
Togo			3,000			3,000
Trinidad & Tobago			15,000			15,000
Turkey				10,000		10,000
Uganda			200	6,000		6,200
Venezuela			500			500
Vietnam					70,000	70,000
Yemen Arab Rep		28				28
Zaire		2				2
Zambia		10				10
	688,531	699,138	181,237	39,494	100,000	1,708,400

*All figures obtained directly by the author from the donor agencies listed.

not a contribution to, but a diversion of resources from, the process of development. It was claimed that people in developing countries reject the means of fertility control unless they are accompanied by a range of other services. This may be true in health delivery systems. At this writing, the abortionists and dealers in commercial and contraband condoms have been too busy to report on this problem. In any case, the capitulation or compro-

mise of the international development community is expressed in the slogan of "integration". It is difficult to question integration as a universal principle without seeming to dismiss the very good things that are meant to be integrated, or to appear to take the position that integration is never appropriate and desirable. Integration is now intoned as an end, however, which should be pursued by family-planning programs everywhere. As a practical matter, other good things are far less likely to be integrated with family-planning services than the latter are to be further integrated into the inadequate and relatively slow-growth systems mentioned above, where population matters are far from the highest priority.

In anticipation of this likely outcome, population specialists might do well to look more closely at the condom and the resources for its promotion and distribution at the commercial end of the delivery spectrum. In the interest of strengthening this effort, it would be more advantageous to enlist the local and international resources of the private sector than to risk their displacement. Much can be done to exploit these resources in collaboration with current programs. First, it is necessary to begin systematic data collection and analysis, encompassing both public and commercial sector activity. For this purpose, a cooperative dialogue between elements in the production and distribution system should be encouraged.

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6

An Overview of Experience with Vaginal Contraceptives in the United States

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The dramatic changes in contraceptive practice in the United States since 1960 have been characterized as the contraceptive revolution (3). The changes have been documented by a series of national fertility surveys beginning in 1955.* The most recent of these surveys, the National Survey of Family Growth conducted in 1976, suggests the revolution may have come to a halt or at least changed direction.

Ample evidence of widespread and effective contraception by families in the United States early in the century is provided by the low fertility and small families of the 1930s. In 1955, 83% of fecund, white couples with wives 18 to 39 years of age had intentionally used some method of contraception other than sterilization (3). A decade later, 93% of couples in this category had done so. From these data, Westoff and Ryder concluded, "Clearly, the norm of fertility control has become universal in contemporary America" (9).

CHANGES IN CURRENT CONTRACEPTIVE PRACTICE, 1965–1976

From the four national surveys between 1965 and 1976, we can trace the contraceptive revolution by examining the changing proportions of couples with wives 15–44 years of age, who are using the various methods of contraception shown in Figure 6-1 (2, 13).

The contraceptive revolution did not lie in the increase in current contraceptive users—a modest rise of only 6 percentage points between 1965 and 1973—but in the changing distribution of methods used. The three most

*National sample surveys of fertility in the United States include The Growth of American Families I and II, conducted in 1955 and 1960, respectively, followed by the two National Fertility Studies of 1965 and 1970, respectively. The National Survey of Family Growth was added to the data systems of the National Center of Health Statistics in 1971, and Cycles I (1973) and II (1976) have been completed. Cycle III, which will include single as well as ever married women, is expected to begin in 1980.

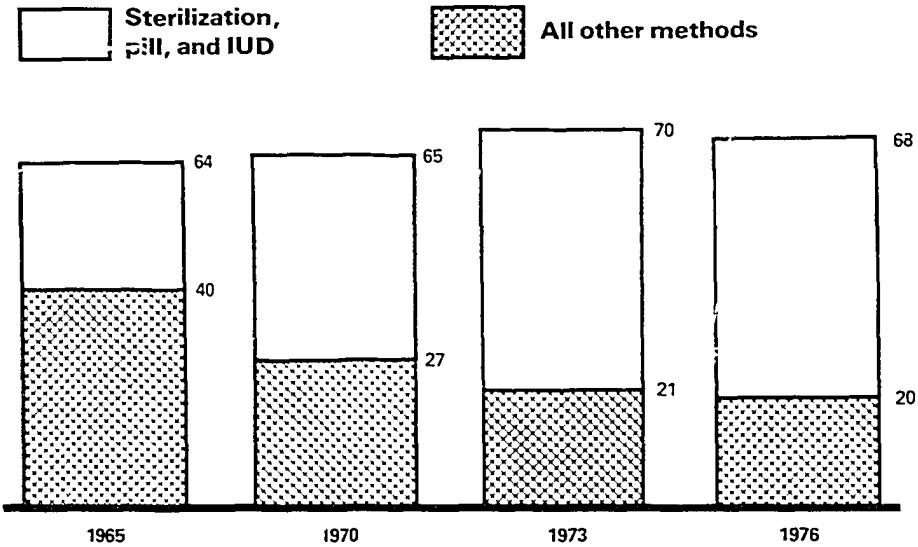

FIG. 6-1. Percent of married couples (wife aged 15–44) using a contraceptive method. (The National Center for Health Statistics, Hyattsville, Md.)

highly use-effective methods—the oral contraceptive pill (the pill), the intrauterine device (IUD), and sterilization for contraceptive (*i.e.*, family limitation) reasons increased from a combined 24% of couples in 1965 to 48% in 1973. Within five years of becoming generally available to the public in 1960, the pill and the IUD were in use by 16% of married couples and their use doubled in the next eight years. Surgical sterilization for contraceptive reasons showed an equally dramatic doubling, from 8% in 1965 to 16% in 1973.

The use of all other methods of contraception was correspondingly diminished by half over this period, from a combined 40% in 1965 to 21% in 1973. Westoff and Ryder compared the most recent methods used by contracepting couples over the preceding decade, 1955–65; the proportion of couples using the diaphragm had declined 60%, the condom had declined 33%, jelly alone 50%, withdrawal and douche by 25%, and rhythm by 40% (9). Possibly these declines are somewhat exaggerated as they refer only to the use of each method by itself and do not include various combinations in which they were used. Nonetheless, over the next eight years, from 1965 to 1973, these methods continued to decline in popularity, a trend shared by each method except foam. By 1973, vaginal contraceptives (diaphragm, foam, cream, condom, jelly, and douche) were being used by only 17% of all couples, and rhythm and withdrawal by just under 5%.

Findings from Cycle II of the National Survey of Family Growth (NSFG), reported by Ford, suggest an emerging change in contraceptive practice by 1976 (2). The overall level of contraceptive practice among currently married women may have declined by as much as two percentage points involving a decline in both the more effective and the more traditional methods, as may be seen in Fig. 6-1. However, this decline in currently contracepting couples is deceptive in two important ways.

First, the decline does not imply an increasing proportion of couples exposed to the risk of an unplanned pregnancy. Overall, the proportion of couples protected from unplanned pregnancy, either by sterilization or by nonsurgical methods of contraception, expanded from 77.0% in 1973 to 79.1% in 1976. This growth was due entirely to the continued increase in both contraceptive and noncontraceptive sterilizations (a combined 6.5 percentage points). The growing acceptability of sterilization as a means to terminate childbearing may prove to be the most dramatic development of the contraceptive revolution.

The rise in sterilizations among currently married couples exceeded the decline in nonsurgical contraception (4.6 percentage points) in these three years. Preoccupation with the rapidly rising popularity of the pill has obscured the continuing decline in nonsurgical methods as a group since 1965, when 56% of couples were using these methods. In 1976, only 49% of couples were relying upon nonsurgical contraception.

The most noteworthy change in nonsurgical methods was the decline in use of the pill and IUD for the first time since they were introduced in 1960. Between 1973 and 1976, these methods declined more than 3 percentage points compared to a decrease of only one percentage point in the more traditional methods taken together. Nonetheless, the proportion of couples currently using the pill or IUD (28.8%) remained well ahead of the proportion using the other nonsurgical methods (20.3%) in 1976.

The second deceptive aspect of the decline in contraceptive practice is that it is largely or entirely due to a change in the question by which sterilizations were classified as contraceptive or noncontraceptive. The change was expected to produce a smaller proportion of sterilizations for contraceptive (*i.e.*, family-planning) reasons than would have been so classified by the 1973 wording. For this reason, we cannot conclude that there was a statistically significant drop in the proportion of contracepting couples. More important, classifying sterilizations as contraceptive or noncontraceptive in motivation is imprecise—an inappropriate dichotomy. In particular, sterilizations for therapeutic reasons, which would not have occurred otherwise, will have replaced the need for contraception by other methods which many couples had been using. For instance, in an estimated 8% of female sterilizations classified as noncontraceptive, the husband had had a prior vasectomy, presumably for family-planning reasons.

The problem of classifying sterilizations by their motivation and the impact (of sterilization) on trends in contraception will be dealt with in a forthcoming analysis, but for the remainder of this discussion, it is appropriate to return to the practice of earlier fertility surveys. Sterilization will be treated as a separate topic, while discussion of contraception will focus on the nonsurgical methods which provide a continuing discretionary control over the risk and choice of pregnancy.

CHANGES IN METHOD PREFERENCE AMONG CONTRACEPTING WOMEN, 1973–76

Although the proportion using nonsurgical methods declined among married women as a whole, it did not decline among those who were fecund

or nonsterile. Ford observed that "about the same percent of women at risk of an unwanted pregnancy (those not sterile, pregnant, postpartum or seeking pregnancy) were using a method in 1976 as were in 1973, 86.3 and 85.9 percent respectively" (2). If we include in the comparisons the most recent contraceptive practices of those currently pregnant, postpartum and seeking pregnancy, the proportion of currently married, fecund women using nonsurgical methods actually increased from 87.2% in 1973 to 88.9% in 1976. In other words, the decline in nonsurgical methods of contraception among all currently married women was exclusively because of the increasing resort to sterilization for whatever reasons, and not to any abandonment of contraception among fecund or nonsterile women.

In Table 6-1 and in the discussion which follows, attention is focused on the pattern of method preference among ever-married, nonsterile women who are contraceptors, and on the changes in preferences between 1973 and 1976. Comparisons are based on the most recent methods of contraception used by women who used any method in the last three years before the interview (contraceptors). For the very great majority the most recent method was the method currently being used at the survey date, but for approximately 12% of women who were currently pregnant, postpartum, or seeking pregnancy, it was the method used prior to seeking pregnancy or becoming pregnant. The more common practice of excluding the currently pregnant from these comparisons creates some bias in the pattern of preferences because those using the less effective methods or no method at all have a higher risk of becoming pregnant at any given time. Also, by this method of classification, postmarried women, who are currently not contraceptors because they are not sexually active, are not excluded from the comparisons. Finally, the distribution of methods shown in Table 6-1 is based exclusively on contraceptors, in order to provide the clearest comparison of user preferences, unaffected by varying proportions of those who are "never users" for whatever reasons. The category of "never users" implied by this classification may include a small portion of those who have used methods sometime prior to the three years preceding the survey, but almost all will be women who have actually never used any method because they have not yet started to use contraception or because of subfecundity, infrequent intercourse, or aesthetic and ethical reasons.

THE PROPORTIONS ABLE TO BEAR CHILDREN

In the first two columns of Table 6-1, the proportions of fecund or nonsterile women in 1973 and 1976 are compared. This comparison is important because those opting for sterilization may have preferred quite different methods or none at all compared to those remaining fecund; that is, they may affect changes in the distribution of nonsurgical methods by drawing more heavily from one group of contraceptors than from others and may be more likely never to have used contraception. While a careful examination of the likelihood of sterilizations according to the previous method used is beyond the scope of this paper, a crude indication is that 25% of those whose most recent method was the pill or IUD were sterile, compared with 31% of those whose most recent method was the condom, foam or diaphragm,

TABLE 6-1. Percent of Ever-Married Women, 15–44 Years of Age, Who are Fecund, Percent of Nonsterile Women Who are Contraceptors,* and Percent Distribution of Contraceptors by Most Recent Method Used U.S., 1976 and 1973

	PERCENT OF WOMEN WHO ARE NONSTERILE		PERCENT OF NONSTERILE WOMEN WHO ARE CONTRACEPTORS		PERCENT OF CONTRACEPTORS WHOSE MOST RECENT METHOD OF CONTRACEPTION WAS								
					TOTAL 1976 OR	PILL OR IUD		CONDOM, FOAM OR DIAPHRAGM		RHYTHM OR WITHDRAWAL		OTHER	
	1976	1973	1976	1973	1973	1976	1973	1976	1973	1976	1973	1976	1973
All women	70.4	76 4	88.3	85.3	100.0	62.2	61.9	24 4	26 4	9.9	7.7	3.5	3.9
15–19 years of age	98 2	99.2	90.7‡	76 2	100.0	82.0	80.8	12.5	11.1	4.8	5.3	0.7	3.1
20–24 years of age	94 8	94.5	92.0	92.1	100.0	76.3	80.0	15.8	14.3	6.1	3.8	1.7	1.8
25–29 years of age	81.6	85.7	93 8	91.5	100.0	65.6	68.0	24.1	24.0	7.0	5.0	3 2	3 0
30–34 years of age	63.4†	72.8	87.9	87.2	100.0	57.8	56.6	26 3	31 6	11 8	8 0	4.1	3.7
35–39 years of age	53.4†	63 9	82.0‡	76.3	100.0	48.3	45.9	32 8	35 2	14.4	13.3	4.5	5.6
40–44 years of age	49.9†	58.6	75.1	73.9	100 0	33 2	31.9	38 2	43 5	21.3	15 8	7.3	8.8
White women	69 8†	76.3	89.6	87.0	100.0	61.7	60.8	25.0	27.6	10.2	8.2	3.1	3.5
Under 30 years	88.1†	90.5	93.4	91.1	100.0	70.9	73.1	20 2	19.8	6.6	4.7	2.2	2.3
30 years and over	54.9†	65.0	84.6	82.5	100.0	48.3	45.6	31.8	37.1	15.4	12.3	4.5	4.9
Currently married	69.3	76.0	90 2	88 2	100.0	59.9	59.7	26.4	28.6	10.8	8 5	3.0	3.3
Postmarried	73.4	79.4	84.6‡	76.1	100.0	77.0	72 3	13.4	17.3	5.8	4.8	3 8	5.6
Black women	73.5	76 7	79.3‡	71.6	100.0	68.6	74.4	18.2	14.6	5.6	2.1	7.6	8.8
Under 30 years	87.7	89.6	88.5‡	83.2	100 0	77.8	85 0	12.5	8.9	4.4	1.6	5.3	4.5
30 years and over	63.6	67.2	70 5‡	60.1	100.0	57.5	59.9	25.2	22.4	6.9	2.9	10.4	14.7
Currently married	75 6	77.3	81.8‡	75.7	100.0	65.0	73.6	20.4	16.0	6.6	2 4	8.0	8.0
Postmarried	69.5	75.6	74.1‡	63.1	100.0	76.8	76.5	13 3	11.3	3.3	1.4	6 6	10.8
Less than high school	63 4	69.5	78 2	74.6	100.0	68 0	64.6	17.8	21.1	9.4	8.4	4.7	5.9
Four years high school	70.1	77.5	89.7	87.0	100.0	63.0	61 3	23.9	27.4	9.9	8.0	3.2	3.2
More than high school	76.6	82.3	93.3	92.9	100.0	57.5	60.7	29.1	29.0	10.2	6.8	3.2	3.5

Protestant	66.5	73.6	88.5	87.2	100 0	65.3	64.2	22.9	26.1	7 6	5.5	4.2	4.2
Catholic	76 0	80.9	87 6‡	81.4	100.0	57.7	56.1	24 8	26.6	14.8	13.6	2.7	3.4
Other	78 7	85.2	91.0	91.0	100.0	58 3	65.1	31.6	29.1	8.4	2.7	1.6	3.1
Fecund	100.0	100.0	94.3	91.4	100.0	62.5	62 8	24.6	26 1	9.7	7.5	3.2	3.6
Subfecund	100 0	100.0	64 0	60 9	100.0	61.2	56.9	23 0	28.5	10.1	8.4	5.7	6.2
No births	90 0	92.8	84 2‡	78 3	100.0	68.0	71.6	21.5	21.0	8.0	4.8	2.5	2.6
1–2 births	77.4	84 2	90.8	87.8	100.0	64 0	63.8	23.9	26.6	8.8	7.0	3.2	3.8
3–4 births	51.7†	61.0	89 9	88.0	100.0	53 0	53.5	27.8	32.4	14.4	10.5	4.9	3.6
5 and more births	43 0	54 2	76.1	80 5	100.0	49.2	53.7	30.0	23 5	15.3	13.2	5.5	9.6
White. Expect more	100 0	100.0	89.6	85.5	100.0	66.7	69.3	22.3	22 7	8.4	5.9	2.6	2.4
Expect no more	54.5†	63.1	89.5	88.4	100.0	57.0	53.4	27.4	32.1	11.9	10.1	3.6	4.4
Black: Expect more	100.0	100.0	81.3‡	72 1	100.0	70.5	79.8	13.8	12.6	7.5	2.4	8.2	5.2
Expect no more	63.8	66.1	78 1‡	71.2	100 0	67.4	70.6	20.9	13.3	4.4	2.0	7.3	11.4

* Contraceptors here include all women who used a method of contraception at any time in the 3 years preceding the survey.

† Decline in proportion nonsterile of at least eight percentage points.

‡ Increase in proportion contraceptors of at least five percentage points.

23% of those using other methods, and 40% of those who never used a method. These percentages, of course, may be affected by differences in the age distributions of women who most recently used the various particular methods.

The sharp decline in the proportion of women who are fecund is observed in every social and demographic category examined except women under 25 and those categories in which 100% are nonsterile by definition. Values which, in 1976, were at least eight percentage points lower than the comparable 1973 figure are marked by a dagger (†) in Table 6-1. The proportions of women who are fecund decreases steadily with increasing age. Among women 25 and older, the size of the decline in the fecund proportion between 1973 and 1976 became greater with increasing age, except among those 40–44 years of age, of whom over 50% were sterile in 1976. Lower proportions of older and currently married white women were still able to bear children when compared to black women, and the difference widened slightly in the three years. The proportons nonsterile were smaller among those with less education and among Protestants. Almost paradoxically, the proportion fecund declines sharply with increasing numbers of children and the decline in fecund women between 1973 and 1976 was far greater for those with three or more children than for those with less than three children. The greater use of sterilization for family limitation among white women than among black women is seen clearly in the much lower proportion fecund among white women expecting no more children (over 9 percentage points lower). In both racial groups, sterilization, whatever the motive, is a greater factor in the termination of childbearing than the leading nonsurgical methods of contraception; among white women expecting no more children, 45.5% are sterile, compared to only 27.8% using the pill or IUD, and among black women expecting no more children the comparable proportions are 36.2% sterile and 33.6% using the pill or IUD.

The decline in the proportion fecund among postmarried women (6.3 percentage points) though practically the same as that of currently married women, involves a significant difference: the sterilizations among postmarried women are all female operations. In 1976, female sterility was reported by 19.8% of currently married women, an increase of 4 percentage points since 1973, compared with 27.0% of postmarried women, representing an increase of almost six percentage points. Although this substantial difference in the proportion sterile between currently and postmarried women is reduced when standardized for race and age, a significant difference remains and raises an important speculation about the possible impact of surgical sterilizations on marital stability.

THE PROPORTION OF FECUND WOMEN USING CONTRACEPTION

As shown in the third and fourth columns of Table 6-1, the proportions of contraceptors among ever-married, nonsterile women increased from 85.3% to 88.3% between 1973 and 1976. All but 3 of the 32 categories compared shared in this increase to some degree, though in many instances the amount of increase was not statistically significant. Those categories in which there was an increase of at least five percentage points are indicated with a

double dagger (‡) in Table 6-1. The greatest single increment in contraceptive practice was 14.5 percentage points among ever-married teenagers. With this increase, the level of contraceptive practice among the teenagers (90.7%) rose to practically the same level as among ever-married women in their 20s (92.9%). Black women reported an overall increase of 7.7 percentage points, more than twice the increase among white women and showed large increases in all subcategories. Postmarried women reported remarkably large increments in the proportions of contraceptors among both white women (up 8.5 percentage points) and black women (up 11 percentage points). While these increases, which were also observed on a current-use basis, may reflect some change in sexual behavior among the widowed, divorced, and separated, they must surely reflect greater candor in the anonymity of the interview. Ever-married Catholic women reported an increase in contraceptors of 6.2 percentage points in contrast to no statistically significant changes among Protestant women and those of other religious preferences. In 1976, no statistically significant difference remained between Catholics and Protestants in the proportions of ever-married women who were using contraception. Women who had not begun their childbearing reported an increase in the proportion of contraceptors that was twice the average, which was probably associated with the great increase among teenagers. Only among ever-married women with five or more children was there a decline in the proportion of contraceptors (down 4.5 percentage points) but, owing to sample size, this decline cannot be judged statistically significant and may be influenced by the increase in sterilization.

METHOD PREFERENCES AMONG CONTRACEPTORS

The overall distribution of contraceptors according to the methods used, which is shown in the remaining columns of Table 6-1, remained practically unchanged between the surveys. The popularity of the pill and IUD with over three-fifths of contraceptors was unchanged and so was that of other methods which accounted for only 3%–4% of users. The 24.4% using the condom, foam or diaphragm in 1976 was a loss from 1973 of 2 percentage points balanced by an equivalent increase to 10% in those using rhythm and withdrawal.

Although the majority of changes in the proportions using each method, within the various social and demographic groups shown in the table, are not statistically significant, the patterns of change are nonetheless worthy of comment for the potential directions which they suggest. Unfortuntely, with this aggregate view of change, it is impossible to disentangle the amount of change in any given method that is due to new contraceptors, to the loss of older ones, or to switching among methods by still others. For instance, if, as was suggested earlier, those who opt for sterilization are more likely to have been former users of the condom, foam or diaphragm, their loss to the population of contraceptors will selectively reduce the preference for those methods among the remaining users unless there are compensating additions from new people beginning contraception or older people switching to those methods. A more complex analysis beyond the scope of this presentation is needed to disaggregate these effects. However, the aggregate changes

are nonetheless important, as they reflect the current demand or preference for each method.

Pill and IUD The popularity of the pill and IUD among all married couples declined for the first time between 1973 and 1976 from 31.8% to 28.8%. This change too was influenced by the trend in sterilization. The decline was much smaller (only about one percentage point) among currently married, fecund contraceptors. When one looks at the most recent methods used among nonsterile, ever-married women using contraception in the last three years, the popularity of the pill and IUD was actually unchanged between the surveys, accounting for about three-fifths of all contraceptors.

Contraceptors in their twenties were less likely to be using the pill or IUD in 1976, while those 30 years and older, who might have been expected to desert these methods in view of the adverse publicity that began between the surveys, reported no change or possibly an increase. White contraceptors continued to use the pill and IUD at about the same rate as in 1973, but black contraceptors, except the postmarried, revealed a marked desertion of these methods, achieving a decline of almost 10 percentage points among those expecting more children. A defection from these methods also appears likely among those with more than a high school education (persons who might be expected to have, on the average, better and more current information about contraception and its side effects) and those with religious preferences other than Protestant or Catholic.

Condom, foam, or diaphragm The decline in the proportions relying upon the condom, foam, or diaphragm appears to have occurred exclusively among white contraceptors 30 years of age and older, and those who expect no more children. These were also the categories in which the highest increases in surgical sterilization were reported. Based on the earlier observation that sterilizations were distinctly more likely among those whose most recent method of contraception was the condom, foam or diaphragm, it would appear that this decline reflects a determination to end childbearing rather than to switch preferences among nonsurgical methods, but there was no compensating adoption of these methods by new contraceptors. Black contraceptors reported increased reliance upon these methods, particularly among those who intend to have no more children. This increase would appear to be very largely a switch in method preferences because there was relatively little increase in sterilizations and a very substantial defection from the pill and IUD.

Rhythm and withdrawal The increase in rhythm and withdrawal may be the most curious development in the 3-year period for, although the percentage gains are small, they occur in every category but one. They represent very sizable relative gains in many cases, considering the generally low proportions relying on these methods to begin with. One of the greatest increases was among women over 30 years of age who also reported the largest increases in sterilization. This observation suggests that a significant portion of the increase in rhythm and withdrawal may be the comparatively lower loss of contraceptors from the over-30 group, possibly because they are at lower risk

of contraception due to subfecundity or less frequent intercourse. But younger contraceptors too, revealed some increased reliance on these methods, perhaps because they are only contracepting to delay the pregnancies they ultimately want and because they have the option of abortion for unwanted pregnancies. Two groups with comparatively large gains in these methods were those with more than a high school education and those with religious preferences other than Protestant or Catholic. Both of these groups had about the average increase in sterilizations, no increase in the already very high proportions contracepting, and significant declines in the proportions using the pill and IUD; in such groups, better informed on the average, such an increase (though small in absolute numbers) is a puzzling development. Currently married black contraceptors also reported above average increases in the proportions relying on rhythm and withdrawal which have customarily had extremely low popularity in the black community. Whether or not this change is merely a short-term choice, the increase in rhythm and withdrawal among black contraceptors appears most likely to be a deliberate switching from the pill and IUD. Again one is puzzled and concerned; are these women accepting the increased risk of pregnancy and planning to use abortion as a back-up procedure, or have they no strategy for dealing with unplanned pregnancies?

CONTRACEPTIVE EFFECTIVENESS

The most salient features of the contraceptive revolution were the remarkable acceptance of sterilization and the speed with which the pill and, to a much lesser degree, the IUD displaced the more traditional methods. At least by contrast to those other options, the newer methods met many of the criteria for more effective contraception. Disturbing research findings in recent years, concerning the safety of the pill, the IUD, and now vasectomies—and the realization that the most effective contraception may contribute to an upswing in venereal disease—have brought about a renewed interest in vaginal contraceptives (as evidenced by this conference).

The questions of the efficacy of different methods continues to be controversial on several grounds which seem to center on two main problems: what constitututes the most appropriate statistical measure of effectiveness and what is the most appropriate study design.

The oldest and perhaps still most widely cited measure of contraceptive effectiveness is the Pearl Index. For at least a decade, however, the inadequacy of this measure has been repeatedly exposed in the literature (7, 10, 11), and only its persistence warrants another summary statement of its limitations.

The Pearl Index is the ratio of the number of unintended pregnancies occurring in a group of women to the number of months they have been exposed to the risk of pregnancy, expressed per 100 women–years of exposure. This measure is valid only in the limiting case that the probability of unintended pregnancy is equal for all months of exposure. Potter has observed that "the experience of a group of contraceptors is advantageously viewed as a process changing through time. As successive months of exposure elapse, the accident-prone are selectively removed by pregnancy to

TABLE 6-2. Effects of Exposure Period on Pearl Index

MAXIMUM EXPOSURE	PEARL INDEX	
	IUD	*Condom*
12 months	2.75	7.33
24 months	2.03	5.69

leave behind a more and more homogeneously low-risk remainder" (8). The problem of loss of comparatively high-risk women in the earliest months is exacerbated if less motivated women remove themselves from exposure by abandoning the given method or stopping contraception altogether. In a report based on data in the 1973 NSFG (9), the effect of the observation period on the Pearl Index is clearly demonstrated in Table 6-2.

The preferred method of measurement proposed by the critics of the Pearl Index uses a life-table procedure. The cumulative product of the proportions of women who "survive" each successive month of a pregnancy interval while using a method of contraception (any method or a specified method) is calculated. The complement of this probability of survival is the failure rate, or the probability of an unintended pregnancy.

However, in following the experience of any given population or sample of women there are many ways, other than a contraceptive failure, in which one may leave the population. One may change methods of contraception or give up contraception altogether; one may cease to be exposed to the risk of conception by separation or marriage dissolution; or one may decide to have a baby. To account for these many sources of attrition a multiple-decrement life-table is calculated, from which associated single-decrement life-tables may be constructed to isolate the various sources of attrition. Thus various rates of discontinuation and their complements—continuation rates—may be calculated. Under a contract with the National Center for Health Statistics, demographers at the Office of Population Research, Princeton University, developed life-table measures of use-effectiveness under varying assumptions, and continuation rates based upon data from Cycle I (1973) of the NSFG (12).

The measure of effectiveness that is used to compare contraceptive methods may be a less critical problem than the comparability of study designs. A common but uncritical distinction is made between theoretical-effectiveness and use-effectiveness. The distinction is essentially one of methodology; of the ability to measure the failure of a method *per se* (theoretical), independent of extraneous human failures in application or regimen (actual use).

In one listing of comparative effectiveness measures for different methods, theoretical and use measures were shown side-by-side, but how it was determined which studies gave theoretical measures and which gave use measures was not described (4). Claims to measure theoretical-effectiveness seem generally to be based on case-control clinical studies which permit highly controlled instructional and observational procedures. Such intensive observation is costly, (usually favoring quite small samples), highly selective or nonrepresentative, and generally does not facilitate interstudy comparisons. Moreover, such intensive observation has its own bias risks such as a "Haw-

thorne effect," in which participants perform better because of the attention which the observation implies.

An alternative, or supplement, to the clinically based, case-control study is the sample survey of a general, household population. The survey, when appropriately designed, can produce use-effectiveness measures and can approximate theoretical-effectiveness rates in the sense that the various sources of failure or method discontinuation can be distinguished in a variety of life-table measures. On the whole, however, we feel that theoretical-effectiveness is a concept which is best suited to methods such as the pill, for which there exists an unambiguous procedure for correct use. We much prefer a measure of failure which reflects the actual experience of a population using a particular method. The outstanding values of the survey lie in the representative character of the sampled respondents, in the ability to assess sampling variability, and in the standard population for which method-effectiveness measures are calculated.

A major objective of the NSFG was to provide a better, nationwide data base for calculating measures of the use-effectiveness of various contraceptive methods. In both Cycles I (1973) and II (1976), a monthly record of the contraceptive status of each respondent during the three years preceding the survey was obtained. This record included information on periods of separation or abstinence from intercourse of at least one month, on the particular contraceptive methods used in each month, on months without using a method and whether this was in order to conceive or not, on months spent in pregnancy and on months of nonuse of contraception following pregnancy. In addition, for each pregnancy occurring in the 3-year period, it was determined whether contraception had been used to prevent an unwanted pregnancy or to delay the next wanted pregnancy, and whether contraception had been intentionally avoided or stopped before conception in order to become pregnant. These data were ordered within "use segments," beginning with marriage or the termination of a pregnancy and proceeding until the method was discontinued or to the interview date.

Failure rates for the first 12 mo of use in a use segment were calculated for a number of the contraceptive methods reported, revealing substantial differences between them. However, notable differences in use-effectiveness were also documented between those who were simply trying to delay their next-wanted pregnancies and those who were seeking to prevent unwanted pregnancies. In the first year of method use (whether it was the first use of that method ever, or resumption after a period of nonuse), preventers had a failure rate of 3.7%, compared to delayers who had a failure rate of 7.3%. If sterilization is excluded, the failure rate for preventers using nonsurgical methods was 5.1% (12).

Contraceptive failure rates during the first 12 mo of use per 100 married women, 15–44 years of age, were calculated for each method used according to contraceptive intention to delay or prevent another pregnancy (Fig. 6-2). The failure rate for the pill was the same for both preventers and delayers at 2.0%. The IUD was next in use-effectiveness, with a 2.9% failure rate among preventers and almost twice the failure rate among delayers. Failure rates for those trying to prevent an unwanted pregnancy using rhythm, the diaphragm, or any one of the foams, creams, or jellies considered as a

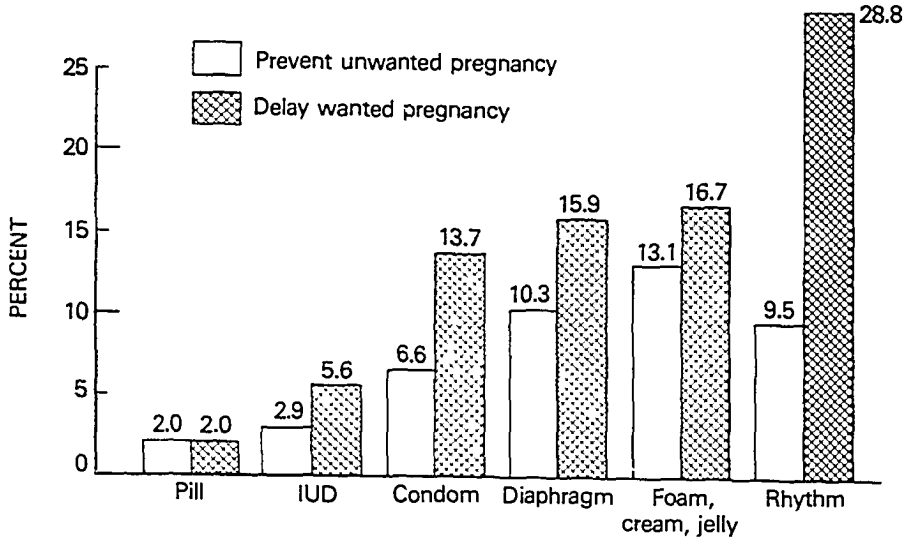

FIG. 6-2. Contraceptive failure rates during the first 12 mo of use per 100 married women (aged 15–44) by contraceptive intention, U.S., 1970–1973 (National Survey of Family Growth. In Vaughan B, Trussel VB, Menken J et al: Vital and Health Statistics, Series 23, No. 5 Hyattsville, Md., The National Center for Health Statistics, 1979)

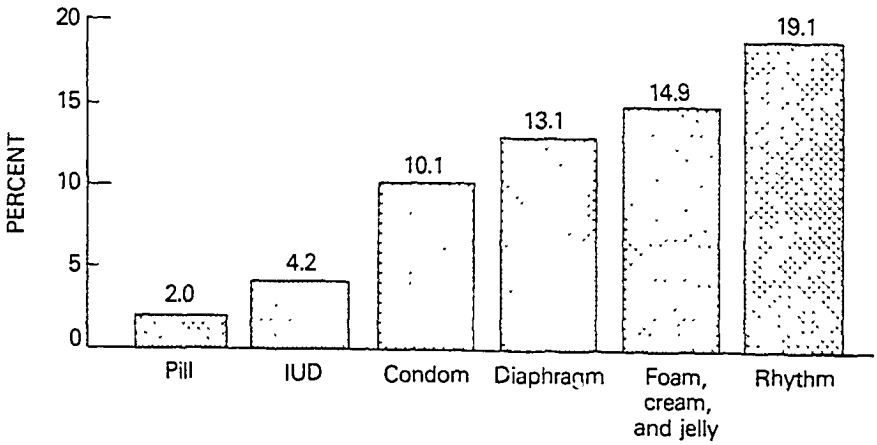

FIG. 6-3. Contraceptive failure rates* during the first 12 mo of use per 100 married woman (aged 15–44) U.S., 1970–1973 (National Survey of Family Growth. In Vaughan B, Trussell VB, Menken J et al: Vital and Health Statistics. Series 23, No. 5, Hyattsville, Md. The National Center for Health Statistics, 1979)

*Rates are standardized for contraceptive intentions to delay the next-wanted birth or to prevent an unwanted birth.

group, followed in increasing order from 9.5% to 10.3% to 13.1% respectively. Among delayers, these three methods also have higher failure rates: 15.9% among diaphragm users, 16.7% among users of foam, creams, or jellies combined, and 28.8% among those using rhythm.

Single overall rates of failure for the various methods were calculated, standardized for differences in the proportions of users of each method who were delaying or preventing another pregnancy (Fig. 6-3). The same rank order prevails, of course, with the pill having a failure rate of 2.0%, followed by the IUD with 4.2%, and continuing with the condom (10.1%), the diaphragm(13.1%), the foams, creams, and jellies considered together (14.9%), and rhythm (19.1%).

Differences in overall failure rates were observed among various subgroups of the population. Failure with contraception generally declined with increasing age, which is understandable in view of declining fecundity and stronger motivation to prevent all further births as age increases. Interestingly, however, there was no systematic association of failure rates with age among those using contraception only to delay the next-wanted child. For both delayers and preventers, failure rates declined notably with increasing education. Although black women are less likely to use contraception in the first place, failure rates among black women trying to delay or postpone the next pregnancy were lower than among white women also trying to delay the next birth. Black women were more likely to be using the most effective methods in 1973. One wonders if delayers among black women in 1976 will still have lower failure rates, inasmuch as they exhibited a strong tendency to move away from the pill and IUD. Among those seeking to prevent future births, however, black couples in 1973 were slightly less effective contraceptors than corresponding white couples. Catholic women have increasingly adopted the more effective methods. Among white women, Catholics who seek to delay the next birth are slightly less successful than others, while those who seek to prevent another birth are slightly more successful.

An examination of continuation rates, so far as the data permitted, for the different methods and classes of users showed that preventers were, as expected, somewhat more likely to continue use over extended periods than delayers. For condom and for foam, cream, or jelly taken together, continuation rates were lower than for the pill and IUD. In general, however, even if accidental pregnancies are avoided, a quarter or more discontinue use of a method within a year.

It is quite likely that these failure rates are too low, though possibly to differing degrees, because the survey did not obtain an accurate account of abortions. Although women were asked for all pregnancy losses they had experienced without any question about how the loss occurred, it is likely that such pregnancy terminations were not reported at all, or were not reported as contraceptive failures. Again, it will be instructive to learn the comparable results for 1976 when a significant number of abortions were openly reported. It is also possible that differences among the failure rates are somewhat understated. It is quite likely that women using some of the more traditional methods were the more successful, longer-term users of these methods in segments of use prior to those observed in the 3 years before the survey; they may be more successful with them or may have relatively lower fecundity compared with all

women who ever used them, some of whom may have switched to other methods by the survey date. Some support for this suggestion would seem to lie in the fact that users of the less-effective methods are older on the average.

"WHAT IS THE BEST METHOD FOR ME?"

This is the fundamental question asked by the person seeking contraceptive protection. Like most questions in life, it has no certain answer. The answer depends on a great many factors: safety, efficacy, constraints on the coital act, problems of privacy, frequency of intercourse, aesthetics and others. The physician can only offer comparisons of the rates of method failure and continuation experienced by groups of women with social and other characteristics similar to the patient's own. More and more, we are able to discriminate the motivations and conditions under which method failures or discontinuation occur.

To date, the most widely available information to physicians, and that provided on the recommended labeling for oral contraceptives, seems to be a cafeteria of study results for each contraceptive method (6). These results are based on a variety of studies, not comparable in several respects, including the sample size, selectivity, and cultural diversity. The great majority are based on the Pearl Index which is biased by the highly variable periods of observations used in the studies. Most troubling are the ranges of these failure rates. They do not even represent the reasonable limits of sampling variability. If they were probability sample estimates, their standard errors would substantially broaden the ranges, which are already greater than those observed in the NSFG. Finally, they provide no data on comparative continuation of these methods, either as to their duration of use or their causes of attrition. In short, they provide virtually no basis for the physician or the patient to choose among the methods.

Being based upon a probability sample, the failure rates from the NSFG are estimates that may differ from sample to sample, around the true value for the population. This variation is summarized in the "standard error of the estimate," which is a measure of these variations. One may conclude that the population value will lie between the estimate obtained from the sample, plus or minus one standard error, about two-thirds of the time, or in 68 out of 100 repeated samples like this one. From the NSFG, the failure rate of the pill, as seen in Fig. 6-3, was 2.0 per 100 married women, aged 15–44 years, with a standard error of 0.4 per 100 women, usually shown as 2.0 (±0.4). The IUD was 4.2 (±1.2) per 100 women; the condom 10.1 (±1.7); foam, cream, jelly as a group 14.9 (±2.1); diaphragm 13.1 (±3.8) and rhythm 19.1 (±4.0). If one wishes greater confidence of including the actual population value, say 95% instead of 68% confidence, it is only necessary to use two standard errors; thus one can say that the probability of failure with the pill is at least 1.2% but not greater than 2.8% with 95% confidence. The Pearl Indices cited in the recommended oral contraceptive labeling, if they are to be generalized to larger populations, also have standard errors but they are unknown because they are not based on probability or representative samples.

One of the limitations of the NSFG is sample size. To reduce the sampling variability in these estimates, the National Center for Health Statistics is exploring the possibility of pooling the results from Cycles I and II for the calculation of use-effectiveness rates. Other limitations of the NSFG, which are expected to be much improved in Cycle III, include the under-reporting of abortions, the exclusion of single women and a lack of information on the reasons for discontinuation of various methods. Cycle III is expected to begin in 1980.

SUMMARY OF PRINCIPAL CONCLUSIONS

Despite an apparent downward trend in the use of contraception between 1973 and 1976, the proportion of currently married women, 15 through 44 years of age, who were protected from unplanned pregnancies actually increased slightly to 79%. This increase was due to the continued and dramatic rise in sterilizations, which may yet prove the most revolutionary aspect of the contraceptive revolution. Nonsurgical methods continued their downward trend among currently married women in general, but solely as the obverse of the rising trend in sterilization. The decline in nonsurgical methods did not reflect an abandonment of contraception by those remaining at risk of an unplanned pregnancy. A noteworthy fall in the proportion of couples currently using the pill or IUD in 1976 was the first observed since these methods became available, and was greater than the associated decline in traditional methods. However, among fecund couples (the only ones to whom these methods pertain) the decline in use of the pill or IUD was only one-third as large. Among current contraceptors, the pill remains the leading single method by a very substantial margin.

Replacing the comparisons of current contraceptive status among only currently married women, which has been customary in recent years, with comparisons of the most recent methods used by nonsterile, ever-married women, provides a sharper picture of the trend in method preferences between the surveys, and makes greater use of the data.

Fertility control among fecund women by nonsurgical methods, far from diminishing, actually increased from 85.3% to 88.3% in the 3-year period. The greatest single increase in contraceptors was 14.5% among ever-married teenagers whose level of contraceptive practice rose to almost equal that of women in their twenties. In all categories of black women the proportions of contraceptors increased by a combined 8 percentage points, possibly reflecting a growing reluctance to use sterilization for family limitation. Postmarried women reported a large increase in contraceptors, probably revealing greater candor at least as much as any greater sexual activity.

Although the pill and IUD were used by about three-fifths of all contraceptors in both 1973 and 1976, black contraceptors (except the postmarried) reported a very sharp defection from these methods.

A small but significant decline in contraceptors using the vaginal methods (condom, foam, and diaphragm) appears to be due entirely to changes among white women 30 years of age and older, and among those expecting no more children. Black contraceptors, on the other hand, particularly those

expecting no more children, increased their acceptance of these methods possibly in lieu of the pill.

Rhythm and withdrawal showed a small but significant increase among contraceptors and this relative gain occurred in every category but one. Some of these increases may reflect subfecundity or lower frequency of intercourse in groups where sterilization attracted relatively more users from the other methods. Nonetheless, the increases in rhythm and withdrawal were greater among those expecting more children than among those expecting no more.

In both Cycles I and II the NSFG collected data which made it possible for the first time to produce use-effectiveness or failure rates by life-table methods, based on a detailed monthly calendar of contraceptive behavior among a probability sample of all ever-married women. Failure rates for specific methods of contraception in the first 12 mo of use segments in the 3 years preceding the survey (1973) were calculated according to the users' motivation to delay or prevent another pregnancy. Failure rates of all methods combined were estimated for specific population groups.

The rank order of methods from lowest to highest failure rates were the same among preventers and delayers, but preventers were significantly more effective contraceptors. Failure rates standardized for intentions ranged from 2.0 (±0.4) per 100 women using the pill to 19.1 (±4.0) per 100 women using the various rhythm methods. The IUD; the condom; the foams, creams, or jellies as a group; and the diaphragm came between the pill and rhythm methods in that order.

Failure rates calculated by life-table procedures from a probability sample of a standard population, provide a comparative basis for individual method choice for members of that population. The scientific merit of such data is greatly superior to comparisons based on biased measures (Pearl Indices) and incomparable data bases. The latter, unfortunately, have all too often been the only information readily available to the public.

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VAGINAL CONTRACEPTION RESEARCH AND DEVELOPMENT

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7

Research in Vaginal Contraception: An Overview

JOHN L. McGUIRE,

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After almost two decades of scientific eclipse, barrier methods of contraception are gaining interest and importance. Increasing concern about the side effects of oral contraceptives and IUDs has resulted in a shift of attention by both scientists and consumers from these methods to the traditional barrier methods of fertility regulation.

New effective and safe barrier methods of contraception will depend on research efforts in public and private sectors, throughout the world. To some scientists, this observation may seem platitudinous. Yet, a wide gap seems to exist between the expectations of health care providers, consumers, and government officials for more effective and safe contraceptives on the one hand; and research efforts currently being committed to meet those expectations, on the other. Actually, a rather small amount of scientific information is available in the area of vaginal contraception, and a paucity of significant current research directed toward new approaches exists today.

The situation is changing, however. Scientific interest in barrier contraception has grown considerably during the past few years. Public agencies have begun to fund research at more realistic levels, and scientific advances are becoming evident. These positive initial steps may lead either to a temporary surge in research activity or to development of needed new methods of fertility regulation for consumers.

The current status of vaginal contraceptive research can best be viewed against a historical background. The idea of barrier contraception dates back to the time when a cause-and-effect relationship between sexual intercourse and pregnancy was first recognized. Coitus interruptus was known at least as early as Biblical times. For centuries pastes, jellies, and various mixtures have been placed in the vagina to prevent conception. In the nineteenth century B.C., the Egyptians were mixing honey, natron (sodium carbonate), and crocodile dung to form a vaginal contraceptive paste. In the fourth century B.C., Aristotle described the use of oil of cedar and frankincense in olive oil to block the cervical os. During the Middle Ages, rock salt and alum were frequently used (2).

The scientific basis of barrier contraceptives probably began in 1678, when Anton van Leeuwenhoek, the inventor of the microscope, reported the existence of animalcula, or sperm, in semen. To recount all the contribu-

tions to the scientific foundations of vaginal contraceptive products would make a long list. In retrospect, however, major creative research in this area has been concentrated in two relatively brief historical periods.

The first began two centuries after van Leeuwenhoek. It began when in 1855, Kolliker in Germany published his findings on the effects of chemical agents on sperm motility. This event initiated a series of studies which could be called the first age of modern-day vaginal contraceptive research. In the 1880s, the diaphragm, invented by Mensinga, came into use (2), and Rendell, an English pharmacist, produced the first commercial vaginal contraceptive: a suppository of soluble cocoa butter containing quinine sulfate. Late in the nineteenth century, Besant, an English feminist leader, recommended a sponge soaked in quinine solution as a spermicidal vaginal barrier (2), and Chunn, in the United States, suggested the use of vaginal contraceptives containing boric acid, tannic acid, or bichloride of mercury. In 1907, Günther in Germany confirmed and expanded Kolliker's work (12), and a spermicidal jelly was introduced commerically in that country.

The second stage of research into vaginal contraception began a quarter of a century later. In 1928, Baker in England compared the effects of chemical agents on guinea pig and human sperm, providing the basis for *in vitro* spermicidal assays using human sperm (1). This was followed by a series of papers by Brown and Gamble establishing standards for human spermicidal testing (4, 5, 6, 7). Research in the laboratories of the Ortho Pharmaceutical Corporation in the late 1930s led to the standard Sander–Cramer test (22) and the Mende–Berliner assay to compare spermicidal formulations (20). In the early 1940s, the first surface active spermicidal agent, Triton X-100, was discovered and developed commercially at Ortho (3), and a few years later, nonoxynol 9 was discovered in the Ortho laboratories (21). During the next two decades, surface-active agents became the principal active ingredients in spermicidal products. The development of Menfegol (17) by the Japanese pharmaceutical company, Eisai, continued this trend. The surfactants are neither strongly acidic nor irritating to the vagina, but have high spermicidal activity. Most other spermicidal ingredients have fallen into disuse, either because of the inferior spermicidal potency of the weak acids or the potential toxicity of mercury-containing compounds. Surfactants are marketed in a variety of dosage forms and are available worldwide (Table 7-1, *Pages 104 and 105*).

Soon after the development of surfactant spermicide-containing vaginal contraceptives, a scientific hiatus began that has lasted to this day. Little new research in vaginal contraception was undertaken, except for the development of such new dosage forms as C film, the water-soluble contraceptive film containing nonoxynol 9. Vaginal methods were overshadowed by the oral contraceptives and intrauterine devices. The use of vaginal agents declined. The time and minds of researchers were increasingly occupied with developing lower-dose oral contraceptives, IUDs, and long-acting parenteral forms of hormonal contraceptives.

As more information about the potential side effects of hormonal agents was gathered, however, scientific interest in vaginal methods was revived. Even so, it was not until the mid 1970s that innovative research into vaginal contraception again began in a few laboratories. Apart from rather modest support of

research into new delivery systems by the World Health Organization, The Population Council, and the Program for Applied Research on Fertility Regulation (PARFR), significant public funding of research in this area has just begun.

Current research in vaginal contraception is centered in four areas: 1) formulation development, 2) assays for efficacy and safety, 3) clinical and epidemiological studies of efficacy, and 4) basic research.

FORMULATION DEVELOPMENT

The major emphasis in current research with vaginal contraceptives centers on dosage form development. The major thrust has been to make products containing surfactants more effective by enhancing consumer compliance. This work began as product-line extensions in the form of aerosol foam products (2), and resulted in foaming tablets and suppositories (2). These dosage forms are not long-acting, however, and must be applied at coitus. Present research emphasis has shifted to development of longer-acting delivery systems, such as sustained release vaginal inserts, and spermicide-releasing sponges, condoms, and diaphragms, which may make these agents temporally independent of intercourse.

Altering the dosage form and increasing its convenience may not seem to be major advances from the viewpoint of medical/scientific progress, but any formulation change resulting in increased convenience contributes to patient compliance. Moreover, animal data, as well as clinical impressions (11, 15, 16), suggest that formulation changes can enhance the inherent efficacy of vaginal contraceptive products.

IN VITRO AND ANIMAL ASSAYS FOR EFFICACY AND SAFETY

In vitro spermicidal assays, although useful in testing new potential agents for vaginal contraception, have three important shortcomings. First, these methods measure only those agents which immobilize sperm. Compounds such as acrosomal enzyme inhibitors, which may block fertilization without affecting motility, would remain undetected by these assays. Secondly, *in vitro* tests are poorly suited to ascertain the relative effects of inactive ingredients of a formulation on its active ingredients, *i.e.*, release of the compound from its vehicle; and the active ingredients plus the barrier effects provided by the vehicle. Finally, spermicidal tests fail to measure the effect of compounds on any other physiologic characteristics associated with the reproductive tract, which could suggest new types of vaginal contraception. These might include compounds that physically change cervical mucus.

For these reasons, many investigators have sought an *in vivo* animal model in which fertility rather than sperm motility is the experimental end point. During the 1950s, research conducted in the Ortho laboratories by Hartman (14) and at the Worcester Foundation by Chang (9), suggested that the rabbit was not well suited to such a test. These results discouraged *in vivo* experimentation in this area for several years. By the mid 1970s, Ortho investigators

TABLE 7-1. Major Vaginal Contraceptive Products

PRODUCT	DOSAGE FORM	MANUFACTURER	GEOGRAPHIC DISTRIBUTION*
Surface active agents			
Nonoxynol 9			
Because	Aerosol foam	The Emko Co.	1
Conceptrol	Cream	Ortho Pharm. Corp	1, 2, 3, 4
Dalkon Foam	Aerosol foam	A. H. Robins	1, 6
Delfen Cream	Cream	Ortho Pharm. Corp.	1, 2, 3, 4, 5, 6, 7, 8
Delfen Foam	Aerosol foam	Ortho Pharm. Corp.	1, 2, 3, 4, 5, 6, 7, 8
Duracreme	Cream	L. R. Industries Ltd.	3, 4
Duragel	Jelly	L. R. Industries Ltd.	3, 4, 5
Encare Oval	Foaming suppository	Norwich-Eaton Pharm.	†
Emko Foam	Aerosol foam	The Emko Co.	1, 2, 3, 4, 5, 6, 8
Immolin	Cream	Schmid Labs. Inc.	1, 2, 3, 8
Koromex Foam	Aerosol foam	Holland-Rantos Co Inc	1
Koromex 11-A	Jelly	Holland-Rantos Co. Inc.	1, 2, 4, 6, 7, 8
Ortho Creme	Cream	Ortho Pharm. Corp.	1,2,3,4,5,6,7,8
Ortho Forms	Suppository	Ortho Pharm. Corp.	3, 4, 5, 6
Patentex	Jelly	Patentex GmbH	1, 2, 3, 5, 6
Patentex Oval	Foaming suppository	Patentex GmbH	3
Patentex Schaum Spray	Aerosol foam	Patentex GmbH	2, 3, 5, 6
Rendells	Suppository	W. J Rendell Ltd.	1, 2, 3, 4, 7, 8
Semicid	Suppository	Gynechemie	1, 2, 4
Staycept Cream	Cream	[illegible]tex Labs. Inc.	4
Staycept Jelly	[illegible]	[illegible]ex Labs, Inc.	4
Staycept Suppositor[illegible]	[illegible]ory	Syntex Labs. Inc.	4

had demonstrated that the implantation rate in rabbits, after intravaginal administration of contraceptive formulations prior to mating, provided an index of vaginal contraceptive potency (11, 15, 16). This *in vivo* model appears to lend itself to evaluation of products containing spermicidal agents, as well as compounds acting on other sperm functions required for sperm transport or fertilization. It also allows evaluation of the effect of inactive ingredients in a formulation, and provides insight into whether a formulation will deliver the spermicide in a more or less bioavailable form or enhances the physical barrier to sperm transport (15). Recent work by Zaneveld with a second species, the stump-tailed monkey, provides another promising model for *in vivo* vaginal contraceptive testing (25).

The validity of these animal models in measuring human vaginal contraceptive efficacy is as yet unknown. There are obvious differences between the reproductive anatomy and physiology of these animals and those of women [illegible]. Further, the clinical data which exist to date do not allow accurate comparison of the efficacy of different vaginal contraceptives, nor do they allow a comparative evaluation of the efficacy of vaginal contraceptives with hormonal contraceptives or IUDs (2). However, at this time these models do appear to be promising research tools.

TABLE 7-1. Major Vaginal Contraceptive Products (Cont.)

PRODUCT	DOSAGE FORM	MANUFACTURER	GEOGRAPHIC DISTRIBUTION*
Triton X-100**			
Genexol Cream	Cream	W. J. Rendell Ltd.	4
Ortho-Gynol	Jelly	Ortho Pharm. Corp.	1, 2, 3, 4, 5, 6, 7, 8
Octoxynol			
Koromex II Cream	Cream	Holland-Rantos Co. Inc.	1
Koromex II Jelly		Holland-Rantos Co. Inc.	1
Hexylresorcinol, dioctylsodium sulfosuccinate			
Prentif Compound	Jelly	Lamberts	4
Polyoxethylenoxy phenol			
CCC	Jelly	Yamanouchi Ltd.	8
p-Methanylphenyl polyoxyethylene ether			
Neo-Sampoon	Foaming tablet	Eisai Co. Ltd.	2, 4, 5, 6, 8
Organometallic compounds			
Phenylmercuric acetate			
Lorophyn Jelly	Jelly	Norwich International	1, 2, 3, 4, 6, 8
Lorophyn Suppository	Suppository	Norwich International	1, 2, 3, 4, 5, 7, 8
Zinc phenosulfonate			
Rendell Foam	Foaming tablet	W. J. Rendell Ltd.	4
Other active agents			
Boric acid			
Ramses Jelly	Jelly	Schmid Labs Inc	1, 2, 3, 4, 8
Polysaccharide-polysulfuric acid ether			
Syn-A-Gen	Foaming tablet	Dr Herbrand KG	1, 4, 6, 8
Syn-A-Gen	Suppository	Dr Herbrand KG	2, 3
Chloramine			
Gynomin	Foaming tablet	H R. Napp Ltd	2, 4, 6, 7, 8

*Distribution—1: U.S. & Canada, 2: S. America, 3: Europe, 4: United Kingdom, 5: Middle East, 6: Africa, 7: Australia & New Zealand, 8: Asia & Far East.

**p-Diisobutylphenoxypolyethoxy ethanol
(Kestelman P, Kleinman RL: International Planned Parenthood Federation (IPPF) Directory of Contraceptives. London, IPPF, 1976)

†U.S. only.
(From the International Planned Parenthood Feueration Directory for 1976 [edited by the authors])

CLINICAL AND EPIDEMIOLOGICAL STUDY OF VAGINAL CONTRACEPTIVES

The third area of research has only recently been brought to general attention (24). It involves the clinical evaluation of the efficacy of barrier methods of contraception. The ramifications of this research are just beginning to be appreciated. First, concepts emerging from this research place the efficacy and difficulties encountered with barrier methods of contraception in better perspective. Secondly, an appreciation of the difficulties involved in clinical trials with these methods makes clear the potential cost of research and development with such products. Owing partly to the latter consideration, the

importance of new approaches to clinical testing of vaginal contraceptives is becoming increasingly evident.

The overall efficacy of a vaginal contraceptive product is the end product of interacting factors. Perhaps the most critical is the spermicidal potency of the active ingredient and its concentration in the product. The characteristics of the delivery vehicle are also important, in that the formulation may control the ability of the spermicide to contact the sperm and produce a physical barrier to sperm transport beyond the cervical os. The motivation and intelligence of the consumer are crucial to the consistent and proper use of the contraceptive product. Convenience, ease of administration, and attractiveness of the dosage form play a significant role in proper use of the product. The consumer's belief in the effectiveness of the product may be essential to its consistent use, and this belief may be shaped by the attitude of the physician (or clinical investigator) concerning the effectiveness of vaginal contraceptives relative to other modalities.

Although *in vitro* spermicidal test systems and animal models generate valuable information concerning vaginal contraceptive effectiveness, only human clinical studies provide real indexes of contraceptive protection. Unfortunately, clinical trials of vaginal contraceptive products conducted over the past 40 years reveal a great variation in effectiveness rates. These studies, reviewed by Belsky (2), involved different types of contraceptives, test populations, and test methodologies. Thus they do not allow comparison of the efficacy of one vaginal contraceptive with another or with other contraceptive modalities.

The problems of assessing vaginal contraceptive effectiveness were recently explored in an interdisciplinary symposium, sponsored by the FDA's panel on over-the-counter contraceptives and other vaginal drug products. This symposium revealed much consumer confusion about the true measure of the effectiveness of a vaginal contraceptive product. Is effectiveness measured in terms of the outcome expected if a product is used consistently and as directed? Or is the level of the effectiveness determined by the success achieved by a large number of women using the product in a variety of situations, with differing degrees of consistency and competence? These alternatives involve the concepts of theoretical- and use-effectiveness in the clinical evaluation of contraceptives.

According to Tietze (24), theoretical-effectiveness is a measure of the capacity of a method or a product to reduce the chance of conception when correctly prescribed, correctly understood, and correctly used. Use-effectiveness, on the other hand, refers to the effect of the method within a particular population which may be more or less motivated and skillful.

Obviously, use-effectiveness is lower than the theoretical-effectiveness. With the IUD, theoretical- and use-effectiveness are essentially the same as long as the IUD remains *in situ* With oral contraceptives and the various barrier methods, patient compliance becomes a major factor. The study of vaginal contraceptive efficacy thus presents special problems to the researcher, the greatest of which is lack of control of their use by the subjects under study.

Some of the problems encountered in conducting a well-controlled, prospective clinical study of vaginal contraceptive effectiveness have been dis-

cussed by Pasquale (24). The ideal would be a *double-blind study*. A placebo control presents no technical problems, merely the preparation of a similar vehicle and dose form without the spermicidal agent. But a placebo control is unacceptable from an ethical point of view. A matched-active control must be used, but this restricts the type of formulations which can be compared. Foam must be compared with foam, cream with cream. Sometimes even minor differences such as consistency of a cream, odor, or instruction can break the blinding.

If a double-blind study is impossible, *comparative trials* with random allocation of subjects may be substituted. Investigator or subject bias cannot be eliminated with certainty, however. Volunteer subjects in a vaginal contraceptive trial may not be representative of consumers of over-the-counter vaginal contraceptives and the results obtained in a clinical study may not necessarily be representative of use in the market-place.

If the design of a clinical study of the method effectiveness of a vaginal contraceptive product is difficult, the study of use-effectiveness is for all practical purposes impossible.

BASIC RESEARCH

Last, but certainly far from least in importance, is basic research in reproductive biology. Basic research is a crucial and indispensable element in the development of new vaginal contraceptives which act by different mechanisms and which are safer and more efficacious than current products. New delivery systems show the most promise for immediate success; the real future probably lies with new types of active agents.

It is often difficult to find ways of applying basic research discoveries to the development of new products. Currently, the most active areas in basic reproductive research are studies of sperm and the process of fertilization (13). It is important that basic researchers keep in mind the pragmatic applications of such research. For example, increased awareness of the interaction of semen and cervical mucus has led to better understanding of the biochemistry and physical composition of cervical mucus. Originally begun in an effort to understand the causes of infertility (10), this work has led to a new approach to improve vaginal contraception, *i.e.*, the search for agents which can alter cervical mucus and thereby prevent sperm migration. Investigations by Stambaugh and Buckley (23), Greenslade *et al* (11), and Zaneveld *et al* (26, 27) of sperm proteolytic enzymes found in the acrosome suggest another new approach to vaginal contraception: theoretically, at least, an inhibitor of the acrosomal enzymes could in itself prevent fertilization.

The objective of all barrier contraceptives, whether occlusive or chemical in nature, is to prevent sperm from reaching and fertilizing the ova. Although investigators are taking different approaches their goal is the same: new products which are inexpensive, long acting, have maximum convenience, independence from coitus, and acceptability for increased consumer compliance.

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8

Collagen Sponge as Intravaginal Barrier Method: Two Years' Experience

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Since 1976, when the idea of using a collagen sponge (CS) as an intravaginal contraceptive barrier method was outlined (1), investigations at the University of Arizona have been involved in various aspects of clinical evaluation of this method (2, 3, 4). Furthermore, several other uses for the collagen sponge in the practice of gynecology have been developed and tested (Table 8-1).

CONTRACEPTIVE SPONGE

Historically, the use of feltlike sponge materials for a vaginal device is one of the oldest contraceptive methods (8). Although the evidence is nearly 3000 years old, nothing is known about the efficacy of this method. Several reports indicate the use of sea sponge, made by nature and formed by a protein spongin, which is a type of collagen. Therefore, the synthetic collagen sponge under investigation is a more sophisticated version of the old types.

The optimal requirements for a sponge which is to be used as a vaginal contraceptive are high resilience of the material, prompt and maximal fluid-binding capacity, easy insertion and removal, and the possibility of incorporating medications such as spermicidal agents into the sponge matrix. The sponge itself should be nonirritating, noncarcinogenic, and stable in contact with the vaginal tissue.

The sponge should continuously cover the cervix as a mechanical barrier against sperm and should be of a size which will minimize the dislodgement of the sponge during intercourse. Proper placement requires insertion of the sponge into the upper vaginal vault. A sponge made of collagen fibrillar protein has been shown to satisfy these criteria (1, 2, 3, 4).

*With collaboration of Karen Betts and Donna Mobley

TABLE 8-1. Collagen Sponge in Various Gynecological Applications

1. Contraception
   A. Cylindrical disk
   B. Disposable spermicide container for diaphragm

2. Topical treatment of vaginal infections
   A. *Herpes simplex genitalis*—zinc-medicated sponge
   B. Various vaginal infections

3. Drug delivery system
   A. For veterinary use (antibiotics)

TABLE 8-2. Modification of Contraceptive Collagen Sponge Tested During its Development into the Final Form

GENERAL PROPERTY STUDIED	TYPE OF MODIFICATION	FINAL RESULT
Resilience	Combination of CS with other fibers made of nylon, cellulose Increase density of collagen Increase cross-linking	CS made of pure collagen with density 50 mg collagen/cm^3, highly cross-linked with glutaraldehyde, no other fibers needed
Size	CS of 6, 7, and 8 cm diameter, 2.5 cm thick	Two sizes should be used, having 6 and 7 cm diameter
Material	Identical size sponges (6 × 2.5 cm) made of collagen, polyurethane, polyvinylalcohol, acetylcellulose	CS proved superior to others in fluid binding, resilience, retention, nonirritation
Removal of CS	Loop or string made of —cotton (umbilical tape) —dacron —polyester —nylon	 —absorbs ejaculate —irritates the male

During development of the present CS, several modifications of the original sponge were tested as summarized in Table 8-2. Table 8-3 describes the current collagen sponge which showed the best performance in animal and clinical testing.

The collagen sponge, as a contraceptive device, is a cylindrical disk, 6–7 cm wide and 2–2.5 cm thick. It is made of pure collagen fibrous protein, isolated from bovine skin. Collagen is reconstituted in the form of a sponge, and the final product contains less than 5 ppm glutaraldehyde, which serves as a collagen cross-linking agent. This minimal presence of residual glutaraldehyde in the sponge is important. Glutaraldehyde is known to be bactericidal and fungicidal, thus preventing the growth of these microorganisms on the surface of the sponge during storage. It must be stressed that glutaralde-

TABLE 8-3. The Characteristics of the Contraceptive Collagen Sponge with Best Performance

Composition	pure bovine skin collagen, 100%
Cross-linking agent	glutaraldehyde <5 ppm residual content
Density	50 mg collagen/cm^3
pH	4.5 to 5.5
Fluid binding (ml water/g)	35–45
Size	6–7 cm × 2.5 cm cylinder
Future options— Incorporation of spermicide	

hyde has been shown to be cytotoxic at concentrations above 20 ppm. The pH of the sponge is adjusted to 4.5 with an acetate buffer. The buffering capacity is sufficient to create a spermicidal environment in the sponge resistant to neutralization by ejaculate of slightly alkaline pH.

The collagen sponge is inserted intravaginally with a syringe-type applicator. A loop made of a soft nylon cord is attached to the collagen sponge for easier removal. The string is anchored through the sponge in such a way that the pulling force is evenly distributed over a large area of the sponge matrix (Fig. 8-1).

The collagen sponge should be left in the upper vault of the vagina for 6–8 hr after intercourse. Removal of the CS for 48 hr following coitus is unnecessary. During this period of time, no malodor is formed within the sponge, due to the chemical reaction of sperm polyamines with diamine oxidase (4, 5, 6). After longer intervals, malodor develops in most users. Rate of malodor formation in the sponge infiltrated with the ejaculate varies from one individual to another.

Various aspects of the collagen sponge (Table 8-2) have been tested by more than 100 volunteers. Sponges with a diameter of 6–7 cm are satisfactorily retained in the upper vagina. The sponge, although resilient, is soft and pliable; users had no significant complaints about discomfort. In early studies, however, several male partners complained about irritation of the penis caused by the consistency of the tape. Therefore, we selected and tested new materials for the loop and the presently used nylon cord has solved this problem.

In early 1977, studies demonstrated that the collagen sponge had good acceptability and convenience to the user (2). The next step in testing of the sponge method, that is, its efficacy as a barrier, was evaluated by a modification of the sperm penetration test as developed by Sims (9) and Huhner (7). Volunteers with ligated fallopian tubes or using an IUD as a contraceptive method were tested during their preovulatory phase for volume and quality

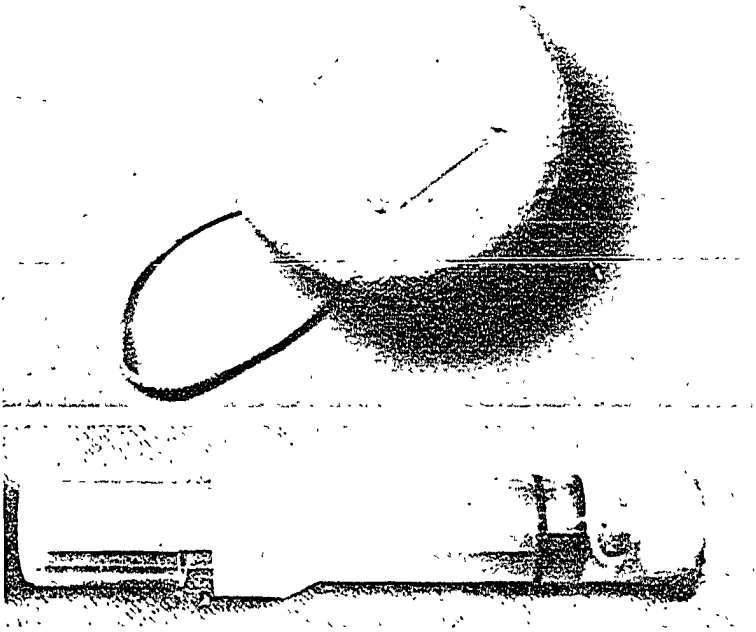

FIG. 8-1. Top, collagen sponge as vaginal contraceptive barrier; note placement of loop **Bottom**, inserter with sponge.

of cervical mucus. Volunteers used 6–7 cm wide CS, inserted in the upper vault of the vagina through an applicator. The couples had intercourse at home and the female subject came to the hospital where the sponge was removed by the gynecologist.

Samples of cervical mucus were collected from the exocervix and endocervix and were analyzed under HPF. For the evaluation of the results of postcoital tests (PCT), the presence of motile sperm in the cervical mucus was considered as a positive test, indicating penetration or bypassing of the CS barrier. During the same or succeeding cycle, each volunteer couple served as their own control. They were tested again, this time without the use of the CS, to verify adequate numbers of sperm present in the cervical mucus.

In the past three years, over 60 sperm penetration tests have been performed using the CS alone as a mechanical barrier. During the developmental phase, several modifications in size, shape, and mechanical characteristics of the sponge were made to design a better mechanical barrier. Irrespective of these modifications, motile spermatozoa were observed in the cervical mucus in 15%–20% of the tests. However, the number of sperm per HPF in the positive tests was significantly lower than the control values.

We will not speculate as to what percentage of the women with positive postcoital tests would have become pregnant. We would like to emphasize

TABLE 8-4. Results of PCT CS with Spermicidal Cream

Total number of volunteers	33*
Number of PCT without CS (controls)	33
Number of PCT with CS—spermicide	33
Negative	31
1 viable sperm/HPF	1 (In exocervix only)
1 viable sperm/slide	1 (In exocervix only)

*Each volunteer provided postcoital testing for collagen sponge alone, followed by collagen sponge plus spermicide.

that our term "failure rate" does not correspond with the usual manner of expressing the effectiveness of a contraceptive method. Any motile sperm observed in the cervical mucus is called a postive test. It is impossible to relate these results to standard pregnancy rates.

Our studies demonstrated that the optimal diameter of a resilient sponge to mechanically obstruct the upper vault should be 6–7 cm for nulliparous females. For multiparous females the diameter of the CS should be between 7–9 cm.

In testing multiparous volunteers with a small diameter sponge (6–7 cm), dislodgment or changes in the position of the diameter of the sponge to the long axis of the vagina was observed. This reinforces the opinion that for a sponge to be effective as a mechanical barrier it must have an elastic memory and the proper size to continuously cover the cervix.

It was postulated that effectiveness of the CS in conjunction with a spermicidal cream would reduce the incidence of positive tests. A total of 33 volunteers were tested at the time of ovulation with the CS in conjunction with spermicide cream. Postcoital tests were performed within 4 hr following intercourse. The average time of sampling the mucus was 1 hr 40 min after intercourse (the range was from 45 min to 3 hr 45 min). The average age of our volunteers was 28 years. One-third of the women were parous and two-thirds nulliparous. As shown in Table 8-4, of the 33 postcoital tests performed with CS spermicide, 31 tests were negative. One of the two positive tests showed one motile sperm per HPF and the other volunteer had one motile sperm on the entire slide of cervical mucus obtained from the exocervix. In neither case were sperm present on the slides from the endocervix.

Both volunteers with positive tests were using an IUD for contraception and even though the exocervix was swabbed with a cotton applicator prior to testing, the positive test may have resulted from mucus surrounding the IUD string.

It was concluded that the combination of a chemical and mechanical barrier will substantially increase the contraceptive efficacy over that of the collagen sponge alone.

At the time of writing this report, we have not decided which type of spermicidal agent to use. Our preliminary testing of the most commonly used spermicide, *i.e.*, nonoxynol 9, demonstrated some adverse effects in animal testing (see chapter 16). However, the collagen sponge as developed and described in this report represents an ideal vehicle for delivering intravaginal

spermicides and other medications. The sponge also insures a continuous release of the drug from the collagen matrix into the vagina. Therefore, the CS spermicide is a potentially promising intravaginal contraceptive barrier method.

Use of the sponge has two beneficial attributes for vaginal contraception. The CS maintains the spermicide in an adequate position to cover the cervical os. Secondly, the sponge is bulky enough that if not inserted into the upper one-third of the vagina, its mechanical presence will be noted by either the male or female.

As a result of our basic and clinical studies, we are presently incorporating a nondetergent spermicidal agent into the sponge. After determining its biophysical characteristics *in vivo,* postcoital tests on a similar group will be repeated. If the results are as satisfactory as the reported data on the CS in conjunction with spermicidal cream, phase three testing will be performed, with couples who will use the CS spermicide as their only means of contraception.

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9

A Clinical Appraisal of a Medicated Polyurethane Sponge Used for Contraception

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JUAN GINER

Intravaginal contraceptive barriers, including sponges, have been widely used for several centuries (1, 4), but since the development of more effective methods of contraception their popularity has decreased. This tendency to set aside the barrier methods is being modified, however, now that the oral contraceptives and IUDs have been shown to produce harmful side effects. Recently, several studies have been implemented in various parts of the world in an effort to increase the efficacy of the sponge against pregnancy, to adapt it to modern life, and to make it widely available.

Encouraged by the positive results of investigations of the vaginal contraceptive sponge reported by Chvapil (2, 3), several investigators undertook a study intended to establish the acceptability and efficacy of a polymeric sponge as a contraceptive method among women in Mexico. The findings of this study are reported here.

MATERIALS AND METHODS

Study participants were 16 women between 16 and 41 years of age, who were attending the Centro de Fertilidad y Esterilidad, A.C., Mexico City. The study participants agreed to use a vaginal sponge as the only contraceptive method used by them or their partners. The polymeric sponge contained the spermicidal compound nonoxynol 9 (constituting 30% of the total weight of the sponge). The women were instructed to insert the sponge deeply into the vagina before intercourse and keep it in place for at least 8 hr. They were then to wash the sponge with tap water and to store it in its original package until it was to be used again. The women were asked to use the sponge during intercourse for a maximum of ten coital acts. Every user was given an appointment to attend the clinic once a month. During the visits information about the frequency of use and performance of the sponge and about the frequency of the subject's menstrual periods was collected.

TABLE 9-1. General Characteristics of Women

CHARACTERISTIC	NO.
Total number of women	16
Average age	30 years (16–41)*
Religion:	
Catholic	14
Other	2
Parity:	
Parous	14
Nulliparous	2
Average number of children	3.5 (0–7)*
Average educational level	6 (0–13)*
Desire for more children	
Yes	3
No	11
Undecided	2
Previous contraception	
Oral contraceptives	5
IUD	5
Rhythm	1
None	5

*Ranges

RESULTS

All the women live in the urban area of Mexico City: fourteen are Catholic, one is Protestant and one has no formal religion. All are married. Their years of education range from 0–13 yr and the average number of years of schooling is 6. All but two subjects have seven children or fewer, with an average of 3.5. Four women have had abortions; eleven do not want more children, two want two more children, and one wants one more child; two women are undecided (Table 9-1).

Previous contraception has been used by 11 patients: 5 used oral contraceptives, 5 used an IUD, and one used rhythm. They reported having sexual intercourse on an average of 4 times a week.

Their reasons for accepting this method were infrequent intercourse (eight women), or absence of serious side effects associated with the sponge (six women). Two women stated no specific reason.

Three women have finished the study after 6 months of using the sponge, and the group as a whole has completed 49 months of observation. To date, no pregnancies have been reported. Nevertheless, some subjects have experienced side effects which have caused them to abandon the method. Seven couples have dropped out of the study: three of them because the sponge prevented proper penile penetration during intercourse, two did not trust the method and changed to a more effective one, and two were lost from follow-up.

Difficulty during sponge insertion was reported by two women and another woman had trouble withdrawing it. One woman reported that the sponge became smaller after being used, and another found that the sponge had turned yellowish.

CONCLUSION

Many couples who have infrequent sexual intercourse are interested in trying a safe barrier method that will avoid the undesirable side effects produced by the more effective contraceptive methods. For these reasons great attention has been given recently to topical contraceptives and investigators in this field have been looking for a simple, effective, and highly acceptable barrier method.

In theory, a polymeric sponge containing spermicides, when properly used, might be a good contraceptive method, however the present study has revealed problems with the prototype, such as discomfort during intercourse and difficulty during insertion and removal due to excessive size of the device. To fully evaluate the merit of this method, further studies with a smaller device are required.

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10

Preliminary Results of a Multiclinic Trial of a Polyurethane–Spermicide Contraceptive Sponge

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In May 1978, a multiclinic trial was undertaken in seven countries to obtain estimates of the use-effectiveness, safety and use-acceptability of a polyurethane-spermicide contraceptive sponge (Collatex, Vorhauer Laboratories, Inc., Costa Mesa, California). The trial is being conducted independently of the manufacturer and employs standardized patient selection criteria, patient instructions, study protocol, and data collection instruments. The ellipsoidal sponge being tested measures 3.0 cm by 5.5 cm, and consists of 70% polyurethane and 30% nonoxynol 9, with a polyester removal loop molded into the perimeter. Laboratory studies conducted prior to initiation of the trial determined that the sponge was safe for human use. Studies have entered the follow-up phase in five countries, but only in the Belgrade, Yugoslavia study have cases completed the six-month follow-up period. Preliminary analysis of the Belgrade data indicates that the device is safe, effective, and associated with an acceptable rate of discontinuation. However, the early, incomplete follow-up reports from Egypt, Bangladesh, Colombia, and Mexico are indicative of less successful use than that reported from Yugoslavia.

The authors wish to express their gratitude to Drs. R Aznar, Mexico City, Mexico; M Mahran, Cairo, Egypt, A. Rahman Khan, Dacca, Bangladesh; and G. Riaño-Gamboa, Bogota, Colombia, for contributing data used in the preparation of this paper, to Glenda Cummings of the IFRP for her help in monitoring the studies, and to Dr B. Vorhauer and Vorhauer Laboratories, Inc., Costa Mesa, California, for contributing the supplies of contraceptive sponges

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INTRODUCTION

Various types of sponge contraceptives have been used throughout recorded history. The earliest known documentation can be found in the records of ancient Egypt and, most recently, in a family-planning program in the United States in 1966. Despite their long history of use, sponges have never been noted for their effectiveness (9). Efforts to further develop and refine sponge contraceptives were abandoned when IUDs and oral contraceptives (OCs) became readily available.

Currently, an increasing proportion of couples are selecting vaginal contraceptive methods instead of IUDs, hormonal contraceptives, or sterilization (5, 10). This shift in preference reflects an increasing willingness to accept the greater inconvenience and higher risk of pregnancy associated with vaginal contraceptives to avoid the permanence of sterilization or the perceived risks of intrauterine and oral contraception. All sponges provide a barrier to sperm passage, and most incorporate a spermicide. This dual physical and chemical mode of action should result in a high level of effectiveness. As sponges do not have to be inserted immediately prior to intercourse, their use does not require the interruption of lovemaking, one of the major problems associated with traditional barrier methods.

Although various developers have operationalized the concept somewhat differently, all sponges provide a barrier to the cervix that is soft and conforms well to the shape of the upper vagina, thereby theoretically providing a barrier to the cervical os. Chvapil, who is primarily responsible for the resurgence of interest in sponge contraceptives, has developed a sponge device consisting of bovine collagen (2, 3, 4)

The subject of this report is the polyurethane-spermicide contraceptive sponge developed by Vorhauer. The Collatex sponge covers the cervical os and blocks the path of the sperm to the uterus. During intercourse, the sponge absorbs ejaculate and a surfactant spermicide renders the sperm immobile. The final choice of the polyurethane-spermicide material came after extensive experimentation with other materials, including bovine collagen, polymer-collagen hybrid materials and pure polymer materials.

The initiation of clinical testing of Collatex followed a program of laboratory testing underwritten by the manufacturer. Tests for local and systemic toxicity, allergenic response, carcinogenicity, and mutagenicity were performed in laboratory animals and human volunteers. The accumulated data indicated that the sponge material was safe for use in clinical trials (6, 7, 8). Additional tests determined that the amount of spermicide released *in vivo* and *in vitro* from the sponge was sufficient to insure a high level of protection if the device were to be used according to instructions (1). The configuration of the device was determined in acceptability testing conducted in Mexico by the Programa para la Introduccion y Adaptacion de Tecnologia Anticonceptiva de Mexico (PIACT de Mexico, A.C.) (11).

The clinical trial of Collatex was initiated in May 1978 in the form of collaborative studies between the International Fertility Research Program (IFRP) and clinicians in Sweden, Guatemala, and the five countries previously mentioned. Specific criteria of evaluation specified in the trial protocol included the incidence of accidental pregnancy, the rates of discontinua-

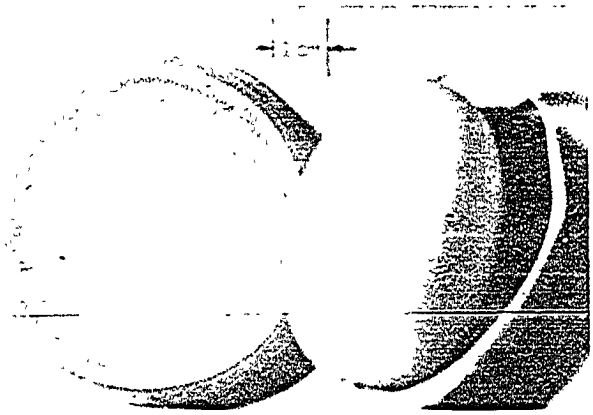

FIG. 10-1. Ellipsoidal Collatex used in clinical trials.

tion of use for various reasons, the incidence of vaginal infection and allergic reaction, the ease and regularity of use, the acceptability of the device to the patients, and the durability of the device.

Data intake was closed for the purpose of this report on April 30, 1979. As previously noted, sufficient follow-up data are available from Yugoslavia to present a detailed evaluation of the success of use of Collatex in that population.

MATERIALS AND METHODS

The sponge used in this trial is an ellipsoidal sponge that measures 3.0 cm by 5.0 cm in the wet state used for insertion (Fig. 10-1). The sponge shrinks to approximately one-half of the wet size when it is allowed to dry. The sponge material is composed primarily of urethane foam and nonylphenoxypolyethoxyethanol 9, commonly referred to as nonoxynol 9, which comprises 30% of the weight of the sponge when dry. Other components include various preservatives and a polyester woven tape molded into the edge of the sponge to serve as a removal loop.

Each woman was instructed to insert the sponge high into the vagina, placing it directly over the cervix. The sponge was removed by grasping the polyester loop, which was accessible under the device. The study protocol allowed insertion up to one week prior to intercourse and removal from 6–48 hr after intercourse. The women were instructed to rinse the ejaculate out of the used sponge gently by wetting and squeezing the sponge no more than three times. The sponge could then be reinserted or stored in its container for later insertion. The amount of spermicide incorporated in the sponge was determined in laboratory testing to be sufficient for about 20 rinsings, but the protocol conservatively specified only ten uses prior to replacement.

Informed consent was received from each subject who agreed to participate in the study. Upon admission to the study, verbal and written instructions in the use of the sponge were given to each subject in her native lan-

guage. Patients were instructed to return for follow-up visits at one, three and six months after their admission to the trial.

Table 10-1 summarizes the characteristics of patients admitted into the studies covered by this report. While the mean patient age in all studies ranges between 26.8 and 30.3 years, the mean parity varies from 1.2 live births per woman in Yugoslavia, to 3.5 live births in Egypt and in Mexico. The mean years of education range from a high of 11.8 years in Yugoslavia to a low of 5.0 years in Egypt. While relatively high proportions of women were practicing some form of contraception immediately prior to their enrollment in the trial—ranging from 65.2% in Mexico to 80.8% in Egypt—only in Yugoslavia, Colombia, and Mexico had any of the women relied on barrier contraception extensively in the past.

RESULTS

COLOMBIA, MEXICO, EGYPT AND BANGLADESH

Table 10-2 contains a summary of the results to date of follow-up of patients admitted into the studies in Colombia, Mexico, Egypt, and Bangladesh. Of the 179 patients admitted to the trial, 97 have made one or more follow-up visits and have an aggregate 277 woman-months of use.

Seven of the eight accidental pregnancies noted in Table 10-2 were reported from Colombia. The other pregnancy occurred in the Egyptian study.

Of the 97 patients returning for one or more follow-up visits, 43 (44.3%) have discontinued use of Collatex. The most prevalent reason, accounting for 55.8% of patient discontinuations, was discomfort during intercourse. In addition, one patient had difficulty in removing the sponge, one developed vaginitis, and one discontinued with complaints of pruritus. Other reasons for discontinuation included lack of confidence in the method, leaving the catchment area of the clinic, and desire for another child.

Complaints in the studies in Colombia and Bangladesh include discomfort during intercourse and the development of an unpleasant odor in the sponge.

YUGOSLAVIA

Table 10-3 presents six-month cumulative gross life-table rates of pregnancy and discontinuation for the study conducted in Belgrade, Yugoslavia. As of the data cutoff on April 30, 1979, the six-month pregnancy rate was 1.1%, the discontinuation rate was 13.1%, and the continuation rate was 85.6%. Of the women admitted into the study, 97 had made at least one follow-up visit

The six-month pregnancy rate of 1.1% women is the result of a single pregnancy that occurred in the second month of use. The patient was admitted into the study with a descended vaginal arch that was the consequence of a prior pregnancy and that presumably contributed to an improper fit of the sponge.

Table 10-4 presents reasons for termination from the study for those pa-

TABLE 10-1. Selected Patient Characteristics by Study Site

CHARACTERISTICS	YUGOSLAVIA	COLOMBIA	MEXICO	EGYPT	BANGLADESH
No. cases	100.0	61.0	23.0	63 0	32.0
Mean age	29.0	28.8	28.6	30.3	26.8
Mean parity	1.2	2.7	3.5	3.5	2.4
Mean years of education	11 8	7.0	7.0	5.0	8.8
Prior contraceptive use (%)	76.0	68.8	65.2	80.8	78.0
Extensive barrier method experience (%)	11.0	3 3	8 7	0.0	0.0

TABLE 10-2. Summary of Follow-Up of Patients in Studies in Colombia, Mexico, Egypt and Bangladesh

REASON FOR TERMINATION	NUMBER OF PATIENTS	PERCENT OF TOTAL TERMINATIONS
Unplanned pregnancy	8	18.6
Intercourse discomfort	24	55 8
Difficult removal	1	2.3
Vaginitis	1	2 3
Pruritus	1	2.3
No confidence in method	2	4.7
Relocation	4	9.3
Planned pregnancy	2	4.7
TOTAL TERMINATIONS	43	100 0
TOTAL ADMISSIONS	179	
TOTAL PATIENTS FOLLOWED-UP	97	
WOMAN-MONTHS OF USE	227	

tients discontinuing use of Collatex. The six-month rate of discontinuation for reasons other than pregnancy (13.1%) is the result of 13 patients choosing to discontinue use of Collatex. The primary reason was discomfort during intercourse, accounting for 11 (78.7%) of the terminations. While the majority of women discontinuing use because of discomfort cited only general complaints, two patients complained specifically of dryness due to excessive absorption of vaginal secretions by the sponge. Other discontinuations included one woman with moniliasis and another who had no coital partner. No cases of allergic reaction or severe vaginal inflammation have been reported.

Table 10-5 presents the types of complaints received from the patients during the follow-up period. Of the 97 patients making at least one follow-up visit, 23 (23.7%) complained of a problem with the use of the sponge. The most prevalent complaint was discomfort during intercourse, which resulted in discontinuation of use for 11 of the 13 patients making the complaint. Ten patients complained that the sponge tore during the removal process, one patient complained of difficulty in removal, and three patients complained of an unpleasant odor developing in the sponge.

Complaints generally occurred early in the follow-up period. While the patients complaining of discomfort during intercourse generally discontin-

TABLE 10-3. Six-Month Cumulative Gross Life-Table Rates per 100 Women in the Yugoslavian Study

TERMINATION REASON	1 MONTH RATE ± S.E.	3 MONTH RATE ± S.E.	6 MONTH RATE ± S.E.
Pregnancy	0.0 ± 0.0	1.1 ± 1.1	1.1 ± 1.1
Discontinuation	5.1 ± 2.2	10 5 ± 3.2	13.1 ± 3.6
Total termination	5.1 ± 2 2	11.5 ± 3.3	14.1 ± 3.7
Continuation	94.9 ± 2.2	88.4 ± 3.3	85 6 ± 3 7
Women at risk of termination	97.5	85.5	40.0
Woman-months of use	97 5	272 5	451.5

TABLE 10-4 Reasons for Termination in the Yugoslavian Study

REASON FOR TERMINATION	NUMBER OF PATIENTS	PERCENT OF TOTAL TERMINATIONS
Unplanned pregnancy	1	7.1
Intercourse discomfort	11	78 7
Monilia	1	7.1
No sexual activity	1	7 1
TOTAL TERMINATIONS	14	100 0

ued use of Collatex, those complaining of tearing, difficulty in removal and odor were able to change their use patterns to overcome their problems.

DISCUSSION

Although the data available from the studies in Colombia, Mexico, Egypt and Bangladesh are limited, the slow recruitment of patients into these studies as well as the number of discontinuations suggests that the use-acceptability of the sponge has not been high in these areas. In addition, the high number of pregnancies reported from Colombia is indicative of potentially low use-effectiveness in that country. This lack of success in the less developed areas presents a strong contrast to the results obtained in Yugoslavia.

With follow-up almost complete in the study in Yugoslavia, the results suggest that the method is acceptable and effective in that society. Women in Yugoslavia and in other Central European countries have traditionally used diaphragms and other vaginal contraceptives with success. This cultural inclination toward acceptance of the intricacies of proper use of barrier contraception may be responsible for the low rate of pregnancy and the moderate rate of discontinuation found in the study to date. A lack of cultural inclination toward successful barrier contraceptive use in less developed areas may have influenced the results in Colombia, Mexico, Egypt, and Bangladesh.

As Collatex is an experimental contraceptive device, this first set of clinical trials was expected to reveal problems that could potentially be remedied by changes in device design and use instructions.

TABLE 10-5. Complaints in the Yugoslavian Study

TYPE OF COMPLAINT	NUMBER	PERCENT OF PATIENTS FOLLOWED-UP
Discomfort		
Continuing use	2	2.1
Discontinuing use	11	11.3
Torn sponge	10	10.3
Difficult removal	1	1.0
Odor	3	3.1
Total number of patients with complaints*	23	23.7

*Note that several patients had more than one complaint during their use of the sponge.

Two hypotheses have been forwarded to explain the low use-effectiveness found in Colombia. The first explanation is that the device was not being correctly positioned in the vagina, while the alternate hypothesis is that the sponges were washed more zealously than was called for in the protocol.

The major complaint, which was also the primary reason for discontinuation in all studies, was discomfort of one or both partners during intercourse. In the Yugoslavian study, approximately 13% of the women had this complaint. A related problem was tearing of the sponge during removal, which was most frequent in those patients complaining of discomfort. Although these problems were often overcome by experience in use, it is possible that the version of the device that was tested was too bulky for some women.

Vorhauer has developed a newer version of Collatex designed to bring it higher into the vagina and to occupy less vaginal volume (Fig. 10-2). The new version is approximately the same diameter as the sponge tested in these clinical trials and has the same amount of spermicide, but is concave rather than ellipsoid. The change in shape has reduced the thickness at the center by one-third, from 3 cm to 2 cm, and allows the device to deploy over the cervix in a manner similar to a diaphragm, thus increasing both the comfort of the device and its effectiveness as a barrier to sperm passage. The concave shape also allows the sponge to fold during removal (Fig. 10-3) which should result in easier removal and less of a tendency to tear.

This change in the shape of the device is expected to increase use-effectiveness as the concave shape should result in more accurate positioning over the cervix. In addition, based on spermicide depletion data gathered in this trial, Vorhauer is now recommending only three washings of each sponge.

Although the proportion of women who complained of an unpleasant odor was found to be relatively low (3.1%) in the Yugoslavian study, it was a frequent complaint in the other studies. Apparently, the odor develops when the sponge remains in the vagina for long periods or as a result of damp storage in its container. To reduce the incidence of unpleasant odor, the use instructions have been modified to advise a maximum of 48 hours between washings, and air drying after washing and prior to storage.

Collatex was originally conceived as a reusable device, thereby reducing its

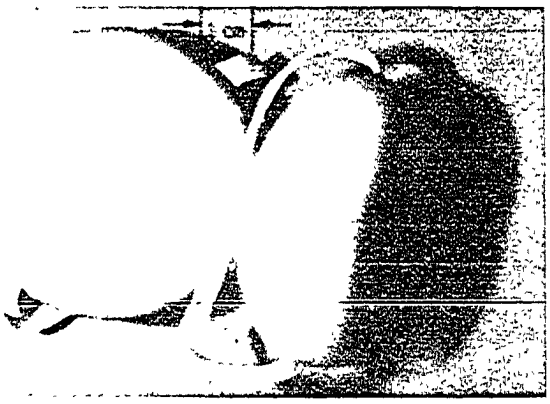

FIG. 10-2. Improved Collatex designed to occupy less vaginal volume.

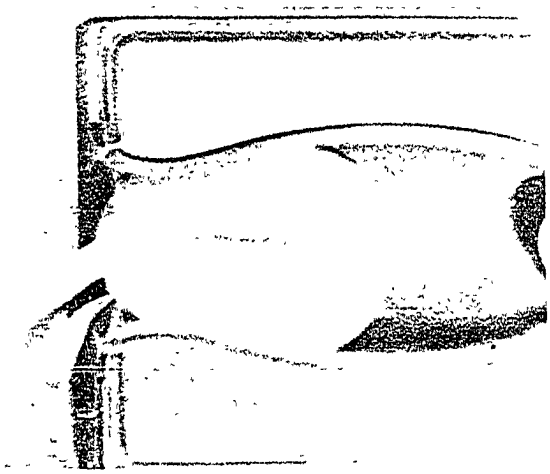

FIG. 10-3. Improved Collatex shown folding upon removal from an artificial vagina.

expense and the frequency of resupply. The success of the study in Yugoslavia demonstrates the soundness of this concept in a society where barrier contraception is well accepted. However, women in other cultures may not find the handling and washing of an ejaculate-laden sponge to be acceptable, as was found in the studies in Colombia, Mexico, Egypt, and Bangladesh. Thus, it seems practical to offer Collatex as a reusable device in areas where such a use-protocol is acceptable, and to offer it as a disposable device in areas where extensive handling and careful washing are not acceptable.

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11

Jost Intravaginal Device: A Spermicidal Sponge (IVD)

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LOIS E. BRADSHAW

The Jost Intravaginal Device (IVD) is a promising new intravaginal contraceptive method which incorporates modern technology with old principals. The IVD satisfies three major concerns in the initial choice and continued successful use of a contraceptive method: these are safety, effectiveness, and acceptability.

There is at present a resurgence of popularity of vaginal methods due to growing concerns over potential serious complications of oral contraceptives, such as cardiovascular mortality and morbidity (4, 7) and hepatic disease (2, 3); and those of IUDs, such as increased risk of ectopic pregnancy (5, 8), and pelvic inflammatory disease (6) with the potential of resultant sterility. The IVD offers women an alternative method of vaginal contraception in what is believed to be a more desirable delivery mechanism than most of the current products now marketed.

THE IVD AND ITS USE

The IVD consists of three disposable pieces: the applicator, consisting of a barrel and plunger, and the device itself, which is composed of a resilient open-and-closed cell polyurethane plug containing the spermicides nonoxynol 9 or 8.

The device, shown with its applicator (Fig. 11-1), is a sponge made of nonoxynol and polyester. The outer cylindrical hollow shell plunger is open at one end and closed at the other end, and includes an integral radially extending flange, adapted for hand use to facilitate insertion of the device into the vagina.

The spermicidal sponge is held within the barrel of the applicator until the applicator is introduced into the vagina. The plunger is then depressed, and the soft sponge is released high into the vaginal canal, where it quickly expands to conform to the shape of the vaginal vault (Fig. 11-2). Under conditions of use, when the sponge is compressed by coital thrusts, the spermicidal nonoxynol is released from the foam; this release continues for periods of 72 hr or longer. In addition to its spermicidal activity, the IVD serves as a physical barrier and has hydrophilic properties which enable it to absorb semen much in excess of its own weight.

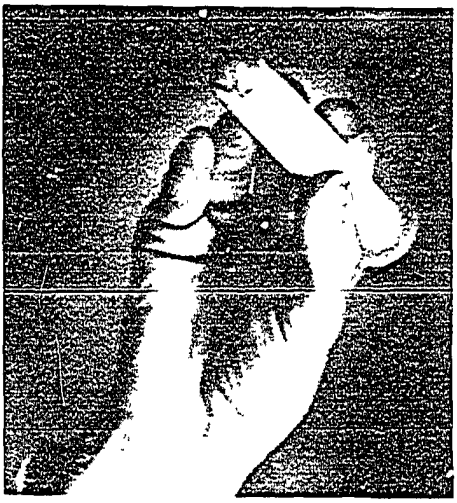

FIG. 11-1. IVD compressed in applicator.

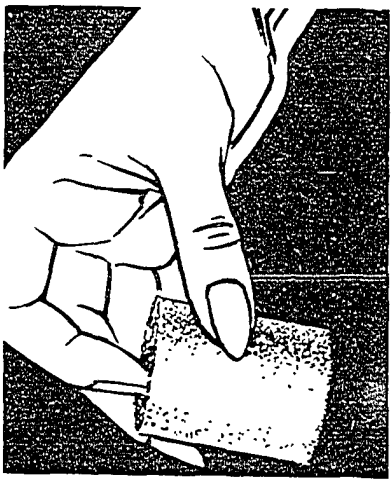

FIG. 11-2. Expanded IVD

PROPERTIES OF THE IVD

Table 11-1 lists properties of the IVD. The presently constructed dry IVD is 4.5 cm high and 3.5 cm in diameter. It has a 0.4-cm deep tab cut in one side approximately one-quarter of the distance from the distal end, for digital removal (Figure 11-3).

Removal is simple. A finger is inserted into the tab slit on the side of the device. This tab elongates when the IVD is saturated so it is not difficult to locate. With the tab compressed between the index finger and the thumb, a gentle tug will remove the IVD from the vaginal canal.

Because of its capability to adapt to the configuration of the vaginal vault,

TABLE 11-1. Properties of the Intravaginal Device

PROPERTY	DRY	SATURATED
Size		
Diameter (cm)	3.5	3.8
Height (cm)	4.5	4.6
Weight (g)	1.9	3.9

FIG. 11-3. IVD removal.

the IVD needs to be made in only one size. The IVD acts as a physical barrier at the cervical os by entrapping the ejaculate within 2–5 min after emission. Its wicking level (absorptive capability) is related to the amount of nonoxynol 9 carried in the foam structure, the quantity of ejaculate, and the length of time between coital acts. There are approximately 50–100 cells/linear in, with 90% open and 10% randomly closed cells to additionally enhance the provision of a physical barrier. The dry weight of the IVD is either 1.9 or 2.0 g, depending on the amount of incorporated nonoxynol 9. If the IVD carries a minimal amount of the spermicide so as to be effective for a single ejaculate, it is capable of absorbing up to 16 times its dry weight. When the IVD carries the maximal amount of spermicide so as to be effective for three to five ejaculations, it is capable of absorbing up to 30 times its dry weight. The heavier the load of nonoxynol, the greater the absorptive capability of the sponge. However, the release potential of nonoxynol in the loaded device is constant and is unrelated to the wicking action.

The IVD eliminates several inconveniences generally associated with the use of vaginal spermicides. After insertion, the active ingredient is not released until the coital act; therefore it may remain in place and does not limit normal activity. Within 2–5 min after intercourse, the seminal and vaginal fluids are absorbed by the IVD which then holds these fluids until the IVD is removed. Additionally, it does not require replacement of a dose of spermicide prior to each act of coitus occurring within a 72-hr period.

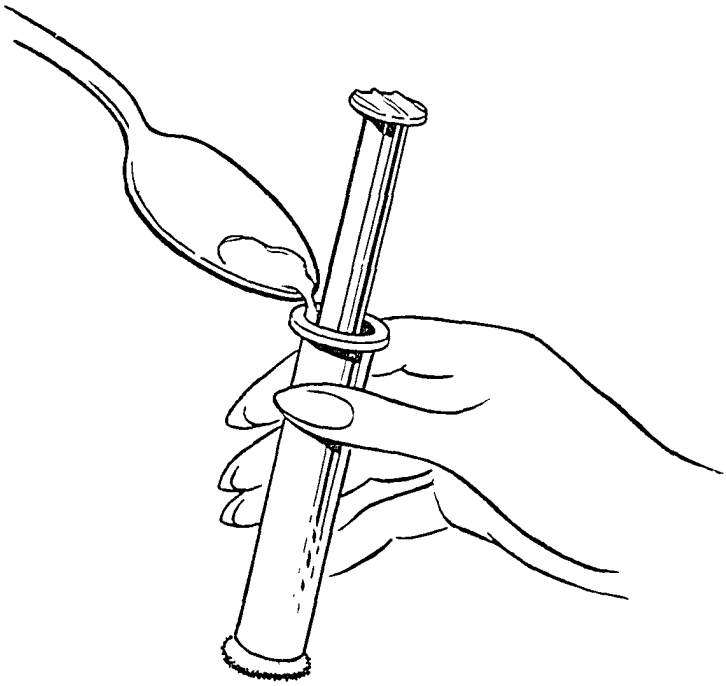

FIG. 11-4. Moistening the IVD for immediate use.

INSERTION AND REMOVAL OF THE IVD

Present investigations indicate that the IVD is effective for contraception up to 72 hr after insertion. If use is planned within 6 hr after insertion, the sponge must be premoistened by placing water in the barrel of the applicator prior to insertion into the vagina (Fig. 11-4). If coitus is planned between 6–72 hr after insertion, the IVD can be inserted in the packaged dry state into the vagina.

Additional testing hopefully will confirm preliminary evidence that coital thrusts activate the release of spermicide from the IVD quickly enough and in great enough quantity to be effective.

The design of the applicator facilitates IVD placement high in the vaginal canal. Due to the convoluted nature of the vagina, the IVD will retain its placement at the cervical os until it becomes heavy enough through saturation to cause it to slide down toward the opening of the vaginal canal.

PRECLINICAL TESTING OF THE IVD

In vivo spermicidal screening tests of the IVD in stump-tailed macaque monkeys has recently been completed by Zatuchni and Zaneveld, of the University of Illinois, and Hahn, of Ortho Pharmaceutical Corporation (1). Fractional subtherapeutic dose levels of the IVD adjusted to the size of the ma-

TABLE 11-2. *In Vivo* Spermicidal Screening Results of IVD Effectiveness in Stump-Tailed Macaques

	MATED AFTER 10 MINUTES OF IVD INSERTION	MATED AFTER 24 HOURS OF IVD INSERTION
Total number macaques	6	6
Dose administration (IVD)	0.25	0 25
Postcoital vaginal fluid specimens aspirated and examined	6	5
Specimens free of motile sperm	4	5
Average motile sperm remaining (%)	17	0

caque vagina were inserted in 12 macaques. Six were mated 10 min after insertion and six were mated 24 hr after insertion. Immediately following coitus, vaginal fluids were aspirated from 11 of the 12 macaques and examined microscopically for sperm activity. In the group of six animals mated 10 min after IVD insertion, 4 of 6 specimens showed no motile sperm. In the other two specimens, the average amount of motile sperm remaining was exactly 17%. In the group of six animals mated 24 hr after IVD insertion, five specimens were collected and examined. All 5 were found to be free of motile sperm. Table 11-2 presents these data.

Human contraceptive effectiveness data are not yet available. However, effectiveness studies of the IVD in Sweden involving over 200 women in two sites have been underway for seven months.

Phase II testing for safety and acceptability of the IVD sponsored by PARFR is about to begin in three Planned Parenthood clinics in the United States. During this planned testing, 200 female volunteers, aged 18–45 years, who have undergone bilateral tubal ligation or who are IUD users will use IVDs. They must be menstruating regularly and have coitus at least 2 times a week. Each participant will be examined by a physician at the initial visit to assure that she is healthy. In addition, each participant will have a Pap smear, vaginal pH recording, and Sims–Huhner test to determine that her sexual partner produces motile sperm and that a hostile environment to sperm is not present.

At the initial visit, each participant will be given a fact sheet describing the research project and will sign an informed-consent form. She will be shown how to use the IVD, will be given instructions for study participation, and will be given a questionnaire/diary to complete as to the length of time each device is worn, when sexual relations occurred, and whether or not any irritation or side effects (itching, burning, odor, discharge, dryness, or discomfort) were noticed by the participant and/or her partner. Each participant, who must have had coitus within the past 72 hr will be randomly assigned to one of three study groups. The first group (30 women) will return to the clinic after wearing the IVD for 24 hr (±4 hours), having had at least one act of coitus. The second group (60 women) will return to the clinic after

wearing the IVD for 48 hr (±4 hours), having had at least one act of coitus. The third group (110 women) will return to the clinic after wearing the IVD for 72 hr (±4 hours), having had at least one act of coitus.

The first IVD will be removed in the clinic at the first follow-up visit. A physical examination, Pap smear, pH recording, and Sims–Huhner test will be done at this visit to determine the incidence of local irritations and/or other side effects. Each IVD will be sealed in a pressure–sensitive plastic bag and be sent for testing for residual nonoxynol.

Each participant will then be given 12 IVDs to use from 24–72 hr during the remainder of a 30–day period as measured from the day of insertion of the first IVD. Each participant will return to the clinic at the end of the 30-day period and approximately two weeks after cessation of IVD use, for clinical observation of any irritations or other side effects, and to complete and return the questionnaire/diary.

Residual nonoxynol in the first IVDs removed at the first follow-up visit will be analyzed using an FDA-approved food coloring known as FD & C blue dye, placed in the sponge to be released into 50 ml of solution buffered to a pH of 4.5–5.7 at 37°C. Results will be plotted to determine residual nonoxynol 9 amounts, according to length of use and episodes of coitus.

Another study is needed to compare the efficacy of the IVD with other vaginal contraceptive products under *in vivo* conditions of simulated coitus.

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SPERMICIDAL FORMULATIONS

35

12

Experience with Barrier Methods of Contraception in Guatemala

LUIS F. GALICH

The Asociacion Pro-Bienestar de la Familia de Guatemala (APROFAM), is a private service association, legally constituted under Guatemala law to collaborate with the Ministry of Health in promoting family-health programs, especially in the area of maternal and child care. The most important service of APROFAM is provision of contraception or sterilization to anyone desiring it. This presentation will describe the experience at the APROFAM Clinics with the contraceptive vaginal suppository Neo-Sampoon.

Neo-Sampoon is a nonionic surface-active agent known as TS-88 or Menfegol (p-methanylphenyl polyoxyethylene ether), which was developed in Japan and produced at Eisai Laboratories. According to results of *in vivo* animal studies, it possesses a strong spermicidal action and is neither irritating nor toxic. It is applied in the form of effervescent intravaginal suppositories with 0.08 g of Menfegol. Early studies involved women who agreed to use them for at least one year, at which time vulvovaginal and cervical secretions were examined, and vaginal pH, bacterioscopy, and Papanicolaou and Huhner tests were performed. The failure rate was 2.3%.

APROFAM EXPERIENCE WITH NEO-SAMPOON

APROFAM began using Neo-Sampoon at its clinics and in its Community Distribution Program in 1971, when a quantity of the product was purchased directly from Eisai Laboratories. At first there was little demand for Neo-Sampoon, but as the public, and especially medical and paramedical personnel became familiar with the product, demand increased. Table 12-1 shows user-acceptance of reversible methods in 1978 at APROFAM. Neo-Sampoon is the intravaginal method requested most frequently.

From the point of view of the user, the advantages of Neo-Sampoon are not having to visit a clinic frequently and not having to undergo a physical examination, which for some women is unpleasant. Most important, Neo-Sampoon is free of the harmful secondary effects of the oral contraceptives and IUDs. However, there are also some inconveniences.

The tablet must be placed as deep inside the vagina as possible, but it has a better effect when it is in front of the cervical opening and not at the posterior fundus of the vagina. Insertion will be made a few minutes before initiating intercourse to allow the tablet to dissolve, otherwise the contraceptive

TABLE 12-1. User Acceptance of Reversible Methods - 1978

Oral contraceptives	56%
IUD	22%
Local*	14%
Condom	5%
Injectables	3%

*Among users of local methods, 70% preferred the Neo-Sampoon and 30% a vaginal cream.

action is not guaranteed. When more than 15 min have elapsed between insertion and intercourse, another tablet must be inserted.

These activities sometimes interfere with the couple's enjoyment. Some users complain of an increase of leukorrhea or of post-coital discharge which soils the clothing. Others say the Neo-Sampoon produces a burning or hot sensation in the vagina, and irritation, which may also be experienced by the partner. The couple must sustain strong motivation to use this method successfully on a continuing basis.

From the point of view of the clinic managers, the advantages of Neo-Sampoon are easy handling and storage, and the almost total absence of logistical problems. Because the product does not require the continuous participation of medical personnel, it is ideal for the Community Development Program (CDP). With an adequate rate of consumption, the product will suffer no alterations as long as the minimum storage conditions exist: glass containers, air-tight package seal, and adequate conditions of temperature and dryness.

The effectiveness of the tablets has proven to be similar to that of the gels and only slightly lower than that of the diaphragm. An accurate failure rate is not yet available but is estimated to be 10% after one year of continuous use by a couple. Neo-Sampoon is useful for distribution to large groups because instructions regarding its utilization are simple, its cost relatively low, and its effectiveness relatively high. Another benefit is that it can be distributed by paramedical personnel.

CONCLUSION

Neo-Sampoon is of great interest to the CDP and is gaining increasing popularity. Good promotional and instructional campaigns by APROFAM personnel have resulted in an increasing acceptance of Neo-Sampoon by couples and by more effective use.

13

Clinical Trial of a Contraceptive Foaming Tablet: A Preliminary Report

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GERMÁN RIAÑO-GAMBOA,

FIDEL ANZOLA,

*DORIS BLANDÓN**†

The introduction of substances or mixtures into the female genitalia for contraceptive purposes goes well beyond history. The earliest Egyptian papyri recommended, among other mixtures, honey and sodium bicarbonate, to be sprinkled in the vulva (7). Aristotle noted that if the lips of the cervix are smooth, conception is difficult; "Whereof since if the parts be smooth, conception is impeded, some anoint that part of the womb on which the seed falls with cedar oil, ointment of lead, or frank-incense and olive oil (7)." Soranus of Ephesus prescribed acid fruit juices, and Casanova recommended half a lemon. The desire of women throughout time has been an easily available, simple, unsophisticated procedure, free of secondary effects, with which to avoid pregnancy, by simply inserting it into the vagina themselves. With such a contraceptive purpose in mind a number of spermicidal creams, jellys, foams, suppositories or tablets have been developed.

In the mid-1960s, Japanese investigators reported their concern about the potential effects of long-term exposure to products containing mercury. At that time, all vaginal contraceptives marketed in Japan contained the spermicide phenylmercuric acetate. In response to the need for an effective nonionic vaginal contraceptive, a surfactant spermicide, TS-88, was developed by the Eisai Company in Tokyo and later marketed as Neo-Sampoon.

This foaming tablet contains TS-88 (60 mg); Menfegol (60 mg); dioctydisodium sulfosuccinate (6 mg); benzethonium chloride (4 mg); starch (111 mg); potassium bitartrate (326 mg); sodium bicarbonate (160 mg); silicanhydride (80 mg); microcrystalline cellulose (33 mg); and polyvinylpyrrolidone (21 mg). The active agent, TS-88 (p-methanylphenylpolyoxyethylene ether),

*This study was supported in part by grants from the International Fertility Research Program and the Office of Population, United States Agency for International Development (AID/pha-G-1172 and AID/pha-G-1198)

†The authors acknowledge the fine assistance provided by Mr. L. F. Rojas and Ms. Camila Botero.

is a nonionic surface-active agent which has been shown by Iwahara (6) and Nagano (8) to have potent spermicidal activity at low concentrations and little bactericidal effect on Döderlein bacilli. It also has been shown to be free of a local stimulant effect and hemolytic action, with oral toxicity as low as 8 mg/kg in mice (5).

As a surface activator, TS-88 is thought to increase the permeability of the sperm to such an extent that the cell surface is damaged, allowing cytochrome c to diffuse out of the cells and, as a result, the motility of the sperm is irreversibly lost (8). Inhibition of sperm fructose metabolism has also been reported.

Clinical trials of Neo-Sampoon conducted in Japan from 1966 to 1972 showed the use-effectiveness of the tablets to be better than that of other vaginal contraceptives; failure rates were in the range of 2.3 to 3.2 pregnancies per HWY (5, 9, 10).

The anatomical problem of spermicides is the difficulty of covering the cervix, which projects into the vagina, during intercourse. The Neo-Sampoon depends upon the foaming action of the tablet when combined with vaginal secretions to disperse the surfactant that kills the sperm. The effervescent disintegration of Neo-Sampoon in the vagina may be experienced by the users and their partners as a sensation of heat. Japanese studies found that 5% to 10% of users considered this sensation unpleasant. In the Philippines, the product is sometimes promoted with the slogan "Neo-Sampoon... for that warm sensation." A few users also report a slight increase in leukorrhea and pruritus. Generally, these unpleasant effects have not resulted in discontinuation of use of Neo-Sampoon (5, 8, 9, 10).

According to the International Planned Parenthood Federation (IPPF) Directory of Contraceptives in 1976, use of Neo-Sampoon is increasing in South America, the United Kingdom, the Middle East, Africa, Asia, and the Far East. To date, however, there has not been a significant Latin American publication of its clinical use.

This preliminary report will present the experiences with the Neo-Sampoon tablet in two urban ambulatory clinics in Bogotá, Colombia. The trial started at the end of July, 1978. The report summarizes the results as of January, 1979.

MATERIALS AND METHODS

The study involved 250 normal fertile women from low socioeconomic backgrounds, attending the outpatient clinics of the Hospital Samaritana and the Instituto Materno Infantil of Bogotá. The women, who voluntarily wanted to avoid pregnancy, were offered the opportunity to use Neo-Sampoon as a contraceptive method. A recording calendar (Fig. 13-1) with a small instructional leaflet was delivered with the tablets to each woman. Auxiliary nurses also gave them instructions and asked them to record menstrual dates, frequency of intercourse, use or nonuse of tablets, and any other relevant information.

The study protocol called for a questionnaire applied at admission and follow-up visits at 1, 3, 6 and 12 mo. Questionnaires were jointly designed

TABLE 13-1 Age by Patient Group

AGE	HOSPITAL LA SAMARITANA		INSTITUTO MATERNO INFANTIL		TOTAL	
	No.	*%*	*No*	*%*	*No.*	*%*
<20	1	2.9	19	17 0	20	13.6
20–24	14	41.2	38	33.6	52	35.4
25–29	4	11.8	36	31 8	40	27.2
30–34	4	11.8	12	10 6	16	10.9
35–40	11	32.3	8	7.1	19	12.9
[illegible]	34	100 0	113	100 0	147	100 0

TABLE 13-2. Parity By Patient Group

PARITY	HOSPITAL LA SAMARITANA		INSTITUTO MATERNO INFANTIL		TOTAL	
	No.	*%*	*No*	*%*	*No.*	*%*
0	1	2 9	6	5.3	7	4.8
1	10	29.4	34	30 1	44	30.0
2	8	23.6	37	32 7	45	30.6
3+	15	44 7	36	31.9	51	34.6
Total	34	100.0	113	100 0	147	100.0

TABLE 13-3. Years of Education by Patient Group

EDUCATION	HOSPITAL LA SAMARITANA		INSTITUTO MATERNO INFANTIL		TOTAL	
	No.	*%*	*No*	*%*	*No*	*%*
None	1	2.9	0	0 0	1	.7
1–3	9	26 5	31	27.4	40	27.2
4–6	14	41.2	48	42.5	62	42.2
7–9	7	20.6	27	23 9	34	23 1
10+	3	8.8	7	6 2	10	6.8
Total	34	100 0	113	100.0	147	100.0

by the International Fertility Research Program (IFRP) and Programa Regional de Investigaciones en Fecundidad (PRIF). Criteria of evaluation were accidental pregnancy, discontinuation of the method, and incidence of complaints.

PRELIMINARY RESULTS

At the time of analysis 169 women had been admitted into the study. Tables 13-1 through 13-4 detail the age, parity, education, and previous contraceptive experience of the study subjects. The characteristics of the women from the two hospitals are similar. They are fertile women of low socioeconomic status of intermediate age, who have had two or more live births, and rela-

CALENDAR FOR THE USE OF THE CONTRACEPTIVE VAGINAL TABLET

Month: _____

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sexual Relations																															
Menses																															

FIG. 13-1. Calendar for the use of the contraceptive vaginal tablet.

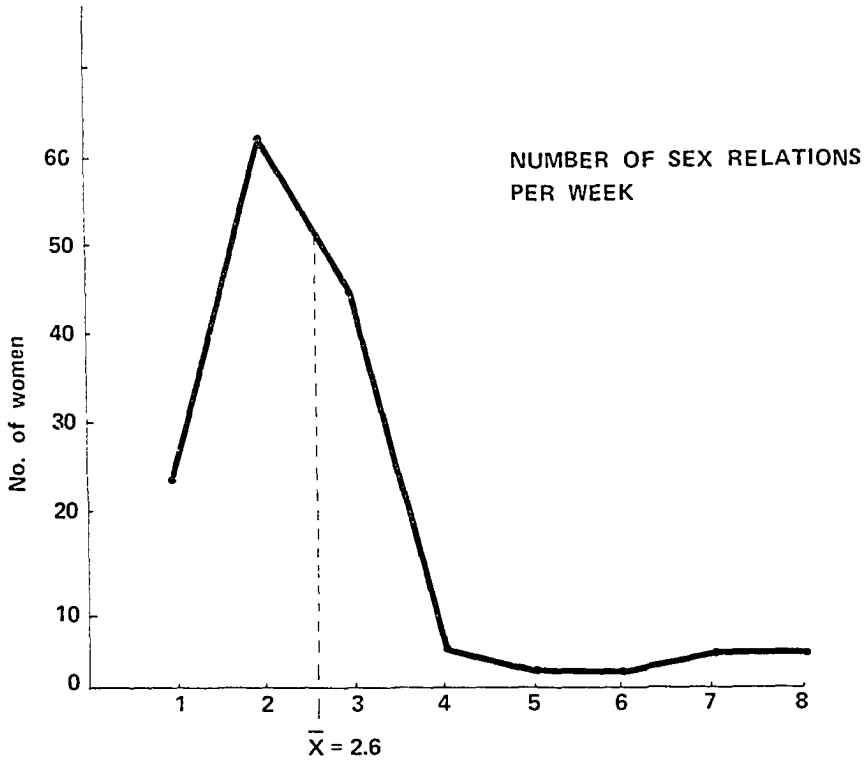

FIG. 13-2. Weekly incidence of sexual relations

tively few years of education; one woman was illiterate. Almost half of the patients, 80 out of 169, reported no use of contraception prior to accepting Neo-Sampoon. The average weekly incidence of sexual intercourse was 2.6 encounters, although a few couples reported up to 8 or more sexual encounters per week (Fig. 13-2). Although most women did not give a specific motive for choosing Neo-Sampoon, reasons mentioned were fear of side effects, or lack of availability of other methods.

Table 13-5 presents the number of women returning for 1-, 3-, and 6-mo

TABLE 13-4. Previous Method of Contraception by Patient Group

METHOD	HOSPITAL LA SAMARITANA		INSTITUTO MATERNO INFANTIL		TOTAL	
	No.	*%*	*No.*	*%*	*No.*	*%*
None	14	41.2	56	49.6	70	47.6
Pills	8	23.5	10	8.8	18	12.2
IUD	6	17.7	42	37.2	48	32.7
Foam/suppository/tablet	3	8.8	3	2.6	6	4.1
Condom	0	0.0	1	.9	1	.7
Rhythm/withdrawal	0	0.0	1	.9	1	.7
Other	3	8.8	0	0.0	3	2.0
Total	34	100.0	113	100.0	147	100.0

TABLE 13-5. Follow-Up Visits by Patient Group

FOLLOW-UP VISIT	HOSPITAL LA SAMARITANA		INSTITUTO MATERNO INFANTIL		TOTAL	
	No.	*%*	*No.*	*%*	*No.*	*%*
One month	19	55.9	64	56.6	82	55.8
Three month	6	17 6	27	23.9	33	22.4
Six month	0	0	3	2.6	3	2.0
Total admissions	34		113		147	

TABLE 13-6. Complaints at One-Month Follow-Up Visit by Patient Group

COMPLAINT	HOSPITAL LA SAMARITANA (N = 14)		INSTITUTO MATERNO INFANTIL (N = 46)		TOTAL (N = 60)	
	No.	*Rate**	*No.*	*Rate**	*No.*	*Rate**
Burning	3	21.4	7	15.2	10	16.7
Irregular menses	0	0.0	1	2 2	1	1.7
Foamy discharge	1	7.1	0	0.0	1	1.7
Total	4	23.6	8	17.4	12	20.1

*Complaint rate per 100 users follow-up at one month.

follow-up visits, as of the date of the 6-mo data analysis. Because not all the women started the trial simultaneously, only 25 out of the 169 had completed the 6-mo segment as of the date of the analysis. Therefore, for this presentation the results are reported only for 1- and 3-mo segments.

Table 13-6 presents the frequency and type of complaints at the 1-mo follow-up visit. The most prevalent complaint was a burning feeling in the vagina; 12 patients found the heat from the tablet during dissolution to be unpleasant. One patient complained of odor and foaming discharge. A few women felt that their discharge had decreased. One additional patient felt that Neo-Sampoon caused her to have two menses in a month. The complaint rate at 1 mo was 29% at Samaritana and 12% at Instituto Materno Infantil.

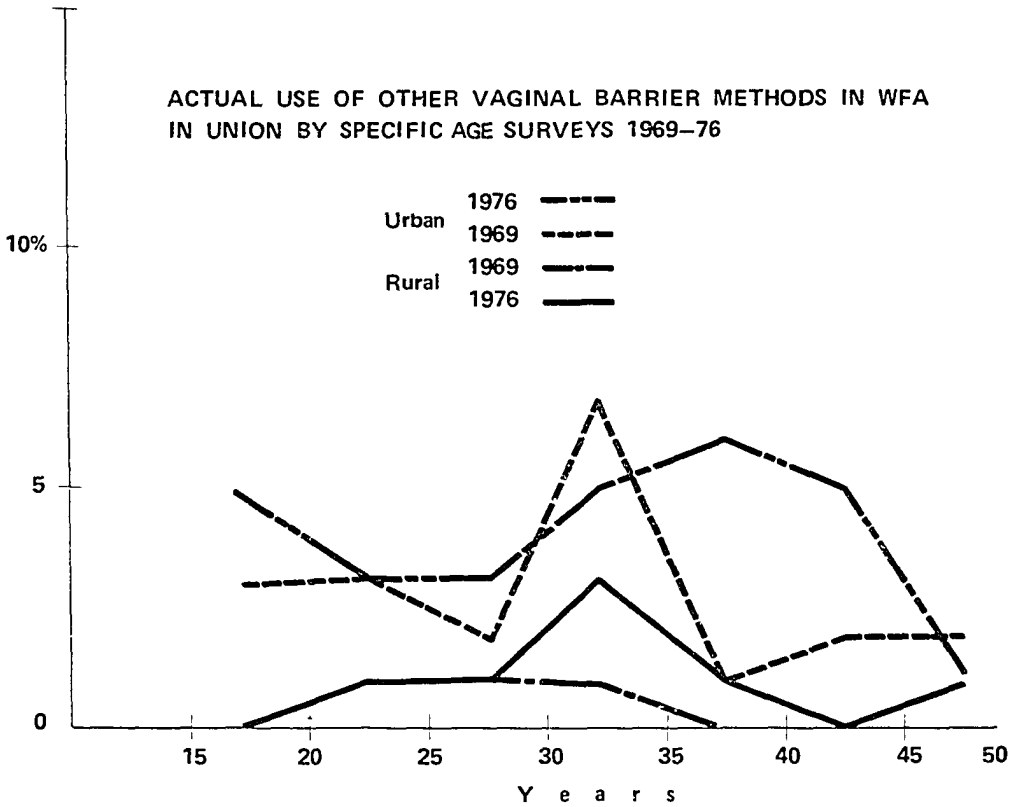

FIG. 13-3. Comparison, by ages of users, of actual use of other vaginal methods. (CCRP, Evaluation Area, Knowledge & Use, ENF-69,76)

At the 1-mo follow-up visit, two patients reported discontinuation of the method. In one case, the woman and her partner both found the heat to be too unpleasant. The other woman did not give any specific reason, stating only that she did not like the method.

TABLE 13-7. Actual Use of Methods of Women in Union Interviewed in 1969, 1976, and 1978 Urban and Rural Zones (Percentages)

ACTUAL METHOD	URBAN			RURAL		
	1969*	1976†	1978‡	1969*	1976†	1978‡
Pills	10	17	19.7	2	10	13.8
IUD	5	11	9 5	1	6	5.3
Condom	3	2	1.8	1	1	1.8
Other methods (vag)	3	4	3.7	1	1	1.8
Female sterilization	2	7	8.6	1	4	5.9

*ENF-69, ASCOFAME

†ENF-C/76, CCRP-DANE

‡Prevalence survey, 1978, CCRP-MINSALUD

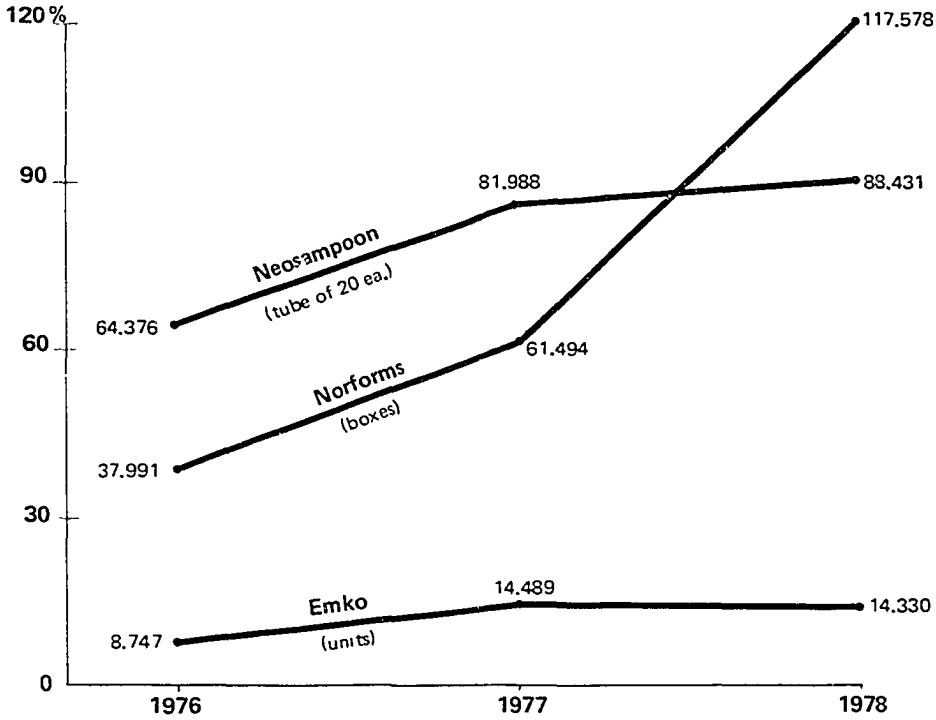

FIG. 13-4. Total sales of other vaginal barrier methods. (PROFAMILIA, Evaluation Bulletins, 1976, 77, 78)

At the 3-mo follow-up no pregnancies were reported.

DISCUSSION

As of the date of the analysis, the trial of Neo-Sampoon in the two clinics had not progressed sufficiently to allow final conclusions as to the value of the product as a contraceptive. Insufficient data are available for the computation of method failure and use continuation rates. In the 3-mo follow-up there were no pregnancies, however, after 3 mo, three pregnancies were reported: one at 3.5 mo, one at 4 mo, and one at 5 mo. The three pregnancies occurred in women who had entered the study in the early part, patients #2 and #4 in the series of the Instituto Materno Infantil, and patient #3 at the Hospital Samaritana. One woman admitted that she had used Neo-Sampoon irregularly, probably indicating that the pregnancy was not a method failure.

From the complaint rate reported at one month it can tentatively be said that Colombian users dislike the vaginal heat produced by Neo-Sampoon in a higher proportion (13.6%) than that previously reported in Asiatic women. This burning sensation starts soon after insertion of the tablet and probably results from distension of the vaginal vault by the foaming action of the tablet as it dissolves. However, the sensation does not follow a specific pattern of intensity, nor is it experienced by all women. In fact, several women used

two tablets each time for safety, without any undue reactions.

Follow-up of study subjects is generally poor in Latin America. In the present trial, although not yet completely analyzed, follow-up seems fairly high. At this stage, it is difficult to ascertain whether failure to return for follow-up indicates actual discontinuation. A contributing factor could be the low socioeconomic status of the study trial group. Also, the need to use the method within 10 min prior to intercourse may constitute another drawback for such patients. One woman in the study reported that her husband rejected the method because when he arrived home in the evening, he always found the tablet on the night table and felt uncomfortable about this daily intercourse forewarning. When the woman was asked why she routinely left the tablet there, she explained that she had to do it, or else her husband would be so anxious that he would not give her enough time to use it.

On the other hand, with all the publicity and information about harmful side effects of oral contraceptives and IUDs, an increasing number of fertile women are turning to vaginal barrier methods and spermicides. Table 13-7 illustrates actual use of barrier methods (other) compared to oral contraceptives, IUDs, condoms, and sterilization in a representative sample of women of fertile age in Colombia, according to two national surveys, one in 1969 and the other in 1976. The estimates made for 1979 by the Evaluation Area of the Corporación Centro Regional de Población, (CCRP) Bogotá, Colombia, (1, 2, 4) shows the comparison of actual use of such "other vaginal methods" by specific age in 1969 and 1976 (3) (Fig.13-3).

Finally, Figure 13-4 indicates the increase in total sales of vaginal methods, including Neo-Sampoon, in one of the family-planning programs in Colombia (PROFAMILIA) (11).

It is anticipated that these sales will continue to increase in the near future.

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14

Evaluating the Clinical Effectiveness of Patentex Oval

LEVIE QUERIDO,

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Patentex Oval is a foaming contraceptive suppository used in West Germany by approximately 400,000 women—that is, by more than 3% of the female population of fertile age. Intrauterine devices (IUDs) are used by approximately one million women and oral contraceptives by four to five million women.

In 1977, the Medical Commission of Stimezo, Netherlands, was informed by clinicians in various abortion clinics of the increased number of German clients who had become pregnant while using Patentex Oval. Data from the Permanent Registration, where all women who seek an abortion in the Netherlands are registered, confirmed this impression. Patentex Oval had become available in West Germany in 1973 and its use had increased fairly rapidly. Random inquiries among more than 19,000 patients in Dutch abortion clinics in late 1974 and the first 6 mo of 1975 indicated that Patentex Oval had been in use by approximately 5% of the women at the time of conception. By 1977, the proportion had increased to around 10%. While it stands to reason that contraceptive practice among abortion patients is significantly less effective than in the general population, the impression was strong that the users of Patentex Oval ran an unacceptably high risk of unwanted pregnancy. These considerations prompted a retrospective study by several Dutch investigators to evaluate the effectiveness of Patentex Oval.

The study was performed during the period from January 1 to April 1, 1978, in nine abortion clinics in the Netherlands, using a group of German women seeking termination of unwanted pregnancies at the clinics. A special registration form was designed for the collection of data regarding use of Patentex Oval. Each German client who stated that she was using Patentex Oval at the time of conception was questioned further as to duration and frequency of use and degree of motivation. A total of 671 women were selected to participate in the study. Their records were compared to the records of the Permanent Registration of 45,130 German women seeking abortion in 1977.

When considering Table 14-1, one should remember that in the general population, the number of Patentex Oval users is almost half the size of the group using the IUDs; whereas, in the abortion population, the users of "other methods"—almost all of whom are Patentex Oval users—constitute a group that is 10 times the size of the group of women who became pregnant while using the IUD. A similar occurrence is noted among oral contra-

TABLE 14-1. Contraceptive Use at the Time of Conception, Among 44,709 German Abortion Patients with Records in the Netherlands Permanent Registration, 1977

METHOD	PER CENT
None	48.4
Coitus interruptus/rhythm	26.4
Other methods*	9 5
Condom	8 0
Oral contraceptives	6 8
IUD	0.9

*The authors estimate that this group consists almost entirely of Patentex Oval users

TABLE 14-2. Marital Status of 652 German Oval Patentex Users Requesting Abortions, Compared to the Marital Status of 44,845 German Abortion Patients with Records in the Netherlands Permanent Registration, 1977 (PR'77)

	PATENTEX OVAL (%)	PR'77 (%)
Married	33	51
Unmarried	60	41
Divorced	7	8

ceptive users. In the general population of West Germany, ten times the number of women used oral contraceptives as used Patentex Oval but, within the abortion population, the number of users of "other methods" (*i.e.*, Patentex Oval) is almost one and one-half times as great. On the basis of these facts, there is a substantially greater risk of pregnancy with Patentex Oval.

Patentex Oval, which has been freely obtainable in West Germany since 1973, has increased progressively in use. Tests made at random among German abortion clients in the Dutch abortion clinics (n = 19,428) during part of 1974 and the first 6 mo of 1975 indicated a 4.8% use rate for the "other methods"; in 1977 this rate had increased to 9.5%. It seems justified to conclude that the increase in the rate of use of the "other methods" in the German abortion clients is largely or entirely due to Patentex Oval use because Patentex Oval was the only new "other method" between 1973 and 1977.

STUDY RESULTS

MARITAL STATUS AND AGE DISTRIBUTION

The proportion of unmarried women in the Patentex Oval study group was higher than the proportion of unmarried women in the overall general registry group (Table 14-2). When the groups are compared according to age

TABLE 14-3. Distribution by Age and Marital Status: Patentex Oval Study Group and Permanent Registration Group, 1977 (PR'77)

AGE (YEARS)	PATENTEX OVAL	PR'77	MARRIED	UNMARRIED	DIVORCED
	(%)	(%)	(%)	(%)	(%)
15–19	25	14	1	42	0
20–24	34	25	18	44	16
25–29	17	22	28	9	36
30–34	12	17	26	3	20
35–39	8	16	17	2	16
40	4	6	10	0	9
	(n = 653)	(n = 45,130)	(n = 217)	(n = 391)	(n = 44)

distribution (Table 14-3), a relatively large number of young girls are found to be users of Patentex Oval. Of the German abortion clients in the Permanent Registration group, 39% were under 25 years of age; among the users of Patentex Oval, 59% were under age 25.

The unmarried users of Patentex Oval are distinctly in excess in the lower-age category and under-represented in the category of 25 years and older. The steep incline in the age distribution with the unmarried users of Patentex Oval is not found among the married women; the distribution here is much more even.

The preference for Patentex Oval especially among young, unmarried women, is understandable. Patentex Oval is freely obtainable and preeminently suitable for women having infrequent intercourse. Patentex Oval might be considered a female equivalent for the condom, in terms of being a method for beginners.

DURATION OF USE

Table 14-4 indicates that in the first 4–6 months of Patentex Oval use, 22% of the married women, 28% of the unmarried women, and 23% of the divorced women became pregnant.

MOTIVES FOR CHOOSING PATENTEX OVAL

Users of Patentex Oval were asked about their motives for choosing this particular method of contraception. Response to advertising was the most frequent motive, followed by the easy obtainability and an "anti-pill" attitude (Table 14-5).

DISCUSSION

Patentex Oval contains 0.075 g p-nonylphenoxypolyethoxyethanol (nonoxynol 9) per unit. Nonoxynol 9 is a spermicidal agent which is also used in other vaginal contraceptives. A nonionic, surface-active agent, it inhibits oxygen uptake and fructolysis and also causes leakage of cytochrome c from cells (1).

TABLE 14-4. Marital Status and Duration of Patentex Oval Use at Time of Conception: Patentex Oval Study Group

MONTHS OF USE	MARRIED* (%)	UNMARRIED† (%)	DIVORCED‡ (%)
1	8	12	4
2	5	13	11
3	9	13	13
4–6	22	28	23
7–12	21	20	30
13–24	22	10	9
>24	11	4	11

*Average duration: 11 mo
†Average duration: 7 mo
‡Average duration: 8 mo

TABLE 14-5. Motive for Choosing Patentex Oval Among 1276 Women

MOTIVE	(%)
Advertising	27
Easy obtainability	19
Antipill attitude	18
Pause in use of oral contraceptive	14
Doctor's recommendation	12
Infrequent intercourse	5
Advice of family or friend	3
Pill complaints	1
Other motives	1

According to the manufacturer, the suppository disintegrates under the influence of body heat, independently of vaginal fluids, forming a fine foam. Information as to why this reaction occurs without relationship to the amount of vaginal fluids is not provided. The quality of the foam and its method of development are the characteristic elements of Patentex Oval. Prolonged and highly effective barrier activity is achieved and spermicidal distribution is good.

EVALUATION OF PATENTEX OVAL

CLINICAL EFFECTIVENESS

Theoretically, for a spermicide to be effective it must immobilize sperm almost instantaneously after the ejaculate is released into the vagina. This condition is dictated by the fact that spermatozoa have been found in the cervical mucus within 90 sec after coitus (16) and in the fallopian tubes within 5 to 10 min after artificial insemination (15).

Until recently, the sole criterion used to evaluate the contraceptive activity

of vaginal contraceptives was a series of *in vitro* tests, in which sperm were incubated with dilutions of the spermicide and observed for motility after certain periods of time (17).

For some reason, the *in vitro* observations do not hold true *in vivo*. Decreased effectiveness may be due to poor distribution of the spermicide in the vagina, the removal or displacement of the spermicide by the coital act, the inactivating effect of vaginal contents, and a position taken during intercourse that may result in poor spermicide contact, etc. These factors cannot be evaluated *in vitro*. To determine the use-effectiveness of a contraceptive, *in vivo* studies are therefore essential.

DISTRIBUTION OF THE SPERMICIDAL SUBSTANCE

For effective prevention of sperm migration, the spermicidal substance must exert its effects on sperm while they remain in the vagina. Also it must form a barrier over the cervical os to block the immediate penetration into the cervical canal.

The foaming ability of the Patentex Oval and the stability of the foam barrier was studied *in vivo* by Rammstedt (11) in 55 women from 18 to 42 years of age. After insertion of the suppository, the vagina was inspected with the aid of a speculum at intervals of 10, 20, 60 and 120 min. The women were encouraged to move around between observations. On the basis of these examinations, Rammstedt concludes that with all women a complete foam development already had occurred after 10 min, that there was a regular distribution of the viscous mass in the entire vagina, and that the foam barrier remained constant and intact, notwithstanding exercise and repeated examination. The possible displacement of the foam by the coital act was not studied.

POSTCOITAL TESTS AND BREEDING EXPERIMENTS

The human postcoital test has been used by several researchers to compare the relative effect of spermicides on the motility and cervical mucus penetrability of sperm (2, 5, 7, 8, 9, 10, 16).

In 1972, Brehm and Albrecht studied the reliability of Patentex Oval (2). One hundred postcoital tests were conducted with 23 couples; three of the women had previously given birth to children. Mucus samples were obtained from the vagina, the os externum, and the cervical canal 5 to 12 min after intercourse. The authors concluded that "the inability to find propulsively mobile spermatozoa in the female genital tract immediately after coitus, offers a clear indication, that no pregnancy can occur." The same results were again published by these investigators in 1978 (4).

Although the postcoital test more effectively indicates the *in vivo* activity of a spermicide than do the *in vitro* tests, it is still not conclusive, since the collected and observed spermatozoa may not be the ones that fertilize. Zaneveld (17) performed both postcoital sperm motility studies and breeding experiments with Delfen vaginal cream, which also contains nonoxynol 9. Although Delfen vaginal cream consistently immobilized all sperm in the postcoital test, half of the animals became pregnant within an average of 3.7

breeding cycles. These results illustrate that even if a compound is 100% effective in the postcoital test, it may not prevent fertilization.

CLINICAL STUDIES

Brehm and Haase (3) studied 10,017 women, of whom 4,588 nulliparas used Patentex Oval as their sole contraceptive during 63,759 monthly cycles. The reasons given for the use of Patentex Oval were pill pause (2950 women) and inability to tolerate hormonal contraception (1729 women). Taken together, these groups accounted for 40% of the cycles studied. Contraindications for using oral contraceptives prompted 2245 women (involving 28% of all cycles) to use Patentex Oval. Only 43 women became pregnant. According to the authors, 15 of these pregnancies were due to patient failures. Brehm and Haase arrived at a crude pregnancy rate of 0.8 and an adjusted one of 0.5.

Salomon and Haase (12) reported a study of Patentex Oval used as the only contraceptive by 1652 women during 34,506 cycles. The average time of use was 21 months. During the study, nine pregnancies occurred. Four were attributed to patient failure, with a crude pregnancy rate of 0.3.

RELIABILITY OF PATENTEX OVAL

The crude pregnancy rate of 0.8 and the adjusted rate of 0.5 for Patentex Oval noted by Brehm and Haase (3) and crude pregnancy rate of 0.3 of Salomon and Haase (12) are extremely low figures—so low, in fact, that they equal or surpass the pregnancy rates for oral contraceptives, IUDs and surgical sterilization. On the basis of the results of these studies the manufacturer assumes that the reliability of Patentex Oval is equal to that of the pill.

In both of the clinical German studies, one can hardly speak of a nonselected population when considering clinical effectiveness (2, 4). On the contrary, one would expect the women in the study groups to have a reduced fertility. Further, the conditions in which Patentex Oval was used in these studies deviates considerably from the everyday situation: the women were selected by gynecologists and examined every three months; and they were advised in detail about the proper use of Patentex Oval, whereas normally Patentex Oval is obtained at a drugstore and brief instructions are given at best. Thus the extremely low pregnancy rates are not representative of those with use of Patentex Oval in the everyday situation.

In addition to reliability, there are other criteria which determine the effectiveness of a method or an agent (14). One has to consider acceptability, attainability, and comfort of use.

ACCEPTABILITY

Although Patentex Oval can be inserted some time before coitus, the application usually takes place during the act of intercourse. This means there must be a pause in the normal coital sequence, so that intercourse may be delayed for another ten minutes. This interruption and postponement of

ejaculation may make the method less acceptable in a number of situations and, again, may lead to incorrect use.

Another factor that influences the acceptability is the existence of side effects, such as itching and burning sensations in the vagina.

ATTAINABILITY AND EASE OF USE

An advantage of Patentex Oval is its easy attainability. The physician need not serve as an intermediary or be informed about intended sexual actions. In young, unmarried women this consideration may be important.

The suppository must be inserted into the vagina as far as possible. This may be a problem to those women with a taboo about handling their own genitals. Obesity or vaginal prolapse also make insertion difficult.

CONCLUSION

The total number of abortions carried out in German women is unknown. It is known that in 1977, 60,000 German women had abortions in the Netherlands, and incomplete registration of West German women showed another 55,000 abortions. It seems reasonable to assume, therefore, that an estimated 150,000–200,000 induced abortions were performed in German women in 1977.

If one were to assume that in West Germany in 1977, no more than the 5000 women who sought abortions in the Netherlands had become pregnant after an average of one year of Patentex Oval use, the Pearl index failure rate of Patentex Oval in West Germany would be one. If the period of use is kept constant but the number of pregnancies resulting during the use of Patentex Oval varied, considering the number of pregnancy interruptions and unintended pregnancies, the Pearl index failure rate is 4 or 5.

A Pearl index figure of less than 10 places Patentex Oval in the group of contraceptives with good effectiveness, that is, in the group of oral contraceptives, IUDs, and surgical sterilization. Within this group it is the least effective method. Considering the great demand for effectiveness placed upon today's contraceptives, a pregnancy rate of more than 3 in developed countries must be considered as a strong indication of that method's ineffectiveness. The claim that Patentex Oval is not only equal to, but even better than, oral contraceptives cannot be sustained. Even the most optimistic extrapolation shows this. The distribution of contraceptive use among West German women seeking termination of unwanted pregnancies underlines that:

*pill users and IUD users are highly underrepresented in the abortion population
*users of other methods (a group consisting almost entirely of Patentex Oval users) are overrepresented in the abortion population.

It is evident that the differences in reliability between the pill and the IUD on the one side, and other methods on the other, are great.

It is our opinion that there is no place for Patentex Oval as a sole method of contraception. In the Netherlands, Patentex Oval is no longer available for sale.

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15

Effectiveness of Vaginal Foam Suppositories: Controversies in West Germany

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SOCIAL ASPECTS OF CONTRACEPTION IN WEST GERMANY

Although the birth rate in West Germany, as in most Western countries, has declined continually since the early 1960s, teenage childbearing, particularly among 17- and 18-year-old girls, has slowly but steadily increased (7). Among the key factors are the shift to earlier physical maturation (*i.e.*, early menarche), a trend toward early marriage, and the liberalization of sexual standards. Despite experience with premarital intercourse at increasingly early ages, young people usually do not desire pregnancy. In addition, teenage pregnancies and deliveries are associated with increased risks to mother and child, including toxemia, maternal death, low birth weight, and prematurity. Even when abortion is performed, serious emotional trauma and psychosocial and economical problems are likely. Thus, a safe, practical, and harmless contraceptive method is needed that is suitable for this group of young patients who are not familiar with the full range of contraceptive possibilities or for whom these are not always available. The phenomenon of "being tired of taking the pill" which has been observed in adult women has also reached the adolescent girl. Considerable concern has been expressed regarding insertion of IUDs in young girls, owing especially to the high risks of pelvic inflammatory disease associated with the IUD. These concerns regarding oral contraceptives (OC) and IUDs have led to a greater use of chemical-mechanical (barrier) methods in the German-speaking countries (8).

Data obtained from a 1977 representative survey by 70 family-planning centers in West Germany and collected by the West German State Department of Health showed that barrier methods were used by approximately

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The PRO FAMILIA–Beratungsstelle (Family-Planning Center) Munster is a member of the Deutsche Gesellschaft fur Sexualberatung Und Familienplanung, E. V. Cronstetten—Str: 30 D-6000 Frankfurt/Main/West Germany.

TABLE 15-1. Distribution of Contraceptive Methods Applied by 700 Female Outpatients, Department of Ob/Gyn, Univ. of Essen, West Germany, Jan. 1977 through March 1978*

CONTRACEPTIVE METHOD	NO. OF PATIENTS	PER CENT
Oral contraceptives	272	39
IUD copper (with chemicals)	133	19
Coitus interruptus	72	10
Sterilization		
Female	63	9
Male	6	1
Combined chem/mech	49	7
Condoms	42	6
Rhythm	28	4
Chemicals	26	4
BBT chart	9	1
TOTAL	700	100

*The ratio of OC users to IUD wearers is 2:1 in this study. This does not reflect the general situation in West Germany, where the ratio is estimated to be approximately 10:1. It is therefore obvious that at this hospital IUDs are more frequently recommended by the physicians. (Tauber PF, Ludwig H. Unpublished data, 1979)

20% of the persons questioned. Approximately 10% to 15% used either condoms or spermicidal substances (9).

The use of a contraceptive method depends on the social level of the user as well as the individual's knowledge about contraception. A clear relationship can be shown between the degree of information about contraceptive methods and contraceptive reliability. It is concluded that the best-informed groups of patients applying any contraceptive method are pill-users, IUD-wearers, and sterilized patients. Of the well-informed couples, 40% use barrier methods, 34% prefer rhythm or keep basal body temperature charts, and only 23% do not practice any contraception except coitus interruptus.

Nevertheless, the amount of information and final selection of a particular contraceptive method are strongly influenced by the understanding, counseling, and supervision of medically trained personnel (mainly physicians), and by their preference for various contraceptive methods. This is demonstrated in Table 15-1, which lists the percent distribution of applied contraceptive methods among 700 female outpatients at the Ob/Gyn Department of the University of Essen, West Germany.

SPERMICIDAL CONTRACEPTIVE PREPARATIONS IN WEST GERMANY

Table 15-2 shows the chemical substances in presently available vaginal contraceptive preparations in West Germany. All preparations can be obtained without prescription from pharmacies, drug stores, hygiene departments of supermarkets, and from specialty shops which sell products associated with

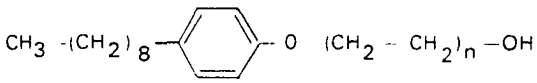

FIG. 15-1. Formula of nonoxynol 9 (Nonylphenoxypolyethoxyethanol)

sex. In addition, mail-order sales are also important in West Germany. The preparations include vaginal creams, jellies, pastes, aerosol foams, suppositories and tablets. The latter are usually prepared as foaming products containing bicarbonate of soda with powder base in which spermicide is incorporated. The only foam suppository presently on the market is Patentex Oval (PO). As with most chemical contraceptives, the preparations contain two principal components: 1) a vehicle that is a relatively inert carrier substance of different water solubility or consisting of a powder base; and 2) a surface active ingredient that is bactericidal or highly acidic and operates as the active spermicidal agent. Frequently, two or more spermicidal components are combined in a single product. Owing to intensive advertising campaigns in professional and lay journals, particularly those directed toward women and teenagers, the most commonly used vaginal contraceptive in West Germany is PO, which is known as Encare Oval in the U.S.. Since its introduction on the West German market in 1973, PO has reached highest priority among all vaginal contraceptive preparations in this country. It is estimated that about 60% to 70% of all vaginal contraceptive preparations sold in West Germany are PO. Other products are offered in much lesser quantities and have achieved only limited distribution.

The aggressive PO advertising campaigns in West Germany imply that: 1) this product is as safe and reliable as the pill; 2) the patented principle of efficacy in PO provides an impenetrable barrier for spermatozoa; 3) PO is highly acceptable without *any* incompatibility to the patient and has no contraindications for its application; and 4) it has become the leading local contraceptive in West Germany because of its great reliability as a contraceptive.

All Patentex products contain nonoxynol 9 (Fig. 15-1). Like all surface-active substances, this agent exerts its spermicidal activity by lowering the surface tension of the spermatozoal cell, leading to a complete loss of motility due to the occurrence of osmotic imbalance. Nonoxynol 9 is considered one of the most effective spermicides and is therefore incorporated in a number of presently used vaginal contraceptives. The total spermicidal power of certain nonoxynol 9 batches had previously been confirmed through *in vitro* tests by the International Planned Parenthood Federation (IPPF) in London (Test Protocol #6450, June 19, 1968, and #74/22, April 4, 1974), although the so-called "foam barrier" had been shown to be insufficient: "Patentex Oval, while satisfying the IPPF Agreed Test for total spermicidal power, failed the IPPF Test for Foaming Capacity" (10).

SUPPOSED MECHANISM OF PO ACTION

Based on the information provided by the manufacturer, PO has two different principles of action. The first is that, following deep vaginal insertion, the suppository melts at body temperature. The resulting foam is distributed

TABLE 15-2. Vaginal Contraceptive Preparations Presently Available in West Germany

BRAND NAME	MAIN SPERMICIDAL SUBSTANCE(S)	CONCENTRATION(S)	COMBINATION WITH	PREPARATION	MANUFACTURER	REMARKS
Delfen	Nonoxynol 9	12.5 g/100 g	—	Aerosol foam	Cilag	—
Delfen	Nonoxynol 9	5.0 g/100 g	—	Vaginal cream	Cilag	—
Ortho	Nonoxynol 9	2.0 g/100 g	—	Vaginal cream	Cilag	Use only with diaphragm
Patentex oval	Nonoxynol 9	0.075 g/Ovulum	—	Foam ovula	Patentex	—
Patentex	Nonoxynol 9	1.0 g/100 g	Alum. acet. tartar.	Foam gel	Patentex	—
Patentex	Nonoxynol 9	8.0 g/100 g	Alum. acet tartar.	Foam spray	Patentex	—
Antibion	Nonoxynol 9	0.024 g/Tablet	Alum. acet. tartar.	Foam tablets	Patentex	—
Contraceptivum E	p-n-nonylphenoxy-polyethyleneglycol	0.024 g/Ovulum*	Lactic acid	Vaginal ovula	Koronis/Mapa	10–60 min prior to intercourse
	Sodiumdioctyl-sulfosuccinate	0.036 g/Ovulum*				
Lady suppositories	p-n-nonylphenoxy polyethyleneglycol	0.024 g/Ovulum*	—	Vaginal ovula	Koronis/Mapa	10–60 min prior to intercourse
Ortho-Gynol	p-diisobutylphenoxy-polyethoxyethanol	1.0 g/100 g	Ricinoleic acid	Vaginal gel	Cilag	—
A-gen 53	Cellulose-polysulfuric acid ester	0.1 g/100 g	—	Non-foaming ovula	Herbrand	10 min prior to intercourse
Semori	8-hydroxychinolinsulfate	0.5 g/100 g	—	Foam tablets	Luitpold	3–4 min prior to intercourse
Confidol	*Dihydrocuprein*	0.1 g/100 g	Boric acid	Foam gel	Pharmasal	Prevents STD and vaginal discharge
	Methyl-p-oxybenzoic acid	0.05 g/100 g	Lactic acid Tartar. acid			
	Propyloxybenzoic acid	0.15 g/100 g	Alum. lactate Calc. lactate *Glycerin* Traganthicum			
Si-O-Safety ovals	Quinine-HCl	0.0625g/Ovulum*	Boric acid	Ovula	Petri	3 min prior to intercourse

*1 *Suppository* = Approximately 1200 mg

within the vagina, particularly at the external os of the cervical canal and at the posterior fornix of the vagina. The manufacturer describes this mechanism as the so-called "barrier function" of the product. It is also claimed that spermatozoa are prevented from ascending the cervical mucus. Secondly, the foam leads to a more even distribution of the spermicide under the condition that the suppository has been correctly applied. The combination of these two mechanisms is supposed to provide complete protection from pregnancy without application of any further contraceptive.

PREVIOUS PUBLICATIONS ON PO

Not many studies have been published on the use-effectiveness of PO since its introduction as a contraceptive because this product is sold without medical prescription and is used without recommendation by a physician. The first publication on the Patentex Oval appeared in 1972 (2). The results were obtained from 100 postcoital tests in 23 couples: 20 of the couples were nulliparous. All couples used PO according to the instructions on the package insert. Smear samples from three different spots (vagina, external os, and cervical canal up to 2 cm) revealed no motile spermatozoa. The major drawback of this study was that all women were taking oral contraceptives (sequential regimen Ovanon; 7 tablets containing 0.08 mg mestranol and 15 tablets containing 0.08 mg mestranol plus 2.5 mg lynestrenol as a progestogen) at the time of investigation. The authors attempted to obtain optimal and also comparable estrogenic stimulation of the cervical mucus on days 9 through 12 of the cycle, when the postcoital tests were performed, and to prevent unwanted pregnancies. Even when only a quarter of the original total amount of spermicide was used, no motile spermatozoa were discovered. Based upon this study, PO was considered as potentially effective as a vaginal contraceptive and was subsequently introduced on the German market. Similarly favorable results from postcoital tests in 18 PO users were recently reported by Hauser (6).

In 1975, the data were published from the largest field trial of Patentex suppositories performed to date in Europe. This retrospective study included 10,017 women who had been using PO for an average 7 months as the only contraceptive, resulting in a total of approximately 64,000 cycles (3). Questionnaires were provided by 287 physicians. Including patient failures, a Pearl index of 0.8/100 woman years was calculated and after correction, i.e. without patient failures, this figure dropped to 0.5/100. From these results, the authors stated that "it is not only favorable, but moreover even necessary to appoint this contraceptive (Patentex Oval) to the safety range of oral contraceptives." This prompted the Patentex GmbH. to initiate its advertising with the statement that "Patentex Oval is as safe as the pill."

Only recently, a first prospective study on PO was published in West Germany (11). Under the supervision of 21 practicing gynecologists, 1652 women used PO over 34,506 cycles, providing an uncorrected Pearl index of 0.3/100. The average duration of PO use was 21 months (range 12 to 54 months). Nine pregnancies were observed, four of them due probably to patient failures. Adverse side effects were reported in less than 1% of the cases

and included heat sensations in the vagina, loss of libido, and distress from increased vaginal discharge.

Controversial results on the use-effectiveness of PO have been mostly the subject of letters to the editors of professional journals. To our knowledge, no further prospective studies have been done so far which could show the true use-effectiveness of PO. Molitor-Peffer (10) reported 25 failures, *i.e.*, pregnancies, with PO use, although incorrect application of the contraceptive was implicated. PO used as the only contraceptive method was considered to be not safe enough and it was suggested to be recommendable only when condoms are additionally applied. A relatively high number of pregnancies under PO has also been reported by Fahrlander and Mall-Haefeli (5). They calculated a 5%–6% failure rate with PO versus 1.3%–1.4% failures in women using oral contraception among all those who sought abortion counseling at the Social-Medical Center in Basel, Switzerland. It was estimated that approximately 6000 women were using PO regularly as the only contraceptive. If one assumes a comparable degree of safety by oral and vaginal contraception, the former would have resulted in a much higher number of pregnancies in women using oral contraception, which was not the case. In this study, the number of women complaining of discomfort with PO was much higher than promised in the advertisements. The authors concluded that the advertisements for PO are overly optimistic and that this contraceptive product should be recommended for use only in combination with other local barrier methods.

RESULTS WITH PO REPORTED FROM PRO FAMILIA CENTERS IN WEST GERMANY

The PRO FAMILIA Pregnancy Advisory Centers, distributed throughout West Germany, are an important source of data concerning the use-effectiveness of contraceptive methods, including PO. As a part of the IPPF, these institutions are particularly well suited for psychosocial and medical counseling of women wanting abortion. Because abortion in West Germany has only recently been liberalized and legalized on certain grounds, and as counseling is required by law prior to the abortion procedure, an increasing number of pregnant women have been seeking mental and practical support for their pregnancy-related problems at the PRO FAMILIA institutions. In 1977, approximately 140,000 counseling sessions were performed in more than 130 PRO FAMILIA centers. Some 40%–60% of the counseled women were pregnant. Patients are usually asked to provide information about which contraceptive method, if any, they were using when they became pregnant, and how it was being used during the cycle of contraceptive failure. As these data are retrospectively evaluated, they cannot be considered representative. For various reasons, such as mistaken questioning by many different interviewers and/or incorrect answering or concealing the primary purpose of the visit, *i.e.*, to receive legal grounds for abortion, the data must be computed or extrapolated to allow any conclusions.

Table 15-3 lists the results obtained from retrospective inquiries, with particular respect to PO contraception, in a multicenter study of 30 different PRO FAMILIA centers and two single urban PRO FAMILIA institutions in

TABLE 15-3 Pregnancies with Patentex Oval (PO) and Oral Contraception (OC), Retrospective Data from Various PRO FAMILIA Centers in West Germany

	OBTAINED DATA					COMPUTED DATA		
	Counseling Period (mo)	*No Pregnant Patients Counseled*	*Pregnancies with PO*	*PO Users Pregnant (%)*	*Pregnant Patients Counseled (%)*	*No. Pregnant Patients Counseled*	*Overall PO Users (Approx. 15%)*	*PO Users Pregnant (%)*
PRO FAMILIA Multicenter (N = 30)	12	19,003	741*	3 9	49	38,780	5,937	12 5
PRO FAMILIA Cologne	20	3,687	231†	6 3	46	8,000	1,200	19 3
PRO FAMILIA Muenster	6	267	11†	4 1	55	485	73	15.1
			Pregnancies with OCs	*OC Users Pregnant (%)*			*Overall OC Users (Approx 25%)*	*OC Users Pregnant (%)*
PRO FAMILIA Cologne	20	3,687	67	1 8	48	8,000	2,000	3.4
PRO FAMILIA Muenster	6	267	4	1 5	55	485	121	3.3

*Include incorrect application of contraceptive

†Contraceptive correctly applied

West Germany. Among all pregnant women counseled at these centers, the percentages of women claiming to have used PO in the cycle of conception varies between 3.9% and 6.3%. Because some of the pregnant women had not been using any contraceptive, as indicated by the cases in Cologne (Table 15-4), the percentages of pregnancies occurring under PO contraception are even higher when calculated only from the number of women who applied contraception. Nevertheless, the above figures compare favorably to those recently published by Fahrländer and Mall-Haefeli (5) in Switzerland and, moreover, express the mostly unpublished opinion and the general experience of many physicians on the real use-effectiveness of PO contraception. Related to the computed number of all counseled visitors, including nonpregnant women who sought the advice of the family-planning services, and assuming a 15% overall PO user rate in the general fertile female population, pregnancies occurring with PO use account for between 12.5% and 19.3%. This means that approximately every sixth and eighth woman will become pregnant while using PO, regardless of her previous experience with this contraceptive. If one compares the rates of pregnancies which were claimed to have occurred under OC, the figures are much lower, ranging from 3.3% to 3.4% in the respective centers (with the exception of the Multicenter study, where the OC failure rates were not available). The risk for a woman to conceive while using PO contraception is therefore approximately five to six times higher than with OC, even when patient failures with OC are not omitted. Although these figures are computed from the original results obtained by retrospective questioning, they represent more or less the true situation and definitely disprove the exaggerated advertising slogan used by the Patentex GmbH, which claimed that "Patentex Oval is as safe as the pill."

Table 15-4 demonstrates the distribution and the percentage of failures by the contraceptive method used in a highly urbanized area, Cologne, West Germany. Undoubtedly, the number of pregnancies reported from this PRO FAMILIA center indicates the preference for certain contraceptive methods recommended by physicians and applied by this mainly urban population. A surprisingly high number of women still practice coitus interruptus or rhythm for contraception or do not practice any contraception at all.

The data from the Cologne center reveal another important problem associated with the use of PO. Among 3,687 pregnant women counseled from April 1977 through November 1978, only 1,906 (52%) used some form of contraception during the cycle of conception. Although the gross failure rates, *i.e.*, number of pregnancies, are even higher with OC (n = 369; 19.4%) as compared to those for women using PO (n = 280; 14.7%), these figures change drastically when one considers whether or not the contraceptive had been correctly applied. From the 369 OC failures, correct use of the pills achieved in only 67 cases, whereas incorrect use was found in the remaining 302 women. The respective figures for correct or incorrect use of PO are almost diagonally different: Among 280 PO failures, a definitely incorrect application was demonstrated in only 49 women, whereas 231 pregnant women believed that they had applied the contraceptive correctly. Related to the total number of pregnant women using a contraceptive in the cycle of conception, the percentages are 3.5% for correct use of OCs versus

TABLE 15-4. Distribution of Contraceptive Failures by Contraceptive Method Used; Retrospective Data from PRO FAMILIA Center, Cologne, West Germany, April 1977–Nov. 1978

CONTRACEPTIVE METHOD		TOTAL NO. PREGNANCIES	(%)*	(%)†	PREGNANCIES WITH CORRECTLY APPLIED CONTRACEPTIVE	(%)*	(%)†	PREGNANCIES WITH INCORRECTLY APPLIED CONTRACEPTIVE‡	(%)*	(%)†
Orals	(s)	369	10 0	19 4	67	1.8	3.5	302	8 2	15.8
IUDs nonmedicated	(s)	14	0.4	0.7	—	—	—	—	—	—
Copper	(s)	83	2 2	4.4	—	—	—	—	—	—
Progestogen	(s)	6	0 2	0.3	—	—	—	—	—	—
Patentex Oval		280	7.6	14.7	231	6.3	12.1	49	1.3	2.6
Other chemical methods		78	2.1	4.1	66	1 8	3.5	12	0 3	0.6
Condoms		262	7.1	13.8	—	—	—	—	—	—
Combination (chem/mech)	(s)	41	1.1	2.2	39	1.1	2.1	2 (1 diaphr)	0.05	0.1
Coitus interruptus		430	11.7	22.6	—	—	—	—	—	—
Rhythm		305	8 2	16 0	—	—	—	—	—	—
BBT-charts		10	0 3	0.5	—	—	—	—	—	—
Sterilization female/male	(s)	10	0.3	0 5	—	—	—	—	—	—
Others		18	0 5	0.9	—	—	—	—	—	—
Subtotal (pregnancies with contraception)		1906	51.7	100.1	403	10 9	21 1	365	9 9	19.1
No contraception used		1781	48.3	—						
TOTAL		3687	100.0*							

(s) Method considered as safe

*Total number of pregnancies: n = 3687(=100%)

†Contraceptive methods used by n = 1906

‡Include patient failures and drug interferences

15.8% for incorrect OC use; and 12.1% with correct use of PO vs. 2.6% for incorrect use. Thus, even the presumably correct application of PO puts the women at an approximately 3.5 times higher risk of becoming unintentionally pregnant as compared to use of OC. It is obvious that this difference in the use-effectiveness derives from the method itself which, like all vaginal preparations, bears an inherent failure rate, even when the substance is correctly used, *i.e.* according to the recommendations given by the manufacturer on the package insert.

DISCUSSION

Although the available data are insufficient to derive calculations of Pearl indices or life-table analyses, they nevertheless reveal a high number of PO failures among the counseled population. In this regard, the advertising statement of the manufacturer, Patentex GmbH, is unjustified, and in fact misleading, because it claims contraceptive safety which is contradictory to the experience of family-planning physicians. When compared to pregnancy rates associated with OC use, the likelihood that a woman will become pregnant while using PO contraception is approximately three to five times higher, regardless of the duration of use and/or the personal experience of the woman with this contraceptive.

With regard to the contraceptive safety and the failure rate of PO, three points are relevant. The first concerns the spermicidal power of nonoxynol 9, which is contained in the PO foam suppository and also in other vaginal contraceptives. Although nonoxynol 9 has been shown to be a potent spermicidal agent with excellent laboratory effectiveness, *in vitro* studies of chemical contraceptives show little correlation with their use-effectiveness in clinical trials (1). This raises a second consideration, *i.e.*, whether or not the application of the spermicides as a PO foam suppository is adequate. The foaming substance in PO has failed the IPPF test for foaming capacity and has thus been proven ineffective. Stone and Cardinale (12) found that 9 of 20 patients in whom the suppository was inserted experienced little or no foam, and the suppository was removed almost intact after 15 min of observation. Lack of solubility and subsequent foaming will result in an uneven and partial distribution of the spermicide and foam in the vagina and will prevent adequate covering of the cervix.

The third concern relates to the proper insertion of the PO foam suppository into the vagina. Considering the findings of the present study, claims by the high number of pregnant women that they correctly inserted the PO suppository are probably incorrect. While they may have believed that insertion was correct, they may have made a mistake. This possibility indicates an additional lack of safety, due primarily to improper or insufficient patient information on the package inserts provided by the manufacturer. Based upon these considerations, it is impossible to believe that the foam from Patentex Oval will exert higher contraceptive qualities than other vaginal contraceptives utilizing spermicides because most of these preparations have identical or at least similar problems, *i.e.*, lack of solubility, low foaming capacity, or improper application. The concept of melting and/or foaming carrier

substances used for application of powerful spermicides as local contraceptives should therefore be reconsidered. New carrier agents should be developed that will provide more effective protection against pregnancy, particularly because OCs and IUDs have been shown to have increasingly limited distribution or are restricted to use by women of certain age groups.

One promising approach to the intravaginal application of spermicides is use of collagen sponges*, as they have been developed by Chvapil (4). Collagen sponges are highly biocompatible and can be combined with spermicides. Clinical trials of such "combined barriers" should therefore be undertaken to improve the prospects of vaginal contraception.

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16

New Data on the Pharmacokinetics of Nonoxynol 9

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The most effective spermicidal agents are detergents, or surfactants. This is not surprising in view of the established ability of detergents to disintegrate cell or subcellular membrane structure, such as lysosomal vacuole and endoplasmic reticulum. Why the deleterious effect of a detergent should be limited to the spermatozoa, however, and avoid such other cells as vaginal epithelial lining or cells of other tissues, has been unclear. Owing to the placement of spermicidal detergents in the upper vagina with rapid resorption capacity, it could be assumed that most of the intravaginally administered detergent is transported through the vaginal wall into the systemic circulation, thus possibly causing a systemic effect.

Publications dealing with pharmacologic-toxicologic aspects of surfactants in animals or in humans are rare. Studies have dealt with spermicidal effectiveness and with the mechanism of sperm lysis by various types of detergents. One source of relevant information about the possible toxic effect of a detergent was a personal report from a veterinarian on liver damage in cattle treated for bloat after large intraruminal doses of a detergent.

In the laboratories of the University of Arizona, during testing of the collagen sponge as a mechanical vaginal barrier, investigators decided to compare the effectiveness of a plain collagen sponge and one containing a spermicidal agent. The choice was nonoxynol 9 (n 9), as the most commonly used and highly effective spermicide (Fig. 16-1). The testing procedure is described below.

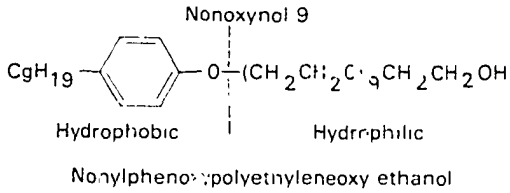

FIG. 16-1. The formula of nonionic detergent nonoxynol 9

RABBIT VAGINAL IRRITATION TEST

Due to the possibility of toxic effects of this detergent residing in the vagina, n 9 was [illegible] sponge (CS) matrix placed intravaginally in rabbits. The [illegible] test is considered by many to be the most sensitive [illegible] spermicidal agents (4, 7).

By an [illegible] re (2, 3), a plain CS or CS containing aqueous n 9 was implanted intravaginally in a total of 15 rabbits. The doses of n 9 corresponded to 200 mg, 500 mg, 1,000 mg and 2,000 mg of human doses.* The sponges were left in the vagina for 10 days, after which the vagina was removed and evaluated by light and scanning-electron microscopes. The sponges implanted intravaginally were also evaluated histologically for cellular infiltrate.

The vaginal tissue showed signs of irritation. The amount of inflammatory change was proportional to the dose of n 9 incorporated into the sponge. The evaluation of the magnitude of morphological change involved: 1) characteristics of epithelial lining, 2) thickness of the submucosal layer, 3) leukocyte infiltration of the submucosal layer, and 4) infiltration of the inserted CS. Each parameter was semi-quantitated by scoring 1+ to 4+. The total score of 0 to 8 was designated as acceptable, 9 to 10 marginal, and over 10 unacceptable. By these criteria, the dose corresponding to 500 mg n 9 should be considered unacceptable. The lowest dose tested, 200 mg, is only marginally acceptable, inducing definite vaginal changes when compared with plain CS (Table 16-1)

This result led us to study several other pharmacological effects of n 9. The outline of the testing program is shown in Table 16-2. It should be emphasized that, in order to identify and quantitate n 9 in biologic fluids and tissues, ^{14}C-n 9 labeled uniformly was utilized in the ethylene repetitive unit. This also permitted us to study the kinetics of vaginal absorption, distribution, and excretion, and the possible metabolism of n 9. No analytic method is presently available to identify and quantitate "cold" n 9 in biologic tissues. Because of the extensiveness of the testing program, this report will present only a summary of the results, without describing all of the methodologic details. These will be published elsewhere.

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*The ratio of size/weight of collagen sponge for rabbit and human vagina is approximately 1:40

TABLE 16-1. Effect of the Dose of Nonoxynol 9 on the Score of Changes of Rabbit Vagina (At Least Three Rabbits in Each Group)

DOSE n 9 (mg/sponge)	MUCOSAL LINING (ulceration)	SUBMUCOUS LAYER (edema)	LEUKOCYTE INFILTRATE IN SUBMUCOUS LAYER	SPONGE	TOTAL SCORE
0	1	0	1	2	4
200	2	2	3	3	10
500	3	4	3	4	14
1,000	4	4	4	4	16
2,000	4	4	4	4	16

TABLE 16-2. Summary of Test Performed to Characterize Nonoxynol 9 Pharmacology

Tissue culture WI-38 fibroblast
- DNA* and GAG† synthesis

Rat ip‡ injections
- liver morphology, TEM#
- liver chemistry
- serum lipids, SGOT§
- lung chemistry

Rat Intravaginal applications
- liver chemistry
- serum, SGOT

Rat
- Resorption, tissue distribution, excretion
- Study on metabolism on nonoxynol 9 (urine, exhaled $^{14}CO_2$)

Rabbit Intravaginal application
- rate of resorption
- rate of excretion in feces, bile and urine
- tissue distribution and retention

Effect of various vehicles on the rate of resorption of nonoxynol 9 from the vagina
- in saline
- in collagen sponge
- in cream

Human volunteers
- nonoxynol 9 and liver function

*DNA = desoxyribonucleic acid
† GAG = glycosaminoglycans
‡ ip = intraperitoneal injection
#TEM = transmission electron microscopy
§ SGOT = serum glutamic oxaloacetic transaminase

EFFECT OF N 9 ON MITOTIC ACTIVITY AND THE SYNTHESIS OF GLYCOSAMINOGLYCANS BY HUMAN FIBROBLASTS W1-38

The cytotoxic effect of cationic detergents in dilution ranging from 1:1,000 to 1:10,000 has previously been demonstrated by a tissue culture technique by Bengmark and Rydberg (1). It has also been shown that the cytotoxicity of detergents increases in the order nonionic < anionic < cationic (5).

In a system of W1-38 fibroblasts, the incorporation of ^{3}H-thymidine as an index of cell mitosis was measured, as was the incorporation of $^{35}SO_4$ into macromolecular compounds as an indication of the synthesis of glycosaminoglycans (GAG). Various amounts of n 9 or other detergents were added to the culture medium together with the radioactive compounds. The system was then incubated for 24 hr.

The results obtained are presented as the concentration of n 9 necessary to inhibit 50% of the incorporation of ^{35}S or ^{3}H into GAG and DNA of the test cells compared to the control cells. ED_{50} for n 9 is between 3 to 5 ppm. The cytotoxic comparison of various detergents showed that the cationic detergent (Cepacol) is the most toxic and the anionic detergent (sodium dodecylsulfate, SDS) is the least toxic. The cytotoxicity of nonionic n 9 approaches that of the cationic detergent (Fig. 16-2).

EFFECT OF N 9 ON RAT LIVER AND OTHER TISSUES

The first *in vivo* study tested saline-diluted n 9 in intraperitoneal injections to 200 g male rats at the dose of 5 mg/100 g body weight/day. According to a formula developed by Hall *et al* (6) relating the drug toxicity in experimental animals to man, this dose corresponds to 200 mg n 9 for 60 kg body weight of man. Each rat received one injection for 5 consecutive days and the animals were sacrificed 24 hrs after the last injection. Control rats received similar treatment with saline.

Chemical analysis of the liver of rats given n 9 (Table 16-3) showed a significant increase in the content of cells (DNA/liver). There was a striking increase in total hydroxyproline content which mainly indicates collagen accumulation. No changes were detected in noncollagenous proteins, in total liver or microsomal fraction or cytochrome P_{450}. The transmission electron micrographs of these livers showed a definite increase in the density of rough endoplasmic reticulum. The lipid content of the liver, *i.e.*, cholesterol, triacylglycerol, and phospholipids, was unchanged. These findings contrasted with the chemical analysis of the lung tissue, in which no change in any of the reported parameters was found. The serum lipids (cholesterol, triacylglycerol) were all significantly decreased in n 9 treated rats.

It should be reiterated that n 9 was administered intraperitoneally in a large dose for 5 consecutive days; however, even a single intraperitoneal dose significantly increases SGOT* (Fig. 16-3). Furthermore, it will be documented below that 5 or more intravaginal administrations of n 9 (aqueous form, 5 mg/100 g/day) to rats also significantly increased SGOT. In order

*SGOT serves as a marker of tissue injury in general, not specifically related to liver damage

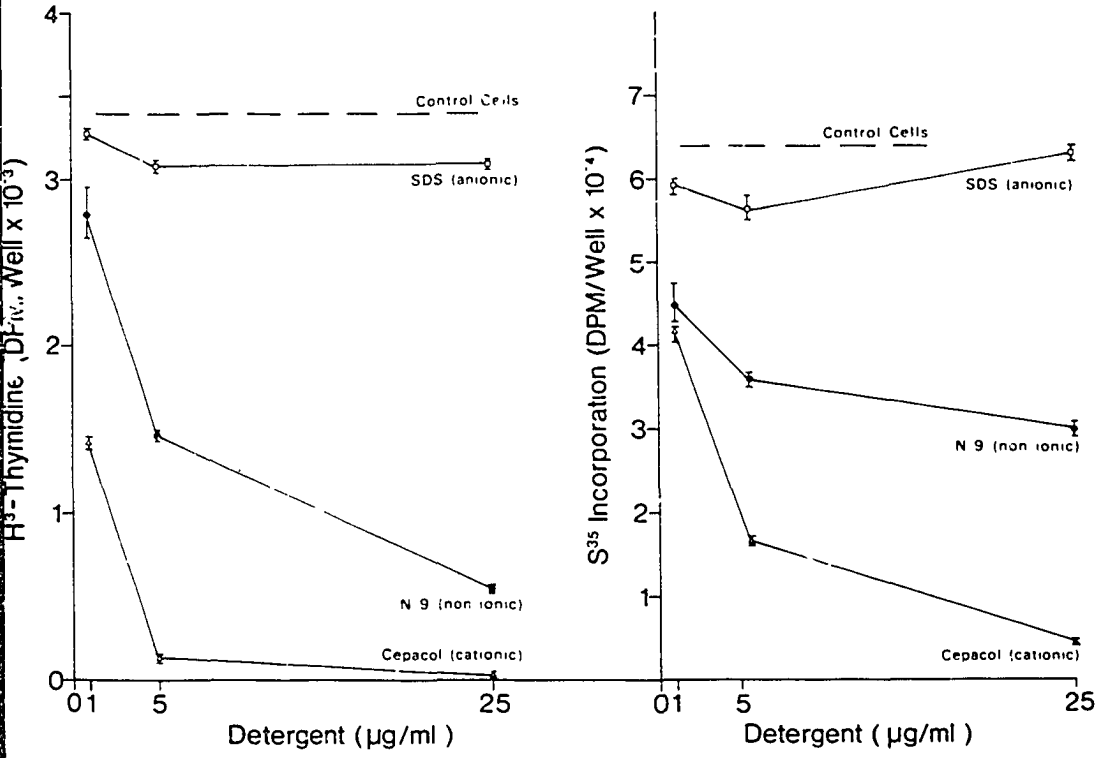

FIG. 16-2. Effect of charge differences of detergents on the function of WI-38 fibroblasts. A given detergent at indicated concentrations was added to cell culture medium with a label and incubated for 24 hr. Each value is the average of three determinations, variability given by SEM

TABLE 16-3 Liver Chemistry; Nonoxynol 9 (rat, 5 × IP, 5 mg/100 g)*

	CONTROL	NONOXYNOL 9	
Weight (g)	9.42 ± 0.36	9.81	
DNA			
mg/g	2.17 ± 0.20	2.67 ± 0.17	P<.05
mg/liver	20.40 ± 1.20	26.16 ± 1.10	P<.005
Collagen-hydroxyproline			
µg/g	127.96 ± 20.01	232.23 ± 21.45	P<.005
mg/liver	1.20 ± 0.17	2.27 ± 0.12	P<.001
Noncollagenous protein			
mg/g	113.20 ± 9.06	116.20 ± 4.41	NS
mg/liver	1.05 ± 0.08	1.14 ± 0.46	NS

*Variability given as $\overline{X}$ ± SEM; content of cholesterol, triacylglycerol and phospholipids unchanged.

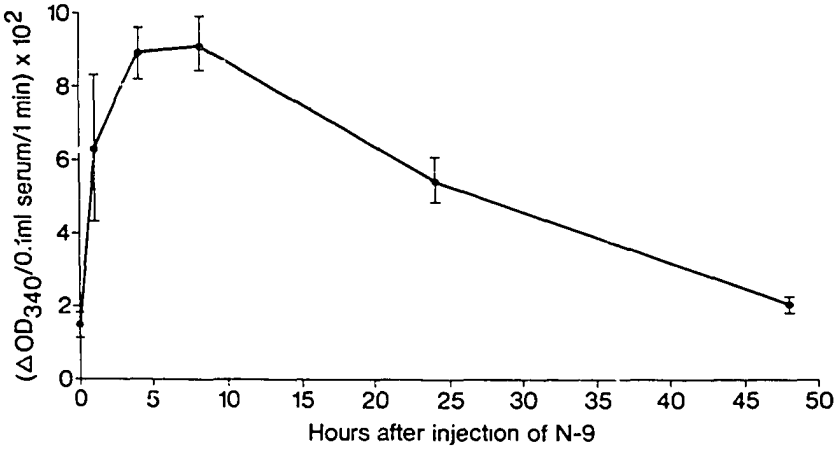

FIG. 16-3. Effect of a single ip injection of nonoxynol 9 on SGOT activity in the serum of rats; 200 g rats were given ip 5 mg n-9/100 g. At indicated time intervals the animals were sacrificed and serum glutamyl oxaloacetic transaminase activity was measured spectrophotometrically at 340 nm. There were 3–5 animals in each group; variability refers to SEM.

TABLE 16-4. Effect of Repetitive Intravaginal Administration of Nonoxynol 9 on SGOT and Liver Chemistry in Rats

NUMBER OF ADMINISTRATIONS*	SGOT ΔOD_{340}/min/100 ml	LIVER HYP†† µg/g
0 (Control)†	13.4	234
5	22.0‡	229
10	18.8‡‡	215
15	22.4‡	339§
20	18.2‡‡	287

*5 mg n 9/100 g weight/day

†9 rats in control group, 6 rats in experiment groups

‡$P < 0.001$

‡‡$P < 0.01$

§$P < 0.05$

††HYP = hydroxyproline (indicates collagen content)

to simulate how this detergent is used by women, rats were injected with aqueous n 9 (5 mg/100 g body weight/day) intravaginally for 5, 10, 15 and 20 consecutive days. Liver, kidney, vagina, and uterus biochemical and morphological analyses were performed and SGOT activity was measured. Some of the results are presented in Table 16-4, showing changes in liver chemistry after intravaginal administration of n 9 similar to those reported for intraperitoneal administration. Collagen content in the liver was significantly increased at 15 days. At all sampling periods, SGOT was significantly elevated.

TABLE 16-5. Excretion of Nonoxynol 9 in Feces and Urine After A Single Intravaginal Dose*

TIME AFTER APPLICATION (HR)	FECES	URINE
	% of original dose	
0– 24	0.53 ± 0.62	20.39 ± 12.30
25– 48	2.09 ± 1.64	5.91 ± 4.79
49– 72	2.06 ± 1.64	5.18 ± 2.81
73– 96	2.43 ± 2.27	3.73 ± 1.89
97–120	1.71†	2.79†
121–144	1.00 ± 0.083	1.84 ± 0.24
TOTAL	**9.80**	**39.85**

*Each value is the average of 3 rabbits; variability given as X ± sd

†Estimated value

RESORPTION OF N 9 FROM THE VAGINA

The kinetics of SGOT changes after intravaginal administration of n 9 indicated a rapid transport of this detergent into the body fluids. A separate experiment was designed to study the rate of resorption, distribution, excretion, and possible metabolism of intravaginally administered n 9. Rabbits were the experimental animal used and a collagen sponge with n 9 was placed intravaginally. The collagen sponge contained 110 mg n 9 and 75 μ Ci^{14}C-n 9.

^{14}C-n 9 was detected in the blood a few minutes after intravaginal insertion of the sponge containing n 9. Further, the rate of n 9 released from the intravaginal collagen sponge depends on the vehicle with which the detergent is mixed (water solution, cream). It was interesting that the level of ^{14}C-n 9 activity in the serum decreased rapidly for several hours. The amount of detergent in the urine decreased from 20% of the total administered dose excreted the 1st day to 2% excreted on the 6th day. While almost 40% of the n 9 was excreted through the urine during the 6 days, only 10% was excreted in the feces (Table 16-5). After intraperitoneal administration, approximately 2% of the n 9 is excreted in bile per hour and the rate of detergent excretion through the bile is linear with time (within 4 hr after administration).

Based on the kinetic data of n 9 in the blood, bile, urine, and feces at various times after a single dose, the conclusions of the study are that

1. N 9 is rapidly transported from the vagina to the blood. As shown in Table 16-6, almost 100% of n 9 is reabsorbed from the sponge within 6 days.
2. N 9 is efficiently cleared from the blood by the kidneys (urine) or the liver (bile).
3. The discrepancy between high excretion of n 9 in the bile and its relatively low content in feces indicates reabsorption of the detergent from the gut by an enterohepatic mechanism.

TABLE 16-6. Recovery of ^{14}C Nonoxynol 9 in the Rabbit Tissues (Single Intravaginal Dose of 111 mg, 6 Days After)

BODY ELEMENT	% OF DOSE
Tissues of the body (Other than skin, bone, and bone marrow)	1.0
Muscle (Estimated assuming 40% of body mass)	28.7
Fat (Estimated assuming 18.8% of body mass)	2.2
Feces (Collected up to 144 hr)	9.8
Urine (Collected up to 144 hr)	39.9
CO_2 (Estimated from 6-hr rat study)	3.0
Sponge (Retained in sponge)	0.4
Total Recovered	85.0
Amount Not Accounted For	15.0

RECOVERY OF N 9 IN THE RABBIT

An attempt was made to account for all the intravaginally administered ^{14}C-n 9 in three adult rabbits. The data summarized in Table 16-6 show that more than 80% of the administered detergent was recovered. Six days after the administration, only half of the dose was excreted in the urine or feces. The major tissue retaining the detergent was the muscle mass, not adipose tissue. The actual content of n 9 in various organs (Table 16-7) indicates that the liver still retains 20–50 times more detergent that other organs 6 days after administration of the n 9 dose. This indicates an enterohepatic circulation of n 9 and suggests that the liver would be the organ most affected by this chemical.

METABOLISM OF N 9 IN ANIMAL TISSUES

In order to test the hypothesis that n 9 is metabolized by animal tissues, the homogeneity of the sample of nonradioactive as well as radioactive n 9 was characterized before its *in vivo* administration to animals. These analyses were compared with the n 9 pattern in one of the commercially available spermicidal formulations. Thin-layer chromatography (TLC) patterns indicated a similarity of all three samples, which contained not only n 9 polymer but also 10%–15% of larger or smaller molecular weight n 9-like components (greater or lesser ethylene in the side chain).

After *in vivo* administration of ^{14}C-n 9, bile and urine were collected. Following appropriate chemical treatment, the TLC analysis did not indicate any changes from the original pattern of n 9.

TABLE 16-7. Tissue Distribution of Nonoxynol 9 (Rabbit, Six Days After a Single Intravaginal Dose)*

Organ	NONOXYNOL 9/ORGAN (DPM × 10^3)	% of Initial Dose
Brain	17.25	0.01
Kidneys	101.14	0.07
Gut	64.61	0.04
Heart	27.19	0.02
Liver	620.20	0.39
Lung	27.46	0.02
Spleen	15.15	0.01
Muscle†	30.85	—
Bone marrow†	3.17	—
Uterus	105.40	0.07
Vagina	140.60	0.09
Collagen sponge	920.00	0.60

*Average of three organ analyses is presented
†Refers to dpm/g tissue wet weight

The finding that $^{14}CO_2$ was detected in the exhaled air a few hours after $^{14}CO_2$ administration may not necessarily indicate that n 9 is being metabolized, because the ^{14}C-n 9 as well as other samples of n 9 tested were estimated to be only 70%–80% pure (by TLC analysis).

At this time there appears to be little evidence to indicate n 9 is being metabolized to CO_2.

HUMAN STUDIES

The information on the chronic effects of a commercially available spermicidal cream, administered to human volunteers for a total of 14 days, is incomplete. The aim was to test ten volunteers prior to, during (at 7 days), and at the end (14 days) of using approximately 150 mg n 9 per day in the cream. Liver function was tested by bilirubin, bile acids, SGOT, SGPT, GGT, blood differential, and serum lipids. Two volunteers showed abnormal values before using the spermicide and were eliminated from the study. Of the remaining eight women, four discontinued use of the spermicide during the testing because of local vaginal irritation, infection, or discomfort. For this reason, the data are incomplete and not conclusive. The only significant finding is the reduction of serum cholesterol in women using n 9 for any time up to 14 days.

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17

Vaginal Contraceptives for Prophylaxis Against Sexually Transmissible Diseases

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For the past several years investigators at the University of Pittsburgh have been working to develop suitable chemical barriers and to utilize vaginal contraceptives for prevention of sexually transmissible diseases (STD). There are a number of reasons to examine this concept of prophylaxis-contraception (pro-con).

Unwanted pregnancy and venereal diseases (VD) are major health problems throughout the world today. In the US, more than one-third of all births are out of wedlock, and two-thirds of the teenage pregnancies and half of teenage births are not intended (8). The health, social, and economic consequences of early childbearing have generally adverse effects on the young woman and on her child, as well as on society. These considerations suggest that the present contraceptive technology and delivery systems are poorly adapted to a teenager's needs.

From epidemiologic perspectives, one can consider unwanted pregnancy as a sexually transmitted condition Although rarely classified as a venereal disease, unwanted pregnancy is transmitted sexually and has many other characteristics of the conventional venereal diseases. The epidemics of adolescent pregnancy and VD are alarming and pose a challenge to public health workers and health care providers. Considering many common parameters between VD transmission and pregnancy, it would seem logical to bring about increasingly interrelated efforts and programs for the prevention of both unwanted and/or unplanned pregnancy, and the transmission of VD, or as they are increasingly designated, STD.

The toll of these infections is very high, in terms of disease, death, and disability. The incidence of gonorrhea, the most common VD, in the United States alone is higher than the incidence of all other infectious diseases except the common cold. It is estimated that, each year, eight to ten million Americans contact gonorrhea, syphilis, genital herpes, trichomoniasis or nongonococcal urethritis. Recent increases of VD around the world have indicated that traditional methods of control have not been completely effective. VD is often transmitted before symptoms occur and treatment is begun. The causative microorganisms have become increasingly drug resistant and now the emergence of penicillinase-producing gonococci, which respond poorly

or not at all to penicillin treatment, has further complicated the situation. Certain features of this disease make its control difficult. No vaccine is available for VD at present and, even if it becomes available, its usefulness will be limited.

Prophylaxis against VD in the male by use of the condom and local application of prophylactic preparations, such as those provided in pro-kits, was well-accepted and widely used in the United States during World Wars I and II. The potential for bringing about self-protective behavior in terms of protection against VD has been well-demonstrated among mililtary personnel, in whom the individual risks were appreciated by significant proportions of sexually active males. Furthermore, the social costs, in terms of absence from duty and need for medical care, resulted in aggressive VD prevention programs by military and civil authorities. It is clear that the success of a preventive program depends upon how the program is promoted and for whom such a program is designed. Moreover one has to learn how to bring about better patient cooperation and utilization of existing and proven health technology.

Prevention of VD through use of mechanical barriers is known but not widely practiced, owing to a variety of factors. Chemical preparations and vaginal contraceptives offer protection against sexually transmitted infections. Their potential for being accepted and utilized should be explored.

In recognition of the interrelationship between pregnancy and STD with respect to population programs, the AID awarded a contract to the University of Pittsburgh for research services toward the development of a combined agent for disease prophylaxis and contraception. It was felt that an intravaginal precoital preparation, offering the woman protection from VD as well as from pregnancy, would complement existing contraceptive and VD-control techniques. Such a preparation could be used alone or in conjunction with another contraceptive and would require no medical prescription or intervention. It would be readily available regardless of age or sex, and motivate sexually active persons to use self-protection. For the first time, women would have a means of protection from infection with STD without having to depend on cooperation from a sexual partner.

Thus, under contract US/AID/CSD/2822, it was possible to study a large number of chemical preparations for intravaginal use as a potential for VD prophylaxis. A number of vaginal contraceptive preparations, marketed in the United States and other counties and approved by the FDA were tested for antimicrobial activity against *Neisseria gonorrhoeae, Treponema pallidum, Trichomonas vaginalis,* and *Candida albicans* (11, 12). The virucidal effect of certain selected contraceptives has also been investigated against *herpes simplex* Types 1 and 2, (10, 13) and more recently on Mycoplasma. These *in vitro* studies were confirmed, utilizing animal models if available.

These laboratory studies were carried out to identify chemical preparations that have sufficient bactericidal and bacteriostatic properties. Chemical contraceptives such as foams, jellies, and creams were tested. Their effects on *Neisseria gonorrhoeae* are shown in Table 17-1. Some of these contraceptives were bactericidal, even at 1% concentration and several at 10% concentration. Gonococci were inactivated within 1 min in the presence of several of these contraceptives. The antimicrobial effects resulted from active

TABLE 17-1. Highest Dilution of Contraceptives Required to Inhibit the Growth of *N. gonorrhoeae* by 2 Methods*

		TIME EXPOSURE METHOD					PLATE DILUTION METHOD		
		Conc.†	*pH*	*Growth after exposure*			*Conc.*	*pH of*	*Growth*§
No.	*Contraceptives*	*%*		*1 min*	*5 min*	*10 min*	*%*	*medium*‡	
1	Certane Vaginal Jelly	10	4.6	+	–	–	10	7.5	–
2	Contra Creme	50	6.9	+	±	–	10	7.5	–
3	Contra Foam	10	7.5	±	–	–	10	7.5	–
4	Cooper Creme	1	6.7	–	–	–	10	7.6	
5	Delfen Cream	20	5.2	+	+	–	10	7.6	–
6	Delfen Foam	50	4.9	–	–	–	20	7.6	–
7	Emko Concentrate	50	7.4	–	–	–	20	7.5	–
8	Emko Concentrate +A	50	7.1	–	–	–	20	7.2	–
9	Emko Concentrate +B	50	7.2	–	–	–	20	7.2	–
10	Emko Concentrate +Spermicide	20	7.0	+	+	–	20	7.3	–
11	Emko Foam	10	7.3	–	–	–	10	7.4	–
12	Immolin Vaginal Cream-gel	50	4.9	–	–	–	10	7.5	–
13	Koromex A Vaginal Jelly	10	6.0	+	–	–	50	7.5	–
14	Lanesta Gel	10	5.6	+	–	–	10	7.5	–
15	Lorophyn Suppositones	10	5.7	+	–	–	10	7.5	–
16	Milex Cresent Jelly	10	5.7	–	–	–	10	7.5	–
17	Ortho Creme	1	6.2	+	–	–	1	7.4	–
18	Ortho-gynol Jelly	10	5.5	+	–	–	10	7.4	–
19	Preceptin Gel	1	5.6	–	–		1	7.4	–
20	Ramses Vaginal Jelly	50	6.7	+	+	–	50	7.5	–

*Bacterial suspension for these experiments contains about 10^6 CFU per 0.1 ml; the inoculated Thayer-Martin selective medium plates were incubated at 37°C in C_2 incubator.

†Only 50, 20, 10, and 1% dilutions in physiological saline solution were tested.

‡pH of media after adding the contraceptive at different concentrations.

§Results from duplicate plates.

(Singh B, Cutler JC, Utidjian HMD: Br J Vener Dis 48:57, 1972)

ingredients of these products and not from artifacts as shown by additional *in vitro* studies. Several other investigators in the United States and other countries (2, 5, 6) have repeated and confirmed these findings. Based on these extensive *in vitro* studies, one chemical contraceptive cream, Conceptrol, was selected for a clinical trial in a high-risk female population. The hypothesis was that topical use of this preparation would reduce the gonococcal infection rate in the test group compared to a control group not

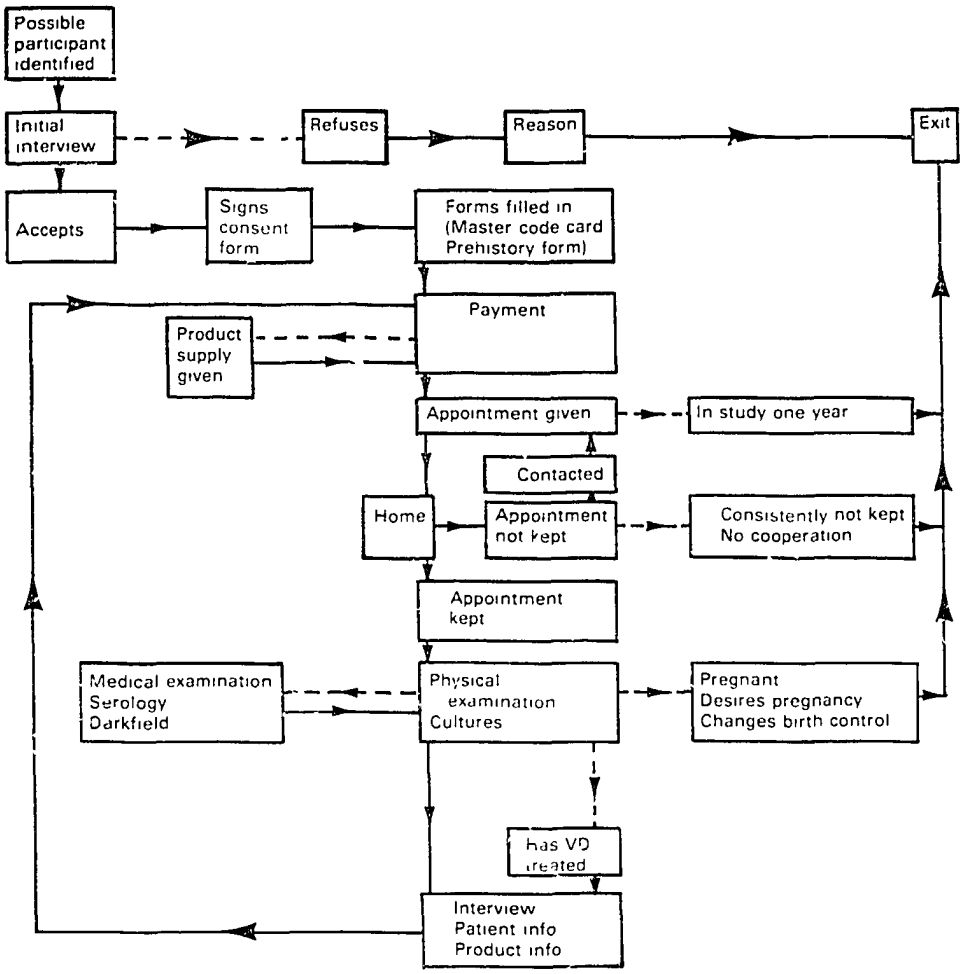

Fig. 17-1. Patient flow diagram.

receiving any prophylactic measures. Steps included in the protocol are shown in Figure 17-1. Participants for the study were enrolled from a local VD clinic. Females who were at high risk of contracting VD were self-identified by their repeated visits for treatment at this clinic. Other considerations for selection were the following: 1) Only adult females over 21 years of age who had at least two gonococcal infections within one year prior to enrollment were selected: Ascertainment of infections was made through clinic records; 2) Only women who were currently using oral contraceptives, IUD, or were surgically sterilized were enrolled. Patients who met the criteria were interviewed by a health educator. The purpose of the trial was explained, and if they agreed to participate, they were asked to sign the consent form. After that they were randomized and entered in the treatment or the control group. Additional information obtained from participants is indicated in Figure 17-2.

1. Date of Birth _____/_____/_____ (Month Day Year) Code No /__/__/__/__/__/__/__/__/

2. Age_____

3 Marital Status Single _____ Married _____ Divorced _____ Separated _____
Other _____

4. Contraceptive practice(s) before participation in study
None _____ IUD _____ Oral Pill _____ Surgical Sterilization _____ Other _____

5. Race: White _____ Black _____ Other _____

6. Educational level completed
7th grade or under _____ 8th to 9th grade _____ 10th to 12th grade _____
College freshman to sophomore _____ College junior to senior _____
Graduate school _____

7 Number of different sexual partners in past 12 months
One _____ Two _____ Three _____ 4-9 _____ More than 10 _____

8 Sex of partners: Male _____ Female _____ Both _____

9. Average number of times of sexual intercourse in a week: 1-2 _____ 3-4 _____
5-6 _____ 7-8 _____ 9-10 _____ 11-14 _____ More than 14 _____

10. Have you ever used anything to prevent yourself from getting syphilis or gonorrhea?
Yes _____ No _____

A If yes, which of the following do you use and how often?

	Always	Most of the time	Sometimes
Douche	_____	_____	_____
Wash	_____	_____	_____
Other	_____	_____	_____

(Specify other _____)

B If no, do you use any of the following in connection with intercourse and how often?

	Always	Most of the time	Sometimes
Douche	_____	_____	_____
Wash	_____	_____	_____
Other	_____	_____	_____

(Specify other _____)

11 Do(es) your partner(s) ever use a condom? Yes _____ No _____
If yes, how often? Always _____ Most of the time _____ Sometimes _____

FIG. 17-2. Pretrial history form I.

A double-blind design with placebo would have been ideal for the trial but due to restrictions imposed by the Committee on Research Involving Human Volunteers, the control group received nothing, and was treated in every other respect in the same way as the test group. Individuals assigned to the treatment group were given a 2-week supply of unlabeled chemical contraceptives. They were given instructions on how to use this intravaginal chemical contraceptive during each and every act of sexual intercourse. Participants in both treatment and control groups visited the clinic every 2 weeks for preventive examination. Cultures were taken for gonococcal and other genital infections including *Trichomonas* and *Candida*. If infection was found, the participant was provided with proper medication. On every visit all participants were interviewed by the health educator. They were also asked to fill out certain forms (Figs. 17-3, 17-4). This provided information

Please complete the following questions; if any questions are not clear, ask the Health Educator to explain them.

Date_____/_____/_____ Code No. /__/__/__/__/__/__/
Month Day Year

1. Any side effect(s) of product:

   None _____ Itching _____ Burning _____

   Itching & Burning _____ Other _____

2. Do you feel that:

   a. The applicator is easy to use? Yes _____ No _____
   b. The applicator is comfortable to use? Yes _____ No _____
   c. The product is convenient to use? Yes _____ No _____
   d. The odor of the product is pleasant? Yes _____ No _____
   e. The taste of the product is offensive? Yes _____ No _____
   f. Using the product interferes with sex pleasure? Yes _____ No _____
   g. The product is easy to carry with you? Yes _____ No _____
   h. The product is messy to use? Yes _____ No _____
   (If yes, explain _____)
   i. Comments _____

In the past month, has (have) any of your partner(s):

   a. Objected to use of product? Yes _____ No _____
   b. Complained of the odor of the product? Yes _____ No _____
   c Complained of the taste of product? Yes _____ No _____
   d. Complained that the product is messy? Yes _____ No _____
   e. Complained that the product interfered with sex pleasure? Yes _____ No _____
   f. Comments _____

FIG. 17-3. Product information sheet.

Date _____/_____/_____ Code No /__/__/__/__/__/__/
Month Day Year

1. Number of sexual partners during last two weeks
   None ____ One ____ Two ____ Three ____ 4-9 ____ More than 10 ____
2. Did you have any new sexual partners in the last two weeks. Yes _____ No _____
3. Total number of times you had sexual intercourse during the last two weeks:
   None ____ One ____ Two ____ Three ____ Four ____ Five ____ Six ____
   Seven ____ Eight ____ Nine ____ Ten ____ Eleven ____ Twelve ____
   Thirteen ____ Fourteen ____ More than Fourteen ____

*4. Number of product left _____

*5. Used test product Each time ____ Most of the time ____ Didn't use ____

6. Exposure to known or suspected case of gonorrhea (clap) during last two weeks
   Yes ____ No ____ Don't know ____

*Control patients skip these questions.

FIG. 17-4. Patient information form.

TABLE 17-2. Infection with Gonorrhea

	FIRST 6 MO	
	Treatment Subject (use of Conceptrol as directed for contraception)	*Control Subject*
No. of participants	37	50
No. of infections	1	11
Average months of participation per subject	3.9	4.1
Patient-months observed	144.4	205.1
No. of infections per/100 patient months	0.69	5.22
	SECOND 6 MO	
	Treatment Subject (use of Conceptrol as directed for contraception)	*Control Subject*
No. of participants	17	27
No. of infections	4	6
Average months of participation per subject	4.1	4.4
Patient-months observed	69.25	120.18
No. of infections per/100 patient months	5.78	4.99

as to the number of partners and sexual exposures the person had encountered. The questionnaire also provided information as to use of the test product. More direct information about the test product was collected from participants in the treatment group on each visit. Their likes and dislikes with regard to the product, as well as the attitude of the partners, indicated the frequency of use of the test product. The data from this clinical field trial are summarized in Table 17-2. In order to get information on trends of infections in the two groups during the period of observation, the data were analyzed using the life-table technique. In the treatment group, almost 100% remained infection-free during the first 6 mo and 80% for up to 8 mo, whereas 15% of controls became infected within the first 2 mo. Thus protective effect of the vaginal contraceptive studied was observed during the first 6 mo after entry into the study (7). After the first 6 mo, possibly the enthusiasm of the treatment group had diminished, or perhaps due to overconfidence, some of the participants in the treatment group neglected to use the test product regularly. Bimonthly interviews of participants by the health educator provided evidence that proper and regular use of vaginal contraception gave considerable protection to women against infection with gonorrhea.

Two other similar clinical trials were initiated, one in Philadelphia, Pennsylvania, using a contraceptive foam, and the other in Bangkok, Thailand, with a group of well-regulated prostitutes using contraceptive suppositories. Both studies were discontinued because of the lack of compliance with the protocol by the study patients. In the latter study, a number of the partici-

TABLE 17-3. Anti-microbial Activity of Chemical Contraceptives With Indications for STD Prophylaxis

Name of Contraceptive	MINIMUM LETHAL CONCENTRATION* (MLC) AGAINST STD PATHOGEN			
	Trepenema pallidum	*Neisseria gonorrhea*	*Trichomonas vaginalis*	*Herpes simplex II*
Cooper Creme	10%	1%	1%	≤10%
Delfen Cream	10%	10%	1%	≤10%
Emko Foam	10%	10%	1%	-
Lorophyn Suppository or Jelly	10%	10%	1%	≤10%
Ortho-Gynol Contraceptive Jelly	10%	10%	1%	-
Preceptin Gel	10%	1%	1%	5%
Neo-Sampoon Loop Tablet	10%	1%	1%	-

*Dilutions (wt/vol) prepared in physiologic saline solution. Germicidal activity determined by an appropriate microbiologic test.

pants had customers who disliked the product and thus the use of the contraceptive was economically unfeasible.

These field trials and other studies have supported clinical observations that an increased prevalance of gonorrhea and other genital infections is associated with the use of modern contraceptives as compared with barrier methods (4). Whether such observations represent a casual association cannot be determined on the basis of these data unless consideration is given to sexual habits and the data are adjusted for known risk factors. Studies of the use of vaginal contraceptive preparations have shown wide variations in effectiveness, which seems most closely related to the motivation of the female and her partner. Based upon these extensive laboratory studies, and the results from the field trial as well as clinical observations made by family planning physicians, it should be apparent that the vaginal contraceptives have sufficient germicidal activity to kill most of the pathogens transmitted sexually. As shown in Table 17-3, vaginal contraceptives were found to have antimicrobial activity against *T. pallidum, N. gonorrheae, T. vaginalis* and *herpes.*

A review of the composition of vaginal contraceptives shows the presence of various bactericides and surfactants in the spermicidal preparations. The chemical group of detergents known as nonionic surfactants is a major class of compounds used as emulsifiers and often as active ingredients in the formulation of vaginal contraceptives. The mechanism of action is similar to that of surface active agents since some of the bactericides act by altering the surface characteristics of bacteria. Surfactants and bactericides together generally have a synergistic effect, making a combined product more effective as a spermicide than any one of the ingredients alone. These concepts are considered by some in developing new spermicidal germicidal preparations. One such preparation was found to inactivate *herpes* at 0.005% concentration (Table 17-4).

Studies of VD prophylaxis have a firm scientific basis and reflect more

TABLE 17-4. Inactivation of Isolates of *Herpes hominis*, Types II and I, by Spermicide-Germicide Compound A (SGCA)

	INFECTIVITY ($TCID_{50}$) AFTER CONTACT WITH INDICATED PERCENTAGE OF SGCA*					
Isolate	*5.0%*	*0.5%*	*0.05%*	*0.005%*	*0.0005%*	0 (Control)
H. hominis, type II						
109	<1	<1	<1	<1	2.0	3.0
116	<1	<1	<1	<1	3.0	3.0
142	<1	<1	<1	<1	2.0	3.0
196-P10	<1	<1	<1	2 0	3.0	3.0
H. hominis, type I						
103	<1	<1	<1	3.0	3.0	3.0
104	<1	<1	<1	3.0	3.0	3.0
105	<1	<1	<1	<1	3.0	3.0
117	<1	<1	<1	<1	3.0	4.0

*Portions of the same viral suspension were incubated with various concentrations of SGCA or medium (control) for 10 minutes at 22°C. Infectivity is expressed as $\log_{10}$ $TCID_{50}$ /0.1 ml of the above suspensions. (Postic B, Singh B, Squeglia NL, Guevarra LO: Journal of the American Venereal Disease Association [now Sexually Transmitted Diseases] 5(1):26, 1978)

than a century of experience. Even before the discovery of chemotherapeutic and antibiotic agents, such prophylactic studies had a high level of medical and public interest because of the devasting human effects of VD and the accompanying social and economic costs. With the discovery of penicillin therapy for gonorrhea and syphilis, the element of local prophylaxis was dropped from VD control programs by both civil and mililtary authorities in the United States. However, interest in VD prophylaxis has revived and in considering the following facts, studies of pro-con are very timely and necessary:

1. The incidence of genital infections through sexual transmission is constantly increasing throughout the world. This includes not only gonorrhea, syphilis, trichomoniasis, and genital *herpes*, but also the lesser known STDs. Epidemiologic data provide support for an association of genital *herpes* infections to cervical cancer. Prevention of genital *herpes* and fear of cervical cancer may become motivational factors, leading to self-protective behavior by concerned individuals.
2. Multiple infections with two or more STDs in the same individual at the same time are not unusual among the sexually active population (14). These multiple infections cannot be treated with a single antibiotic and require more than one type of therapy. Quite often a proper diagnosis of simultaneous multiple infections is not made. However, a single method of prevention can be developed and, for high-risk populations, the use of preventive methods is essential. The impact of prophylaxis on VD epidemics can be shown by statistical methods (9). One can further consider this advantage in terms of cost benefit—the cost of prevention versus the cost of treating a VD patient and of the various complications ensuing from sexually transmitted diseases.

3. Many developing countries report a very high incidence of VD. In some countries, 18% or more of the females coming to family-planning centers have a sexually transmitted disease. In certain countries, 20% or more of the sterility cases are due to gonococcal infections. These factors affect demographic growth; therefore it has been suggested that, in the interest of good public health practice, family-planning programs should be combined with VD control efforts.
4. Vaginal chemical contraceptives or topical contraceptives deserve a second look because more effective spermicides and more convenient packaging have been developed (3). These product improvements, coupled with the need for contraceptives which can be disseminated through nonmedical channels (possibly vending machines), suggest that the vaginal contraceptives can once again play an increasingly useful role in family-planning programs. There are many parts of the world in which long-standing folk support of vaginal contraception makes this approach more acceptable initially than the newer techniques.
5. In the United States, more than one million teenagers become pregnant each year. This epidemic of adolescent pregnancy is a major concern today. The highest incidence of VD is also found among the adolescent population. It is evident that the pro-con approach could well provide another method of combating these problems and would be more attractive to certain individuals. It is also true that using any method of contraception to prevent pregnancy is more effective than using no method at all.
6. Interest in pro-con work, as shown by national and international organizations, further merits the investigation of this public health approach. Therefore, it is essential that the work on pro-con, which was started again in recent years, with such a tremendous investment, be continued for both reference and research.

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NEW DEVELOPMENTS IN BARRIER AND SPERMICIDE METHODS

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Vaginal Rings Releasing Spermicides

WHO SPECIAL PROGRAMME OF RESEARCH IN HUMAN REPRODUCTION TASK FORCE ON VAGINAL AND INTRACERVICAL DEVICES FOR FERTILITY REGULATION †*

INTRODUCTION

One of the objectives of the WHO Special Programme of Research, Development and Research Training in Human Reproduction is to develop vaginal rings with the capacity to provide a reliable local contraceptive effect without the drawbacks of any possible systemic effect. The use of a vaginal ring saturated with a spermicidal drug which would be released at a constant rate over a period of several weeks or months was given early consideration. The aim was to produce a device which would combine simplicity of use with a high degree of contraceptive efficacy. Essential features of such a device included

1. Easy vaginal insertion by the subject herself without the need for prior medical or paramedical pelvic examination and concurrent measurement of vaginal capacity
2. Comfortable self retention for 2–3 weeks in each menstrual cycle to circumvent the need for repetitive insertion prior to each act of coitus
3. A degree of softness and pliability to avoid interference with the act of coitus
4. Nonirritant capacity so that, during the period of use, vaginitis or increased vaginal discharge does not occur
5. A degree of contraceptive protection with proper usage, greater than

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†Presented by Dr. Alfredo J. Gallegos, Medical Officer, Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland, on behalf of the investigators.

TABLE 18-1. Nonoxynol Content of Vaginal Rings*

G ± SD
3.79 ± 0.08
3.56 ± 0.10
3.60 ± 0.06
3.60 ± 0.07
3.56 ± 0.03
3.54 ± 0.07
3.58 ± 0.11
Loading Average = 3.60 + 0.08 SD

*Each ring cut into 4 equal segments and assayed separately.

that associated with the use of presently available vaginal contraceptive methods.

An attempt was made to meet these criteria. A limited number of silicone rubber vaginal rings were manufactured. The same toroidal shape and material developed for use in other studies concerned with the release of steroids from vaginal rings were considered to provide a suitable platform for the constant release of the spermicide nonoxynol 9 as one of those chosen for trial. This communication is intended to provide interim information on preliminary results emanating from this ongoing study.

MATERIAL AND METHODS

According to a similar process previously described (1), Battelle Pacific Northwest Laboratories designed and tested and Alza Mexicana manufactured 40 torus-shaped silicone rubber (Dow Corning Silastic Medical Grade Elastomer) vaginal rings with an external diameter of 5.5 cm and a cross-sectional diameter of 0.95 cm.

They were produced to meet specifications requested by the WHO Task Force on Vaginal and Cervical Devices for Fertility Regulation, that is, to release more than 5 mg/day of commercially available nonoxynol 9 and to maintain this release at a constant rate for a minimum of 30 days.

The physiochemical characteristics of the silicone rubber and nonoxynol 9 are such that a maximum of approximately 4.0 g of the latter may be incorporated in a single device at manufacture. Table 18-1 exemplifies the nonoxynol 9 content of the rings under trial from a study of seven sample rings by UV absorption at 274 nm.

The *in vitro* release rate of nonoxynol 9 from four other sample rings, as shown in Figure 18-1, illustrates the continuous flow system used. "Sink" conditions are defined as sufficient flow of solution over the surface of the device to remove all nonoxynol which has diffused to the surface of the device; it is the condition in which the concentration of nonoxynol in the solution close to the surface of the device approximates zero. Under these con-

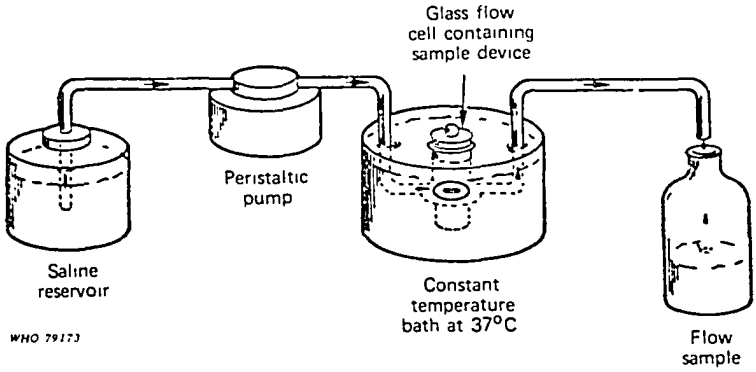

FIG. 18-1. Continuous flow system, designed to allow sufficient flow of solution (saline) past surface of device to remove all nonoxynol which has diffused to surface of device (sink condition). Resultant flow sample is then analyzed by UV spectrophotometry at 274 nm.

ditions it should be noted that, while the release rate was constant from day 10 to day 30, an initial 'burst' up to 22 mg/day was observed (Fig. 18-2).

PHASE I CLINICAL TRIAL

A detailed protocol to assess the sperm immobilization properties of nonoxynol 9 when released from vaginal rings was designed. The following summarizes certain important features of the study being conducted in collaborating centers in Japan and Mexico:

1. Only sterilized volunteer women are recruited on the basis of these criteria: they must have regular menses, lead an active sex life, and have no evidence of vaginitis or infective cervicitis.
2. During the month prior to vaginal ring insertion at midcycle, the state of the vagina is recorded and aliquots of venous blood and cervical mucus are taken postcoitally for base-line data.
3. In the succeeding cycle, the vaginal ring is inserted on day 7 and worn continuously for 10 days. During this cycle, postcoital tests are made on days 12, 14, and 16 for the evaluation of sperm motility and for the estimation of nonoxynol 9 levels* in the cervical mucus. At the same time venous blood samples are taken to assess plasma levels of nonoxynol 9.
4. The vaginal ring is removed on day 17 $\pm$ 2, rinsed in cold water and retained in the clinic until the next subject visit on day 7 $\pm$ 1, of the following and final cycle under study, when all the tests are repeated.

*Estimates of nonoxynol 9 levels in cervical mucus are made with high pressure liquid chromatography (hplc) in the United Kingdom.

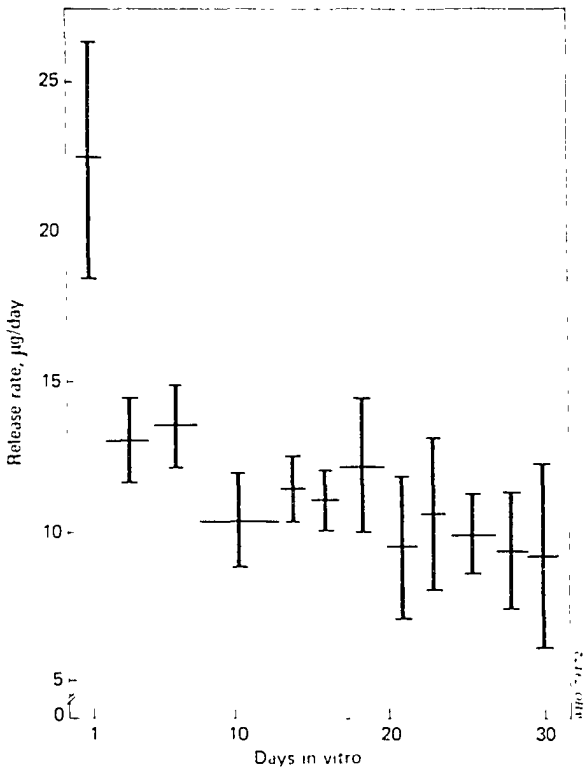

FIG. 18-2. Flow testing results under "sink conditions" for four nonoxynol-releasing vaginal rings. Average release rate for days 9–31, 10.38 mg/day ±1 05 SD. Note the burst around day 1.

RESULTS

To date, although only the immediate results of 39 postcoital tests from 11 subjects are available, they are of great interest. While they certainly show a marked decrease in the number of motile sperm in cervical mucus in the presence of the vaginal ring, evidence of motile sperm still remains but "progressive" motility was disrupted. This would suggest that, at this level of release of nonoxynol 9, a contraceptive effect by sperm immobilization cannot be ensured. Whether these remaining motile sperm have the capacity to fertilize normally poses another question. No complaints of discomfort, vaginal irritation, or interference with the act of coitus have been noted, nor have any of the rings been expelled.

RELATED STUDIES

The results of studies run almost concurrently at the WHO Collaborating Center in Los Angeles, under the supervision of a Task Force Steering Committee member, may help to explain the aforementioned preliminary findings in the Phase I Clinical Trial.

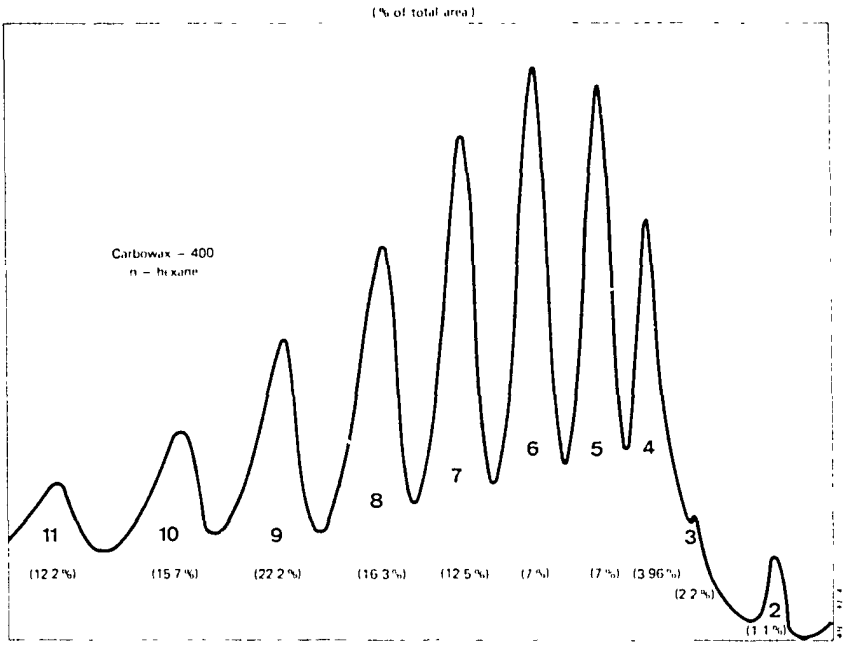

FIG. 18-3. High pressure liquid chromatography profile of commercially available nonoxynol 9 (% of total area). The fraction numbers correspond to the numbers of ethoxy groups with the proportion of each fraction shown in parentheses.

Several samples of commercially available nonoxynol 9 were analyzed at Battelle Northwest by hplc with similar results. A typical profile is shown in Figure 18-3 At least 9 different nonoxynol 9-related fractions were identified and fractions 5 and 6 were further characterized by mass spectrometry.† A molecular ion mass of 440 was obtained for fraction 5 and one of 484 for fraction 6. This corresponds to molecules containing 5 and 6 ethoxy molecules per molecule of nonylphenol. It is intended to conduct similar studies in other centers to provide further evidence concerning these findings.

In a further study performed in the same research center, the *in vitro* spermicidal potency of all those fractions was then investigated on three different pool batches of fresh semen, appropriately diluted with a saline, to contain a standardized number of motile human sperm cells (10×10^6 per ml). The results are shown in Table 18-2 according to the effect of the different fractions on specimens from the three pools of standardized semen. They show that the spermicidal potency of fractions 2, 3, 4, and 5 is markedly lower than that of fractions 6–11.

The possible significance of these results becomes more apparent when they are considered in relation to the findings obtained in the (hplc) separation of the various fractions as shown in Figure 18-3. Fractions 2, 3, 4, and 5

†Finnigan quadrapole mass spectrometer model 1015D using a heated direct inert probe.

TABLE 18-2. Different Nonoxynol 9 Fractions; Spermicidal Potency (μg/ml)*

FRACTION	TESTS 1	2	3
2	> 295	> 295	> 295
3	> 295	> 295	> 295
4	> 280	> 280	> 280
5	> 290	> 290	> 290
6	14.8	29.5	7.4
7	26.0	26.0	13.0
8	17.0	34.0	17.0
9	13.5	27.0	13.5
10	23.0	46.0	23.0
11	35.0	35.0	17.5
Unfractionated	12.5	25.0	25.0

*Spermicidal potency of each fraction was determined, under conditions stated in text, at 30 sec. Fractions 2–5 had very low activity whereas fractions 6–11 had the highest potency.

of weak spermicidal potency constitute 14% of the molecules of the commercially available nonoxynol 9 under investigation. Furthermore, because it is known that those fractions with lower molecular weights could be released much sooner than those with greater molecular weights from the silicone rubber polymer, a considerable proportion of the spermicidal compound initially released from the vaginal ring should comprise fractions 2–5. The findings may, in part, explain the lack of complete inhibition of sperm motility by the use of this first prototype of a spermicide-releasing vaginal ring.

Similar studies are now being conducted in other centers, directed toward verification of the analytic results presented and to gain more information on the desirable chemical components for incorporation into a vaginal ring, in order to provide consistent and highly effective local spermicidal activity.

The results of the Phase I Clinical Trial, together with the unexpected analytic results of the spermicide are now being taken into consideration in the design of future prototypes of spermicidal vaginal rings.

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Prospects and Problems in the Development of an Intravaginal Contraceptive Device (IVCD) and Method

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RUDOLPH N. PETERSON

An intravaginal contraceptive device (IVCD) is described which is of similar shape and intermediate in size between a diaphragm and a cervical cap. The device is made of a synthetic membrane or matrix which is impregnated with a spermicidal drug, such as nonylphenoxypolyethoxyethanol, nonoxynol 9, that is bound to or incorporated into a mechanically stable artificial matrix, such as a hydrophilic polymer. The IVCD may be inserted into the vagina by the woman; it then swells and is used as a cervical cap. The drug is released by the membrane at a controlled rate and the IVCD dissolves only after its function is complete; that is, the membrane passes through solid, gel, sol, and liquid stages in a timed sequence. This contraceptive approach involves applying a tested and accepted compound that will inhibit sperm motility and fertilizing capacity at low concentration and developing a new drug delivery system based on a hydrophilic polymer which will mechanically block the initial rapid phase of sperm migration.

The device consists of a relatively flexible gel which swells upon absorbing water from the vagina. The gel consists of macromolecules, with great affinity for water, which have been cross-linked to form a three-dimensional network, making them insoluble. Therefore, instead of dissolving, they swell and take up large amounts of liquid, becoming a soft elastic material. The swollen gel is, therefore, a three-dimensional network composed of cross-linked polymers which act as the structural material (which gives it substantial mechanical stability) and the spaces within the gel are filled with liquid. The majority of the space within the gel is liquid. The drug may be adsorbed on the surface of the particles of the gel bed. The release of the drug is accomplished (at a controlled rate) by a form of gel chromatography, that is called restricted diffusion chromatography. The drug is partitioned first between the gel phase (polymer) and the sol phase (liquid) of the membrane and then between the sol phase of the membrane and the vaginal fluid (plus semen). Many of the chemical properties of these commonly used membranes—ion exchange, isoelectric separation, electrophoresis, buffering capacity, agglutination, desalting of proteins, denaturing of proteins and nucleic acids, temperature effects, and "stickiness"—remain to be explored and exploited for their barrier contraceptive potential.

MECHANICAL AND BIOCHEMICAL PROPERTIES OF SYNTHETIC MEMBRANES

In order to construct a useful membrane for a vaginal contraceptive, several membrane properties are to be considered basic: 1) mechanical stability and ease of manipulation at room temperature; 2) mechanical stability and impenetrability to sperm for a specified period of time *in situ* followed by slow dissolution; and 3) capacity to incorporate a chemical contraceptive which can be released *in situ.*

The membrane should have a consistency that permits easy insertion without membrane damage and without any abrasive discomfort to the recipient. It should be stable for long periods at temperatures below that of the body. After insertion, mechanical stability and impermeability should be retained long enough to prevent sperm passage into the cervical mucus, especially during and immediately after ejaculation. The membrane must slowly develop instability *in situ* so that its eventual dissolution obviates the necessity for removal. Finally, membrane dissolution should be accompanied by the release of the spermicidal agent to insure a complete contraceptive effect.

A concurrent alternate approach offers possibilities. This approach is based on the use of a water-soluble case of biopolymer (for example, dextran, polvethylene oxide, or polyvinyl alcohol) to form an IVCD as a thin, firm package which encloses a less firm gel. The water-soluble base would be $\cong$ 0.1 mm (3–4 mil) thick, or less, with the convex side facing the vagina. This would be chemically tailored to dissolve quite rapidly ($\cong$2–3 min), while the other side of the package (the concave side, facing the cervix) would dissolve more slowly ($\cong$60 min). This sequence of events would permit the gel and the added spermicidal drug to become active in a matter of 2–3 min after insertion, while a mechanical barrier would continue to cover the cervix for 60 min or more, if required.

The use of such a water-soluble case of biopolymers would greatly simplify the problems of gel formulation because the gel would not have to be as completely dehydrated, but could be partially hydrated. This means that cross-linkage need not be as extensive and drug release and subsequent liquefaction could proceed more rapidly and completely. The materials for the case must be firm but flexible in the formation of the gel package. This would yield a soft, flexible, but strong IVCD. The case would be tailored to swell, become weak, and dissolve or disintegrate at a controlled rate upon insertion into the vagina, as described. Both the dextrans and the polyvinyls can be formulated as water-soluble biopolymers to meet the requirements of the IVCD case.

The time sequence for the IVCD is as follows. The transition from solid (partially hydrated) to gel would begin upon insertion and take only a few minutes. If a water-soluble case is used, the case would dissolve quite rapidly (2–3 min) and the partially hydrated gel and its associated spermicidal drugs would be released within 2–3 min. If agar and/or dextran is used by itself, the solid to gel process would take 3–5 min and would be a matter of moving from the partially hydrated form to the more hydrated form.

The transition from gel to sol would be gradual and would take about 60 min. This gel-sol would provide long-term mechanical protection of the cer-

vix and prevent sperm passage into the cervical mucus, while the spermicidal drug would kill the sperm in the vagina. Moreover, the sol will remain in the vagina for some hours along with the semen (particularly if the woman remains recumbent) and will, therefore, kill any remaining sperm. It will drain out of the vagina along with the semen.

There should not be any appreciable lag time from insertion of the IVCD to protected coitus. First, the IVCD is inserted by the woman over the cervix. The optimum procedure for insertion, whether manual or with the aid of a disposable inserter, such as is used with tampons, remains to be determined (after the IVCD prototype is developed and tested and when human testing is begun). If the woman fails to seat it completely over the cervix, the IVCD will be pushed into place at first intromission. This will occur because the IVCD imbibes fluid and swells in place over the cervix; therefore, by the time intromission takes place, the IVCD will be ready to be pushed onto the cervix. The IVCD will have mechanical stability to prevent sperm passage into the cervical mucus, especially during and immediately after ejaculation. Moreover, within 2–3 min after insertion, the diffusion of spermicidal agent from the gel will begin. In use, the IVCD, as are contraceptive creams or foams, will be inserted prior to initiation of coital activity. The IVCD will provide the combination of a mechanical barrier to sperm passage into the cervical mucus and of a spermicidal action on the sperm in the semen pool in the vagina.

The total amount of water taken up by the IVCD is estimated to be of the order of 2–3 ml or less. This is less than the sum of the lubrication of the vagina plus the volume of the ejaculated semen and, therefore, it is improbable that there will be any effect on the epithelium. Moreover, the dissolution and disintegration of the IVCD will yield additional fluids to the vagina.

The membranes and gel will finally disintegrate into a flowing jelly-like consistency and will come out of the vagina with the semen after coitus. While it is theoretically possible to design biopolymers so that they will finally flow like water, this is a most difficult technical problem and is probably not worth the effort. A final form for the biopolymer material which resembles the consistency of human semen is practical. We believe that the woman will not be able to notice any difference in consistency or nature of the outflow from the vagina after coitus with an IVCD as compared to unprotected coitus.

There are several facts that we have about this problem that indicate that it will be minimal: 1) the volume of semen ejaculated into the vagina is about 2–5 ml or more; 2) the volume of vaginal lubrication is not known, but Masters and Johnson (5) describe "copious amounts" and "many drops" of it; 3) the total volume of the IVCD in the sol phase will not exceed 3–4 ml; 4) the measured dose applicator for Delfen Contraceptive Cream contains 2.5 ml and the measured dose applicator for Delfen Contraceptive Foam contains 5 ml; and 5) a large number of women remain recumbent after coitus, which means that drainage takes place slowly. Thus, the IVCD sol is in the same volume range as currently accepted and widely used vaginal creams and foams and should not present any aesthetic problem. It should also be pointed out that there will be no dripping or draining during

coitus with the IVCD, which is one of the major drawbacks of creams and foams.

CHEMICAL STRUCTURE OF THE MEMBRANE

A number of the gel-forming polymers commonly used in biochemical analyses have properties similar to those set forth above. Moreover, methods that are used to prepare these polymers are capable of being modified to produce gel membranes which have a wide range of physical and biochemical stability. Some of these materials and their properties relevant to the design of an IVCD are listed.

Hydroxyethyl starch This is a starch derivative which consists of more than 90% amylopectin and, when the polymer is composed of D-glucopyranose units, its degree of polymerization can be carefully controlled during preparation. Moreover, current medical application uses it as a plasma volume expander and as a cryoprotective agent for erythrocytes. The degree of cross-linking can be controlled to permit entrapment of molecules of the size proposed for use in this study.

Agar and Agarose gels These gels, which are widely used in chromatography and electrophoresis, are composed of mixtures of linear polysaccharides in cross-branching networks that allow for penetration and entrapment of molecules. The gels are generally stable in the pH range of 4.5–9.0 and at temperatures up to 35°C. Stability decreases with increasing temperature, leading to gradual melting of the gel. Because agar and agarose preparations consist of a heterogeneous population of molecules varying in size and cross-linking, fractionation of these preparations should yield polymer mixtures suitable for the purposes proposed.

Dextran gels Dextran is a linear polymer of glucose formed by an α-1,6 glucoside linkage during the bacterial fermentation of sucrose. The polymer is soluble in water but solubility is decreased and gels are formed when polymer chains are cross-linked with glycerol residues. The commercial product, Sephadex, is a dextran gel which is stable over a wide pH range and is insoluble in water. Solubility and other physical properties can be altered by changing the type and degree of cross-linking. An interesting property of these gels is that they swell upon exposure to water. The degree of swelling depends on the extent of chain cross-linking and the rate of swelling depends on the ambient temperature. The ability of a contraceptive membrane to swell after insertion would have obvious contraceptive value.

Cellulose and cellulose esters Membranes composed of this material do not appear as suitable as the agar and dextran gels but exhibit certain properties that may be exploitable. Certain polymers of cellulose acetate, for example, have a paper-like consistency when dry but swell into gels after reaction with water. The matrix of these gels is capable of retaining a drug used for sper-

micidal effects. Recently, Loewit (6) reported that human sperm, *in vitro*, are permanently immobilized by a 1%–3% solution of hydroxypropylmethylcellulose.

CHEMICAL CONTRACEPTIVE TO BE USED WITH THE MEMBRANE

Detergents have been widely used in conventional creams and jellies. The nonionic surfactant nonoxynol 9 has achieved particular popularity because of its effectiveness against sperm and its apparent lack of effect on the vaginal mucosa. It will be used in the IVCD.

Other detergents (surface active agents) which are currently in use in marketed intravaginal products, include diisobutylphenoxypolyethoxyethanol, dodecaethyleneglycol monolaurate, methoxypolyoxyethyleneglycol 550 laurate, polyethyleneglycol monisocetylphenol ether, and polyoxyethylenenonylphenol.

INCORPORATION OF CHEMICAL CONTRACEPTIVE INTO THE MEMBRANE STRUCTURE

Three methods can be used to bind the chemical contraceptive molecule to the membrane matrix. The first involves trapping the molecule in the gel lattice. This is done by preparing monomer solution in the presence of the molecule to be occluded and then polymerizing the monomer. The inhibitor is then trapped inside the cross-linked networks of the gel matrix. Upon dis-

solution of the membrane, the inhibitor would be released into the surrounding medium. Such a method could also be used to trap encapsulated membrane-solubilizing enzymes in the gel matrix. Thus, the comparatively stable dextran gels could be slowly solubilized by trapping a controlled-release, colloid-encapsulated cellulase or polysaccharidase in the gel matrix.

The second method involves direct covalent bonding of the molecule to the gel matrix. This procedure has been used successfully to bind fully active enzymes, antibodies, and enzyme inhibitors to gel matrices.

The third method involves adsorption of the molecule on the preformed gel. This method depends upon an electrostatic interaction between the gel surface and the binding molecule. Thus, a gel such as agar, which has a negative surface charge due to the presence of sulfate groups in some of the polymer chains, should be an effective binder of spermicidal cationic surfactants.

IN VITRO STUDIES: PHYSICAL AND CHEMICAL PROPERTIES OF MEMBRANES

Prior to experiments with animals, membrane preparations will be tested extensively *in vitro* Such studies will include assessments of the following.

Thermal and water solubility Polymer membrane preparations will be formulated and screened to select those that retain stability in the dry state at

room temperature but which swell and become soluble at body temperature in an aqueous environment. These properties, of course, will depend on the degree of polymerization and cross-linking of various preparations.

Nonylphenoxypolyethoxyethanol release Detergent release from membranes will be measured *in vitro* in physiologic saline at 37°C, as a function of time, by photometry. The several polymers proposed will be tested with the drug to find the optimal combination and configuration to use in tests of spermicidal activity.

Spermicidal activity The ability of membrane preparations to release spermicide (nonoxynol 9) and immobilize and kill sperm will be tested. Some of these tests will involve mixing weighed amounts of membrane with various dilutions of human semen. This method is similar to a general method that has been used to rate the spermicidal activity of conventional contraceptive jellies, creams, and foams (3, 4).

Mechanical properties We plan to test the mechanical properties of the membrane as affected by simulated physiologic stress (*i.e.*, penile thrust and mixing of vaginal contents).

IN VIVO STUDIES

In view of the problems of extrapolating from *in vitro* testing to the *in vivo* situation, the necessity for an animal model is apparent. Earlier work with vaginal spermicides in the rabbit includes that of Carleton and Florey (1), Millman (8), and Chang (2). In this connection, the work of Eckstein *et al* (3) with the rabbit and the monkey is of significance. More recently, Homm *et al* (4) compared the relative antifertility activity of Delfen foam, Delfen cream, and Preceptin gel in the rabbit with data from *in vitro* tests with human sperm. They concluded: "The rabbit does appear to provide a model for the *in vivo* evaluation of relative potencies of vaginal contraceptive preparations." Emphasis in our work will be placed on the rabbit as an animal model. IVCD prototypes will be tested *in vivo* for efficacy in rabbits by artificial insemination tests and natural mating tests, which are standard in this laboratory.

FDA-acceptable animal tests for irritation will be carried out on rabbits by "the rabbit vagina test" method described and standardized by Eckstein, *et al* (3) and summarized by Sobrero (9). Measured quantities of biopolymer are introduced daily for 10 days into the vagina of mature rabbits. Their effects on vaginal mucosa are determined histologically after sacrifice and autopsy of animals on day 11 and are compared to tissues from control animals. No material which fails to pass the rabbit vagina test will be used in this project.

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Water-Soluble Condom and Vaginal Contraceptive Film Insert*

RAYMOND BELSKY

The study described here was carried out between September, 1977 and May, 1978. It was designed to determine if a water-soluble condom could be produced using bio-compatible films and plasticizers. A water-soluble condom or penile cap could be marketed and distributed without concern about side effects and might increase contraceptive use among couples who find the latex condom unacceptable because it reduces sensation. A rapidly dissolving, easily inserted vaginal film might find acceptance among pill and IUD dropouts who consider foams and suppositories too messy or who experience a burning sensation with foaming tablets. Soluble film as a vehicle for spermicide also has the advantage of introducing less material to the vagina.

METHODOLOGY

Sixteen film resins and plasticizers already approved by the Food, Drug and Cosmetic Act (FD&C) were investigated and listed prior to being tested in combination with the effective spermicide nonoxynol 9 (CO-630) which has FDA and International Planned Parenthood Federation (IPPF) approval and is presently used in vaginal contraceptives. Film used as a penile cap or wrap-around sheath and acting as a spermicidal barrier should be fast-dissolving to facilitate introduction of a spermicidal agent over the cervical os.

Film samples of 0.003 in. (3 mil) thickness were cast from solutions of resins and plasticizers and evaluated against the following criteria.

Clarity/exudation: a visual test Clarity indicates compatibility of water-soluble resin with nonoxynol 9 and other ingredients. Under certain conditions nonoxynol 9 may exude from the cast film as an oily layer, rendering it aesthetically and functionally undesirable.

*The work was performed with the participation of Springborn Laboratories as a feasibility study under contract to the Program for Applied Research on Fertility Regulation (PARFR), Northwestern University Medical School.

Handleability Film is considered too brittle or weak when it cannot be handled at 40% relative humidity (RH); that of a heated room in a cold climate in winter. Film that sticks to the fingers is too sensitive to moisture.

Drape Film has sufficient "drape" (softness, lack of springback) or "tackiness" when it can be draped onto the penis (or inserter) and remains in place without requiring added moisture. Drape is measured by placing a clamp along the long edge of a 2.2 in. by 3/8 in. piece of film with 2 in. of the film projecting vertically. The strip sags to the left or right for 30 sec and the angle achieved with the drape is measured. A sag of 180° represents complete sag or drape.

Self-adhesion Slight tackiness or cohesiveness, when the film is pressed back on itself, is desirable. The film should not stick to itself permanently, however. A talc coating overcomes excessive tack, but produces some unacceptable effects. Lecithin is being evaluated as a coating and has shown promise in preliminary testing.

Aging in humidity Shelf life in tropical climates is determined with a test in which two pieces of 3 mil film 0.5 in. by 1.0 in. are stapled together and stored for 20 hrs at 75% RH and then 90% RH. Film is considered "failed" if the sections cannot then be peeled apart. For films that pass the 75% RH test, the peel test is repeated at 90% RH.

Solubility rate Going into solution quickly to release the spermicidal agent is an especially important characteristic of film, or alternatively, slow dissolution with the as-yet undissolved film acting as a mechanical barrier to sperm. The test to determine solubility involves a 50 ml charge of distilled water (pH 5.5) placed in a test tube 4 cm in diameter. The water is stirred with a thermometer and heated to between 98° F and 99° F with a heat gun. A piece of 0.003 in. film 0.25 in. by 0.75 in. is added to the water and is stirred slowly for 5 min (300 sec). The times when disintegration begins and when 95%–100% dissolution occurs are recorded. An acidity of pH 5.5 simulates a normal vaginal condition.

After determining which film seemed to be most promising in terms of these criteria, various configurations of film were developed according to the following considerations:

Use For penile use, the product should easily fit over the glans—either as a cap or film wrap—with some extension over the shaft. It should remain in place on the erect penis until insertion into the vagina, whereupon the film should dissolve readily at the cervix. An easily draped, flat film would be appropriate for direct pre-coital vaginal insertion using manual digital insertion by the woman or her partner or using a specially designed inserter.

Manufacture Film production should require a minimum of complicated machinery. The cost of a flat film insert will not exceed that of a condom or foam tablet. A fabricated penile cap may cost as much as the condom, tablet or other suppository.

TABLE 20-1. FDA Status of Polymers for Use in Water-Soluble Condom (PARFR)

MATERIAL	TRADE NAME	USE	FDA STATUS
Polyvinyl alcohol	Gelvatol	Film	OK for contact with food
Polyvinyl pyrrolidone	PVP	Plasticizer	OK for skin contact
Polyvinyl methyl ether	Gantrez M	Plasticizer	OK for skin contact LD_{50} > 6.4 gm/kg
Mono alkyl ester of poly (methyl vinyl ether/ maleic acid)	Gantrez ES	Film	OK for skin contact LD_{50} > 10 gm/kg
Carboxylated vinyl acetate	Resyn 28-1310	Film Cast with AMP	OK for skin contact LD_{50} > 2 gm/kg
Ethylene maleic anhydride	EMA	Film	No FDA data available
Alkanolamide	Monamid 716	Plasticizer	OK for skin contact LD_{50} > 4.85 g/kg
Carboxymethyl cellulose	CMC	Film	Edible
Hydroxy propyl cellulose	Klucel	Film	Edible
Methyl cellulose	Methacel	Film	Edible
PVP/Vinyl acetate 70/30	PVP/VA E-735	Plasticizer	OK for skin contact 1958
Glycerine		Plasticizer	Edible
Dipropylene glycol		Plasticizer	Edibility LD_{50} 14.8 ml/kg; skin penetration > 20 ml/kg
Sorbitol		Plasticizer	Edible
Polyethylene oxide	Carbowax 1000	Plasticizer	Used in cosmetic hair spray
Triethyl citrate	Citroflex	Plasticizer	OK for contact with food

Packaging Packaging, often the most costly part of a product as delivered to the user, should involve a low-cost design capable of maintaining product integrity when the film is stored in the tropics.

RESEARCH FINDINGS AND THEIR SIGNIFICANCE

Table 20-1 indicates the FDA status of 16 films and plasticizers selected from the polymers that are acceptable to the FDA on the basis of safety in skin contact, in food packaging, or that are considered edible.

A wide range of films in various combinations of plasticizer were screened. Wherever nonoxynol 9 (CO-630) was used, it comprised 25% of the final formulation. Film 0.003 in. thick in pieces 5 cm by 5 cm, and yielding approximately 65 mg of spermicide, was tested by the Potter & Clarke Company in England, and passed the IPPF Standard Test for spermicidal activity. The vaginal film insert is presently commercially available in England under the name C-film.

Over 40 film formulations utilizing different combinations of resins and plasticizers, with nonoxynol 9 representing 25% of the final product, have been screened by Springborn Laboratories against C-film as a standard.

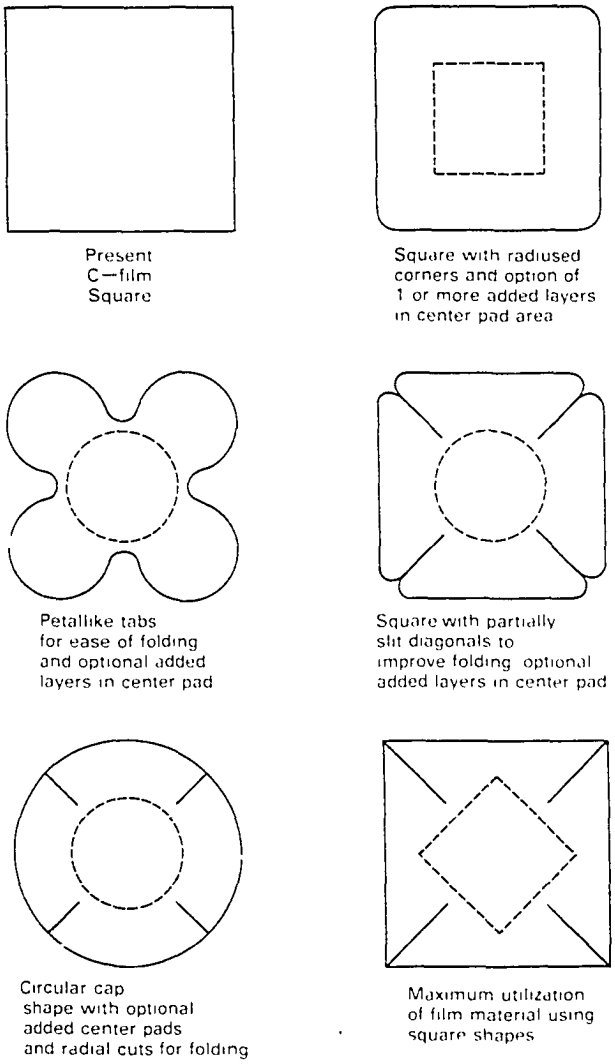

FIG. 20-1. Nonfolded flat film shapes.

Polyvinyl alcohols (similar to C-film), polyethylene oxide, and some carboxylated polymer films proved to be fast-dissolving, while various cellulosics were slower to dissolve and too stiff. Plasticized polyvinyl alcohol (PVA) and plasticized polyethylene oxide showed the most promise. A plasticizer adds strength and drape to polyvinyl alcohol and assists film solubility. Polyvinyl pyrrolidone (PVP) and high PVP copolymers proved to be too hygroscopic for plasticizer use. Polyethylene oxide, sorbitol, and triethylcitrate showed promise as plasticizers. Exudation may be a problem if any quantities of nonoxynol 9 are lost along with the plasticizer. Hydrolyzed PVA (75%) and

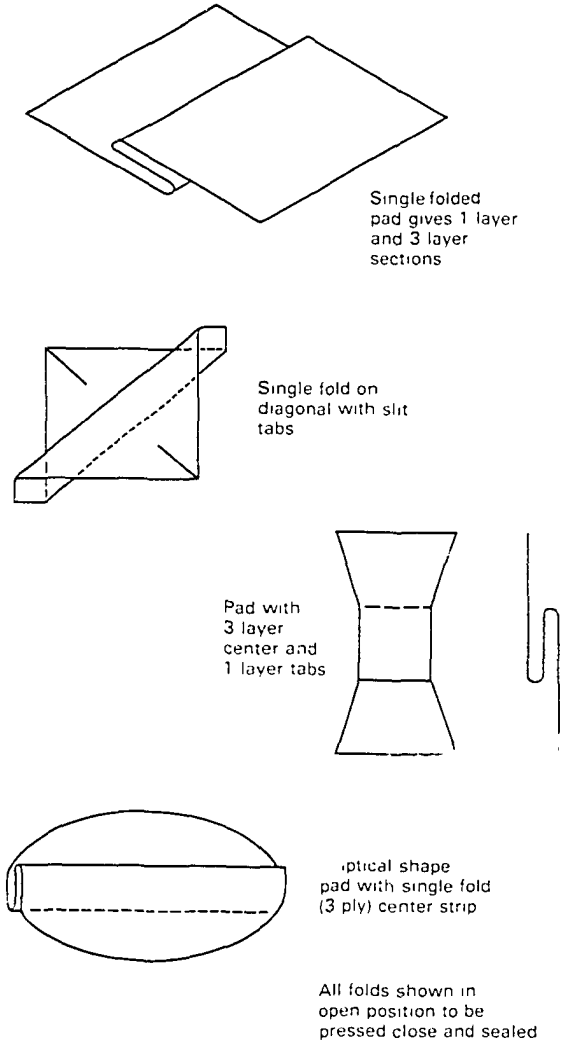

FIG. 20-2. Folded film shapes.

vinyl acetate copolymers are highly compatible with nonoxynol 9. Development of films containing nonoxynol 9 which have good draping qualities and high humidity re- ance, but which will dissolve more rapidly than C-film *in vitro* , seems feasi le.

Product des as centered around creating shapes which could concentrate spermici -laden film at the center while leaving the edges thin enough for draping around the penile shaft. A number of these shapes are shown in Figures 20-1, 20-2, and 20-3.* Various methods of shaping spermicide films

*Patent disclosures have been filed.

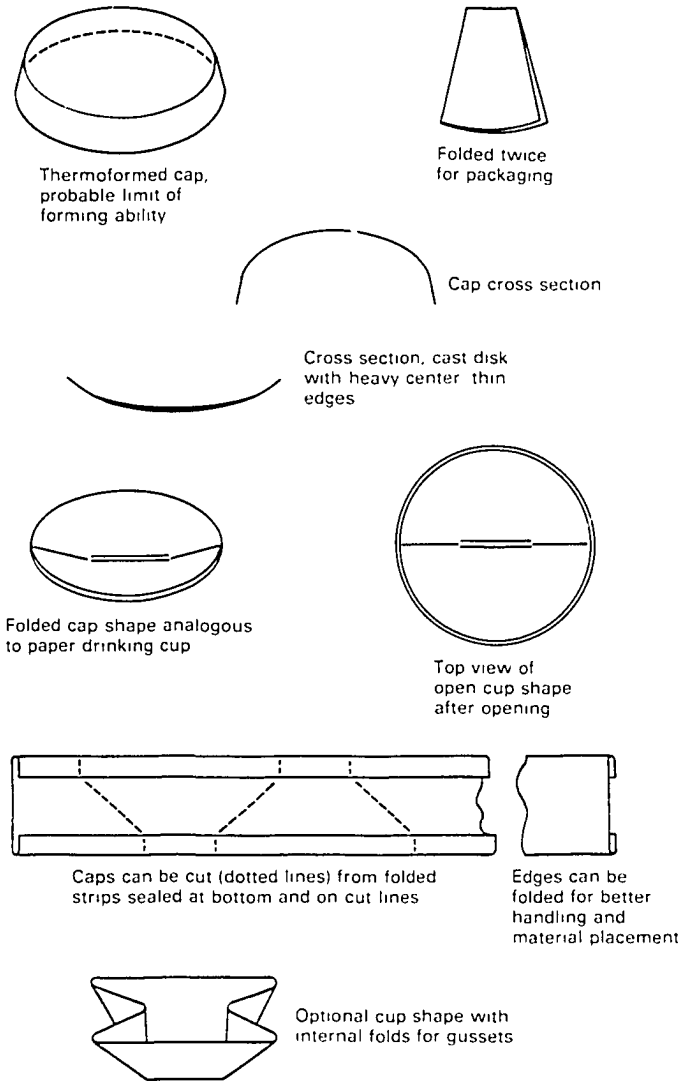

FIG. 20-3. Shaped caps.

for better application were investigated in this study. From a production viewpoint, a flat film would be most practical. If the film is concentrated at the center and the edges are kept pliable and conforming, heavier central areas could be provided with precut patches adhering to the already cast film, with moisture serving as the cement. Slitting radially from the corners appears to increase conformability but may render the edges less manageable. Folding the samples concentrates film in the center area and may permit a better grasp of the item. Folded shapes can also be readily produced in quantity. Two folded shapes have been tucked in such a manner as to

present a shallow penile cap shape to the user and still be packaged flat. A disadvantage is that the heavier spines show less tendency to conform and may be uncomfortable for the user.

Thermoforming C-film shows a moderate ability to be heat-shaped. The heating cycle stiffens the film; presumably, regaining moisture will make it flexible again. This suggests that a formulation with plasticizer, permitting deep thermoforming into a condom-like shape, may be feasible.

Casting Film solution was cast in various shallow and deep concave dishes made from Teflon, glass, or nylon. The dried film stuck to the glass and nylon, despite parting agents, but separated readily from the Teflon surface. The solution gave edges no thinner than 4 mil, but can probably be refined to yield thinner edges and reasonable shape control, with a thicker central area. Production of cast samples would be feasible but probably not as efficient as a flat film for the final shape.

It should be noted that the films are, as expected, moisture sensitive, and become very difficult to handle with moist fingers. Packaging and handling by the user must allow for this. Water was used as a bonding agent for folds or overlays. A solution of the film material itself may be tried as the bonding agent.

The most plausible shapes were a flat flower, or rosette, shape with additional material in the center, and the cup shape (either folded from flat film or made of two flat halves of a sheath bonded together at the closed end with additional material). The cup shape would be suitable and easy to use as a penile cap. It would be complicated to produce if the halves were folded or bonded, however. Further, it would require a complex and expensive package to protect product shape and keep the film from sticking to itself.

The flat film rosette shape would be easier to produce, because the center portion would be bonded flat to a previously die-cut shape. If packaged flat, it could be folded in half with an interleaf of finished paper to protect it from sticking to itself or to other sheets. Because it is not condom or cap-shaped, its use would require the user to develop the notion of placing the [illegible] over the glans and wrapping the thinner, outer edges around the shaft for use as a condom.

CONCLUSION

The more rapidly dissolving films in this feasibility study may offer an improvement over the performance of C-film, particularly with their better capability for insertion and the opportunity to deliver more spermicide to the area of the cervix. As a vaginal contraceptive, a water-soluble flat film with an overall dimension of 3 in. by 3 in. or less may be produced with relatively simple, low-cost manufacturing and packaging processes. A compactly packaged, easy-to-use, nonprescription product would have the advantage of fitting into both clinical and community-based contraceptive distribution programs.

The disintegration and dissolution rates of the films under investigation suggest that a number of the films have good potential for use as a penile

cap or condom, but designs must be identified which would be acceptable to the user. Studies should be undertaken to determine whether the films can dissolve rapidly enough to act on the ejaculate when used as a penile contraceptive product.

Present cup and sheath designs may be refined to facilitate mechanized manufacturing and packaging processes. Prospects for a low-cost penile cap in a suitable package are not promising, however, even though the cap shape has proven to be the most amenable of the designs to use on the penis. Less costly wrap-around shapes should be tested by consumer panels, to determine if men can readily learn proper use.

The development of new film combinations for use as either vaginal film contraceptives or penile caps or sheaths, with capabilities for fast dissolution and good drape and handleability, appears promising, based on the preliminary findings by the author and his associates. Yet to be determined, however, are *in vivo* spermicidal activity, dispersion within the vagina, and the long-term stability and shelf life of the films.

EVALUATION OF VAGINAL CONTRACEPTIVES

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Quality Assessment of Barrier Contraceptives

MICHAEL J. FREE,

GORDON W. DUNCAN

National family-planning programs, as well as major donors, have expressed the need for assistance in assessing the quality of various contraceptive products and in developing an indigenous capacity to carry out independent, in-country testing. The capability is desired not only to assess the quality of recently received goods, but also to assist in monitoring the quality of these items as they move through the family-planning programs to the ultimate users.

Latex condoms from most established manufacturers are generally strong, uniform, and free from holes—a testimonial to careful quality control at the factory and by public-sector standards institutions. However, little is known about the effects of suboptimal storage conditions, especially in tropical and subtropical climates; so that condoms shipped to and stored under these conditions are essentially out of control.

Various claims of premature condom deterioration have been made in recent years. In light of these, it is clear that the major problem is the complete lack of stored condom quality data available to program managers and distributors; to reassure them or enable them to make meaningful accept/reject decisions.

Managers in the field deal with a variety of condoms from different sources and at different stages of deterioration. These include the following:

1. New condoms from large, established manufacturers
2. New condoms from small plants or from manufacturers in the starting-up phase of production, sometimes with no electronic testing equipment or inadequate routine quality control procedures
3. New condoms from either of the above sources with, or without, independent quality checks
4. Aging condoms stored under various conditions
5. Condoms of unknown vintage transferred from other programs

A system of quality control is needed that is geared to these conditions. It must be simple, practical, rugged, require no special skills to operate, calibrate or maintain, and have a low capital cost. At the same time, the quality of the tests themselves should not be compromised. It will usually be operated at the level of the major distribution centers within any country so that

it does not have to be adapted to rural conditions. However, the ability to transport it to, and use it in, remote sites may be an advantage. Quality tests selected for use in the field must relate in some meaningful way to tests recommended by national or international standards organizations and authorities. However, a heavy emphasis can be placed on *monitoring* programs, whereby the quality of condoms aging in storage can be continually related back to the same condoms at delivery. This approach would avoid problems associated with comparison among different brands, types, shapes, or sizes which inevitably fall into dispute because of different philosophies of latex curing, different aging characteristics, and differences in data related to size, thickness, or geometry. The relative testing approach would provide information on rate of deterioration, sudden changes in strength or uniformity of a population of condoms and, if degree of deterioration can be related to failure rate during use, the overall acceptability of the condom stocks in question even beyond their shelf life expiration date.

Of course, comparison among different brands of condoms cannot be avoided in some situations. Therefore, some absolute quality value must be obtained from the test parameters, and newly delivered condoms or existing stocks at the start of a monitoring program must fall within a prescribed range of strength, freedom from holes and uniformity.

With these thoughts in mind, Program for Introduction and Adaptation of Contraceptive Technology (PIACT) initiated a program to develop a comprehensive package of equipment, information, training, and calibration for field testing of condoms. At the outset of this program, three questions arose:

1. What happens to condoms when they deteriorate?
2. Can tests measure deterioration with sufficient sensitivity and precision?
3. At what stage of deterioration do condoms become unacceptable? Based on materials consideration, field trials, and laboratory tests it seemed most likely that decreased strength of the latex was the most important mode of deterioration since pinholes were either a manufacturing defect or appeared only in the very advanced stage of condom degeneration, when the latex could be broken by even gentle handling.

In order to evaluate and compare the sensitivity and precision of potential tests for condom deterioration, a test model was needed. Fortunately, it turned out that UV light reduced the strength of condoms by 80%–90% in 8–10 hr of exposure, and could be applied in a reasonably consistent fashion. Therefore, UV-exposed condoms were used as the model in selecting appropriate tests.

FIELD TESTS

Simple, low-cost equipment has been developed to perform two types of strength tests. These are the air inflation test (*volume* and *pressure* at burst) and the surface stress tests of the latex membrane (*biaxial tension* and *tear tests*). In addition, an apparatus for performing the water test for pinholes has been developed. This battery of tests, together with detailed operating

procedures, sampling protocol, calibration checks, data collection forms, and ancillary equipment for handling condoms and performing standard dimension checks, constitutes the PIACT Field-Testing Package for Condoms. These tests are not represented as being the final answer to the problems of quality control in the field. Rather, they are offered as a new approach to the monitoring of condom quality. Hopefully, they can be refined and selected and will benefit from the continued international debate on absolute standards for condom quality.

The equipment and tests are described briefly in the following paragraphs followed by a discussion of experimental evidence of the effectiveness of the strength tests in determining deterioration of condoms. Data are also given for condoms judged unacceptable on the basis of reports from the field after being stored for a prolonged period in a hot climate.

CONDOM STRENGTH TESTS

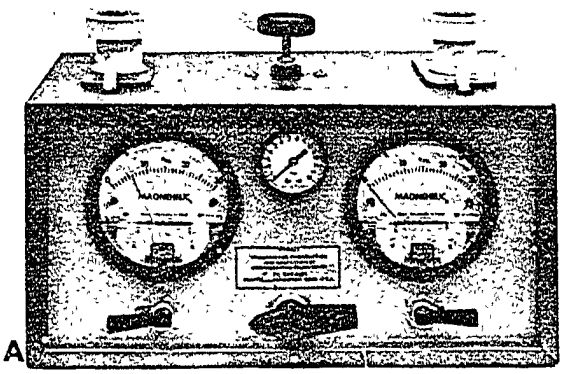
Tests for condom strength include the air inflation test, reflecting the strength of the whole condom, and the biaxial tension and tear strength tests, reflecting the strength of selected sites on the wall of the condom. All of these tests can detect deterioration of rubber condoms. However, different shapes and sizes (in the case of the air inflation test), thicknesses, textures, and curing philosophies among the various manufacturers make comparisons among different brands difficult, except in terms of variability around the mean (homogeneity of the population). These tests are, therefore, much better suited to monitoring condom deterioration over time by periodic sampling and comparison of results with zero time values for the same population of condoms.

In cases in which newly delivered or stored condoms being tested for the first time are found to have a wide range of strength, it is most likely that the distribution of results will be skewed toward the low values and that normal statistics such as means, standard deviations, coefficients of variation (SIDA Y test) or t tests lose their value. The same applies if, during monitoring, the range of strength data for condoms in storage becomes significantly broader. Under both circumstances a pass/fail test is called for and accept/reject decisions are made on the basis of the numbers of condoms bursting under 10 liters. As long as the data stay uniform, however, mean and range charts for condom strength can be used as an effective monitoring tool for condoms in storage.

Air Inflation Test The air inflation apparatus (Fig. 21-1A) is designed to test condoms for bursting volume and pressure according to specifications laid down by the following authorities:

1. SIDA (Swedish) Specifications for Rubber Condoms, p. 4, Paragraph 7
2. International Standards Organization Proposed Standards ISO/TC 157 N62.

It is a compact portable unit composed of two identical air-metering and dispensing systems, condom holders, and pressure gauges. Air is supplied to the condoms at a constant mass flow rate through a pressure-controlled ori-



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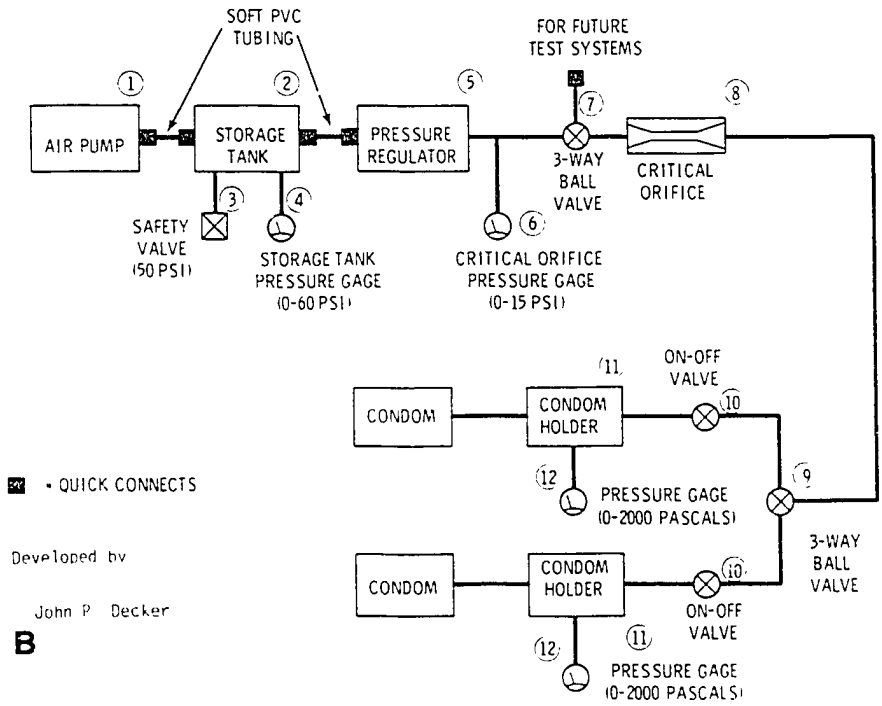


FIG. 21-1. Apparatus to test condoms for pressure and volume at burst. **A.** Front view. The left-hand condom holder contains a condom in the process of being inflated. **B.** Block diagram of the air inflation apparatus.

fice. Volume at burst can be obtained by recording the time to burst. Bursting pressure can be read directly off the gauges. The system is arranged as shown in Figure 21-1B.

Biaxial Tension Test The biaxial tension test for condoms (Fig. 21-2) is a new test designed to provide information on the strength of the rubber. Its advantages are that it does not require large, expensive, carefully calibrated equipment as is required for standard *elongation at break* and *tensile strength* measurements; that it avoids the problem of edge effects with the consequent dependence on sharp dies and perfectly cut specimens that are essential for reproducible results in complying with standards such as *ANSI/ASTM D-412-75 Rubber Properties in Tension;* and that multiple tests can be performed on each condom, therefore isolating intracondom variation and increasing precision.

The components of the system and their arrangement are shown in Figure 21-2A. A holder, similar to those used with the air inflation apparatus (Fig. 21-1A), is used to hold a circular area of the condom membrane over a closed chamber while suction is applied to the chamber. The vacuum level at bursting point is recorded. The uniqueness of the test is derived from the FLANGE configuration, which has a cylindrical hole. Most of the elastic strain in the material is expended in stretching it downward through the cylinder. The membrane assumes a hemispherical configuration, which remains stable until failure stress is reached. At failure, the membrane bursts, leaving a circular hole indicative of symmetrical stress distribution. Since the FLANGE diameter is small and defines the radius of the surface at failure, vacuum levels attained are directly proportional to surface stress. Two or more tests can be performed on the same condom, and the results can be averaged.

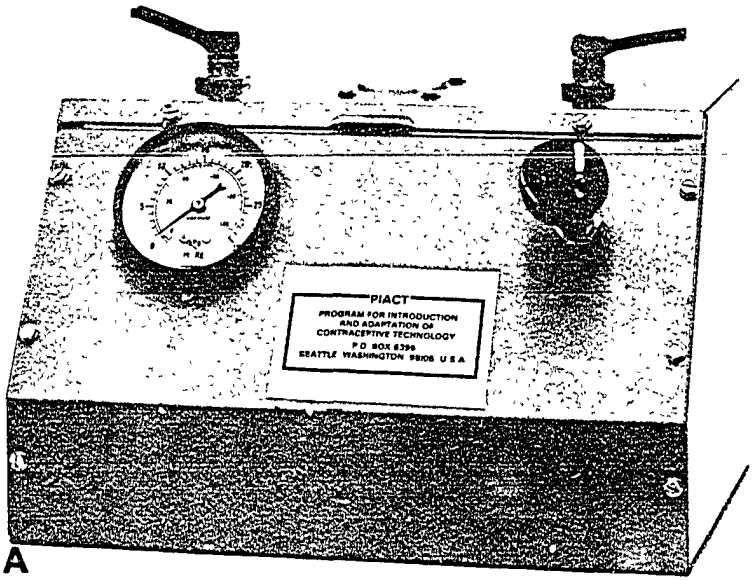
Tear Strength Test The condom tear test attempts to reproduce the type of stress that might result from rough handling of a condom during use; *i.e.*, small breaks in the rubber, followed by stretching.

This test is performed on the same instrument used for the biaxial tension test. After the test condom membrane is deliberately punctured in the center of the test region and positioned on the FLANGE, it is covered by an additional membrane. This additional membrane places a strain on the punctured test membrane as a vacuum is drawn in the chamber. A floating rod, its lower end resting on the upper membrane, moves downward as the membrane is drawn into the cylinder. The upper end of the rod moves against a scale (calibrated in millimeters) so that the displacement at the moment of failure can be recorded. As in the biaxial tension test, more than one test can be performed on each condom. In addition, the tear test can be done on the same condoms used for the biaxial tension test.

THE WATER TEST FOR PINHOLES

The water test apparatus (Fig. 21-3A) is designed to test condoms for pinholes, according to specifications laid down by the following authorities:

American Society for Testing and Materials ANSI/ASTM D3492-77; Paragraph 7.2.2.



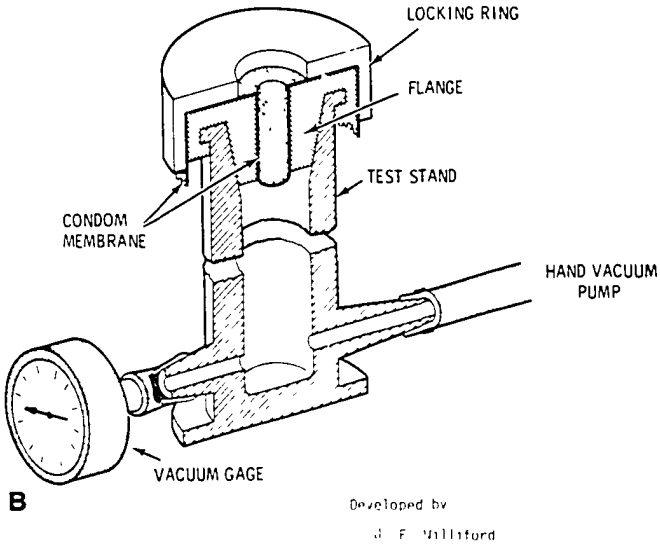


FIG. 21-2. Apparatus to test condoms for biaxial tension. **A.** General view. **B.** Cross-sectional view.

SIDA (Swedish) Specifications for Rubber Condoms P. 4, Paragraph 6.1
British Standards Institution, BS3704 Revision 1977 Appendix A
International Standards Organization Proposed Standards ISO/TC 157, doc N5.

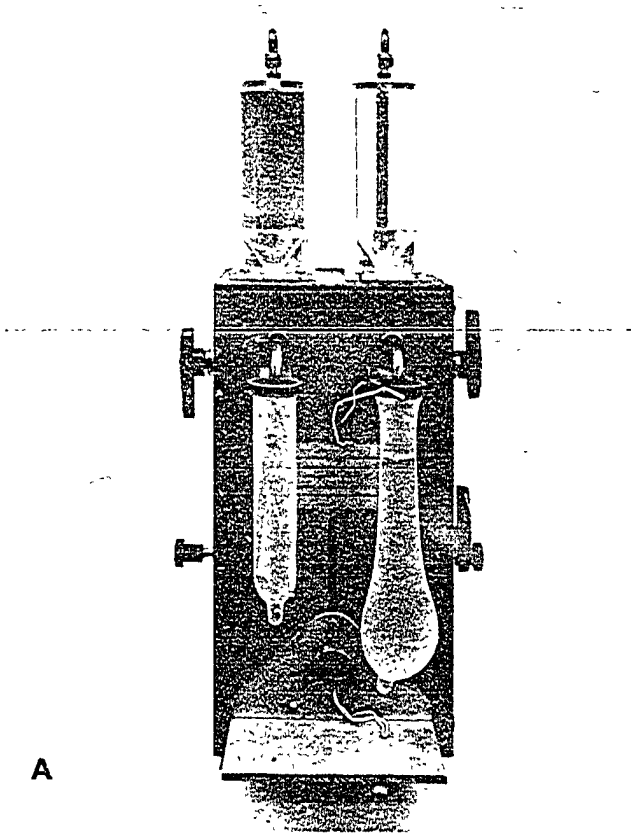
The apparatus is a compact, portable unit composed of two identical water metering and dispensing systems with condom holders, arranged as shown in Figure 21-3B. In this test, water-filled condoms are examined for water leakage by direct inspection and by rolling on (green) blotting paper. Strict accept/reject criteria for a population of condoms based on multiple sampling plans have been generated by the above mentioned authorities. Because pinholes are primarily a manufacturing defect and are unlikely to result from deterioration processes, this test is included in the field-testing package to meet the need for independent testing of newly acquired condoms or existing stocks at the beginning of a monitoring program. It should be performed prior to strength tests because a significant number of pinholes can skew the distribution of strength data and make interpretation of air inflation data difficult.

EFFECTIVENESS OF STRENGTH TESTS IN MEASURING DETERIORATION OF CONDOMS

Condoms were exposed in a standard fashion to UV light for periods ranging from 2–8 hr before being tested by the three strength tests described previously. The condoms were uncolored and 52-mm wide.

Results of the tests are shown in Figure 21-4, expressed for comparison purposes as percent of unexposed condoms. In the case of the biaxial tension and the tear tests, the *unexposed* data were obtained from masked areas of the exposed condom membrane, which was cut open and laid flat prior to exposure. It is evident from these data that all tests were capable of detecting progressive deterioration, even after only 2 hr of exposure to UV light. All of the deterioration curves were bi- or triphasic, with an initial slow rate of decline, followed after 2 hr by a markedly more rapid increase. The burst volume fell rapidly to around 20% of unexposed value by 8–10 hr of exposure. Burst pressure leveled off at 40% of unexposed value by 6 hr, while biaxial tension and deflection at tear were both around 50%. Subjectively, the condoms given 8–10 hr exposure were easily torn apart manually and were clearly beyond usable strength. On the other hand, 2–3 hr exposed condoms could not be subjectively differentiated from unexposed. It was concluded that these tests can be used to monitor deterioration of uniform, normally distributed populations of condoms.

The tear test was used in another preliminary trial to compare a limited batch of condoms (an American brand stored in Bangkok) with condoms of the same brand purchased in the U.S.A. (Table 21-1). The condoms stored in Bangkok were judged unacceptable by the program managers on the basis of package damage, yellowing of lubrication, general appearance, and claims of breakage during use. From these tear data, it is apparent that the Bangkok condoms were 14% less resistant to tear than the comparable U.S.-purchased product. Based on the UV deterioration curve (Figure 21-4C), this



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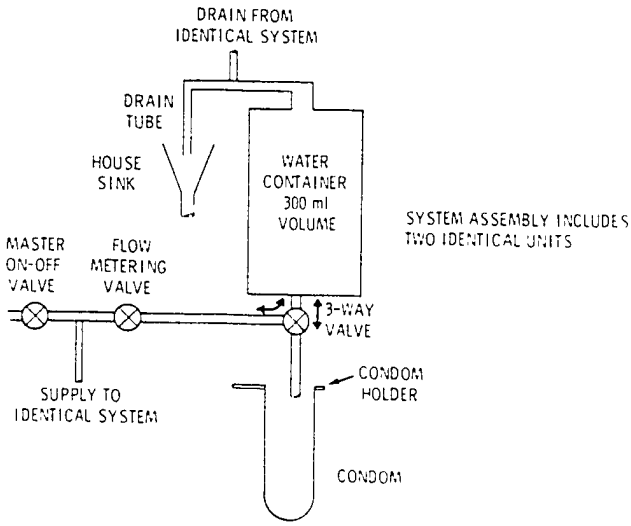

FLOW RATE TO FILL CONTAINER

300 ml/15 sec = 20 ml/sec

$\simeq 7 \times 10^{-4}$ ft^3/sec

B $\simeq 1.2 \times 10^{-5}$ ft^3/min

FIG. 21-3. Apparatus to test for pinholes in condoms **A.** Front view. The right-hand condom is filled with 300 ml of water **B.** Schematic diagram of the water test apparatus

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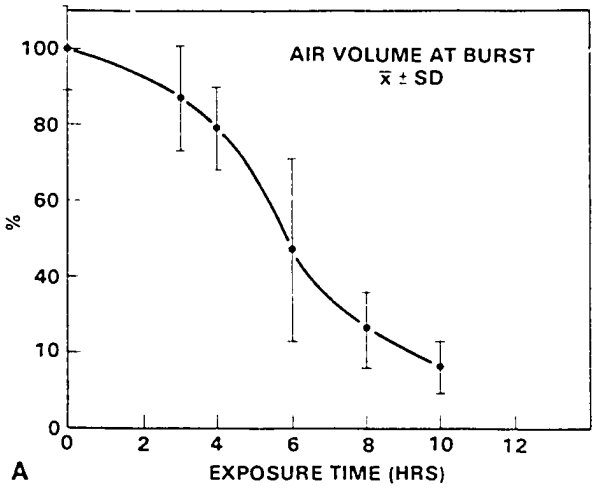

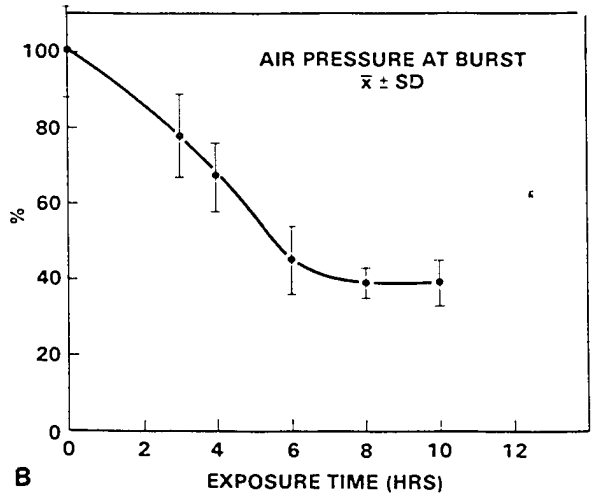

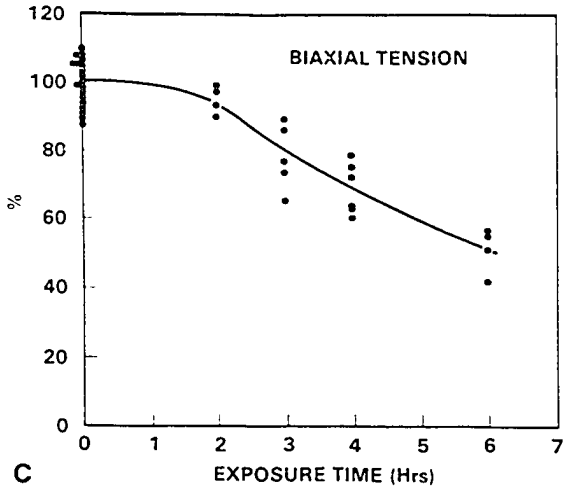

FIG. 21-4. Sensitivity of the condom strength tests in detecting deterioration of condoms. **A.** Effect of exposure to ultraviolet light on condom burst volume. **B.** Effect of exposure to ultraviolet light on condom burst pressure. **C.** Effect of exposure to ultraviolet light on condom biaxial tension.

TABLE 21-1. Comparison of American-Made Condoms from Bangkok with U.S.-Purchased Condoms of the Same Brand

SOURCE	BANGKOK (COMMUNITY-BASED FAMILY PLANNING)	U S.-PURCHASED	U.S.-PURCHASED TESTED AT 70°C/100% HUMIDITY FOR 256 HR
Quantity	19	13	10
Date of manufacture	5/75	6/77	6/77
Nominal width (mm)	49	52	52
Mean deflection at tear (mm)	21.3	24 9	23.9
Range (mm)	19.1 -24.4	21.6-28.5	21.6-30.5
Standard deviation (mm)	1 27	1.78	2.54
Value of t (t test for two independent means, assuming normal distribution)	6 49		1.22
Percent difference	14		4
P	<0 001		0 24

difference would be equivalent to about 3 hr of UV exposure. The Bangkok condoms were 2 years older than domestic stocks, and no data were available to indicate the normal aging curve for this brand of condoms. Also, it was not known whether aging had been accelerated in the Bangkok environment. However, the standard temperature (70°C) for accelerated aging tests, as specified by the British Standards Institute, resulted in only a 4% decrease in tear strength of the condoms purchased in the United States, even when exposure time was increased 20-fold beyond specifications (Table 21-1).

PRESENT STATUS OF THE PIACT CONDOM FIELD TESTING PROGRAM

Few data are available on aging of condoms under multiple adverse conditions of temperature, humidity, electrical storm activity, exposure to natural or artificial light, abrasion, and mechanical load. Furthermore, the interaction of these environmental factors with packaging, materials, lubricants, powder, color dyes, and other design features has never been explored. Much of this information can be generated by the field-testing program outlined here, providing suitable attention is paid to sampling and data collection.

Condom-testing facilities have been set up at PIACT de Mexico in Mexico City and at the Community-Based Family-Planning Services headquarters in Bangkok. Data from these and similar facilities are being used to check quality of newly acquired condoms and to permit program managers to compare deterioration of their condom stocks over periods of months or years with respect to brands, packaging, storage conditions, color, lubricant, and other

factors. These data and those from other centers presently being established, are being collated and, wherever possible, will be related to data from studies of rates of failure of condoms during use.

At the same time clinical product failure trials are being conducted with condoms exposed for different intervals to UV light. These studies will provide initial data relating deterioration level with failure during use. It is hoped that such data may lead to a consensus on a *rejection point*. These decision points can be refined as more field data accumulate.

It is anticipated that the inherent low cost of this equipment and ease of operation will make feasible the installation of a testing facility at all central condom storage sites. These facilities will do much to ensure the effectiveness of condom distribution programs and will provide a wealth of information on optimum storage and packaging of condoms under adverse conditions. PIACT believes that this package provides a meaningful approach to condom monitoring in the field that can be refined and improved with the cooperation of all interested parties.

22

Vaginal Contraception: Current FDA Status

ELIZABETH B. CONNELL

In the Federal Register of January 5, 1972 (37 FR 85), Charles C. Edwards, M.D., then Commissioner of the U.S. FDA, announced a proposed review of the safety, effectiveness, and labeling of all over-the-counter (OTC) drugs by independent FDA advisory review panels. He pointed out (1) that there were close to half a million OTC drugs being sold in the United States. Up to that time, the FDA response to such products had been sporadic and based almost entirely on concerns about safety. No system existed for their routine review and there were no guidelines for the development and approval of these agents.

It was decided, therefore, to undertake a thorough evaluation of all over-the-counter products. As Dr. Edwards wrote (2),

> The Agency will deal with all OTC drugs through rulemaking that will establish, define and describe therapeutic classes or categories of these products on an industrywide basis and will outline parameters for each class by means of a monograph. Those OTC drugs that meet the established standards of safety and effectiveness and are not misbranded under prescribed, recommended, or suggested conditions of use for their category may be marketed as before. Those not meeting the requirements, to continue on the market, may either file a New Drug Application for FDA approval or submit data in support of a monograph amendment.
>
> Under this method of classifying drugs, FDA will appoint advisory review panels of qualified experts from outside the Agency to evaluate the safety and efficacy of OTC drugs, to review OTC drug labeling, and to advise the Agency on the promulgation of the monographs establishing conditions under which OTC drugs in the specific categories will be generally recognized as safe and effective and not misbranded. Separate advisory panels will consider at least 25 designated categories of drugs. The FDA will appoint these panels and a chairman of each from nominating lists submitted by organizations representing professional, consumer, and industry interests. Each panel after its study will recommend a monograph for an entire drug category. This monograph will include acceptable active ingredients and certain combinations when appropriate, acceptable dosage ranges of ingredients, acceptable indications for use, guidelines for labeling, and directions for consumer use.

In May, 1972 (2), the Commissioner published the final regulations providing for the OTC drug review under S330.10, which were made effective immediately. To this end, 25 panels were initially created, each to review a specific group of products. Requests for the submission of data and information were published in predetermined order in the Federal Register; 60 days

being allowed for the relevant manufacturers to respond. The panels were convened in the same order. Each panel consisted of a chairman and six members. Two nonvoting liaison representatives were also appointed, one from industry and one from the consumer groups. The general mandate to all the OTC panels was to review all the active ingredients submitted in their category of drugs and then place them in the appropriate category. The categories were as follows:

Category I Conditions under which OTC contraceptives and other vaginal drug products are generally recognized as safe and effective and are not misbranded

Category II Conditions under which OTC contraceptive and other vaginal drug products are not generally recognized as safe and effective or are misbranded

Category III Conditions for which the available data are insufficient to permit final classification at this time

PANEL SELECTION, MANDATE, AND ACTIVITIES

In May of 1973, the Commissioner issued a request (3) for data and information on all of the active ingredients used in OTC contraceptives and other vaginal drug products. He also appointed a panel to review the data and information submitted and to prepare a report pursuant to S330.10(a)(1) on the safety, effectiveness, and labeling of those products. The panel consisted of four obstetrician-gynecologists (one, the chairman), a pediatrician, a pharmacist, and a Ph.D. in biochemistry. The panel first convened on August 2, 1973 and then held two-day meetings at roughly 1–2 month intervals, ending its deliberations in December 1978.

The charge given to this particular panel was the review of approximately 50 products, including more than 30 active ingredients (Table 22-1) found in vaginal contraceptives (the subject of this report) and more than 80 ingredients used in other vaginal drug products. In preparation for this review, the FDA Medical Library staff had carried out a literature search of the pertinent American publications in the field, covering the years from 1950 to 1973. At the time of the original convening of the panel, it was quickly recognized that the amount of valid data in the field of vaginal contraception was extremely limited. Most of the safety information given to the panel had been generated 10-30 years before and very few of the studies cited had been performed under guidelines which would satisfy today's criteria for excellence. The efficacy data were also extremely limited and all were calculated using the Pearl index, not the more accurate and acceptable life-table technique.

Somewhat appalled by the minimal amounts of information made available to it, the panel commissioned additional literature searches and individual panel members carried out their own reviews on the ingredients assigned to them. Where a particular area of concern existed, speakers were invited to come to address the panel. More than 20 such individuals met with the panel and several company presentations were also made.

TABLE 22-1. Active Ingredients Reviewed by FDA

CONTRACEPTIVE INGREDIENTS	CONTRACEPTIVE INGREDIENTS (cont.)
Acacia	Nonoxynol 9 (nonylphenoxy polyoxyethylene ethanol, polyoxyethylenenonylphenol, nonylphenoxypolyethoxyethanol)
Alcohol	Octoxynol
Benzethonium chloride	Perfume
Boric acid	Phenylmercuric acetate
Butyl paraben	Polyethylene glycol of mono-iso-octyl phenyl ether
De-ionized water	Preservatives
p-Diisobuytiphenoxypolyethoxyethanol	Propyl paraben
Dodecaethylene glycol monolaurate	Purified water
Glycerin	Sodium borate
Hydroxyethyl cellulose	Starch
Laureth 10S	Stearic acid
Menfegol (p-methanylphenyl polyoxyethylene (8.8 ether)	Tragacanth
Methylpolyoxyethyleneglycol 550 laurate	
Methylbenzethonium chloride	
Methylparaben	
Methyl polysiloxane	

During the course of its deliberations, the panel also organized two symposia. The first one was held in January, 1975, and brought together experts from many fields including physiology, genetics, toxicology, and teratology to review all the current information relevant to the field of vaginal contraception and to look at data from ongoing research. The second symposium was held in April, 1978, and the panel invited an outstanding group of consumer advocates, industry representatives, basic researchers and clinicians to attend. This meeting dealt with four issues related to the effectiveness of vaginal contraceptives. The first was consumer concern about having more detailed labeling on both the box and the package insert, to be written in language easily understood by the average consumer. The second was the problems encountered in the development of clinical protocol for the testing of vaginal contraceptives. The third part of the program dealt with the current use of vaginal contraceptives, and where and how new data on their effectiveness might be generated. Finally, study design and statistical analyses were looked at, including the necessary components of future studies which would lead to more accurate use-effectiveness data.

Thus the panel attempted, using every possible means, to gather and review all of the information available on vaginal contraception before arriving at its conclusions and recommendations. Unfortunately, these combined efforts only served to substantiate their original observation that very little good work had been done in this field in recent years.

PANEL RECOMMENDATION

During the course of its deliberations, the panel had to deal with three major issues: safety, efficacy, and labeling. Regarding safety, the panel con-

cluded that proper study of any of these ingredients encompassed four areas: 1) the safety of the pregnant and nonpregnant users; 2) the safety of the very young fetus; 3) the safety of the fetus through the later stages of pregnancy up to the time of birth; and 4) the safety of the neonate if the ingredient were to be transmitted through breast milk. In the case of efficacy, given the fairly primitive data then available, the panel elected to draw up its own standards and guidelines for what would be appropriate testing of a vaginal contraceptive. Finally, finding that the consumers felt that the current labeling ranged from virtually none to rather inadequate, the panel developed a list of approved and approvable claims and an outline of patient instructions.

SAFETY

The panel found its greatest concerns to be in the area of safety. Its review of the literature suggested that it was only in the past few years that the vagina has generally been considered to be anything other than a totally inanimate space. Recent studies, however, have clearly pointed out the fact that the vagina has a great ability to absorb or transport a wide variety of materials. Therefore, the panel found it virtually impossible to evaluate completely many of the agents under its review because only the local effects of the various drugs had been studied. There was almost no information on the absorption of any of these ingredients through the vagina into the systemic circulation and there were no studies on the effects of these agents on the developing human fetus or the nursing infant.

Because the human fetus is known to be susceptible to teratogens as early as the 11th or 12th day after fertilization, the panel was concerned that the use of any agents prior to the diagnosis of pregnancy might produce fetal damage. For example, the fetal kidneys only begin to function at about the 14th week after conception and, therefore, any drugs administered before this time may not be cleared from the fetal circulation. In addition, the enzyme systems of the baby's body are poorly developed at this time and cannot be expected to be very effective in the detoxification of drugs. Because of these factors, the panel was concerned that certain chemicals might accumulate in the fetus and produce damage. It is well known that the cause(s) of a number of spontaneous abortions remain unknown. The panel felt that it was possible that exposure to environmental contaminants or theoretically benign agents, such as the ones under its review, could be the reason for such anomalous development.

The panel has recommended to the Commissioner of the FDA that certain studies be carried out, first in several animal species and, following this, if safety is established, in the human (Fig. 22-1). These guidelines will apply to ingredients placed in Category III by the panel because of safety concerns and, hopefully, in addition, to any new vaginal contraceptives to be tested in the future. There was considerable discussion as to which animals should be used for the initial screening; the panel recognizing that no animal data can be immediately transposed to the human because of the wide range of species variability.

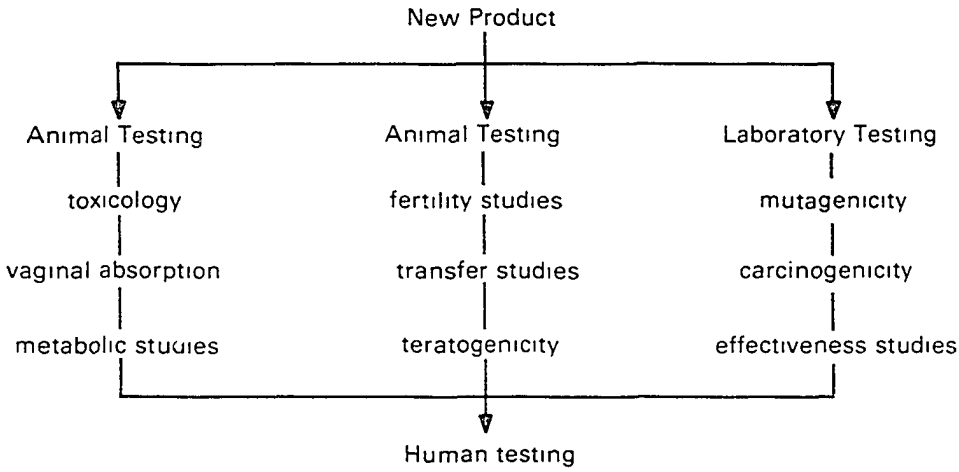

FIG. 22-1 Vaginal contraceptive development.

Table 22-2 Vaginal Contraceptives Laboratory Evaluations

TYPE OF TEST	TEST MATERIAL	DATA SOUGHT
Mutagenicity—*in vitro*	Bacterial assays (Ames Test) Chinese hamster ovary CHO cells Hamster lung V-79 cells Mouse lymphoma cells Human fibroblasts Human lymphoblasts	Mutations at individual loci DNA damage and repair Clastogenic events Breakage and repair of chromosomes
Mutagenicity—*in vivo*	Mouse	Somatic damage • Micronucleus changes • Sister chromatid exchange • Recessive coat color spot Germ cell damage • Dominant lethal test • Heritable translocation assay • Sperm morphology • Germ cell specific locus test
Carcinogenicity	Hamster embryo cells Hamster	Morphological transformation Tumor induction

Toxicity Studies

The following guidelines were established for animal and human testing for toxicity (Table 22-2). First, regarding acute toxicity, it was recommended that studies first be carried out in the rat or the mouse, looking for potential hazards. It was believed that, for the determination of the LD_{50}, the intravenous route of administration was appropriate for water-soluble ingredients, and the intraperitoneal or other parenteral routes for water-insoluble or particulate ingredients. It was recommended that the oral route not

TABLE 22-3. Vaginal Contraceptives: Animal Testing

TYPE OF STUDY	ANIMAL SPECIES	DATA SOUGHT
Metabolic—*in vivo*	Rodent Nonrodent	Clearance rate Turnover time Half-life Tissue analysis for ingredient & metabolites
Metabolic—*in vitro*	Tissue slices	Enzyme systems Cell membranes Cell division
Vaginal absorption	Two species not phylogenetically related Pregnant and non-pregnant animals	Degree & rate of absorption Levels of ingredient & metabolites in blood urine and tissues

be used because of major differences in the degree of absorption in different species.

As regards subacute and/or chronic testing, it was recommended that this be done in one nonrodent species with 12 mo of exposure and one rodent species with 24 mo of exposure. The data to be collected include information on body weight, food consumption, and behavior; hemogram and blood coagulation studies; liver and kidney function tests; metabolic studies; and, following sacrifice of the animals, gross and microscopic examination of body tissues, particularly the liver, kidney, brain, and reproductive organs.

It was further recommended that local toxicity studies be conducted using the vaginal route of administration, inasmuch as these products might be used frequently and over a considerable period of time. The panel believed that the rabbit would be an excellent animal model for evaluating agents for potential vaginal irritation and that an intradermal test or a cutaneous test on the guinea pig would be appropriate for screening potentially sensitizing ingredients. Obviously, the final and only totally valid tests for irritation and sensitization would be those carried out in human subjects, but this would be permitted only after negative results had been obtained in the animal experiments.

Vaginal Absorption Studies

Vaginal absorption studies are particularly important, inasmuch as many compounds are now known to be absorbed freely across the vaginal walls. The panel has, therefore, recommended that two species of animals which are not closely related phylogenetically be evaluated, including both pregnant as well as nonpregnant animals (Table 22-3). It recognized that great care must be taken in the selection of animals to be studied, being sure that the dosage form of the test preparation is retained within the vagina. Rats and sheep are particularly useful for this type of testing, solid dosage forms and creams frequently being reflexively expelled from the vagina of the rabbit and the dog. Liquid formulations may be applied in many species, provided that prolonged retention of the drug is not critical to the experimental

design. Nonhuman primates were felt to be eminently suitable for testing for vaginal absorption, but they would have to be restrained so that they could not remove the inserted test agents.

The degree and rate of vaginal absorption can be determined by measuring the levels of the ingredient and its major metabolites in blood, urine, and certain body tissues. By comparing the test results with the dose levels previously found to induce toxic or embryotoxic effects, the potential hazards and the margins of safety may then be extrapolated for the human fetus and the pregnant and nonpregnant woman. Finally other factors, such as the vehicle used for the administration of the agent, may appreciably affect the rate of vaginal absorption and need to be taken into account.

Metabolic Studies

The panel recommended that any ingredient which demonstrated toxicity undergo further *in vivo* and *in vitro* testing because vaginal absorption in significant amounts might occur if it were used over a considerable period of time (Table 22-3). Thus it was felt that analysis for the ingredient and its major metabolites should be carried out in one rodent and one nonrodent species, following the systemic administration of the ingredient. The clearance rate and the turnover time, as well as the half-life of the test ingredient should be calculated for the entire body and for various organs and tissues. The rate of accumulation of the toxic ingredient on repeated or continuous exposure at various dose levels could then be predicted.

In addition, studies should be performed *in vitro* determining the effect of the test ingredient on critical enzyme systems, using tissue slices, and looking at such things as cell membrane structure and cell division.

Maternal-Fetal Transfer Studies

The panel has recommended that any ingredient which produces embryotoxic effects in the pregnant animal should be studied in order to determine the rate and magnitude of the transfer of the ingredient and its major metabolites from the maternal to the fetal compartment (Table 22-4). Following the systemic administration of the ingredient to the pregnant animal, analyses for the ingredient and its major metabolites must be carried out in the fetus, placenta, and amniotic fluid and certain maternal tissues, such as the blood, liver, kidney, brain, and reproductive organs. The site of localization of the test ingredient in these various tissues should be determined by histochemical studies.

Teratogenicity Studies

The panel has recommended that the test ingredient be administered systemically throughout the period of organogenesis to at least two species of animals that are not phylogenetically closely related (Table 22-4). Litter size and the number of stillborns should be determined as well as the number and weight of fetuses at different stages of gestation. Autopsies should be carried out on dead offspring, anatomical malformations noted, and gross

TABLE 22-4. Vaginal Contraceptives: Animal Testing

TYPE OF STUDY	ANIMAL SPECIES	DATA SOUGHT
Fertility	Two species not phylogenetically related	Pregnancy rates and outcome
Maternal—fetal transfer	One or more species showing embryotoxicity	Levels of ingredient and metabolites in maternal and fetal tissues
Teratogenicity	Two species not phylogenetically related	Number & weight of fetuses Litter size & number of stillborn Gross and microscopic examinations Effect on lactation and analysis of milk

and microscopic examinations performed. Live-born animals should be observed for neurologic and behavioral abnormalities. The effectiveness of lactation, the nutritional quality of milk, and the growth curve of the young during the suckling period should be charted. If there are adverse effects on the offspring, analyses must be made for the test ingredient and its major metabolites in the milk.

Mutagenicity and Carcinogenicity Studies

The panel has recommended that tests for mutagenicity and carcinogenicity be required when evaluating safety (Table 22-5). Vaginal preparations containing chemicals with carcinogenic potential, if used during early pregnancy when the woman is not cognizant of the fact that she is pregnant, may be hazardous to the preimplantation blastocyst, the embryo, or the developing fetus; the carcinogenic effects becoming manifest some time after birth. Transplacental carcinogenesis has been shown in animal studies and, in the case of diethylstilbestrol, in the human.

It appears that certain tissues are more susceptible to some carcinogens during fetal and infant life than they are in the adult. Since carcinogenesis via mother's milk has been shown in animal experiments, there is always the possibility that an infant who is breast fed by a mother who uses vaginal preparations containing an unsuspected carcinogen may ingest it in the milk. While the woman herself may be less susceptible to the action of carcinogenic agents than is the fetus or infant, she may undergo prolonged exposure with continuous use.

The panel believes that the most reliable test of carcinogenicity requires exposure of the test animal to the suspected carcinogen during nonpregnancy, early pregnancy, and lactation using the vaginal route of administration. It has recommended that certain short-term predictive tests may be used as alternatives to the lengthy and costly animal assays for carcinogenic activity. One such test is the host-mediated *in vivo* and *in vitro* combination assay, in which the chemical to be tested is injected intraperitoneally into a

TABLE 22-5. Vaginal Contraceptives: Animal Toxicity Studies

TYPE OF TEST	ANIMAL SPECIES	TESTING REQUIRED
Acute	Rat or mouse	LD_{50}
Subacute and/or chronic	Non-rodent	12 mo of exposure
	Rodent	24 mo of exposure
Local	Rabbit	Vaginal application
	Guinea pig	Intradermal or cutaneous

pregnant animal. Embryo cells are then cultured, the appearance of morphological transformations suggesting the chemical's carcinogenic activity. In another assay, cultured embryo cells from untreated pregnant animals are exposed directly to the chemical to be tested and observed for morphological transformations.

It is currently believed that a positive response in one of these systems suggests that the chemical is potentially hazardous, and that testing with more sophisticated bioassays is indicated.

Certain other test procedures are used to identify potential mutagens. While not all mutagens are carcinogens, many, but not all, carcinogens are mutagens. These prescreening tests are relatively inexpensive, quick, and reasonably easy to perform. The majority of the tests have as endpoints some form of genetic damage. The first of these is mutations at individual loci as in the bacterial mutagenic assays, (the Ames test) and in certain mammalian cell culture systems, such as the Chinese hamster ovarian (CHO) cells, hamster lung V-79 cells, mouse lymphoma cells, and human fibroblasts and lymphoblasts. The second endpoint is the measurement of DNA damage and repair and the third is the measurement of blastogenic events including deletions, chromatid and chromosome breakage, and the repair of chromosomal material.

The panel has recommended that a battery approach to testing should be followed, using at least three of the following types of tests: bacterial mutagenesis, cultured mammalian cell mutagenesis, cell transformation, DNA damage and repair, and whole animal mutagenesis or chromosomal damage. It believes that no single test can be used to assess carcinogenic potential because all tests may be expected to yield a fraction of false positive and false negative results. Moreover, conventional long-term testing for carcinogenicity may be indicated if positive results are obtained using the short-term predictive tests.

Effectiveness

At the time the panel was convened, there were no specific guidelines for testing contraceptive effectiveness of vaginal products or for verifying the validity of numerically expressed claims of effectiveness. The panel therefore developed a series of guidelines for *in vitro* and *in vivo* testing of vaginal contraceptive ingredients and products.

In Vitro Testing

The panel recommended that *in vitro* tests be designed to support the postulated mode of action of the contraceptive agent, *e.g.*, spermicidal, sperm-immobilizing, inhibiting the ability of sperm to fertilize ova, and promoting resistance of the cervical mucus to sperm transport. At the present time, in order for a compound to be considered an effective contraceptive agent, it must meet one of two requirements: it must either kill or immobilize all sperm on contact or it must render the sperm incapable of fertilization. Several systems for *in vitro* testing are currently being used in various laboratories, such as the Brown-Gamble, the Sander-Cramer, and the International Planned Parenthood Federation (IPPF) Agreed Test. All of these tests are based on the use of human semen, the IPPF Agreed Test being used most often as the standard spermicide screening procedure.

Vehicles serving multiple functions may require evaluation as well. For example, the vehicle may act not only as a carrier for the spermicide but may serve also as a physical barrier. However, the vehicle may also have negative effects. For example, a vaginal suppository or tablet requires proper placement and time for melting, and may have a limited duration of action. Therefore the panel recommended that the spermicidal effectiveness of the final formulation must be tested.

In Vivo Testing—Animal

The panel recommended that testing for contraceptive effectiveness be required in two appropriate animal species, the animal to be used depending upon the mechanism of action. For example, in man, most nonhuman primates, and ruminants, semen is deposited in the vagina, whereas in the horse, pig, dog, and in murine rodents, semen is deposited directly into the uterine lumen. Therefore, the latter group of animals would not be appropriate as animal test models if interference with sperm transport is postulated. The rabbit may be used, although pregnancy is not completely inhibited because recent studies have indicated that implantation rates can be used as a measure of vaginal contraceptive potency. The stump-tailed macaque (*Macaca arctoides*) has also been used more recently. The use of farm animals, particularly sheep, may be useful in the evaluation of vaginal contraceptive agents, particularly because the reproductive performance of domestic animals is well known.

In Vivo Testing—Human

The panel observed that testing for contraceptive effectiveness of vaginal products had been poorly standardized, leading to wide ranges of method- and use-effectiveness of the same product in different studies. Failure rates as low as 3% and as high as 40% had been reported. Because of this wide variation, the panel was unable to establish an acceptable standard of effectiveness and therefore devised its own suggested protocol for long-term prospective studies for these products.

The panel further recommended that all data be statistically evaluated using the life-table method. Although the older data calculated using the

Pearl formula might be salvaged, new data will be required for a more precise evaluation of effectiveness.

Phase I The panel recommended that a rising dose study, based on initial evaluation in animals, be performed in 10–20 subjects using the product for at least 10 days, looking for any evidence of local or generalized reactions. The tests described by Huhner and Johnson and Masters might be conducted during this phase.

Phase II At least 50 subjects should use the product for 6 mo to determine short-term effectiveness. The panel set up a number of criteria for the selection of test subjects for this phase, how the study was to be carried out and how the data were to be collected.

Phase III (method-effectiveness) If acceptable pregnancy protection rates are demonstrated in Phase II testing, the panel recommended that a similar protocol be used for long-term studies, using a minimum of 750–1,000 volunteers.

Phase IV (use-effectiveness) The panel did not recommend that use-effectiveness data be required in order to prove the effectiveness of a vaginal contraceptive product. It established Phase IV guidelines only for the substantiation of numerically expressed claims of effectiveness. It believed that an effort should be made to obtain data not only on users within the health care system, but also those outside this system because most users of OTC vaginal contraceptives come from the latter group. Moreover, because use-effectiveness may change over a period of time as the characteristics of the population of women using the method change, the panel recommended that the studies be repeated at reasonable intervals.

Extended use-effectiveness As in the case of Phase IV testing, the panel did not recommend that extended use-effectiveness data be required. Extended use-effectiveness guidelines were developed only for the further substantiation of numerically expressed claims of effectiveness.

The panel believes that a household survey should be used for evaluation of extended use-effectiveness. The survey should include (but not be limited to) information on age, race, marital status, parity, educational level, employment, history of pregnancies, coital frequency, contraceptive intent, contraceptive history, and use status at the end of the study.

Finally, it was recommended that retrospective studies be carried out, looking for possible local or systemic toxicity and teratogenicity, mutagenicity, and carcinogenicity.

LABELING

As its third mandate, the panel reviewed the general and specific labeling requirements previously adopted by the FDA for OTC contraceptives and other vaginal drug products (21 CFR 201.61), as well as the labeling for all of the OTC contraceptive products submitted. During the course of its review, the panel became increasingly aware of the growing importance of vaginal contra-

ception because of the many concerns about immediate and possible long-range side effects of the oral contraceptives and IUDs. Also, because vaginal contraceptives are sold without prescription and used without professional guidance and because the effectiveness of any vaginal contraceptive is directly related to the accuracy and consistency with which it is used, the panel felt that it was particularly important that their labeling be as informative and as explicit as possible.

The panel therefore concluded that, in order for women to obtain the maximum protection against unwanted pregnancy with these products, new labeling guidelines should be developed. These fell into 4 major areas:

Indications for use The indications for use should be simply and concisely stated so that the consumer has a clear understanding of the results which can be anticipated from the use of the product.

Directions for use The label should contain a clear statement of the usual effective dose, the maximum-allowable total daily dose and the duration of usage. When a drug is known to have a somewhat higher than average incidence of hypersensitivity reactions, this fact should also be so stated on the label.

Ingredients The panel concluded that the consumer should be made aware of all of the ingredients in a product because of the possibility of allergic states and/or idiosyncracies. Although current statutes require that only the active ingredients be listed, the panel strongly recommended that all inactive ingredients also be listed.

Effectiveness and claimed advantages After reviewing all of the claims made by manufacturers of the various products, the panel concluded that certain claims for effectiveness have been made in the past without adequate, valid supporting data. Therefore, it recommended that any language which promises specific health benefits which are not substantiated by scientific data may not be used to promote the sale of these products. For example, manufacturers may not make use-effectiveness or comparative effectiveness claims unless valid scientific data have been provided upon which to base them. The panel recognized that this type of labeling would be of great help to the consumer, but did not believe that there are currently any valid studies which could support a method-effectiveness or use-effectiveness labeling claim. Moreover, it believed that many of the currently used terms are vague and poorly defined, thus promoting impressions of effectiveness which have not been proven. Finally, the panel disallowed all claims and phrases which included superlatives and terms which ascribed medical or authoritative approval because it believed that these claims were clearly misleading.

SUMMARY

After more than five years of work, the FDA OTC Panel on Review of Contraceptives and Other Vaginal Drug Products has almost completed its

assigned review and its monograph for the Commissioner is virtually done. The various ingredients found in vaginal products have been categorized and new guidelines for safety and efficacy testing and labeling have been drawn up. These guidelines will mandate the requirements for Category III ingredients to move to Category I. It is the understanding of the panel that, because there are currently no FDA standards for vaginal contraceptives, they will also serve as the official standards for all new vaginal products.

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23

Preclinical Evaluation of New Vaginal Contraceptives

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Vaginal contraceptives represent one of the oldest methods of contraception, and today they remain the only medical method of birth control used exclusively by women which does not require physician intervention. Thus, vaginal methods play an important role in overall fertility-control programs. Although a variety of dosage forms have evolved throughout the centuries (5), new dosage forms and more convenient packaging are needed to improve patient compliance and efficacy of vaginal contraceptives.

During the past several years investigators in the Ortho laboratories have been studying various means of evaluating vaginal contraceptive formulations. As a result of this effort, the first quantitative *in vivo* vaginal contraceptive evaluation procedure was developed, using the rabbit as an animal model (18, 22, 23). During our efforts to evaluate and improve vaginal contraceptives, we have also critically reappraised the methodologies used for the *in vitro* testing of spermicidal agents and vaginal contraceptive formulations. The purpose of this chapter is to describe a methodology we have developed and modified which can be employed in evaluating preclinical efficacy and safety of the spermicidal contraceptives.

EVALUATION OF EFFICACY

BACKGROUND

The development of currently available spermicidal vaginal contraceptive products has utilized almost exclusively *in vitro* testing procedures for the screening and evaluation of the spermicidal potency of the active ingredient and the formulation. Various *in vitro* tests have been devised to measure the efficacy of spermicidal agents. Although the testing for spermicidal activity of chemical agents has a history dating back to Kolliker's work of 1855 (25), Baker's comparison of the effects of chemical agents on the guinea pig and human sperm in 1932 was the basis of human sperm testing (1). It was also Baker who in 1935 first recognized the need for testing the spermicidal activity of the formulation rather than the active ingredient alone (2). Various

TABLE 23-1 Vaginal Contraceptive Products Tested

PRODUCT	LOT#	ACTIVE INGREDIENT	DOSAGE FORM
Delfen Contraceptive Foam	N-1083	Nonoxynol 9	Aerosol foam
Neo-Sampoon Loop Tablet	A17FBA	Menfegol	Foaming tablet
Delfen Contraceptive Cream,			
Conceptrol	03R534	Nonoxynol 9	Emulsion cream
Ortho-Forms	11P0629	Nonoxynol 9	Melt suppository
Ortho-Gynol Contraceptive Jelly	11M330	Triton X-100	Jelly
Encare Oval	103221	Nonoxynol 9	Foaming suppository

modified spermicidal tests were subsequently developed by Brown and Gamble (6, 7, 9, 10), Sander and Cramer (29), Millman (27), Davidson (14), Carruthers (13), and Harris (20). The similarities and differences of these tests were previously reviewed by Hardy and Wood (19). In 1964 many of these modifications were incorporated into what is known as the International Planned Parenthood Federation (IPPF) Agreed Test for Total Spermicidal Power (24). This test is the result of the work of Harris (20) and combines the principal feature of Baker's test and the method of Sander and Cramer.

In reviewing the literature dealing with *in vitro* spermicidal tests, it is apparent that new methodology has not been published since the work of Harris in 1962 and the tests most commonly used at present are the Sander-Cramer and the IPPF Agreed Tests. The effectiveness of vaginal contraceptives depends on a number of interacting factors, including: 1) the spermicidal potency of the active ingredient; 2) the release of the active ingredient from the dosage forms; and 3) the physical properties of the formulation as a barrier to sperm penetration through the cervix. We therefore decided to reevaluate the respective merits of the Sander-Cramer and the IPPF Agreed Tests. We used four commercially available vaginal contraceptives available from Ortho (aerosol foam, emulsion cream, jelly, and melt suppository) and two examples of other dosage forms not currently manufactured by Ortho (foaming tablet and foaming suppository) as shown in Table 23-1.

IN VITRO TESTING METHODS

Sander-Cramer vs. IPPF Agreed Tests

The Sander-Cramer Test, which was developed in the laboratories of Ortho Pharmaceutical Corporation in 1940, involves the addition of 1.0 ml of diluted test compound or formulation to 0.2 ml of human semen at room temperature. The endpoint is the greatest dilution of the test material which immobilizes all sperm within 20 seconds.

In the IPPF Agreed Test, all spermicides are diluted with 0.9% saline to a constant concentration of 1 g/11 ml. For a product to "pass" the IPPF Test, 1 ml of this solution at 35°–37°C must immobilize the sperm in 0.2 ml of semen from each of three different donors or from five of six donors within 40 sec. Major variables between these two tests, as shown in Table 23-2, in-

TABLE 23-2. Methodological Differences Between the Sander-Cramer and IPPF Agreed Tests

VARIABLE	SANDER-CRAMER TEST	IPPF AGREED TEST
Semen quality	Examine volume, sperm count and motility	≥50 M/ml, 40–50% rapid forward motion
Semen age	≤1 hour	≤4 hours
Semen donors	Not specified	Minimum of 3, maximum of 6
Temperature	Room temperature (22 ± 1°C)	35–37°C %
Testing solution	Serial dilutions	1gm/11ml
Mix time	5 seconds	10 seconds
Elapsed time	20 seconds	40 seconds
Slide preparation	Hanging drop	Slide plus coverglass
Endpoint	Greatest dilution that immobilizes sperm in <20 seconds	Must immobilize sperm from 3 or 5 of 6 donors
Confirmation	Retest endpoint dilution	Unable to revive motility with buffered glucose solution

clude semen age, temperature, number of different semen donors, and test solution preparation.

It must be noted that while there are several procedural differences between these two tests, the principal difference is in the endpoint of the tests. The Sander-Cramer Test can provide quantitative potency data, whereas the IPPF Agreed Test only provides qualitative data with respect to the activity; a product either "passes" or "fails" the IPPF test (Table 23-2).

The results obtained for the spermicidal potency of the six different vaginal contraceptive formulations tested by the IPPF Agreed Test and the Sander-Cramer Test are shown in Table 23-3. In the IPPF Agreed Test, all formulations immobilized sperm obtained from six different donors in 40 sec or less with the exception of Encare Oval. Encare Oval was capable of immobilizing sperm in 40 seconds or less from three of the six donors used in this study. As also shown in Table 23-3, the Sander-Cramer test provides an index of spermicidal potency for the six vaginal contraceptives tested. They are listed in descending order with respect to their spermicidal potencies. The spermicidal potencies of Delfen Contraceptive Foam (12.5 mg of nonoxynol 9/100 mg of foam); Neo-Sampoon Loop Tablet (7.5 mg of Menfegol/100 mg); Delfen Contraceptive Cream; Conceptrol (5 mg nonoxynol 9/100 mg); Ortho-Forms (2 mg nonoxynol 9/100 mg); and Ortho-Gynol Contraceptive Jelly (1.0 mg Triton X-100/100 mg) are all approximately related to the amount of active ingredient contained in the formulation. Encare Oval (2.3 mg nonoxynol 9/100 mg), a foaming suppository, was the only exception to this pattern and showed the lowest potency. Nonoxynol 9 and Menfegol possess approximately similar spermicidal potencies, while Triton X-100 is one-half as potent as either nonoxynol 9 or Menfegol. The Encare Oval, which contains approximately one-fifth the amount of the active ingredient of Delfen Contraceptive Foam, had a spermicidal potency at least 100 times less than that of Delfen Contraceptive Foam. One might speculate that some component in Encare Oval suppository formulation

TABLE 23-3. Spermicidal Activity of Six Different Vaginal Contraceptives Tested by the IPPF Agreed and Sander-Cramer Tests

DOSAGE FORM	IPPF AGREED TEST (1000 mg/11 ml)*	SANDER-CRAMER TEST (mg/ml)†
Aerosol Foam (Delfen Contraceptive Foam)	6	0.99 ± 0.0
Foaming Tablet (Neo-Sampoon Loop Tablets)	6	4.8 ± 0.1
Emulsion Cream (Delfen Contraceptive Cream; Conceptrol)	6	5.1 ± 0.1
Melt Suppository (Ortho-Forms)	6	10.6 ± 0.3
Jelly (Ortho-Gynol Contraceptive Jelly)	6	48.6 ± 1.4
Foaming Suppository (Encare Oval)	3	~100

*Number of donors in which sperm were immobilized in <40 seconds at this concentration (n = 6)

†Lowest concentration (mean ± SE) capable of immobilizing sperm in <20 seconds (n = 6)

limits the spermicide's availability to contact sperm. In all trials of both test procedures where sperm were instantaneously immobilized, sperm motility could not be revived with the addition of a buffered glucose solution to the test mixture.

FACTORS AFFECTING SPERMICIDAL ACTIVITY

It has been the general consensus that there is a large difference in criteria for spermicidal testing and various factors have been known to affect the result (20, 27). In order to assess the extent to which each test criterion may influence the results, we have reevaluated major variables between the Sander-Cramer and IPPF Agreed Test using six different vaginal contraceptive formulations.

The following variables were studied for their influence on spermicidal activity: pH of formulations, semen age, temperature, and semen donor variations.

pH of Formulations

Sperm are susceptible to changes in the pH of cervical mucus. Acid mucus immobilizes sperm, whereas alkaline mucus enhances their motility (28). Many vaginal contraceptive formulations are buffered at a pH of 4.5–5.0, which is comparable to the pH of the human vagina and is also detrimental to sperm survival. pH determinations are not required by the Sander-Cramer Test but are routinely conducted in the IPPF Agreed Test. We have examined pH values of all final test preparations which immobilize sperm instantaneously (Table 23-4). The pH of semen obtained from the six donors for

TABLE 23-4 pH of Test Preparations Used in the Sander-Cramer and IPPF Agreed Tests

DOSAGE FORM	SANDER-CRAMER TEST		IPPF AGREED TEST	
	Test Solution	*Test Solution Plus Semen**	*Test Solution*	*Test Solution Plus Semen**
	(*pH*) *Mean* ± *SE*		(*pH*) *Mean* ± *SE*	
Aerosol Foam (Delfen Contraceptive Foam)	5.6 ± 0.1	7.8 ± 0.0	4.3 ± 0.0	6.9 ± 0.1
Foaming Tablet (Neo-Sampoon Loop Tablets)	6.1 ± 0.1	7.3 ± 0.1	7.4 ± 0.1	7.8 ± 0.0
Emulsion Cream (Conceptrol; Delfen Contraceptive Cream)	4.8 ± 0.0	7.2 ± 0.0	4.6 ± 0.0	6.4 ± 0.1
Melt Suppository (Ortho-Forms)	3.7 ± 0.0	7.4 ± 0.0	3.9 ± 0.1	6.2 ± 0.0
Jelly (Ortho-Gynol Contraceptive Jelly)	4.2 ± 0.0	6.7 ± 0.0	4.3 ± 0.0	6.4 ± 0.0
Foaming Suppository (Encare Oval)	5.4 ± 0.1	7.1 ± 0.1	4.9 ± 0.5	5.8 ± 0.5

*Semen pH 7.9 ± 0 (N = 6)

all the tests was 7.9, while the saline used to dilute the contraceptives had a pH of 5.2. In the Sander-Cramer Test, the test solutions used (greatest dilutions which immobilized sperm) were all acidic (pH 3.7–6.1). When these test solutions were mixed with semen (1.0 ml + 0.2 ml of semen), the pH changed to near neutrality or slightly alkaline (pH 6.7–7.8). In the IPPF Test, the test solutions (83.3 mg/ml) of all formulations were also acidic (pH 3.9–4.9, except for Neo-Sampoon Loop Tablets, in which the pH was 7.4. After mixing with semen, the pH remained slightly acidic (5.8–6.9), with the exception of Neo-Sampoon Loop Tablets, in which the pH was nearly that found for semen (7.9). The optimal pH for sperm migration and survival in cervical mucus is between 7 and 8.5. This is also the pH range of normal midcycle cervical mucus (28).

Our results indicate that vaginal contraceptives are effective even at an optimal pH for sperm migration in the cervix. Therefore, spermicidal activity does not seem to be influenced by the pH of the semen's environment in the vagina.

Effects of Semen Age and Temperature

Figure 23-1 illustrates the results of comparative studies of the effects of age of semen, room temperature (22 ± 1°C), and 37°C on six different contraceptive formulations. Statistical analysis of the data indicates that spermicidal potency was not affected by altering temperature when 30-min ejaculates were used. When 2-hr-aged semen was used, there was also no significant ($P < 0.05$) difference in the spermicidal potencies obtained for all formulations, with the exception of Ortho-Forms, a melting suppository tested at 37°C. A significant ($P < 0.05$) difference in the potency obtained for Ortho-Forms was found when semen was used 4 and 6 hr following ejaculation at room temperature and 2, 4, and 6 hr following ejaculation when tested at

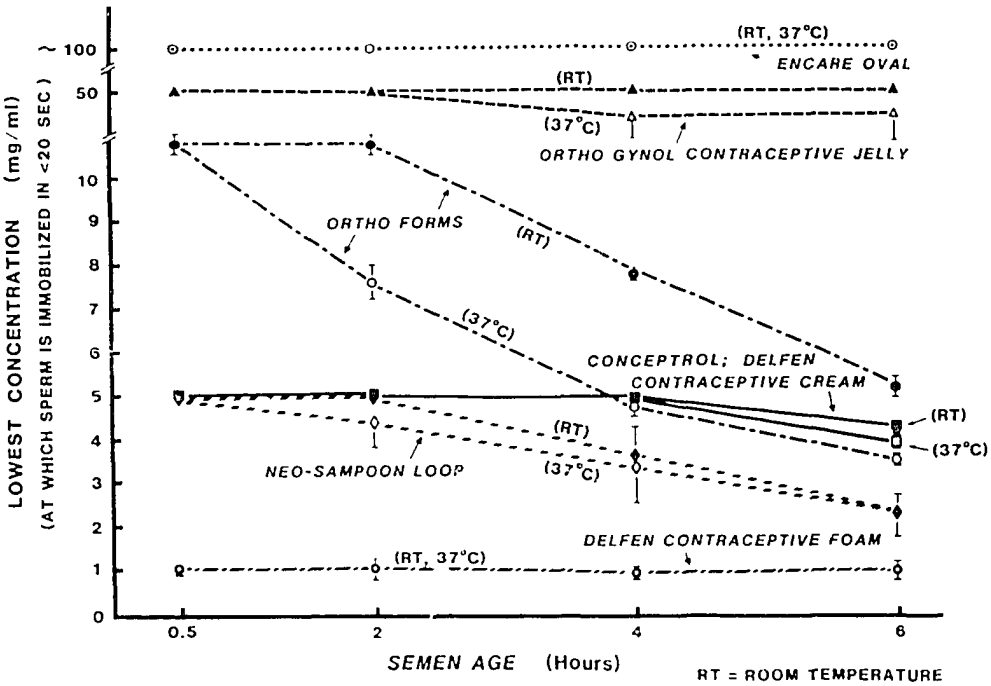

FIG. 23-1. Effects of semen age and temperature on spermicidal potency of six different contraceptives.

37°C. For Neo-Sampoon Loop Tablets, there was a significant ($P < 0.05$) difference found in the potency when semen was used 6 hr following ejaculation and tested at both temperatures. There was no significant ($P < 0.05$) difference in the spermicidal potency obtained for Delfen Contraceptive Foam, Delfen Contraceptive Cream (Conceptrol), or Ortho-Gynol Contraceptive Jelly, regardless of semen age or temperature at which they were tested. Encare Oval had no different spermicidal activity at the highest concentration of the test solution, regardless of semen age or temperature. The finding that altered temperature had no effect on spermicidal activity of any formulation with the exception of the Ortho Form melting suppository is consistent with the previous reports of Harris (20) and other investigators (8, 27). Because sperm are subjected *in vivo* to 37°C temperature, it may seem logical to subject them in the *in vitro* tests to spermicides at 37°C. However, we feel that it is not necessary to evaluate spermicidal potency at 37°C because evaluations conducted at room temperature using fresh ejaculates yield similar results and are more convenient.

Effect of Semen Donor Variations

As shown in Table 23-5, there are large differences in spermicidal potency of nonoxynol 9 between semen donors. Sperm from semen donor JK was the most susceptible to nonoxynol 9, whereas semen donor RP had the most

TABLE 23-5. Spermicidal Variations Obtained Between and Within Semen Donors for Nonoxynol 9

SEMEN DONOR (INITIALS)	μg/ml*
JK	115.8 ± 9.4
ML	121.2 ± 3 8
WM	125 8 ± 6 8
RG	134 8 ± 8.2
JG	143.0 ± 0 0
RP	152 8 ± 14.2

*Lowest (mean ± SE) concentration of nonoxynol-9 which immobilized sperm in <20 seconds (N = 4)

P < 0 05 JK vs. JG, JG vs. ML

resistant sperm. While there was no significant ($P < 0.05$) differences in the spermicidal potency obtained for nonoxynol 9 when tested on sperm from donors JK vs. ML, WM, RG, or RP, significant differences were found between donors JK vs. JG and ML vs. JG. Although variations in spermicidal potency were observed within each semen donor when tests were conducted on six different occasions over a one-year period, the difference was not significant ($P < 0.05$). The problem of semen variation among different donors has been pointed out by many investigators in the past (4, 6, 20, 27), and there appears to be no single solution. It has become our research practice to test each formulation with three different donors' semen in order to minimize variations due to "susceptible" or "resistant" sperm.

IN VIVO TESTING METHODS

The need for *in vivo* testing procedures for the evaluation of vaginal contraceptive formulations is well recognized. However, very little work had been done in this area until our laboratory proposed the first quantitative *in vivo* vaginal contraceptive evaluation procedure using the rabbit as an animal model (18, 22, 23).

While the anatomy of the rabbit vagina differs from that of the woman and the extrapolation of animal data to clinical efficacy can obviously not be known until valid comparative clinical data with the same products are available, studies indicate the rabbit has certain fundamental advantages over other laboratory animals. First, the rabbit ovulates in response to a copulatory stimulus. Thus, the animal is available for contraceptive experimentation at any time, with the time of ovulation known. With other laboratory animal species, special efforts must be made and experiments planned accordingly. Secondly, the fertility endpoint can be evaluated within a span of days, rather than in months required when other animals, such as the monkey, are used. Thirdly, the time interval between formulation insertion and coitus can be more precisely controlled. Finally, the model can be evaluated with much less effort and cost than with the monkey. While no animal model completely

simulates the conditions of human reproductive behavior, anatomy, and physiology, our experience with the rabbit has shown that this species provides valuable preclinical information which aids in evaluation and selection of potential new active ingredients and dosage forms. We have shown that this model lends itself to estimation of contraceptive potencies of various formulations and relationships between the relative roles of the active ingredient and the delivery vehicle in vaginal contraceptive potency (18).

Zaneveld *et al* (32) have recently described another animal model using a primate, the stumptailed macaque, to test the effectiveness of a vaginal contraceptive. Although this primate model might be considered an alternative to the rabbit model, its use for comparison of vaginal products seems limited due to the general unavailability of this primate species and the lengthy time involved for studies. However, more recent collaborative studies between our laboratories and that of Zaneveld suggest that the monkey might be more useful if contraceptive products were administered prior to mating, and a postcoital test were conducted to determine the viability of sperm in the vaginal cavity. This approach, because of the long gestation period of this species, would have practical advantages over the use of fertility data as the index of vaginal contraceptive efficacy (See Chap. 24 for a more detailed discussion).

EVALUATION OF SAFETY

GENERAL CONSIDERATIONS

The major goal of animal toxicity studies of vaginal contraceptives is to characterize the local and/or systemic functional and morphologic effects. Such information provides a guide for assessing potential human risk and delineating particular adverse effects which might warrant special monitoring in clinical trials.

Observations from animal toxicity studies suggest at least potential adverse effects in humans. On the other hand, recognizing that there are limitations in extrapolating animal toxicity data to humans is equally important. For example, toxicity in animals may sometimes reflect a drug effect related to specific physiologic or pharmacokinetic characteristics peculiar to that test species and not related to humans.

In the past, evaluation of vaginal contraceptives has been limited to vaginal irritation studies in rabbits and monkeys, which assess the potential for local tissue irritation without reference to systemic toxicity. However, toxicology is a rapidly evolving field, and many basic principles which are accepted today are based on information which was unknown even a few years ago. Toxicology has also been broadened to include the input of many other disciplines, such as molecular and cellular biology.

A number of recent studies have shown that the vagina has the ability to absorb and transport to the systemic circulation certain substances placed within it. Furthermore, it is well established that substances in the mother's blood stream may penetrate the placenta to some extent unless destroyed or altered during passage (15, 21). It is also possible that a pregnant woman

might use a vaginal contraceptive during early pregnancy, before she is aware of her pregnancy. Therefore, in addition to studying possible effects of a new vaginal contraceptive on the vaginal mucosa, today we also focus on four additional areas: 1) The safety of the nonpregnant or early pregnant user; 2) the safety of the conceptus through the embryonic stage; 3) the safety of the fetus up to birth; and 4) the safety of the neonate, should the ingredient be secreted in the milk.

With these points in mind, the objective of this section is to present the vaginal irritation test, which is routinely used at Ortho, and to provide an overview of the types of local and systemic safety studies which we feel should be considered when developing new vaginal contraceptives.

LOCAL TOXICITY (VAGINAL IRRITATION) STUDY

Because the rabbit vaginal irritation study which we use at Ortho is rather specialized and information on the method is not readily available in the literature, the detailed procedure will be described below. It is important to note that this test, when conducted over a prolonged period (up to 2 years), provides information not only about the potential for local irritation but also the potential for absorption and local carcinogenicity. Inasmuch as a vaginal contraceptive will be used over extended periods, one must always be cognizant of tissue changes other than those which we term irritation.

Obviously, local toxicity studies should ultimately be carried out in women as well as in animals. We believe, however, that animal screening tests should first be conducted in species with a vaginal irritation threshold which is lower than that of women. The vagina of the dog, rabbit, and monkey (3, 12) have been proposed as models and tested (as has the eye of the rabbit), but most have a variety of practical and theoretical disadvantages. The two methods which have been most fully explored and documented are the vaginal irritation tests in rabbits (performed in the Ortho laboratories) and monkeys (Birmingham University, England) (16). It has been shown that the rabbit is a good, albeit highly sensitive, animal model for testing agents for potential vaginal irritation (17). The greater sensitivity of the rabbit vagina may be due to the absence of the cornified epithelial layer, which is present in women and the monkey. Since the rabbit test is quicker, cheaper, more sensitive, and more easily conducted, it is generally considered preferable to the monkey test (17).

Vaginal irritation is determined after instillation of the vaginal contraceptive into the vaginas of at least three rabbits once daily for 10 days. The instilled dose is usually a multiple of the proposed human dose. Two or more additional rabbits are included as sham and untreated controls.

Rabbits are restrained on their backs while a rubber catheter attached to a dosing syringe is inserted into the vagina to a depth of approximately 4–6 in. As the product is expressed from the syringe the rubber catheter is steadily retracted. The method of delivery of the substance will vary with its nature (samples of foams, creams, suppositories, tablets, etc.).

Rabbits are sacrificed on the day following the last treatment (11th day) and the vaginas examined grossly, removed, and fixed in 10% neutral buffered formalin. Sections are taken through the proximal, middle and distal

portions of the vagina of each animal and processed for histopathologic evaluation.

The vaginal sections are evaluated for the condition of the epithelium (degeneration, metaplasia, erosion, and ulceration), the degree of leukocytic infiltration, edema and congestion. Each parameter is scored on a scale of 1–4, with a total of 16. Based on our experience, comparing scores in this test with observations in the clinics we consider total scores of up to 11 as acceptable and above 12 as unacceptable.

SYSTEMIC TOXICITY STUDY

With respect to questions about systemic toxicity, we believe that *new* vaginal contraceptive agents should be subjected to acute oral and vaginal toxicity (LD_{50}) studies in several species. If all of the LD_{50}, are of the same order of magnitude, it is probably safe to estimate a similar LD_{50} for humans (11). The presence or absence of systemic signs following any of these studies of the new vaginal contraceptive may be an early indication as to whether the material is absorbed from the vagina. Often a study of absorption is not done at this step of development because an assay method sufficiently sensitive to detect the presence in the blood stream of the vaginal contraceptive ingredient is not available.

If data on absorption are not available and there is some indication from the initial acute studies that absorption may occur, we believe an intravaginal subacute toxicity study should be conducted in which systemic evaluations are made to determine systemic toxicity including hematologic studies, clinical chemistry, and gross and microscopic pathology.

As mentioned above, a vaginal contraceptive might accidentally be used during the period of embryonic organogenesis; we believe, therefore, that any indication of absorption from the intravaginal route necessitates an evaluation of the teratogenic potential of the contraceptive product.

DISCUSSION AND CONCLUSIONS

The development of currently available vaginal contraceptive products made almost exclusive use of various *in vitro* spermicidal testing methods which had been established prior to 1962. The search to find better products continues and reexamination of the tests for evaluating new products is critical, to be certain that they can be applied safely. Thus, a test method which does not provide the comparative quantitative value has very little meaning to investigators who are searching for new improved products.

To establish some predictability and standardization in assay methodology, the two most commonly used *in vitro* spermicidal tests, the Sander-Cramer and IPPF Agreed Tests, were reevaluated. Among the factors examined which could have an influence on the results of spermicidal activities were the pH of the formulations, semen age, temperature, and semen donor variations.

Although the test solutions used in both procedures were generally acidic, there was no evidence that pH had an influence on the spermicidal activity.

TABLE 23-6. Methodological Differences between IPPF Agreed Test and Modified Sander-Cramer Test

VARIABLE	SANDER-CRAMER TEST	IPPF AGREED TEST
Semen quality	≥50 M/ml, 40–50% rapid forward motion	≥50M/ml, 40–50% rapid forward motion
Semen age	≤1 hour	≤4 hours
Semen donors	Minimum of 3	Minimum of 3, maximum of 6
Temperature	Room temperature (22 ± 1°C)	35–37°C
Testing solution	Serial dilutions	1gm/11ml
Mix time	5 seconds	10 seconds
Elapsed time	20 seconds	40 seconds
Slide preparation	Hanging drop	Slide plus coverglass
Endpoint	Greatest dilution that immobilizes sperm in <20 seconds	Must immobilize sperm From 3 or 5 of 6 donors
Confirmation	Average value of donors	Unable to revive motility with buffered glucose solution

Age of semen and temperature, however, had a significant influence on the spermicidal activity of Ortho-Forms (melting suppository) when semen was used 4 and 6 hr following ejaculation at room temperature, and at 2, 4 and 6 hr following ejaculation at 37°C. However, there was no significant difference in the spermicidal potency obtained for all six formulations regardless of temperature, when 30-min ejaculates were used. These studies support our criteria that fresh semen should be used, ideally within 2 hr after ejaculation, to assure consistent spermicidal results. While temperature may not have a critical influence on the spermicidal activity when fresh ejaculates are used, new dosage forms should initially be assayed at room temperature and 37°C to determine whether any unusual differences in spermicidal potency can be detected. Although the Sander-Cramer Test does not indicate the number of semen samples that should be used for each evaluation, our studies show that variability is more likely to occur among rather than within semen donors. When nonoxynol 9, the active ingredient contained in most of the products examined, was tested with semen from each of the six donors, a significant difference was found among donors, whereas the differences among samples from the same donor were not significant. It is now our research practice to test each formulation with semen obtained from three different donors in order to minimize variations (Table 23-6).

The development of a number of new barrier methods, such as spermicide-releasing sponges and spermicidal condoms are underway. Evaluation of such new products and even formulations such as foaming suppositories and tablets raise totally new questions some of which create a need for devising appropriate assay procedures. How much and at what rate is the spermicide released? Is the amount released enough to immobilize sperm? Do the sponges absorb semen? If so, what is the rate and capacity of absorption in relation to the mass of these sponges? Do these characteristics change in

the presence of cervical mucus? Those factors which have been found to influence current *in vitro* testing methods should be carefully considered when developing new assay procedures. For example, in our studies, Encare Oval (a foaming suppository) had relatively low *in vitro* spermicidal activity when compared to other formulations in the Sander-Cramer test and failed the IPPF Agreed Test when conducted under experimental conditions reported here. Another approach for testing Encare Oval was recently reported by Stone and Cardinale (30) who showed good spermicidal activity when foam generated from adding saline to Encare Oval was tested. Although this report did not quantitate the amount of foam tested, it may represent yet another method for evaluating this type of product. The authors also raise the question of the solubility of such a formulation *in vivo*.

In combination with an improved *in vitro* technique, we use an *in vivo* animal model in the selection of potential new active ingredients and dosage forms for future clinical evaluation.

In the safety evaluation, in addition to assessing topical effects, we have become increasingly aware of the need to study the potential for absorption from the vagina and the potential systemic effects of a product.

To date, the most fundamental questions pertaining to preclinical efficacy studies remain unanswered. Is there a direct correlation between preclinical efficacy as judged by various *in vitro* and *in vivo* test procedures and clinical efficacy as judged by valid clinical trials? To what extent does the barrier effect provided by the vehicle contribute to the overall clinical efficacy of the product?

The answers to these questions will certainly open new perspectives in the development of improved vaginal contraceptives. However, it is reasonable to assume that any product which can demonstrate high standards of *in vitro* and *in vivo* preclinical efficacy may also show similar effects in clinical trials.

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24

Animal Testing for Potency of Vaginal Contraceptives: Development of a Primate Model*

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INTRODUCTION

One of the important aspects in the development of new vaginal preparations is the use of an animal model in which to test the formulations before clinical studies are initiated—an essential step in the evaluation of formulations not yet approved for human use. Additionally, animal experimentation aids in assessing the potential usefulness of a compound before starting clinical trials. Finally, animal tests can be performed under much more stringent and carefully controlled conditions, so that the properties of the preparation can be estimated more accurately. Under clinical conditions, factors may be present that may lead to erroneous conclusions. For instance, the lapse of time from application of the compound until intercourse takes place, the time of the menstrual cycle during which the agent was used, and coital duration, are some of the human factors that are extremely difficult to control during clinical trials, particularly when the studies are carried out on a small number of subjects. It is also very difficult clinically to pair test and control subjects so that they are of approximately equal fertility. One is forced to rely on random selection, which may not always be accurate, especially when dealing with small groups.

After being found active in an *in vitro* screening test, vaginal spermicides should undergo further tests to assure that they are also active *in vivo*. The final test is the determination of the pregnancy rate when the compounds are clinically used. While there is no substitute for such studies, they are time consuming, very costly, require extensive organization, and are often unreliable unless performed with many individuals over an extended period of time. It is much more sensible to do such experiments first in animals to insure a good chance of success before initiating the clinical studies.

A good animal model for the evaluation of the effectiveness of vaginal contraceptives was not available until recently. Some experiments with the

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dog and rabbit as experimental animals were performed by Carleton and Florey (3) and Millman (9). More intensive studies were performed by Chang (4), who tested eight spermicides in the rabbit and found that none of the preparations were very effective in inhibiting fertilization and by Hartman (7), who claimed that the rabbit was unsuitable for these purposes. The rabbit was also used by Zaneveld *et al* (17) and Newell *et al* (10) to test the effectiveness of vaginal contraceptive preparations. Subsequently, Homm *et al* (8) and Greenslade *et al* (6) seriously attempted to develop the rabbit as an animal model for the *in vivo* evaluation of vaginal contraceptives. A correlation was found between the *in vitro* spermicidal activity of the three compounds tested (Delfen Contraceptive Foam, Delfen Contraceptive Cream, and Preceptin Contraceptive Gel)* and their contraceptive activity in the rabbit. It was concluded that the rabbit appeared to provide a suitable model to determine the relative *in vivo* potency of vaginal contraceptive preparations.

A concern that is always expressed when using the rabbit, dog, or any other nonprimate for this type of work is that there may exist significant differences in the reproductive processes between these species and the human being. The only species which has a reproductive tract similar to that of the woman and which cycles in the same fashion is the nonhuman primate. Thus, unless one uses the human or the nonhuman primate in an *in vivo* study, the validity of the results, as they apply to women, may be open to question. Therefore, in our laboratory, we decided to study the primate for the purpose of evaluating the effectiveness of vaginal contraceptives *in vivo*.

SELECTION OF THE PRIMATE

The first obstacle was the aggressiveness of most primates. In order to conduct the studies correctly, it is essential that the female animal is not anesthesized or tranquilized during the insertion of the formulation into her vagina so that she can mate immediately. A short interval between the insertion of the vaginal preparation and breeding is necessary to measure the optimal effectiveness of the formulation because, with time, some of the preparation may leak from the vagina, or may be locally inactivated. To insert the formulation correctly, the female needs to be bent over, an applicator inserted into her vagina as deep as possible then slowly withdrawn while ejecting the preparation from the applicator. It is almost impossible to do this with the primates that are usually employed for laboratory research, *i.e.*, the *Macaca mulatta* (rhesus monkey), the *Macaca fascicularis* (cynomolgus monkey) or the papio species (baboon). These primates are so aggressive that handling them is difficult unless the animals are trained for long periods of time.

Optimally, the male should start the coital act as soon as the female is placed in his cage, so that little chance exists for precoital loss of the spermicide. Additionally, prolonged intercourse should be avoided because this

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may also cause loss of the preparation from the vagina and thus decrease its contraceptive effectiveness. Finally, the coital act should take place under supervision so that the primates can be separated immediately after ejaculation and the vaginal fluid collected for examination. Commonly used laboratory primates often wait a long time before mating and frequently do not do so under supervision.

However, the *Macaca arctoides* (stumptailed macaque), a less commonly used primate, appeared to satisfy the conditions. The females are generally cooperative and can readily be handled without much training. The males breed as soon as the female is inside their cage, normally within 2–3 min. A further advantage of this species is that the females conceive readily under caged conditions. The College of Medicine of The University of Illinois, in Chicago, has a colony of stumptailed macaques and the use of this primate for the study of vaginal experimentation was evaluated.

FERTILITY EXPERIMENTS

Our first experience was directed primarily to the fertility aspect, *i.e.*, the ability of some agents to prevent pregnancy (15). The stumptailed macaque proved to be an excellent animal model for these studies from a handling standpoint. It was friendly and cooperative. An occasional problem was that the male did not let the female go after coitus. Since the animals were in a squeeze cage, however, separation could be readily achieved.

The experiments consisted of inserting the vaginal preparation four times each day during the midcycle period, and breeding the female each time after insertion (15). After each coital act, the male and female were separated for about 1.0–1.5 hr, following which the insertion and breeding were repeated. The midcycle period of the animal was estimated from the time of menstruation because the stumptailed macaque ovulates approximately 12 days after the onset of menstruation (12). Thus, the breeding experiments were performed for 5 days, starting with the 9th day after the onset of menstruation. The 1st day of menstruation was found by swabbing the vagina of the animals. The contraceptives were applied with a 3 ml syringe from which the tip had been removed. The syringe was placed as deep into the vagina as possible, next to the external cervical os, and was withdrawn slowly while the product was being ejected. The size of the stumptailed macaque vagina was found to be approximately 15% to 25% that of the human vagina. Thus, 25% of the woman's dose was employed, *i.e.*, 1 ml.

The products studied were K-Y Jelly (Johnson and Johnson, New Brunswick, New Jersey), a neutral lubricant vaginal jelly, and Delfen Contraceptive Cream. Both male and female animals were of proven fertility. Detailed breeding records were available on the females so that it was known how many times the females had become pregnant and how many breeding cycles were required for pregnancies to occur. The relative fertility of each animal could thus be assessed. This was expressed as the Fertility Quotient (FQ), calculated as follows.

$$FQ = \frac{\text{Total number of pregnancies}}{\text{Total number of breeding cycles required to obtain these pregnancies}} \times 10$$

The FQ was calculated for each animal and was used in conjunction with the number of times that each primate had been pregnant, to separate the animals into groups of equal fertility, consisting of six animals each. The FQ is a good index of fertility and its use in breeding colonies may provide a uniform method to describe the relative breeding ability of the animals.

All the animals that received the K-Y jelly became pregnant in the first breeding cycle, with the exception of one that never became pregnant. This primate probably developed some kind of genital tract pathology, and it was removed from the study. The experiments with Delfen Cream were repeated approximately 1 yr apart with two different groups of animals, and essentially the same results were obtained. During the 1st yr, three of the six females became pregnant, after two, three, and four breeding cycles, respectively. During the 2nd yr, four of the six monkeys became pregnant, after two, two, three, and four breeding cycles, respectively. Thus, a large difference was present between the conception rate obtained in the K-Y jelly (control) series and in the series with Delfen Cream. The suitability of the stumptailed macaque as an animal model for the study of contraceptive effectiveness was, therefore, demonstrated.

Additional fertility studies were performed in this animal model to determine if inhibitors of acrosin (a sperm enzyme essential for the fertilization process) could also prevent conception (14). A total of six different groups of animals were used and the results further emphasized the usefulness of the stumptailed macaque for measurement of the contraceptive activity of vaginally placed formulations (see section on Other Considerations).

POSTCOITAL EXPERIMENTS

Although the fertility experiments demonstrated that the stumptailed macaque was a good animal model to evaluate the contraceptive activity of vaginal formulations, they did not show that the primate could also be used for postcoital spermicidal tests. Even though they are less expensive than clinical tests, primate fertility experiments still require approximately 1 yr to perform and are costly. Before entering into such studies, it is useful to have a good appraisal of the *in vivo* effectiveness of a vaginal spermicide. Even though a preparation may have high *in vitro* spermicidal activity, this may not be the case in the vagina, as our results indeed showed. It is advisable to test the spermicidal activity of a vaginal formulation *in vivo* before fertility experiments are initiated. Thus, subsequent experiments were performed aimed at studying the stumptailed macaque for this purpose.

Preliminary postcoital tests with the stumptailed macaque were reported by Zaneveld *et al* (15), but only one agent (Delfen Contraceptive Cream) was used. The experiments performed showed that, as expected, a decrease in the spermicidal activity of the Delfen Contraceptive Cream occurred when an animal was mated repeatedly without reinserting the precoital dose of the

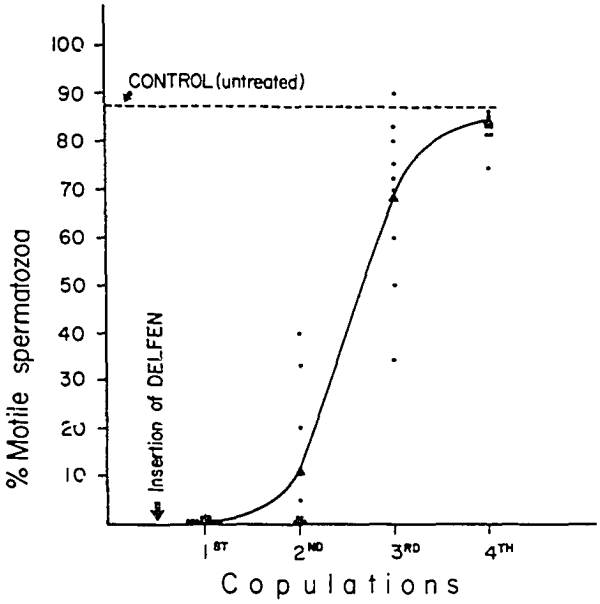

FIG. 24-1. The antimotility effect of Delfen Contraceptive Cream on repeat breeding without reinsertion of the cream. All coital events were 30–45 min apart. Spermatozoa were collected immediately after each copulation. △-△ average of nine different experiments. (Zaneveld LJD, Bhattacharyya AK, Kims DS: Am J Obstet Gynecol 129:368, 1977)

cream. The decay of the spermicidal activity followed a sigmoidal curve (Fig. 24-1) indicative of the loss of spermicidal activity on repeat breeding. The more slanted the curve, the longer the preparation remains active after subsequent intercourse without reinserting another dose. Comparisons of the curves obtained after testing various formulations will show which of these preparations has the longest lasting effectiveness on repeat intercourse without inserting a new dose.

More extensive postcoital experiments were needed, however, comparing a number of vaginal formulations at various concentrations in order to establish if the stumptailed macaque could be utilized as an animal model to compare the spermicidal effectiveness of different formulations during a single coital act. This was done recently (18). In this study, several different vaginal preparations were compared: Delfen Contraceptive Foam*, Delfen Contraceptive Cream*, Preceptin Contraceptive Gel*, and Encare Oval Suppository†. Four different levels of the products were tested to determine if dose-response curves could be obtained. The formulations were inserted by the method described previously. The animals were bred immediately, except in the case of the suppository because the manufacturer recommends a 10-minute wait before coitus. This interval was observed. The animals were separated immediately after coitus and the vaginal fluid was collected by entering a tuberculin syringe with 0.2 ml of physiologic saline into the vagina until it reached the cervix. The saline was injected and suction was applied with the syringe while slowly removing it from the vagina. The small amount of saline proved useful in recovering ejaculated spermatozoa because the

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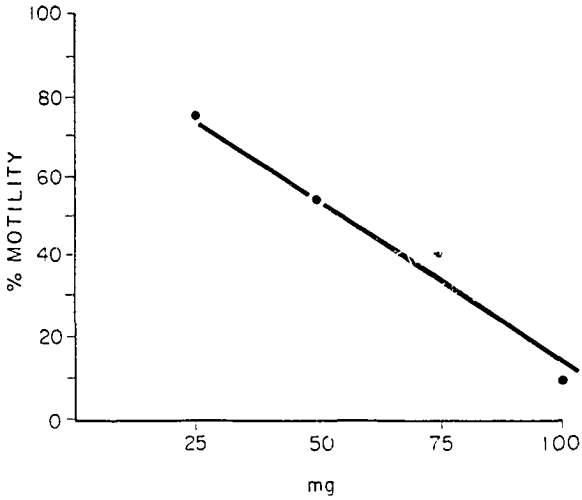

FIG. 24-2. Typical example of a dose response curve obtained with a test compound placed vaginally before coitus (see text for experimental detail). Each point represents the mean of six different experiments.

fluid portion of the ejaculate of a primate is often very small (0.1 to 0.5 ml). A drop of the collected fluid was immediately placed on a slide and observed for motility by counting 100–200 spermatozoa.

Significant individual variations were obtained. At a certain dose level of a preparation, one animal may show as much as a 60% higher sperm motility than is seen in another animal. This is not surprising because the effectiveness of a formulation depends on its distribution in the vagina, the volume of the ejaculate, the sperm concentration, and possibly some other factors. Therefore, the relative contraceptive potency of a formulation varies with each coital event. The higher the dilution of the preparation, the greater the variability. With an excess of formulation, at the higher dose levels, such individual variations largely disappeared.

When the data of a group of animals were averaged, consistent results were obtained, however. It was found that an average of six individual experiments produced repeatable results. This was tested by repeating the experiment at the same dose level several weeks later. Each time, almost exactly the same results were obtained. Additionally, a dose between two previous dose levels was tested. This was performed three times with different preparations, and each time the results fell almost exactly on the line connecting the results at the other two dose levels. When the averaged data are plotted, dose-response curves are obtained from which the relative activity of the compounds can be calculated using the parallel-line assay (5). Besides the compounds mentioned above, five others have been evaluated in a similar fashion, each giving smooth dose-response curves. A typical example of such a dose-response curve is shown in Figure 24-2. According to this, the stumptailed macaque seems to be an excellent animal model to study the postcoital spermicidal activity of vaginal formulations.

In vitro experiments with the formulations using a modification of the Sander-Cramer test (11) showed that the primate spermatozoa (collected from the stumptailed macaque by electroejaculation) were equally as sus-

ceptible as human spermatozoa to the spermicidal activity of Delfen Contraceptive Foam, Delfen Contraceptive Cream, and Preceptin Contraceptive Gel. Interestingly, the formulation that required time to dissolve in the vagina, *i.e.*, the Encare Oval Suppository, showed some difference between its *in vitro* spermicidal activity towards human and primate spermatozoa. To produce the same decrease in percent motility of the human spermatozoa as was needed for the primate spermatozoa, approximately a ten times higher concentration of the Encare Oval preparation was required. It is possible that the vehicle causes this differential effect.

The relative *in vitro* spermicidal potency of the preparations does not run parallel with their postcoital effectiveness. For instance, a compound that was less active than the Delfen Contraceptive Cream under *in vitro* conditions was more active in the postcoital experiments. Furthermore, in collaboration with Drs. N. Alexander (Oregon Primate Research Center, Beaverton, Oregon) and F. J. Trapani (Walla Walla, Washington), sixteen vaginal formulations prepared from natural substances were tested. All of these had shown good spermicidal activity *in vitro*. However, in the postcoital test, only a few of the natural preparations proved to be active spermicides. These results emphasize the need for postcoital tests before beginning fertility experiments.

OTHER CONSIDERATIONS: NEW VAGINAL CONTRACEPTIVE AGENTS

Presently available vaginal contraceptives have a failure rate associated with different formulations (1). As described in other chapters of this book, several methods can be used to decrease such a failure rate. All these methods aim at improving the spermicidal activity of the agents or their method of delivery. However, because of the nature of the reproductive process, spermicidal activity alone may never be sufficient to provide a high degree of contraceptive effectiveness. It would appear useful to incorporate agents into the spermicidal preparations that work on an entirely different principle.

In a previous publication (2), we discussed the use of agents that prevent the liquefaction of the seminal coagulum. A large number of spermatozoa are often trapped in the coagulum, and if its liquefaction were interfered with, penetration of these spermatozoa into the cervix would be prevented. Additionally, this would allow more time for the spermicides to affect the spermatozoa. Another agent that may be incorporated in a vaginal suppository is one that alters the physical properties of the cervical mucus so that sperm penetration is no longer possible or is severely delayed. Neither antiliquefaction nor anticervical mucus penetration agents are presently available for testing but it is important to consider and explore these research possibilities.

A third type of agent is one that, once bound to the spermatozoon, prevents its union with the female gamete (egg). Research in this area has shown very encouraging results. Spermatozoa, in order to pass through the zona pellucida of the egg require the activity of acrosin, a proteinase located in the sperm acrosome (16). In nonhuman primate species, synthetic, low-

molecular-weight acrosin inhibitors have been shown to prevent fertilization when mixed with sperm or when placed in the vagina before coitus (15).

Recently performed experiments with synthetic acrosin inhibitors, using the primate as an animal model, and employing the experimental fertility test protocol described previously in this chapter, showed that one acrosin inhibitor, p-nitrophenyl-p'-guanidino benzoate (NPGB), had high contraceptive activity when applied vaginally (14). When mixed with K-Y jelly at concentrations of 0.09 mg/ml, this compound was equally as effective as Delfen Contraceptive Cream. Interestingly, another inhibitor, N-α-p-tosyl-L-lysine chloromethylketone (TLCK), which was a highly effective antifertility agent when placed vaginally in the rabbit, had little contraceptive effect in the primate. This illustrates the species differences that can occur when testing vaginal preparations, and emphasizes the need for using an animal model that is closely related to man. Toxicity experiments in mice showed that the three acrosin inhibitors tested, NPGB, aminobenzamidine, and benzamidine, had LD_{50} values of, respectively, 180, 240, and 580 mg/kg. The toxic dose of these compounds is between 1,000 to 10,000 times greater than the dose at which they exert vaginal contraceptive activity; this fact encourages the continued study and development of these agents. Present efforts in our laboratory are aimed at developing inhibitors that are specific for acrosin.

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25

In Vivo Testing of Intravaginal Contraceptives

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VIRGINIA E. JOHNSON-MASTERS

In recent years the limitations and adverse side effects of oral contraceptives and IUDs have been well documented. Consequently, increased public and research interests have been directed toward intravaginal chemical or mechanical barrier contraceptive agents. To aid in the evaluation of intravaginal contraceptive agents, a controlled *in vivo* testing technique has been developed by investigators at the Masters and Johnson Institute. This technique is designed to assess the contraceptive efficacy of intravaginal contraceptive products under carefully controlled *in vivo* conditions. The proposed study mode should be employed only after *in vitro* testing of an intravaginal contraceptive product has been completed, and before the product has been released for testing in clinical settings.

Although *in vitro* studies lead to valuable information about the spermicidal capacity of chemical contraceptive agents, such testing approaches are limited in the following ways: 1) concentrations of the contraceptive agent to which spermatozoa are exposed are not always equivalent to concentrations of the contraceptive material within the vagina; 2) assessment of interactions between the microbiologic or biochemical environment of the vagina and the contraceptive agent is difficult—these interactions may either reduce efficacy, produce a synergistic effect, or entail no alteration in efficacy; and 3) unique anatomic and mechanical aspects of *in vivo* contraceptive use that may modify efficacy cannot be adequately evaluated by *in vitro* methods.

In vitro techniques are unsatisfactory for evaluation of mechanical barrier methods designed for intravaginal contraceptive purposes, because laboratory techniques have been inadequate for replicating the varying degrees of involuntary distention of the vaginal barrel occurring during sexual stimulation (5).

Commonly used evaluation techniques sometimes overlook other important factors influencing contraceptive efficacy. For example, conducting studies at different time intervals after the insertion of the contraceptive agent into the vagina is vital, because in actual usage, the duration of time from contraceptive insertion to intravaginal ejaculation varies considerably from one couple to another as well as for the same couple on different occasions.

In such circumstances, the efficacy of the contraceptive product is influenced not only by the expected chemical effect of the agent on the intravaginal environment, but also by alterations in intravaginal distribution of the contraceptive material due to changes in coital positioning, levels of sexual excitation (with consequent variations in degrees of vaginal vault expansion and lubrication production), and redistribution of contraceptive material occasioned by marked differences in penile thrusting patterns. Furthermore, because in actual practice a couple may have coitus (and intravaginal ejaculation) more than once during a given time period, evaluation techniques must also consider the effectiveness of a contraceptive method when seminal fluid is introduced intravaginally two or more times within a specified time interval.

IN VIVO MODEL

The first report of an *in vivo* study of intravaginal chemical contraceptives using artificial coital techniques was published in 1962 (1). Further reports followed in 1963 (2), and 1970 (3). The following is a description of the controlled *in vivo* testing technique used at the Masters and Johnson Institute.

SELECTION OF FEMALE STUDY SUBJECTS

Women between the ages of 21 and 45 who have had tubal ligations are recruited as study subjects. Volunteers complete a screening questionnaire containing data about current and past medical history, menstrual cycle, contraceptive use, and pregnancy. Each potential study subject listens to a tape recording describing the purposes and investigative methods and procedures of the project, method of payment, and risks of participation. A physician investigator then interviews the prospective participant and answers whatever questions she may have. If the woman then gives her written informed consent to participation, she will proceed to the second phase of screening.

Each potential study subject undergoes a number of laboratory tests to determine general state of health. These include a complete blood count; blood type, serologic test for syphilis; erythrocyte sedimentation rate; 20-channel chemistry screening profile (Technicon SMAC), including glucose, BUN, creatinine, sodium, potassium, chloride, uric acid, calcium, inorganic phosphorus, iron, total protein, albumin, cholesterol, triglycerides, total bilirubin, alkaline phosphatase, glutamate oxalacetate transaminase (GOT), lactate dehydrogenase (LDH), glutamate pyruvate transaminase (GPT), creatine phosphokinase (CPK); thyroxine; serum estradiol and estrone; serum testosterone; serum sperm-agglutinating antibody test; urinalysis; pregnancy test; vaginal culture; and vaginal cytology. Hormone determinations are done by radioimmunoassay methods; the sperm-agglutinating antibody test is done by a modified Franklin-Dukes method.

Each prospective study subject undergoes a complete physical examination. Women are excluded as study subjects for the following indications:

1. Use of prescription medications on a regular basis
2. Current use of illicit drugs
3. Anemia (hematocrit below 33% or hemoglobin less than 12g%)
4. Endocrine disease: diabetes mellitus, thyroid dysfunction, other known endocrine disorders
5. Hepatic or renal disease
6. Cardiovascular disease
7. Vaginal infection
8. Amenorrhea or other significant menstrual disorders
9. Abnormal pap smear or dysfunctional vaginal cytology

In the selection of female study subjects, parous women are specifically included (along with nulliparous women), because in the parous woman, the vaginal barrel generally is enlarged, which might cause intravaginal distribution of a chemical contraceptive to be more problematic, and placement of a mechanical barrier device to be less secure.

Each study involves a group of 15 female subjects. To insure a final group of 15, and to protect against invalidation of study results, owing to incomplete data, intercurrent health problems in a subject, or withdrawal of a subject from the study, 20 women are initially recruited and evaluated.

SELECTION OF MALE DONORS

Male donors, aged 18 to 35, are also recruited from the community. Donors are screened for health problems by the use of a medical history questionnaire, a physical examination, and a laboratory evaluation. The laboratory screening includes a complete blood count, blood type, serologic test for syphilis, 20-channel chemistry screening profile, thyroxine, serum testosterone, urinalysis, and seminal fluid examination for sperm count, evaluation of motility and morphology, and seminal fluid culture. Seminal fluid from donors is checked against serum from female study subjects to be certain that sperm-agglutinating antibody reactions do not occur.

Only donors with sperm counts of 40 million/ml or higher who have no current health problems are accepted as sperm donors. Additional criteria are evidence of fewer than 15% immotile sperm per ml ejaculate, less than 5% abnormal sperm forms, and a seminal fluid volume of not less than 2.5 ml. Cultures of specimens from the potential donor's urethra and seminal fluid are obtained before he is admitted to the investigative program.

Purpose and details of the study are explained to the donor, and he is required to give written informed consent. At least 30 male donors are selected for possible study participation.

OVULATORY CERVICAL MUCUS

The availability of ovulatory mucus is a necessary requirement for any clinical test of sperm penetration of cervical mucus. Theoretically, cervical mucus is penetrable for approximately 3 days of each menstrual month. Tests are

routinely scheduled for each study subject on only two days of a menstrual month. In some woman, however, a number of months of observation are necessary to determine individual variability in the timing of ovulation. Only one test is conducted with each study subject in any 24-hr period.

Testing sperm penetration of cervical mucus is of little value unless ovulation has occurred. To ascertain this occurrence, the following techniques are employed. Ovulation is anticipated from routine use of vaginal cytology. Prior to experiments, the cervical mucus is checked for the spinnbarkeit phenomenon. After the 2-day testing period per each menstrual month has been completed, blood is drawn to determine LH and serum progesterone levels. If hormonal indications of ovulation are inconclusive or negative, the statistics from the particular testing period are discarded.

METHODS

Each female study subject is tested on 11 occasions for each contraceptive product evaluated. The first test is a physiologic Sims-Huhner test, during which a seminal fluid specimen is injected intravaginally without the prior insertion of any contraceptive agent. This test controls for the possible presence of an intravaginal lethal factor that would render meaningless the results of contraceptive-use data (4). During this test, specimens are withdrawn from the vagina and the external cervical os at 1 min, 5 min, 10 min, and 20 min, to ascertain the presence of spermatozoa and estimate the degree of motility. The physiologic Sims-Huhner test is conducted only during an estimated period of ovulation.

The study subject is given the contraceptive product and the packaged commercial literature describing its use and, after reading the instructions, she inserts the contraceptive material intravaginally while in a supine position. The insertion technique is observed and recorded by a paraprofessional investigator, but no coaching or answering of questions is allowed. If the material is incorrectly inserted, this is noted, but testing continues in a routine manner. Timing of the individual experimental episode begins as soon as the product is inserted. A semen specimen is mechanically injected into the vagina at specified time intervals in a short series of spurts simulating ejaculation, with deposition of semen sequentially in the vaginal cul-de-sac, in the midvagina, and towards the vaginal outlet. Deposition of semen occurs at 1 min, 5 min, 10 min, 15 min, 30 min, and 60 min after insertion of contraceptive material (Table 25-1). Four additional experiments are conducted. In two of these experiments the study subjects are inseminated in the female-superior coital position because varied coital positions may influence distribution of the intravaginal contraceptive or the positions of a mechanical contraceptive device as well as patterns of seminal fluid deposition. The first of the female-superior depositions takes place at the 10 min interval, and the second at the 15 min interval. In the final two experiments, a second semen specimen is utilized in each case to simulate repeated coitus and ejaculation. The first specimen is injected at 10 min and the second specimen is injected at 2 hr in one test and 6 hr in the other test. By these measures the range of contraceptive effectiveness can be more definitively determined.

TABLE 25-1. Screening Schedule for Intravaginal Testing of Contraceptive Products

TIME INTERVALS FOR SEMINAL FLUID DEPOSITIONS (ROUTINE SCREENING)*	
1 min	15 min
5 min	30 min
10 min	60 min

**Five additional tests are performed*

1) The initial Sims-Huhner test to insure absence of vaginal lethal factor.
2) 10-min test with subject in female superior coital position
3) 15-min test with subject in female superior coital position
4) Multiple seminal fluid depositions (10 min and 2 hr)
5) Multiple seminal fluid depositions (10 min and 6 hr)

The ten tests of spermicidal efficacy and the initial Sims-Huhner control test total 11 specific investigative episodes per female study subject for each contraceptive product evaluated. For each study subject and each test, an experimental log is maintained. On each occasion, a pre-experimental vaginal smear is taken to check for the presence of spermatozoa, infection, or other factors. Characteristics of the specific seminal fluid specimen to be used in the test are recorded, including seminal fluid volume, sperm count, and estimated sperm motility (rated on a 4-point scale). Only seminal fluid produced one hour or less before onset of the specific test episode is used.

Coitus is simulated by the use of dildoes for 3–4 minutes immediately before intravaginal deposition of the seminal fluid specimen. With the 1 min test only that amount of dildo usage is involved. The subject's attainment of orgasm is noted.

When measuring results, three intravaginal specimens are withdrawn immediately after deposition of semen. These samples, taken from the cul-de-sac, transcervical area, and vaginal outlet, provide information as to continuing sperm motility and presence or absence of sperm clumping. Immediately after the three vaginal samples have been obtained, a specimen also is taken from the external cervical os. Vaginal specula have been specifically designed that enhance exposure of the intravaginal area without significant displacement of the vaginal contents.

After each testing session, the study subject is interviewed by a female professional staff member for subjective data. Included in the questions are specific requests for personal interpretation of the aesthetic qualities of the particular intravaginal contraceptive method tested. Following the testing episode, the study subject undergoes a thorough douching routine after which vaginal smears are examined to check for sperm presence and the status of

TABLE 25-2 Screening Schedule for Intravaginal Testing of Contraceptive Products

TIME INTERVALS FOR SEMINAL FLUID DEPOSITIONS (IN-DEPTH PRODUCT EVALUATION)*	
0.5 min	15 min
1 min	30 min
2 min	60 min
5 min	75 min
8 min	90 min
10 min	105 min
12 min	120 min

**Five additional tests are performed*

1) The initial Sims-Huhner test to insure absence of vaginal lethal factor
2) 10-min test with subject in female superior coital position
3) 15-min test with subject in female superior coital position
4) Multiple seminal fluid depositions (10 min and 2 hr)
5) Multiple seminal fluid depositions (10 min and 6 hr)

the contraceptive material. The study subject is not released until the vagina has been thoroughly cleansed.

DATA ANALYSIS

Data analysis is routinely conducted using standard methods, including chi-square testing, analysis of variance, and other suitable techniques.

IN-DEPTH SCREENING

The techniques described above have been designed to screen and compare a multiplicity of intravaginal contraceptive agents. Yet another clinical application exists. This type of *in vivo* evaluation technique is useful when an intravaginal contraceptive technique is in the process of development and the developers want an in-depth study of product strengths and weaknesses.

The in-depth study is conducted with study subjects recruited, evaluated, and controlled as described above. However, a more detailed schedule is used so that the product may be evaluated in far greater depth (see Table 25-2).

In addition, 1 hr and 6 hr tests are conducted using two sperm specimens, and 10 min and 2 hr tests are conducted with the subject in the female-superior coital position.

SUMMARY

The current practice of releasing an intravaginal chemical or a mechanical barrier contraceptive product to public consumption without establishing its efficacy *in vivo* should be reconsidered. Reasonably effective methods are available to conduct such *in vivo* studies and if conducted routinely, they would provide an additional dimension of contraceptive protection for the consumer.

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CLINICAL TRIALS

26(2)

26

Clinical – Effectiveness Studies of Vaginal Contraceptives

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Phase I and II testing of contraceptives gives some estimate of their potential for preventing pregnancy, but the final measure of clinical effectiveness must be obtained through clinical trials in which many couples use the method over a period of time. These studies also yield other data, including side effects that may not have been apparent in the preliminary trials, as well as consumer acceptance of the method under investigation.

Studies of this type may appear to be simple clinical experiments in which a number of couples volunteer to use a particular contraceptive under close supervision of monitors, who record the number of subjects who become pregnant, the types of side effects that occur, and the reasons why the participants may decide to stop using the product. In fact, there are a number of variables in the design and execution of the study that may alter the outcome of the investigation. These include the study population, the investigational staff, and the interaction between these two groups. While these factors are important in any clinical study, they are particularly significant in the evaluation of vaginal contraceptives, whose successful use depends heavily on the compliance and motivation of the subjects involved.

This chapter will consider the ways in which these variables can combine to influence the apparent efficacy of the vaginal method being investigated.

EFFECTIVENESS OF VAGINAL CONTRACEPTIVES: TERMINOLOGY

Contraceptors may become pregnant because they do not use their method, because they use it incorrectly, or because the method fails even though it is used exactly according to instructions. Pregnancies that occur for the first two reasons are considered to result from "patient failure," while those that occur for the third cause are considered to be due to "method failure." This conventional terminology about pregnancy can be restated in the following way:

Psychological failure:	occurs because contraceptor failed to use the method
Procedural failure:	occurs because contraceptor used method incorrectly
Physiologic failure:	occurs because method did not protect against pregnancy even though it was used correctly

In the case of the barrier methods, it may be difficult to differentiate between a procedural failure and the other types, but it is an important distinction. Poor motivation may lead to improper use, but it can result from inadequate instruction by clinic or office personnel or from inadequate package inserts.

Theoretical-effectiveness refers to the pregnancy rate obtained for those participants in a study who always use the method correctly, *i.e.*, only those pregnancies due to method failure are counted. This measurement reflects the biological effectiveness of the method. *Use-effectiveness* refers to the overall pregnancy rate, including pregnancies from all causes.

Theoretical- and use-effectiveness are identical for tubal sterilization, they are similar for those contraceptive methods that require little or no motivation for the contraceptive to be successfully, such as the IUD, but in the case of vaginal contraceptives [illegible] large disparity between theoretical- and use-effectiveness [illegible] may vary depending on the way studies are planned and conducted. The following discussion will deal with some of the factors that can [illegible] results of a clinical trial and that should be considered when data are interpreted or studies are designed.

STUDY SUBJECTS

[illegible] groups are involved in the conduct of a clinical trial, the study subjects [illegible] the investigator's staff. The women participating in contraceptive trials [illegible] usually must be within the reproductive age group, must be sexually active, of proven fertility, and have normal menses. These criteria are used to [illegible] that the participants are capable of becoming pregnant and are regularly exposed to the risk of pregnancy. Within these guidelines there is still considerable leeway for selection by the investigator, and the selection process can influence the outcome of the study.

SELECTION OF SUBJECTS

There is relatively little information about the performance of nulligravid women in prospective studies of vaginal contraceptives. One could speculate that the pregnancy rate would be high because the group would contain many young women in their early reproductive years who might lack the motivation to use a vaginal method successfully, and, in general, contraceptive failure rates are higher for younger women (10, 11). On the other hand, the group would also include women in their twenties and early thirties who have conscientiously avoided pregnancy in order to continue their education or pursue a career and who would tend to be careful contraceptors. In addition to the variable of motivation, there may be biologic differences between nulligravid women and those who have been pregnant that may cause them to have a high or low rate of failure while using a barrier method.

The error incurred by using subjects of unproven fertility would depend on the incidence of unsuspected infertility in the group selected. There can be a similar type of error even in the population of women with "proven" fertility, because this criterion means only that the individual had a pregnancy

sometime in the past, but not that the individual or her partner are fertile at the time of the study. Some of the women may have become infertile in the time between their last pregnancy and their enrollment in the investigation. Generally no inquiries are made about the fertility of the male partner, who may also have had a decline in fertility or may not be the person who fathered the subject's last child.

Nulligravid women should be included in clinical contraceptive trails. The potential subjects can be screened to eliminate those with a probable cause of infertility, such as a history of severe salpingitis or oligomenorrhea. If the study were large enough, the data for this subgroup could be analyzed separately in addition to including them with those of the total study population.

EXPERIENCE WITH THE METHOD

A study of a barrier method could be biased if a large number of the patients had used the same or a similar method for a substantial period of time. The group would be preselected for successful users because those who had become pregnant would have been previously eliminated from the population. The removal of the careless users would improve the use-effectiveness of the method, but if this were the only factor involved, one might correctly interpret the data. The major error would be that many of the early physiologic failures would also be screened out, which would lead to an apparent improvement in the theoretical-effectiveness of the product under study.

Some consideration must be given to previous users both in patient selection and in data interpretation. This is particularly important if the product being studied is one that is already on the market. Excellent results would be expected if all of the study subjects had used the product for a long time before they enrolled in the clinical trial. The study design may include the contraceptive history of the study population, but this information is not usually taken into account in the interpretation of the data.

MOTIVATIONAL FACTORS

Motivation is an important factor for the successful use of a vaginal method of contraception. If the study population contains a large proportion of women who are poorly motivated, there will be a high failure rate. This would not only decrease the use-effectiveness rate, but it could also change the apparent theoretical-effectiveness rate, because it is not always possible to distinguish between physiologic and other types of failures.

It is possible to introduce some bias with the selection methods. There is a natural tendency to recruit subjects who seem reliable and conscientious, because they are more likely to continue in a study and not be lost to follow-up. These subjects may also be more apt to use the method correctly.

Another factor is the subjects' plan for future pregnancies. Those couples trying to space, or delay, a pregnancy are more likely to have a contraceptive failure than those attempting to prevent further childbearing (10, 11), al-

though this may be influenced by other variables, such as age and the length of time the subjects have used their contraceptive method (12). The study design should provide some information about the contraceptor's plans for future pregnancies. The obviously casual user would be considered unreliable and probably would not be enrolled, but some guide to the motivation of those who do participate may be useful in interpreting the results of the study.

INTERACTION BETWEEN RESEARCH STAFF AND PATIENTS

The conduct of clinical studies may be significantly affected by four factors: 1) the attitude of the staff members toward the contraceptive product; 2) the care they use in instructing the subjects; 3) their attitude toward the study population; and 4) the attention they give to the follow-up of the participants.

ATTITUDE OF STAFF TOWARD THE PRODUCT

The staff must convey confidence in the method while being frank in explaining that the effectiveness of the product depends on how carefully the subject follows instructions. If patients do not have faith in the method, they may use a second contraceptive without informing the staff, or they may not be willing to exert the necessary effort to use a product that they consider to be relatively ineffective. Women may stop using a vaginal method effectively when they learn that some of their friends have become pregnant while using the same product. The patient should have some concept of theoretical- and use-effectiveness and should have enough rapport with the clinic staff to consult with them about any doubts they may have about the preparation they are using.

INSTRUCTIONS IN THE USE OF THE METHOD

Success or failure can depend on how carefully and thoroughly the staff instructs the patients in the use of the method. This is particularly important when the subject has not previously used a vaginal contraceptive. A contraceptor who has little understanding of the physiology and anatomy of the reproductive tract can easily misunderstand instructions unless they are explicit. The staff should use audiovisual materials and let the patient practice using the product on an anatomic model and, if feasible, also on herself. Supplemental written instructions are also useful in the event that the subject forgets any details and is embarrassed or neglects to ask about them at a later time. If the method involves a device, the patient should insert it under supervision and a physician or nurse clinician should verify that the device was properly positioned, as is customary in many settings when a women is fitted with a diaphragm (3).

Those experienced in clinical research with contraceptives are aware of the spectrum of misunderstanding that can occur. Patient's errors range from the humorous to the bizarre, but unfortunately they may result in an unwanted pregnancy.

FOLLOW-UP

Rapport between patients and staff depends not only upon the initial contact but also on the continuing care provided by the medical facility and how well the staff maintains contact with the contraceptors. Frequent contact, particularly in the early phases of the study, may help to maintain the motivation of some subjects and reinforce the proper use of the product (2, 5). If the staff is indifferent or antagonistic to the subjects' questions, problems, or need for reassurance, the subject may lose confidence in the method and either stop using it, use it less effectively, or stop returning to the clinic with questions that arise.

INTERPRETATION OF THE RESULTS OF CLINICAL STUDIES

Clinical effectiveness studies should provide some measure of the theoretical- and use-effectiveness of a method and some information about how well the product may prevent pregnancy when it is used by the general public rather than the study group. Given the variables associated with clinical trials, however, there are numerous problems and questions about the interpretation of study results.

One problem is how to interpret the wide range of pregnancy rates obtained from different studies in which the same type of product is evaluated. For example, pregnancy rates ranging from 1.8 to 38.7 have been reported for a contraceptive foam (3) and from 1.9 to 28.9 for the diaphragm (8). There are similar variations for other barrier methods including the condom (1, 6). Different patient populations are probably the major cause of the variable results, although all the other factors described can contribute to the outcome of the investigations. For any of these studies, the overall results obtained reflect the efficacy of the product as used by a particular patient population under the conditions of the investigation.

A further question is, should an attempt be made to determine theoretical-effectiveness in addition to use-effectiveness, and can this value be determined? The theoretical effectiveness should take into account only those pregnancies that result from a physiologic failure of the method. Since it is not always possible to distinguish between physiologic and other types of failures, the value obtained for theoretical-effectiveness is only an approximation. Even so, it can be a guide to the efficacy that can be expected under the best conditions of use. The most effective use of the data presently available is to establish a range of effectiveness that informs the consumer about the results that may be expected when a method is used correctly with every episode of coitus, in comparison to the outcome that can occur if the method is used carelessly or inconsistently.

It is also difficult to determine the *relative* effectiveness of different vaginal contraceptives because most studies have been done by independent investigators using different study populations and settings. It is not accurate to compare the results, because variations between centers, as determined by existing studies of the same product, would obscure any differences between products. This problem is not unique to the study of vaginal contraceptives.

Similar difficulties exist in dealing with oral contraceptives, as noted by Goldzieher and Rice-Wray (7), and the IUD as discussed by Mishell (9).

Ideally, to avoid the variations inherent in separate studies, products should be compared by distributing them randomly to the same patient population under the supervision of the same staff of investigators. This could be difficult to achieve with vaginal contraceptives if the products were dissimilar. Patients may not object to the random assignment of two similar products, *i.e.*, two kinds of oral contraceptives or IUDs or even foams, but they may be less inclined to accept a randomly assigned diaphragm versus a vaginal cream, because the methods are so different. It would also be difficult to compare a new type of vaginal contraceptive with a "standard" product, such as foam because, while many women may be willing to accept a new and presumably "better" contraceptive, not many would volunteer if they might receive a product that is already available to them, possibly without cost, at a local clinic or even commercially available without the inconvenience of a medical examination and clinic schedule.

The problems of comparing data from different studies become exaggerated if one attempts to use information from clinical studies to predict the efficacy of a vaginal contraceptive when the product is eventually marketed. The relatively controlled environment of the clinical investigation is lost and results are not likely to be as good as those achieved in clinical trials. In the case of prescription products, the clinician may not be as selective as the investigator in prescribing the method or as careful as the research staff in instructing patients in product use and sustaining motivation of the study subjects. Worse results can be predicted for non-prescription products, because users may not be motivated enough to use the method well, and the consumer must rely on the package insert for instructions which may not be complete or clear enough to assure correct use. In both instances, better patient education by clinicians and clinic staffs, and package inserts that are more simply and clearly written could improve the effectiveness of both prescription and over-the-counter vaginal contraceptives.

DISCUSSION

Clinical studies are necessary to evaluate new methods of contraception. They cannot be supplanted by *in vitro* laboratory experiments or animal studies that simulate conditions in the human female reproductive tract at the time of coitus. In considering the design of new vaginal contraceptives, it is important to recognize the ways in which a method can fail to prevent pregnancy in clinical use. The types of failures have been divided into three rather than the usual two categories of patient and method failures, even though they may, at times, be very difficult to differentiate. One emphasis in developing new vaginal methods has been to devise a method that will avert some *psychological* failures because the product can be placed in the vagina well before its anticipated need (4). A product that could be used independent of coitus would also prevent some *procedural* failures because it could be inserted at leisure rather than in the moment of need when the user is more apt to be hasty and careless. Other procedural failures could be eliminated

by more explicit instructions and better consumer education. In addition, a well-designed method might compensate for some patient error in placement and also effect a reduction in procedural failures. Until now little consideration has been given to the influence of the method itself on the outcome of the clinical trial, but a product that is simple and convenient to use, that may be inserted well in advance of coitus so as to allow for some inexpertise in insertion, should provide better clinical results than a product that did not have these attributes.

Despite their drawbacks and the fact that they have not always been conducted under ideal conditions, clinical studies of vaginal contraceptives have been valuable. Reports of such studies should include details about patient selection, methods of instruction, and follow-up. Both the health professional and the consumer will be misled if the study subjects are instructed to use their method every night, whether or not they plan to have intercourse, or if they are advised to use a double dose of spermicide, and these facts are not included in the professional or consumer literature. Clinical studies, perhaps of improved design, will continue to be a mainstay of contraceptive research. It is important to appreciate the weaknesses of these studies however, and to keep their results in perspective.

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Components of an Epidemiologic System for the Surveillance of Adverse Effects Due to Vaginal Contraceptives*

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As newer and more efficacious vaginal contraceptives are developed, they must be monitored for side effects. Immediate adverse reactions to these contraceptives will probably become apparent during the early clinical trials, particularly if these immediate effects occur at a high incidence. Of greater concern, and more difficult to detect, are adverse effects which occur only after long-term or chronic usage; are delayed in appearance; and occur at low frequencies. If these three conditions hold, such adverse effects may indeed be difficult to detect unless an organized system is in place to permit their discovery.

Several epidemiologic strategies may be used to monitor and detect adverse reactions due to ingestion of a pill or use of a vaginal contraceptive. These strategies are discussed in this chapter (8).

STRATEGIES TO DETECT ADVERSE REACTIONS TO VAGINAL CONTRACEPTIVES

THE CONTROLLED CLINICAL TRIAL

During Phase III studies of vaginal contraceptives, clinical trials will be carried out to assess their efficacy and toxicity. Usually these clinical trials involve seven hundred to several thousand subjects but, in the case of a topically applied contraceptive, they would probably be much larger. An adverse effect that occurs in the order of 1/1000 women/year and appears immediately might be detected with these early clinical trials. If the adverse effect mimics a very common disease such as vaginitis, however, it may be ob-

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scured, as it has no peculiar manifestation. If the clinical trials are controlled, the relationship to the use of the contraceptive may reveal itself. Thus the importance of a control group in clinical trials is illustrated.

COHORT STUDIES

Cohort is the term used by epidemiologists to describe a group of persons who are followed forward in time (1). Cohort studies of vaginal contraceptives would compare users of these contraceptives to nonusers or to those persons who choose some other method of contraception. The difference between a cohort study and a randomized controlled trial is the inability of the investigator to randomly allocate to any one group persons entering the study. The cohort approach is not as powerful as the experimental method because the differences that are observed in the users as contrasted to the nonusers may be due to a variety of selection factors. Another difficulty is attrition due to members of a cohort moving out of the area, changing to another form of contraception or discontinuing it, dropping out of the study, and so on. Furthermore, cohort studies are expensive and time consuming.

Cohort studies permit the evaluation of a whole range and variety of possible adverse and beneficial effects, the possible discovery of delayed effects, and the calculation of an incidence rate or absolute measure of risk (as contrasted to the relative risk calculation which is usually the only one possible in the next research strategy, the case-control method).

CASE CONTROL STUDIES

The case control method is the research strategy best suited to eliciting the possible relationship of a *rare* illness to drug exposure (5). In the case of vaginal contraceptives, if it were suspected that a vaginal tumor (a rare type of tumor in younger women), had been caused by certain agents, medical records of these women could be collected and any past exposure to vaginal contraceptives compared to that of a suitable comparison or control group. The case-control method, therefore, starts by locating persons with the disease of interest and searching the patient's history to determine if exposure to the suspected agent is more common among these patients than in a comparison group. It requires initial suspicion that the contraceptive may cause a particular illness; the first clue is usually arrived at by reports from astute clinicians.

Like the cohort method, the case-control strategy is observational and nonexperimental, and therefore interpretation, bias, and confounding can be troublesome factors. Nevertheless, it has been useful in elucidating the adverse effects of oral contraceptives such as phlebitis or pulmonary embolism and it is inexpensive, rapid, and possibly the only method feasible when one is studying very rare adverse effects.

ROUTINE CASE-CONTROL SURVEILLANCE

A new method of monitoring adverse effects has been pioneered by members of the Boston Drug Epidemiology Unit of the Boston University Medical Center (BDEU) (7). These investigators regularly interview persons who

enter hospitals in various parts of the United States and Europe to obtain drug histories using a detailed standardized questionnaire. When the data file becomes large, associations between diseases and past drug usage may be revealed. This system has additional versatility in that if an adverse effect is suspected, an *ad hoc* case-control study can then be rapidly mounted because the interviewers are in the field and can simply give high priority to finding and interviewing patients who are admitted to hospitals with illnesses that are suspected to be related to a particular drug exposure. For example, if vaginal cancer were thought to be due to the long-term use of vaginal contraceptives, the interviewers in the various hospitals could quickly begin collecting such cases. Furthermore, if a new contraceptive were to become very popular shortly after being marketed, patients suffering adverse effects would begin to enter hospitals and their conditions would possibly be picked up under this routine surveillance system. It is important to note that if the adverse reaction does not lead to hospitalization, this system will probably fail to identify it.

SURVEILLANCE SYSTEMS IN AMBULATORY CARE SETTINGS

It is theoretically possible to develop a surveillance system for adverse reactions that occur in outpatient settings (and this includes reactions to vaginal contraceptives that may be troublesome but may *not* lead to hospitalization); in practice, however, such systems have not functioned well. Physicians in large group practices have the potential capability of linking diagnoses to past drug exposures but, presently, data linkage systems to accomplish this are not effectively operating in the United States. Large group practices are monitored in this fashion in the United Kingdom as a part of a feasibility study, and ambulatory care surveillance systems have been established and tested in Sweden. A study in a large group practice in the USA has recently reported on the relationship of uterine cancer to estrogens (3).

CONGENITAL MALFORMATION AND CANCER REGISTRIES

Should vaginal contraceptives increase the incidence of congenital malformations in women who become pregnant while using them, or lead to particular tumors among those exposed, registries which collect records of such malformations and tumors can sometimes be used as a source of cases that can later be reviewed, and the patients interviewed, to ascertain drug exposure. This is a valuable source of cases for the case-control or retrospective method. Congential malformation registries now exist in the United States, United Kingdom, and Finland, as well as in other countries. In the United States, tumor registries that have been useful in linking drug exposure to subsequent cancers are located in Connecticut, New York State, California, and other states (2).

THE QUESTION OF NUMBERS

In choosing between the cohort and case-control research strategies, an important factor to consider is the number of subjects needed in each of the two study designs

TABLE 27-1. Number of Subjects Needed to Detect a Relative Risk of 3.0 with Error Rates α = 0.05 (Two-Sided) and β = 0.20 (One-Sided) Using the Cohort Study Design and the Case-Control Study Design

			DISEASE INCIDENCE AMONG NON-EXPOSED INDIVIDUALS			
	STUDY DESIGN		*0.001*	*0.01*	*0.10*	*0.30*
Drug Exposure Rate in Target Population	0.01	Cohort	7823	767	62	9
		Case-Control	803	803	803	803
	0.10	Cohort	7823	767	62	9
		Case-Control	99	99	99	99
	0.30	Cohort	7823	767	62	9
		Case-Control	55	55	55	55

For both study designs, the sample size depends upon the lowest relative risk that the investigators consider important to detect as well as the chosen error rates, α and β; α signifies the chance of obtaining a statistically significant estimate of relative risk when there is no association between exposure and disease; β signifies the chance of not detecting such an association when one does indeed exist. The sample size increases as the smallest important relative risk decreases and also increases as the error rates, α and β, decrease. Thus, more observations are needed to detect a smaller increase in risk or to have greater confidence in our inferences. The sample size for a cohort study also depends upon the incidence of the disease under study in *nonexposed* individuals during the period of follow up; the sample size increases as this incidence of disease decreases.* The sample size for a case-control study depends upon the rate of exposure to the suspected drug during the period of interest in *nondiseased* individuals (usually estimated by the overall exposure rate in the target population); the sample size increases as this exposure rate decreases.*

Table 27-1 shows the number of subjects needed in each study group in order to detect a relative risk of 3.0 with error rates $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (one-sided) (6). The initial sample size needed for a cohort study will actually be larger than that tabulated due to loss to follow-up during the study period. Generally, the cohort design is to be preferred when the incidence of disease is high among nonexposed individuals but exposure to the drug is rare, while the case-control design is to be preferred when the incidence of disease is low but exposure to the drug in the target population is common.

For both research strategies, two additional factors should be considered in the determination of sample size. A larger sample is needed to look beyond an overall association, *e.g.*, to detect increased risk of disease associated with exposure in particular subgroups of the target population, to detect increased risk of a particular type or severity of the disease associated with exposure, or to detect increased risk of disease associated with a particular type or level of exposure. Second, the tabulated sample sizes do not take into

*This relationship holds over ranges of low rates.

account paired matching of individuals in the two study groups. Such matching tends to increase the efficiency of the study design and decrease the necessary sample size. It is extremely difficult, however, to include the effect of the matching in the sample size calculations before the study is conducted, so that a sample size which disregards the matching is usually used as a conservative guideline.

To sum up, the case-control research strategy is usually chosen in the investigation of a rare disease thought to occur in association with a drug. The cohort method is often feasible if there is a high incidence of the disease thought to be associated with the drug. For example, chloramphenicol causes aplastic anemia in about 1 of every 60,000 persons who take it. A cohort study would have to be impractically large to detect this risk whereas a case-control study (where persons with aplastic anemia were interviewed and their drug histories sought), would be of a reasonable size and answer the question. Conversely, a cohort study of a rash associated with ampicillin, which occurs in about one in five persons exposed to this drug, would be feasible and the method of choice since the incidence is so high.

CONCLUSION

The monitoring and surveillance of vaginal contraceptives for possible adverse effects should continue after the contraceptives have been marketed. A variety of monitoring strategies have been outlined in this presentation. Health professionals should realize the importance of such systems.

Dr. Kenneth Ryan of Harvard Medical School, in writing about oral contraceptives, recently observed (4):

> In the realm of human research, epidemiologic studies will probably play an increasingly important role in reproductive medicine. The possible benefits and risks of different drugs and synthetic hormones can only be determined through long-term well-organized studies of the effects of these agents on human populations. This has been demonstrated in the past; English physicians were able to gather information on the effects of the birth control pill much faster than were researchers in the United States, because England's national health insurance program and record keeping facilitated the collection of the necessary information. At present, much more research is devoted to getting a drug on the market than to following the effects of that drug once it enters public use. This unbalanced situation must certainly change.

It would be unfortunate if we did not learn from the example of the oral contraceptives, and thereby fail to have surveillance systems in place if and when vaginal contraceptives become more widely used.

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28

An Agenda for Vaginal Contraceptive Development

RICHARD J. DERMAN

At present there is no single agenda for vaginal contraceptive development. That one is needed, however, is demonstrated by the distinct and opposing needs expressed by consumers. On the one hand consumers are demanding new, safe, and effective vaginal contraceptives; on the other hand, these same consumers are calling for stringent and rigorous government regulations for new contraceptive products, to insure their absolute safety and effectiveness. The situation is compounded by the growing awareness of major side effects attributed to systemic hormonal preparations and to the IUD and concern that pharmaceutical industry spokesmen and medical practitioners are not being candid about the problems associated with presently available contraceptives—particularly with regard to side effects, pregnancy rates, and potential long-term complications.

All the potential new products, some of which may soon become available as well as those presently on the market, are designed to protect against unwanted pregnancy in one of two ways: by creating a physical barrier that prevents the entrance of spermatozoa to the cervical canal and/or by providing a direct action on the sperm—either killing or immobilizing them. Is it realistic, therefore, to anticipate increased method-effectiveness with new product forms?

A review of the vaginal contraceptive literature regarding effectiveness claims provides little assistance in the selection of a specific product or even a product category. The FDA position that "there is fragmentary evidence that foam preparations are somewhat more effective than the others" may be correct, or may simply reflect our longer experience with this type of preparation (4).

The FDA has approved only three chemical agents in Class I as being both safe and effective; all are nonionic surfactants and, despite complete inactivation of sperm *in vitro*, all products containing the active ingredients have been associated with pregnancy rates varying from less than 2% to 30% (6). It is no wonder that clinicians are often reticent to prescribe vaginal contraceptives. Disregarding economic motives, clinicians tend to prescribe medications almost solely on the basis of their efficacy, *i.e.*, so much antibiotic per kilogram of body weight to adequately eliminate a given organism and elicit a therapeutic response. It is frequently stated that reported clinical trials, for a variety of reasons, do not permit efficacy or comparison claims.

This may imply that any new product containing ingredients already deemed safe and effective may enter the marketplace on the basis of comparability with previously approved product formulations, without first undergoing carefully controlled clinical trials. If this situation continues, it probably represents no advantage to the consumer. It has already become evident that product sales are a reflection of marketing dollars spent rather than of consumer awareness of use-effectiveness data.

Restrictive labeling should stimulate pharmaceutical companies to reassess their present products, and to collect carefully monitored prospective clinical data utilizing the life-table approach. If the protocols are consistent with FDA recommendations, data on method-effectiveness and use-effectiveness may be translated into claims which would be consistent with FDA requirements, and might even permit the manufacturer to suggest product superiority. At the same time it would be appropriate for a government agency or a foundation to support similar trials comparing product categories. In this way the consumer and the provider can be assured of an informed choice in the selection of a vaginal contraceptive.

Investigations of presently marketed products may lead to their approval for other indications besides contraception. The *in vitro* gonococcocidal activity of nonoxynol 9 is well known (3); whether this formulation carries full or only partial protection against certain forms of sexually transmitted diseases (STD) in the *in vivo* state requires clinical trials that are ethically difficult to construct in a prospective manner. The four-fold to seven-fold relative risk of pelvic inflammatory disease associated with IUD use (1), coupled with the endemic state of gonorrhea, should stimulate the Center for Disease Control, the U.S. Department of Health, Education, and Welfare, and private industry to take a closer look at available products with the potential for protection against these conditions. Both *in vivo* and *in vitro* testing against the *Chlamydia* organism may be more socially acceptable, as this condition presently accounts for more nonspecific urethritis and perhaps cervicitis than the gonococcus (2). In addition Singh, Postic, and Cutler have demonstrated inactivation of the virucidal effect of type 2 *Herpes* virus utilizing a 10% solution of two different chemical contraceptives. It has been reported that a number of viruses including herpes are inactivated by benzalkonium chloride and related quarternary ammonium germicides. There has been recent discussion at the FDA as to potential systemic toxicity of these compounds. In light of new evidence as to the therapeutic benefits of quarternary ammonium germicides, additional studies may be in order before urging manufacturers to alter their present formulations (5).

Recently, Wright, Vessey *et al* (7) corroborated other reports of a decreased incidence of dysplasia and neoplasia among diaphragm users as compared to a controlled population. The study indicated that even if one adjusts for age at first coitus and frequency of intercourse, as well as for multiple partners, the protective ratio for barrier methods appears to approach an order of four.

Recently a decline has been seen in the United States in the number of new acceptors of oral contraception or the IUD. This decline will most likely continue if additional serious risks are established for these methods of contraception. A number of commercial and research organizations are predict-

ing that just such a decline in use will, in fact, occur. Recognizing this, investigations into new product forms are proceeding rapidly. Whether it is a chemical that alters cervical mucus or sperm capacitation or an impregnated barrier with potential for high rates of effectiveness, each approach will require FDA testing. The following steps are proposed as essential to an effective evaluation.

In vitro tests should be designed to support claims for the mode of action of a given contraceptive agent. Where appropriate, testing for the penetration of sperm through cervical mucus at midcycle should be performed. Bovine cervical mucus might be substituted for human. The *in vitro* testing for spermicidal activity can utilize any of the five standard tests available which prove rapid sperm immobilization. The vehicle providing the spermicide must also be evaluated because placement, dispersion, melting time, and duration-of-action all relate to method-effectiveness.

Many products now marketed have such data available. It is with *in vivo* testing that stringent requirements are proposed; initially with animal models and finally through testing of effectiveness in humans. While admittedly selection of animal models is imperfect and not totally agreed upon, the use of rabbits, sheep, and primates holds considerable promise.

For effectiveness claims to be proven in the human, clinical trials must employ sufficient numbers of patients to provide statistically acceptable data. These overall proposed requirements are not unlike those for a new ethical pharmaceutical. These trials comprise four phases, beginning with phase I, or short-term tolerance studies, in which the product is employed on a rising dose scale for at least 10 days in 10–20 subjects. Careful assessment of local and general reactions must be made prior to initiation of the next phase of testing. During phase I, postcoital studies should be included.

Phase II trials must be carried out in recommended dosage forms for 6 mo to determine short-term effectiveness prior to initiating broader-based trials. At this level, at least 50 patients must complete the testing period with strict adherence to the predetermined protocol.

Assuming that the preliminary data appear promising, phase III trials will then continue over a period of one additional year with recruitment of at least 1000 patients to insure completion at one year of 200. The results over the 18-mo period, assuming the trials are conducted properly, may be translated into method-effectiveness claims. If use-effectiveness data are desired, phase IV activity or postmarketing data must be monitored and accurately reported.

What we are witnessing is the establishment of requirements calling for a minimum of 2 yr at the clinical testing level with expenditures of approximately one million dollars for each dosage form or change in formulation. Given this fact the number of new entries into the field will surely decrease.

Perhaps the most important factor in new product acceptance is how the consumer responds to the product. Even if a safe and effective vaginal method were developed consumer acceptance would not be assured. Consumer market research should be initiated by pharmaceutical companies long before capital is invested in phase II and phase III clinical trials.

In conclusion, we are witnessing a rejuvenation of interest in vaginal contraception, particularly by the consumer. Government and industry must

now combine forces to develop an agenda which calls for the critical assessment of new topical agents, new modes of delivery, and new barrier methods. However, until these new products become available and their promotion founded on firm clinical data, the additional responsibility of education concerning the use of those present-day products which we believe to be safe and effective should not be overlooked. Finally, we must begin to inform the public not only on the contraceptive benefits or risks of an agent, but also make available information which covers ancillary health benefits.

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INTERNATIONAL PERSPECTIVES ON VAGINAL CONTRACEPTION

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29

The Cultural Acceptability of Vaginal Contraceptives*

SUSAN C. M. SCRIMSHAW

The search for new contraceptives, and better versions of old ones, is going on rapidly and with considerable success. These devices, no matter how effective and good in many technical respects, have to pass a final test. People must use them, and use them consistently and properly.

For a long time the assumption has been that if technology provided solutions to problems, people would gratefully embrace the new products of technology. As anthropologists Steve Polgar and Jack Marshall were fond of saying, the tendency in family planning has been to attempt to fit people to the technology rather than changing technology to fit people (11). In reality, technical development as well as actual inservice testing and long-term use of vaginal contraceptive methods are needed.

The purpose of this chapter is to share and to extend some of the work by anthropologists, sociologists, and psychologists involving cultural and individual factors affecting the acceptability of vaginal contraceptives. For those working on contraceptive development, this should provide an insight into the potential acceptability of methods. For those who will be distributing the methods through programs they direct, the intent is to provide guidelines for assessing the acceptability of these methods, in order to assist people in accepting and using the technology, and also to provide further, specific information to guide contraceptive development.

CULTURE AND ACCEPTABILITY

When technological developments, such as modern contraceptives, and the systems to distribute them are developed in one culture and applied in many additional cultures, the perception and use of these methods and systems will be guided by differing cultural beliefs, behaviors, norms, and expectations.

The acceptability of family-planning programs by a given cultural group is often described in undifferentiated terms. "Africans want many children so they won't accept family planning." "Pakistani women didn't respond to the government program; they didn't want family planning." Such descriptions lump together the concepts of desired family size and the acceptability of a

* The author expresses her indebtedness to her research assistant, Ellen Iverson and to Elena Hurtado for her very valuable comments

particular method or delivery system. Further differentiation can serve to generate more specific questions, leading to more productive analyses. An appropriate analysis of cultural values and family planning requires the separation of various factors into at least four steps which provide a progression from the recognition of existing cultural norms regarding family size to responses of potential contraceptive acceptors within a culture to specific programs offering methods of fertility control. These steps include the following.

1. *The cultural population policy* The overt recognition of cultural norms regarding family size and the behaviors which help to maintain those norms
2. *Specific details of that policy* Cultural values influencing the acceptability of family planning; of specific steps taken to produce a specific family size and, frequently, specific intervals between births
3. *Method acceptability* The group's reaction to the array of methods currently available to regulate fertility
4. *Delivery system acceptability* The acceptability of various aspects of the mode of delivery of these methods

Most countries include a range of subcultures or even cultures, as distinguished by religion, linguistic groups, ethnic groups, social strata, and other elements. These groups may have differing values for the four elements of the framework.

Family-planning programs can and should address themselves to all four areas. This chapter focuses on only one, that of method acceptability. However, as Bernstein and Nakamura discuss in Chapter 26, method acceptability is affected by the knowledge and availability of the method, how it is explained, and how the individual is instructed in its use. All these are aspects of family-planning services. The importance of these and other factors cross-culturally is explored in another paper entitled "Anthropology and Population Research: Application in Family-Planning Programs" (15).

THE ACCEPTABILITY OF VAGINAL CONTRACEPTIVE METHODS

Given the diversity of the societies using vaginal contraceptives, it is not surprising that a method which is highly regarded and widely used in one culture may be totally unacceptable in another. It would be virtually impossible to find one method which satisfies everyone, but it is useful to know what characteristics are likely to be acceptable more often than not, and what modifications may increase the acceptability of a given method. For example, in some societies, disposing of a contraceptive method after use is a problem when little garbage is generated under conditions of poverty, and what is generated is highly visible. This has made condom use a drawback in several Latin American squatter settlements in Ecuador, Colombia, and Peru, as well as in India (2). This problem would indicate that the water-soluble condom and films now being developed have a good potential for acceptance in instances where disposal is considered a major obstacle to use. However, one of the difficulties in assessing acceptability is that contraceptive methods have many attributes, and seldom are rejected on the basis of a single one.

TABLE 29-1. Inherent Attributes of Vaginal Contraceptives. Use-Related

	Condom	Foam	Vaginal Suppositories	Diaphragm & Jelly or Cream	Sponges	Cervical Cap	Cream or Jelly Alone	Water-soluble Films	Microcapsules	Cervical Ring	Douche	Summary No of Methods
1. Gender of user												
a. Male	X							X				2
b. Female		X	X	X	X	X	X	X	X	X	X	10
2. Relationship to coitus												
a. Before sexual activity initiated			X	X	X	X	X		X	X		7
b. After sexual activity initiated	X	X	X	X	X		X	X				7 (2)
c. After sexual activity concluded											X	1
3. Requires handling of genitalia	X	X	X	X	X	X	X	X	X	X	X	11
4. Demands collateral equipment		X			X(some)		X				X	4
5 Repeated application needed if coitus more than once in a 6-hr period	X	X	X	X (Jelly or Cream)			X	X			X	7
6. Requires professional fitting				X		X				X		3
7. Nonprescription	X	X	X		X		X	X	X		X	8
8 Must be removed after coitus	X			X	X							3
9. Must be washed and stored				X	X						X	3

As discussed by Marshall (8), methods of fertility regulation are viewed as a cluster of attributes, not simply as material objects. Each attribute has cultural meanings which influence the overall acceptability of the method. Attributes can be divided into two classifications, inherent and perceived (8). Inherent attributes of contraceptive methods are the properties of those methods, the physical characteristics of the methods and their modes of use.

Table 29-1 presents the inherent attributes of vaginal contraceptives which are related to use. The table includes notations which check off the specific attributes of specific methods. For example, condoms and water-soluble films are used by the male, while all other vaginal methods are used by the female (although it is obvious that both partners are ultimately involved in the use of these methods, the primary user is indicated here). Seven of these methods can be applied before sexual activity is initiated, but all but two (the cervical cap and the microcapsules) are also normally applied after sexual activity has been initiated if the partners prefer that timing. Two methods (condom and C-film if used by the male) cannot be applied until enough sexual activity has taken place to produce an erection. All eleven methods discussed here require the handling of the genitalia, but only two require collateral equipment (foams, jellies, or creams need applicators). However, some sponges have been designed to be used with applicators, which should reduce their acceptability. Three methods require professional fitting, while the other eight are nonprescription methods. Three must be removed after

TABLE 29-2 Additional Inherent Attributes of Vaginal Contraceptives

1. Color	12. Cost
2. Odor	13. Overall effectiveness
3. Taste	14. Reversibility
4 Size	15. Mode of action
5. Texture	a Systemic
6. Shelf life at home	b. Topical
7. Length of effective period during use	c Barrier
8. Need for resupply	16. Potential irritant
9. Disposability	17. Increases vaginal discharge
10. Packaging	18 Ability to prevent venereal disease
11. Name	

TABLE 29-3. Perceived Attributes of Vaginal Contraceptives

1. Local irritation	11 Uncomfortable
2 Inhibits sexual spontaneity	12 Too complicated
3. Inhibits sexual pleasure	13 Harms woman's body
4 Can get lost in vagina	14 Harms man's body
5 Can get stuck in vagina	15. Harmless, safe
6 Too big to fit in vagina	16 Messy
7. Convenient to use	17. Association with morality
8. Inconvenient to use	18 Feels hot
9 Easy to use	19 Feels dry
10 Difficult to use	

coitus and two must be washed and stored for reuse. Seven require another application if coitus takes place more than once in a 6-hr period.

Table 29-2 lists additional inherent attributes of vaginal contraceptives. No attempt was made to classify each method in terms of these characteristics because listing all possible colors, costs, and other items would have been cumbersome. Here, the researcher or program director can use the list to classify the methods being studied or offered, and then question users or potential adopters as to their perceptions of the methods and their feelings about specific attributes. For example, it is useful to know people's *perceptions* of the effectiveness of a method irrespective of the actual effectiveness. A researcher or program director could assess his community's actual or potential perceptions of these attributes on a positive, negative, or neutral basis, thus deriving an acceptability score for each method. This concept is based on a suggestion made by Elena Hurtado.

From the point of view of acceptability, all of the inherent attributes listed in Tables 29-1 and 29-2 are only important in how they are perceived by potential and actual users. For example, while it is a fact that a diaphragm must be removed, washed, and stored, this only affects acceptability if the user finds that too difficult to be worthwhile or even possible. Thus, when assessing acceptability, we are really looking at the perceptions of inherent attributes as well as the perceived attributes of methods.

Table 29-3 lists potential perceived attributes of vaginal contraceptives. While the methods may not possess these attributes, in some cases people

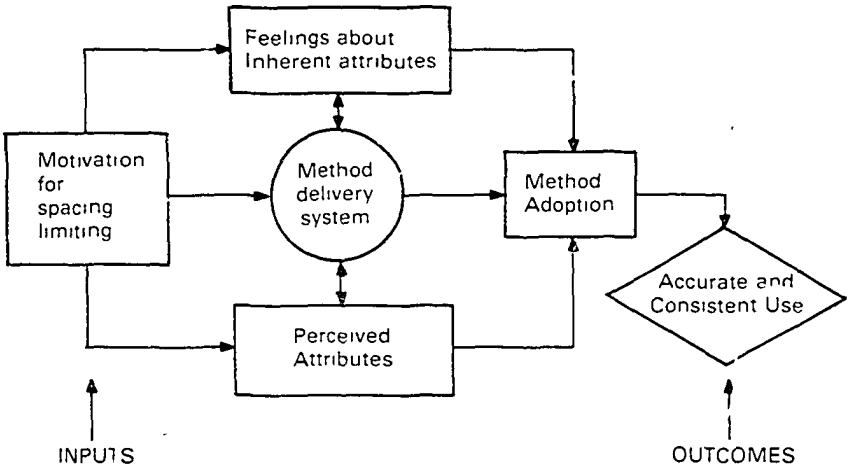

FIG. 29-1. Contraceptive method acceptability and use model.

think they do, and this is what affects behavior. An example of a common perceived attribute of both the diaphragm and the condom is that they can get lost in the vagina (10). In a study of pregnant women of Hispanic origin in New York City, it was found that most women did not have detailed knowledge of their internal anatomy, and believed that what went into the vagina also penetrated the uterus (17). When this is added to a Central American folk belief that things like air and harmful objects can get into the body and float around it freely (1), it becomes easier to understand this concern. However, in New York and in Colombia, it was clear that women can rapidly acquire enough knowledge of their anatomy to reassure them on this point. When requested to draw the reproductive organs into a simple line drawing of a female figure, one Colombian woman did an excellent job, then asked the interviewer to write in the name of the organs she had named correctly, explaining she was illiterate. When she was asked how she knew so much anatomy, the woman said she had remembered the drawings and explanations at the local family-planning clinic (16). This was not an isolated instance. Thus, the perceived attributes of vaginal contraceptive methods must be interpreted for each culture, and reinterpreted at intervals in order to measure and further influence change. While body image drawings, such as the one described above, are difficult to interpret, they provide useful, rough indications of knowledge of reproductive organs, and of attitudes towards them because women approach the tasks with varying degrees of shyness and discomfort.

Although the questions must be asked with care so as not to bias the potential recipients, culture-specific perceptions of vaginal contraceptives could also be included in the acceptability score mentioned earlier.

Fig 29-1 presents a model for assessing the impact of attitudes towards methods on the actual adoption and use of those methods. First, the individual or couple's motivation for spacing or limiting their families is an important factor. In general, the higher the degree of motivation the more nega-

tive attributes people will tolerate. Thus, this motivation affects both feelings about inherent attributes and perceived attributes. It also influences use. If one method is presented as more difficult to use than another method potential adopters are likely to pick up on this. On the other hand, if people demand a method the clinic personnel do not regard highly, they may force the clinic to provide that method rather than see the woman leave with no method at all. This happened with foam tablets in at least one Ecuadorian clinic.

All of these factors influence method adoption, which is only the first step. Accurate and consistent use is ultimate proof that a method is acceptable to an individual or to a couple. This is true even when the couple may dislike some of the attributes of the method. This measure is particularly important where vaginal contraceptives are concerned. As other chapters in this volume discuss, the discrepancy between theoretical-effectiveness and use-effectiveness is greater for vaginal methods.

EXISTING DATA ON ACCEPTABILITY

Some 400 studies of knowledge, attitudes, and practices related to family planning (KAP Studies) have been conducted for about 25 years, with results that vary in reliability and validity from poor to excellent (13). Because so many projects were carried out, one would expect a great deal of data on contraceptive acceptability. This is not the case. The vast majority of these studies focus on the acceptability of family planning, rather than on specific methods. When specific methods are discussed, they tend to be surgical sterilization, the pill, and the IUD; all methods which were emphasized during the 1960s and early 1970s at the expense of vaginal methods of contraception. Clinical trials of methods focus on factors such as safety and effectiveness, and may also focus on whether or not the method seems acceptable. However, less emphasis is placed on why methods are acceptable, or on cross-cultural factors in acceptability. This historical inattention to the acceptability of specific vaginal methods is changing, as evidenced in discussions by Campbell and Berelson (3), Pohlman (10), Lane, Arceo, and Sobrero (6), Lane (5), and Population Reports (12). For example, Campbell and Berelson discussed psychosocial factors relating to acceptability, and presented tables on method attributes, relative effectiveness, and limitations of each method (3).

KAP studies have also tended to focus on knowledge and use of specific contraceptives rather than attitudes towards them. Differences in these three areas may be revealing. For example, a 1971 study in Guayaquil, Ecuador queried men and women about knowledge, use, and attitudes relating to contraceptive methods. When this information is summarized for vaginal contraceptive methods (see Tables 29-4, 29-5, and 29-6), men and women differ slightly in their knowledge of condoms, foam tablets, foam, and diaphragms when the chi-square significance test is applied. Significantly ($P < 0.005$), more men than women know about condoms, while more women than men know about foam tablets ($P < 0.005$). Women also appear to know more about foam and diaphragms, but the levels of significance for this are

TABLE 29-4. Knowledge of Vaginal Contraceptive Methods for Urban Ecuadorian Men and Women

METHOD	VOLUNTEERED N	VOLUNTEERED %	PROBED N	PROBED %	NO KNOWLEDGE N	NO KNOWLEDGE %	TOTAL N	TOTAL %
CONDOM								
Women	190	6	1023	35	1722	59	2935	100
Men	237	21	613	53	302	26	1152	100
FOAM TABLET								
Women	416	14	687	23	1833	62	2935	99
Men	101	9	289	25	760	66	1150	100
JELLY/CREAM								
Women	98	3	274	9	2563	87	2935	99
Men	32	3	109	9	1011	88	1152	100
DOUCHE								
Women	230	8	904	31	1801	61	2935	100
Men	48	4	341	30	764	66	1152	100
FOAM								
Women	19	1	67	2	2849	97	2935	100
Men	9	1	31	3	1112	96	1152	100
DIAPHRAGM								
Women	74	2	251	9	2610	89	2935	100
Men	30	3	133	11	990	86	1153	100

somewhat lower ($P < 0.05$ and 0.02, respectively). The only significant difference in use is with condoms, which more men than women report as their contraceptive method ($P < 0.005$). This is partly because men in this population often have sexual unions with more than one woman. It appears that the condom is often used for such liaisons.

Men and women also differ in their attitudes towards foam tablets, jellies and creams, and diaphragms. Women are more negative than men about the diaphragm but more positive about foam tablets. Women often felt the diaphragm was too large, would hurt them, or was too complicated, but equated foam tablets with other types of suppositories, which are commonly used in this culture as a way of applying medication. These differences were statistically significant at the 0.005 and 0.01 levels, respectively, when the chi-square test was applied. Women were more negative than men about douching ($P < 0.005$). Men and women agreed they did not like condoms much, and slightly more than half of both sexes liked foam while slightly less than half did not. However, the differences were not statistically significant for methods other than the diaphragm, foam tablets, and douching. These differences may mean that, although use patterns are similar for men and women, knowledge and attitudes are not, so that acceptability is affected more by one partner than the other in some cases. Ever-use of *all* methods for women in this population was 44%, while 22% were currently attempting to contracept (18). In some instances, women used contraception without their partner's knowledge, which is distinctly difficult in the case of vaginal contraceptives.

This last is an example of several generalizations applicable to the consideration of the acceptability of vaginal contraception which emerge from the

TABLE 29 5. Use of Vaginal Contraceptive Methods for Urban Ecuadorian Men and Women

	CURRENT		PAST		NO USE		TOTAL	
METHOD	N	%	N	%	N	%	N	%
CONDOM								
Women	6	1	131	5	2792	95	2931	100
Men	16	2	192	17	947	82	1155	101
FOAM TABLET								
Women	31	1	145	5	2755	94	2931	100
Men	12	1	39	3	1104	96	1155	100
JELLY/CREAM								
Women	5	1	41	1	2885	98	2931	100
Men	5	1	9	1	1141	99	1155	101
DOUCHE								
Women	53	2	203	7	2675	91	2931	100
Men	10	1	57	5	1088	94	1155	100
FOAM								
Women	0	0	10	1	2920	100	2931	101
Men	2	<1	4	1	1149	100	1155	100
DIAPHRAGM								
Women	4	1	11	1	2916	99	2931	101
Men	1	1	4	1	1148	99	1153	101

literature and from current research. One of these is that good husband-wife communication is important for the effective use of vaginal contraceptives, and less so for methods like pills or injectables, which the woman may use alone. Kar and Talbot report that in Venezuela, discussion between spouses is the most important determinant of current use (4). When such discussion is not possible, women take action on their own, although this is seldom the case for men (18).

Another underlying issue is that some cultures expect one partner to be responsible for contraception. For example, Shedlin and Hollerbach report that the women they surveyed in Mexico said they and their partners did not use condoms because contraception is the woman's responsibility (19). However, Pohlman reports that more husband dominance is associated with less effective contraceptive practice (10). Obviously, it is easier if both partners agree on the need for, and the mode of, contraception.

Another set of factors which affects the acceptability and use of vaginal contraceptives relates to enjoyment of sex and attitudes towards touching the genitalia. Pohlman summarizes several studies on this, including Rainwater's pioneering work in the early and mid 1960s (14). In general, the greater the acceptance of sexuality, the more this permits couples to discuss contraception and use vaginal contraceptives as part of sex play rather than something to deal with hurriedly and surreptitiously (10). He also mentions that in cultures or in individuals where sexual pleasure is not emphasized for one sex (usually women), some methods such as the condom may serve as a reassuring, symbolic barrier (10). In a study on psychological factors influencing women's selection of contraception, Metzner and Golden found that women who disliked methods which necessitated vaginal or genital manipulation also did not use tampons, thought masturbation was repulsive, and

TABLE 29-6. Attitudes Towards Vaginal Contraceptive Methods for Urban Ecuadorian Men and Women

	NEGATIVE		NEUTRAL		POSITIVE		TOTAL	
METHOD	N	%	N	%	N	%	N	%
CONDOM								
Women	726	75	0	0	249	25	975	100
Men	539	71	0	0	223	29	762	100
FOAM TABLET								
Women	322	37	0	0	561	63	883	100
Men	131	45	0	0	159	55	290	100
JELLY/CREAM								
Women	193	68	0	0	90	32	283	100
Men	64	59	0	0	44	41	108	100
DOUCHE								
Women	275	24	283	25	576	51	1134	100
Men	154	43	95	27	106	30	355	100
FOAM								
Women	25	44	0	0	32	56	57	100
Men	14	41	1	3	19	56	34	100
DIAPHRAGM								
Women	159	49	75	23	91	28	325	100
Men	71	62	2	2	41	36	114	100

were bothered by the idea of having something inside their vaginas. They also described their family sexual upbringing as "strict" (9). Because all vaginal contraceptives involve touching the genitalia, acceptability of these methods will obviously be influenced by such attitudes, although attitudes do change. Fifteen years ago it was virtually impossible to find tampons in Latin America. They are now available, although it would be interesting to obtain sales figures by socioeconomic status and subculture. For example, Guatemalan Indian women do not remove their skirts to bathe, have sexual intercourse, or to give birth. They also have an aversion to touching their genitalia. Even without economic limitations, they are unlikely candidates for tampons and many forms of vaginal contraception.

Another generalization which has come out of the work of the WHO Task Force on Contraception Acceptability is that contraceptives which resemble existing indigenous contraceptives or even other types of medication will be more acceptable than alien forms of contraception (11). A good example of this is the contraceptive sponge. Many societies have a long history of using a sponge or sponge-like material as a vaginal contraceptive. Obviously, the refinements of this method should be welcome in these cultures if care is taken to keep the method simple. Another example is vaginal suppositories, which have analogs in rectal suppositories that are commonly used in many cultures.

SUMMARY OF EXISTING KNOWLEDGE

While it would take too much space to summarize existing data on acceptability for each method, several generalizations can be made about vaginal

methods. The main counts against acceptability are the need to touch the genitalia, messiness, storage, resupply, disposal, and direct relationship to coitus. They also require planning and a certain degree of compulsiveness on the part of the couple to assure consistent use. All of these problems occur to some extent in most cultures. The counts in favor are reversibility, local rather than systemic action, relative lack of side effects, and similarity to indigenous methods.

On this basis it might be interesting to postulate ideal vaginal methods. One possibility would be a vaginal ring which could be inserted and forgotten, requiring replacement approximately once a year. The sponge meets many criteria, but the ideal sponge would need no additional spermicide, would need no applicator, and could be left in place for several days at a time without any difficulties. Water-soluble films and condoms eliminate the problem of disposability, but may be perceived by some couples as being too messy. The message that emerges is one which many social and medical scientists have been trying to convey for years: *choice.* Although existing methods may be improved and new methods developed, a range for selection is a necessity. The appropriate array of methods will vary with the culture and other circumstances such as economic factors, but the choice must be there.

CONCLUSIONS

Consistent and accurate use of vaginal and other methods of contraception is strongly affected by many factors, only some of which involve acceptability. For the investigator developing new methods and the clinician or administrator delivering services, however, acceptability should be a central issue. As health educators and development experts have learned worldwide, people have strong beliefs about what is right for them, and act according to those beliefs.

Marshall suggests three areas for action:

1. Modify fertility regulating methods;
2. Modify cultural beliefs;
3. Modify the image of the fertility regulating mechanism (8).

Efforts are underway to modify existing methods of fertility regulation. These are based on a combination of data indicating safety and effectiveness, with experience relating to acceptability, although more attention should be paid to the latter.

The other two areas which should not be neglected concern people working at the programmatic end. Too often, there is a tendency to underestimate people's ability to change. For example, it has long been stated that "Latin American women won't use diaphragms;" however, several programs have shown good results with this method because considerable time was invested in working with patients on appropriate knowledge and skills. The importance of high-quality service delivery cannot be underestimated, and health workers at all levels should be involved in improving those services. Areas of special importance for health education are increased husband-wife

communication regarding family planning and specific methods of contraception, increased instruction in human anatomy, and increased sexual awareness and understanding of the range of permissible sexual activity. The latter is already being done by the popular press in many countries.

All three areas required additional data indicating present behavior and specific needs. Such data are in short supply. The variables discussed in this chapter are intended to serve as guidelines for research at all levels, from taking a brief reading of a patient population to testing the acceptability of a new method with a sample of thousands. Such studies should not be confined to survey questionnaires, which often measure ideal attitudes and behavior rather than what people are really thinking and doing; surveys should be preceded and supplemented by in-depth interviews, informal discussions, and observations. It is to be hoped that future studies will not be limited to provision by family-planning programs of only those methods thought to be most effective and acceptable, but will seriously explore the variations in attitudes towards all methods, and the feelings and thoughts behind those attitudes.

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Social Marketing of Contraceptive Products

LUIS DE LA MACORRA

Social marketing is the art and science of researching, developing, selling, promoting, and advertising a given product or service to fill a perceived need of the consumer and to provide a social benefit to the community.

The social marketing of contraceptive products began not many years ago, when a family-planning program manager realized that the traditional commercial distribution system could be employed to reach the consumer more efficiently. Preliminary research indicated that the commercial distribution channel covered a larger percentage of current and potential contraceptors than all other distribution systems put together. It was also determined that prices and, in some cases, legal limitations, are the main barriers for a substantial increase in sales and coverage. In some countries, retail prices of contraceptive products have placed them out of reach of the vast majority of the population. In many places, sale of contraceptives is restricted to certain outlets and a doctor's prescription is required. When these barriers are conquered and the products are offered to the public in as many points of purchase as possible, a substantial increase of sales, and, therefore of usage, occurs.

During the past few years, a number of countries around the world have either increased the coverage of their current commercial-social marketing of contraceptive products and programs or have created new ones. In either case, even though a definite, clear evaluation of results is rather difficult, latest reports (1) indicate that

1. Commercial programs have increased the availability of contraceptive products. This is very simple because, by distributing products through regular commercial channels, a much larger number of points-of-sale can be reached. It is interesting to note that even though social marketing programs require an initial commercial monetary transaction, every country where these programs exist has noted an increase in coverage and penetration.
2. Even though the penetration of these programs varies from country to country (for example, India's 2% of total potential population to Brazil's 29%), there are certain important factors similar to all programs. In most cases the acceptors are less than 30 years of age, come from small families with only one or two children, and have little or no previous contraceptive experience.

3. The continuity of most commercial programs has achieved positive results when compared to that of other systems. For example, in Indonesia, clinical programs have achieved a 66% rate of continuation after one year and 33% after three years. Commercial programs, however, indicate a continuation rate of 76% after one year and 48% after three years.
4. Most important of all, the overall cost-benefit analysis made in every case indicates a substantial improvement particularly after the initial expenditure phase of the program has been completed. Just as important is that commercial programs do not require specially trained, expensive personnel and facilities. Thus, the traditional health system is free to provide the needed, routine health services. This is the reason at least seven countries are currently developing newer, larger, social marketing programs. Eleven are adding commercial divisions to their official programs, and various others are planning to increase their existing coverage.

It is not proposed that commercial distribution programs alone be used for family-planning purposes. Clinical programs have a definite need because they help to answer more specific questions and to solve problem cases. Community distribution programs also fill a definite gap. Without them, the lower economic individuals who cannot pay for services received would not be covered. Additionally, community-based distribution programs have been found very appropriate where strong supportive effort is required to educate couples about contraception.

It is felt that a commercial distribution program of contraceptive products will provide support for a nationwide plan and that the final results will depend on a number of variables, such as commercial penetration, degree of positive motivation towards family planning on the part of the public, price differential between regular retail and social marketing program prices, absence of legal restrictions, and the range of products offered. The wider the answer to all variables mentioned above, the better the results that we can expect to obtain.

In Mexico, a nationwide education and distribution program of contraceptive products has been initiated, directed toward the general public, and particularly toward marginal urban and rural areas through regular commercial channels. A little over a year ago, it was determined that the current commercial sector (a total of 13,000 drug stores) serviced almost half of the total contraceptors in Mexico. This was the case, even though the retail price of products was high, promotion was totally absent, and brand distribution was limited; all of which indicate a high degree of inefficiency. It was planned, then, to develop a social marketing, commercial distribution program that would be offered through drug, self-service, and food stores, and would have a wide variety of high-quality products at half of the current consumer price. The distribution plan is supplemented by a complete training program for the retail store owners and their employees. Additionally, a program to inform and educate the general public has been developed through mass media and descriptive pamphlets have been circulated in stores. The object of the campaign is to increase contraceptive usage by giving the consumer, at the right moment and at an affordable price, the product required for responsible family-planning action (3).

To reach these objectives a nonprofit organization called PROFAM has been established. A sales force consisting of 30 promoeducators, properly trained to sell PROFAM products nationally, has been structured. Merchandise is distributed in vans, together with the necessary supportive educational materials, including a Retailers Training Manual, a Consumer Guide, an audiovisual orientation program for retail employees, a product display unit, and promotional pamphlets.

PROFAM products being sold include a box of two condoms for 5.00 Mexican pesos* (compared to 14.00 pesos, the current competitive price), a contraceptive foam for 44.00 pesos (compared to 85 pesos), cream for 33 pesos (compared to 65 pesos), suppositories at half price, and a cycle of oral contraceptive tablets for 9 pesos (compared to 20 pesos).

All products are manufactured by the leading laboratory with the most acceptable formulation. For example, PROFAM oral contraceptives are the same formulation as Neogynon and are made by Schering Mexicana. The suppositories are made by Norwich, the condoms by Kopsa, and the cream and foam by Lemery. In this manner it is hoped to gain the confidence of the consumer.

During the first year of operation it is estimated that PROFAM will reach at least 18,000 outlets. Before the program was started, contraceptive products were sold in only 11,000 stores. Consequently, the addition of PROFAM activities to the market will substantially increase overall sales. We estimate that the total market will double in 2 years, with PROFAM representing 20% of this total. Therefore, all other manufacturers will have a larger participating market but a smaller percentage of the total.

The programmed activities of PROFAM, as previously mentioned, include a number of alternative distribution solutions to be investigated and additional promotional efforts to be tested. Starting in the summer of 1979, PROFAM test marketed distribution of condoms through vending machines, distribution of all products on a house-to-house basis, a special promotion directed to physicians, and the introduction of new products.

For the purpose of the vending machine test, 300 units are located in key public places in Mexico City. A box of two condoms is sold for 5.00 Mexican pesos. Hopefully, brand awareness and product acceptance will improve substantially, thereby increasing the total percentage of condom usage in Mexico. Results will be available after one year of sales.

The house-to-house distribution test will investigate results of a selling vs. a sampling promotional program to improve product acceptance. For this test, four cities in the interior of Mexico will be employed, two for the test and two for control purposes. We expect results to be available early in 1980.

To promote PROFAM products to physicians, a direct-mail program has been developed, starting late in 1979. This program will be continued for at least 2 years before any careful evaluation can be made. In addition to the plans mentioned above, a lower-priced, individually packed condom will be introduced at 2.00 pesos, and a higher-priced carton, with three condoms, sold in a fancy package at regular retail price, to help generate at least a

*In March, 1979, $1.00 (U.S. currency) was worth 22.80 Mexican pesos.

minimum sales income to somewhat offset program costs. Other new presentations are planned, such as a handy double pack of suppositories and a higher-priced, fancy package cycle of the same formulation of oral contraceptives at the regular market price. As for new products, it is PROFAM's intention to introduce a wide range of nonclinical contraceptive products. An effervescent vaginal tablet is currently under development.

All commonly known marketing practices are being applied to the development of PROFAM programs. We have developed purchasing and packaging elements. The necessary distribution strategies have been implemented and a carefully planned and tested advertising and promotional campaign will soon commence.

The primary premise is, "The reason is the consumer." And on this basis, the details of PROFAM's program have been developed. In 1978, we started what is probably the most comprehensive research program on family-planning motivations, knowledge, attitudes, and practices ever carried out. When the PROFAM distribution program was planned, the first consideration made was to learn as much about the consumer as possible. Although sufficient information was available in reference to usage and knowledge of contraceptive methods among women in general, little or no information was found for what motivated the behavior of women, and even less information with regard to men. It was then decided to carry out a three-phase, complete research program that would hopefully throw light on these motivational reasons, plus positive and negative attitudes, not only in reference to family planning, but also with regard to products, methods, and concepts (4).

The initial phase of the program consisted of a motivational analysis, the second of a quantitative research effort, and the third of a comprehensive retail KAP study. For the qualitative study, 44 group sessions were carried out in various areas of Mexico. Each group was homogeneously integrated, representing male and female users and nonusers of contraceptives in urban and rural areas. Also studied were two economic and two age groups. Each session was taped and monitored by psychologists to follow a preset theme guide. After all sessions were completed, each was individually analyzed and correlated with the others. Then conclusions were made and a formal report prepared. This document served as the basis of a questionnaire to be given to 2250 individuals, representing a statistically correct sample of PROFAM's potential consumers. What we hoped for was the development of certain behavioral hypotheses from the motivational results and, where possible, a degree of confirmation from the quantitative study.

The two initial phases have been completed and final conclusions are being written. A few initial results are as follows:

1. Previous government-sponsored motivational campaigns have been successful in increasing the awareness and acceptance of family planning. The great majority of people (over 80%) are in favor of contraception and more than half of all couples living in consensual union have used or are now using a contraceptive method.
2. Acceptance of family planning is higher among young, urban, well-educated, more affluent women, than among older, rural, uneducated, poor men.

3. Physicians and peer-group friends, whether the husband's or wife's, play the most important roles for or against family planning. The church influence was not considered of substantial importance, even in rural communities.
4. Oral contraceptives, injectables and IUDs are the best known methods, in that order. All are considered to cause side effects but are nevertheless widely used because they offer effectiveness.
5. Although both knowledge and practice were found to be higher than initially expected, there still exists a widespread lack of correct and complete knowledge of most contraceptive methods, characteristics, advantages and disadvantages.
6. The great majority of people favor a national program for education and distribution of contraceptive products. This acceptance includes educational efforts through mass media, such as magazines, radio, cinema and television.

More detailed results, which will consider motivational attitudes and behavior, will soon be available with the publication of final results.

The third phase of the study used a representative sample of retailers. A total of 36 cities in Mexico were visited and 580 food and 800 drugstore owners and employees were interviewed. The results were analyzed as to type of store, city size, use or nonuse of contraceptive products by the respondent, age, and work status.

Basically, attitude results corroborated those of the previous study. Most retailers indicated a definite approval of family planning. Also interesting was the high degree of importance the general public gave to the pharmacist's recommendation, even though the research indicated his relatively poor level of information and education about contraceptive methods. When specifically questioned about their individual support for a national contraceptive sales effort, over 80% of all retailers were clearly in favor of it. This support included willingness to place display units and promotional materials in the stores.

In addition to the large-scale program mentioned previously, a number of smaller, specifically directed research projects provided the following information (2):

1. A study indicated the approval of consumers for the name PROFAM for contraceptive products since it was found to have positive connotations.
2. A separate consumer analysis demonstrated that the right color for the oral contraceptive should be white, which connotes "medical effectiveness" and "no unhealthy side effects".
3. Another project helped to determine the final graphic details of the package (color, logo and figures).
4. Another helped to properly write the text of the instruction leaflets to provide correct understanding.

The above information shows that every possible step taken to develop the PROFAM program has been checked and analyzed for errors and, most important, has been based on the consumer's wants and needs. We have yet

to determine PROFAM's success. We have only started to distribute the products and to reach the consumer. Problems have been encountered, but it is more hopeful than before that the official 1982 objective of 2.5% annual population growth for Mexico will be achieved due to the social marketing of contraceptive products started by PROFAM. We are now certain to improve the quality of life for our children. PROFAM is expected to contribute significantly to this goal.

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Commercial Techniques to Promote Condom Use

MANUEL YLANAN

The Condom Marketing Research Project of the Population Center Foundation in the Philippines has completed its first year of implementation and results indicate that commercial communication and distribution techniques can produce a significant increase in the acceptance and use of condoms for family-planning purposes. Condom acceptance was achieved through an initial intensive combined effort of advertising, coupled with door-to-door sampling and selling. The result was a three- to fourfold increase in condom use over pretest levels. Six months afterwards, this high initial trial response had declined, as expected, but was held at levels representing two- to threefold increases over pretest levels.

Increased condom use was achieved, while the levels of use of other contraceptive methods available from the national program were maintained, resulting in a net overall increase in contraceptive practice in the test areas. On the basis of these findings, an estimated 300,000 to 600,000 new users of contraception could be added to the national program by the nationwide application of these commercial marketing techniques.

RESEARCH OBJECTIVE AND PLAN

The purpose of this research study is to determine whether or not, and to what degree, various combinations of commercial communication and distribution techniques are capable of bringing about a significant increase in the continuing use of condoms purchased from commercial retail outlets.

The commercial marketing combinations tested consisted of variations in retail price (10–25 centavos per condom), and variations in intensity of door-to-door effort, (5 rounds of sampling and selling vs. 2 rounds of sampling vs. no organized door-to-door effort, but rather, sampling at public markets and around stores by the salesman), combined, in all test areas, with an intensity of advertising effort judged to be optimum for a product introduction.

These marketing combinations were implemented in five test area modules of 10,000 homes each in the provinces of Pangasinan and Isabela, as indicated below. A control area is included in this research plan.

Area P-1 The towns of Urdaneta, Villasis, Rosales, and Sto. Tomas in the Province of Pangasinan.

Area P-2 The towns of San Jacinto, San Fabian, Mangaldan, and Manaog in the Province of Pangasinan.

Area I-1 The towns of Santiago, Cordon, Echague, and Alicia in the Province of Isabela.

Area I-2 The towns of Cauayan, Luna, Cabatuan, San Mateo, and Ramon in the Province of Isabela.

Area I-3 The towns of Ilagan, Tumauini, Sto. Tomas, Cabagan, Sta. Maria, and San Pablo, in the Province of Isabela.

Control Area The towns of Laoag, San Nicolas, Batac, Bacarra, Paoay, and Sarrat, in the Province of Ilocos Norte.

The effects of the various marketing combinations on the 10,000 couples in each test area were evaluated through three sample surveys. A sample of 500 married women of reproductive age (MWRA) was interviewed in each of the three surveys in each of the test areas. The first survey was conducted in all test areas and the control area in October 1977, just before implementing the test. This provided the baseline data.

A first follow-up study was conducted immediately after the initial intensive effort. For areas P-1 and I-1, the study was conducted in January, 1978. For areas P-2, I-2, I-3 and the control, the study was conducted in April, 1978. Six months after the first follow-up study, a second follow-up study was conducted, for areas P-1 and I-1 in July, 1978, and areas P-2 and I-2, I-3 and control, in November, 1978.

TEST OBJECTIVES AND PLAN

The overall test plan was divided into four phases, each with activities designed to meet a given objective. The preoperating phase was carried out over an 8-mo period preceding the actual test plan implementation. The objective of this phase was to select specific commercial communication and distribution approaches appropriate to the effective marketing of condoms for family planning.

The philosophy that finally emerged from this, and the strategy adopted for the application of the commercial technique, was that condoms should become a standard item of household use, to be purchased on a regular basis from retail outlets where most household needs can be bought. Condoms were thus classified into the low-retail-unit-cost, frequent-purchase category of packaged consumer products. The communication and distribution approaches appropriate and proven to be effective for this class of goods were also established. The choice of sari-sari stores (small neighborhood retail outlets carrying household needs), the choice of the pricing structure, of the door-to-door effort, and of the advertising approach were logical consequences.

The second objective of the preoperating phase was to determine the specific advertising, door-to-door sampling and selling, and retail distribution activities that would be implemented in each test area and subjected to the research evaluation. Research studies and actual field trials were conducted to establish which of several possible ways of carrying out these activities was

optimum for purposes of the test. Each of the marketing combinations to be tested needed to be operationally feasible and affordable when applied on a national scale.

The implementation of the test plan was divided into three sequential phases. The endpoint of each phase would be the availability of data which would permit a decision about whether or not to proceed with the subsequent step. phase I was launched on November 5, 1977 and completed by the end of October, 1978. The results of the research studies to evaluate phase I are the subject of this report.

The objective of phase I was to determine whether commercial communication and distribution techniques can bring about a significant increase in the use of condoms for family-planning purposes. The capability of the commercial system to accomplish this is unproven and must be established before additional resources are committed to the implementation of the plan.

Phase II is presently underway, having been launched on February 5, 1979 in all test areas. The objective of this phase is to determine whether the continuation of the commercial communication and distribution approaches at maintainance levels (as opposed to the intensive initial levels of phase I) can maintain a high level of use of condoms purchased from commercial retail outlets so that condoms become a standard trade item, regularly stocked by the commercial distribution system.

The crucial questions that will be answered in phase II are: Will the couples who have experienced satisfactory trial usage in phase I now go to their neighborhood retail stores to buy condoms? Will enough couples buy enough condoms regularly enough to provide the continuing volume of sales that justifies trade stocking? The follow-up research study, the retail sales distribution records, and the response of the trade channels will provide answers. Phase II should be completed by the end of November, 1979.

Phase III, is scheduled for implementation in 1980 in the entire Northern Luzon area, covering 14 provinces with a total population of 5,800,000. The objective of this phase is to validate the optimum marketing plan indicated by the results of the earlier, controlled, laboratory-scale, 10,000-home modules of phases I and II; but now, under actual field operating conditions and on a sufficiently broad scale to provide realistic bases for detailed operational planning and costing, preparatory to a nationwide launching. The manpower and organizational structure, the scheduling of working phases, and an accurate cost estimate for the subsequent nationwide launching, must be based on actual field experience.

PHASE I IMPLEMENTATION

The specific test activities carried out in each test area for phase I are outlined below. For all test areas and the control area the prestudy baseline research was conducted in October 1977. Implementation of the test activities started in all test areas on November 5, 1977.

For the areas P-1 and I-1, the initial intensive period covered the months of November and December with heavy, introductory-level radio advertising, retail distribution coverage, and 2 rounds of door-to-door sampling of

10,000 homes in each area with 6 condoms. The first follow-up study for these areas was conducted in January 1978.

For the areas P-2 and I-2, the initial intensive period was from November 1977 through March 1978, with heavy, introductory-level radio advertising, retail distribution coverage, and 2 rounds of door-to-door sampling with 6 condoms followed by 3 rounds of door-to-door selling of condoms with premium offers, for a total of 5 rounds of coverage of 10,000 homes in each area. The first follow-up study for these areas was conducted in April, 1978.

For area I-3, the initial intensive activity was from November 1977 through March 1978, with heavy, introductory-level radio advertising, retail distribution coverage and sampling, with 6 condoms, of housewives doing their marketing at public markets and of homes surrounding neighborhood retail stores by the retail distribution salesman. The first follow-up study for this area was conducted in April 1978.

There were no test activities of any kind carried out in the control area and the first follow-up study was conducted there on April 1978.

In all test areas, for the 6-mo period following the first follow-up study, the test activities consisted of continuing radio advertising at heavy, introductory levels and continuing retail distribution coverage to maintain availability and accessibility of condoms. Of all meaningful retail outlets in the test areas, 75%–85% were carrying condom stocks during this period. The second follow-up study was conducted in July 1978 for areas P-1 and I-1 and in November 1978 for areas P-2, I-2, I-3 and the control area.

Since the objective of phase I is to determine whether commercial communication and distribution techniques can bring about a significant increase in condom usage for family planning, the specific test activities, which are combinations of these techniques, are designed to attain this objective. The variations being tested represent various cost levels and expected sales income levels. The test is intended to identify which of these variations is optimum when implemented on a national scale.

The variation in retail price, (25 centavos per condom in P-1 and P-2 vs. 10 centavos per in I-1, I-2, and I-3) is intended to determine what volume of consumer purchasing can be generated at these retail prices, and therefore, what total sales income can be generated at each of these retail price levels.

The variation in door-to-door sampling and selling activity (2 rounds of sampling in areas P-2 and I-1 vs. 5 rounds of sampling/selling in areas P-2 and I-2 vs. market sampling and store neighborhood sampling in area I-3) is intended to determine what levels of trial usage of condoms can be generated by varying intensities of door-to-door coverage. Each intensity level represents a correspondingly different cost level. The rationale for the door-to-door coverage is that satisfactory trial experience with condoms for family planning will result in regular usage and that repeated trial opportunity will produce higher levels of regular usage.

DATA ANALYSIS APPROACH

The research results discussed here are derived from the studies conducted in the five test areas and the control area of the Condom Marketing

Research Project of the Population Center Foundation in the Philippines. The test activities being subjected to research evaluation are being implemented in test modules of 10,000 homes each. A sample of 500 married women of reproductive age (MWRA) from each module were interviewed for these studies. The data from these interviews reflect the effect of the test activities on the MWRA in the test areas.

Although these test areas and the control area are fairly typical of rural Philippine areas, they were not selected for this research study on a statistical basis and are not presented in the following discussions as statistically representative of total rural Philippines. However, we do make projections and extrapolations of the data and we must caution the reader that although the research data provide the bases, the inferences and conclusions drawn rely, to a large extent, on informed personal judgment and professional operating familiarity with the social and economic dynamics of the process being evaluated.

This approach to data analysis does not look for mathematically precise distinctions. It uses the research data to provide indications and directions and establish general parameters within which the project can be reasonably expected to operate. It is adequate and appropriate for our purpose at this point in the development of the research project.

Our purpose in the following discussion is to establish a ball-park figure for the possible national condom usage levels and consequent national sales volume that can be reasonably expected from the application of commercial communication and distribution techniques on a national scale. Similarly, the desired mix of commercial techniques now indicated by the research can be costed on the basis of a national scale implementation. With these general estimates of income and expense, it will be possible to make an informed judgment as to the economic feasibility and operational viability of the project on a national scale.

If at this early stage, the general indications are that we do not have a feasible and viable project, prudence dictates that all further test efforts be abandoned. If, as is the case in this instance, the early results provide the basis for proceeding with the test plan, we can look to the research results from phases II and III to further refine and enlarge our knowledge and capability to design and implement a cost-effective commercial marketing system for condoms for family planning.

PHASE I RESEARCH RESULTS

Table 31-1 shows past-month condom usage. It can be seen from comparing Column A to Column B that a three- to fourfold increase in condom usage took place in all test areas immediately after the initial intensive effort. To facilitate comparison the percentages are indexed with the baseline usage level at 100. The control area, it will be noted, experienced no increase in usage.

Six months after the first follow-up study in all test areas, the usage had declined as expected (comparing Column B to Column C). However, the usage levels recorded were still two to three times greater than the pretest

TABLE 31-1. % MCRA* Using Condoms in Past Month

	A (%)	B (%)	C (%)	D (%)	E (%)
Pangasinan I	7 (100)	27 (385)	18 (257)	9 8	8.2
Isabela I	5 (100)	20 (400)	13 (260)	7.0	6.0
Pangasinan II	9 (100)	35 (388)	24 (266)	12.6	11.4
Isabela II	4 (100)	19 (475)	12 (300)	5.6	6.4
Isabela III	4 (100	14 (325)	8 (200)	5.6	2.4
Control Area	5 (100)	5 (100)	7 (140)		

*Married Couples of Reproductive Age

Column A Prestudy baseline conducted October 1977.

Column B First follow-up study conducted January 1978 in Pangasinan 1 and Isabela 2 and April 1978 in Pangasinan 2, Isabela 2, Isabela 3, and control area.

Column C Second follow-up study conducted in July 1978 for areas P-1 and I-1, and in November 1978 for areas P-2, I-2, I-3, and the control area.

Column D Use level at normal growth trend (40%).

Column E Net additional use.

levels (comparing Column C to Column A). The control area registered a 40% increase in past-month use.

If we assume that the 40% increase in past-month use in the control area reflects the growth trend in condom acceptance normally experienced by the national program during the period, we should discount the two- to three-fold increase in use experienced in the test areas by this value. Column D of Table 31-1 shows the effect of this "normal" 40% growth on the pretest use levels (Column A) and Column E shows the percentage points of use increase attributable solely to the commercial communication and distribution efforts in these areas.

This 6% to 11% range of additional use from the test activities in areas P-1 [illegible] P-2, and I-2, when applied to the total estimated married couples of repr[illegible]ve age (MCRA) in the country in 1979 (5,775,600) indicates 346,5[illegible] to 635,300 new users could be added to the national program by these commercial techniques when applied on a nationwide scale. The significance of this can be appreciated when it is noted that the national program target for new acceptors of all methods in 1979 is only 477,500.

That the additional condom use brought about by the use of commercial techniques is in addition to the all-method use normally brought about by the national program is evidenced by the research results. Table 31-2 shows the use, during the month preceding the interview, of all program methods. Note that the use of all program methods had increased significantly in all test areas except I-3. The control area had also experienced growth of 6%.

However, the growth experienced by the test areas can be almost entirely accounted for by growth in condom use. The other program methods are relatively stagnant, with oral pills even showing some decline. The notable exception is rhythm, which shows growth in all areas except P-1.

TABLE 31-2. % MCRA* Using Program Methods in Past Month

	P-1			I-1			P-2			I-2			I-3			CONTROL		
	A (%)	*B* (%)	*C* (%)	*A* (%)	*B* (%)	*C* (%)	*A* (%)	*B* (%)	*C* (%)	*A* (%)	*B* (%)	*C* (%)	*A* (%)	*B* (%)	*C* (%)	*A* (%)	*B* (%)	*C* (%)
Condoms	7	27	18	5	20	13	9	35	24	4	19	12	4	14	8	5	5	7
Rhythm	10	11	10	9	13	15	9	14	15	9	10	16	7	7	12	11	16	20
Oral pills	9	8	10	7	8	7	6	7	7	9	6	8	9	7	7	5	3	6
Fem. ster.	4	4	4	5	5	2	2	3	—	4	5	1	5	6	2	5	6	—
IUD	2	2	1	1	1	1	2	1	2	3	3	3	4	3	2	3	3	2
Vasectomy	—	—	1	2	2	—	—	—	—	—	1	—	1	1	—	—	—	—
TOTAL	32	52	44	29	49	38	28	60	48	29	44	40	30	38	31	29	33	35

*Married Couples of Reproductive Age

Column A Prestudy baseline conducted October 1977.

Column B First follow-up study conducted January 1978 in Pangasinan 1 and Isabela 2 and April 1978 in Pangasinan 2, Isabela 2, Isabela 3, and control area.

Column C Second follow-up study conducted in July 1978 for areas P-1 and I-1, and in November 1978 for areas P-2, I-2, I-3, and control area.

These research results are consistent with trends in national program statistics which indicate growth for condom and decline for oral pill acceptance. The control area shows condom use growth, though not to the same significant degree as in the test areas where the commercial techniques had been applied.

Other data obtained through the research studies support and reinforce the findings on past-month use. The data on condom trial (See Table 31-3) indicate the high level of trial use of condoms obtained after the initial intensive period. Similarly the data on condoms found in the home at the time of interview (See Table 31-4) reflect the effects of the initial intensive effort. All these results consistently point to the fact that the commercial marketing techniques tested are capable of securing a high level of condom acceptance and use. The conclusion can be drawn, therefore, that the objective of phase I has been attained.

PROJECT VIABILITY

The research results reported here cover only the activities of phase I and the possible additional usage indicated above is the result only of the initial intensive effort consisting of heavy, introductory-level advertising and door-to-door activities. What still remains to be established by phase II research is whether these levels of use will be maintained or perhaps even increased in the 2nd year of applying the commercial marketing techniques when the intensive introductory support is reduced to normal maintainance levels.

In order to reach a conclusion about the viability of a national application of the commercial marketing techniques, however, it is necessary to make some judgments about the use levels that can be expected to result from the first few years of national application. The reason for this is that the intensive initial effort required to launch a new product requires a heavy invest-

TABLE 31-3. % MCRA* Ever Tried Condoms

	A (%)	B (%)	C (%)
Pangasinan I	16 (100)	37 (231)	40 (250)
Isabela I	14 (100)	33 (236)	34 (243)
Pangasinan II	21 (100)	49 (233)	54 (257)
Isabela II	12 (100)	36 (300)	38 (314)
Isabela III	16 (100)	28 (175)	30 (187)
Control Area	15 (100)	18 (120)	19 (130)

*Married Couples of Reproductive Age

Column A Prestudy baseline conducted October 1977.

Column B First follow-up study conducted January 1978 in Pangasinan 1 and Isabela 2 and April 1978 in Pangasinan 2, Isabela 2, Isabela 3, and control area.

Column C Second follow-up study conducted in July 1978 for areas P-1, and I-1, and in November 1978 for areas P-2, I-2, I-3, and the control area.

ment in the first years. The income from the sales of product, on the other hand, starts at low levels in the first years and eventually grows to normal, going-basis levels. The viability of the project is gauged by the capability of the sales income to completely recover the initial heavy investment in a reasonable period of time.

Based on the early research data provided by phase I (Table 31-5) and, without the sales volume results still to be produced by phase II, we have made the judgment that the nationwide application of the commercial marketing techniques being tested can reasonably be expected to produce sales income sufficient to completely recover the initial introductory investment in 4.5 years. In the subsequent years, the project is expected to generate sufficient sales income each year to completely recover its communication and distribution expenses for that year.

This means that a significant number of new users (roughly equivalent to the entire new acceptor target of the national program) can be added to the national program. And, if the phase II results confirm this, the initial level of use could be maintained over the succeeding years and even enlarged gradually. Most importantly, this can be achieved by the national program with no cost for the communication and distribution effort. The only cost would be for the acquisition of the condoms themselves. A substantial cash outlay will have to be made in the first two years but as seen in Table 31-5, this amount could be completely recovered in 4.5 years.

The important assumptions that underlie the figures in Table 31-5 are as follow:

Sales Volume The basis for the sale income figures in Table 31-5 is the estimated volume of sales which can be reasonably expected from the project. The first 2 years' sales volume is a reflection of the capability of the sales

TABLE 31-4. % MCRA* With Condoms in the Home When Interviewed

	A (%)	B (%)	C (%)
Pangasinan I	6 (100)	50 (833)	24 (400)
Isabela I	4 (100)	31 (775)	14 (350)
Pangasinan II	10 (100)	50 (500)	25 (250)
Isabela II	6 (100)	31 (516)	18 (300)
Isabela III	6 (100)	11 (183)	8 (133)
Control Area	7 (100)	7 (100)	9 (128)

*Married Couples of Reproductive Age

Column A Prestudy baseline conducted October 1977.

Column B First follow-up study conducted January 1978 in Pangasinan 1 and Isabela 1 and April 1978 in Pangasinan 2, Isabela 2, Isabela 3, and control area.

Column C Second follow-up study conducted in July 1978 for areas P-1, and I-1, and in November 1978 for areas P-2, I-2, I-3, and the control area.

force to make initial placements with the retail outlets, numbering about 30,000, and with drugstores and wholesalers. Subsequent years reflect the effect of consumption (actual use of condoms) on sales. Table 31-6 indicates that the 2nd year assumes sales of 212,000 gross representing the use level of 696,000 regular user-couples or 11% of the total MCRA. This calculation accepts the high end of the range (5% to 11%) shown by the research of possible additional new users from the application of the commercial marketing techniques being tested.

Subsequent years are shown on Table 31-6 to account for the regular use of 14%, 15%, and 16% of total MCRA. This is considered a reasonable growth expectation. However, the actual sales volume experience of phase II will eventually provide a more factual basis for making this forecast of sales.

Retail Pricing The research results do not show any significant differences in use and acceptance that can be attributed to the differences in retail price between areas. Because the sales income from the 25-centavo retail price is

TABLE 31-5. Economic Viability of Project (In Millions of Pesos)

	YEAR I	YEAR II	YEAR III	YEAR IV	YEAR V
Estimated Cost of National Application	7.4	5.3	5.0	5.0	5.0
Estimated Income from Sales	1.6	5.1	6.7	7.4	8.1
Net Gain (or Loss)	(5.8)	(0.2)	1.7	2.4	3.1
Cumulative Gain (or Loss)	(5.8)	(6.0)	(4.3)	(1.9)	1.2

TABLE 31-6. Forecast for Sales and New Users

	YEAR I	YEAR II	YEAR III	YEAR IV	YEAR V
Estimated Income of From Sales (millions)	1.6	5.1	6.7	7.4	8.1
Estimated Sales (in thousand gross)	69	212	304	336	369
Estimated Users (thousand)*	207	695.9	913.1	1008.6	1108.2
Total MCRA (thousand)†	6136 8	6326.2	6522.3	6724 5	6926.2
% Users to Total MCRA	3%	11%	14%	15%	16%

*Research results from the test areas indicated that the average number of times couples engage in sexual intercouse in one month is 4

†Assume Year I to be 1981; Year II, 1982, etc

substantially greater than the 10-centavo retail price, the calculations of sales income, in Table 31-5 assume a 25-centavo retail price.

Distribution Cost The need to make condoms easily and conveniently available to rural couples dictates that the sales effort be initially concentrated on retail outlets. This is an expensive approach because the retail outlets are numerous and their individual purchases are only in dozen pieces. The possibility of reducing this cost by sharing the retail distribution effort with other products which have the same coverage objectives is being explored. High nutrition products for children are being seriously considered.

Door-to-door Cost The research results of phase I indicate that considerable savings in cost could be attained without significantly reducing the trial use effects of the door-to-door effort. For purposes of cost estimating, we have assumed that trial use of condoms will be sought through sampling at public markets and around stores (as was done in I-3) and door-to-door selling of condoms with premium offers (as was done in areas P-2 and I-2). Market and store sampling does not require specialized door-to-door teams and door-to-door selling costs can be offset, in part, by the income from its sales.

The research results for phase I provided the bases for the judgments that are incorporated in the assumptions previously discussed. In addition to the past-month use, the research provided data on the effects of advertising and door-to-door sampling and selling, on the attitudes of consumers towards advertising condoms and selling condoms through neighborhood stores, attitudes towards the use of condoms for family planning, and their perceptions of the various product and use characteristics of condoms. These research results will be analyzed in depth and will become part of the documentation for this project.

In general, it can be said that the optimism reflected in the judgment that the national application of the commercial marketing techniques being tested will be economically feasible and operationally viable stems from the generally favorable tenor of the research results. The condom is basically ac-

ceptable as a family-planning method and there are no serious objections to its use. The advertising of condoms, and the sale of condoms through neighborhood retail stores was not considered objectionable by the people of the rural communities in the test areas. The active cooperation of local government officials and community leaders was easily obtained. This receptive environment actually experienced by the test areas is in sharp contrast with earlier expectations of hostility and opposition to the commercial marketing of condoms. This positive atmosphere provides the confidence that the forecasts of use levels we have made are reasonable. It now remains for the sales and regular use data from the phase II implementation to indicate whether the projections and extrapolations we have made from phase I results are valid.

COMMUNITY-BASED DISTRIBUTION PROGRAMS

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32

Community Distribution Programs and Barrier Methods in Guatemala

ROBERTO SANTISO-GALVEZ

The Asociación Pro Bienestar de la Familia de Guatemala (APROFAM) is legally constituted according to local law and affiliated with the International Planned Parenthood Federation (IPPF). APROFAM started its clinic services in 1965.

In 1976 APROFAM initiated a Community Distribution Program (CDP) in two densely populated zones of Guatemala City with extensive poor areas. Prior investigations had demonstrated that other family-planning clinics were having difficulties in attending to the needs of the users, especially because

1. There was too much demand for clinic services;
2. Patients had to wait an average of 1 hr at the clinic to obtain a contraceptive method;
3. Patients were subjected to impersonal treatment by the clinic personnel, who were poorly motivated and faced excessive work;
4. The clinic was open for too few hours, considering the large number of potential users who worked.

The target population to be served by the APROFAM clinic was studied and a goal was set to reach 30% of the women of fertile age; this meant that 5,756 new contraceptive acceptors were to be served by the CDP.

SELECTION OF PERSONNEL

Promoters of the program were selected and given special training. Promoters were selected for this role on the basis of their recognition as natural community leaders and because of their support of family planning. They were expected to promote and disseminate information on contraceptive methods through group meetings and house calls and to supervise the contraceptive distribution activities and keep statistical records.

As it was a pilot program, each promoter worked with 10 distributors. Four promoters and 40 distributors were involved initially.

PROGRAM SUCCESS

During the first year 5,400 new acceptors entered the program, constituting 93% of the set target. This was considered a success, given the opposition

TABLE 32-1. Reasons Given for Requesting Family-Planning Services

REASON	(%)
No more pregnancies desired (limiters)	54
Pregnancy spacing	44
Health	1
Economic	1

TABLE 32-2. Contraceptive Method Chosen by APROFAM Users During 1976

METHOD	%
Oral contraceptives	90
Neo-Sampoon	5
Condom	4
Foams and vaginal gels	1

TABLE 32-3. Clinic Services: Accumulated Admissions, 1968–1978

METHOD	NUMBER	%
Oral contraceptives	74,347	57
Intrauterine device	22,876	17
Female sterilization	13,921	11
Local methods	9,150	7
Injections	8,007	6
Vasectomy	2,690	2
Total	130,991	100

of influential medical and paramedical personnel in several sectors.

After 1 year, a survey of 540 acceptors (10% of the total group was made (5). Table 32-1 lists the primary reasons given for requesting family-planning services and Table 32-2 gives a breakdown of the group according to contraceptive methods chosen: 90% used oral contraceptives (OC) and 10% used local methods.

Following the survey, and informational campaign on surgical birth control methods was initiated, which resulted in increased acceptance of surgical contraception. By the end of 1978, female sterilization procedures and vasectomies accounted for 13% of all the methods provided by the clinical systems (2) (Table 32-3). The proportion of persons selecting barrier methods was 7%. However, analyzing specifically the clinical services of 1978, acceptance of the condom and other barrier methods increased markedly to 19% (Table 32-4).

Owing to the success of the CDP in Guatemala City, other projects were started that involved sectors of organized workers (cooperatives, "Ligas

TABLE 32-4. Temporary Contraceptive Methods Chosen by APROFAM Clinic Users, 1978

METHOD	%
Oral contraceptives	55
Intrauterine devices	22
Local or barrier methods	14
Condom	5
Injectables	4

Campesinas") as well as production sectors (coffee and cotton growers), an integral development project called "Tac-Tic," and a project with special emphasis on person-to-person communication complemented by community distribution. Tac-Tic Project is located in an Indian community, where conservative sociocultural standards do not permit easy acceptance of innovative programs (2). The cotton and coffee growers project had limited influence, owing to the high proportion of migratory workers who visit for only 3 mo during the harvest. This migratory working population expressed no interest in family planning. The reasons for this are being investigated. The success achieved by the other programs was acceptable: from 51.6% for the Communication Project and Person-to-Person Services to 106.5% for Campesino Leagues.

The CDP has had a significant increase from its initiation in 1976. It has grown from 5,406 new acceptors in 1976 to 13,237 in 1978. In 1976 it accounted for 29% of all new acceptors of APROFAM and, by 1978, this percentage had increased to 57%.

Of the 13,237 CDP acceptors in 1978, 9,600 (73%) chose oral contraceptives and 3,637 (27%) chose various barrier methods. The number of contraceptives distributed by CDP is given in Table 32-5.

The Guatemalan CDP was designed as a service activity, and therefore it has no built-in systems for evaluation, for recording secondary side effects of the various contraceptives, reasons for withdrawal from the program nor for discontinuing use by method. Qualitative and quantitative systems for evaluation are presently being designed.

The expansion of the CDP has met various obstacles due to the particular characteristics of the Guatemalan population (3).

Distribution

Rural 66%, urban 34% (4)

Ethnic groups

50% Latin, 50% Indian; special problems of communication arise because there are four main languages and approximately 22 dialects.

Illiteracy

In the 1973 census, the illiteracy rate was 52%; in rural areas, it reached 72%.

High infant mortality rate

79:1000 live births.

TABLE 32-5. Community Distribution Program, 1978

CONTRACEPTIVES	AMOUNT DISTRIBUTED	REGISTERED ACCEPTORS	% OF TOTAL REGISTERED
Oral contraceptives	59,012 cycles	9,600	73
Condoms	18,127 dozen	3,637	27
Neo-Sampoon	2,700 containers		
Gels and foams	1,273 containers		

TABLE 32-6. Types of Contraceptives Sold by Pharmacies in Quiché, 1978

METHOD	%
Oral contraceptives	50
Condom	22
Vaginal tablets	21
Injectables	7

Child labor

Working minors especially in the rural areas; children as young as 6 years old provide some working help to their parents.

Religion

It is estimated that 95% of the Guatemalan population is Catholic.

For these reasons, other channels for the distribution of contraceptives in the rural areas and specifically in the regions inhabited by the native population are being investigated. A study in the province of Quiché (1), where the population is 85% Indian, revealed that although the percentage of women of fertile age using contraceptives was very low, the main distribution source of contraceptives was the National Health Services, followed closely by the drug stores. This study also showed that sales of barrier methods reached 43%, in 1978 (Table 32-6). A study is presently underway to determine the usage of different contraceptive methods on a national basis. Therefore, new strategies are being designed which will permit greater coverage.

CONCLUSIONS

1. The Guatemalan Community Distribution Program has grown rapidly since its inception in 1976.
2. The use of barrier methods has increased notably in these programs.
3. It is believed that the use of barrier methods will continue to increase.
4. The relatively high cost of contraceptive methods that can be utilized without medical or health professional intervention is an obstacle to their utilization by the economically poor population. Usually barrier and other local contraceptive methods are not among the subsidized or free commodities supplied by international assistance programs and foundations.

Providing these methods to the population at a nominal price would facilitate their acceptability and use.

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The Condom in Rural Bangladesh

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The Cholera Research Laboratory (CRL) has assessed the knowledge and practice of condom use in two areas of rural Bangladesh; in one, condoms and instructions were distributed to all interested couples in August 1976, and the other received no special effort. Survey results confirmed field reports that many men initially identified condoms as balloons or children's toys. Colored condoms provided to half the intensive distribution area did not result in higher rates of use. In the nondistribution area a minority of men (37%) were able to identify a family-planning use for the condom. Although two-thirds of all men knew where to obtain condoms and the majority also knew the cost, only 16% could correctly describe the use of a condom. By contrast, in the intensive distribution area, 89% could identify the condom as a contraceptive, 93% knew where to obtain supplies, 86% knew it was free, and 45% could describe the correct use of condom. However, the condom practice rate increased only modestly from 1.2% to 3.8%. It seems that considerable educational and promotional work will be required to substantially increase condom use in rural Bangladesh. Social marketing efforts may be helping to correct this problem.

The condom has been a versatile contraceptive for centuries and is now being promoted and distributed by a variety of techniques in many countries, including South Asia (3). The Indian Nirodh condom sales increased considerably from 1968-1973 and this method was being used by an estimated 2.9 million Indian couples (2.7% of reproductive-age couples) in 1976 (3,4). In Pakistan, the condom was reportedly the most popular method for promoters in the field, yet there were concerns that large quantities had been misused, even though the details were unclear (3,4). The effectiveness of a method cannot always be assessed by the quantities distributed.

A pilot project to provide oral contraceptives and condoms to all eligible couples was undertaken in one thana (county) of rural Bangladesh by the CRL in October, 1975. The purpose of this project was to determine the acceptability and effectiveness of a simple house-to-house delivery system of contraceptives. Contraceptives were distributed in 143 villages, half the 260,000 population of the Matlab Thana field surveillance area (FSA). The other half—the nondistribution area—received family-planning services from the national programs.

EARLY EXPERIENCE WITH CONDOMS

This study arose from the need to examine some of the factors related to the low level of condom use and the lethargic response to our promotion of the condom. Our field workers reported that some men did not know the condom could be used for family planning and, more importantly, they seemed reluctant to consider it as a method they might use because of its association as a child's toy. We found that plain (noncolored) condoms, the same as were provided through the national family-planning program were being sold through village shops and local bazaars, children reportedly being the principal purchasers. Condoms had been regularly sold during the preceding 2–3 years. Furthermore, our female village-level workers (dais) who carried oral contraceptives and condoms with them daily during home visits sometimes complained that children would pester them to obtain condoms. When our male field workers visited households to provide condoms and instructions, children often urged their parents to take the supplies. In turn, parents who received condoms (usually 1 dozen) would sometimes placate the child with a few condoms and place the remainder in safe-keeping.

The extent to which children were familiar with the condom as a toy was not so important to us as was the extent to which adults were unfamiliar with the condom as a contraceptive. That many adults did not perceive the condom as a contraceptive seemed consistent with our observation of a low baseline level of condom practice, despite moderate availability through local markets and government workers. Full availability through the CRL dais (who carried condoms through the village daily) resulted in only a modest increase in use. Admittedly, the main emphasis was on oral contraceptives during the early months of the program, as this was considered a more effective method, and the vigorous introduction of only one method at a time seemed appropriate for this noncontracepting population. However, as pill acceptors began dropping out, many were using no method, and a special intensive promotion of condoms seemed appropriate 9 mo after the start of the program.

METHODS

The special distribution of condoms included new educational materials with explicit pictorial instructions. These were developed at the suggestion of Bangladeshi staff with the help of villagers. The instructions could then be given to the husband or, if he was not present during the interview, to his wife. The community may also become more sensitized to the intended use of condoms. Even though the distribution was conducted during the monsoon, when many men were unemployed and more likely to be at home, only 25% were present during the visit. Therefore, the instructions and one dozen condoms were usually provided to women. Colored condoms were given in half of the distribution area and the other half received plain condoms.

The proportion of eligible couples using condoms and other methods of contraception was assessed every 3 mo, by means of a prevalen Twenty per-

cent of the villages in the condom distribution and nondistribution areas were included.

The impact of our efforts on the knowledge of condoms was assessed by a survey in November 1976. We selected 510 baris* (the sampling units) in the contraceptive distribution area and a similar number in the nondistribution area. This number was chosen because we wished to interview at least 250 male respondents in each area, and our pretesting interviews suggested that only 50% of baris would have an eligible male at home.

Following a random start, a systematic sample of 10% of villages in each area was identified and equal numbers of baris from each village within an area were sequentially identified from the CRL census. This procedure resulted in the selection of a total of 32 villages with an average cluster size of 32 baris each. If the designated number of baris could not be obtained in one village, the next adjacent village was then included to obtain the required cluster size.

Eligible males were defined as husbands of nonmenopausal women, aged 15–44 years. Only one respondent was selected from each bari because pretesting indicated subsequent interviews in the same bari were invariably contaminated by the first. If the first household did not contain an eligible man the interviewer proceeded sequentially to the next house according to the CRL census numbers until he found a respondent or exhausted all the houses in that bari.

The interviewer showed several condoms (one of which was in clear view through the transparent wrapping) to men and asked six questions about the identity and use of the condom as follows: 1) "What is this used for?"; 2) (Asked of respondents indicating a noncontraceptive use on the first question) "Can it be used for anything else?"; 3) "From whom would you obtain it?"; 4) "At what distance from your house could you obtain it?"; 5) "How much would it cost?"; and 6) "Can you explain how this should be used as a family-planning method?" An understanding of how the condom was to be applied, used, and removed was given credit as being "correct." Less than a complete understanding was considered "partially correct," if the man understood the condom should cover the penis during intercourse. For practical purposes the interviewer's distinction between these latter two categories was fairly arbitrary.

RESULTS

Based on the quarterly prevalence surveys, condom use was very low before the contraceptive program was begun in Matlab Thana. The prevalent rate of use increased from 0.02% to 1.2% in the contraceptive distribution area over 9 mo and remained at 0.2% in the nondistribution area. With intensive educational and distribution efforts, 35% of couples received condoms, but the active user rate increased only ot 3.8%. The villages receiving colored condoms did not report a higher rate of use (Table 33-1). This finding was

* A group of patrilineally related households containing an average of 5–6 families with 30–35 members

TABLE 33-1. Contraceptive Use Rate for Married Fecund Women Aged 15–44; Colored and Plain Condom Areas; Prevalence Survey, Matlab, November 1976

	COLORED CONDOMS DISTRIBUTED		PLAIN CONDOMS DISTRIBUTED		COMBINED AREAS	
Women interviewed	2507		1757		4264	
Method Currently Used	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Oral contraceptives	280	11.2	158	9.0	438	10.3
Condoms	88	3.5	73	4.2	161	3.8
Other	20	0.8	17	1.0	37	0.9
Total	388	15.5	248	14.1	636	14.9

consistent with field worker impressions that colored condoms as such produced little reaction, positive or negative. Condom use remained much lower than pills or injectables, where these alternative methods were offered in competition.

To compare the condom distribution with an earlier distribution of oral contraceptives, 69% of all "eligible" couples initially received pills and 17% were using this method 3 mo following the distribution. The special condom distribution raised the overall contraceptive use rate from 14% to 15%, whereas the addition of condoms *and* injectables in selected villages raised the rate from 14% to 21%. The vast majority of new users in these villages chose the injectables. The reluctance to use condoms was thereby established.

When initially asked to identify a condom, almost four times as many in the contraceptive area identified it initially as a method of family planning (46.5%), compared to 12.8% in the nondistribution area (Table 33-2). However, more than half in the contraceptive area and 82% in the nondistribution area identified it first as a balloon or toy, or could not identify it.

A degree of modesty was detected on the pretest, possibly resulting in some reluctance to specify the contraceptive purpose of the condom. Therefore, the second question was asked to those who did not initially identify a contraceptive function. With this additional question a total of 88.6% and 36.8% were able to identify a family-planning use for the condom in the contraceptive and nondistribution areas, respectively (Table 33-3).

TABLE 33-2. Initial Identification of Use of Condom; Matlab, November 1976

	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
Contraceptive	139	46.5	37	12.8
Balloon, toy or other	142	47.5	158	54.9
Contraceptive and balloon, toy or other	8	2.6	15	5.2
Do not know	10	3.3	78	27.1
Total	299	99.9	288	100.0

TABLE 33-3. Ability to Identify the Condom as a Contraceptive on Either Initial or Secondary Response*; Matlab, November 1976

USE IDENTIFIED	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
Contraceptive	265	88.6	106	36.8
Noncontraceptive only or not known	34	11.4	182	63.2
Total	299	100.0	288	100.0

*Men initially identifying the condom as a balloon, toy or "other" (Table 33-2) were then asked if they knew of any additional use for the product. Those indicating a contraceptive use were added to those in Table 33-2 to determine the maximum number aware of a family-planning use for the condom.

The large majority in the contraceptive area correctly named the CRL female village worker as a source of condoms in their village and some named additional sources (Table 33-4). Only 6.7% did not know where to obtain a condom in the contraceptive area in contrast to 32.6% in the nondistribution area. The majority in the nondistribution area identified a market or shop as the place to obtain condoms, although there was no official commercial marketing activity in Matlab Thana.

Availability was assessed by asking at what distance from his home the man could obtain a condom. In the distribution area, 75% correctly named their own village as the nearest point to obtain condoms (Table 33-5). Only 1% of men in the nondistribution area named their own village; however 50% knew a source within 2 miles of their homes.

The cost of a condom was indicated as less than 20 paisa (1.3 cents U.S.) by over half those in the nondistribution area and most of the remainder did not know the cost (Table 33-6). Over 90% in the distribution area indicated the condom was either free (as provided by CRL) or less than 10 paisa.

TABLE 33-4. Reported Sources of Condoms*; Matlab 1976

SOURCE	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
CRL field worker	257	86.0	2	0.7
Market or shop	47	15.7	156	54.2
Government worker	20	6.7	49	17.0
Fertility res. clinic (Matlab)	0	0.0	4	1.4
None known	20	6.7	94	32.3
Total	344	115.1†	305	105.9†

*Men were asked "From whom would you obtain this product"?

†Percentages total to more than 100 because more than one source could be named by each respondent.

TABLE 33-5. Distance From Household Where Condoms Could be Obtained; Matlab, November 1976

LOCATION OF SOURCE	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
Within own village	224	74.9	3	1.0
Outside village -				
< 1 mile	55	18.4	93	32.3
1-2 miles	0	0.0	51	17 7
3-4 "	0	0.0	37	12.8
5+ "	0	0.0	7	2.4
None known	20	6.7	97	33.7
Total	299	100 0	288	99.9

One-third of men in the distribution area and two-thirds in the nondistribution area could not explain how the condom could be used as a family-planning method (Table 33-7). This question was inadvertently omitted during some of the first interviews; however, the overall results would not have been substantially influenced. Reluctance to describe the correct use of the condom might be greater in the nondistribution area, although the responses are fairly consistent with the initial low number correctly identifying the condom as a family-planning method (Table 33-2). More than four times as many in the distribution area could correctly describe the use of a condom.

The survey has confirmed that men outside the special distribution area generally could not identify the condom as a contraceptive. The situation was improved in the contraceptive distribution area, although, even there, almost half initially identified it as a toy. Consistent with these findings was the widespread inability by men in the nondistribution area to correctly describe the use of the condom, despite the fact that it had been generally available for several years. Most of these men knew who provided condoms, where to find the product, and how much the condom cost. The widespread

TABLE 33-6. Reported Cost of One Condom; Matlab, November 1976

COST	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
Free	256	85.6	37	12.8
*1-10 Paisa**	15	5.0	76	26.4
11-20 "	0	0.0	44	15.3
21-30 "	0	0.0	3	1.0
31-40 "	0	0.0	2	0.7
41+ "	0	0.0	1	0.3
Not known	28	9.4	125	43.4
Total	299	100.0	288	99.9

*15 Paisa = $0.01 U.S.

TABLE 33-7. Ability to Describe the Use of the Condom as a Contraceptive; Matlab, November 1976

RESPONSE	CONTRACEPTIVE DISTRIBUTION AREA		NONDISTRIBUTION AREA	
	Number	*(%)*	*Number*	*(%)*
Correct	133	44.5	28	9.7
Partially correct	35	11.7	18	6.3
Incorrect	1	0.3	1	0.3
Could not respond	99	33.1	197	68.4
Question not asked	31	10.4	44	15.3
Total	299	100.0	288	100.0

unofficial marketing of condoms in the nondistribution area was confirmed, the price generally being below the 20–30 paisa price of commercial balloons.

Records show that condoms were regularly received by the local Government program from October 1971 to 1977 (6). Previous records were reportedly lost in the War of Liberation. From 6,000–11,000 dozen condoms were received annually from 1973 to 1976. Based on the above supply data, between 2.1% and 3.4% of the estimated 24,300 eligible Matlab Thana couples should have been active users from 1971–1976 (assuming 12 condoms/mo/couple). However our baseline survey in November 1975 found 0.2% reporting active condom use. This information is consistent with our findings that the condom is not readily used by men in this area.

DISCUSSION

One might ask if our findings are likely to be unique only to this one area of Bangladesh. National reports for the quarter ending December 31, 1975 indicate sufficient condoms were being distributed to supply 2.7% of Bangladesh's 16 million fertile couples (7). However, the Bangladesh Fertility Survey (BFS) conducted in late 1975 and early 1976 found 0.9% of couples reporting active condom use (8). By contrast, pill supplies would protect 2.8% of couples in the same period and the BFS reported 3.4% active pill users. The difference between condoms supplied and used might be explained if a large proportion of condoms were being misused. However, other explanations may also be considered, including the possibility that condom use may be selectively underreported.

This latter possibility may contribute to the large difference between national program commodity distribution and the CRL reported baseline level of condom use. The BFS questions on contraceptive practice probed for responses more than ours, and thus may have increased reporting. Underreporting of contraceptive practice has been noted in other family-planning surveys in Bangladesh (9). However, at least for pills, we found overreporting to be a problem once we started our distribution system. To summarize, the accuracy of reporting condom use would be very difficult to

confirm, short of assessing the pregnancy experience of condom acceptors. This latter task may be undertaken for the Matlab experience.

Matlab is not an unusually conservative Muslim area and we are not aware of other factors that might inhibit the use of condoms. However one should exercise caution in extending the assessment of any experience in this limited area to the larger population of Bangladesh. Nonetheless, BFS data also indicate a disturbingly low level of condom use.

Progress has been slow, not only in attaining higher use rates with the condom, but also in achieving recognition of the condom as a method of family planning. The previous general availability of the condom without adequate information about its intended use probably contributed to this difficulty. We feel some success has been made by our direct and explicit educational efforts about condom use. However, a vigorous ongoing effort will likely be needed to sustain increases in usage. An energetic approach through social marketing, mass media, and personal education may help to achieve this goal.

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34

Procurement and Use of Drugs: Managing the Process to Advantage

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Health and family-planning programs in developing countries, whether government, donor, or privately sponsored, typically face the problems of material scarcity coupled with mismanagement of resources. To achieve greatest impact, resources must be used effectively and wisely. It is our experience in developing countries that the greatest constraint to effective health programs is often availability of supplies rather than health workers. A public health program, to achieve consumer acceptance and positively affect public health, depends substantially on the capacity to deliver drugs and/or medical equipment. In family-planning programs the story is the same; impact is more likely when contraceptives can be made available. Because contraceptives are usually procured and delivered through the same channels as other drugs, field experience in public health supply systems in developing countries is relevant to the supply problems of family-planning programs.

Transmission of drugs and other medical supplies from producers to users requires a broad range of activities, interactions, and interinstitutional relations. They combine to form what may be called the "procurement and use process." Though the procurement and use process is critically important to most programs, health decision makers frequently view it as a process with an inertia of its own—something which they do not really understand and something over which they have no control. Our observations in many developing countries suggest, however, that when managers make efforts to improve the procurement and use process, there can be substantial positive impact on drug availability and the subsequent effectiveness of public health programs.

For the past 8 years, Management Sciences for Health (MSH) has actively participated in the design and implementation of national pharmaceutical supply systems in Afghanistan, Nepal and Bolivia, in collaboration with USAID and UNICEF. In addition, for the past 18 mo, in collaboration with WHO, MSH has conducted a survey of pharmaceutical supply systems in

Asia, Africa, and Latin America. To date, ten countries have been visited and their supply systems studied in detail.

This chapter is based on the observations, reports, and case studies in these 13 countries, and considers various problems typically encountered in the procurement and use process of pharmaceuticals and contraceptives in developing countries. It will review reasons why this process is important, enumerate the activities which comprise it, describe the most commonly observed problems, and present encouraging examples which confirm that developing countries increasingly can, and do, manage the process to their own advantage.

IMPORTANCE OF THE PROCUREMENT AND USE PROCESS

Three interrelated factors underlie the importance of the procurement and use process:

1. The *economic impact* of drug costs on programs and consumers
2. The *availability* of drugs as a key factor in consumer interest and *program effectiveness.*
3. The large number of *practical opportunities for improvement* in all segments of the procurement and use process

In Europe and North America, drugs constitute 10%–20% of expenditures for health care, making them an important economic factor in this area (4). In developing countries, the economic impact of drug costs for government programs is immense, often representing as much as 50% of health-care budgets. In some countries, for example Afghanistan, import costs of wholesale drugs are equal to entire health operating budgets for salaries, services, and other supplies (13). At the household level, expenditures for medicine make up a sizeable chunk of household budgets. In rural Afghanistan, 7% of total household income, cash and noncash, is spent on health needs and 37% of this figure goes for drug purchases in the commercial sector. For the average 50,000-person target population of a government rural health center in Afghanistan, the estimated annual value of drugs purchased on the open market is about $43,470 (5). This is 47 times the annual value of drugs dispensed through the center (6). Therefore any step taken to reduce drug cost may have significant impact on the economic and health status of a family.

Availability of drugs is a key factor in maintaining consumer interest and achieving significant impact in public health programs. The credibility of health workers depends largely on their ability to supply these commodities. A rural health survey in Afghanistan showed that villagers value drugs more than health workers or a clinic. In a Latin American country just embarking on a rural health program, community health workers turn to private pharmacies to replenish their stocks when program supplies fail them. This is necessary, they say, for without drugs, they cannot maintain interest in preventive services and health education. Adequate and timely supply of contraceptive drugs and devices is especially critical in family-planning programs in order to have substantial impact on fertility..

Typically, these supply systems are hampered by programs arising out of systems design, people, policy, and technical issues. It is seldom possible to completely rebuild a supply system so that it meets every expectation, but it is frequently possible to make improvements in specific problem areas which visibly improve overall service. A major goal of this chapter is to demonstrate that there are viable approaches to solving problems involved in the procurement and use of drugs, including vaginal contraceptives. Important examples exist in a number of developing countries. Improved service need not await technological breakthroughs. Despite ever-present constraining influences of political and private interests, improvement can be made if practical approaches are taken.

THE PROCUREMENT AND USE PROCESS

Interactions and relationships among suppliers, planners, outlets, and users of drugs are interinstitutional and complex. An overview or description of the entire procurement and use process is useful for identifying problem areas and placing them in an organizational context. The process is divided into four activity areas: selection, procurement, distribution and use.

Within each area, a number of critical activities must be performed to insure a continuous supply of goods. The various organizations and activities involved in the procurement and use process combine to form a system because lapses of judgement or performance in one area may cause disruptions in another. For example, a mistake in drug selection may be the source of problems in the areas of distribution or use. Likewise, if information is not made available on consumption rates of drugs or which drugs are currently in stock, inappropriate selections and procurements may follow.

Figure 34-1 shows the principal areas of the process with activities grouped under them. *Drug selection* addresses issues such as what products should be available for what problems and in what quantity? *Procurement* includes considerations of finance, purchasing methods, terms of payment, sources of supply, decisions to make or buy, and quality assurance. *Distribution* includes forecasting needs and inventory management, storage, transport, and waste management. *Use* includes consideration of prescribing and dispensing practices, packaging and labeling, matching supplies to appropriately trained personnel, and educating consumers. Each of these activities is a potential source of disruption but also a potential opportunity for improvement.

Complex relationships between institutions, both public and private, complicate, but do not prevent, effective analysis of the process. Circumstances vary from country to country but some generalization is possible. Figure 34-2 is a model of these relations. The pharmaceutical industry is dominated by a few large multinational manufacturers. Large numbers of small local processors and packagers of intermediate drug forms transfer finished goods from manufacturers to government and private procurement agencies in each country. These agencies distribute directly to hospitals, health programs, pharmacies and shops, and these, in turn, provide drugs to users, either directly or through various levels of health workers.

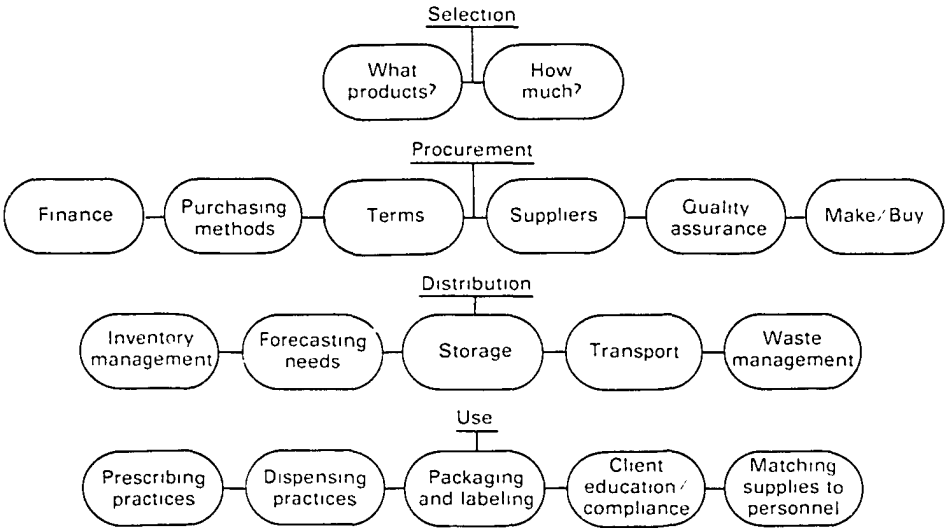

FIG. 34-1. Activities in the procurement and use process.

COMMON PROBLEMS

Each system has a unique combination of constraints and deficiencies which contribute to its own particular set of difficulties. Experience in a number of countries in the developing world suggests, however, that some of these difficulties recur frequently enough to be regarded as typical problems of the drug procurement and use process.

One problem which cuts across all four areas of the process concerns the information used to make decisions. Information systems which regularly provide decision makers with reliable data on public health conditions, consumption rates, effectiveness of various drugs, and quantities of supplies on hand are seldom found. Critical decisions on what drugs to procure, what quantities to stock and how to distribute them should be based on users' needs but frequently are not. Scarcity of information on needs results in procurement of nonessential drugs, shortages of essentials, and ultimately, lower-quality service.

In the area of *selection*, there is often an unnecessarily large number of different types of drugs available. Problems associated with this situation include use of expensive brand name products in place of cheaper, generically named drugs, procurement of disproportionate amounts of nonessential drugs (combination products and over-the-counter symptom relief drugs), and procurement of drugs whose effectiveness has not been scientifically demonstrated. Inability to regulate the types of drugs available contributes to a wide range of prescribing practices and obligates supply systems to stock an unnecessarily large number of different items.

Problems relating to procurement that consistently demand attention in-

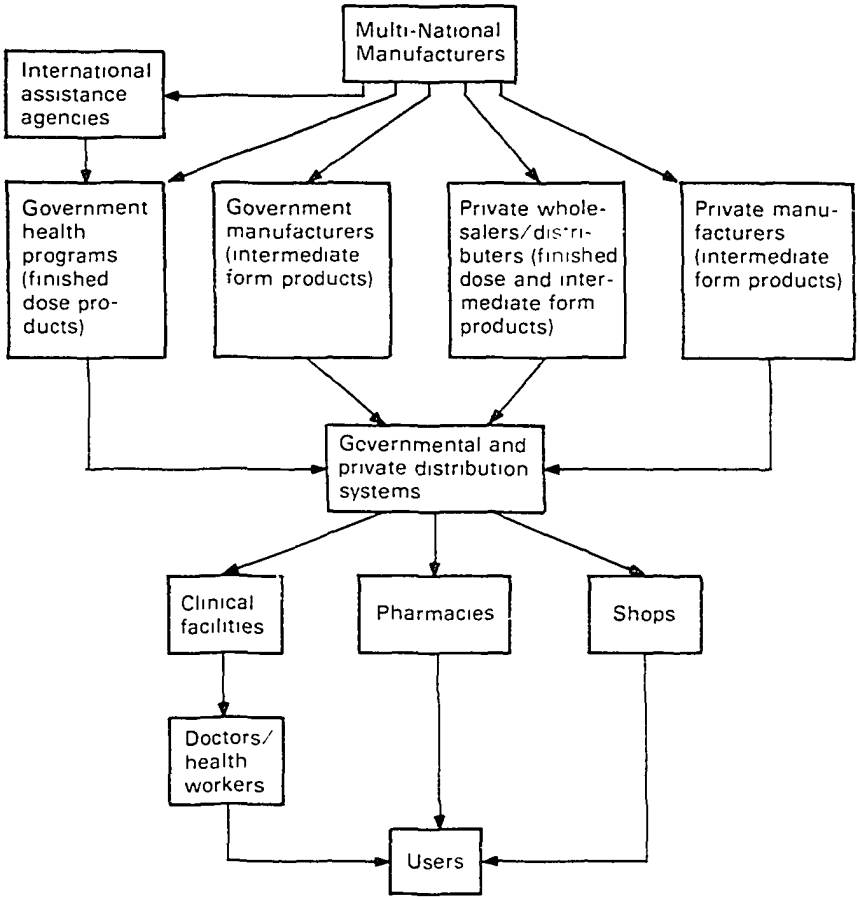

FIG. 34-2. The pharmaceutical procurement process.

clude supplier performance, quality assurance, and the question of whether to make various products within the country or to buy from outside. Suppliers may withdraw offers or change bids during the tender process, deliver substandard products or goods about to expire, or fail to replace bad batches.

Quality should be checked when drugs are first received and reverified when they reach the outlets that distribute them. Reverification is important because drugs may be acceptable upon arrival in the country, but may deteriorate after long periods of time in the supply system. Environment, poor handling, storage, and packaging all contribute to this problem. Unfortunately, quality assurance laboratory facilities and personnel are frequently not available.

Many countries would save money and expand services if they could man-

ufacture some products in local facilities. In order to be truly economical, the "make or buy" decision must be based on sound demand and cost projections. It is often difficult to bring the necessary information and analytic skill together so that useful projections can actually be made. Another problem associated with make or buy decisions is production inefficiencies at manufacturing plants. In order for government plants to be able to provide products more cheaply than commercial suppliers, they themselves must be well managed.

Commonly seen problems associated with *distribution* include inadequate storage facilities, insufficient transportation resources, inefficient stock management, and loss due to theft or spoilage. Storage facilities are often overcrowded with incoming supplies stocking up, spilling into aisles, or simply being left on loading docks. In addition to problems of quantity of space, there are problems of quality. Moisture and pests destroy supplies as they sit in warehouses and poor security causes additional losses from theft. As materials move through the supply system, outward from the center, storage standards usually become worse; regional warehouses are often little more than shacks and clinical facility storerooms only dirty closets. Also the limited space available is often poorly used. Scarcity or inefficient management of rolling stock keeps supplies bottled up at central warehouses when there is space available at regional warehouses. Information systems, as suggested above, are usually inadequate, so that managers are frequently unaware of what supplies they have on hand or where they are. Supplies needed in one region may gather dust in another, simply because their presence is unknown, or because mechanisms for transferring stocks do not exist.

Problems associated with *use* fall into three main categories: prescribing and dispensing practices, misuse of drugs by patients, and problems of packaging and labeling. Lack of a mechanism to promote uniform prescribing and dispensing habits results in incorrect prescribing and over- or underuse of drugs by patients. These have obvious drawbacks in terms of quality of care, but they also have implications for the supply system. Use of noneffective drugs (incorrect prescribing) or unnecessary multiple prescriptions requires the supply system to procure, store, and deliver nonessential items. This increases the strain on the system without achieving improved care. Dispensing of drugs is frequently carried out in unsanitary conditions with dirty utensils. Creams and liquids go out in unwashed bottles and pills are simply wrapped in paper. Frequently, only oral instructions are given to the patient by the dispenser. Imagine a case in which a mother receives multiple prescriptions for several children with each drug placed in an unlabeled container.

Packaging and labeling are not only important to safe use of drugs, they are critical to whether or not they are used at all. Users exposed to brand name drugs from commercial suppliers have come to expect fancy packaging. They may reject generic products which do not meet their expectations of what good medicine should look like. This is often the case with drugs used in government programs which are unpacked from bulk sources and distributed in shoddy looking packages.

Up to this point, problems related to specific activities in the procurement and use process have been discussed. There is another set of behavioral

problems which create obstacles to good management from within the system. Obviously, such lapses as theft, misappropriation of supplies, or professional indifference are detrimental to effective management of the process. Often these problems can be traced to particular individuals, but widely held attitudes are built into many systems that frustrate goal achievement. Material scarcities in developing countries make available supplies valuable commodities. Control systems often are elaborate and many people view their primary responsibility as conserving supplies rather than promoting effective use. This attitude is reflected in the multiple signatures usually needed to allocate small amounts of drugs and equipment. Supplies become a source of tactical leverage in bureaucratic infighting. Officials resort to rewarding their allies and punishing their enemies by giving out or withholding supplies. Manipulating supplies for political purposes often becomes the *de facto* goal of materials management in some systems, and public health considerations assume a secondary role (3).

ENCOURAGING EXAMPLES OF PROCESS MANAGEMENT

Each part of the procurement and use process is important and must be dealt with, whether by action or default. Progress has been made in many areas, but we know of no country where all activities are performed well. Moreover, there is no solution that is universally applicable. Each country has its own constraints and resources. Solutions to specific management problems must be designed with these in mind.

One practical approach to developing solutions for procurement and use problems is to investigate encouraging examples of process management wherever they are found. Comparison of problems on a case by case basis will encourage development of situation-specific solutions. The following examples illustrate approaches which different countries have adopted for various management problems.

SELECTION

Prior to 1972, the national formulary in Sri Lanka contained 2100 items. This number was far in excess of needs and proved unmanagable for government programs. In 1972, the State Pharmaceutical Corporation (SPC) was organized as a state monopoly for exclusive importation of pharmaceutical raw materials and finished dose products. SPC's role has been subsequently modified in that its monopoly in the commercial sector has been eliminated, but it remains the sole procurer of pharmaceuticals for government programs.

Among the SPC's objectives are to save foreign exchange, reduce the number of available drugs, improve drug information reaching prescribers, expand quality testing facilities, promote domestic drug manufacturing, and reduce prices to consumers. SPC has not met with success in all areas, but work with the national formulary has contributed to notable improvements in stock management. Shortly after being founded, SPC collaborated with the National Formulary Committee to reduce the number of drugs stocked

for government programs. The original list of 2100 items was narrowed to 800, of which the SPC purchases only 50 by brand name.

The decrease in number of separate stock items, plus improved forecasting procedures has reduced the number of stockouts (shortages) from an average of about 250 items at any one time to about 25 items. Shortages that endanger health are now virtually nonexistent (7).

Afghanistan is also benefiting from the adoption of an improved drug formulary. In 1973, a committee of local professionals appointed by the Ministry of Health, and assisted by MSH, redrafted the national formulary. The Ministry was, at that time, procuring and delivering drugs which were too expensive in some cases and not effective in others. The committee's goal was to simplify and improve health practices through identification of each drug by its generic name, limitation of available drugs to those of proven effectiveness, elimination of most fixed combination drugs, and maintenance, where possible, of drugs customarily used by Afghan physicians.

The committee produced a new formulary of about 400 drugs, one-third of the number previously listed. As a result of this work, the government enacted a national policy to procure drugs for its programs by generic name only. Although the economic effects of this policy have not yet been assessed, the adoption of the new formulary has resulted in the development of a basic drug list for the rural health program. This 40-drug standard formulary is easier to order, store, and transport, with the result that annual shipments to health centers are now completed in one-third of the time previously needed (1).

Issues of selection are not critical in some family-planning programs because many of the commodities are preselected by donor agencies. However, many of the drugs necessary to support family-planning programs, such as pain medications and antibiotics, are vulnerable to section problems.

PROCUREMENT

Malaysia has been able to solve enough of the management information and production problems to permit economical local manufacture of many pharmaceutical products. Prior to 1964, supply and production operations for the Ministry of Health were undertaken in 18 separate locations ranging from old garages to rented warehouses. In 1964, the Ministry of Health established the State Pharmaceutical Laboratories and Stores (SPLS) at Petaling Jaya. This complex replaced all existing facilities. Tablets, injectables, and liquid medications are all produced at SPLS and many formulations are developed to suit local needs.

In all, the Ministry of Health has reduced drug procurement costs by an estimated 34% by producing pharmaceuticals at Petaling Jaya. Petaling Jaya's success stems from a number of factors, including availability of accurate information on consumption, the high quality of pharmaceutical education in Malaysia, careful selection of the products, low domestic wages, absence of import taxes on raw materials, packaging in bulk and absence of payments for research, marketing, and return to investors (8).

Not every country has the capacity to manufacture pharmaceuticals economically enough to allow drug production for all its needs. When, as is

usually the case, most drugs must be purchased, financial resources can be stretched by careful management of purchasing. Papua, New Guinea has developed an effective system based on regulated indenting (ordering) and competitive bids. The Department of Health has in New Guinea a system of six regional storage facilities called Basic Medical Stores (BMS).

In order to coordinate ordering and receiving and to minimize stock-holding costs, a system of regulated ordering is used. All pharmaceutical supplies are divided into three categories depending on whether the item is to be purchased once, twice, or three times a year. List I items are the highest volume items for which considerable savings are achieved by bulk buying. List II items tend to be cheaper per unit, so that bulk rates are not as critical. List III is for items with high unit cost, highly variable consumption or short shelf lives. When each BMS completes estimates for each supply period, it records the rate of overstock as well as needs. From these documents, the Pharmaceutical Services Section of the Department of Health executes transfer orders to move stock between the regional storage facilities.

Purchase quantities for each store are set after the transfers have been considered. Collated estimates are then sent to the purchasing office which circulates tenders to lists of known suppliers and bids are approved through a 3-tier selection process. This system has the advantages of encouraging competitive pricing among acceptable suppliers and making efficient use of the purchasing staff. Its principal shortcoming is that there is no inventory control below the BMS (9).

DISTRIBUTION

Peru's Ministry of Public Health does not have enough central storage space for its 57 health districts. It has been able to get around these difficulties by arranging for suppliers to deliver drugs direct to each district hospital, from which the Ministry arranges for further distribution to health centers and clinics. Contracts with suppliers are "ex-works" which means that the supplier is responsible for packaging and delivering to the buyer at specific times and places. Preparation of delivery timetables is computerized. Supplies are delivered at eight quarterly intervals over a 2-year contract period. In addition, supplemetary deliveries are made on a monthly basis. Suppliers use a combination of independent commercial transport companies. Computerized timetable formats are used to indicate the types and amounts of each item to deliver to each facility and the desired delivery date. The printout includes spaces for dates and signatures so that it can be used for record-keeping purposes. Though these measures have minimized the transportation resources needed by the ministry, problems do remain. In particular, district and subdistrict storage space is inadequate for climatic conditions, arrangements to redistribute supplies are too slow, and the distribution system does not produce accurate consumption data from which more reliable demand projections could be made (10).

In Costa Rica, inadequate regional warehouses and poorly qualified personnel made the decentralized distribution system unsatisfactory. To overcome this, the Ministry of Public Health set up the General Inventories Department (GID). This office coordinates all deliveries directly from the

central warehouse. Health Centers submit requests every 2 mo and delivery occurs about 2–3 weeks after the central warehouse receives a requisition. In case of shortages at the warehouse, there are procedures for stock transfers between facilities and for commercial purchases. PERT/CPM procedures are used to schedule staff time, warehouse personnel, and delivery trucks. These charts indicate when each facility should prepare its requisition, the times for filling the requisition by the warehouse, delivery times, log times, and other information. This system has improved deliveries overall, though central storage space is insufficient to accommodate the expanding number of facilities and available regional storage space is not yet well utilized (11).

USE

In Malaysia, tablets were initially distributed in bulk and then repacked for dispensing in paper envelopes and small plastic bags. Drawbacks to this system include mixups during packaging and dispensing, breakage during transport, and problems of identity if labels come off bulk packages. To overcome these difficulties, Petaling Jaya has coverted to foil-backed polyvinylchloride blister packaging. Although this improved packaging and labeling will hopefully cut down on breakage and improve dispensing practices, its principal disadvantage is expense. Initial capital, personnel, and daily operating cost of the blister packaging operation are all several times those of the bulk packaging operation (12).

For ministries experiencing packaging and dispensing problems similar to those of Malaysia, but lacking comparable financial resources, there are cheaper alternatives to blister packaging. Both Afghanistan and Bolivia have introduced course-of-treatment packaging into their village health worker programs by employing heat-sealed plastic bags. These dispensing units are especially suitable for village programs with their basic level of training and limited facilities. Precounted courses of therapy can be turned over to patients without unpackaging and counting drugs and thus continually exposing them to moisture and contamination. The machinery and equipment for the heat-sealing operation is simple and it can be set up in almost any clean, dry room which is large enough and has electricity (2).

CONCLUSION

Health managers in developing countries are acutely aware of the problems involved in the selection-procurement-distribution use cycle associated with pharmaceutical and contraceptive commodity supply systems. They want to take action but are often not aware of effective alternatives. The issues involved in proper management of this process have not been extensively studied or documented. Few hard data exist and future research needs to be directed to the resolution of these problems.

The technically perfect contraceptive device awaits discovery. Yet, in many countries fertility rates can be lowered by regular supply and appropriate use of existing technologies and commodities. Operational supply system manuals need to be developed which can be used by anyone. Use of the manuals

should be augmented by onsite technical assistance because each system has its own specific difficulties that require individual attention.

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AGENCY PROGRAMS ON VAGINAL CONTRACEPTION

35

Intravaginal Contraception: United Nations Fund for Population Activities

JC DONAYRE

From its inception, the United Nations Fund for Population Activities (UNFPA) has had a broad mandate in the general field of population. This mandate became apparent with the early attempts by the Fund administrators to mobilize the considerable potential of the UN Specialized Agencies for work in population, and later with the general perspective achieved when the UNFPA was located within the UN Development Program. The UNFPA has been built into the development program of the United Nations, maintaining a large degree of autonomy, but representing an overall development approach to the problems of population.

Although the founders of UNFPA may have had other goals in mind, the evolution of the Fund prior to the Population Conference in Bucharest in 1974, where significant international policy decisions were made, and in the years since, reflects a growing commitment to the development of effective, multifaceted population programs addressing the problems of less-developed countries in response to international consensus.

A steady growth in UNFPA resources since 1969 has allowed a considerable expansion of population programs, as shown in Table 35-1. By the end of 1977, $312.6 million had actually been spent and another $125.5 million had been allocated for expenditures in 1978. By the end of 1978, over half a billion dollars had been allocated to these programs. Of the seven categories in which the UNFPA program is subdivided (Fig. 35-1), support for family-planning activities represented 37.3% of all expenditures up to 1972, growing to 45.5% in 1975 and remaining at that approximate figure through 1978. This four-year plateau is, on the one hand, indicative of a leveling off in implementation rates, expressed here in actual expenditures and is, on the other hand, a reflection of heavy emphasis on sectors other than family planning, such as basic population data or communication and education programs. These categories are not mutually exclusive, however; communication or education programs may be directly related to, or in support of, family-planning programs.

Most of the national programs in family planning supported by the UNFPA are integrated into, or form part of, maternal and child health operations. Although it is impossible to determine the importance of family-planning services relative to maternal and child health care programs, because

TABLE 35-1 Program Trends by Population Sectors, 1969–1978 (As of September 1978)

	PROJECT EXPENDITURES (US$ 000)						
Population sectors	1969–1972	1973	1974	1975	1976	1977	1978
Basic population data	$ 2,057	$ 3,817	$ 9,073	$11,221	$12,511	$ 9,848	$20,655
Population dynamics	3,425	3,992	6,616	7,759	8,347	8,350	13,986
Population policy	684	538	989	1,309	1,137	1,046	2,821
Family planning	9,890	8,803	18,726	30,560	31,755	30,413	57,222
	(37.3%)	(30 3%)	(34 6%)	(45.5%)	(45.4%)	(45 9%)	(45 6%)
Communication and education	3,262	4,179	7,773	8,718	8,668	8,531	17,598
Multisector activities	3,405	4,488	6,124	2,826	1,508	1,166	3,281
Program development	3,778	3,254	4,787	4,748	5,915	6,876	9,943
TOTAL	$26,501	$29,071	$54,088	$67,141	$69,578	$66,230	$125,506

the degree and modes of integration vary widely and the cleavage lines are often not easily established; a considerable part of UNFPA financing aims to strengthen the related maternal and child health programs.

More than 50% of UNFPA support is oriented to activities other than family planning and, when directed to family planning, includes support of maternal and child health operations. While it is difficult to determine with any degree of precision what part of UNFPA support nominally directed to family planning actually goes to effective and direct support of contraceptive services, the expenditures for the purchasing of contraceptives are shown in Figure 35-2. As of 1978, 10.5% of family-planning resources and only 4.5% of total UNFPA program resources had been utilized to provide contraceptives for national programs. After a peak in 1975, resulting from a now discontinued advance order of contraceptives, the relative importance of contraceptive supplies in UNFPA programs steadily declined, reaching 6.8% of all family planning and 3.1% of all program expenditures in 1978.

A further breakdown by regions (Fig. 35-3) shows that countries in Asia and the Pacific received about 50% of the cumulative funding of UNFPA for family planning in the decade of 1969–1978. These are followed by Latin America, with 24.2% and the region of Europe, the Middle East, and the Mediterranean with 17.8%. Figure 35-3 shows expenditures in family planning in absolute and relative terms as compared to other expenditures in various regions. The most notable variations occurred in Latin America, where family planning expenditures rose from a low of 11.4% of all programs in that region between 1969 and 1972, to 56.2% in 1975, remaining in that vicinity until 1978. Less marked variations have occurred in other regions also, with the exception of Asia and the Pacific, where family-planning programs have received more than 60% of all UNFPA resources allocated to that region.

The expenditures shown in Figure 35-4, according to region, reveal a decrease in the proportion of funds designated for purchase of contraceptives, in 1977 and 1978. Only cumulative figures are available up to 1976, but in all regions, these are higher than the 1977–1978 figures. It is also evident that although in the countries of Asia and the Pacific, where more than 60% of all UNFPA support was earmarked for family-planning programs, only 5.9% of that was for the provision of contraceptive supplies, with only the programs in Africa having a similar designation for contraceptive supplies. The highest outlays for contraceptive supplies occurred in Europe, the Middle East, and the Mediterranean, essentially as a reflection of the very high levels of support for this aspect of the program in the period from 1969 to 1976.

Although complete figures are unavailable to allow differentiation among the various types of contraceptives provided to programs by UNFPA for all years, Figure 35-5 compares expenditures in two representative years, 1974 and 1975. Oral contraceptives (OCs), IUDs, and injectables constitute the major group, with OCs predominating. For these three modalities, the UNFPA provided $2,503,895 or 88.5% of all its contraceptive resources in 1974. The remaining 11.5% of the funds ($326,853) went to the provision of intravaginal contraceptives, including condoms and spermicides. For 1975, the proportional difference in expenditures for the two groups was

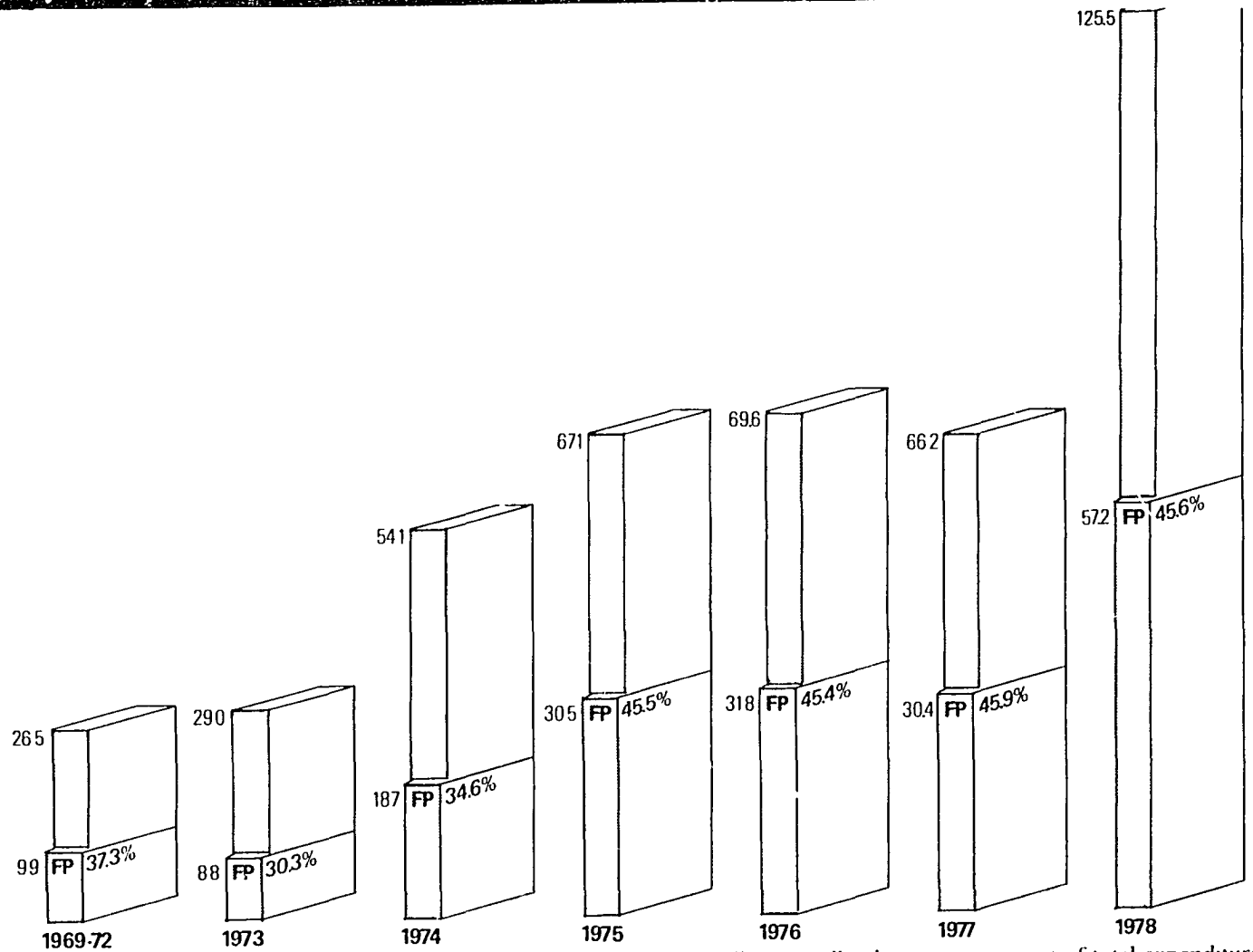

FIG. 35-1. Project expenditures 1969/1972–1978 in millions of U.S. dollars. Family planning as percent of total expenditures (as of September, 1978)

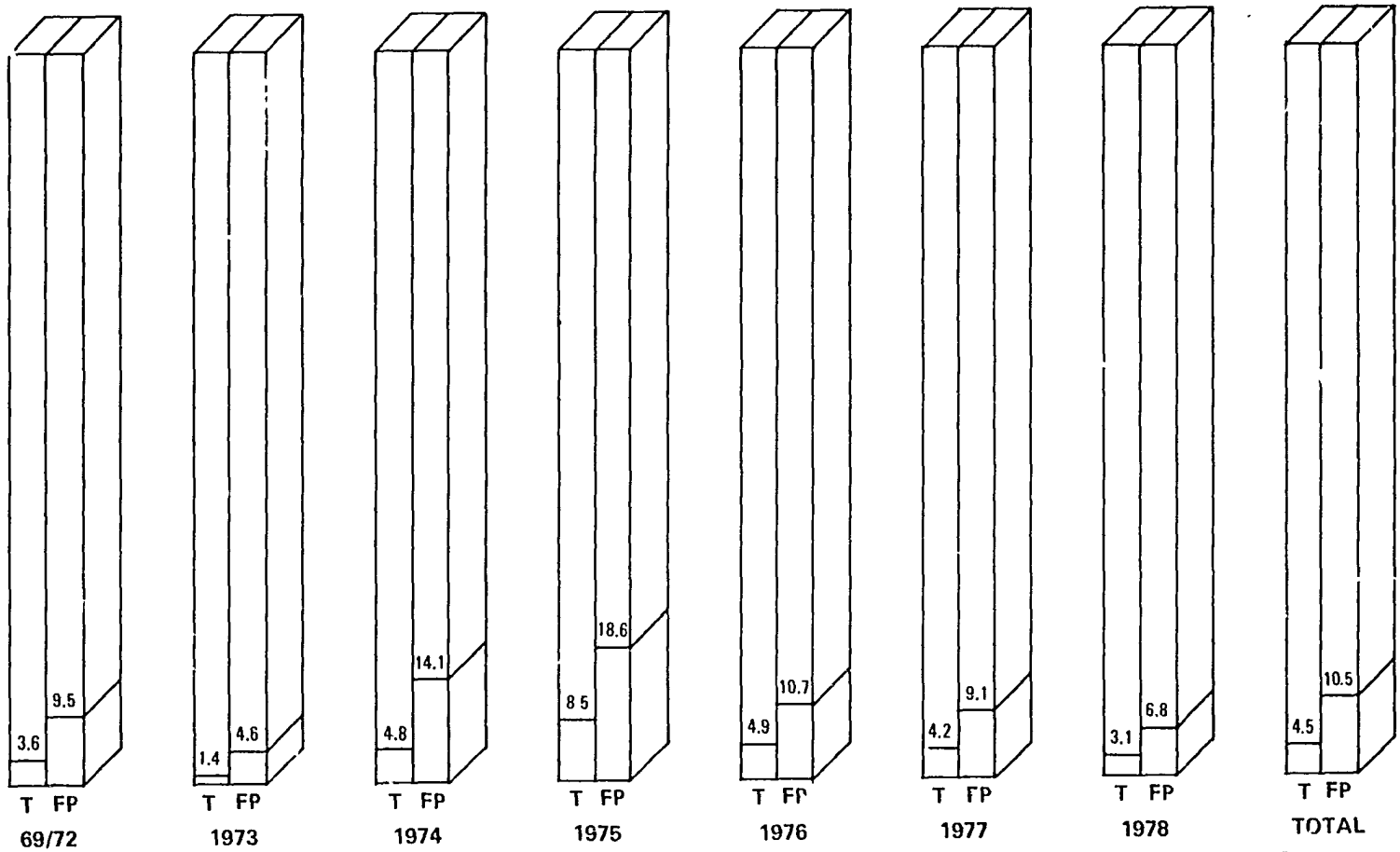

FIG. 35-2. Contraceptive expenditures as percent of total (T) and family-planning (FP) expenditures 1969/1972–1978 (as of September 1978)

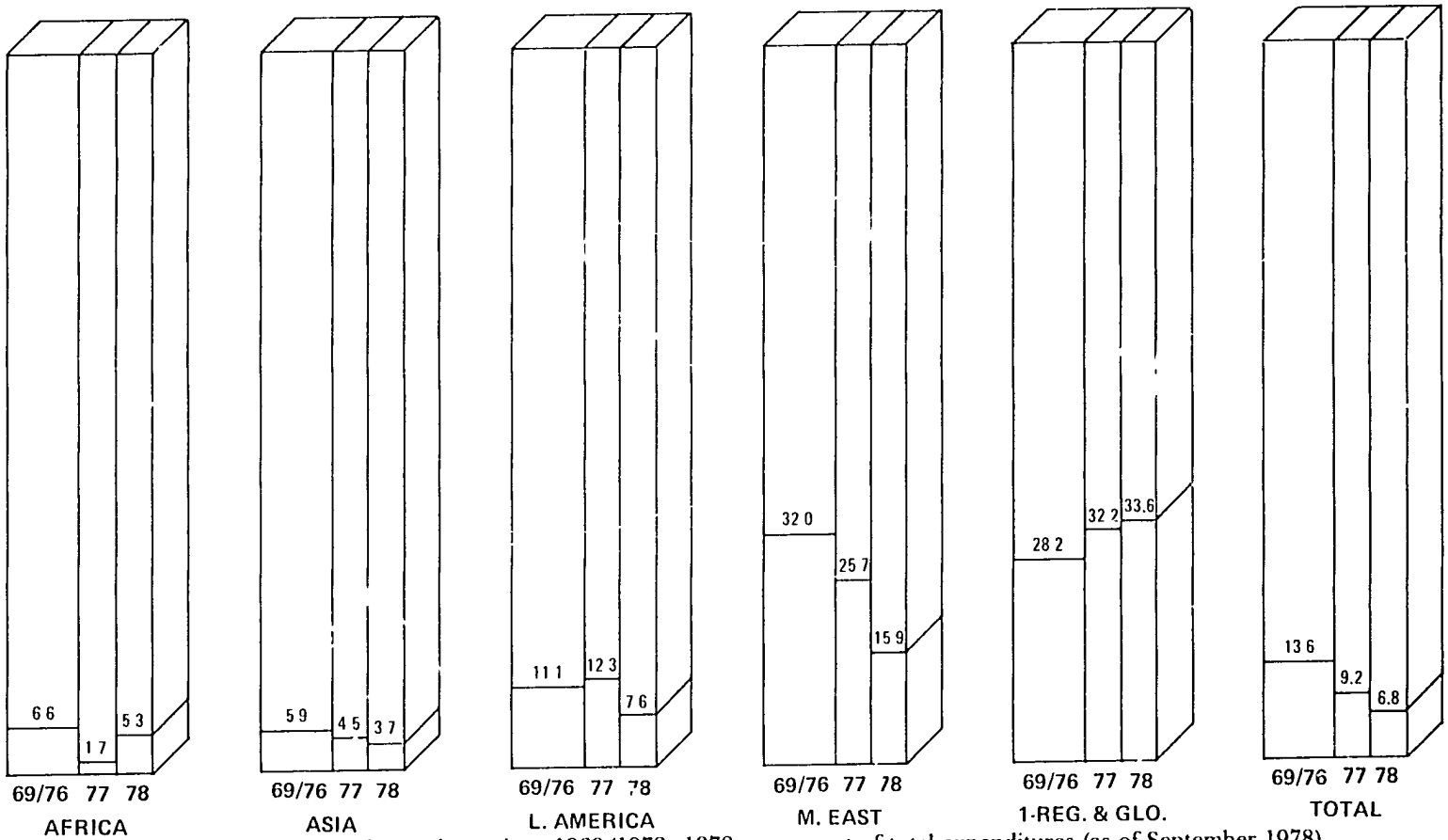

FIG. 35-3. Family-planning expenditures by regions 1969/1972–1978, as percent of total expenditures (as of September 1978).

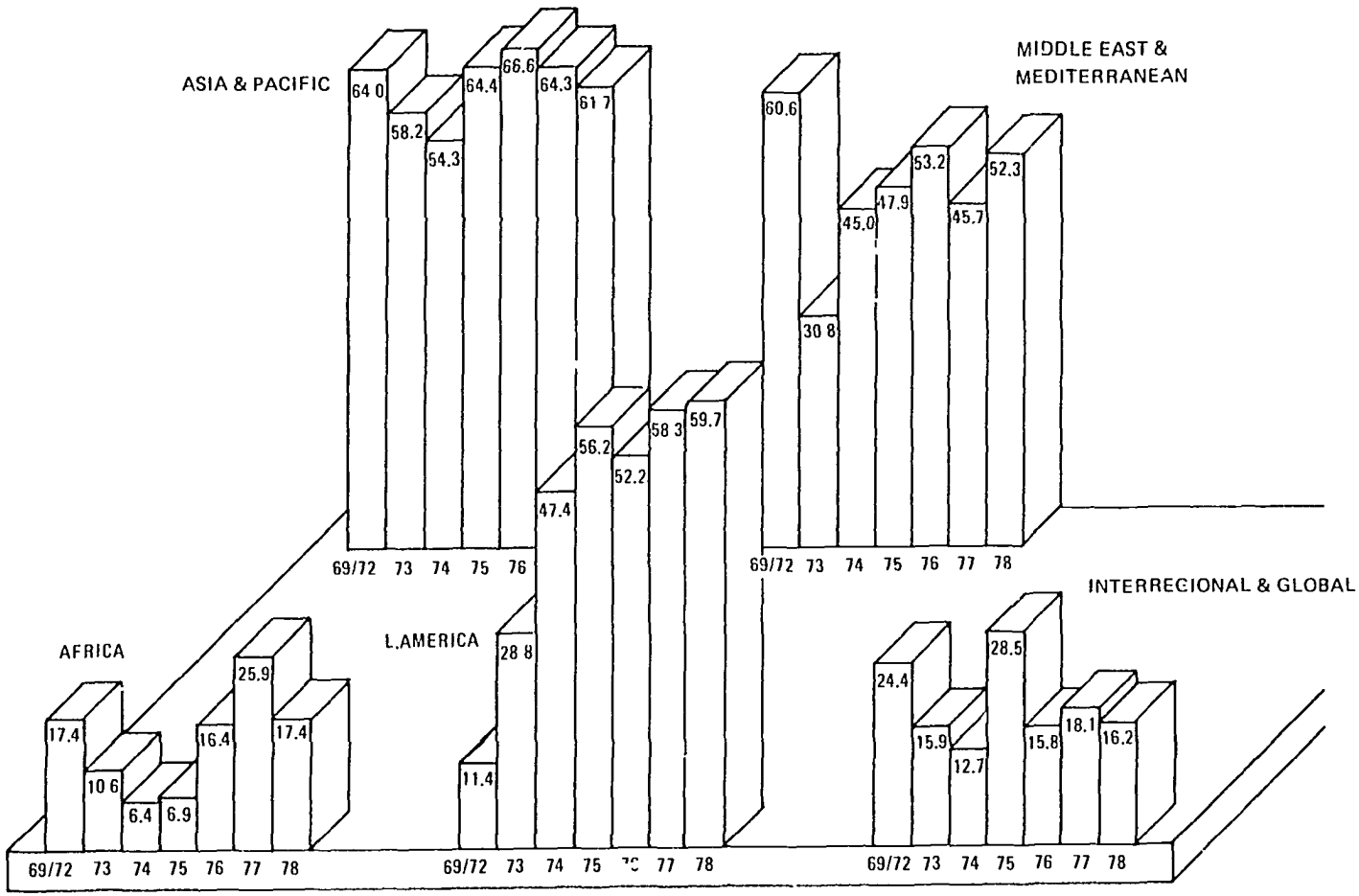

FIG. 35-4. Contraceptive expenditures by regions 1969/1972–1978 as percent of family-planning expenditures (as of September 1978).

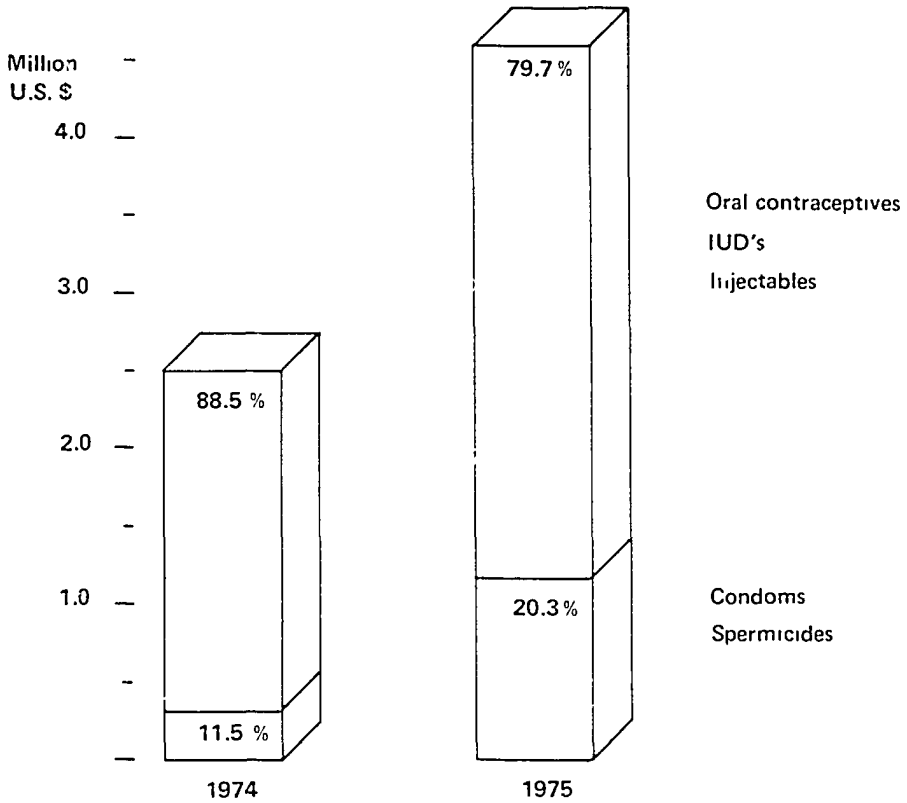

FIG. 35-5. Contraceptive expenditures by type in two sample years.

less marked, reflecting a disbursement of condoms from the stockpile five times greater than that in 1974.

CONCLUSION

The UNFPA has provided contraceptive supplies to a large number of countries in the context of its support to family-planning service programs, involving approximately 45% of all UNFPA-financed operations. Those programs have most often integrated maternal and child health services with family-planning programs and, in consequence, have required UNFPA resources for components other than the purchase and distribution of contraceptives. From 1969 to 1978 the total contribution to the latter constituted 10.5% of all UNFPA support to family planning and 4.5% of total UNFPA program funds. Of these distributed funds, only 11.5% in 1974 and 20.3% in 1975 were utilized for condoms and spermicides. These figures are probably representative of the overall UNFPA allotment for these contraceptive methods.

Although in absolute terms, UNFPA is probably among the main providers of international funds for contraceptives, the composition of its support for population programs is extremely varied. The supply of contraceptives is not the most important component of its general programs, nor does it constitute the major part of its support to family-planning programs.

The increasing evidence on the improved acceptance, utilization, and effectiveness of vaginal methods of contraception, shown also at this meeting, and the continuous problems affecting other methods, should soon be reflected in a switch in demand worldwide. What is happening in developed countries in this regard, where the use of vaginal methods is on the upswing, should soon be evident in less-developed countries. To that end, and for the benefit of programs, information should be widely disseminated on recent data such as shown in this workshop. The Fund would collaborate utilizing the channels open to it and would be prepared to respond to this newly created demand.

36

The Importance of Vaginal Contraception

MALCOLM POTTS

Vaginal contraceptives are to family planning what a buffalo cart is to a modern transport system; more certain ways of solving the problem may exist, but to overlook the usefulness and potential acceptability of a simple solution to a common problem, especially a method that is of proven usefulness and perhaps also open to improvement, is shortsighted.

SOCIAL SIMPLICITY

Most likely the interest of scientists and physicians in the glamorous and highly effective contraceptive methods has been responsible for the glacial progress of vaginal barrier methods. In 1931, Marie Stopes wrote, "While preparing the third edition of my textbook *Contraception, Its Theory, History and Practice* I tracked down, through several indirect references, the fact that the rubber vaginal cap, which is now of such technical value as a contraceptive and which has universally been attributed to Dr. Mensinga, was in use by Dr. Wilde over 40 years before" (5). Wilde wrote in 1838 about the condom, coitus interruptus, tubal ligation, therapeutic abortion, and a rubber vaginal cap. He fitted the cap with the use of a speculum and described it as something "to let persons, to whom childbearing is impossible, wear a rubber pessary constantly; the pessary having no opening, covering the os uteri completely and closing it tightly, to be removed only during the menstrual period."(7)

Wilde also referred to the earlier literature of 1823: "Most peasant families had only two to three children, then no more. Careful investigation showed that a midwife possessed this secret. At the end of the child bed, she brought the woman, unknowingly on her part, a foreign substance which, applied to the os uteri, closed the entrance" (1).

It is against the grass-roots and crocodile dung (one ancient Egyptian form of vaginal barrier) beginnings that the contemporary importance of vaginal contraception should be seen. Most of the world's people live a life not greatly different from the German peasant of 1823.

I once flew out of Bombay with an Indian doctor who had practiced in the Caribbean for the whole of his professional life. He was leaving Bombay after his first visit to India in 20 years. Like me, he was appalled at the poverty and the effects of the population explosion.

"Do you know what I would do?" he said. "Cottonseed and mustard oil. . .!" Apparently this was the traditional Indian remedy, and he probably had more

insight than most family-planning program advisors in New Dehli, by recommending a peasant solution to a peasant problem.

The contemporary view of vaginal contraceptives may still be too clinical. In the nineteenth century, a dichotomy occurred with regard to vaginal contraceptives and the dichotomy still exists today. On the one hand, the condom and spermicides enjoyed an expanding over-the-counter trade; on the other hand, the diaphragm became the tool of the physician working in a family-planning clinic.

The marriage between family-planning clinics and vaginal contraceptives took place in Holland, where the check pessary had been developed by the Flensburg physician Mensinga (hence the English name, Dutch Cap) and the first birth-control clinic was opened by Aletta Jacobs. Until recently family-planning programs almost exclusively trod this second, clinic-oriented path. The work of the Japanese Family-Planning Association and the RFSU in Sweden, and more recently PSI-initiated programs in developing countries, are beginning to cause a shift in attention to the over-the-counter approach that, as the triumph of the PSI Bangladesh Program (Huber, Chap. 33) and the promise of Mexico (Macorra, Chap. 20) show, is more relevant, cost-effective, rapidly implemented, and probably more culturally acceptable than the physician-delivery approach.

Until the development of oral contraceptives and the rediscovery of the IUD after World War II, vaginal methods of contraception were the only option a doctor could offer to a woman seeking contraceptive advice. At the peak of its popularity in America, the cap and cream method of family planning was used by approximately one in three Americans who attempted any form of contraception. The Population Investigation Committee survey of contraceptive use in England in 1959 found a vaginal barrier the method of choice among one in eight couples who were using some form of birth control. Vaginal contraception has always been a method used more by schoolteachers than shop assistants, and the method lost ground to oral contraceptives in all social classes and in all countries during the 1960s. Only recently have vaginal contraceptives begun to increase in popularity (Pratt, Chap. 6).

Perhaps the first conclusion that can be drawn from any broad historical and geographic perspective is that simple, do-it-yourself methods of contraception might well play a more significant role in fertility control in the developing world than we have considered possible. When I first took part in clinical family planning, in Britain during the 1950s, Marie Stopes's Clinic still sold sponges through a mail system. At the present time, I continue to use one of these sponges to wet my postage stamps. When I first joined the International Planned Parenthood Federation (IPPF) in the 1960s, the widely used *Medical Handbook* still gave instructions for "homemade barriers and household material of spermicidal value." It described making vaginal barriers from "clean, soft, white cloth . . . cut into pieces about 6-in. square." Small sea-sponges can also be used. A variety of homespun spermicides were also recommended. "One part of acetic acid mixed with 20 parts of warm, boiled water is an effective spermicide." "Any clean or sweet or cooking oil (mustard oil) or fat, including butter or margarine if suitably smeared over the plug or sponge." The *Handbook* warned women against carbolic soap and detergents.

In the 1950s, washable, reusable sheaths were still being sold in Britain. A place may exist for a similar product in developing countries. The sheath might be made of plastic, which has good heat transmission and high tensile strength.

There is a need for promotion of existing vaginal contraceptives through nonclinical channels. Implementers of social marketing and CBD programs should review the potential of vaginal contraceptives. Anyone considering possible improvements should remember that an over-the-counter method has a more significant social input than one that requires advice from an "expert." Those striving to extend the choice of family-planning services to a greater number of individuals will hopefully avoid the paternalism of Marie Stopes who particularly recommended the sponge and olive oil for "poor and illiterate, often overburdened, women whose husbands are either lascivious, careless or drunken."

If vaginal contraceptives are important largely because they are simple, then this advantage should not be eroded by technological overkill. A disposable vaginal sponge is likely to be unreasonably expensive and demand too much of the distribution system for regular use in developing countries. A long-lasting vaginal contraceptive device may make insupportable demands on the technology.

DISTRIBUTION SIMPLICITY

By the 1890s most methods now with us, and some possibilities we have forgotten, were advertised and sold. W. George, around 1900, had a wholesale and retail trade in "all kinds of rubber preventive appliances." He sold condoms for from two shillings to ten shillings ($.25–$1.00) per dozen; the "capote anglaise—a wonderful appliance for use by married ladies desiring to regulate the number of their offspring" cost five shillings and sixpence. Rendell's pessaries (still successfully marketed in 1979) sold for two shillings per dozen, cervical caps for two shillings and threepence; and a sponge with quinine for two shillings. (2) The Gem pessary "fitted with a specially prepared sponge dome that acts as an absorbent, preventing any fluid from passing beyond the rim of the pessary" is reminiscent of the collagen sponge (Chvapil, Chap. 8). However, a combined sheath and pessary that could be "rolled into the shape of a check Pessarie, and can be so used by the wife" has no modern analogue, except that it could be "used, unrolled, as a sheath by the husband." Like the original, the C-film concept, it was appropriate for either partner to use (Belsky, Chap. 20).

Over-the counter (and mail-order) sales of social marketing and of community-based distribution programs have received some support over the past five or ten years. The concept of CBD has gained greater acceptance than seemed possible when we launched the idea in the early 1970s. But, although global policies have been so set, the over-the-counter trade in contraceptives is still not reaching its full potential. The careful demonstration of the acceptability and cost-effectiveness of social marketing in the Philippines (Ylanan, Chap. 31) has not been translated into a nationwide policy. Even nations such as Thailand, with established family-planning pro-

grams, levy tariffs on the import of contraceptives. Indonesia maintains an anachronistic law adopted in colonial times that forbids the unsolicited dissemination and display of contraceptives; in Ireland, restrictive legislation is being considered that would limit contraceptive sales to pharmacies. In Great Britain and the U.S., the use of television to promote contraceptives is forbidden—in Britain the statute setting up the commercial television companies specifically forbids advertisement of undertakers, astrologers, and contraceptive products; in the United States a brief experience in California showed that television sponsors, possibly pressured by religious minorities, withdrew their support if contraceptives were promoted.

Laws regulating the manufacture, display, and advertisement of contraceptives should be repealed. Contraceptive products should be subject only to existing trade description acts. Tariffs against contraceptive imports should be abolished. The experience and self-confidence of the Bangladesh (Chap. 33), Guatemalan (Chap. 32), and Mexican (Chap. 30) programs should be expanded to countries such as Nigeria, Egypt, and Brazil.

PHYSIOLOGIC SIMPLICITY

Condoms almost certainly fail more frequently because they are not put on than because of mechanical defects. No direct, or even indirect, link can be found between the tests that manufacturers run (Free, Chap. 21; Hahn, Chap. 23), which are an aspect of quality control of the physical properties of condoms or *in vitro* powers of spermicides, and the physiologic possibility of pregnancy. In the case of methods with a low failure rate, especially those distributed directly to the consumer, many decisions about use must be made by inference rather than by observation. For example, in testing spermicidally lubricated condoms, it became apparent that assembling and following the number of users necessary to demonstrate, on a statistically sound basis, that the addition of a spermicide would reduce the already low pregnancy rate of a condom, would be impossible. All that can be said is that concurrent use of a spermicide is a reasonable step to take (3). In developed countries, conducting large-scale Phase III clinical trials (Stollev, Chap. 27) is increasingly difficult, partly because of expense and, more important, because couples who are likely to volunteer for clinical follow-up of intrinsically nonclinical methods are few in number and nonrepresentative of those very groups most likely to benefit from such methods. Studies of contraceptive failures (Hoffman, Chap. 15) through women seeking abortion may be helpful and human (Masters, Chap. 25) and animal testing (Zaneveld, Chap. 24) seem promising.

Biologically, the vaginal barrier, combined with a spermicide, is the most logical approach to interruption of the process of human reproduction. Sperm must make the quick but hazardous journey from one partner to the other, and surely it ought to be possible to arrest their progress and destroy them without any local or systemic harm to the man or woman.

If humans had the anatomy of a number of our mammalian cousins, perhaps of the bull and the cow, or of the red kangaroo, then spermicides would solve all of our problems. Unfortunately, we must live with the anato-

my of the human vagina, which is a curiously perverse organ from the point of view of hydraulics (Masters, Chap. 25; Flowers, Chap. 2). The problem is that the cervix protrudes into the vagina and spermicides are often pushed into the posterior fornix during intercourse. The female vaginal barrier is not a sperm-tight trap; it is mainly a device for holding an adequate supply of spermicide, whether margarine or nonoxynol 9, between the tip of a moving penis and the entrance to the cervix.

In terms of effectiveness, vaginal barrier methods are unlikely to approach the systemic method of contraception with their widespread effects and ability to prevent pregnancy in a number of different ways. The widespread steroid action gives the method its side effects, however, and rare but measurable hazards. Voge (6) concluded a scholarly review of *The Chemistry and Physics of Contraceptives* over a generation ago with the words

> To those who still clamor for the one hundred percent efficient contraceptives, the views which have been discussed [a realistic summary of the limitations of vaginal methods] may appear depressing and savor of pessimism, but after mature consideration, I am ready to affirm that we not be despondent.... Clinic reports seem to put the 'irreducible minimum' [of failures] at about two percent.

In many ways, changes have been slight since Voge wrote in 1932, except that the cost of research has escalated. Gamble financed the National Committee on Maternal Health studies in contraception in 1934, with $5000 (8). Perhaps a new generation of biologically more sophisticated agents will be discovered to interrupt fertilization (Zaneveld, Chap. 24).

One pressure sometimes mentioned as a reason for increasing emphasis on vaginal methods is the clinical hazard associated with long-term use of the pill or IUDs. This is probably misguided, as contraceptive methods are complementary, not competitive, with each method offering a different balance of advantages and disadvantages (Scrimshaw, Chap. 29).

Vaginal barriers are without significant short-term side effects and probably have no long-term risks, although even this can be challenged (Chvapil, Chap. 16). The condom and sheath may reduce the risk of cancer of the cervix, and both barriers and spermicides have the potential of helping to control venereal disease (Cutler, Chap. 17). In any country where abortion is legal, or safe abortion is accessible, the combination of vaginal barrier methods of contraception with first trimester abortion presents less risk to the user than adopting IUDs or oral contraceptives (4).

When barrier methods are promoted honestly, without unverifiable claims, they find many acceptors. In the developing world their marginally inferior performance in relation to effectiveness is perhaps less significant than in the West.

STRAIGHTFORWARD DECISIONS

"Why can't a scientific community that has sent a man to the moon solve the problem of contraception!" wails the press. That is perhaps the wrong way to pose the question, and we should ask instead, "What can we do for the thousands of millions of people who, in an age when a handful of men

have been to the moon, are still using their bullock carts to take themselves and their produce to market?" For these people our sophisticated technology may not be relevant.

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