CONTRACEPTIVE UPDATE

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I.
INTRODUCTION

Worldwide, there has been a dramatic increase in contraceptive use over the past thirty-five years. The number of couples using systems of fertility control (the prevalence rate) has increased more than tenfold. In developing countries, the number of contraceptive users increased from under 30 million before 1960, to almost 400 million in 1996. The percent of couples in the reproductive age group using contraception has increased from 8 percent to over 50 percent and is continuing to rise in most of the developing world.[1]

Consequently, fertility has been steadily declining. In developing countries, the number of children a woman will have in her lifetime has decreased from approximately six in the 1960s, to less than four today.[2] Most industrialized countries are at, or even below, replacement levels of fertility.

National surveys have provided detailed information on the methods that people choose to prevent pregnancy. Around the world, contraception is practiced chiefly by women. Surgical sterilization, primarily tubal ligation, ranks first among methods chosen by American couples.[3] Oral contraception is the most widely used reversible method.[4] In other countries, the pattern is different. In Sweden and France, the intrauterine device (IUD) is the preferred reversible method.[5] In Japan, modern hormonal methods for women are not openly available, and the predominant method of birth control is the condom.[6] Given the high failure rate of condom use, this means that many women ultimately must resort to having an abortion. Over one quarter of pregnancies in Japan are voluntarily terminated.[7]

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1. Sheldon J. Segal, *Trends in Population and Contraception*, 25 ANNALS OF MED. 51, 51-56 (1993).

2. U. N. DEP'T OF ECONOMIC & SOCIAL INFORMATION POLICY AND ANALYSIS, POPULATION DIVISION, WORLD POPULATION PROSPECTS, THE 1994 REVISION 107 (1994).

3. SUSAN HARLOP, K. KOST, J.D. FORREST, PREVENTING PREGNANCY, PROTECTING HEALTH: A NEW LOOK AT BIRTH CONTROL CHOICES IN THE UNITED STATES 30-31 (1991).

4. Nancy J. Kim, *J&J Back in IUD Business; GynoPharma Sale Is in the Works*, RECORD, Aug. 3, 1995, at B1.

5. Sheldon J. Segal, *Contraceptive Development and Better Family Planning*, 73 BULL. N.Y. ACAD. MED. 92, 92-95 (1996).

6. Ed Gutierrez & Guy Netley, *Japan's Ban on the Pill Seems Unlikely to Change*, 348 LANCET 886 (1986).

7. Martha Shirk, *Japan May Allow Woman to Use Pill Finally*, ST. LOUIS POST-DISPATCH, March 18, 1997, at 3A.

In Latin America and Africa, male use of contraception is negligible.[8] In India, on the other hand, where surgical sterilization is the chief method used to prevent pregnancy, there was a period in the recent past when vasectomy was emphasized.[9] Presently, most sterilization operations are tubal ligations. Male methods account for about 15 percent of the contraceptive prevalence rate, which has climbed in recent years to about 40 percent of couples.[10] Some provinces of China rely heavily on vasectomy. Nevertheless, in the developing world, as well as in most industrialized countries, when couples wish to prevent pregnancies, contraception usually involves methods that women use.

Even with the availability of so-called modern methods, contraceptive failure is not uncommon. Surgical sterilization by tubal ligation, for example, usually assumed to be the gold standard with respect to effectiveness, does not always succeed. During the first year after such procedures, about four women per thousand will become pregnant.[11] Among reversible methods, failure rates for one year of typical use are lowest with copper-carrying IUDs or progestogen-releasing intrauterine systems, contraceptive implants, and injectable progestogens (in each case, less than 1 percent). The conventional pill, the mini-pill, and inert plastic IUDs fail at a rate of 3-5 percent. Failure rates with use of the condoms, vaginal sponges, spermicides, cervical caps, diaphragms, periodic abstinence and withdrawal range from 8.3 to 28 percent.[12]

In order to calculate the number of pregnancies that result from contraceptive failure, one need only multiply the number of users of each method by its annual failure rate. Of the 3.2 million pregnancies that occur annually in the United States, fully one half occur while a couple is using a method of contraception. Studies show that about half of these are carried to term and the other half are terminated by abortion.[13]

Presently available methods of contraception are profoundly inadequate. Failure rates are unacceptably high and side effects are often severe. This article surveys the current landscape of contraceptive technology in an effort to illustrate the need for more research in this area.

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8. Jan Gehorsham, *Now Contraception Gains as World's Attitudes Change,* ATLANTA J. & CONST., July 2, 1991, at B3.

9. Arthur Golden & Matt Miller, *Mexico Puts Away the Scalpels to Promote Male Sterilization,* SAN DIEGO UNION-TRIB., Sept. 11, 1994, at A27.

10. INTERNATIONAL INSTITUTE FOR POPULATION SCIENCES, BOMBAY, NATIONAL FAMILY HEALTH SURVEY (MCH AND FAMILY PLANNING): INDIA 49-50 (1994).

11. ROBERT A. HATCHER ET AL., CONTRACEPTIVE TECHNOLOGY 380-81 (16th ed. 1994).

12. Elise F. Jones & Jacqueline D. Forrest, *Contraceptive Failure Rates Based on the 1988 National Survey of Family Growth,* 24 FAM. PLAN. PERSP. 12, 14 (1992).

13. J.D. Forrest, *Epidemiology of Unintended Pregnancy and Contraceptive Use,* 170 AM. J. OBSTETRICS & GYNECOLOGY 1485, 1485-88 (1994).

II.
CONTRACEPTIVE ADVANCES: 1960-1996

Since the initial wave of contraceptive innovations in the 1960s, several major advances have been made in contraceptive technology. Most notable among the new products introduced have been the copper-bearing IUDs, the levonorgestrel-releasing intrauterine contraceptive system, the five-year subdermal contraceptive, and injectable progestogens.

The Copper T 380A, the most effective copper-bearing IUD, and the Copper 7 IUD were marketed initially by the G.D. Searle Co.[14] Within months after Searle was acquired by the giant chemical corporation Monsanto in 1985, both of these IUD products were pulled from the market.[15] Monsanto executives cited as the reason for this decision the mounting cost of defending law suits and their unwillingness to risk the entire assets of the corporation for the sake of products which, though medically safe,[16] were vulnerable to litigation and added little to total corporate revenues. Ortho Pharmaceutical of New Jersey, which also distributed a Copper T IUD, followed Monsanto out of the U.S. market.[17] Consequently, IUDs virtually disappeared from the United States for several years,[18] until a single-product company (GynoPharma. Inc.) was formed to market the Copper T 380A. Because distribution has been limited, IUDs are used by relatively few American women.[19]

IUDs are the birth control method of choice in many countries. IUDs are used by 30 percent of women using contraceptives in Sweden and more than 50 percent of women using reversible contraceptives in China and Cuba.[20] IUDs are appealing because they are simple to use, inexpensive, and remarkably effective. A World Health Organization (WHO) study found that the pregnancy rate associated with the Copper T 380A is below two pregnancies per 1000 women per year, a success rate that is equivalent

14. THE POPULATION COUNCIL, THE COPPER T 380A INTRAUTERINE DEVICE (1992) (on file with author).

15. Peter L. Riley, *The Copper 7 Intrauterine Device: Survey of a Decade of Litigation,* J. HEALTH & HOSP. L., Aug. 1989, at 240.

16. There is substantial epidemiological evidence that American women, living in stable monogamous relationships, have no increased risk of pelvic inflammatory disease when they use an IUD. N. C. Lee, G.L. Rubin, R. Boruck, *The Intrauterine Device and Pelvic Inflammatory Disease Revisited: New Results from the Women's Health Study,* 72 OB. & GYN. 1-6 (1988).

17. *Searle Withdraws from IUD Market,* AM. FAM. PHYSICIAN, Mar. 1996, at 17.

18. *Id.*

19. C. Huntinton Kooiker & F. Douglas Schutchfield, *Barriers to Prescribing the Copper T 380A Intrauterine Device by Physicians,* W. J. MED., Sept. 1990, at 279.

20. Sheldon J. Segal & W.P. Mauldin, *Contraceptive Choices: Who, What, Why?, in* FERTILITY REGULATION TODAY AND TOMORROW 305, 313 (E. Diczfalusy and M. Bygdeman eds., 1987).

to surgical sterilization.[21] The WHO also has reported that the Copper T 380A maintains its effectiveness for ten years.[22]

Another intrauterine contraceptive system gaining popularity in European countries is the levonorgestrel-releasing intrauterine system.[23] It is as effective as the Copper T 380A, and some studies have shown that it possesses the added advantage of reducing the incidence of sexually transmitted disease. The levonorgestrel-releasing intrauterine system has a life span of five years.

The Norplant system, a long-acting contraceptive that releases a steroid hormone from an elastomer polymer, has been marketed in the United States since 1991. The subdermal Silastic capsules slowly release the synthetic progestogen levonorgestrel, establishing a blood level above the threshold required to inhibit ovulation and preventing sperm passage through a thickened cervical mucus. An effective blood level can be maintained for at least five years, although a user may remove the capsules at any time. The effectiveness of Norplant is comparable to that of surgical sterilization. The main side effect of Norplant is irregular vaginal bleeding.[24] By 1997, Norplant had been registered in 26 countries and was being used by over 8 million women in 44 countries.[25]

Shortly after the FDA announced its approval of Norplant, the press and some legislative bodies raised the specter of "social engineering." Editorial writers were quick to suggest that women (particularly adolescents) receiving welfare payments from government might be offered incentives to accept Norplant to avoid unwanted pregnancy.[26] Legislative proposals similar to those written of in the press were introduced in several states. None of the proposals were enacted. However, a state judge in California offered a woman convicted of child abuse the choice of Norplant insertion or prison. The researchers who developed Norplant unequivocally and publicly opposed the aforementioned uses of Norplant.[27] Nevertheless, Norplant became the target of criticism by consumer, feminist and human rights advocates who perceived with trepidation the potential for Norplant to be used in a coercive manner by the state.

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21. World Health Organization, Special Programme of Research, Development and Research Training: Task Force on Safety and Efficacy of Fertility Regulating Methods, *The Tcu 380A, Tcu 220, Multiload 250 and Nova T IUDs at 3, 5, and 7 Years of Use—Results from Three Randomized Multicentre Trials*, 42 CONTRACEPTION 141-69 (1990).

22. The Population Council has reported that the Copper T 380A is effective for up to 12 years. F. Gary Cunningham & J. Whitridge Williams, Obstetrics § 61, at 1368 (20th ed. 1997).

23. T. Luukkainen & J. Toivonen, *Levonorgestrel-Releasing IUD as a Method of Contraception with Therapeutic Properties*, 52 CONTRACEPTION 269, 269-76 (1995).

24. THE POPULATION COUNCIL, NORPLANT CONTRACEPTIVE SUBDERMAL IMPLANTS: MANUAL FOR CLINICIANS (1990).

25. THE POPULATION COUNCIL, ANNUAL REPORT (1997) (on file with author).

26. *Norplant and the Right to Have Children*, BALTIMORE SUN, Apr. 25, 1991, at A15.

27. Sheldon J. Segal, *The Uses of Norplant*, BALTIMORE SUN, Feb. 19, 1993, at A10.

Medical and scientific findings regarding the safety and effectiveness of Norplant have been affirmed and reaffirmed by both the FDA and the WHO. Norplant also has received strong backing from an expert committee of the American Society for Reproductive Health, the nation's largest professional organization of reproductive health professionals.[28] Despite these findings and recommendations, Norplant nevertheless has become the target of product liability litigation in the United States.[29] Although none of the thousands of claims that have been filed against the distributor of Norplant, Wyeth-Ayerst Laboratories, and physicians who have provided the Norplant system has been upheld in court, the avalanche of litigation threatens the survival of the product. The adverse publicity associated with the lawsuits has had a dramatic effect on Norplant use in the United States and has influenced behavior in other countries. According to a *New York Times* report, sales in the United States have dropped from a peak level of about 5000 per week to less than 500.[30] In the United Kingdom, after an initial burst of consumer interest immediately after the introduction of Norplant in 1993, the level of sales has declined. After seeking and obtaining regulatory agency approval in France, Wyeth-Ayerst International has postponed introduction Norplant in that country.

As American use of Norplant has declined, interest in injectable contraceptives has risen. Contraceptive preparations based on injectable forms of synthetic progestogens are not new, but they have experienced a revival in recent years. Depo-Provera, an injection of the progestogen medroxy-progesterone acetate that lasts for three months, finally was approved for use as a contraceptive in the United States in 1992, after having been used in over ninety other countries for decades.[31]

III.
NEW SUBDERMAL CONTRACEPTIVES

Even as use of the Norplant system declines in some countries, research on subdermal contraceptives is progressing. The most advanced research project is the levonorgestrel 2-rod system.[32] The 2-rod system has two advantages over the current Norplant system. The first is that the same contraceptive effect can be achieved with two subdermal inserts instead of the conventional six used in the Norplant system. Reducing the

28. AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE, STATEMENT ON NORPLANT (1995).

29. Alicia Ault Barnett, *US Norplant Product Liability Suits Fail*, 349 LANCET 708 (1997).

30. Gina Kolata, *Will the Lawyers Kill Off Norplant?* N.Y. TIMES, May 28, 1995, § 3, at 3.

31. Joseph Anthony, *Choosing a Contraceptive: What's Best for You?*, AM. HEALTH, Apr. 1994, at 68.

32. George F. Brown, *Long-Acting Contraceptives: Rationale, Current Development, and Ethical Implications*, HASTINGS CENTER REP., Jan. 1995, at S12.

number of subdermal inserts results in easier insertion and removal procedures, and reduces the incidence of any attendant complications. The second advantage is that the levonorgestrel 2-rod is simpler to manufacture than Norplant.

The two-rod system has been studied extensively and has been proven to be as effective as the original Norplant system.[33] The FDA has ratified a modification of the original Norplant new drug approval (NDA) that authorizes the sale of the levonorgestrel 2-rod system. When introduced, the levonorgestrel 2-rod system can be expected to renew interest in the use of subdermal contraception.

There are three additional subdermal insert systems under development that attempt to simplify the insertion and removal procedure by reducing the insert number down to one. One of these is the Uniplant method. The active progestogen in Uniplant, nomegestrol, has an excellent record for safety. As a subdermal contraceptive, it is used for one year before being replaced. Another system called Implanon currently is being tested by a company in Holland. Implanon prevents contraception by inhibiting ovulation. The product is designed to be effective for up to three years. An issue that needs to be researched further with regard to Implanon is the pattern of menstruation-like bleeding that some women experience while using the product. The third single-rod product is the Nesterone system.[34] It is designed to last for two years.

IV.
VAGINAL CONTRACEPTIVES

One method of vaginal contraception is the vaginal ring. Vaginal rings are an appealing contraceptive option because they can be inserted and removed without the assistance of a physician. Vaginal ring contraception has been under investigation for over 25 years.[35] There has been commercial interest in bringing a vaginal ring contraceptive to market, but this has not yet materialized.

The conventional oral contraceptive is also effective when used vaginally. A large international study demonstrated that two popular brands of "the pill," used vaginally on the usual dosage schedule, are just as effective as when taken by mouth.[36] This procedure has the advantage of

33. S.E. Olsson, *Contraception with Norplant Implants and Norplant-2 Implants (2 Covered Rods): Results from a Comparative Study in Sweden*, 37 CONTRACEPTION 61, 61-73 (1988).

34. S. Diaz, V. Schiappacasse, M. Pavez, A. Zepeda, A.J. Mooyoung, A. Brandeis, P. Lahteenmaki, H.B. Croxatto, *Clinical-Trial with Nesterone Subdermal Contraceptive Implants*, 51 CONTRACEPTION 33, 33-38 (1995).

35. D.R. Mishell, M.Talas, A.F. Parlow, D.L. Moyer, *Contraception by Means of a Silastic Vaginal Ring Impregnated with Medroxyprogesterone Acetate*, 107 AM. J. OB. & GYN. 100, 100-07 (1970).

36. Elsimar M. Coutinho, F.Alvarez, J.C. DeSouza, A.R. DaSilva, O.M. De Acosta, V. Brache, J. Garza Flares, L. Vasquez-Estrada, R. Santa, S. Bassol, *Comparative Study on the*

by-passing the liver when the drug first enters the bloodstream. Women who experience nausea or gastric upset when using an oral contraceptive can benefit from using the pill vaginally.[37] A Brazilian company is seeking authorization to market the first vaginal pill. The company has received preliminary notification of approval from the Brazilian Ministry of Health.[38]

V.
A MORNING-AFTER PILL

Although most people are unaware of the fact, effective post-coital contraception methods have been available in the United States for several decades. Post-coital contraception has been called America's best kept secret. Until recently, there was no commercial interest in post-coital contraception product development and few health care providers were aware of the effectiveness of "off-label" use of existing products for this purpose. There is now an emerging interest in post-coital contraception.[39]

During the 1960s, orally active estrogenic products were shown to initiate menstrual-like bleeding when taken within a few days after unprotected intercourse. The product that women used most frequently to prevent contraception after intercourse was diethylstilbestrol (DES).[40] One study conducted at a university student health service, found that no pregnancies occurred among 1,000 young women who took DES within six days of unprotected intercourse.[41] The main disadvantage of DES was that it caused severe nausea and vomiting.

In the 1970s, a study demonstrated that a high dose of the conventional pill, taken up to 72 hours after intercourse, could prevent pregnancy.[42] This method has been adopted mainly by emergency room physicians treating rape victims and by student health services on university campuses. Companies marketing oral contraceptives in North America have been unwilling to label their products to indicate this possible use. This is true even though identical pills have been approved and marketed for post-coital use in several European countries. In the United States, the

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Efficacy and Acceptability of Two Contraceptive Pills Administered by the Vaginal Route: An International Multicenter Clinical Trial, 53 Clinical Pharmacology & Therapeutics 65, 65-72 (1993).

37. Nausea may not be fully eliminated. C.L. Cook, L.J. Wiist, S.L. Kraft, *Pregnancy Prophylaxis: Parental Postcoital Estrogen*, 67 OB. & GYN. 331, 331-4 (1986).

38. *Vaginal Contraceptive Pill Developed in Brazil*, PHARMACEUTICAL BUS. NEWS, Oct. 5, 1993.

39. C. Ellertson, *History and Efficacy of Emergency Contraception:Beyond Coca-Cola*, 28 FAM. PLAN. PERS. 44, 44-48 (1996).

40. Marion Block & Marvin C. Rulin, *Managing Patients on Oral Contraception*, 33 AMER. FAM. PHYSICIAN 154, 154-168 (1985).

41. L. Kuchera, *Post-coital Contraception with Diethylstilbestrol*, 218 JAMA 562, 562-563 (1971).

42. A.A. Yuzpe, and W.J.Lancee, *Ethinylestradiol and dl-norgestrel as a Postcoital Contraceptive*, 28 FERTILITY AND STERILITY 932, 932-936 (1977).

FDA convened a panel of experts to discuss post-coital use of birth control pills. The panel unanimously approved the conclusion that this birth control method is both safe and effective.[43] None of the companies with appropriate products on the market, however, have taken steps to describe this use on their product's labels, and no company has come forward to sponsor a new drug application.[44]

Studies of the anti-progesterone mifepristone as an emergency contraceptive are extremely encouraging.[45] The compound is as effective as the high-dose combination pill method and causes far fewer side effects. There is evidence that some progestogens, without estrogen, can have this same advantage.[46] There is a progestogen-only product on the market in some countries and interest in this approach is beginning to intensify.

VI.
A Pill to Terminate Early Pregnancy

An adequate level of progesterone in a woman's blood is necessary to establish and maintain pregnancy. Progesterone antagonists that occupy progesterone receptor sites on target cells prevent conception.[47] The progesterone antagonist mifepristone (RU 486) has been used to induce abortions. When combined with a drug that induces contractions, RU 486 has a success rate exceeding 95 percent.[48] The combination is highly effective even up to nine weeks after the last menstrual period.[49]

Political opposition to RU 486 in the United States has prevented its availability as a medical abortifacient in this country. The French company that sells RU 486 sold all of its North American rights because it did not want to be at the center of the controversy. An American clinical trial, however, has been completed and an NDA is pending before the FDA. The relevant advisory committee at the FDA has recommended approval and the agency itself has declared the product approvable. Final approval could occur as soon as arrangements for manufacturing and labeling the drug are completed.

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43. Joanne Kenen, *FDA Wants Applications on "Morning-After Pill"*, Reuters World Service, Feb. 24, 1997.

44. Tamar Lewin, *An Improved Morning-After: US Agency Spotlights New Use for Birth Control Pills,* Int'l Herald Trib., July 2, 1996.

45. A. Glasier, K.J. Thong, M. Dewar, M. Mackie, D.T. Baird, *Mifepristone (RU 486) Compared with High-dose Estrogen and Progestogen for Emergency Post-coital Contraception* 327 New Eng. J. Med. 1041, 1041-1044 (1992).

46. E. Kesseru, *The Hormonal and Peripheral Effects of d-Norgestrel in Post-coital Contraception,* 10 Contraception 411, 411-24 (1974).

47. Sheldon J. Segal, *Mifepristone (RU 486)*, 322 New Eng. J. Med. 691, 691-93 (1990).

48. M. Bygdeman & M-L Swahn, *Progesterone Receptor Blockage: Effect on Uterine Contractility and Early Pregnancy*, 32 Contraception 45, 45-51 (1985).

49. *Id.*

A second abortion pill procedure has begun development. The pill contains the abortifacient drugs methotrexate and misoprostol.[50] Methotrexate has been used at low doses for the non-surgical management of some ectopic pregnancies.[51] Now the abortifacient use, discussed over thirty years ago but never pursued because of concern over potential toxicity, is being reconsidered and is currently under investigation by clinics of the Planned Parenthood Association in the United States.

The main advantage of this procedure would be that the two drugs employed are already approved and are used for other purposes. Therefore, they could be prescribed for "off-label" use without further FDA authorization. The main disadvantage is the prolonged time required to initiate and complete a medical abortion by this procedure. In addition, health care providers may be reluctant to prescribe an off-label purpose that might be difficult to defend in the event of malpractice litigation.

VII.
A CONTRACEPTIVE VACCINE FOR WOMEN

Efforts to develop a contraceptive vaccine are ongoing. The most comprehensive program toward the development of a contraceptive vaccine is based on the use of a pregnancy hormone, human chorionic gonadotropin (hCG).[52] The underlying rationale is to develop antibodies that will interfere with or prevent the action of hCG, which is essential for the establishment and maintenance of an early pregnancy. Without the action of hCG, the uterine lining loses its progestational support and, at the time of the next expected menses, sloughing and menstrual flow occur whether or not the preceding ovulatory cycle was fertile. A clinical study was completed in India in 1992. Pregnancies did not occur in women who developed antibody titers that exceeded the threshold adequate to neutralize the hCG of early pregnancy. A report of this work was published in the United States in 1994 in the Proceedings of the National Academy of Sciences,[53] but it has failed to stimulate commercial interest or further scientific research.

The Indian vaccine induces a temporary immunization. Frequent booster shots are required to maintain antibody levels above the threshold

50. Mitchell Creinin & Phillip Darney, *Methotrexate and Misoprostol for Early Abortion*, 48 CONTRACEPTION 339, 339-348 (1993).

51. Toshinobu Tanaka et al., *Treatment of Interstitial Ectopic Pregnancy with Methotrexate: Report of a Successful Case*, 37 FERTILITY & STERILITY 851, 852 (1982).

52. U.S. Deshmukh, G.P. Talwar & S.K. Gupta., *Antibody Response Against Three Epitopic Domains on Human Chorionic Gonadotropin (hCG) in Women and Rodents Immunized with a Beta hCG-Based Immunocontraceptive Vaccine*, 14 J. CLIN. IMMUNOL. 162-8 (1994).

53. G.P. Talwar et al., *A Vaccine that Prevents Pregnancy in Women*, 91 NAT'L ACAD. SCI. PROC. 8532, 8532-36 (1994).

required for effective hCG neutralization. This feature is sometimes overlooked by critics who are concerned about the potential irreversibility of an hCG vaccine. Work is needed to develop a product that will produce longer immunization periods.

Research on the development of contraceptive vaccines has become politically controversial. Some feminist groups and women's health advocates have expressed grave concern about the potential for misuse of an anti-fertility vaccine. They fear its involuntary or coerced application in order to sterilize women forcibly. Given this perceived potential for abuse, they question the ethics of working on contraceptive vaccines and call for restraint on the part of scientists and organizations that support scientific research. At least one start-up biotechnology company that initially undertook a development program for an anti-hCG vaccine has discontinued its investment in the project.

VIII.
A MALE PILL

The most extensive clinical experience with a systemic male contraceptive has been accumulated with a pill containing gossypol, the yellow pigment found in cottonseed. First tested as a male contraceptive in the 1970's by a team of Chinese investigators, the idea sprung from the serendipitous observation that uncooked cottonseed oil (which contains gossypol) had been responsible for an epidemic of infertility in a rural area in China.

The anti-fertility effect of gossypol has been achieved without lowering plasma testosterone levels so that hormone replacement therapy to maintain libido and other secondary sexual characteristics is not required, as it is with other approaches to male contraception.[54] Several studies on the effect of gossypol have raised hypokalemia (reduction in blood potassium levels) as a concern,[55] but others have produced no evidence of this side effect.[56] The more significant problem with gossypol inheres in its reversibility, which appears to decrease with higher doses and longer duration of use.[57] Even though most men who use gossypol for a year or longer are able to resume spermatogenesis after cessation of treatment, it is not possible to assure an individual user that fertility will return within a specified time period. Accordingly, gossypol may have application as a medical alternative for men seeking surgical vasectomy. An international, multicenter trial is being carried out to test the use of gossypol for this purpose.

54. National Coordinating Group for Male Contraceptives, *Gossypol—A New Antifertility Agent for Males*, 4 CHIN. MED. J. 417, 417-28 (1978).

55. C. Wang & R.T. Yeung, *Gossypol and Haypokalaemia,* 32 CONTRACEPTION 237, 237-52 (1985).

56. Elsimar M. Coutinho, J.F. Melo, I. Barbosa, S.J. Segal, *Antispermatogenic Action of Gossypol in Men*, 42 FERTILITY & STERILITY 424, 424-30 (1984).

57. Gossypol also poses a toxicity risk. James Craig, *Firm Says Male Birth-Control Pill Safe,* Reuters Financial Service, Aug. 28, 1996.

A Brazilian company has achieved industrial levels of extraction and purification of gossypol from cotton plants.[58] This product is undergoing laboratory and clinical testing for effectiveness and safety.

IX.
A Male Implant System

Male implants are effective at preventing spermatogenesis, but the side effects are substantial. Men using such implants require androgen replacement therapy to maintain libido, potency and other secondary male sex characteristics, and this treatment can interfere with the implants' inhibatory effect on spermatogenesis.[59] Potential toxicity and metabolic issues further complicate the development of appropriate androgen replacement therapy. Unlike estrogens and progestogens, androgens that can be used orally are not available. When androgen therapy is used for the treatment of sexual dysfunction or hypogonadism, frequent intra-muscular injections are required. Although studies with alternative delivery systems suggest that injectable preparations that would last for 6 months may be feasible, no such preparations are commercially available.

X.
A Male Injectable Contraceptive

It is unlikely that current research into male injectable contraceptives will lead to the development of an acceptable and practical system for male contraception. Steroidal suppression of gonadotropins has been extensively studied as an approach to male contraception; however, some basic uncertainties remain.[60] The daunting challenge when using an androgenic steroid to suppress gonadotropins, is to establish a dose that will remain within normal limits for all men, without reaching hyper-androgenic levels in some.

Any method that risks exceeding physiological blood levels would be viewed with skepticism because of the critical role of androgens in cardiovascular events and prostate stimulation.[61] It is hard to visualize the acceptability of a contraceptive product based on the use of the same hormones that disqualify athletes from international competition. One need only observe the controversy aroused by the approval of occasional

58. *Brazil: Male Contraceptive Pill,* Chemical Business News Base, Nov. 15, 1996, *available in* Reuters Textline.

59. E. Michel et al., *Failure of High-Dose Sustained Release Luteinizing Hormone Releasing Hormone Agonist (Buserelin) Plus Oral Testosterone to Suppress Male Fertility*, 23 Clin. Endocrin. 663, 663-75 (1985).

60. B.N. Barwin, *Recent Advances in the Pharmacologic Regulation of Fertility in Men,* 119 Can. Med. Assoc. J. 757, 757-59 (1978).

61. Population Briefs: Rep. on Population Council Res., Male Methods Under Investigation, Jan. 1995 (on file with author).

medical use of marijuana to predict the outcry that would greet the suggested contraceptive use of a controlled substance.

XI.
A Vaccine For Men

Scientists are currently exploring immunologic means to suppress male fertility. One line of research is based on a vaccination accompanied by androgen replacement therapy to ensure normal male secondary sex characteristics and functions. Some men with prostate cancer have been safely treated with such a vaccine, but the preliminary studies have not addressed the issue of androgen replacement, which is essential to a regime of controlling fertility in normal men.[62]

The role of the pituitary hormone FSH in stimulating the production of sperm by the testis is not fully understood, although it is known that it contributes to this process. Some studies are attempting to develop an anti-FSH vaccine, which might avoid the problems associated with suppression of testicular hormones.[63]

XII.
Percutaneous Vasectomy

Simplification of the operative procedure may enhance the popularity of vasectomy. There are short-term complications of the conventional operation, which include hematoma, infection, epididymitis and spontaneous recanalization of the vas. A recent development perfected by surgeons in China has been popularized as the "no-scalpel" vasectomy. The scrotal skin is punctured at the midline and the vas is visualized through the tiny puncture hole. This procedure minimizes bleeding and other side effects. No sutures are required to close the entry site. In addition to its widespread use in China, the "no-scalpel" vasectomy procedure has been in use in the United States since 1986.[64]

XIII.
Conclusion

Despite the substantial scientific and political obstacles, government agencies and non-profit organizations have funded significant contraceptive research. This work, however, cannot yet be characterized as fully successful. There remains a dire need for viable contraceptive technology.

62. The Population Council, *supra* note 25.

63. *See, e.g.*, N.R. Moudgal et al., *Responsiveness of Human Male Volunteers to Immunization with Ovine Follicle Stimulating Hormone Vaccine: Results of a Pilot Study*, 12 Hum. Reprod. 457, 457-63 (1997).

64. L.E. Davis & M.D. Stockton, *Office Procedures: No-Scalpel Vasectomy*, 24 Prim. Care 433, 433-61 (1997); S.Q. Li et al., *The No-Scalpel Vasectomy*, 145 J. Urol. 341, 341-44 (1991).

The problems are daunting, and they can only be resolved if the private and public sectors invest heavily in vigorous research.[65]

65. Although beyond the scope of this article, it bears emphasis that men and women throughout the world face a growing risk of infection with HIV and other sexually transmitted diseases. Vaginal sheaths, vaginal virucidal creams or gels, medicated condoms and other means to reduce the risk of infection urgently need greater attention. This is a complicated line of research that cannot depend on laboratory results alone. Ultimately, clinical trials will be required, and the design of such trials present daunting challenges of ethics as well as pharmacology. Some explorations are in progress, but this line of research should receive a much higher allocation of resources. *See, e.g.*, C.J. Elias & C. Coggins, *Female-Controlled Methods to Prevent Sexual Transmission of HIV*, 10 AIDS S43 (1996).