Contraception—A Look Forward, Part I: New Spermicides And Natural Family Planning

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Abstract: **The number of contraceptive choices for couples in the United States has declined in recent years, as has public and corporate sponsorship of the development of new contraceptives. Nevertheless, there are many possibilities for future birth control methods under active investigation. Six of the most interesting of these are described in this three-part review. Part I examines new spermicides and natural family planning.**

Current spermicides, though popular, are limited in number, have strict requirements for effective use, and cause a number of side effects. Investigational agents promise greater efficacy, simpler use, longer duration, and fewer adverse effects.

Natural family planning methods are the only ones acceptable to a large number of couples, but they are seriously flawed by unacceptably low use-effectiveness and intensity of training requirements. Home chemical assays for biological markers of the fertile period, including urinary hormones and cervical enzymes, may improve the acceptability and effectiveness of natural family planning. (J Am Board Fam Pract 1991; 4:33-46.)

Of the 860 million couples of reproductive age in the world, only about 43 percent use an effective, modern form of contraception.[1] Not surprisingly, most nonuse is in the developing world, where the rate of use is only 10 to 30 percent. Contraceptive methods chosen most frequently are, in descending order, surgical sterilization, intrauterine devices (the Chinese use about 71 percent of those produced), and oral contraceptives.[1] In addition, between 40 and 45 million abortions are performed worldwide each year, about half of which have followed contraceptive failure.[2] In all countries, actual family size is almost universally greater than desired family size.[3] Furthermore, the number of deaths resulting from pregnancy is a greater problem than is generally appreciated. This fact has been dramatically phrased by Potts and Bhiwandiwala:

> . . . 99 percent of all maternal deaths occur in Third World countries . . . . More women die in one month in India from pregnancy, childbirth, and illegal abortion than die in the whole of North America, Eastern or Western Europe and Scandinavia, Japan, Australia and New Zealand in *one year*. At a global level, maternal mortality is equivalent to crashing a jumbo jet full of parturient or aborting women every 5 hours, day after day.[3 p 4]

Clearly, there is a need for more effective and acceptable methods of contraception and for better promotion and distribution of those methods.

Despite this, as Mastroianni and colleagues observed, "Since the introduction almost three decades ago of the pill and the IUD, no fundamentally new contraceptive method has been introduced in the United States."[4] The exponential population growth of recent years has been accompanied by a *decrease* in constant-dollar expenditure for contraception research and development in this country.[5] An estimated 75 percent increase in the funding of the eight major public-sector contraception research and development organizations is needed to pursue the new methods likely to be useful in the foreseeable future.[6] These organizations support approximately 70 projects, each one receiving about $1 million per year. The cost, however, of bringing a new drug to market may be as high as $125 million.[7]

The decline in contraceptive research funding has been particularly steep in the private sector. Most United States and European pharmaceutical firms have abandoned the field entirely. Certainly, the threat of major liability, which has

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reduced the potential profitability of a new drug or device, has dampened their interest.[8] Despite serious legislative proposals to reduce the impact of this problem on birth control development,[4] Lincoln and Kaeser[7] have argued convincingly that numerous other factors, such as a shortage of trained researchers and opposition by both feminist and antiabortion groups, make it unlikely that liability reform alone will attract drug companies back to contraceptive research.

Among these other factors, though, is not a lack of imagination. Even incomplete lists of proposals[6] provide an impressive breadth of strategies for interrupting every known step in human fertility, and the number of possible points of attack increases with our understanding of reproductive physiology. (Barnes, for example, offers a summary of recent research on the process of fertilization.[9])

In this review, rather than briefly examining each of the dozens of new methods that have been proposed, I have selected six methods to discuss in depth. Before proceeding to these topics, however, it is worth mentioning the following large areas of promising research that will not be covered in detail in this paper:

1. *New sterilization techniques.* These include methods that are more readily reversible than standard operations (e.g., the Shug device for men[10] and the Filshie clip for women[11]) and methods that can be performed without an incision (e.g., chemical occlusion of the vas deferens[12] and tubal occlusion with silicone plugs[13]). All these techniques should receive increased acceptability.
2. *Delivery systems for female hormones.* Many possible methods of administration exist for conventional hormonal preparations (progestins with or without estrogens). These include a variety of subcutaneous implants, vaginal rings, and depot injections.[14-17] Such devices are likely to be the most important new birth control methods in much of the world for many years. Part III of this series will consider brain-specific estrogen delivery.
3. *Immunologic methods.* Active or passive immunization shows much promise.[18,19]
4. *Plant-derived compounds.* The World Health Organization has outlined its strategy for development of useful contraceptives from plant material.[20] Of the more than 5000 plants reported to have fertility-regulating properties, a high-priority list of 365 has been selected for effectiveness screening, purification of active principles, and toxicology studies. The most advanced of these, gossypol, is reviewed in Part II of this series. The literature has been broadly reviewed by Farnsworth, et al.[21] and Kong, et al.[22]
5. *Spermatogenesis inhibitors.* These include both hormonal and nonhormonal compounds. A collection of thorough reviews of these agents is found in Zatuchni, et al.[23]
6. *Gonadotropin-releasing–hormone (GnRH) analogues.* Dozens of GnRH agonists and antagonists have been synthesized and tested in both male and female animals.[24-26]

Ideal contraceptive methods would be failsafe, have no toxicity or subjective side effects, require only one decision for long-term use, be immediately reversible, cost nothing, require no health professional, be usable by men or women, and prevent transmission of microbial diseases. Obviously, no current or imagined method meets all of these criteria; compromises must be made in some of the desirable features. All of the methods under investigation are designed to improve on one or more of the defects of current contraceptives. The main goal of contraceptive research, however, is not the discovery of the "philosopher's stone" of a single perfect method but, rather, the production of a wide variety of effective methods to allow better matching of features for each couple.

With this objective in mind, this review examines six of the most interesting contraceptive methods proposed. Part I deals with two examples of improvements on current birth control methods: new spermicides and natural family planning. Part II reviews two compounds that are or have been in use in other countries: mifepristone and gossypol. Finally, Part III introduces clinicians to two examples of methods that are radically different from any currently available: inhibin and brain-specific estrogen delivery. My focus, where possible, is the clinical

applicability of the methods rather than the basic science behind them.

Statistics Used in This Review

"Method effectiveness" refers to the success rate with perfect use of the contraceptive and, as a general rule, should not vary with the study population. There are exceptions, such as the different effectiveness of the vaginal sponge in multiparous versus nulliparous women. "Use effectiveness" refers to the success rate occurring with flawed or inconsistent use of the contraceptive and can be expected to vary with the study population. It is usually the more important measure for clinical work.

Either of these measures can be calculated from a clinical trial in a variety of ways. Only two are used in this review. "Pearl index" is the number of pregnancies per 100 women-years of exposure, unadjusted for other factors. The Pearl index is sensitive to the length for which some method has been used by the study group, and it will improve with time as less-motivated users discontinue it and others gain familiarity with it. "Life-table" rate is the probability that a woman using the method will have a pregnancy during some specified period (usually 1 year) after beginning use. This value more accurately reflects the expectations for a given patient.

While the Pearl index is a crude instrument, it is readily calculated from raw data and has been in use for several decades, allowing retrospective comparisons. The life-table method is more sophisticated, but it is not as commonly reported in clinical trials (especially small ones), has not been in use as long, and varies in the details of its calculation from study to study. These two indices are by no means identical, but they are comparable. That is, while no mathematical rule requires their values to be the same, for most clinical trials the differences are small enough to allow at least semiquantitative comparisons even when different indices are used for effectiveness calculations. For a critical and insightful review of the effectiveness statistics used in contraceptive research and a sensible proposal for their standardization, see Trussell, et al.[27]

New Spermicides

Vaginally applied spermicides are among the most accessible contraceptives. They are available as creams, gels, foams, suppositories, sponges, and, in other countries, films and effervescent tablets. They can be used alone or in conjunction with a barrier method for added effectiveness. A recent survey reports spermicides, used alone, to constitute the third most popular form of reversible contraception in the United States.[28]

Compounds that have been produced as spermicides can be divided into four major classes: surfactants, sulphydryl-binding agents, bactericides, and electrolytes.[29] Six agents have been deemed safe by the U.S. Food and Drug Administration, but only three are considered effective. These are the nonionic surfactants — nonoxynol-9, octoxynol, and menfegol.[29] Of these, only nonoxynol-9 and octoxynol are currently used in commercial products in the United States, and nonoxynol-9 dominates the market. Other spermicides, including some mercuric compounds, are available elsewhere in the world.[30]

In addition to their easy availability, spermicides are active against a number of sexually transmitted diseases. Nevertheless, currently available spermicides possess a number of disadvantages that restrict their usefulness. The following comments are directed particularly at nonoxynol-9, but they are generalizable to other surfactants:

Effectiveness

While spermicides are adequately effective when used perfectly (3 percent first-year pregnancy rate), they are sensitive to user error, including, not least, failure to use them at all. One review found reliably reported failure rates of 11 to 31 percent, with studies in specialized populations ranging from 0.3 to 60 percent.[30] A British group of older (25 years or greater), married, well-educated women, who were experienced with the method, had an 11.9 percent failure rate.[31] *The Medical Letter* cites use-effectiveness as 21 percent first-year pregnancy rate.[32]

Inconvenience

Many users find that spermicides interrupt sex, are messy or difficult to apply, or have an unpleasant smell or taste. The timing requirements, both before and after intercourse, can be

an annoyance, and they are probably the reason for a significant fraction of failures.

Side Effects

Although sperm cells are unusually sensitive to membrane disruption, surfactants by their very nature cannot avoid some degree of destruction and, hence, irritation of other cells, particularly mucosa. Antibodies against the spermicide can be formed,[33] and true allergies occur.[34]

Safety

No systemic side effects are known to occur from use of nonoxynol-9.[30] Safety concerns have primarily focussed on possible teratogenicity from use in early, undiagnosed pregnancy. Although there have been several reports of increased risk of spontaneous abortion or birth defects,[30] the article most often cited is that of Jick, et al.[35] Two of the authors of this study have subsequently backpedaled about its significance, writing, "[I]ts conclusion is unsupported by more complete evidence from its subjects,"[36] and "I believe we did not have enough information to warrant publication."[37] The methods of the investigation have been discredited, and subsequent reports with better designs have failed to replicate the results.[38-40] Nevertheless, Ortho Pharmaceutical has lost at least one multimillion-dollar lawsuit based on the alleged teratogenicity of octoxynol, and the judgment was upheld on appeal, despite the acknowledged preponderance of scientific evidence to the contrary.[8,41] There is a real possibility that a few more such cases could cause the removal of current spermicides from the market.

For all of these reasons, better spermicides are needed, and I have selected a number of products under development to review. They all share the potential to correct one or more of the deficiencies of current spermicides. My list is by no means comprehensive; it omits, for example, all plant-derived compounds, for the simple reason that there is an impossibly large number to review. This sampling should, nevertheless, be sufficient to show the improvements that could be realized by aggressive development of new spermicides. The term "spermicides" is used, somewhat imprecisely, to include all those topical agents that kill, immobilize, or otherwise render sperm incapable of fertilization.

RS-37367

Syntex Laboratories have experimented with an imidazole derivative, which they have labelled RS-37367.[42] This compound in aqueous solution is about 25 times more potent than nonoxynol-9 for immediate immobilization of dog sperm in vitro. In gel formation, it is about 50 times more potent than nonoxynol-9 for human sperm immobilization. The compound's low molecular weight also allows zero-order kinetic release from a polymeric Silastic™ matrix formed into a soft vaginal ring.

In vivo primate studies showed the 1 percent gel to immobilize all ejaculated sperm, and about 200 times fewer sperm were recovered from the endocervix of treated animals than from controls. The 0.1 percent gel was equivalent to 5 percent nonoxynol-9. (Commercial preparations of nonoxynol-9 in the United States use concentrations of 2.27 percent to 12.5 percent.[43 p 714]) The 1-inch, 0.5 gram vaginal rings performed equally well and could be removed before coitus (after several days in place) without loss of efficacy.

In addition to its immobilizing effects, RS-37367 induces acrosome-reaction-like changes (leakage of acrosomal contents) and may inhibit sperm cytochrome a_3, necessary for cellular respiration. RS-37367 also mixes with cervical mucus and changes its ultrastructure; the mucus increases in the complexity of its cross-linked matrix, thus becoming less penetrable.[42]

At this point in the product development, Syntex decided not to continue research. Part of the reason was difficulty in finding a formulation that produced consistent dispersement of the active drug. VLI Corporation, manufacturer of "Today™," a contraceptive sponge, purchased the licensing rights and was investigating the possibility of incorporating RS-37367 into a future version of its sponge. VLI Corporation was subsequently (1988) purchased by Whitehall Laboratories and no longer exists as a separate entity. An official spokesperson for Whitehall reported that no generic name has been assigned to the drug and that she knew of no published information on it having been produced in recent years. She refused to comment whether it was still under active development (Karen Richard, personal communication, February 1990). It is impossible, therefore, at this time to estimate the likelihood of this promising agent coming into use.

ORF 13904

Ortho Pharmaceutical received a patent in 1984 for a long-chain sulfonated polystyrene polymer with molecular weight of about 500,000 that appears to have contraceptive efficacy and duration of action greater than nonoxynol-9. This compound, known only as ORF 13904, is described in two publications.[44,45]

ORF 13904 had no effect on human sperm motility in vitro, but when dissolved in cervical mucus, the mixture limited sperm penetration to a few millimeters. It was clearly not behaving as a typical spermicide.

In vivo testing in rabbits showed effectiveness several times that of nonoxynol-9 when both were used in 5 percent gel formulations. Furthermore, it maintained significant, though somewhat diminished, effectiveness for several hours longer than nonoxynol-9, even with multiple matings. If this characteristic could be extended to human use, it might lengthen the short period recommended between application and intercourse and obviate the need for repeated application.

The second series of experiments was designed to elucidate the mechanisms by which ORF 13904 acts. The following multiple modes were found:

1. ORF 13904 agglutinates sperm. The tails persist with normal movement, but there is no forward progress. This flocculation is greatly enhanced by some unidentified component(s) of normal seminal plasma.
2. Sperm pretreated with ORF 13904, then washed free of the compound, had decreased ability to penetrate cervical mucus in vitro, and severely decreased fertility in vivo, implying some irreversible direct effect on the cells.
3. Cervical mucus pretreated with ORF 13904 became less penetrable.
4. Human sperm acrosin, a protease essential for successful fertilization, was inhibited by ORF 13904. Fifty percent inhibition was achieved with a drug concentration of only 0.01 percent.

Like RS-37367, ORF 13904 is no longer reported in the medical literature. A spokesperson for Ortho said that development was finally terminated in 1989 because of inability to produce satisfactory purity and concerns about carcinogenesis (R. Homm, personal communication, February 1990). It is unfortunate that negative findings such as these are not published as readily as the early encouraging results. Dr. Homm noted, further, "Ortho has no new spermicidal compounds under development at the present time," a significant loss for future contraceptive prospects.

Propranolol

Propranolol is primarily a cardiovascular drug, a nonselective β-adrenergic antagonist. It is also known to have some efficacy as a local anesthetic. This property is commonly, if loosely, called "membrane-stabilizing activity" and may be partially responsible for propranolol's antiarrhythmic effects.[46,47] Because this action resembles that of quinidine, and quinidine has some spermicidal value, propranolol was investigated as a spermicide in vitro and found to inhibit sperm motility.[48] Animal studies confirmed the phenomenon,[49] and human trials were undertaken quickly because the general safety of the drug was already known.

Pharmacokinetic data show dramatically greater serum propranolol levels after vaginal administration than after oral administration of an identical tablet; peak levels are more than two times, and total area under the absorption curve more than three times those resulting from an oral dose.[50] The difference was attributed to first-pass hepatic degradation after enteric absorption. No local vaginal symptoms were noted by these few subjects. Cardiovascular and pulmonary effects were consistent with nonselective β-blockade and were measurable, but asymptomatic. As the β-blockade appears to be independent of the membrane effect,[48] it was postulated that use of the dextro isomer alone, rather than the racemic mixture that is commercially produced, would eliminate such effects. The *d*(+enantiomer)-isomer has less than 1 percent of the adrenergic potency of the *l*(–enantiomer)-isomer but equipotent membrane-stabilizing activity.[47]

Pearson, et al.[51] found that *d*(+)-propranolol, after oral administration, was concentrated from serum into cervical mucus by a factor of about 45, and the elimination half-life from mucus was

132.5 hours. However, the peak concentration of the drug in the cervical mucus after one 80-mg dose was a thousandfold lower than that needed to immobilize sperm in vitro. They performed no in vivo studies of spermicidal effects.

A fourfold greater concentration of *d*(+)-propranolol is needed for immediate immobilization of sperm than with nonoxynol-9; nevertheless, sufficient concentrations appeared readily achievable with vaginal preparations.[52] The mechanism of immobilization is uncertain, but may be inhibition of sperm adenylyl cyclase; this decreases the intracellular concentration of cyclic AMP, an important regulator of sperm motility.[53]

The first clinical trial was with 198 parous Chilean women.[48] The usage regimen was novel for a spermicide: one standard 80-mg *d*(+)/(–)-propranolol tablet was to be inserted vaginally each evening (except during menstruation), without regard to when intercourse occurred, for 11 months. There were five pregnancies (none of which manifested fetal abnormalities at autopsy after abortion); the life-table 1-year pregnancy rate was 3.4 per hundred women-years, and the Pearl index was 3.9. The drug is believed to inhibit nidation, and this possible effect could not be separated from the true spermicidal effect in this study design. There were no effects on menstrual patterns and no systemic reactions. Local discomfort was present only early in the study and was reported to be mild.

A subgroup of 30 women was chosen for study of the duration of spermicidal effect. They were asked to have intercourse in the periovulatory period 10 hours after tablet insertion. Postcoital examinations in these women showed no motile sperm in the endocervical mucus, demonstrating delayed efficacy of vaginally administered propranolol. None of them became pregnant.[48] It seems likely that this prolonged action is due to the marked concentration and retention of propranolol in cervical mucus, as discussed previously.

Finally, it has been reported that postcoital tests show complete sperm immobilization with propranolol, but not with nonoxynol-9.[54]

Whether *d*(+)-propranolol is truly more effective than nonoxynol-9 can only be determined by direct comparison of two randomized user groups. The apparent prolongation of action of propranolol when compared with nonoxynol-9 certainly warrants further exploration and, if confirmed, exploitation.

Benzalkonium Chloride

Benzalkonium chloride is a cationic surfactant. It has been in commercial use for more than 50 years as a surface antiseptic. It acts by altering microbial membrane permeability. It is available in such innocuous over-the-counter products as Bactine™, Visine™, and contact lens cleaning solutions.

Nevertheless, there are problems with its use, such that a standard pharmacology text reports, "In aggregate, the disadvantages would appear greatly to outweigh the advantages."[55] These disadvantages include skin and mucus membrane irritation by a mild desquamating effect; unpredictable inactivation by a variety of agents including simple soap; adsorption onto rubber, plastics, cotton, and other porous surfaces, with consequent decreased efficacy; very long contact time needed for bacterial killing; occasional cutaneous necrosis[43 p 1525,55]; and contact dermatitis.[56] Such a compound might seem an unlikely candidate for a vaginal contraceptive, but the known spermicidal effect of benzalkonium chloride has led to proposal of its use for that purpose.

A large phase III clinical trial was conducted in Spain.[57] A vaginal suppository containing 1.2 percent benzalkonium chloride was used. For comparison, the highest concentration in an over-the-counter product is Bactine™, 0.13 percent. The trial included 653 women for a total of 9517 woman-months. Life-table failure rate was 3.7 percent at both 12 and 24 months, as all failures occurred in the first 10 months. There were 23 pregnancies; Pearl index was 2.9. Twelve pregnancies could be attributed to erroneous use or nonuse of the spermicidal suppository. Because there was no comparison group using a standard spermicide, it is impossible to know whether these impressive results are due to a true superiority of the product or to the intensity of training and follow-up. Local itching and burning early in the study was the most common (22 percent) side effect, with most of these described as "slight." Continuation rates were 72.8 percent at 12 months and 65.9 percent at 24 months.

Mendez, et al. mention an earlier clinical trial that enrolled 1998 women for 19,917 woman-months with only 17 pregnancies (Pearl index 1.1).[57] Because their references to this study are all published in foreign languages, and a computerized search found no English-language publications for those authors, I am unable to comment on the conditions of the trial. The preclinical studies of the spermicidal effects of benzalkonium chloride cited by Mendez, et al. are similarly difficult to evaluate; without exception, they are published in foreign languages or are listed as "unpublished."[57]

A more recent paper reports an observation that may account for some of the contraceptive effect of benzalkonium chloride:

> When exposed to benzalkonium, the filaments in cervical mucus become thickened, severed, retracted and agglutinated, giving the appearance of coagulated mucus. Macroscopically, it was observed that the liquid transparent cervical mucus became thickened and gelatinous once exposed to benzalkonium, somewhat resembling luteal secretion, although more profuse . . . The changes induced by benzalkonium suggest that the cervical mucus is rendered impervious to spermatozoa.[58 p 110]

The importance of this effect relative to the direct spermicidal action is unknown.

As discussed earlier, currently available spermicides are adequate, though far from ideal. Any new spermicide must demonstrate that it has some advantage over the old (especially in effectiveness) to justify its development. Benzalkonium chloride, which has a known potential for adverse effects, has no conceptual advantages over nonoxynol-9, the current standard. Unless benzalkonium's superiority can be shown by direct comparison, there will be little reason to add it to the contraceptive market.

Chlorhexidine

Chlorhexidine is ubiquitously used as an antiseptic skin cleanser (Hibiclens™) and as an antimicrobial oral rinse for the treatment of gingivitis (Peridex™). Compared with benzalkonium chloride, its germicidal action is much faster, lasts longer, is not inactivated by soaps, and is not reduced by adsorption onto porous surfaces. Its principal disadvantage is that prolonged, repetitive use may cause contact dermatitis in up to 8 percent of users.[55]

The first clinical use of chlorhexidine as a spermicide was for irrigation of the ligated vas deferens during vasectomy in the early 1970s. Its spermicidal activity was not quantified until 1985 when Louis and Pearson found the spermicidal potencies of chlorhexidine and nonoxynol-9 to be essentially identical.[59] The following year, however, Pearson was the senior investigator for a paper in the same journal, reporting that a different assay showed the spermicidal potency of chlorhexidine to be about 40-fold less than that of nonoxynol-9; no comment was made on the rather marked discrepancy between these results.[52] The study by Sharman, et al. confirmed the earlier work of Pearson by finding nearly identical in vitro potency for chlorhexidine and nonoxynol-9.[60]

More importantly, though, Sharman, et al. provided a basis for believing that chlorhexidine is likely to be more effective in vivo.[60] They point out that because of pooling in the posterior vaginal fornix, some sperm can enter the cervical os with very little contact with vaginal fluids, which contain the nonoxynol-9. For added effectiveness, a spermicide should prevent sperm migration through cervical mucus. In cleverly designed experiments, they showed first that chlorhexidine, but not nonoxynol-9, diffuses into cervical mucus, and second, that chlorhexidine, but not nonoxynol-9, maintains spermicidal efficacy when mixed into cervical mucus. They speculated that this compatibility is due to charge interaction between the sialic acid and sulfate residues of cervical mucus and the cationic form of chlorhexidine present at vaginal pH.

Chlorhexidine is known not to be absorbed through intact skin and has very poor absorption from the gastrointestinal tract. It is reported to be well tolerated by the vaginal epithelium.[59] The first human study of its use as a spermicide is now underway at the University of Manchester.[54]

Acrosin Inhibitors

Acrosin is a protease found in the heads of sperm. It is believed to be required for at least three crucial steps in the fertilization process: (1) the acrosome reaction, (2) sperm binding to the

egg, and (3) penetration of the zona pellucida.[61] Acrosin inhibitors act by inactivating this enzyme, thus removing the fertilizing capacity of the sperm. This contraceptive effect can take place independently of sperm killing or motility impairment.

The most potent acrosin inhibitors are the guanidinobenzoates.[61] Early experiments found members of this class of compounds that were as effective in primate reproductive tests as commercial preparations of nonoxynol-9. These agents have been further modified to reduce the toxicity and to increase the degree of binding of the drug to the acrosin molecule. The result has been the development of three guanidinobenzoates that reduce rabbit fecundity by 93 percent or more when vaginally applied in a concentration of only 0.01 percent. By comparison, 1 percent nonoxynol-9 produced only 80 percent fertility reduction in the same test. These compounds also inhibit the fertilizing capacity of human sperm in the zona-free hamster ovum penetration test.[61] The predictive value of this test, however, has been seriously challenged.[62] The antiproteolytic effect has been found to occur within the first 2 minutes of contact with human ejaculate.[63]

Animal testing of these more recently tested guanidinobenzoates has shown lower systemic toxicity than nonoxynol-9.[61]

In addition to topical application, the guanidinobenzoates can be released slowly from polymeric devices. Implantation of such a device in rabbit uteri was 100 percent effective at preventing pregnancy.[64]

A different series of guanidinobenzoates is being explored in India.[65] These compounds have good anti-acrosin potency, but reports of experiments to determine the fertilizing capacity of treated sperm have not been published.

Other classes of chemical compounds are inhibitors of acrosin in vitro and demonstrate corresponding antifertility effects when applied vaginally in laboratory animals. These include tetradecyl sodium sulfate (TDSS),[66] sterol sulfates,[67] and amino acid esters.[68] These agents are less potent than the guanidinobenzoates, but as long as safe, effective doses can be used, this difference in potency may not be clinically important. TDSS and a sterol sulfate can also be released from silicone rubber or polyurethane vaginal rings with impressive contraceptive efficacy (in rabbits) and with lower doses than are effective in gel preparations.[67,69]

The acrosin inhibitors, as a group, represent a significant development in contraceptive technology. Because their mode of action is independent of that of true spermicides, it may be possible to combine an acrosin inhibitor with a surfactant to increase the method-effectiveness of the latter by a considerable margin. This possibility, of course, depends on the active compounds being shown not to interfere with each other.

Enzymes other than acrosin, such as hyaluronidase and phospholipase, are also required for successful capacitation and fertilization. Inhibitors to some of these enzymes have also shown promise in preclinical studies.[70]

Seminal Liquefaction Inhibitors

Human semen coalesces into a gel-like coagulum in the vagina, aided by proteins secreted by the seminal vesicles. During the ensuing 15 to 30 minutes the semen liquefies, freeing the sperm; this is accomplished by prostatic agents that are still unidentified.[71] Although sperm have full tail motion upon ejaculation, the viscosity of the semen is a major barrier to effective forward motion until liquefaction occurs.

Mandal and Bhattacharyya[71] have proposed exploiting the dependence of fertilization on the liquefaction of semen. It is reasonable to expect that a vaginal contraceptive that is both spermicidal and inhibitory to seminal liquefaction will have greater effectiveness than a spermicidal agent alone.

These researchers screened 101 known enzyme inhibitors for evidence that they slow the liquefaction process. Of these, 27 showed no effect, 36 accelerated the reaction, 20 inhibited liquefaction, and 18 arrested it entirely. Ten of this last group were also potent spermicides, killing all sperm within 15 seconds. Three of this subgroup were heavy-metal compounds, probably unacceptable for human use. Of the remaining seven compounds, at least one—potassium permanganate—seems unlikely to be a successful product because of its staining of skin and potential for causing cutaneous necrosis in its concentrate form.

That an initial screening such as this could identify several compounds with the properties sought is quite encouraging. It will be interesting to see whether in vivo animal studies confirm this approach to vaginal contraception.

Miscellaneous Agents

The compounds discussed below have spermicidal potential. Most are at the preclinical level of development.

4-Bromo-7-Hydroxyindan Oxime

Yu, et al.[72] screened a series of chelating agents for spermicidal activity. The most potent one also proved the least toxic to various rabbit tissues. Initial teratologic screening revealed no induced abnormalities.

Alkylphenoxy Polyethoxy Ethanol (10)

"Agent 741" is a nonionic surfactant made from a petroleum by-product and is used in many vaginal contraceptives in China. Both its potency and toxicity are equal to those of nonoxynol-9.[73] Its primary advantage is markedly lower cost of production.

Seminal Plasma Motility Inhibitor

Iwamoto and Gagnon[74] purified from human seminal plasma a protein that inhibits sperm motility in the presence or absence of seminal plasma. "Seminal plasma motility inhibitor" is a single peptide chain of about 20 kilodaltons. It appears to inhibit dynein, the ATPase used by sperm for motility. The authors have suggested that this factor could play a significant role in some cases of male infertility. They do not mention a possible future contraceptive potential, but one can speculate that this protein could be produced in large quantities by genetic engineering techniques and formulated into a vaginal contraceptive.

Lubricants

Products for sexual lubrication (K-Y Jelly™, Lubrin Inserts™) are clearly marked as not for contraceptive use. Nevertheless, they have a considerable adverse effect on sperm motility in vitro, and their use is discouraged for couples attempting to conceive.[75,76] Their activity is not the immediate paralysis induced by spermicides but appears to be sufficient to constitute a real clinical effect. It seems reasonable that the ingredients of these products (glycerin and polyethylene glycols) could be used as the carrier base for spermicides, thus enhancing their efficacy, if no antagonism to the primary active ingredient is found.

Natural Family Planning

No matter what advances are made in hormonal, mechanical, or surgical forms of contraception, there are segments of the world population to whom these methods will be unacceptable. These include persons with concerns about side effects, those for whom cost is prohibitive, and adherents to the teachings of the Roman Catholic church on "artificial" birth control. These persons, too, deserve access to the benefits of modern advances in reproductive technology, in the form of improvement in techniques of natural family planning (NFP). ("Natural family planning" is the in-vogue term for awareness of the fertile and infertile segments of the menstrual cycle to achieve or avoid pregnancy and is used in this paper. But it is not obvious that temperature charting and cervical mucus examination, taught worldwide by advocates of NFP, are inherently more "natural" than other methods of contraception.)

The most prominent disadvantage to current natural family planning techniques is the high failure rate. Many studies have been conducted to ascertain this rate, which is found to vary enormously with education levels, motivation to avoid pregnancy, regularity of the individual woman's cycles, nationality, experience with the method, age, parity, skill of the instructor, and intensity of follow-up counseling. In fact, such variables influence the efficacy of natural family planning more than that of any other method of contraception.[28] An extensive review of studies of the most widely taught methods[77] found, for the cervical mucus method of Billings, a range of 0.4 to 39.7 and a median of 20 pregnancies per 100 woman-years (Pearl index). Two of the best-designed studies, though, both reported Pearl indices of about 35. For the sympto-thermal method (combining calendar, temperature, mucus changes, and other symptoms), the same review found reported failure rates ranging from 4.9 to 34.4, median of 16, and Pearl index 13.7 and 26 in the two large

studies. It is clear that the multiple indicators of the sympto-thermal method provide better protection than the Billings method, but it is equally clear that neither approaches the effectiveness of other modern methods.

Without question, most failures are due to conscious departure from the required abstinence during the fertile period. While NFP proponents correctly argue that this is "use failure" rather than "method failure," the clinical significance of the distinction is minimal; this cause of failure seems refractory to educational efforts[77] and is only dependent on user motivation.

Another concern of natural family planning, unique among contraceptive methods, is the increased relative fraction of conceptions occurring at the margins of the fertile period. Worrisome—though far from conclusive—evidence links such conceptions with higher rates of congenital defects and alterations in the sex ratio at birth.[78]

It seems reasonable to suppose that precise identification of the beginning and end of the fertile phase would improve the success rate and simultaneously reduce the method's very high discontinuation rate by reducing the number of required days of abstinence. Reliable markers of the fertile phase would also presumably reduce the second most common cause of failure, which is difficulty interpreting the mucus or temperature fluctuations, and the possible risk of conception at the end of the fertile phase. This is the goal of the World Health Organization's sponsorship of natural family planning research. At present, though, the number of potentially useful new indicators of the fertile period is quite limited.

It is noted that various devices have been marketed to automate the daily temperature monitoring or to assist in cervical mucus collection.[79,80] Even at their best, such devices could produce only marginal improvement in NFP efficacy because of the inherently variable nature of temperature and mucus texture as fertility markers. Such devices are not discussed further in this paper.

The rapid rise of luteinizing hormone (LH) just before ovulation seems an obvious choice for a marker. In fact, there are now available over-the-counter home assays for urinary LH that have proved reliable at predicting impending (within 24 hours) ovulation.[81] But while this marker is useful for promoting fertility, its applicability in preventing pregnancy is limited to use as a confirmatory test for other symptoms. Due to the period of viability of sperm in the female reproductive tract, any marker of the fertile period must be able to precede ovulation by at least 3 days, and preferably 4 or even 5. More than this would result in days of unnecessary abstinence. This limitation also applies to attempts to improve natural family planning by measurement of salivary LH content.[82]

The World Health Organization task force assigned to this problem reported that a 5-day block in each menstrual cycle accounts for more than 90 percent of pregnancies and tried to use laboratory assays of daily urinary estrone-3-glucuronide and pregnane-3α-glucoronide to identify that block.[83] The amount of intersubject variation of quantity of hormone, though, presented a formidable challenge to their stated goal of a "universal" test. Their best formula would require periods of abstinence as shown in Table 1.

While far from ideal, these results are a considerable improvement over the average of 15 to 18 days of abstinence required in each cycle by the Billings method.[28,77] Using the calendar rhythm method alone—possibly the most widely used NFP method in the world—requires an average of 16 days of abstinence.[84] (I am unaware of similar reliable reports of the amount of abstinence required by the sympto-thermal method in actual use.) There remains, though, a serious question whether the laboratory assays used in this study could be successfully converted into home kits. There was also consider-

Table 1. Determining the Fertile Period: Number of Days of Sexual Abstinence for Method-Effectiveness.*

Required Days of Abstinence	Percent of Cycles
5	10
6	15
7	20
8	15
9	15
10	10
>10	15

*Data from World Health Organization Task Force on Methods for the Determination of the Fertile Period.[84]

able international variability in the assays, a puzzle currently being investigated.[83]

An Australian group has focussed on colorimetric home assays.[85] They envision a woman measuring urinary estrogens daily from early in the cycle until a rise is established, marking the beginning of the fertile period. She then switches to daily testing for urinary pregnanediol. When this is found to exceed a threshold value, indicating infertility, intercourse may resume and testing is discontinued until the next menstrual period. These authors claim to have developed kits for such testing that are nearly as accurate as the best laboratory assays, use no noxious chemicals, cost less than 10 cents each, can be easily manufactured in quantity, and "involve less labor and cost than does making a cup of tea." They have published the results of actual home testing for only the pregnanediol test,[85] which requires only the accurate volumetric mixing of morning urine and tap water and visual reading of the result (against a color standard or with an electronic meter) as very negative, negative, plus-minus, positive, or very positive.

While this plan appears very promising, the estrogen assay is obviously the more important one because it defines the start of the fertile period, and it has not yet been tested under home-use conditions. Unfortunately, it is also the more difficult one because of the smaller absolute amounts of estrogen present and the great intersubject variability in the natural course of its rise. See also Albertson and Zinaman[79] for a brief discussion of other commercial kits for measuring urinary steroids. Some of these are or will be marketed for home use.

As a general rule, estrogen and progesterone levels in saliva parallel the serum levels but would be more readily accessible for home assays.[79] No home kits have yet been proposed, and it is difficult to see how such a system would have intrinsic advantage over urinary assays.

A group at the University of Illinois has studied cyclical variations of guaiacol peroxidase (GP) in cervical and vaginal secretions.[86] It appears that this enzyme catalyzes the cross-linking of mucin polypeptide strands, making the mucus thicker and less penetrable. Competitive inhibition of this enzyme may be the mechanism by which guaifenesin thins bronchial secretions, for ease of expectoration, and cervical mucus, enhancing fertility in some women.[87] GP activity is at a nadir 1 day before ovulation, allowing the mucus to remain lubricative and penetrable; from 6 days before ovulation to this nadir, the levels drop exponentially, and after the nadir, they rise exponentially. Cervical and vaginal GP production is believed to be inversely related to the level of circulating estrogen, while GP in the saliva shows no cyclic variation. Cervical GP does not have a midcycle drop during anovulatory cycles or in women on oral contraceptives. These researchers used a colorimetric assay with guaiacol and hydrogen peroxidase, which they say could be readily produced as a home kit. They do not discuss the problem of daily home collection of mucus from the cervical os, where the GP concentration is greatest.

Three papers have evaluated the relation between salivary electrical resistance (SER), as measured by a commercial device, and ovulation.[88-90] Albrecht, et al. reported a remarkably consistent interval of 5 to 6 days between the SER peak and the LH surge and suggested this as a clinically useful marker of the onset of the fertile phase.[88] Roumen and Dieben, however, were not able to replicate these results, finding no consistent relation between the two events, even when analyzing only cycles of ideal length (26–30 days). They further found that in consecutive months, a given patient was unlikely to repeat her SER peak-LH peak interval. They attributed the results of Albrecht, et al. to random variation among a small number of subjects.[89] Jacobs, et al. found a correlation coefficient between that of the other two studies, with a range of 4 to 9 days separating the SER peak from the LH peak, and concluded that the measuring device's potential as an adjunct to NFP methods was "limited."[90]

Two of these three papers also examined the relation between the monthly nadir of vaginal electrical resistance (VER) and LH surge.[88,90] Because of the temporal proximity of these two events, it appears that VER, like urinary LH assays, is better suited to fertility promotion than prevention. Its applicability to NFP is likely to be limited to identifying the end of the fertile phase.

Saliva contains a number of enzymes that show monthly variations in concentration in

normally cycling women. Personal Diagnostics, Inc., was developing a spectrophotometric device for quantitating four of these enzymes simultaneously.[79] This project has been abandoned, partly because of complexity of use. The system relied on assessing rates of change in the enzyme levels. It was originally intended for the promotion of fertility by ovulation forecasting and was often able to give a 3-day advance prediction, but this would be insufficient for NFP purposes.

Two commercial devices have been developed to assess the volume of cervicovaginal fluid, which demonstrates cyclic variation: the Ovu-Trac™[79] and the Rovumeter™.[80] These devices, too, even under ideal conditions, may become useful adjuncts to NFP but probably will not give sufficient advance prediction of ovulation to act as markers of the beginning of fertility.

It is to be hoped that one of these methods—or one yet undiscovered—will provide a breakthrough in accurate prediction of monthly fertility, and will, in turn, bring to natural family planning levels of contraceptive effectiveness rivaling those of other modern methods.

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