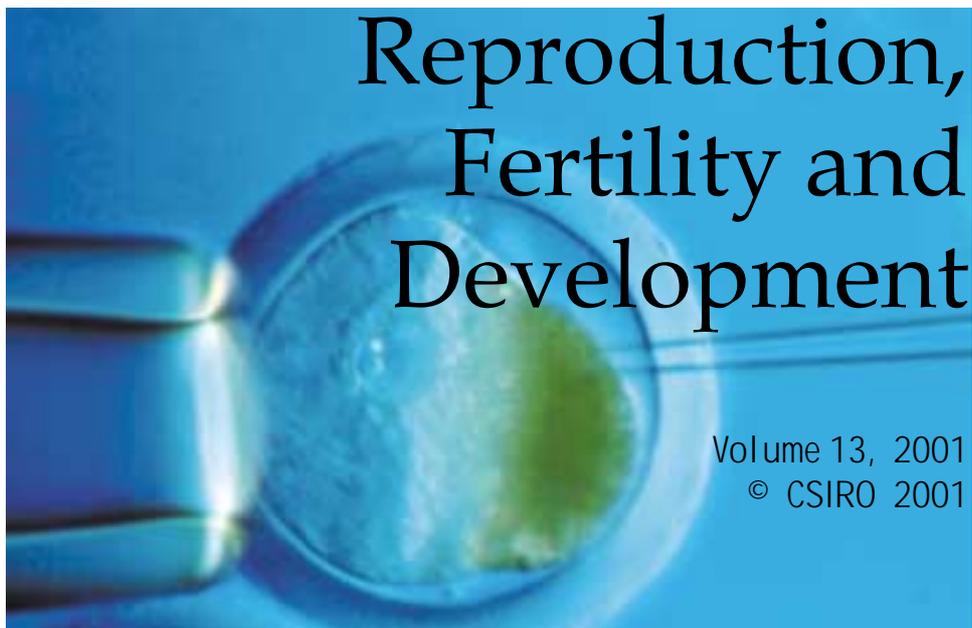


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Meeting the contraceptive and AIDS prevention needs of people living on a dollar a day

Malcolm Potts

Warren Hall, Room 314, School of Public Health, University of California, Berkeley, CA 94720, USA.
email: potts@socrates.berkeley.edu

Abstract. The new millennium sees the largest cohort of young people in history entering its fertile years. Many of these people are too poor to pay the full cost of modern contraception, but the money available for subsidizing their needs is exceedingly limited. The AIDS pandemic is placing additional, unprecedented demand on already overstretched resources. Existing methods of contraception that are well established and off-patent can be produced in bulk at low cost, and will remain the backbone of future programmes. The use of misoprostol as an abortifacient is likely to spread rapidly. New methods must take into account the limitations of the health infrastructure in developing countries and the imperative of low cost. Given the constraints of money, skills and facilities, it is essential to set realistic priorities for future contraceptive research and development. It is suggested that the greatest needs are for a woman-controlled method of preventing HIV transmission and for a non-surgical method of female sterilization.

Introduction

For ten years, Roger Short was chairman of Family Health International (FHI), and helped lead that organization's research on contraception. He also helped take FHI into the field of AIDS prevention, as well as working with the Global Programme on AIDS in Geneva for a year. In the coming decades a major factor limiting the wider use of contraceptives for family planning and the greater use of condoms for AIDS prevention might not be shortcomings of the methods, but insufficient commodities at affordable prices. Additional research on contraceptives will have to give greater priority to considerations of cost.

The largest cohort of young adults in history is entering its fertile years. HIV continues to spread exponentially in several parts of the world. Family planning is impossible without access to contraceptives, and AIDS prevention cannot proceed without access to condoms and antibiotics to treat sexually transmitted diseases (STDs), which facilitate HIV transmission. Access to safe abortion is also an essential element in any realistic approach to fertility regulation and in any serious effort to improve reproductive health. Empirical evidence shows that it is impossible to achieve either replacement level fertility or a low maternal mortality without access to safe abortion (Potts 1997).

Three-fifths of the world's population, living in the poorest 61 countries, receive 6% of the world's income. Almost half the world's population lives on less than \$2 US a day (Table 1) (World Bank 2000). Most of these 2.8 billion people are too poor to afford the full cost of manufacturing, promoting and distributing modern methods of contraception, or to pay all the costs of diagnosing and treating reproductive tract infections. International assist-

ance is one essential element in helping to solve these problems, but some hard choices need to be made in the allocation of the limited resources available. Inevitably, highly constrained budgets also influence research priorities.

Services must work to obtain sufficient commodities and thus there must be an effective logistic system in place; the needed commodities must be distributed at affordable prices, backed up by appropriate information and promotion. Research must focus on one or two key topics that are likely to have the greatest leverage on the reproductive health of the poor.

Globally, the gap between rich and poor is growing wider, and we are further from the goal of universal access to effective contraception than we were some years ago. A crisis is arising in the supply of contraceptives and AIDS prevention commodities. Since the mid-1990s, the donor contribution to commodity costs has fallen markedly.

The need

Predicting contraceptive needs is relatively straightforward. All those entering their fertile years over the next decade and a half are already born and enumerated, and the relationship between the percentage of couples using contraceptives and the total fertility rate of a country is well understood.

The Demographic and Health Surveys demonstrate a large unmet demand for family planning in nearly all countries (Potts 2000a). If the financial resources were available, it would be possible to meet this need relatively rapidly. Social marketing is a particularly cost-effective, culturally appropriate way of expanding the use of oral contraceptives, condoms, injectables and even intrauterine devices (IUDs). The problem is how to secure high quality commodities and to find the money for advertising and

distribution. Unfortunately paying for contraceptives is not a popular initiative among donors and international agencies. In the 1980s, the World Health Organization (WHO) Global Programme on AIDS spent tens of millions of dollars on international conferences, but only a few hundred thousand dollars buying condoms. The support given by international donors is only enough to provide the equivalent of three condoms per man per year in sub-Saharan Africa, hardly sufficient to make an impact on the most disastrous epidemic since the rise of modern scientific medicine.

To date, the international community has not even attempted to supply antibiotics to treat STDs on a significant scale.

Manufacturing commodities

Most of the family planning and AIDS prevention commodities needed are made by capital-intensive industries that employ relatively few people, many of whom are specialists. Fortunately, a competitive world market exists for the supply of oral contraceptives, condoms, IUDs and antibiotics. The patents on many of the most needed products have expired. Some commodities used in poor countries, such as oral contraceptives, are manufactured in the same factories that also supply a higher priced western market. Both development costs and the capital costs of the manufacturing equipment have been largely written off and, as a result, prices are remarkably low. The cost of oral contraceptives is one of the few things that has fallen over the past 40 years. Western manufacturers charge under 20 cents per cycle for bulk supplies. Recently, an Indian manufacturer who bid on a UNFPA contract at approximately 5 cents monthly has undercut even these low prices.

Condoms cost more than contraceptive pills to make. The variable that cannot be altered is the cost of the high quality latex used in manufacture. The AIDS crisis has increased the need for latex gloves in the west and, as these are made on the same machines as condoms, gloves end up competing with condoms for manufacturing space and raw materials. Consequently, the cost of condoms, unlike oral contraceptives, is likely to rise.

Widely used antibiotics, such as tetracycline, are low cost, but more and more drug resistant forms of disease including STDs are arising, and the cost of prescribing appropriate antibiotics is also likely to rise.

Table 1. Population (billions) living below \$2 per day
(World Bank 2000)

| Region | 1987 | 1998 |
|--------------------|-------|-------|
| South Asia | 0.911 | 1.096 |
| Sub-Saharan Africa | 0.357 | 0.475 |
| Remaining nations | 1.281 | 1.223 |
| Total | 2.549 | 2.801 |

It is sometimes suggested that the solution to the contraceptive commodity problem is to build local factories. Unfortunately, there are two reasons why this could make the problem worse. First, it would divide production into small units, increasing costs and perhaps decreasing quality. The low prices are achievable only with large production units for economies of scale. Second, even if a condom factory is built, for example in Bangladesh, most people will still be too poor to buy the product. There is no way to short circuit the need for some degree of subsidy.

Fortunately, low-cost manufacturers serving large domestic markets already exist in China, India, Mexico, Brazil and Egypt. Ways are needed to open up South-South trade routes so that these manufacturers can compete in the international market as suppliers of smaller countries that do not have significant local production. In June 2001, a meeting of Partners in Population and Development in Cochin, India, suggested that developing countries collaborate in expediting approval of generic drugs for import from developing country manufacturers.

Buying commodities

There are only three sources of money to buy commodities: (i) the consumer; (ii) subsidy by the consumer's government; and (iii) subsidy from the international community. It is reasonable for those who can pay for commodities to do so. Unfortunately, poorer people spend the greatest proportion of their total income on health care. However, the contribution of people living on less than two dollars will necessarily remain limited. Observations suggest that most individuals will spend up to approximately 1% of their disposable income in order to control family size. Once cost goes above this level, it seems virtually impossible to persuade more than a small percentage of the population to use modern contraception (Harvey 1994).

If the 1% rule is combined and with widely accepted estimates of the cost per couple per year of contraceptive protection to sub-Saharan Africa, it can be calculated that over 95% of people are unable to meet the full cost of manufacturing, promoting and distributing modern methods of contraception. (Table 2) (R. Green, Bay Area Inter-

Table 2. Percent who can afford the full cost of family planning

Assumption: users will invest 1% of their disposable income to buy contraceptives (R. Green, Bay Area International Group, University California, Berkeley, personal communication)

| Region | Percentage |
|---------------------------|------------|
| Sub-Saharan Africa | 3 |
| Asia | 7 |
| Arab State/Eastern Europe | 29 |
| Latin America | 49 |
| All aid-dependent nations | 16 |

national Group, University of California, Berkeley, personal communication).

In a few countries, such as China and India, the government has taken a lead in providing contraceptives, but most African governments have not been in a position to meet commodity needs from their own tax base. Moreover, the horror of AIDS is going to further weaken the economies of these already desperately poor nations, so it is not realistic to expect much help from this source.

This leaves the international community. Here the record is uneven. In the 1960s, first Sweden and then the US Agency for International Development (USAID) (under the leadership of the then director of the Office of Population, Dr Rei Ravenholt) started to buy contraceptives for Third World countries. Britain and the Netherlands joined the contraceptive club, but most countries stayed outside. France once bought a few condoms, but none of the other Catholic countries of mainland Europe have helped. Japan makes some of the world's finest condoms, but they have never donated a single condom to fight AIDS in Africa, or to combat unintended pregnancies in Asia.

After almost 40 years of carrying an unequal share of the burden, the traditional donors are feeling fatigued. Administrators like to support interesting projects; they are unlikely to be promoted merely for buying 10 million condoms, important as that may be to family planning or AIDS prevention.

The picture is doubly worrying, because the total flow of aid from the international community is so limited. During the 1990s, at a time of unprecedented growth in wealth, the total international aid contribution of the Organization for Economic Cooperation and Development (OECD) countries stagnated. Of the limited amount available, only 1–2% goes to international family planning. Allowing for inflation and growing numbers of people, the world is hardly half way towards the modest targets set in 1994 at the United Nations International Conference on Population and Development in Cairo, for assistance to international family planning and reproductive health (Potts *et al.* 1999; Casterline and Sinding 2001). Allowing for inflation and the increase in the absolute number of women and families in need of family planning and reproductive health care, then USAID gives no more than it gave in the 1960s.

Distribution

Once the commodities are secured, distribution is not always easy. Some countries with national family planning policies, such as India, put duties on contraceptive imports. It often takes time—and sometimes bribes—to get consignments out of customs. Many distribution systems run by ministries of health are inefficient. Breaks in the supply line are common.

Commodities can be stolen or misused in corrupt ways. In the case of contraceptives, anything that is stolen or smuggled out of the country usually still ends up being used

as contraceptives by relatively poor people. Antibiotics are another matter. For example, the World Bank found that in Kenya in the 1980s, antibiotics intended for STD treatment aimed at slowing HIV were corruptly channelled into other areas of use.

Social marketing

Thirty years of international family planning experience demonstrates that the most cost-effective way of distributing contraceptives is through social marketing (Harvey 1999). Social marketing is the organized sale of subsidized products at very low prices in commercial markets. This system of distribution:

- uses business skills and management techniques and rewards for social profit;
- sets the price of the commodity to suit the consumer;
- uses the existing infrastructure of small shops and kiosks found throughout the world;
- creates a strong brand image (e.g. Raja condoms in Bangladesh, or Prudence in Zaire);
- uses professional advertising agencies (e.g. the Janani programme in Bihar is the largest purchaser of radio advertising in the state); and
- ensures that everyone, including the vendors who detail the products to retail outlets and the vendor, enjoy a small profit margin tied to volume.

Poor people are great entrepreneurs. If they weren't, many of them would not survive. The key to social marketing is to set the right price, find the right outlets and have the freedom to advertise. Once these factors are in place, social marketing is the most cost-effective, rapid-to-implement, culturally appropriate way to distribute any preventive or therapeutic commodity where the consumer makes the decision about use in their own home. Social marketing is ideal not only for contraceptive distribution, but also for oral rehydration salts to treat infant diarrhoea, bed-nets for malaria control and probably antibiotics to treat reproductive tract infections in men. In women, unfortunately, the symptoms of an STD are not specific enough to permit self-diagnosis and home treatment.

A major step in oral contraceptive use was to secure a non-prescription status for 'the Pill'. This battle is still being fought in relation to antibiotics and STDs even though, as with oral contraceptives, it is merely recognizing and trying to improve the *de facto* situation currently applicable throughout the developing world.

New methods

A great deal of excellent research on reproductive physiology takes place in academic institutions and universities all over the world. However, only a small group of not-for-profit institutions—the Medical Research Council (MRC) Unit in Edinburgh, FHI in North Carolina, the Contraceptive Research and Development programme (CONRAD) in

Washington, and the Population Council in New York—actually attempts to develop new methods of contraception and AIDS prevention for human use. Chinese research units in Shanghai and Beijing, and the India Council of Medical Research in New Delhi, also work in these fields.

Given today's needs and available resources, what should be the research priorities for these organizations?

One way to plan future strategies is to look at past successes and failure. Although China has brought a number of innovative hormonal methods into use, the record of western-based organizations over the past 30 years has been deeply disappointing. The whole field of contraceptive development is in disarray, and any new methods of family planning and AIDS prevention are reaching the market place at a glacial rate.

In 1982, the US Office of Technology Assessment (OTA) tried to predict the range of new contraceptive technologies that would be available in the year 2000 (Office of Technology Assessment 1982) (Tables 3 and 4). At the time, even Djerassi (1987), whose background in industry has often made him a more realistic commentator on contraceptive development than most others, overestimated the pace of introducing new methods.

The few new methods that have reached the market place all took longer than predicted to gain regulatory approval. Some, such as Norplant, have given disappointing results. Quinacrine sterilization, a successful new method, which probably has a huge potential to help women in poor communities make choices over childbearing, is mired in controversy. Research in some areas thought promising in

Table 3. Predictions made in 1982 and disappointments in 2000

(Office of Technology Assessment 1982)

| Prediction 1982 | Comment 2000 |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <i>Highly likely before 1990</i> | |
| Safer oral contraceptives | No. 'Third generation' progestins no safer than earlier oral contraceptives |
| Improved IUDs | No. Levonorgestrel releasing IUDs available in 1990s, but too expensive for most people |
| Improved barrier methods for women | Yes. But only one new method: female condom. Low volume use and high cost. Other new barrier methods stalled |
| Improved long acting steroid injection | No |
| Improved ovulation-detection methods | No |
| Steroid implants | No. Norplant use increases after 1990, but US market collapses |
| Steroid vaginal rings | No. Not on market by 2000 |
| LRF-analogue contraceptives for women | No. Not by 2000 |
| Prostaglandin analogues for self-administered induction of menses | No. Not by 2000 |
| <i>Possible by 1990</i> | |
| Monthly steroid based contraceptive pill | No. Not by 2000 |
| Improved monthly injections | No. Available by 2000 |
| New types of drug releasing IUDs | No |
| Mini dose vaginal rings | No |
| Antipregnancy vaccine for women | No. Nearly all worked stopped by 2000 |
| Improved barrier methods for men | No. Work on plastic condom stalled |
| Sperm suppression contraceptives | No |
| Reversible female sterilization | No. Work virtually stopped by 2000 |
| Simplified female sterilization | Yes. But subject to controversy and not in large scale use |
| LRF analogues for self-administered menses induction | No. Not by 2000 |
| <i>Unlikely, but possible by 2000</i> | |
| Antifertility vaccine for men | No. Work practically stopped |
| Antisperm drugs for men | No. Work practically stopped |
| Antisperm maturation drugs for men | No. Work practically stopped |
| Lactation-link contraceptive | No |
| Ovulation prediction methods | No |
| New types of anti ovulation drugs for women | No |
| Drugs to disrupt ovum transport | No |
| Reversible male sterilization | Some interesting work in China |
| Pharmacological or immunological sterilization for women | No |
| Pharmacological or immunological sterilization for women | No |
| Agents other than LRF analogues for self-administered induction of menses. | No |

Table 4. Options not foreseen in 1982

| Option | Comment |
|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antiprogestational agents for medical abortion | RU486 (+ prostaglandin) successful, but commercialization held back |
| Antiprogestational agents for emergency contraception | Mifepristone (RU486) is produced in China in 25-mg and 10-mg tablets, but developing countries are not yet accepting without European or US FDA approval |
| Stable, low-cost prostaglandin for self-induced abortion | Available, but commercialization held back |
| Microbicides to slow HIV transmission | Limited trials with disappointing results |
| Surgical male circumcision to slow HIV transmission | Controversial, no services developed |
| 'Chemical' male circumcision to slow HIV transmission | Chemical entities known, but no research taking place |

1982, such as contraceptive vaccines, has practically come to a halt.

The record of the pharmaceutical industry is also a paradox. Mifepristone (RU486) has performed well, but the company that developed it has turned its back on the commercialization of the product. The company manufacturing the prostaglandin misoprostol (Cytotec; Pharmacia) explicitly denies its efficacy in reproduction and its control, and tries to restrict its sales for gynaecological purposes.

HIV was just being recognized as the OTA document went to press in 1982. The advent of HIV/AIDS has turned the world upside down and defined urgent new needs for barrier methods (i.e. vaginal and possibly also penile chemical compounds). Even in the face of a fatal, incurable disease that infects 16000 people a day—many of them young women on the threshold of adult life—no new method to prevent HIV transmission has been developed since the beginning of the epidemic (Potts 1994).

Roger Short is an outstanding reproductive scientist with a strong commitment to family planning. Roger is responsible for many scientific achievements, but has also experienced the frustrations of working specifically in contraceptive development. As Director of the MRC Reproductive Biology Unit in Edinburgh, he assembled a talented team of scientific researchers, yet that team was not able to produce any new method of family planning. As noted earlier, Roger Short was also Chairman of FHI for much of the 1980s, at a time when I was President and CEO of that organization. We conducted many clinical trials of Norplant, but the method took decades to reach the marketplace and it is likely to be overtaken by a more user-friendly product from industry. We kept monthly injectables alive, but they were a modification of a method known since the 1960s. The work we did together did not produce any fundamentally new method of contraception, nor did it contribute to any significant reduction in the spread of HIV/AIDS. Plastic condoms made a promising beginning in the 1980s, but their development came to a virtual halt in the 1990s.

What went wrong?

- *The easy leads in reproduction had already been exploited.* Oral contraceptives were the most logical

means of interrupting human fertility. Controlling male fertility, for example, is an order of magnitude more difficult, and if it can ever be achieved it is unlikely to bring the additional benefits of reducing uterine and ovarian cancer that 'the Pill' provides.

- *The work done by not-for-profit organizations in contraceptive development and AIDS prevention has been grossly undercapitalized.* The Cairo conference marked a policy shift from a focus on family planning to a broad agenda of reproductive health and women's empowerment. As has been noted, less than half the budget estimated as needed to pursue this new agenda has become available. Broader goals, combined with less money, are a recipe for further stagnation in research and development.
- *Some not-for-profit organizations did not have the management structure appropriate to bring new products into widespread use.* Inadequate funding and poor management extended the length of time it took to make subdermal implants available for widespread use. Partnerships with industry were flawed. For example, when mifepristone was brought to the American market, the Population Council did a number of expensive clinical trials in the US, although these were never used in the final FDA application. The levonorgestrel-releasing IUD has performed extraordinarily well, but the developers lost control of its price and it now costs \$400 per device in the US. Although it is cheaper in bulk, it is still far too expensive to use on a significant scale in the developing world.
- *The pharmaceutical industry had little interest in developing new methods of contraception or AIDS prevention.* They had the money and experience to take new drugs and devices through regulatory approval processes, but the area was perceived to present little profit, and high profile medico legal cases, especially the debacle of the Dalkon Shield, further deterred commercial investment. Interestingly, there has been one important case against an IUD manufacturer in the past decade and the company won it. However, IUD development remains a dead area.
- *Groups that might be thought to support contraceptive development have become some of its worse enemies.*

In India, women's groups have removed injectables from government programmes, even though, for example, this method is increasingly popular in neighbouring Bangladesh. Research on anti-pregnancy vaccines, and on the use of quinacrine to occlude the Fallopian tubes as an alternative to surgical sterilization, has been halted by vitriolic attacks from small, but highly committed, groups of women.

- *The regulatory environment in the west for developing contraceptives and AIDS prevention drugs and devices has become increasingly expensive and difficult.* Research on human beings always requires the highest standards, but, with the passage of time, regulations tend to become increasingly demanding without necessarily adding anything to the quality of research. For example, in the 1980s, FDA regulations forced Organon to spend about \$8 million on small-scale pre-marketing clinical trials on US women as a prerequisite for sale in the US. The facts that Marvelon was already the most widely used contraceptive pill in Europe, and that the most useful information on rare events nearly always comes from post-marketing surveillance, were ignored. Pedantic FDA requirements account, in part, for the slow progress of new barrier methods in the 1980s and 1990s. Progress on possible life-saving microbicides has been brought to a virtual halt by FDA regulations and the ethical framework some US researchers have constructed.

What succeeded?

Not-for-profit institutions working in contraceptive development have often contributed more to contraceptive development by making important incremental improvements in existing methods, rather than developing novel methods. Both the MRC Reproductive Biology Unit in Edinburgh and FHI did extensive research on the suppression of ovulation during lactation. As a result, more precise guidelines were given to breastfeeding women. This might seem a trivial contribution, but in some developing countries, anovulation associated with breastfeeding averts more births than modern methods of contraception.

There is a large gap between the use effectiveness of oral contraceptives and failure rates observed in well-conducted clinical trials. The FHI did work on the instructions given to women using oral contraceptives. Again, this might seem pedantic, but 100 million women use 'the Pill' and a 1% reduction in the failure rate would avert more unintended pregnancies in a year than any new method of contraception might do in a decade.

Roger Short has made important contributions to the demonstration that male circumcision has a powerful preventive effect on HIV acquisition (Szabo and Short 2000). Indeed, by an order of magnitude, male circumcision has almost certainly prevented more HIV infections in Africa—perhaps as many as 8 million cases (Potts 2000b)—than all

the programmes of condom distribution, STD control and education put together.

What is needed?

The limitations of resources, the reality of HIV and the continuing need for family planning should set our priorities.

There is an outstanding unmet need for a HIV prevention method that women can use when they cannot compel their partners to use a condom. The barrier method most needed is a chemical compound that will kill or block HIV in the vagina (or on the foreskin) without damaging human tissue. Over the last 30 years, no country has achieved a high prevalence of contraceptive use purely through the availability of a single method of fertility regulation. The greater the number of contraceptive methods available, the higher contraceptive prevalence tends to be (Ross and Frankenberg 1993). Yet we are attempting to slow the spread of HIV with a single method—condoms. For sound biological reasons, women tend to be more cautious decision-makers than men in relation to reproductive health and family planning, and it is imperative to offer them a method they can control.

In the 1980s, FHI demonstrated that commercially available spermicides using nonoxynol-9 reduced the transmission rates of gonorrhoea and chlamydia, but caused a small increase in monilial infections (Rosenberg *et al.* 1987). To date, a similar effort to control HIV has failed. (Roddy *et al.* 1998). Fortunately, there are very large numbers of chemical entities that destroy HIV. It has been apparent since the first part of the 1980s that research in this field was urgently needed. Experience also suggests that it might take several iterations of formulations of one or more possible microbicides before an effective product is found.

In the contraceptive field, there is an urgent need for a non-surgical method of female sterilization. Voluntary sterilization is the single most widely used method of family planning in the US, Britain and several other parts of the world. As more and more women choose to have smaller families, voluntary sterilization is likely to become more and more popular to cover the increasingly longer interval between the last wanted child and the menopause. In south Asia and Africa, it is difficult to offer an acceptable quality of surgery when basic health services are weak. Research on transcervical methods to block the fallopian tubes have a long history, but only the use of quinacrine pellets has reached large-scale clinical use (Hieu *et al.* 1993) and unfortunately the method then became mired in controversy.

Mistakes that were made in the development of microbicides

Problems included a lack of funding and a lack of clear priorities. Institutions followed too many leads, rather than focusing on one or two achievable goals. In the case of microbicides, there were bureaucratic battles with possible sponsors arguing over whether work on microbicides fell under family planning or AIDS prevention budgets. There

was an almost total failure to appreciate that when dealing with a new disease that is growing exponentially, even a poor product today is better than a perfect product some years down the road. The NIH, NRC and USAID have all funded projects in this field by writing requests for proposals and planning peer-reviewed research. There is a fierce debate about the nature of appropriate clinical trials, and only a few candidate formulations are now moving through the US FDA approval process. At the present rate, it will take years, or even decades to bring a needed product into widespread use. Meanwhile, UNAIDS estimates that there are 15 000 new HIV infections every day.

One of the good things about microbicides is that they are a relatively low technology. The field would move much more rapidly if money had been used in a more directed way. What is urgently needed is a management system that carefully selects chemical entities with a plausible likelihood of being effective and then allots the available resources in the appropriate way between laboratory research and expedited Phase I, II and III clinical trials.

It is the large-scale clinical trials that are most expensive. There has been poor management, a stubborn refusal to use any but US FDA guidelines and a reluctance to review more than one ethically acceptable system for conducting trials. As a result, the pipeline is bursting with promising products that the clinical trial system is incapable of exploiting.

The US FDA is pushed and pulled by a variety of forces. It is set up to regulate the wealthiest market in the world and keeping costs low for manufacturers is not a priority. The FDA perceives the risk of making a mistake as high, and in the case of microbicides it feels little pressure to act quickly.

In designing protocols for clinical studies of possible efficacy, it has been asserted that only a placebo-controlled trial would give valid results. It is then argued, not unreasonably, that if using a placebo exposes a volunteer to an incurable, lethal disease, then every volunteer must be counselled to use a condom. The outcome that is then measured is the rate of infection among the relatively small number of volunteers who fail to use condoms in the way they were counselled, but who continue to use microbicides. Those promoting this ethical framework feel they have shouldered their responsibility as investigators. Those critical of this framework suggest that they are merely shifting the possibility of using the placebo with the associated risk of death to those least able to organize their lives and who are socially, economically and educationally the most vulnerable, raising questions of both ethics and a biased sample (Potts 2000c).

In the case of microbicides, information on theoretical effectiveness will be of little value. No one suggests testing a new contraceptive against a placebo. There is a consensus that a new method needs to be tested against the 'gold standard'. Thus, a new IUD has often been compared with the existing Lippes loop, or more recently copper IUDs.

What is needed is information on use effectiveness. One rational, cost-effective and rapid way to proceed in this potentially life-saving technology is to randomly allot microbicides and condoms among carefully informed volunteers. On biological grounds condoms are likely to have a higher theoretical effectiveness than microbicides, but microbicides may be used more consistently, because the woman is in control. It is reasonable to suggest that the use effectiveness of condoms and microbicides may be similar, as has proved to be the case when diaphragms and spermicides were compared with condoms in controlling bacterial STDs. Once a single effective microbicide is developed, it could be used as the benchmark against which to test new and improved microbicides.

Abortion

All societies use a mixture of contraception and abortion to control family size. On average, every woman alive will have approximately one abortion before she reaches menopause. Obviously, in practice, some women have many abortions and others will have none, but there can be no doubting that abortion is common. It is also true that no nation has achieved replacement level fertility without broad access to safe abortion.

Abortion raises profound ethical problems and sincere people have different beliefs about when life begins. In the 16th century, Europe pulled itself apart over different beliefs over life after death. In the 21st century, the US is engaged in a political war—sometimes with real bullets—over the status of life before birth. It is time for Americans to return to their origins and to understand the value of religious tolerance. Given that several abortion providers have been murdered and that there are only a few thousand doctors doing even first-trimester operations in the US, vacuum aspiration abortion has become the first operation in the history of medicine where the operator is more likely to be killed for performing the operation than the patient is to die from the procedure.

Medical abortion

The anti-progestational agent, mifepristone (RU486), was the first successful therapeutic agent where the pharmaceutical company that developed it initially tried to take it off the market. Mifepristone was approved only on the orders of the French Minister of Health. It remains on patent, expensive and available in only a few countries. Clinically, it is always used with a prostaglandin to induce abortion. The most effective low cost and heat-stable prostaglandin has turned out to be misoprostol, sold under the brand name Cytotec by Pharmacia (Pharmacia took over the Searle Company, which developed Cytotec for treating stomach ulcers.)

In the 1970s, prostaglandins generated a great deal of interest as possible fertility regulating agents (Karim 1975),

but initial research was disappointing. Recently, it has been shown that misoprostol has a great many gynaecological uses, from controlling post-partum haemorrhage to inducing early abortion. (Goldberg *et al.* 2001). Even without mifepristone, misoprostol appears to be 70–85% effective in terminating an early pregnancy. When misoprostol alone fails to induce an abortion, it usually still induces uterine bleeding. In countries where abortion remains illegal, such bleeding is enough to take the women to hospital for treatment of miscarriage using dilatation and curettage or manual vacuum aspiration to empty the uterus. Where this drug is available, as it has been in Brazil and parts of Central America, women learn about its powers and the number of septic abortions decline dramatically.

Policy implications

The need for a global commodity purchasing agency

Given rising needs and limited resources, maximum benefit would be obtained from the donor community by dividing the limited money available between commodities and programmes at a level above the implementing agencies, such as the UNFPA. If these agencies are left to divide the resources there will always be a risk that they will cut back on commodities, rather than on staff or other aspects of programmes, such as conferences. It would be simple to launch a global commodity-purchasing agency that receives money from the donor communities and places orders for contraceptives and the drugs needed for reproductive health. A small team of professional people, placed anywhere in the world with modern communications, could do this job. They could be financed by imposing a small handling charge on every order.

Setting research priorities

Unless any new method can compete in cost with existing contraceptive pills and condoms, it is unlikely to reach a significant number of people. For example, it would be highly counterproductive to cancel orders for 10 million oral contraceptives to purchase 1 million male pills (Potts 1996). If a male pill reaches the market place, it is likely to cost considerably more than the female pill, whose development costs have largely been written off and where a large and profitable western market enables donors to bulk purchase these commodities at a remarkably low price. Given the very limited resources, research should not be supported beyond the purely laboratory work on animals, unless a plausible case can be made that the method, if developed, would cost less than 20–25 cents a month to use.

Appropriate regulations

The US FDA does not wish to be, and should not be made, the world gatekeeper in contraception and AIDS prevention research and development. For example, mifepristone in

small doses has been shown to be effective for emergency contraception, but attempts to make it available in several developing countries have been frustrated this year by the importing countries' insistence on European or US FDA approval. Scientific research is an unequivocally international enterprise. In particular, the development of microbicides would be greatly accelerated and many human lives would be saved, if knowledge were to be shared across frontiers, and if local researchers, for example in South Africa, were to develop their own clinical protocols and to identify their own ethical framework for conducting clinical trials.

Competition with antiretroviral drugs

In the west, and in the US in particular, those who are HIV positive have become well-organized advocates for their needs. There is no comparable body of lobbyists representing those who are about to be infected with HIV. Indeed, many of those likely to be infected in the near future, may well be at risk for the very reason that they deny their susceptibility to infection. In short, prevention is often overshadowed by the drama of new therapies.

Retroviral drugs, even if produced by non-western manufacturers at the lowest possible cost, are too expensive for large-scale use in low-income communities. The minimum cost for the supervision and supply of antiretroviral drugs in developing countries is going to be several hundred dollars a year, compared with a single digit per capita government expenditure on all aspects of health.

Thailand has a good record of setting evidence-based policies on HIV/AIDS. They can demonstrate a high degree of condom use among sex workers and a decline in STD rates. Nevertheless, a recent decision to fund a pilot project to treat 2000 HIV positive people with retroviral drugs (there are 1 million HIV positive people in Thailand) is swallowing half the total money set aside by the Ministry of Health for all aspects of AIDS prevention and care. Condom purchases by the government have fallen.

It is possible that the advent of retroviral drugs and efforts to use these in low-income settings will spark a second wave of HIV infections as budgets for the limited prevention programmes are eroded by demands to pay for therapies.

Conclusions

Anyone working on the international aspects of reproductive health and family planning should advocate more resources in this field. Had the money now being spent on AIDS in Africa been available in the 1980s, it might have had an impact. As it is, if the international community is serious about trying to slow the spread of HIV, it has to be recognized that it has become a multi-billion dollar problem.

If poor people are to be helped, commodity supplies must be secured. The international community must accept that

those living on one or two dollars a day cannot afford the full cost of modern methods of contraception and hundreds of millions of people will need some degree of subsidy. A serious crisis is arising in the money available to purchase the commodities needed for family planning and reproductive health. At this time of stalled or falling budgets, contraceptive purchases tend to get squeezed out. It is not difficult to calculate the number of people or to estimate the level of subsidy required. The figures are large, but there is no way of escaping them.

Like a ship weathering a serious storm, the decks may need to be cleared. In the last analysis, it may be more important to buy condoms and contraceptive pills than to conduct additional research on a possible new method of contraception, especially when it is shown that, even if the method were to succeed, it would be too expensive to buy in bulk.

The limited resources available should to be focused on areas of greatest need with the highest possibility of success. Microbicides stand head and shoulders above every other possibility. At a second level, I would rank the need for a non-surgical method of female sterilization, and it is regrettable that this area has become the subject of such polarized, ill-informed debate. Finally, we should continue to look for cost-effective ways of making incremental improvements in the methods that we do have.

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When I was doing embryological research in the Anatomy Department at Cambridge, Roger Short was the guru of young researchers engaged in studying mammalian reproduction. We became good friends and began to share a common interest in world population problems. Each of us helped introduced the other into our slightly different worlds of animal and human reproduction. When I went to the USA in 1978 as president and CEO of Family Health International (FHI), Roger was kind enough to join my board. During his 10 years as Chairman of the Board, and taking up many of his fountain of exciting ideas, the organization grew and entered new fields, such as research on lactation and pregnancy spacing. Roger also helped move FHI into the field of HIV/AIDS prevention, as well spending a year at the Global Program on AIDS in Geneva. My paper in this volume discusses the key issues affecting the provision of low-cost contraception in the developing world and, in so doing, pays homage to Roger's own contribution to this important field. The most wonderful personal gift that Roger has given me is a delight and fascination in Darwinian evolution. While we worked together at FHI we began our joint authorship of 'Ever Since Adam and Eve: The Evolution of Human Sexuality'. Because of Roger, evolu-

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