Still Waiting for the Contraceptive Revolution

By Michael Klitsch

In the mid-1960s, when the oral contraceptive and the newly introduced IUD began to transform contraceptive practice around the world, hopes were high that even more effective methods would soon follow. Researchers’ imaginations produced visions of hormonal injectables, implants, vaginal rings and transdermal patches, methods of nonsurgical sterilization, improved IUDs, menses inducers—even systemic methods that could be used by men. As recently as 1982, a U.S. government report contended that 10 new methods were likely to reach the market during the 1980s, and another 20 by the year 2000.

Thirty years later, much of the enthusiasm about contraceptive advances has waned. Only three new contraceptive methods received Food and Drug Administration (FDA) approval in the 1990s, none as soon as hopeful advocates had expected: the hormonal implant (now enveloped in lawsuits), an injectable hormonal method that took more than 20 years between its first FDA submission and its approval, and the female condom. The only other important changes were the gradual adjustment of pill formulations to expose users to a smaller total dosage of hormones and the introduction of new hormones already widely used in Europe.

The lack of decisive advances is not the result of a paucity of candidate methods. In 1993, an estimated 100 experimental contraceptive methods were being studied around the world. Yet many of those methods had been in the works for years, and others were only slight modifications of products already on the market.

The slowing of the “contraceptive revolution” has not gone unremarked. In the late 1980s, the National Academy of Sciences (NAS) sponsored a series of meetings on the problems inhibiting contraceptive research and in 1990 published a book summarizing the conclusions. The 1990s brought even more expressions of concern. Many have asked why, after years of intensive research activity, the appearance of new methods with the revolutionary impact of the pill and IUD remains far away.

What Are the Problems?
A core set of factors has been identified as key to why contraceptive reality has failed to match 1960s expectations. The three main obstacles noted in recent evaluations were identified 10 or more years ago.

Regulatory and Legal Issues
Over the course of the 1970s and 1980s, many pharmaceutical companies in the United States gradually cut back or eliminated their contraceptive research efforts. This flight from research has usually been attributed to, among other factors, liability concerns;6 it said, noting that liability issues are simply a recognized cost of doing business in the United States.

Recent developments involving the hormonal implant (Norplant) dramatize how high the “cost of doing business” can sometimes climb, however. Nearly 200 lawsuits were filed against the implant’s manufacturer, Wyeth-Ayerst, in 1994, of them class-action suits. These lawsuits alleged a variety of problems caused by the implant, ranging from scarring and emotional distress attributed to removal difficulties to claims of autoimmune disorders resulting from exposure to the silicone in the implant’s shell.

Concurrently, implant sales fell from a rate of 600 per day in the early days following the method’s introduction to only about 60 per day by early in 1995 (although some of that decline probably occurred because the initial demand for the implant had been satisfied). Felicia Stewart, deputy assistant secretary of health for population affairs, has said that “it’s clear watching what’s happening with Norplant why a company thinking about marketing a new contraceptive product might say it isn’t worth making an investment.”

• Product liability costs. Manufacturers of IUDs, pills and spermicides have all paid sizable damage claims in the past several decades as a result of death or injury arising from contraceptive use. Not only have a few of these judgments been quite large, but the costs of defending against such lawsuits are high as well. Even noncommercial research organizations have been affected: According to the 1990 NAS report, liability costs for two not-for-profit groups active in contraceptive research, Family Health International and The Population Council, more than doubled over a two-year period during the 1980s.

Although that report concluded that product liability litigation had “contributed significantly to the climate of disincentives for the development of contraceptive products,” an analysis prepared by the Program for Appropriate Technology in Health (PATH) for a 1993 meeting on reproductive research reported otherwise. Some pharmaceutical executives downplayed the impact of liability concerns; it said, noting that liability issues are simply a recognized cost of doing business in the United States.

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to meet higher standards of safety before they could market a new drug. The demands for additional animal and human trials, as well as more exacting FDA evaluation of the results, added years—and millions of dollars in additional costs—to the drug development process.

In recent years, concerned about the effects of overregulating the pharmaceutical industry, the FDA began to streamline the process of drug evaluation and approval. In particular, the agency relaxed requirements for contraceptive methods that also protect against the acquisition of sexually transmitted diseases (STDs), and opened the way for the easier acceptance of data collected in foreign studies.

On the other hand, recent FDA plans to revise the approval process for compounds such as spermicides have renewed regulatory anxieties in the family planning community. For years, manufacturers of vaginal contraceptives have not had to receive formal FDA approval for their products as long as they were formulated following guidelines published by the agency in 1980. Early in 1995, though, the FDA proposed that each over-the-counter vaginal contraceptive be "tested in appropriate clinical trials under actual conditions of use" to establish its efficacy. This change would require new tests for some products that have been on the market for decades. Rather than perform expensive tests for products that yield only a small profit, some manufacturers could stop selling spermicides altogether.

Public Opinion and Politics

Changes in attitudes toward contraceptives. In terms of their effectiveness and ease of use, the pill and IUD represented a drastic improvement over barrier methods that they were adopted with great enthusiasm. Over the years since then, however, public opinion over the side effects of the methods grew, and researchers soon saw how media reports of complications (or potential complications) affected contraceptive use.

The coinciding growth in influence of the consumer movement and the women’s movement produced more critical analyses of contraceptive side effects, and fed rising public perceptions that since contraceptives are marketed, their potential for complications and side effects should be as small as possible. Such expectations added an extra layer of difficulty to the development of any new contraceptive method, and probably also contributed to the pharmaceutical industry’s hesitation to do much more than tinker with existing methods.

The explosion in STDs during the 1980s, and particularly the emergence of the human immunodeficiency virus (HIV) and AIDS, further complicated public attitudes. Only “low tech” barrier methods like the condom and spermicides offer protection against STD infection; the newer, more “high tech” methods, from the pill to the implant, offer little or no such security. In recent years, pressure has risen for a wider selection of methods that can prevent the transmission of pathogens—and against methods that cannot.

The abortion debate. Almost since the earliest days of the battle over the legal status of abortion in the United States, contraceptives have been caught in the crossfire. For years, some antiabortion activists denounced contraceptive methods such as the pill and the IUD, charging that if they disrupt implantation rather than prevent fertilization, they are in fact abortifacients.

Such arguments, in turn, have had an effect on contraceptive research. For example, among a number of types of contraceptive vaccines now under development, the most advanced is a vaccine to prevent or interrupt implantation. Critics, however, condemn it as an abortifacient. Similar concerns have slowed development work on a monthly menses inducer.

Financial Issues

Profitability. According to the 1993 PATH report, many companies view the limited potential of new contraceptives to attract additional customers in the United States to be the greatest deterrent to contraceptive research. According to this argument, contraceptive markets in developed countries are mature and have little additional profit potential; in the absence of a revolutionary new method that could force its way into a crowded market, most companies prefer to continue selling their existing product line rather than to invest large sums in research on methods that might not produce any greater profits. In addition, some companies probably fear that instead of attracting new customers, a new product would simply be substituted for the company’s other methods, adversely affecting the market share of existing, highly profitable products.

Research funding. Although contraceptive research becomes more expensive as ever more exotic approaches are explored, the funds available for such research have not kept up with demand. An evaluation of funding for contraceptive research conducted in the mid-1980s found that in 1983, about $57 million was being spent worldwide on contraceptive development, down nearly 25% from the high of $74 million (in constant 1983 dollars) spent in 1972. Federal spending on such research, according to the 1990 NAS report, became increasingly dominant in the 1980s, in part because of the steady decline in both industry and foundation support for contraceptive research.

Who Sponsors the Research?

For reasons outlined earlier, a number of American pharmaceutical companies instrumental in developing or marketing the first generation of modern contraceptives gradually left the field of contraceptive research. By 1995 there were only four private companies in the world that were known to be conducting research on new contraceptive methods. Two of these—Ortho and Wyeth-Ayerst Laboratories—are American companies, and two others—Schering AG and Organon—are European concerns. All market a number of contraceptives and have conducted research on various methods. Beyond these four, most private entities that participate in contraceptive research are fairly small start-up companies pursuing one or two approaches.

As the research role of private pharmaceutical interests faded, a host of U.S. public-sector organizations either stepped up their contraceptive development activities or initiated contraceptive research. These include such nonprofit institutions as Family Health International and The Population Council, each of which has had a long involvement in basic biomedical research and the shepherding of new methods to the market.

In addition, the Contraceptive Research and Development Program (CONRAD), which is supported primarily by the U.S. Agency for International Development and is based at Eastern Virginia Medical School, funds research on a wide variety of contraceptive approaches at research institutes, universities and private companies around the world. Its primary aim is helping to advance promising methods through the initial stages of safety and efficacy testing.

The U.S. government also directly supports U.S. contraceptive research through the Contraceptive Development Branch of the National Institutes of Child Health and Human Development (NICHD). In particular, the Contraceptive Development Branch often provides grants to fund clinical trials of new fertility regulation methods.

Internationally, the most important supporter of contraceptive research is probably the World Health Organization (WHO). Its Special Programme of Research Development and Research Train-
ing in Human Reproduction helps to coordinate international research efforts through task forces devoted to such areas as long-acting systemic methods, male fertility–regulating methods and vaccines.

In addition, there are several research programs established in developing countries, the most notable of which is the Indian Council of Medical Research, which has spearheaded important contraceptive vaccine studies. Another is the Programme of South-to-South Cooperation in Reproductive Health, which encourages a network of developing-country researchers to follow up on leads ignored or passed over by large pharmaceutical companies or developed-country research programs.

Finally, several private foundations, such as The Rockefeller Foundation, the Ford Foundation and the Andrew W. Mellon Foundation, contribute varying amounts of funds in support of programs or particular projects, both in the United States and overseas.

What’s in the Works?

Spermicides and Barrier Methods

Arguing that vaginal methods are ignored in favor of systemic hormonal methods, women’s health activists have persistently pressed for increased research on barriers and spermicides. In the early 1980s, only a strong campaign by feminist groups kept the cervical cap from being removed from the U.S. market after the FDA questioned its efficacy. Their efforts led to clinical trials that eventually brought FDA approval of the cap.16 A few years later, the rising prevalence of STDs and HIV infection among women of reproductive age finally led to a reevaluation of the worth of barrier methods.

A new vaginal sponge made of polyurethane foam is under development; it contains low levels of three different agents—nonoxynol-9, benzalkonium chloride and sodium cholate—that are meant to serve as a combined spermicide and microbicid.22

The new sponge is just one illustration of the proliferation of research on spermicides, virucides and microbicides. Early in 1995, NICHD announced the funding of three large projects on microbicides.21 Both are now in clinical trials: Femcap has begun small-scale safety studies, while Lea’s Shield has entered a comparative trial (with the diaphragm) intended to test the device’s safety and efficacy.

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At the same time, investigators are exploring the development of long-acting spermicidal suppositories, the addition of new chemicals to existing spermicides, and even entirely new products. (Neem oil, which is extracted from a tree native to India, is an example of the latter: When combined with two other natural compounds, neem extract has proven a potent spermicide in vitro and animal studies.24)

One highly promising, but long-range, approach is the use of recombinant DNA technologies to create monoclonal antibodies to combat microbes.25 Combining these antibodies and dispensing them either topically (as with a traditional spermicide) or via a vaginal ring might offer the user highly specific protection against sexually transmitted infections.

Injectables

Injectable progestins were developed in the late 1950s, and Schering AG marketed the first injectable, norethisterone enanthate (known as NET EN), in Peru in 1967.26 At about that time, Upjohn applied to the FDA for approval to sell depot medroxyprogesterone acetate (DMPA, also known as Depo-Provera) in the United States. However, early animal studies suggested that DMPA use might lead to an elevated risk of cancer; after nearly 25 years of controversy, expert panels, rejection and reappraisal, the FDA finally approved DMPA in 1992,27 on the basis of reassuring data from WHO multicenter studies.28 In the intervening years, DMPA and NET EN became widely used around the world.

In addition, several combined injectables active for about one month per injection have also become available in Europe and a number of developing countries. Combined injectables were developed because of the tendency of progestin-only methods to disrupt usual menstrual bleeding patterns: By adding estrogens to the long-acting progestins, researchers hoped to create a method that would give women better cycle control. In 1964, Upjohn conducted clinical trials of a combination of DMPA and an estrogen, estradiol cypionate, but the company terminated its contraceptive research in the mid-1980s. WHO continued work on the injectable, however, and by 1994 the preparation (known as Cyclofem) had been registered in six developing countries (Bolivia, Guatemala, Indonesia, Mexico, Peru and Thailand), with preliminary steps toward marketing under way in another six.29 In 1995, Upjohn exercised an option on U.S. rights to the injectable and announced that it would soon seek FDA approval for Cyclofem (to be marketed as Cyclo-Provera in the United States).30

Of the three other combined injectables, one consisting of NET EN and estradiol valerate was created by WHO and licensed to Schering AG, which has registered it in several Latin American countries.31 Schering has not indicated whether it plans to market the injectable (called Mesigyna) in the United States, however. In addition, two other combined injectables are very unlikely ever to be used in the United States. One, marketed widely in Latin America, contains rel-
ately large doses of estrogen and progestin; the other, known as Injectable No. 1, is not used outside of China.

**Vaginal Rings**

Research on vaginal rings—small silicone rubber devices that release a contraceptive hormone—also began in the 1960s. As the years passed, the number of vaginal rings under development proliferated, without any of them reaching the point of FDA consideration and approval. Two types of rings are currently being studied: one that releases only a progestin, and another that releases both a progestin and an estrogen. The biggest advantage of the progestin-only rings is that they can be used by women who are breastfeeding; their chief disadvantage is one shared by other progestin-only contraceptives—irregular menstrual bleeding.

A few years ago, among four progestin-releasing rings at various stages of development, a levonorgestrel-releasing ring developed by WHO was closest to going into general use. This device had a projected lifespan of three months, had undergone extensive testing in Great Britain and was about to enter large-scale production there. However, its introduction was postponed at a very late stage when vaginal irritation was detected in a small number of users.

A vaginal ring with a projected lifespan of one year or more has been developed by The Population Council; this ring steadily releases a very low dose of a progestin called Nestorone. Efficacy trials are expected to begin in late 1995. The method’s developers anticipate that both breastfeeding women and normally ovulating women will be able to use this ring. Finally, Population Council researchers have also developed a ring that releases progesterone, a natural progestin, and will be used exclusively by breastfeeding women. This ring has been licensed in Chile and is expected to make its debut there shortly.

The Population Council is also responsible for two vaginal rings that release a combination of progestin and estrogen: The first releases norethindrone acetate and ethinyl estradiol and can be used for up to one year; the second contains Nestorone and ethinyl estradiol, and is expected to be effective for 6–12 months. Both are in early phases of human trials; the Council is expecting to wait until full data have been collected on both versions of the combined ring, and then proceed to market with the better design.

Although small-scale clinical studies of various vaginal rings have produced generally positive results, none of these devices have been marketed in the more than 25 years that they have been under development. Research efforts were slowed by two serious problems. In 1987, Dow Corning stopped producing a chemical crucial to the fabrication of one of the materials used in many of the vaginal rings. As a result, most had to be redesigned, with concomitant delays in testing and development.

Then came the discovery in 1992 of vaginal lesions in some women using the WHO ring. Most work on vaginal rings was halted while special studies of the vaginal effects of ring use were conducted. Preliminary results indicated that such lesions also occurred among nonusers and did not appear to be associated with the ring itself. Nevertheless, the WHO ring was redesigned to be more flexible, and studies of the new ring design have been undertaken.

A vaginal ring may yet become available for consumer use, but whether this method is marketed in the United States will depend in part on the developers’ success in finding a commercial partner willing to sell the device. Other complications may still occur, however. For example, some chemical companies that produce medical-grade silicone rubber materials (such as those used in the ring) are considering withdrawing their products from the U.S. market because the manufacturers have repeatedly been included as plaintiffs in liability lawsuits over medical devices that use their materials.

**Implants**

Although the introduction of the six-capsule contraceptive implant to the U.S. market has been problematic, its developers, The Population Council and Wyeth-Ayerst, are moving ahead with a second-generation implant, a two-rod system known as Norplant II; a new drug application for this method was officially submitted to the FDA in mid-1995. The two rods, which release small amounts of levonorgestrel (the same hormone used in the six-capsule version), are expected to have an effective lifespan of at least three years. The use of two rods rather than six capsules will probably ease both insertion and removal difficulties.

Other hormonal implants are in much earlier stages of development, and may debut outside of the United States before they are marketed here. For example, Organon is conducting large-scale human trials of a single-rod, desogestrel-releasing implant (known as Implanon) that will be effective for at least two years. In addition, the nonprofit consortium known as South-to-South Cooperation in Reproductive Health has begun early human studies of Uniplant, a single implant that releases the progestin nomegestrol acetate and will be effective for about one year. Finally, The Population Council is working on a rod-like implant that will release Nestorone.

A drawback common to all of these implants is that they need to be removed surgically. Thus, researchers are working to create biodegradable implants. One such implant, known as Capronor, is a capsule that releases levonorgestrel and is expected to provide one year of contraceptive protection before the capsule biodegrades.

Another approach being studied involves the injection of 4–6 small pellets consisting of norethindrone and cholesterol; this method is also expected to be effective for about one year. Although both of these implants have been studied in women, at least several more years of human research may be needed before they can be referred to the FDA for approval.

**Intrauterine Devices**

The IUD is one of the oldest and one of the most effective of modern contraceptive methods, but currently has low prevalence and limited availability in the United States. Two IUDs are currently sold domestically: a Copper-T IUD also widely used around the world (the 380A) and a hormonal IUD with a useful life of only one year.

Although the introduction of new IUDs in the United States might raise the method’s prevalence, there is little reason to anticipate new arrivals anytime soon. A hormonal IUD with a lifespan of three years, the LNG 20, is already approved for use in Finland and in Sweden. Its Finnish manufacturer, Leiras Oy, has not yet sought FDA approval for the device.

WHO has been conducting trials on a new frameless IUD (called CuFix 330) that lacks the IUD’s usual stiff plastic skeleton; instead, the CuFix consists of a string of six copper beads suspended from the upper portion of the uterus by a nylon thread. The design is expected to produce less pain and bleeding than other types of IUDs, although early research has produced mixed results.

**Methods for Men**

For most of the history of contraceptive research, scientists have focused on female methods. A consensus is forming, though, that systemic male methods should also be developed and promoted. An international symposium involving contracep-
tive researchers and women’s activists that was held in 1990, for example, concluded that there was a clear need to increase the investment in research on male methods (as well as to convince men to become more personally involved in fertility regulation and reproductive health). Even the 1994 International Conference on Population and Development included in its final document a statement that “high priority should also be given to the development of new methods for regulation of fertility for men.”

Moving beyond condoms to systemic methods for men may prove difficult, however. For example, although WHO has studied hormonal approaches to male contraception for more than two decades, no usable method has yet been produced. Recent WHO research has shown that weekly injections of the androgen testosterone enanthate will suppress sperm counts so that annual pregnancy rates are only about one per 100 person-years of use. However, weekly injections would not be commercially viable, and developing acceptable dosages and injection schedules remains a stumbling block. WHO hopes eventually to develop a treatment that is either oral or can be administered by means of an implant.

Combining testosterone enanthate with a progestin (such as DMPA) or with another androgen may lead to a long-term injectable method for men. WHO and CONRAD have tested such approaches in only a handful of men, however.

A dual-implant system for men is being examined by The Population Council. One implant releases a luteinizing hormone-releasing hormone analog that halts sperm production; the other releases a male hormone to prevent loss of potency and libido. These implants are only now entering the first stages of human trials, however, and are a number of years away from general use.

Several other concepts for male systemic methods are even farther back in the development process. Mifepristone is believed to interfere with sperm motility, but the use of this drug as a male method still must be tested in animals before human trials can begin. The serendipitous discovery by infertility researchers in New York that a hypertension drug, nifedipine, had produced infertility in a group of men has led to hope that it may serve as a reversible male method. Although animal tests will not be needed for the drug, which is already FDA-approved, dose-finding research must be conducted before efficacy trials can begin.

Along with such new possibilities, researchers are also reexamining an old lead—gossypol. Derived from cottonseed oil, gossypol stops sperm production but does not affect androgen levels. Studies published in the early 1980s revealed that the drug also reduced body levels of potassium, leaving users prone to temporary paralysis and irregular heartbeat. In addition, infertility proved irreversible among some of the users. However, subsequent research has suggested that reduced doses of gossypol may avoid these problems but still maintain the antifertility effect. Over the next few years, South-to-South will be conducting a multicountry international trial of gossypol.

Vaccines
Nearly 100 years ago, scientists learned that spermatozoa could provoke an immune reaction if they were injected into the body. Efforts at translating this information into a contraceptive vaccine began in the mid-1960s and focused on inducing an immune reaction to sperm.

In the mid-1970s, researchers realized that human chorionic gonadotropin (hCG) would also be a good candidate for a contraceptive vaccine, since this hormone is produced only during early pregnancy. After 20 years of research, though, the first small-scale human trial of an anti-hCG vaccine showed that nearly 20% of the women who received injections failed to develop an effective immune reaction. Research continues on two anti-hCG vaccines, one created by India’s National Institute of Immunology and one produced by WHO. Meanwhile, other researchers continue to explore the feasibility of developing vaccines targeting a variety of proteins on the surface of the egg or on the surface of the sperm, in the belief that if either gamete could be coated with antibodies, fertilization would not take place. Another potential vaccine is aimed at disrupting a chemical that assists in the fusion of the sperm and egg. Scientists have found it harder than expected to identify molecules peculiar to the gametes or to the fertilization process, however, a necessary step so as not to provoke an autoimmune reaction among similar molecules elsewhere in the body.

Moreover, research into immunologic contraception is expensive, and only limited funding for such research has been available. Adding to the complexity of the situation is that contraceptive vaccine research has come under heavy criticism from both antiabortion and women’s health activists. Those opposed to abortion object to the anti-hCG vaccines as being a form of abortion. For that reason, no U.S. government research money has gone to study these vaccines, even though they are closer to actual large-scale human trials than an antisperm vaccine.

Meanwhile, in 1993, a network of women’s health activists, the Women’s Global Network for Reproductive Rights, began a drive to halt all contraceptive vaccine research around the world. The group’s objections range from worries that a successful vaccine could be administered to women against their will and that manipulating the human immune system may prove unnecessarily dangerous to concerns over the ethics of conducting such experiments and the “population control” perspective from which they believe the concept of contraceptive vaccines is derived.

Some of this opposition arises from a misapprehension that at one time was shared by the research community: that a contraceptive vaccine would prevent pregnancy permanently, much like vaccines against certain diseases. Most studies of candidate immunologic contraceptives have suggested, however, that the immunity wears out fairly soon, and that for extended contraception a number of booster injections would probably be needed. Thus, a contraceptive vaccine may prove to resemble current injectables more than it will disease vaccines.

Menses Induction
A reliable menses inducer would have several distinct advantages over other methods: the need to administer just one pill per month, rather than one per day; a smaller likelihood of long-term side effects; and the user’s lack of awareness about whether fertilization had in fact occurred that month. Yet two decades of searching for a usable menses inducer, by WHO and by other institutions, has not been successful. Throughout the 1970s, researchers studied the use of prostaglandins to induce menses on a regular basis. The drugs proved fairly reliable, with efficacy rates approaching 90%. However, they also caused women much nausea and diarrhea. As a result, research on them gradually waned.

In the 1980s, investigators turned their attention to antiprogestins as another means of interrupting implantation. WHO studies and research performed by Roussel-UCLAF demonstrated that the antiprogestin mifepristone, when combined with a mild prostaglandin, was a very effective early abortifacient. However, mifepristone has less promise as a...
monthly menses inducer, in part because it can delay the start of the next menstrual cycle, making it difficult for a user to determine when to take subsequent doses.60

The development of a menses inducer is another area of research that has been slowed by abortion politics. First, because of differences in the wording of abortion laws around the world, menses inducers that interfere with implantation might be legal in some places but illegal in others. Similarly, a drug used after a woman knew that her period was late might be classified as an abortifacient, while the same drug used at—or just before—the time the woman expected her menses to occur might not be.

**Will Research Awaken?**

Continuing high levels of abortion and of unintended pregnancy suggest that many couples are in need of a new approach to contraception. The reanimation of contraceptive research in the United States would help meet these needs and eventually could reduce the level of unintended pregnancy.

A concerted effort is now being made to accelerate research on contraception so as to recover some of the momentum lost in the 1970s and 1980s. In May 1995, the Institute of Medicine convened a workshop to discuss ways in which to promote public-private collaboration in contraceptive research. One month before, the Rockefeller Foundation sponsored a conference in Bellagio, Italy, on public- and private-sector collaboration in contraceptive research and development. The conference brought together, for the first time, senior representatives of the pharmaceutical industry and of public-sector programs to discuss how the process of contraceptive development could be reinvigorated by means of public-private collaboration. And in late 1994, the Institute of Medicine held a workshop on how contraceptive research efforts can take advantage of novel leads growing out of research into molecular biology.

These conferences were part of a larger Rockefeller Foundation–funded initiative entitled “Contraception-21,” intended to “launch a second contraceptive technology revolution” for the 21st century.61 Contraception-21 entails a five-component plan to mobilize new resources for contraceptive research: focusing research on methods that women feel a need for; reengaging the pharmaceutical industry in contraceptive research; applying new findings in molecular biology to the problem of preventing fertilization and pregnancy; accessing the technical and human resources of developing countries; and increasing the commitment of international donors.

How to reestablish the pharmaceutical industry’s interest in contraceptive research is the principal focus of one area of the initiative. PATH, in particular, has analyzed why public-sector organizations have experienced difficulties in “handing off” newly developed products to private-sector manufacturers.62

Among the reasons is an important difference in the process by which public-sector and private-sector organizations develop products. While public-sector agencies often choose an approach based simply on what will work, pharmaceutical companies usually use market research to determine customers’ preferences regarding the ideal and the minimum acceptable combinations of characteristics for a particular product. The findings of such research then may be used to guide product research, permitting the developer either to refine a drug that is under development or to halt work on one that will never satisfy users’ minimum criteria of acceptability.

The authors of the PATH report observe that in particular, public-sector organizations often lack a mechanism for terminating work on leads that may ultimately prove unpromising. The end result can be an inefficient use of the limited funding available for contraceptive research, very slow progress for all methods under development and the creation of a drug or device with limited commercial appeal.

Although in the past, public-sector research organizations have often worked together with private-sector companies to market new methods (such as the Population Council’s licensing Wyeth-Ayerst to market the hormonal implant in the United States), such collaboration has usually occurred late in a product’s development cycle. In an emerging alternative model for private-public collaboration in contraceptive research, a public-sector organization seeks to involve a private company at an earlier stage of product development than is currently typical, perhaps by using market research to demonstrate the commercial potential of a method well before it is actually ready to be marketed. (Both CONRAD and FHI have successfully used this approach in recent years.) Alternatively, a public-sector agent works with a private company to supply the expertise needed to move the private company’s product toward FDA approval, with a quid pro quo of a low public-sector price or a share of royalties.

One recent example of public-private collaboration concerned efforts to bring the combined injectable Cyclofem to market. WHO took on the research responsibility for Cyclofem after Upjohn halted their contraceptive development work, and sponsored a series of studies evaluating the method’s effectiveness and side effects. In the late 1980s, WHO awarded rights to the drug to the Program for the Introduction and Adaptation of Contraceptive Technology, which then licensed Cyclofem to the Concept Foundation, a nonprofit foundation in Thailand. This foundation, in turn, sought manufacturers for the drug and obtained approval for the drug in a number of developing countries. Subsequently, Upjohn exercised an option to pick up Cyclofem’s U.S. rights from the Concept Foundation, and may soon be selling Cyclofem in the United States.

The PATH report also suggests that the pharmaceutical industry is in the midst of a massive transition that will probably reduce the likelihood that drug companies will conduct all of the development work for a product in-house. As a result, it could become common for pharmaceutical companies to collaborate with small outside public or private organizations, especially on exotic or unusual drugs and devices. Such collaborative efforts will probably become particularly important as contraceptive research embraces new developments in molecular biology and biotechnology.

**Is the Concern Misplaced?**

In 1995, an American woman seeking a reversible method could choose from among oral contraceptives (more than 30 formulations), IUDs (two types), an injectable, an implant and a variety of barrier methods. Do such methods represent enough of a choice, or is a wider variety of methods needed? Although Americans are believed to be discontented with their current array of contraceptive choices, no good data currently exist to confirm individuals’ opinions about the need for new methods or what contraceptive research priorities should be. (A poll conducted in 1988 suggested only that 82% of American adults favored continued government funding of contraceptive research.)63

Several factors suggest that the current mix of reversible methods is inadequate, however. One is that approximately 1.5 million abortions are performed annually in the United States; likewise, there are about two million births each year that are considered either mistimed or unwanted. Surely many of these abortions and births could be avoided if more acceptable
methods of contraception were available. Yet what hope is there that more contraceptive choices will become available at any time soon?

Liability reform (which was urged in the 1990 NAS report) may bring the pharmaceutical industry back into contraceptive research. The tort reform measures under consideration in Congress could change liability issues facing contraceptive manufacturers. For example, the broad product liability bill passed by the House of Representatives in March 1995 included language known as the “FDA defense”—that manufacturers cannot be liable for punitive damages if their product was approved by the FDA (so long as the information that they provided to the FDA was honest and complete). The Senate version of the bill, which as of October 1995 had not been voted on, does not contain such language. Thus, even if the latter were passed, it would take a House-Senate conference to decide the provisions of a final bill.

However, with the pharmaceutical industry in the midst of important change, legislative actions such as tort reform may not be sufficient—or even necessary—to provoke movement on contraceptive research. Companies are now merging and rethinking their research and development strategies. Some may choose to reenter the business if they are better insulated from lawsuits; others might decide that even favorable changes in the liability laws will not be worth the expense of reinitiating a contraceptive research effort, especially if new methods might endanger steady profits from established contraceptives.

Without reform, though, major change in the current situation seems unlikely, given the near impossibility of obtaining insurance against liability claims. In the past, some companies have “self-insured” methods by building a premium into the price of the method and then diverting a portion of the income to an insurance fund. However, self-insuring the pill was simple, because sales were high and expenses low. Self-insurance for the IUD and the implant, on the other hand, led to high initial prices for these devices. If a similar strategy is used with other novel methods needing infrequent resupply, the resulting high initial charges for them may blunt their potential.

Even in the event of tort reform sought by the pharmaceutical industry, however, the role of large companies will probably remain limited. Indeed, in the early days of the “contraceptive revolution,” many of the most important developments were spearheaded by individuals or small companies that later grew into large manufacturers. Similarly, many new methods either marketed in the last few years or in advanced trials (such as the female condom, the polyurethane condom, new caps and diaphragms, and new sponges) were developed by small, single-product companies (often with substantial assistance from public-sector entities such as CONRAD and NICHD).

Such firms will likely continue to be the engine for contraceptive development in the United States. First, they often are willing to take research risks that larger enterprises will not. In addition, although a shortage of capital can sometimes slow their research efforts, they are less attractive targets for liability suits because they lack “deep pockets.”

On the other hand, small firms may be more suited to marketing niche products than to developing major new methods. Even the larger, better funded nonprofit organizations (such as The Population Council) have experienced problems in completing their research in a timely manner when a new method presents technical problems. Such situations may require closer collaboration between small entities (either for-profit or nonprofit) and major manufacturers, and at an earlier stage than is presently the case.

Regardless of the results of liability and regulatory change, funding remains a key problem in contraceptive research. Worldwide, pharmaceutical companies are estimated to take in as much as $2.9 billion on contraception, but probably spend only about $22 million on contraceptive research. Likewise, in 1992, the U.S. Center for Population Research targeted only about $14 million of its $140 million reproductive research budget at contraceptive development. A recent attempt at estimating current spending on contraceptive research produced a figure of only $57 million for 1993, substantially less than the $69 million estimated for 1983. Both of these figures are lower than previous estimates; either estimate indicates little real growth or actual reductions in constant-dollar spending for contraceptive research.

The future of contraceptive research may lie in greater private-public collaboration in the funding and conduct of research. However, such coordination may require public-sector organizations to reconsider the appropriateness of some of the methods they have focused on, as pressure grows to justify expenditures to a for-profit partner with an emphasis on developing a marketable product. Furthermore, seeking the closer involvement of private pharmaceutical companies may increase the difficulty of proceeding with potentially controversial methods, such as menses inducers or certain kinds of vaccines.

Overall, rather than being revolutionary, any new methods that reach the U.S. market before the end of the century will probably represent the kind of steady evolutionary change that has characterized contraceptive development over the past decade or more. If methods that would transform contraceptive practice (as the pill and IUD did in the early 1960s) are to appear in the longer run, increased public support, a mobilization of ever-scarcer resources and closer cooperation between public-sector and private-sector entities will be needed.

References
4. Ibid., p. 137.
5. Ibid., p. 141.
8. Ibid., p. 1.
15. L. Mastroianni, Jr., P. J. Donaldson and T. T. Kane, 1990, op. cit. (see reference 3).