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Prospects for Improved Contraception

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Introduction

Like most revolutions, the contraceptive revolution disappointed some whose expectations of it were unrealistically high. Two decades ago, when the oral contraceptive was brought to market and the IUD was reborn in antiseptic plastic and stainless steel, many scientists voiced optimism that that was only the beginning. A new reproductive age was said to be dawning, and it would not be long, we were told, before the perfect contraceptive would become available—highly effective, safe, acceptable, inexpensive and simple to administer and distribute. By now, it is generally recognized that there can never be such an ideal contraceptive, and that an array of methods is needed for people who live under different circumstances and have differing preferences and requirements. Each method has its unique advantages and drawbacks, and it is likely that there will always be some trade-off between effectiveness and risk.

Granted all these qualifications, the distance from the scientist's imagination to the couple's bedroom has proved to be greater than some had believed. The array of vaccines, menses inducers, male pills and chemical sterilants first heralded a dozen or more years ago are for the most part still in early stages of development—for want of money, knowledge, manpower or all three. Not a single new contraceptive chemical entity has reached the marketplace since the introduction of the synthetic steroid norgestrel in 1968. What is more, the need for improved contraceptives has become ever more acute as the reputations of the pill and the IUD have been tarnished by an accumulation of

Some important new birth control methods have been developed in the postpill, post-IUD era; others are on the way. But shrinking dollars for research (especially R&D), inadequate coordination and planning by donors and programs, and costly and complex regulatory requirements frustrate efforts to use current knowledge to make major breakthroughs.

medical reports indicating that while they are not nearly as dangerous as some had feared, neither are they as safe as some had hoped.

Population growth rates in developing countries (where three-quarters of the world's people live) remain high, implying a doubling of the 3.3 billion inhabitants of Third World countries in the next 34 years, slowing progress in economic and social development.¹ In most developing countries, more than half of women of reproductive age want no more children, but typically, two-thirds of them are not using any means to prevent childbirth.² Even in highly developed countries, where contraceptive practice appears to be nearly universal, unintended pregnancies remain common. In the United States, for example, an estimated 2.8 million unplanned pregnancies occur each year, half of them terminated by induced abortion.³

Does all this mean that the contraceptive revolution itself was aborted? Although we have not been propelled from the contraceptive stone (or rubber) age directly into a High-Tech, perfectly contracepting society, neither have we stood still in the development of more effective and safe birth control methods and in their successful wide-scale use.

Among the new methods marketed since the pill and IUD made their debuts 20 years ago are outpatient female sterilization by means of laparoscopy and minilaparotomy, simplified aspiration abortion, copper and hormone-releasing IUDs, long-acting injectable progestational agents, prostaglandins

for second-trimester abortions and — not least in importance — a much safer but still highly effective oral contraceptive, with just a fraction of the dose of steroid hormones contained in pills marketed two decades ago. What is more, long-acting hormonal implants, vaginal rings, new injectable preparations, prostaglandins to induce early abortions, IUDs causing less bleeding and pain and cervical caps are in advanced field trials with thousands of women, and should be widely available within the next three to five years. Somewhat further down the line, but with an excellent chance of being introduced into wide-scale use, are long-acting biodegradable steroidal implants that do not require removal. By any standard, these technological advances constitute a considerable improvement in the available contraceptive repertoire.

Increasingly widespread utilization of the most effective modern methods of birth control associated with vigorous national family planning programs in a number of developing nations — including some very populous ones such as China, Indonesia, Mexico and Thailand — have helped bring down birthrates and explosive population growth rates dramatically. Although specific estimates differ, there is now general agreement that the rate of population growth in the developing world has been slowed, and that barring unforeseen safety problems with current methods or significant alterations in the social climate, the trend toward further decline in growth rates is likely to continue.⁴

Unprecedented control over reproduction (however still imperfect) has helped women

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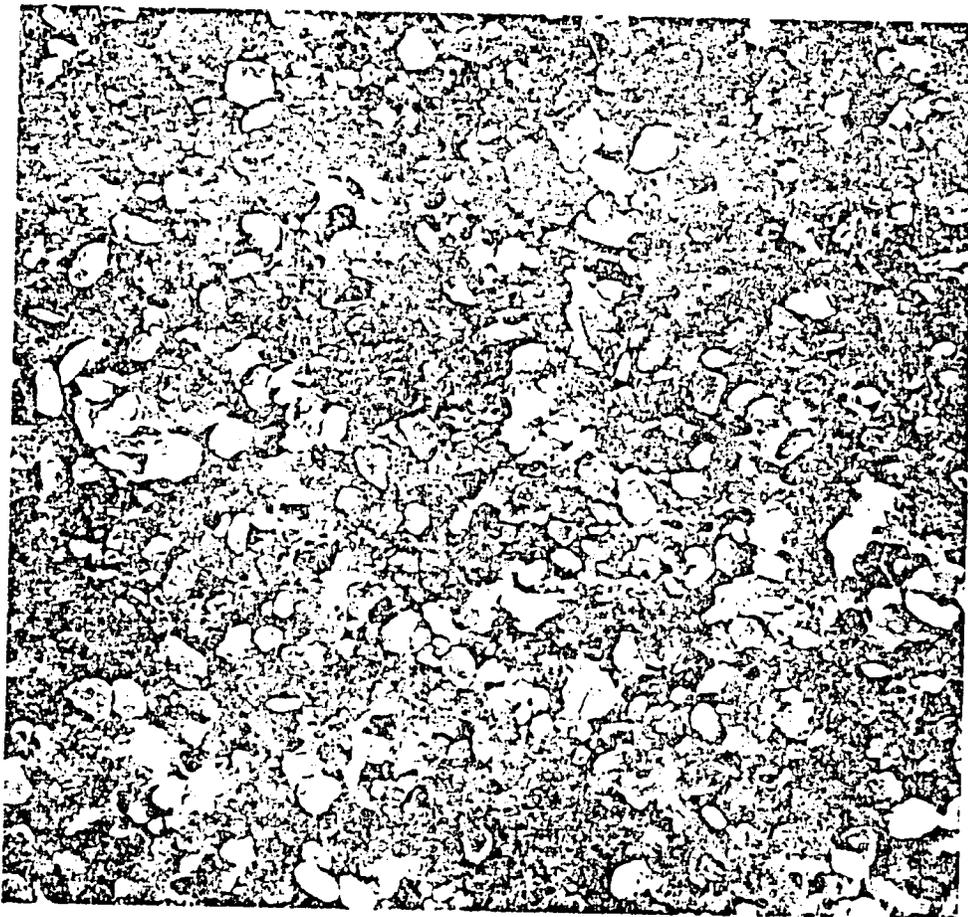
Prospects for Improved Contraception

to take advantage of opportunities for educational and economic advancement and to press for realization of those opportunities where they are not available. The strong pressures exerted on the scientific community to find safer alternatives to the pill and the IUD are themselves evidence of the growing power of the women's movement, which, in turn, has been spurred by the availability of these very methods.

It seems almost certain that with improved service delivery programs employing currently available methods, birthrates will come down even more rapidly in the years to come as couples are enabled to improve con-

in countries where all current methods, including abortion and sterilization, are widely available, however, is evidence that today's methods are not sufficient to enable couples to realize their reproductive intentions even under very favorable circumstances, much less under conditions where storage, distribution and administration of contraceptives are problems.

Oral contraception, the IUD and sterilization are the cornerstones of current service delivery programs. The pill, although highly effective, is considered unsafe for older women who smoke or have other conditions (such as obesity or high blood pressure) that



A long-acting steroidal implant might be marketed in three years (above, silastic implant surface).

control over their own reproduction. The decline will be especially marked if the trend toward liberalization of sterilization and abortion laws and policies continues. As has been noted in several country studies, not only do family planning programs help couples to have the number of children they desire, but the very success of these programs appears to influence them to reduce their family size ideals, especially when some (even very modest) improvements in levels of modernization and women's status are occurring simultaneously.⁵

The very large number of unintended pregnancies and births that continue to occur

place them at high risk of cardiovascular disease. The advisability of the IUD, on the other hand, is questionable for young women who have not yet begun childbearing, because of the danger, however small, of infection that might compromise future fertility. Widely publicized information about health risks — sometimes sensationalized — has led a number of young women in developed countries such as the United States to abandon the pill and the IUD. Many of these women have switched to traditional, less effective methods, depending on legal abortion as a backup in the event of contraceptive failure. As family planning programs expand,

pill and IUD use in developing countries continues to increase, but both acceptance and continuation rates are undoubtedly affected by adverse publicity. In any case, discontinuation of both methods is often relatively high, and their extended use-effectiveness is below that obtained in clinical trials with highly motivated users. Both effectiveness and continuation of use are lower in developing than in developed countries, reflecting such adverse social conditions as poor health services, low income and low education levels. As a result, it is not uncommon in Third World countries to see pregnancy rates associated with these methods that are many times higher than those recorded in developed countries; and first-year discontinuation rates in developing countries run as high as 20–40 percent of new pill and IUD users.⁶ There are even more problems of acceptance and consistent long-term use with coitus-related methods. Although the demand for contraceptive sterilization outruns the technical and logistic capacities of many developing countries to provide services, couples often turn to this permanent method only after failing to prevent unwanted births with reversible methods. Without the backup of induced abortion, as we have noted, the incidence of unplanned births would be more than twice as high as it is, even in a country such as the United States where contraceptive use is widespread. And it is unlikely that the political and religious controversies over abortion will be settled in the foreseeable future. In a number of countries, especially in the Muslim world, it is probable that abortion will remain illegal for some time to come.

Under these circumstances, it seems unlikely that the present technological base for birth planning will be adequate to support the addition of 500–600 million more users over the next few decades. New reversible methods for men and women, as well as less intrusive and simpler means of sterilization, continue to be desperately needed in industrialized and in developing countries.

What is the current state of contraceptive development, and what are the prospects for the future?

The Contraceptive R&D Process

Producing and marketing a new contraceptive involves investment in six major types of activity: the training of scientists to conduct research and the support of those institutions that educate them; basic scientific research in reproduction; mission-oriented research; applied research and development (R&D); product introduction; and evaluation of the effectiveness and safety of methods in use.

For any type of research, basic or applied,

the training of scientists and support of the academic institutions that produce them is essential.

Basic research from a wide range of scientific disciplines is the source of fundamental knowledge needed to supply leads for development of contraceptive methods. It is generally undertaken without an applied objective in mind, and includes laboratory, animal and field research devoted to improving knowledge about reproductive processes.

Mission-oriented (or directed) research generally refers to efforts aimed at accomplishing a specific contraceptive end; examples include a means of arresting spermatogenesis or a luteolytic agent. Mission-oriented research may include both basic and applied efforts, and may be conducted simultaneously in academic institutions and applied R&D organizations. (For example, efforts to develop a male pill may involve toxicology and efficacy studies by R&D organizations even as fundamental studies of the male reproductive physiology are undertaken to elucidate how points in the reproductive process might be interrupted to provide a more effective means of fertility control.)

The direct source of new products and technologies is applied R&D, which endeavors to utilize fundamental knowledge and understanding to develop new materials, new techniques and new processes in order to create a new product. Narrowly defined, applied R&D consists of using scientific research procedures in conjunction with engineering and manufacturing capabilities to design, test and refine new prototype products. In the case of applied R&D directed at obtaining new contraceptive methods, the major organized R&D programs are currently being conducted by more than a dozen private pharmaceutical companies, by three nonprofit R&D organizations, by a UN agency and by a U.S. government agency. In addition to the work they carry out within their own institutions, these organized R&D programs also use grants and contracts to fund a wide variety of other organizations to perform specific applied R&D tasks.

Product introduction converts a newly developed prototype product into a widely available manufactured item. This final step of the overall contraceptive development process comprises product acceptability and marketing studies, design and engineering of production plants, pilot trials of manufacture, package design, regulatory filings, establishment of distribution channels and other activities designed to ensure local introduction and use of new products. Product introduction activities are sometimes defined and conducted as part of the applied

R&D process. In other instances, they are viewed as part of the family planning service delivery system or of private-sector marketing, distribution and sales systems.

A sixth type of scientific activity — evaluation of the performance of existing contraceptive techniques — complements and provides an essential frame of reference for the contraceptive development process. It entails epidemiological research and is generally conducted by government agencies or by specialized nonprofit groups in collaboration with universities and health centers. Studies of existing methods provide benchmark information on the safety, health effects and effectiveness of products in current use.

While this article touches on all aspects of reproductive research and contraceptive development, its main focus is on applied R&D and on public-sector support for developing new contraceptives.

Funding and Organization

Reproductive and contraceptive research did not benefit from the rapid expansion of funding for biomedical research by the governments of the United States and other industrial nations in the two decades that followed World War II, largely because of the traditional taboos against the study of sex and reproduction and the moral and religious controversies over government involvement in birth control. Indeed, until 1959, the U.S. National Institutes of Health were prohibited from supporting research having any explicit relationship to birth control. (Today, the controversy over abortion similarly inhibits research in that area.) During the 1950s, biomedical research in the field of reproduction was largely funded by two major private foundations — Ford and Rockefeller — and a few individual philanthropists.

The oral contraceptive was developed with the support of private philanthropy and some sectors of the pharmaceutical industry, but without any government funding. By the mid-1960s, however, worldwide concern about the problems caused by rapid population growth spurred increased support for research to find better birth control methods.

In 1967, an Office of Population was established within the U.S. foreign assistance agency, the Agency for International Development (AID). While most of its funds are expended for family planning service programs, 3.5 percent of its budget has gone for research related to contraceptive development.* The Center for Population Research (CPR), now the major source of funds worldwide for reproductive and contraceptive research, was established as part of the U.S. National Institute of Child Health and Hu-

man Development in 1968. In 1969, the United Nations Fund for Population Activities (UNFPA) began its large multinational population assistance efforts. Its investment in fertility regulation research has never exceeded one-half of one percent of its budget, and has been used mainly for institution-building, although very recently, UNFPA has begun to make small expenditures for contraceptive development through annual contributions to the Human Reproduction Programme of the World Health Organization (WHO).

During the late 1960s, other developed countries — Britain, Canada, France, Sweden and West Germany — also began to fund reproductive and contraceptive research. Smaller efforts — most of them supported by international assistance agencies — were undertaken in some developing countries; the largest of these was in India.

The result of this increased concern can be seen in Figure 1 (page 178) and Table 1 (page 179). Funding for all aspects of reproductive and contraceptive research rose rapidly, from an estimated \$31 million in 1965 to \$117 million in 1973. Although this total research budget has continued to climb as measured in current dollars (to an estimated \$155 million in 1979), expenditures corrected for inflation peaked in 1973. By 1979, constant-dollar expenditures were below what they had been in 1971.

Although U.S. government contributions for reproductive research have been increasing since the mid-1970s in constant as well as current dollars (see Table 2, page 179), the investment of private philanthropies has declined somewhat and contributions of other governments apparently have not grown. The investment of the private pharmaceutical companies is believed to have plateaued in the late 1970s at about \$14 million (current dollar figures not shown in table) and apparently has declined in constant-dollar terms because of increased concern about the profitability of investment in research into new methods.†

The U.S. government is currently spending about \$89.3 million for all types of reproductive and contraceptive research, contrib-

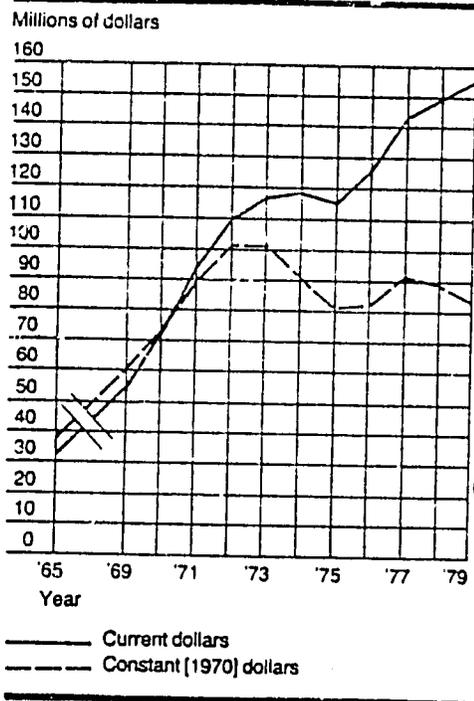
(Continued on page 178)

*A very small proportion of AID's research expenditures have been for specified basic research believed to offer promise of generating new leads for applied contraceptive R&D, e.g., prostaglandins and thyrotropin-releasing hormone research.

†Survey data from governments other than the United States and from pharmaceutical companies are not available after 1976. There is some indication that the efforts of private industry may have increased during the last two years because of interest in a few specific research areas, especially in the brain hormones.

(Continued from page 175)

Figure 1. Worldwide expenditures for reproductive research, 1965-1979



uting primarily through the CPR with smaller amounts expended through other of the National Institutes of Health and the AID. The proportion of total world funding for reproductive research provided by U.S. government agencies has increased from just 30 percent in 1965 to 35 percent in 1970, 45 percent in 1975 and 58 percent in 1979. Private philanthropies and nonprofit agencies, which accounted for about one-fifth of total funding in the latter half of the 1960s and the early 1970s, are now responsible for less than one-tenth of total research expenditures. U.S. industry, which financed about one-quarter of reproductive research in the late 1950s, was, by the late 1970s, believed to be responsible for less than one-tenth of expenditures.

Although all aspects of funding for reproductive and contraceptive research have declined when measured in constant dollars, it is the expenditures for contraceptive development that have fallen most sharply, as may be seen in Table 3 and Figure 2 (page 180). Whereas about 30 cents of every dollar spent on reproductive research went into contraceptive development in 1974, only

*Among the governments were those of Denmark, Finland, Great Britain, Norway, Sweden, the United States and Canada's specialized foreign assistance agency, the International Development Research Centre (IDRC). The foundations were the Ford Foundation and The Rockefeller Foundation; the multilateral agency was the UNFPA.

about 23 cents per dollar was spent for this purpose in 1978 (the most recent year for which data are available). Even in inflated current dollars, funds for contraceptive development have not increased. (They were about \$35 million in 1974 and \$33.7 million in 1978). Although expenditures by pharmaceutical companies may have increased somewhat in the last two years, it is notable that public-sector funding for contraceptive development has clearly declined since the early 1970s. At the present time, only 15 percent of all reproductive research financed by governments, private philanthropies and multinational organizations is devoted to contraceptive development.

In 1974, the authors of a Ford Foundation-sponsored study estimated that funds for applied contraceptive R&D would have to be increased by three times to take advantage of leads developed through basic research;⁷ today, expenditures in constant dollars are only three-quarters of the extremely inadequate 1974 levels (see Figure 2).

Yet basic science has uncovered numerous new leads in the 1970s — most spectacularly, Guillemin and Schally's Nobel-prize-winning work on releasing factors, which has opened up new opportunities for applied research that could lead to revolutionary new birth control methods for men and women (as well as new means to stimulate fertility in the infecund). Expenditures for basic reproductive research and for training new scientists, which were estimated in 1974 to be at about 40 percent and 30 percent, respectively,⁸ of what were then current needs, have not done as badly as support for contraceptive R&D, but they, too, have not grown rapidly enough to do much more than keep pace with inflation. Expenditures for evaluation of the safety of current fertility control methods — estimated in 1974 to be just at 15 percent⁹ of the levels needed to protect the health of users — have remained about the same in current dollars, but have declined by more than one-fifth when inflation is taken into account. This decline has occurred despite the widespread publicity given to safety problems associated with available modern methods.

Given the failure of funding institutions, both public and private, to meet the challenges documented by the 1974 Ford Foundation study, it is perhaps remarkable that the postpill, post-IUD phase of the contraceptive revolution has been as successful as it has. And it is not at all surprising that expenditures for research into new methods of contraception have tended to be restricted to so-called low-risk efforts promising relatively quick returns with minimum investment.

Public-Sector Contraceptive Development

During the late 1960s and early 1970s, the foreign assistance agencies of governments in several developed countries, two private U.S. foundations and one multilateral agency* took steps to create new public-sector programs to help develop new birth control methods. These programs were financed mainly through foreign assistance funds, since their primary purpose was to contribute to a foreign policy goal: namely, a reduction in unwanted births and an improvement in the individual health and well-being of couples in developing countries through provision of more appropriate birth control techniques than those currently available.

The rationale of the principal donors was based upon their realization that technologically feasible improvements in birth control techniques could contribute to improving individual health and well-being while reducing rapid population growth rates in developing countries. Unwanted fertility in these countries not only constituted a substantial proportion of childbearing, but also was viewed as hampering the efforts of national governments to improve the social, economic and health conditions of their people.

The donors recognized that private industry, which had traditionally been depended upon to develop new drugs and medical devices, had little incentive to develop birth control products geared to the special needs of developing-world couples because of what was perceived as poor profit potential offered by such markets. National medical research councils in developed countries, despite their growing interest in reproduction, concentrated almost all of their efforts on fundamental research. What is more, their priorities were determined mainly by the health needs of their own people, rather than by the needs of people who live in developing nations.

Few developing countries had (or have) national medical research councils focusing on reproduction or contraception (an exception is the Indian Council for Medical Research); those that did generally lacked the scientific capacities for highly technical applied R&D efforts. With the experience before them of international public-sector programs in applied R&D that had helped to enhance rice, wheat and maize production, the foreign assistance agencies reasoned that similar programs could be established to develop new birth control technologies that would be useful in Third World nations.

Over the course of a few years, five new scientific organizations were created that focused on the contraceptive needs of couples in developing countries: The Special Pro-

Table 1. Total expenditures for research in the reproductive sciences and contraceptive development, by country of origin, 1965 and 1969-1979 (in 000s of current and constant [1970] U.S. dollars)

Country of origin*	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
Current dollars												
Total	31,022	54,546	71,462	94,483	110,224	117,430	118,723	115,553	125,836	142,800	149,000	154,800
United States	25,926	41,537	55,009	71,663	79,724	82,070	79,104	73,992	82,787	97,300	104,800	111,600
Other industrialized countries	4,886	11,992	15,267	21,126	28,811	33,039	38,029	39,176	39,720	45,600	44,200	43,200
Developing countries	208	1,017	1,186	1,694	1,689	2,321	1,590	2,385	3,329			
Constant dollars												
Total	38,270	57,893	71,462	90,390	100,825	100,957	91,146	79,721	82,104	91,400	88,700	82,600
United States	32,010	44,188	55,009	68,906	73,819	71,991	62,287	53,232	56,318	62,300	62,400	59,500
Other industrialized countries	5,992	12,634	15,267	19,908	25,505	27,093	27,771	25,046	23,874	29,200	26,300	23,100
Developing countries	268	1,070	1,186	1,577	1,501	1,873	1,088	1,443	1,912			
% distribution of expenditures (based on constant U.S. dollars)												
United States	83.6	78.4	77.0	76.3	72.4	69.9	68.3	66.8	68.6	69.6	70.3	72.0
Other industrialized countries	15.7	21.8	21.3	22.0	26.1	28.1	30.5	31.4	29.1	31.4	29.7	28.0
Developing countries	0.7	1.8	1.7	1.7	1.5	2.0	1.2	1.8	2.3			
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*Countries reporting 1965-1974: United States; other industrialized countries—Australia, Belgium, Canada, Denmark, Finland, France, Germany, Great Britain, Israel, Italy, the Netherlands, New Zealand, Norway and Sweden; developing countries—Africa, Egypt, Hong Kong, India, Iran, the Philippines, South Korea, Thailand and Turkey.

Countries reporting 1975-1979—data for governments other than the United States are based on 1976 estimates (e) and reports (r): United States; other industrialized countries—Australia (r), Belgium (e), Canada (r), Denmark (r), Finland (e), France (r), Germany (r), Great Britain (r), Israel (r), Italy (r), Japan (r), the Netherlands (r), New Zealand (e), Norway (r) and Sweden (r); developing countries—Africa (e), Egypt (e), Hong Kong (e), India (r), Iran (e), Latin America (r), the Philippines (e), South Korea (r), Thailand (r) and Turkey (e).

programme of Research, Development and Research Training in Human Reproduction of the WHO; the Population Council's International Committee for Contraception Research (ICCR); the Program for Applied Research on Fertility Regulation (PARFR); the International Fertility Research Program (IFRP) and the Program for the Introduction and Adaptation of Contraceptive Technology (PIACT).^{*} A sixth R&D program, the Contraceptive Development Branch of the CPR,

was also established during this period to develop new and improved contraceptives for the American people. All are successfully operating today.

The WHO Human Reproduction Programme, launched in 1972, has a number of components besides contraceptive R&D, including the development of scientific institutions and manpower in Third World countries; the setting of scientific and technical standards; the provision of supplies and

equipment needed for research; and establishment of information about the performance of existing methods of birth planning. The Programme has established a series of task forces, each devoted to the development of a potential contraceptive lead. The task forces plan and organize mission-oriented and applied R&D directed at new birth planning technologies. Of the WHO Programme's total budget of \$16 million in 1978, only \$4.3 million was allocated to applied contraceptive R&D.

The ICCR program, established in 1971, focuses intensively on product development, basing most of its activities on technological leads that are at or near human trial. The ICCR is the only one of the programs that conducts extensive product formulation and development work in its own laboratories. It conceives its mission as closely analogous to the role traditionally played by pharmaceutical company research divisions in the development of new contraceptive technologies. Its annual budget for contraceptive de-

Table 2. Estimated worldwide funding for reproductive biology and contraceptive development, 1965 and 1969-1979, by sector (in millions of constant [1970] U.S. dollars)

Sector	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
United States												
Total	32.0	44.2	55.1	68.9	73.9	72.1	62.4	52.9	54.7	62.3	62.4	59.6
Government	11.4	19.9	25.3	32.0	43.3	44.8	38.0	36.8	41.4	44.6	45.8	47.7
Philanthropic & nonprofit	8.2	11.1	16.8	22.8	16.9	14.2	12.7	6.2	3.8	8.5	8.3	4.4
Industry	12.4	13.2	13.0	14.3	13.7	13.3	11.7	9.9	9.5	9.0	8.3	7.5
International												
Total	8.3	13.7	16.4	21.5	27.8	28.9	28.7	30.1	30.7	29.1	26.3	23.1
Governments	6.2	3.7	18.3	21.2	24.7	24.4	23.3	24.8	25.8	24.3	22.6	20.3
Nonprofit	0.07	0.04	0.06	0.28	3.1	4.5	5.4	5.3	4.9	4.8	3.7	2.8

*Survey data are not available for after 1976. It is assumed that expenditures remained at 1976 levels.

*The WHO program is funded by the governments of Canada, Denmark, Finland, Great Britain, India, Mexico, Norway, Sweden, Thailand and the UNFPA. The ICCR is supported by private foundations, the U.S. government and Canada's IDRC. The PARFR is funded entirely, and the IFRP principally, by the U.S. government. The PIACT is supported by the U.S. and British governments, the UNFPA and private foundations.

velopment is approximately \$2.7 million.

The IIRP, founded in 1971, concentrates on large-scale clinical trials of contraceptive technologies. It specializes in setting up national networks in developing countries for clinical trials of contraceptives in order to evaluate their performance and to promote their local introduction and use. Its overall budget is about \$4.4 million, of which about \$1.5 million is for contraceptive development.

The PARFR program was originally established in 1969 to provide scientific venture capital to promising ideas for potential new methods that were not funded by the two larger programs. Although the PARFR now operates a more directed grant program and is establishing its own clinical testing network, it seeks to avoid overlap with the WHO and the ICCR programs. Its annual budget for contraceptive development is about \$900,000.

The PIACT, founded in 1976, is the most recently established of the five organizations. It was created to close the gap between contraceptive development and actual production, adaptation and introduction of new methods in developing countries. The PIACT generally concentrates on packaging, manufacturing, informational materials, product servicing and repair capacities and product distribution needs associated with the development of new technologies. Its annual budget is about \$400,000.

These five international programs have established close working ties with the Contraceptive Development Branch of the CPR. The Branch conducts a centrally designed and coordinated contraceptive R&D program through the use of government contracts. Expenditures of the Contraceptive Development Branch in 1979 were about seven million dollars, 14 percent of the CPR's entire research budget.* Although none of the five international contraceptive development programs receive CPR support, all of them benefit substantially from its research program — especially from the leads developed from CPR-backed basic and mission-oriented research.

Close working ties between the R&D organizations and the pharmaceutical industry have been established, enabling the public-sector programs to draw upon industrial experience and proprietary information and to arrange for industry to manufacture and dis-

Table 3. Percentage distribution of expenditures in the reproductive sciences and contraceptive development, by purpose, 1965 and 1969-1978

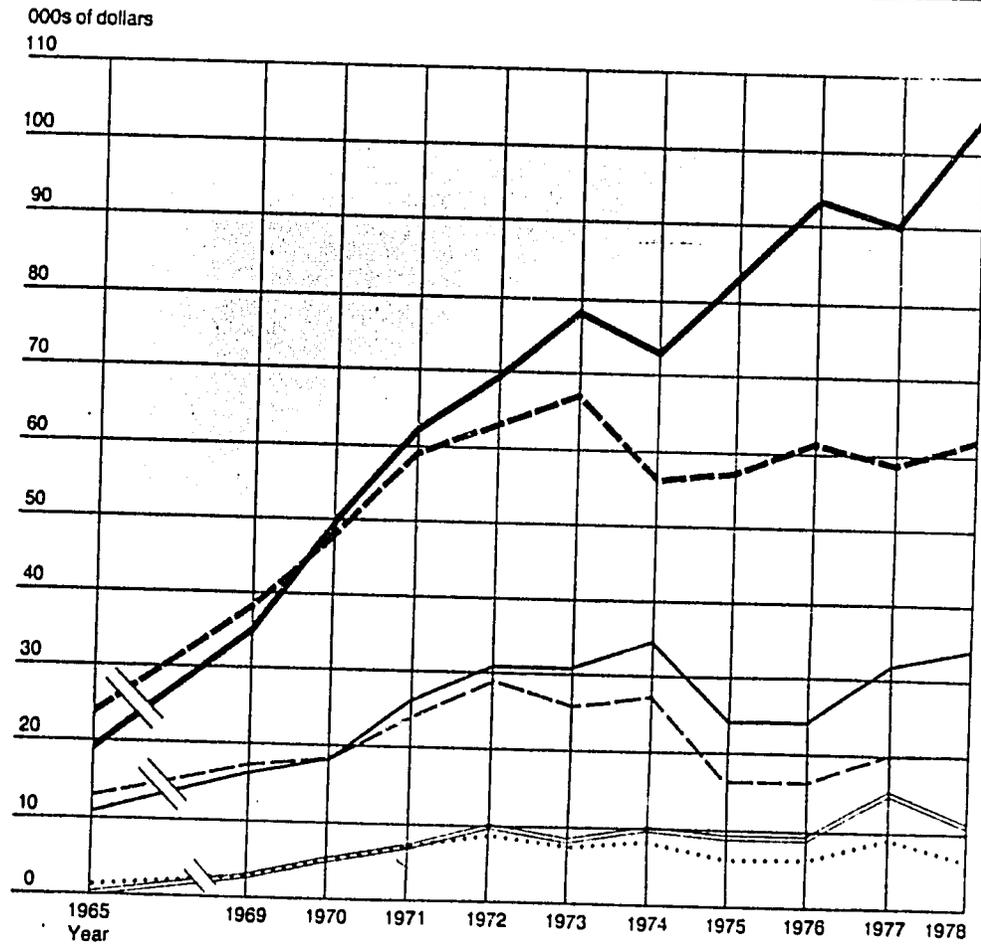
Purpose	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Fundamental studies, training	62.0	65.0	68.0	65.4	62.6	66.8	61.8	71.8*	73.8*	68.0	70.1
Contraceptive development	35.3	30.0	24.7	27.1	28.3	28.2	29.5	20.5	19.4	22.0	22.8
Safety	2.7	5.0	7.3	7.5	9.1	7.2	8.7	7.7	6.8	10.0	7.1
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*Includes unclassified expenditures.

tribute new products they have developed. They have also been successful in engaging scientists and scientific institutions from developing countries to participate in R&D activities. More than two dozen new centers for

laboratory and clinical research have been established in developing countries through links with these six organizations. In addition, working ties have been established with Third World national medical research insti-

Figures 2. Worldwide expenditures for fundamental reproductive studies and training of scientists, contraceptive development and evaluation of contraceptive safety, 1965-1978 (in 000s of current and constant [1970] U.S. dollars)



Current \$
 ———
 Constant \$
 - - - -
 Safety evaluation
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*The CPR is by far the world's largest funder of basic and mission-oriented reproductive research through its grants program. It also carries out evaluation research on the safety and performance of existing contraceptives, provides scientific training and institutional support and conducts a small intramural research program of its own as well.

tutions, such as the Indian Council for Medical Research.

Current Areas of Effort And Funding Levels

The six R&D organizations are currently working on more than two dozen potential new contraceptive methods. As Table 4 indicates, the current allocation of resources for contraceptive development by the public-sector institutions. More than 70 percent of research expenditures are directed to new contraceptive methods for women; only six percent are devoted to finding new male methods. (The remainder go to research into methods that might be applicable to either sex or both sexes, such as releasing factors or periodic abstinence.) In recent years, considerable effort has been made to find a male method. The current concentration on female methods is not a reflection of a male chauvinist bias among researchers, but is the result of the fact that there are more potential possibilities for developing female than male methods and that more is known about the female than the male reproductive system.

Thirty-seven percent of the public-sector investment in contraceptive development is going to new approaches to steroidal contraception for women: subdermal implants, improved orals, injectables, vaginal rings and intranasal sprays. Ten percent is going for various approaches to an antipregnancy vaccine. Eight percent is being devoted to various experimental antifertility and anti-implantation agents; seven percent is devoted to intracervical devices and improved IUDs. Five percent is being spent on menses-inducing and abortifacient drugs. New approaches to barrier methods and to female sterilization are each receiving about two percent of public-sector funding.

About five percent of development expenditures are being devoted to research on releasing factors, which have potential for suppressing ovulation in the female (and, possibly, inducing menses also) as well as blocking the generation of sperm in the male. About six percent of public-sector funds are going for other male contraceptive drugs. About four percent are being devoted to research into various plants that might be useful as abortifacients or antiimplantation agents.

The heavy emphasis in current research expenditures on female steroidal approaches partly reflects the low-risk, quick-return decisions dictated by the relatively small (and shrinking) share of research dollars accorded to contraceptive development. Since these approaches involve finding new combinations and methods of delivery for agents that are already well-known and tested, they seem to donors and programs to offer the

most promise of delivering marketable contraceptives at reasonable cost within a fairly short period of time. In addition, the proportionately large current investment in these approaches reflects the fact that most of them are now in advanced clinical trials — the most expensive segment of contraceptive research — and some can be expected to be available for widespread use in the next three years.

There is no question that these methods will offer some advantages over those currently available, and can be expected to increase the ability of couples in the developing world to exercise control over their fertility. These improvements, however, do not appear to offer the kind of radical advances in birth control technology that many had hoped for, and which the current scientific base seems capable of providing.

In the following section, we discuss the prospects for the development of five potential methods, any one of which, the authors believe, would significantly increase current use; combined, the methods could revolutionize current contraceptive practice in developing as well as in developed countries. These are a nonsurgical means of female sterilization, a reversible method for men, an antipregnancy vaccine for women, a self-administered menses inducer and a postpartum IUD. While all of these potential methods are currently under investigation by public-sector contraceptive development programs, together they account for less than one-third of public-sector investment in new method development, and not one of them accounts by itself for more than 10 percent of public-sector research efforts.

The profiles of the five potential methods are presented not only to assess the prospects for their development, the problems associated with their use and their potential utility in worldwide family planning programs, but also to shed light on what needs to be done to make applied contraceptive R&D more effective and efficient.

Five New Methods:

I. Nonsurgical Female Sterilization

Description. Current efforts to develop a nonsurgical method of female tubal sterilization involve the delivery of a sclerosing agent to the uterotubal opening via the vaginal cervix and uterus. By irritating the tissue of the fallopian tube, the substance causes the lumen of the tube to close from scarring. Ideally, the method could be delivered by paramedical personnel trained to insert IUDs, and delivery could be accomplished without pain, using local anesthesia. Effectiveness should be as high as that experienced with current methods of surgical ster-

Table 4. Percentage distribution of public-sector expenditures for development of new contraceptive methods, 1978

Type of method	%
All female methods	71.2
Steroidal	37.2
Subdermal implants	(16.9)
Improved oral contraceptives	(9.9)
Injectables	(5.4)
Vaginal rings	(4.4)
Intranasal sprays	(0.5)
Vaccines against pregnancy*	10.1
Sterilization	2.0
Reversible	(0.4)
Nonsurgical	(1.6)
Antifertility and antiimplantation agents	8.3
Intra-cervical (ICD) and intrauterine (IUD) devices	6.9
ICDs	(1.6)
Postpartum IUDs	(1.6)
Other IUDs	(3.7)
Menses-inducing and abortifacient drugs	4.5
Barrier methods	2.2
All male methods	6.1
Systemic	5.5
Reversible sterilization and improved vasectomy techniques	0.6
Methods for couples and unclassified	22.7
Releasing factors*	5.1
Plant agents	3.9
Periodic abstinence	4.8
Other and unclassified	8.9
Total	100.0

*The percentage of total expenditures for releasing factors, derived from 1978 data, is almost certainly higher because of increased interest in this line of research, while the proportion devoted to steroidal male methods and to antipregnancy vaccines has probably decreased because of problems encountered with research on these methods.

ilization. These methods would need to be nontoxic. Sterilization would be irreversible. *Status of research.* Two substances and various means of delivery are now under investigation. Methylcyanoacrylate and quinicrine hydrochloride are now being used in clinical trials. The former is a widely used "tissue glue" that polymerizes in the tube, forming a plug to which the tissue adheres. The plug eventually biodegrades, leaving behind scar tissue which permanently closes the tube. A specially designed instrument which does not require visualization of the tubal openings is used to place the methylcyanoacrylate inside the fallopian tube.

Quinicrine is a drug that has been used for treatment of malaria. When placed in the uterine cavity in the form of crystalline pellets or in a thick suspension, the chemical enters the oviducts, initiating a scarring process that results in tubal closure. A potentially more effective way of introducing the quinicrine into the tubal opening, by attaching pellets of the drug to the transverse arms

or fundal portion of an IUD, is being tested. In this procedure, the pellets are held in place for several days, providing a longer time for the drug to penetrate the tubes. If complete tubal closure is not accomplished, the IUD is still in place to provide protection until a second application can be made.

Both of these sclerosing agents, and several instillation procedures, are being tested in small clinical trials to determine the effectiveness of tubal closure and to evaluate levels of safety and freedom from side effects. Long-term follow-up of subjects is necessary to observe the effective duration of closure as well as such possible problems as increased risk of ectopic pregnancy. At present, the methylcyanoacrylate seems to be only 80 percent effective in completely closing the tubes on just one application. It is believed that with two applications, an effectiveness rate of 95 percent could be achieved. Efforts are being made to improve delivery. Modifications of the instrument used for instillation are being investigated that would reduce its cost and improve its performance.

Researchers are currently making three instillations of quinacrine pellets at monthly intervals to get a closure rate more satisfactory than the 90–95 percent rate heretofore obtainable. It is hoped that by using the IUD as a carrier, only a one-time application will be necessary.

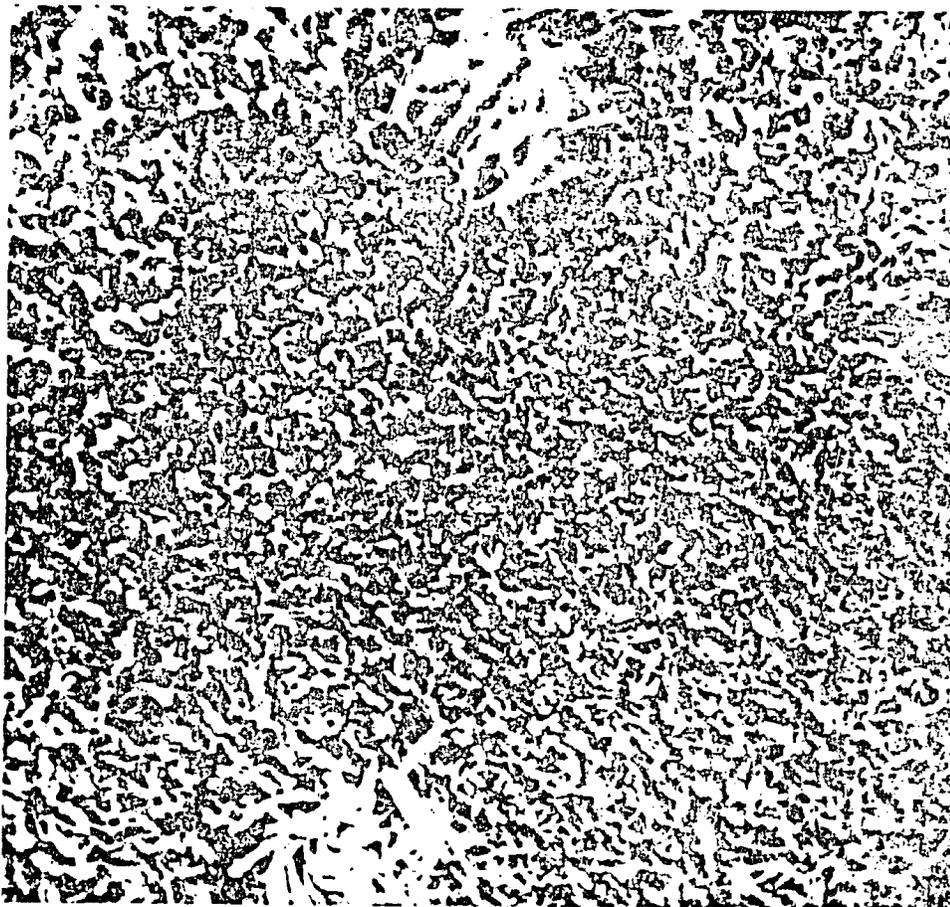
Because of the need for long-term follow-up, the clinical trials, even though small, are costly and time-consuming. Toxicology tests for both the quinacrine and methylcyanoacrylate applications will be required. To achieve better than a 95 percent effectiveness rate for any of these methods, it is probable that prolonged clinical testing will be needed to obtain the optimal combination of instillations, time between instillations, drug carriers and instrumentation, especially if the technique is to be used by paramedical personnel.

Research into other potential chemical sterilants, possibly in conjunction with tube-relaxing drugs, is being considered by investigators, but as yet has not obtained funding. It is likely that it will be several years before these experimental techniques are sufficiently advanced to merit wide-scale field trials. There will need, in turn, to be several years of field trials to ascertain effectiveness, safety and acceptability. Thus, it is likely to be as much as 10 years before a highly effective chemical sterilant is generally available. **Advantages.** A nonsurgical method would involve far less pain and discomfort than do sterilization methods now in use. The user would not require hospitalization nor the unavoidable long recovery period necessary with surgical methods. The risk of morbidity

and mortality associated with general anesthesia (used with some current methods) and opening the abdomen to reach the fallopian tubes should be eliminated. Although risks with current methods such as minilaparotomy and laparoscopic sterilization are already quite low in developed countries, they tend to be somewhat higher in developing countries, especially if the sterilization is performed outside a hospital. The cost of nonsurgical sterilization should be lower than that of minilap, and much lower than that of laparoscopic sterilization.

A major advantage of the method is the possibility that it could be delivered by para-

Incomplete closure could increase the risk of ectopic pregnancy — but since this is a life-threatening event, the method certainly would not be introduced if it involved a substantial risk. Concern about this problem however, will add to the research required before such a method can be made widely available. In addition, there may be rare complications associated with the chemical used. (For example, quinacrine hydrochloride has been observed to cause adverse reactions in the central nervous system: if it gets into the general circulation in large amounts.) Even the simplest approaches currently under study require operators with



Scientists seek way to chemically seal tubes (above, microphoto, hamster oviduct surface).

medical personnel, which would make it possible to meet the increasing demand for sterilization from women in areas where there are few surgical facilities. Presumably, the sclerosing methods, at any rate, could be utilized in any setting where IUDs can be inserted.

Drawbacks. It is possible that none of the agents currently under investigation will be capable of yielding effectiveness rates as high as those of surgical techniques because of incomplete closure or recanalization of the damaged section of the tube. This could mean that up to five percent of women who undergo the procedure would get pregnant.

fairly high level of technical skill and will probably require a clinic setting where sterile instruments are available. Ideally, only a one-time application of the sterilant would be required. However, it is currently necessary to perform the procedure twice with at least a one-month interval to ensure tubal closure. In the meanwhile, an alternative method of contraception has to be used.

Organizations involved. Currently, the CPR, the WHO, the IFRP and the PARFR are the major agencies supporting this type of research.

Current funding. As of 1978, roughly two percent of public-sector funds for applied



contraceptive R&D were being spent on these methods—or somewhat less than \$300,000 annually. About half of the funds went to the IFRP's research with quinacrine, and the other half to research on methylcyanoacrylate conducted by the PARFR and the WHO.

Future requirements. Current funding is inadequate to finance a comprehensive effort to exploit the technological opportunities associated with nonsurgical approaches. Just to bring current investigations through the initial clinical trials will require a minimum of \$2–3 million over the next five years. It would require an investment of some \$750,000 annually over about 10 years to cover the costs of clinical studies, formulation development, and toxicology studies for an effort that pursues multiple approaches simultaneously (for example, studies of a variety of types of pellets and different kinds of IUD carriers), as well as a search for other types of sterilants and for drugs to facilitate their entrance into the fallopian tubes. Such a comprehensive effort is probably needed to develop a method with an efficacy rate of over 98 percent with just a single administration.

Institutional constraints. Only a small number of researchers are working to develop a nonsurgical sterilant. Although they have been extremely productive and creative, their efforts would benefit from a more broadly based institutional approach. The CPR has limited its interest in this method to the funding of a few projects, possibly because nonsurgical sterilization is considered to have its major usefulness in developing countries where laparoscopic sterilization is unavailable. The WHO has also pursued this approach with only a small-scale effort. No institution, including those sponsoring this approach, has invested in studies to determine whether a nonsurgical sterilant would be acceptable to potential users, programs and medical authorities in developing countries if no better than a 95 percent effectiveness rate can be attained, and if more than a single application of the sterilant is necessary. There is also an ethical limitation on the clinical testing of potential new sterilants in countries where minilap and laparoscopy are available, in light of the fact that the experimental methods are likely to be less effective than the proven ones.

II. A Reversible Method for Men

Description. There are three approaches to male contraception: stopping the production of sperm, blocking the transport of sperm during intercourse, and affecting the quality of sperm so that they are incapable of fertilization. All male methods currently in use —

vasectomy, the condom and withdrawal — are based on the second approach. What is being sought by contraceptive R&D organizations is a highly effective, reversible, self-administered, coitus-independent contraceptive that does not interfere with libido, is free from dangerous side effects, is inexpensive and is easy to distribute.

Status of research. It has long been known that massive doses of steroids will usually cause infertility in men by shutting down sperm production. Until recently, investigations into a possible male method have concentrated on different combinations of various steroidal hormones.

“By now, it is generally recognized that there can never be . . . an ideal contraceptive, and that an array of methods is needed”

Another promising method for arresting spermatogenesis has recently entered early clinical trials: a chemical analog of the brain hormone luteinizing hormone-releasing hormone (LHRH). The effects of this decapeptide, which stops sperm production in male rats, is being carefully observed in a small group of volunteer men. (The same chemical is being tested as an ovulation inhibitor in women.) The LHRH analogs now being tested must be administered by nasal spray or injection; however, it is believed that if an analog proves successful in inhibiting spermatogenesis in men, a more convenient form of administration will be developed (for example, a daily pill or a yearly subdermal implant).

There has probably not been sufficient basic research to understand the effects of LHRH on the reproductive processes. Thus, synthesis of better analogs and new dosage formulations will have to be developed simultaneously. If the analogs now in limited clinical trial prove successful, it will still be at least seven years and, if new analogs are needed, possibly 10–15 years, before they become generally available.

Another method under investigation that is apparently highly effective in stopping sperm production is gossypol, a derivative of cottonseed oil. Chinese scientists claim to have administered gossypol pills for at least six months to some 4,000 men, with an efficacy rate of 99 percent. Some of the men have been on the pills for more than six years. The pills are taken daily for about two months until sperm are no longer observed, and then are taken weekly to maintain infertility. Fer-

tility generally returns to normal in about three months after discontinuation of treatment. Gossypol apparently works by incapacitating the sperm-producing cells.

Several research organizations outside China are investigating possible long-term adverse side effects of gossypol through animal studies, and more clinical information is being sought from China. At least three to five years will be required for widespread human testing in other countries after current toxicology studies are completed. If side effects prove to be significant, a gossypol analog synthesis and screening program will be required to discover safe but effective compounds, and it would be 10–15 years before a marketable product would be generally available.

Little progress has been reported in finding an acceptable method which would cause infertility by inhibiting sperm maturation or motility. Chlorinated sugars were found to arrest the maturation of sperm in marmosets, but discovery that they were toxic to the marmosets' central nervous systems caused the WHO to abandon this line of research.

Important mission-oriented research remains to be done on sperm maturation and capacitation in order to make this type of research truly productive.

Some scientists are also intrigued with the potential of inhibin as a male contraceptive. If this naturally-occurring substance could be structurally identified and synthesized, it is thought, it could be effective in suppressing the secretion of follicle-stimulating hormone (FSH), necessary for normal spermatogenesis. However, considerable mission-oriented research would have to be undertaken before inhibin could be considered a potential male contraceptive. Not only does inhibin itself have yet to be isolated in its pure state, but evidence needs to be accumulated that it can inhibit the secretion of FSH in a mature male.

Advantages. All of the methods under investigation have an advantage over current reversible male methods in that they are not associated with sexual intercourse. If they can be self-administered, men will be able to share contraceptive responsibility with their partners.

Based on clinical experience to date, it is thought that the LHRH analogs will have few systemic side effects.

In addition to being effective as a contraceptive, gossypol should have little or no effect on libido, since it does not seem to affect the cells producing the male sex hormone, testosterone. The raw material is widely available, and the product should be relatively inexpensive. Neither LHRH nor gossypol would require clinical or surgical

facilities, and both should be relatively easy to distribute.

E-raunchbacks. In addition to their contraceptive effect, the steroids also reduce testosterone synthesis, sometimes resulting in loss of libido and development of female secondary sexual characteristics (such as enlarged breasts). Studies undertaken over the past 10 years, using several types of steroids and regimens, including or omitting testosterone to protect against feminizing side effects, have shown not only that exceedingly large steroid doses are required, but also that the method is of unreliable effectiveness. That is, sperm counts are not reduced to zero in all men. In addition, testosterone has to be administered by injection at fairly frequent intervals, requiring clinical facilities; and recovery of fertility takes up to six months in some subjects.

LHRH analogs may decrease the synthesis of testosterone (and therefore libido); thus, testosterone supplementation may be required. Both LHRH and gossypol would

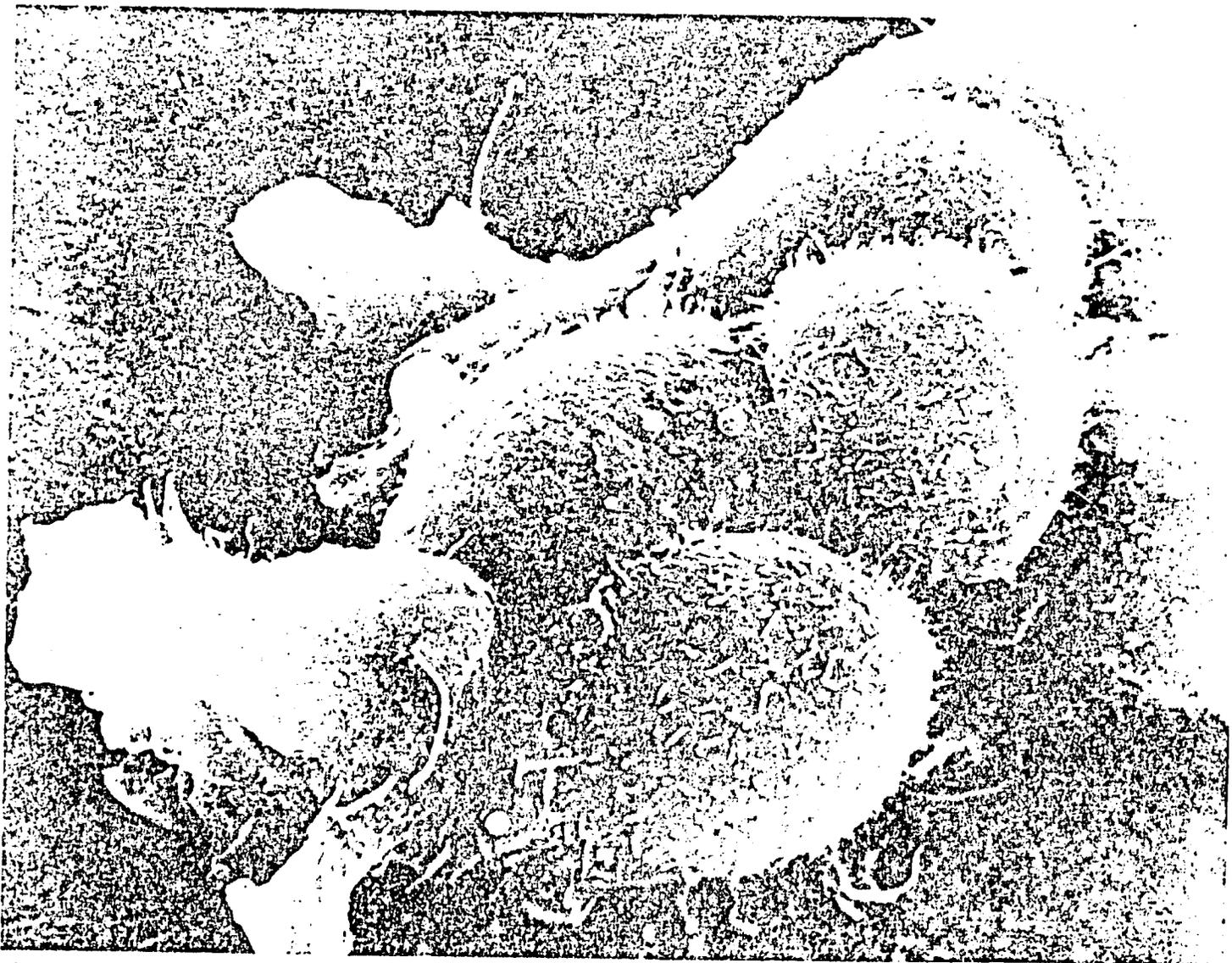
probably require one to two months of daily administration before they completely suppress sperm production. Therefore, another method of birth control would have to be used until a zero sperm count was achieved. Similarly, another method of birth control would need to be used during the approximately three months required for return of normal sperm counts and sperm quality.

At present, the reversibility of the effects of these drugs on the testes is not well understood. Obviously, if there is permanent damage to the sperm-producing cells, neither product would be approved as a contraceptive. At any rate, it is likely that a very long recovery period would be required for any method that blocked sperm production. To demonstrate reversibility will require extensive long-term clinical studies, contributing to the relatively long period that will be needed to make such methods generally available. Gossypol may well have some adverse side effect in humans since it is known to be highly toxic in some animal species. Its

effects on organ systems (other than the reproductive organs) may depend on diet or general health; and evidence of low serum potassium levels in some of the Chinese subjects requires further investigation.

While in some cultural settings, a male pill may prove very popular, it may not be acceptable in others.

Organizations involved. LHRH agonists are being explored as a male method by the CPR as well as the ICCR. At least five pharmaceutical companies have begun fairly substantial programs involving LHRH analogs as potential contraceptive agents; however, the total size of these programs, and the amount devoted to male methods, is unknown. Outside of China, animal research with gossypol is being undertaken under the auspices of the ICCR. The WHO is considering work on gossypol and conducted a modest research program to investigate inhibin as a potential contraceptive. It also supported work on steroids (as did the ICCR) and on chlorinated sugars until the recent discovery that they



Ideally, male contraceptive methods should not interfere with testosterone production—above, electron micrograph of testosterone-producing cells in culture.

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were toxic. However, the WHO has indicated that because of lack of funding, it will disband its task force on male contraception unless there is some major progress reported on gossypol research from China.

Current funding. In 1978, about six percent of funding for contraceptive development went into research on male systemic methods. Since that time, however, work in steroidal approaches, which accounted for most of the expenditures, has been largely discontinued, and the WHO program may be entirely abandoned. The CPR has awarded one \$300,000 contract for the study of LHRH in males and is currently negotiating another contract of similar size. The ICCR is spending an estimated \$168,000 in 1980 for gossypol and LHRH research. As we have noted, five pharmaceutical companies are also involved with LHRH analogs, but the amount of expenditures is unknown.

Future requirements. If donors are seriously interested in developing a male contraceptive within the next decade, they must be prepared to embark on a major mission-oriented research program that will involve very large expenditures for toxicology studies on current analogs and, if these are shown to be safe, subsequent clinical trials. At least \$15 million will be needed for development of a male contraceptive based on an LHRH analog. If inhibin is to be followed up as a possible contraceptive, at least \$3 million will be needed over the next two to three years to isolate and collect the protein, and another \$10–20 million over 10–15 years before a product could become generally available. More precise cost and time estimates are impossible to make at present. Donors should encourage R&D programs to develop comprehensive plans and cost estimates for developing male methods by indicating their real interest in providing long-term funding for mission-oriented research.

Institutional constraints. All public-sector agencies have expressed interest in development of a systemic male contraceptive. At present, there is considerable support by the U.S. government for the LHRH-analog approach, and much of the toxicological and dosage formulation research may be undertaken by the pharmaceutical companies which are keenly interested in these peptides for ovulation induction and suppression.

A major constraint has been the inadequacy of understanding about the male reproductive process. As a result, much of the current work had to proceed, at least partially, in the blind. Another major institutional constraint has been the lack of commitment to long-term pursuit of leads that may require five to 10 years of intensive R&D

before they can yield marketable products.

When the only potential male method involved steroid research, all of the R&D programs, under pressure to come up with a male method, picked up on one or another steroid approach. Because there was insufficient data-sharing and research collaboration, some of these efforts tended to be duplicative rather than mutually reinforcing. It is to be hoped that current research involving LHRH analogs, gossypol and other approaches will not repeat that mistake.

III. An Antipregnancy Vaccine

Description. Contraception would be achieved by vaccination with protein antigens specific to pregnancy or to an organ involved in the reproductive process. Circulating antibodies would interfere with ovulation, corpus luteum function, fertilization, early implantation or maintenance of pregnancy, depending on the antigen selected. Ideally, the method would be administered in one injection. After a period of months required for the antibody titers to build up to sufficient levels, contraceptive effectiveness would be maintained for one to three years. Such an immunological method should be reversible with declining antibody titers, but effective contraception could be renewed by means of a single booster vaccination administered in the final months of the effective period.

Status of research. The principle of antibody reaction in response to an injection of a protein derived from the beta chain of human chorionic gonadotropin (hCG) has been shown in human clinical trials. However, the effectiveness of the antibodies and the safety of the method have not yet been demonstrated.

Two major approaches have been utilized: The first involved immunizations with an antigen consisting of highly purified beta-hCG chemically linked with tetanus toxoid. Menstruation and ovulation continued normally, but some pregnancies ensued. A more active antigen appears to be needed.

Theoretically, one problem with this approach is the possibility that cross-reactive antibodies could neutralize other similar pituitary hormones, stopping the function of the target organ permanently, inducing autoimmune tissue injury to the pituitary gland or forming circulating immune complexes that could result in kidney damage.

Although no such cross-reactivity was found in experiments with women, some researchers have sought to protect against this possible problem; their work has constituted the second major approach to an antipregnancy vaccine. Those researchers have concentrated on finding a vaccine against a

unique fragment of the beta-hCG chain which does not cross-react. However, the difficulty of finding a powerful enough adjuvant to create an effective antibody reaction is even greater when dealing with such a small fragment than when the whole beta-hCG molecule is the target.

Investigation at a much more basic level is also proceeding on antigens derived from the zona pellucida, the outer coating of the ovum at the time of ovulation and before implantation. Such antibodies are thought to form a deposit on the outer surface of the zona, which prevents sperm penetration and thus inhibits fertilization. Such antigens have not yet been isolated in pure form, and it is unlikely that an effective human vaccine could be made available in the near future.

Sperm antigens are also being studied, but so far they have proved relatively ineffective in animal tests. Research in this area is therefore at a basic level.

Given the very early stage of R&D in this area, a minimum of 10–15 years of sustained, high-priority effort will be needed to produce a vaccine using either the beta-hCG or one of the other approaches.

Advantages. Vaccination is a universally appreciated and understood medical intervention. The method is unlikely to require any special facilities for delivery, since in most countries there are already facilities for vaccination programs, and paramedical personnel and barefoot doctors are already trained to give injections. Effectiveness should be high, and the antifertility effect would be limited to one event in the reproductive process. Thus, short-term side effects should be minimal, and regular menstrual cycles should be maintained. Women would have no problems of storage, disposal or genital manipulation. The eventual cost would probably be similar to that for other types of vaccinations offered by public-health programs in developing countries.

Drawbacks. Long intervals of effectiveness imply a relatively long time period for return to fertility, which might in itself reduce acceptability among some women. During the initial period — about three months — when antibody titers were being built up, and in the final months of declining titers, another method of contraception would be needed. Although paramedical personnel could administer the injections, they would have to be specially trained to deal with allergic reactions inevitable among a small percentage of recipients. What is more, a vaccination program requiring periodic inoculations is known to be difficult to mount and maintain in some developing-country settings. Use of family planning outlets could make this problem more manageable. While there are likely

to be few or no direct side effects, there would be medical concerns about long-term health hazards with this as with any other immunization procedure. Acceptability may also be reduced if women confuse this long-acting method with sterilization.

Organizations involved. The ICCR, the WHO, the CPR and the PARFR have all been involved in one or another aspect of vaccine research. The WHO was one of the major agencies involved in beta-hCG vaccine research and in zona pellucida and sperm antigen approaches; the ICCR is continuing its beta-hCG research; the CPR is funding work on zona pellucida approaches; and the PARFR is working on sperm antigens. At least two pharmaceutical companies are also believed to be active in investigations into a vaccine.

Current funding. About 10 percent of public-sector funding for applied R&D was being expended annually by the public sector on all of these approaches as of 1978. The largest share, about \$1.2 million, was going into

Not a single new contraceptive chemical entity has reached the market since . . . the synthetic steroid norgestrel in 1968.

beta-hCG research. Private-sector involvement is believed to be small.

Future requirements. At this early stage of development, concentration on any single approach would involve a very high risk that no usable vaccine will result. A broad-scale effort, involving research into a variety of antigens and approaches, is required. Such a mission-oriented approach would involve costs on the order of \$3-6 million per year over at least 10 years, but would appear to offer an excellent probability of producing an effective vaccine.

Institutional constraints. In the past, donors and programs have taken a short-term approach, and have concentrated mainly on beta-hCG rather than making a long-term commitment to a large, multiapproach, sustained effort. When initial efforts did not result in an immediate payoff, enthusiasm cooled. Because of budget cutbacks, the WHO may disband its entire immunological task force, and the ICCR may be forced to decrease its activities involving the beta-hCG approach because of the high cost of adjuvant development. Unless there is a commitment to a sustained, multiapproach effort, backed by sufficient funds, it is unlikely that a usable product will result.

Such an expanded R&D program would require strengthening of connections between immunologists and reproductive biologists, and application of their combined expertise to the perplexing problems involved in vaccine research, working closely with the R&D programs that thus far have had relatively little experience in this area. Greater participation by the CPR would be highly desirable because of its capacity to fund the relevant basic and mission-oriented research needed. To date, the CPR has not been very active in this field, perhaps because of a perception that a vaccine is essentially a method for developing countries, while its mission is to address the health problems of Americans.

IV. A Self-Administered Menses Inducer

Description. Scientists have long been interested in developing a pill, liquid, nasal spray or vaginal tampon that could be self-administered at the expected time of menses (or shortly thereafter) to induce menstruation and evacuation of the uterus. A desirable agent would have few side effects and would totally evacuate the uterus. It should be readily available through commercial sources as well as family planning programs.

Status of research. Several approaches are currently under investigation. The most advanced work is with prostaglandin analogs. These induce uterine contractions, thus terminating pregnancy during the first eight weeks (and during the second trimester) of pregnancy. No such product has yet been developed which can be taken orally without unacceptable gastrointestinal effects; but with additional research and development efforts, some prostaglandin analogs may be found suitable, although the costs, at least initially, may be high. By the nature of their action, all prostaglandins will probably cause some gastrointestinal tract stimulation; however, such reactions have been reduced greatly, and can probably be reduced even further without diminishing uterine action. Compounds now available in the form of vaginal tampons or injections appear to be at least 90 percent effective in completely evacuating the uterus when administered during the first eight weeks of pregnancy. Current products have already gone through final testing in several countries, and will soon be available for widespread use. (In the United States, clinical trials are still in progress and general availability may still be some two to three years away.) Analogs with greater efficacy and reduced side effects may not be available anywhere for another three to five years.

In some animal species, prostaglandins have been shown to stop progesterone production by the corpus luteum — a process

called luteolysis. However, no prostaglandin analog has yet been proven to be luteolytic in humans. New prostaglandins are now being tested for the characteristic in nonhuman primates. One to two years of monkey trials will be needed, and, if successful, will have to be followed by toxicology and clinical trials. LHRH analogs also appear to be able to decrease progesterone production and have terminated pregnancies in rats. However, analogs currently under study have not proved powerful enough to terminate progesterone production by the corpus luteum in human subjects once pregnancy has occurred. Some basic R&D work is under way to isolate agents from medicinal plants such as the *Montana tomentos* (zoapatle) that are known to have abortifacient effects.

At least five to 10 years will be needed for development of a luteolytic prostaglandin, a luteolytic LHRH analog or a medicinal plant agent.

There are a number of other biological approaches that could be pursued in an all-out mission-oriented approach. Among these are chemicals which are toxic to specific placental or embryonic cells; chemicals that alter the blood supply or hormone production of the corpus luteum; and chemicals that bind to hormone receptors. Little applied R&D is yet going on in any of these areas, largely because it is not likely that a usable product could be developed within a decade. Yet, if efforts to find a suitable prostaglandin or LHRH analog or plant extract fail, and if other approaches are not pursued, further development of a method about whose usefulness there is wide agreement among scientists and family planning program professionals could be delayed.

Advantages. If a self-administered method was relatively inexpensive and did not require an extensive medical infrastructure (except when rare problems such as incomplete evacuation of the uterus occurred), it would have wide acceptability in many developed and developing countries. It would need to be administered no more than once each month or, if use was restricted to those times when menses is delayed, only three or four times a year. Depending on its mode of action, the method probably would not cause irregular bleeding — in fact, if taken monthly, some of the agents would serve to regularize the menstrual cycle. In addition, the method would be similar in its form of administration to folk medicines (such as herb teas) that are widely used by women in many developing areas, but would not provoke the disastrous consequences attendant upon ingestion of some of those substances.

Drawbacks. Side effects currently associated with available prostaglandins include nausea

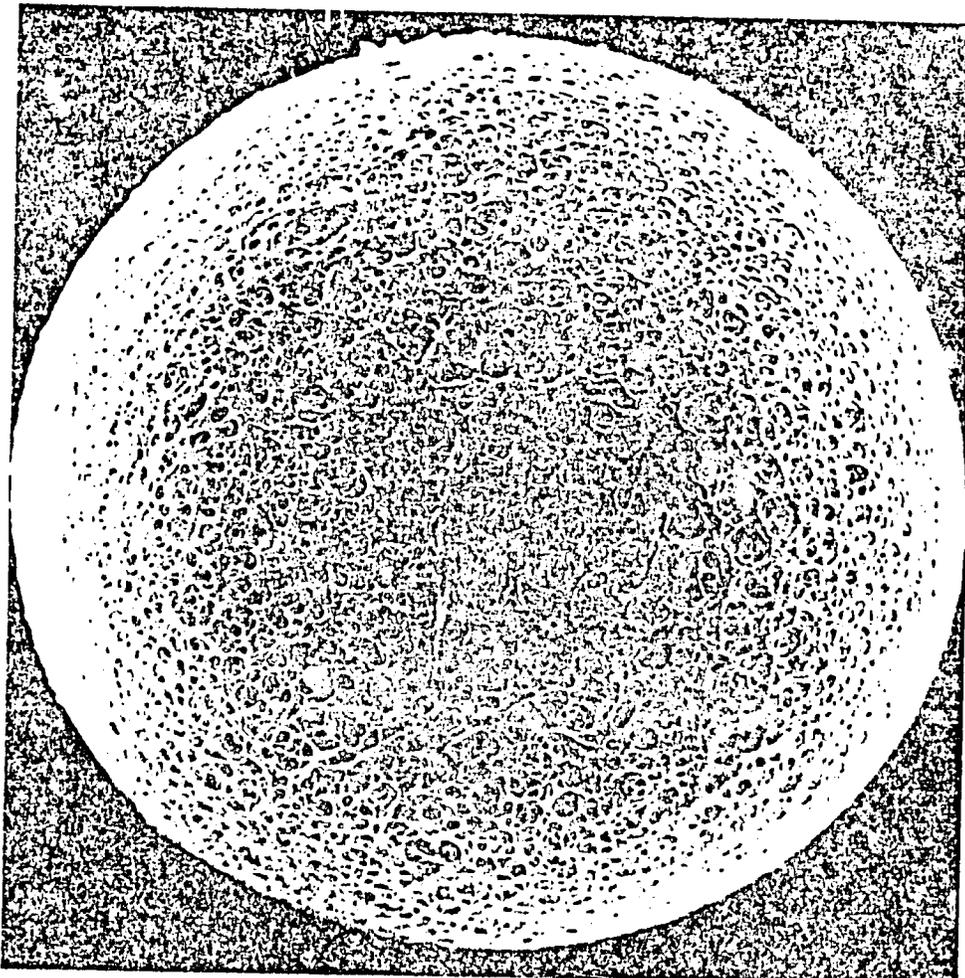
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and diarrhea. However, administration of the prostaglandins in conjunction with antiemetics and other drugs has helped to control these side effects. In addition, uterine evacuation is not complete in all cases, requiring medical backup to complete the abortion. In countries where abortion is illegal, it is doubtful that this product would be acceptable. If a uterotonic analog (that is, one that causes uterine contractions) could be developed that did not affect other organs (such as the smooth muscle of the intestinal tract), it would be quite useful because of the advantage of self-administration.

A method that would stop the production of progesterone by the corpus luteum (which is necessary to prepare the uterus for implantation of the fertilized egg and to maintain a pregnancy during the first few weeks) would have none of the side effects common with uterotonic preparations; evacuation of the uterus should be complete; and, since the product would be administered at the time of expected menstruation, without determination of pregnancy, it might be acceptable even in countries where abortion is not legal. However, couples morally opposed to abortion might still find such a method unacceptable because of the possibility that they were terminating an established pregnancy rather than preventing a conception. In addition, considerable educational efforts would be needed to discourage women from using such a method too late after the time of their expected period (since the corpus luteum is needed to sustain pregnancy for only a few weeks after implantation).

Organizations involved. The CPR has a broad-based R&D program to develop new LHRH analogs for use in ovulation suppression; and some of this work could indirectly benefit research on menses-inducing agents. The WHO is providing the major public-sector funding of testing of uterotonic prostaglandin tampons and injectable products. The AID is also funding some prostaglandin research. Both the WHO and the CPR are funding research to isolate plant products, and some of these may be useful in the eventual development of menses inducers or early abortifacients. The ICCR is investigating the luteolytic activity of LHRH analogs.

Current funding. Total annual funding by public-sector agencies for research into development of a menses inducer is about 12 percent of total public-sector expenditures for contraceptive research. Roughly half of this is going to prostaglandin research, with the rest divided between plant research and research into LHRH analogs. It is not known to what extent industry is investing in such products, although it has played a considerable role in prostaglandin research and is



Research is starting on zona-pellucida-derived antigens for a pregnancy vaccine (above, hamster zona).

interested in LHRH analogs for ovulation inhibition.

Future funding needs. To complete the development of uterotonic prostaglandin analogs with diminished side effects and greater efficacy will probably take another three to five years and cost a total of \$5 million in public-sector funds. A luteolytic prostaglandin, if it can be identified, probably could not be developed in less than eight to 10 years, and total cost is likely to be well in excess of \$10 million. The cost of developing a suitable LHRH analog is likely to be similar, or greater (again, with some uncertainty about the outcome).

Costs of developing other products and uncertainties about success would be similar or greater, and the development time is likely to be 10–20 years, in areas where considerable mission-oriented research is needed. It should be emphasized that all of these projections are highly speculative; R&D in this area involves high risk but has potential high payoff. The more avenues that are explored simultaneously, the greater the likelihood of a successful outcome.

Institutional constraints. The CPR is constrained by legislation from developing new abortifacients. It does, however, contribute

indirectly to such work through its general funding of prostaglandin and LHRH receptor research, as well as basic research on the corpus luteum and the implantation process. The WHO, the major organization supporting R&D in prostaglandins and plant substances, is slowed because of its growing focus on building up research capacities in developing countries. In general, the WHO, the PARFR, the ICCR and the IFRP have tended to shy away from large investments in avenues of research if they cannot promise donors that human testing and new products are likely to result in a relatively short period of time. Yet a vigorous and comprehensive R&D effort in this area would necessarily entail both mission-oriented research and a major screening program of new chemical agents. Only the CPR currently has the capacity for such screening and for extensive mission-oriented research. However, as noted, it is constrained by legislation from actively pursuing research into abortifacients. The other R&D programs do not have sufficient funds to pursue such comprehensive efforts. Either (like the IFRP and the PARFR) they do no work in this area, or (like the WHO and the ICCR) they do so in such a limited, piecemeal way that they are unlikely

to develop a new menses-inducing agent (other than uterotonic prostaglandins) without many years of effort and a substantial amount of scientific good fortune.

V. A Postpartum IUD

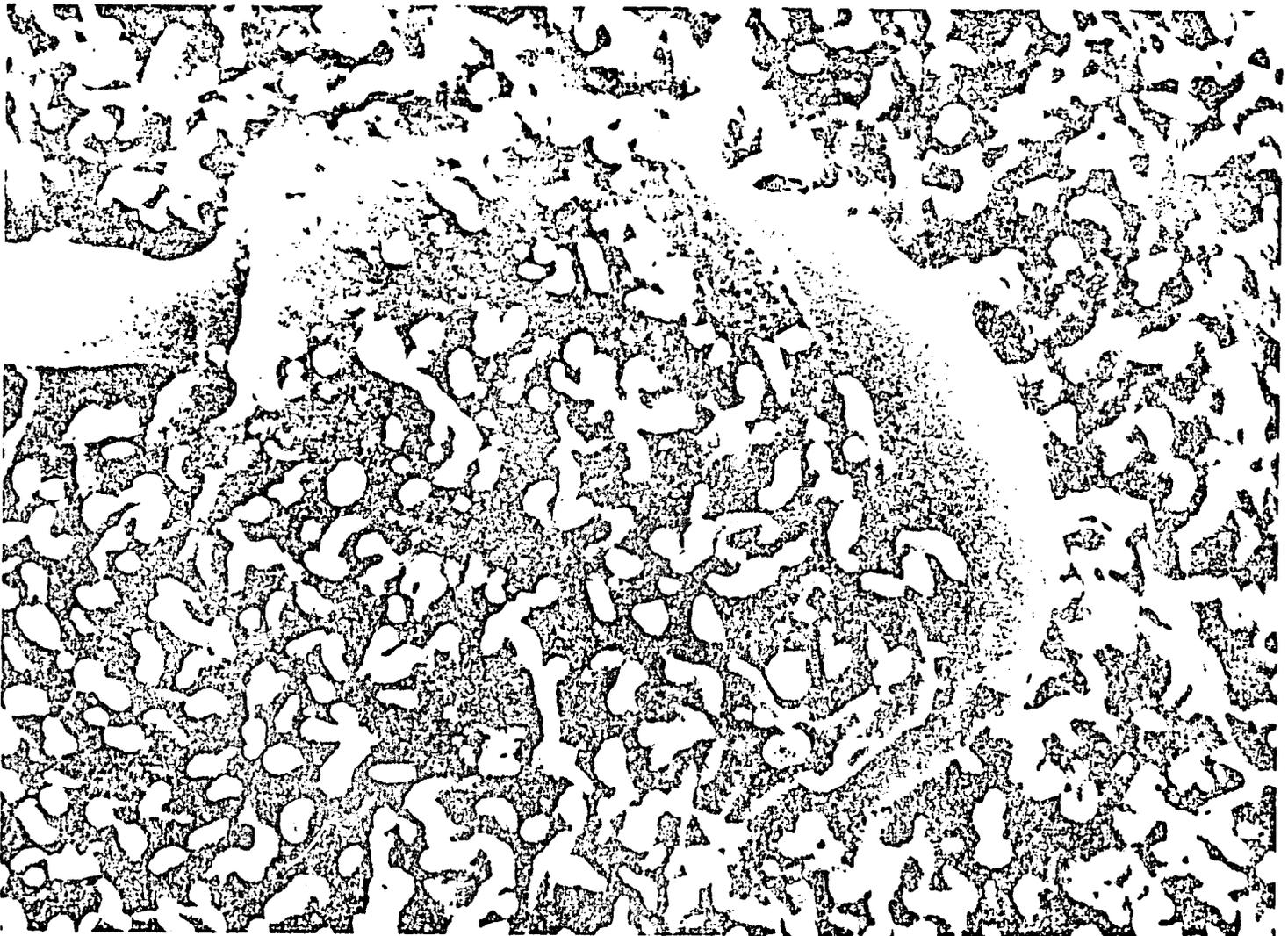
Description. An intrauterine device that would be retained when it is inserted immediately after the placenta is delivered could reach all women who have assisted deliveries. Conventional IUDs inserted during the postpartum period are likely to be expelled about three times more often than when they are inserted during the menstrual cycle. (The high rate of expulsion occurs be-

attendant should be feasible. At least a 95–99 percent effectiveness rate should be obtained.

Status of research. Several types of postpartum devices are currently being investigated. One is simply a Lippes loop with three surgical sutures attached to the uppermost curve. The sutures anchor into the fundus of the uterus and slowly dissolve, so that by the time uterine involution is complete, the sutures have disappeared, and a conventional IUD remains in place. A second device, a modification of the Nova-T, a copper-bearing device, has plastic flanges near the base of the stem. If placed high in the fundus of the

shortly. If efforts to develop inserters, informational materials and packaging are accelerated, and if training programs could be set up in use of the method, a postpartum device could become widely available in less than five years.

Advantages. If a traditional birth attendant could be trained to insert such a device properly at the time of delivery, the method could reach large numbers of women in developing countries at a time when motivation to avoid pregnancy is generally high. Unlike the pill, IUDs do not interfere with lactation, and they do not introduce drugs or steroids into the breast milk. Many women in the devel-



A self-administered menses inducer would bring on menses, whether conception had occurred during the month or not (above, fertilization in the hamster).

cause the postpartum uterus is in the process of contracting to its prepregnancy size. Unless the IUD can be anchored high in the uterine fundus, uterine contractions can easily displace it.)

Ideally, such a device would be effective over a woman's entire reproductive lifespan, and would need certainly to be effective without replacement for several years. Insertion by a specially trained nonphysician birth

attendant, the flanges brace against the walls of the involuting uterus, preventing downward displacement. The first device has achieved encouragingly low expulsion rates in limited clinical trials, and it is planned to expand these clinical studies quite rapidly. Since the IUD and suture materials are already approved for clinical use, toxicology requirements are minimal. Field trials to determine effectiveness of both devices will be initiated

opening world are not routinely seen by medical or paramedical personnel after the postpartum period, so that it is much more difficult to reach them to insert conventional IUDs during the menstrual cycle.

Drawbacks. The postpartum IUD would possess the same side effects associated with conventional devices — notably, disturbed menstrual bleeding patterns, pain and risk of pelvic inflammatory disease (PID) and, pos-

sibly, subsequent infertility. Indeed, these devices may tend to increase postpartum bleeding, spotting and cramps, and special care would be needed to prevent infection. For women who deliver in hospitals, skilled medical services would presumably be available. But traditional birth assistants would need to have special training to insert these IUDs.

Organizations involved. The major organizations involved are the IFRP, which is developing the sutured loop, and the PARFR, which has begun a study of both devices. The ICCR and the WHO have also been involved to a lesser extent in developing such devices.

Current funding. About two percent of current public-sector funding for contraceptive development is going toward research on postpartum IUDs. The IFRP is spending about \$210,000 annually on its device; the PARFR has a three-year study under way, with a total investment of \$200,000; the ICCR is spending about \$45,000 annually at present; and the WHO, about \$13,000. In all, the current annual investment in this method is about \$300,000.

Future requirements. The current strategy of selecting and testing a very small number of potential designs can probably be executed at current annual funding levels (with allowance for inflation) over the next three to four years. If several designs were tested simultaneously, about five times the current annual funding level would be needed, but a substantially superior product could result within five to seven years.

Institutional constraints. The involvement of industry could speed up the timetable for development of this kind of method, but major pharmaceutical companies are not likely to be interested in developing a low-cost IUD for Third World family planning programs. Public-sector agencies have attached lower priority to this approach than it would seem to merit, considering the potential worldwide usefulness of such a device. This is perhaps because it has lacked some of the "glamour" attached to such other leads as a male method or menses inducer.

Different investigators, working independently, have developed their own ideas about optimal design, and they have gone on to manufacture and test these, often using different types of clinical protocols and applying very different scientific standards for evaluating performance. They have tended to place emphasis on proving that their particular designs are superior and worth marketing, rather than working closely with other R&D groups to develop the optimal device even if a longer process of development and testing is required.

Limitations of Current Arrangements And Funding

There is a good chance that some of the methods described in the preceding section could be made available to the public within the next decade if public-sector funding for contraceptive development were increased by some four times, if donors made that funding available on a secure, long-term basis, if there were improved coordination and planning by donors and research programs, if there were more reasonable requirements by regulatory agencies and if there were more effective harnessing of the potential of industry.

Funding for all contraceptive development programs is shrinking and is increasingly insecure. The United States and other governmental donors have decreased their expenditures for contraceptive development since the mid-1970s. The WHO Human Reproduction Programme, the largest of the five international R&D organizations, is probably going to eliminate its R&D task forces on new male contraceptive agents and contraceptive vaccines because of budget cutbacks from several donors. Budget-tightening by the U.S. Congress has led to restriction of contract programs, precisely the mechanism through which the U.S. government finances contraceptive R&D. None of the R&D programs has been able to keep pace with inflation in recent years; what is more, increased costs for overhead have left relatively smaller proportions of expenditures for actual research. These shrinkages are occurring at a time when R&D costs are increasing because of the relatively large number of potential new methods now in advanced clinical trial — the most expensive part of the R&D process. Because of lack of funds, R&D programs have had to reduce the number of toxicology studies, clinical trials and product formulation efforts that they would otherwise undertake. As we demonstrated in our analysis of five potential new methods, the R&D programs have had for the most part to restrict their work to a few technological approaches, usually the least costly, and they have been unable to pursue multiple avenues of investigation simultaneously in order to speed up the development process.

Funding limitations prevent these R&D programs from making substantial enough investments in longer term mission-oriented research to bring new breakthrough technologies to the general public in the next decade. Indeed, at today's pace of development, most of these methods will probably not reach the market before the end of this century.

Cutbacks in funding have been exacer-

bated by donor pressures on programs to minimize expenditures in developed countries. Such pressures, although consistent with the objective of developing scientific and technological capacities in Third World nations, are not consistent with the fact that 95 percent of the world's R&D efforts are conducted in developed nations, where the bulk of scientific, technical and engineering capacity is located. This problem is particularly notable for R&D efforts entailing chemical syntheses of new compounds, drug screening, studies of toxicology, studies of the mechanism of action of new agents and of their effect on metabolism, studies of product formulation and the organization and coordination of highly sophisticated clinical trials. The involvement and training of developing-country scientists in these endeavors should be (and has been) pressed by R&D organizations to the extent that funds are available, and more programs of scientific training and institutional development for such countries are clearly needed. But reducing expenditures for R&D in developed countries will inevitably slow R&D efforts. In the case of the largest of the R&D programs, the WHO Programme, these pressures have led to increasing emphasis on clinical trials of existing methods and on operational research involving family planning service delivery. Only one-quarter of the WHO's current research budget is going to contraceptive development.

Beyond problems associated with funding, there are a number of organizational problems that appear to be reducing the effectiveness of R&D programs. Greater coordination among the contraceptive-development organizations — especially sharing of technical information, data, protocols and research plans — could increase efficiency and improve allocation decisions. Senior scientific staff from the six R&D organizations now exchange technical information about various projects on an ad hoc basis, and meet formally each year at a two-day meeting sponsored by the WHO to exchange information about ongoing work and future plans. But such contacts are not sufficient to permit the effective sharing of information about projects that is needed. What is more, the organizations tend — partly out of scientific conviction, but also in order to make their programs more visible and attractive to their donors — to identify themselves with particular technological approaches and undertakings, and to ignore (and sometimes disdain) complementary approaches undertaken by other groups.

In part, this problem stems from a lack of joint planning and coordination among the major donors to these R&D programs. His-

torically, particular donors have been closely associated with particular programs.* The only time the donors meet as a group is at conferences held for a few days every few years to discuss all aspects of the population-related programs that they support. Many governmental donors are poorly informed about programs they do not fund, and they tend to restrict their interests in contraceptive development principally to the activities and functions of the organizations they support. The result has been sharp competition among the recipient organizations to maintain their traditional sources of funding.

Constructive competition, even if it involves some redundancy of effort, is probably desirable in contraceptive research as in other activities. It encourages creativity and exposes waste. The current level of competition, however, has become counterproductive.

As a result of the competition for funds, some investigators have tended to oversell their programs, underestimating the time and funds necessary to bring a new method through clinical testing, or neglecting to make clear to donors that in the very nature of the development process, some promising leads will have to be abandoned along the way. The result has been to make donors impatient with the slow progress between the initiation of an idea and its realization as a marketable method. The paradox is that as donors' interests cool and their pocketbooks tighten, it becomes ever less possible to pursue multiple leads simultaneously — an approach that could produce results more rapidly than the current typical practice of working on one lead at a time.

A different kind of problem arises from the fact that the work of the major R&D organizations is conducted principally by scientists who do not have field experience in family planning programs where the new technologies will eventually be used. Too often, it has been assumed that newer is better, without adequate research into the acceptability or practicality of a particular method under developing-country conditions. In the past few years, the R&D programs with an international focus have made progress in establish-

ing mechanisms to help ensure that the methods they are developing meet the needs of eventual users. One of the R&D organizations, the PIACT, specializes in research related to the adaptation and introduction of new technologies — for example, their packaging, their instructional materials and their shelf life under tropical conditions. Other programs now routinely conduct acceptability surveys as part of their clinical trials of new methods. Nevertheless, the ultimate acceptability of many of the technologies now under development remains uncertain and, in some cases, questionable. Partly, this is because of a lack of suitable research methodologies, but it is also because there continues to be insufficient linkage between the research organizations and the family planning service delivery programs.

Another problem has grown out of the success of the R&D organizations in developing new technologies. From the outset, it was envisioned that these public-sector organizations would rely on private-sector companies for manufacturing and distributing the new products they developed. In some instances, however, difficulties have arisen in establishing a low enough price for the manufactured product so that public-sector family planning programs can afford it. Even when the R&D organizations have been successful (for instance, in the case of the Copper T, which is available to public programs for less than one dollar), problems have arisen in the marketing and distribution of the new products to family planning programs. Although many companies have been willing to manufacture products developed in the public sector, they have not been eager to distribute and promote them at special concessional prices to public agencies through their commercial marketing networks. Consequently, even when the methods are inexpensive, potential public-sector buyers and users of the new technologies in developing countries often fail to hear about them or to learn where they can obtain them. Again, several agencies have begun to address this problem, and one of these (the PIACT) has specialized in this area.

Current drug regulations, especially those promulgated in the United States, constitute another obstacle to rapid development of new contraceptives. Increasingly stringent regulations imposed over the course of the last two decades have tremendously increased the costs and the time required for new drug development in the United States and, to a lesser extent, in Europe as well. The increased costs are alleged to have discouraged industry from participation in birth control research, especially with regard to high-risk efforts. None of the internationally fo-

cused applied contraceptive R&D organizations have sufficient funds to take their drug-based potential products through all of the toxicology and clinical trial requirements that the U.S. Food and Drug Administration (FDA) is likely to establish for new chemical entities.

What Can Be Done?

Clearly, the most important action that could be undertaken to spur the development of new and improved contraceptive methods would be the provision of substantial additional funds for this purpose. In the first place, expenditures need to be sufficient to ensure the rapid completion of development of advanced leads already in the R&D pipeline. Second, other methods believed to have great promise for improving control over reproduction among couples in the developing and developed world (such as a male method, an antipregnancy vaccine and a menses-inducing agent) should be selected by donors and programs for large-scale efforts involving simultaneous pursuit of all promising technical approaches. (To produce an antipregnancy vaccine, for example, work would be undertaken on various placental antigens, ovarian antigens, gonadotropin antigens and egg and sperm antigens.) Such projects would require long-term financial commitment, long-term R&D planning and a technological organization of much broader scope than is currently available for pursuit of these important but still elusive leads.

An increase of at least two times current annual expenditures for applied contraceptive R&D will be required to complete the development and fielding of methods now in the R&D pipeline and twice that much again would be needed to take advantage of the most promising opportunities for the five new methods described earlier. In addition, it is essential that donors devise a mechanism to commit such funding on a sustained basis for the 10 years or so needed to bring a new method from the laboratory to the marketplace.†

Increases in expenditures for fundamental research are also needed to nourish contraceptive development efforts and supply new leads when old ones fail to work out. Continued expenditures are also needed for evaluation of safety of existing methods, and of new methods as they are brought to market, to build confidence in these methods and to guard the health of couples who employ them. Finally, ongoing funding is needed to train new scientists and support research institutions to assure continuity of research efforts over the long term.

It is unlikely that such increases will be forthcoming unless there is a radical shift in

*The largest donor, the U.S. government (through AID), provides its funds exclusively to the four U.S.-based organizations, two of which it created. Seven of the remaining nine governmental donors provide their funds exclusively to the WHO program.

†Contraceptive development expenditures in the public sector have declined by about one-quarter since 1974 when, it was estimated, a threefold increase was needed to take advantage of current knowledge. To reach that goal would require a fourfold increase. Important new leads uncovered since that time further increase the possibilities for further productive R&D activities.

donor research priorities. The U.S. National Institutes of Health (NIH) is the world's major funder of reproductive and contraceptive research. Even during the peak of world concern in the early 1970s about the severe social and economic problems engendered by rapid population growth, only two percent of the NIH research budget was devoted to studies in reproduction, and only about four-tenths of one percent was going for applied contraceptive R&D.¹⁰ Today, the proportion devoted to reproductive research is under two percent, and the proportion devoted to contraceptive development is less than three-tenths of one percent.¹¹ Increases in the share of total funds the NIH devotes to population research could be an appropriate and important source of new money for contraceptive R&D. However, some modification of the current grants and contracts mechanism would need to be devised so that the CPR could provide institutional support to the major R&D programs.

Increased funding from the Office of Population of the AID is also critical for the survival of the four U.S.-based R&D programs. AID support of these programs has come under criticism from some who believe that scientific research is out of place in a foreign assistance agency, and that research activities would more appropriately be concentrated in the NIH. The emphasis of the NIH, however, on the health of Americans rather than on the needs of people who live in developing countries sometimes conflicts with the priorities of the internationally oriented R&D organizations. Broader program support rather than narrowly focused project support by the AID is needed, perhaps with assistance in selecting programs and setting quality standards provided by an outside advisory panel established for this purpose by the AID.

The fact that world population growth rates have begun to slow in a number of countries of Asia and Latin America has led to complacency among some policy-makers that the "population problem" has been solved, and that no major initiatives, such as the development of a new contraceptive technology, are needed. The long time frame that appears to be necessary for the development of any new method discourages those donors who are still convinced of the need for action to meet population problems. Many of them have become convinced that the only solution lies in more efficient organization of services and the initiation of community pressures and incentives "beyond family planning."

In fact, the demonstration of receptivity to family planning efforts in countries around the world, and the responsiveness of couples

to these programs as measured by increased contraceptive use and declining birthrates and growth rates is a persuasive argument for assigning high priority to research in contraceptive development.

There is no technological fix for problems engendered by population growth. But new methods of fertility control that better meet individual needs and preferences and that are effective, safe and require less costly and sophisticated delivery systems than those now available can accelerate fertility declines now taking place, as well as help initiate them in places and among couples where current methods are inappropriate. Without sterilization and legal abortion, conventional family planning programs using available methods have limited effectiveness in bringing down birthrates. This is because of relatively high rates of discontinuation as well as problems of acceptability and safety. Religious and political opposition have inhibited the development of sterilization programs and the legalization of abortion in many countries, and will probably continue to do so — especially where legal abortion is concerned — for some time to come. What is more, epidemiologic research has made us aware of the limitations of current methods based on safety problems. Even in developed countries, as we have noted, the inappropriateness of current methods has resulted in continued high rates of unintended pregnancy, though these are masked to some extent by the considerable recourse to legal abortion.

Donors from government, multilateral agencies and private philanthropies have created a highly productive international contraceptive research and development apparatus which, if provided with expanded and continued support, is virtually certain to develop a wide range of extremely useful new birth planning technologies during the next decade. It is to be hoped that greater appreciation of this fact and of the urgent need for new methods will persuade donors to provide the needed additional funds even in the face of the current climate of financial austerity.

Institutional Changes

Whatever the level of funds available, there are a number of changes in institutional arrangements that could help bring about their more efficient utilization. One of these would be insistence of the donors on detailed data-sharing among technical personnel of the R&D organizations that they support. Such data-sharing is unlikely to take place, however, without improved coordination and joint planning among the donors themselves — beyond the annual meeting sponsored by

the WHO and the irregular conferences sponsored by the private foundations.

The kind of mission-oriented approach suggested here, involving the simultaneous pursuit of various technological leads to achieve a particular type of method (such as a menses inducer, a male pill or an antipregnancy vaccine), would certainly require — in addition to greatly increased funding — far greater coordination among developers and donors than now exists, in order to choose the methods for research concentration and to allocate the various approaches to those organizations that are best suited to pursue them.

The provision of substantial additional funding is the most important action that could be taken to spur method development.

Various models have been suggested to improve coordination and planning and evaluation. One is the Consultative Group for International Agricultural Research, which coordinated governmental and private foundation efforts to bring about the so-called Green Revolution through applied research to development of new agricultural techniques in Third World countries. The Consultative Group is assisted by a Technical Advisory Committee which monitors progress on various avenues of investigation and helps evaluate which is worthy of further investigation and which should be abandoned.

Another approach that might lead to improved donor coordination and involvement is for the United States government, which is responsible for 60 percent of worldwide reproductive research, to end its refusal to fund the WHO Programme. By taking its place on the WHO's Council of Donors, the U.S. government could seek to encourage that Council to strengthen its role in contraceptive applied R&D.

At another level, it has been suggested that most of the contraceptive development efforts of the AID and the CPR be concentrated in a new international agency, the Institute for Scientific and Technical Cooperation (ISTC), the organization of which was authorized by Congress, but for which no funds have yet been appropriated.

Clearly, further in-depth exploration of feasible means to achieve the kind of coordination needed among donors and programs is required.

In addition to regular data-sharing, R&D

organizations could benefit by strengthening their procedures to periodically assess the potential utility of the technologies they are developing for Third World clients. These assessments could be based not only on formal marketing research studies, but also on informal discussion with service program personnel. They should include analyses of the programmatic requirements of new methods to identify user needs, preferences and potential problems.

Some way needs to be found to speed up the regulatory process for new methods required by the FDA. For example, a comprehensive review and reconsideration of current requirements for animal toxicology might provide a means for developing new sets of standards that would offer greater flexibility and speed. Numerous attempts have been made to change these regulations, without success, because of disagreement among scientists as well as political pressures from consumer advocacy and feminist groups on the one hand and pharmaceutical companies on the other. While it is clearly unacceptable to allow human trials of products which are likely to cause serious health problems, many of the current regulations for clinical trials clearly inhibit and make more expensive the entire process of contraceptive development (and, it should be added, development of all other categories of drugs and devices). Action is needed to simplify regulations without sacrificing health protection. In addition, governments should be encouraged to establish their own standards, based on the risk-benefit equations applicable in their own countries. The WHO's efforts to develop institutional capability in Third World countries is helping to achieve this goal.

The claims of Carl Djerassi and others that industry is refusing to participate in this type of research because costly and time-consuming regulatory procedures have made it unprofitable¹² are probably exaggerated. At least five companies are known to be engaged in research on LHRH, for example, in search of a more acceptable ovulation suppressant than the current oral contraceptive. In certain areas (e.g., vaccines), it is possible that the participation of industry may only be obtained if the government takes over liability coverage, as it did in the case of the mass swine flu inoculations. Government reimbursement for expensive toxicology studies and extension of patent protection may also be needed. Concessions to industry, however, should be carefully hedged with agreements requiring the companies to sell and promote the resulting products at low cost to public-sector programs.

In our view, the kinds of increases in the

level and nature of funding that we have discussed, and the appropriate changes in institutional arrangements, could result in the development of major new methods in the next decade that could revolutionize contraceptive practice the world over by greatly increasing rates of acceptance and continuation, while providing options that are as effective as the pill and the IUD, but safer than either of those methods.

It would be unfortunate if donors, feeling the pinch of inflation, impatient with the pace of current progress and complacent over falling birthrates, were to fail to take advantage of the extraordinary opportunity now available to accelerate these declines and help advance social and economic progress not only through improving family planning service delivery, but also by making available desperately needed new methods of contraception.

Exhortation, of course, is easier than persuasion. It is difficult to pry loose increased funding for research in any area in this period of budget tightening, and it is colossally difficult to change the perception of priorities that are built into the funding system. Current institutional arrangements reflect different perceptions of what needs to be done in this field as well as intercountry and intracountry personal and bureaucratic rivalries. Change is always difficult; but in this instance, it is essential. It is urgent that the major governmental and private donors examine the current situation and find ways to solve the problems we have discussed. Perhaps one persuasive means of accomplishing this is the appointment by a consortium of the key governmental and nongovernmental donors of a blue-ribbon international committee of scientists to assess the current research situation and report its findings within a year.

Clearly, if present trends of shrinking real-dollar R&D budgets continue, with the consequent slowdown of R&D activities of the major research organizations, we will certainly not obtain any of the "breakthrough" methods described in this article in the foreseeable future, and we are in danger of further delaying even those methods that are in advanced clinical trial.

References

1. Population Reference Bureau, "1980 World Population Data Sheet," Washington, D.C., 1980.
2. M. Kendall, "The World Fertility Survey: Current Status and Findings," *Population Reports*, Series M, No. 3, 1979; and additional data from first country reports, World Fertility Survey.
3. J. Dryfoos and J.D. Forrest, "Evaluation of the Role of the Public Sector Family Planning Program in the U.S.," paper presented at the annual meeting of the Population

Association of America, Denver, Apr. 11, 1980.

4. W.P. Mauldin and B. Berelson, "Conditions of Fertility Decline in Developing Countries, 1965-1975," *Studies in Family Planning*, 9:5, 1979; and D. Kirk, "World Population and Birth Rates: Agreements and Disagreements," *Population and Development Review*, 5:387, 1979.
5. C.F. Westoff, "The Unmet Need for Birth Control in Five Asian Countries," *International Family Planning Perspectives and Digest*, 4:9, 1978; and R. Freedman, "Theories of Fertility Decline: A Reappraisal," *Social Forces*, 58:1, 1979.
6. W.P. Mauldin, "Experience with Contraceptive Methods in Developing Countries," in National Research Council, *Contraception: Science, Technology and Application* (Proceedings of Symposium on Contraceptive Technology, May 16-17, 1978), National Academy of Sciences, Washington, D.C., 1979, p. 50.
7. R.O. Greep, M.A. Koblinsky and F.S. Jaffe, *Reproduction and Human Welfare: A Challenge to Research*, MIT Press, Cambridge, Mass., 1976, p. 435.
8. *Ibid.*
9. *Ibid.*
10. *Ibid.* p. 428.
11. U.S. Bureau of the Census, *Statistical Abstract of the United States: 1979*, Washington, D.C., 1979, p. 622.
12. C. Djerassi, *The Politics of Contraception*, W.W. Norton, New York, 1980, Chapters 5 and 11.

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