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Research approaches to new sterilization technology

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INTRODUCTION

In this paper it is intended to provide an overview of the current status of research underway on new and improved sterilization techniques and to highlight neglected research areas related to sterilization.

The usual definition of sterilization is that it is a procedure by which an individual is made incapable of reproduction. It has most frequently been achieved by the surgical removal of some portion of the reproductive system which precludes the union of sperm and egg, either by removal of their site of origin or by interruption of transport processes. Such procedures include gonadectomy, vasectomy, and salpingectomy.

However, with growing knowledge of processes fundamental to conception and widespread discussion of the concept of reversible sterilization, it seems appropriate to include in this paper methods which fall into a broader definition of sterilization. Such methods encroach, to some extent, on what has heretofore been considered "contraception." They encompass methods which, following a single treatment or, at most, a few subsequent or infrequent treatments, result in a protracted period during which pregnancy cannot occur. This definition would include, and we will discuss briefly, research approaches to male "chemosterilants" which require infrequent usage or application. Although IUDs also fit this definition, they will not be discussed.

Research on sterilization technology will be most relevant if it is formulated with an appreciation of the acceptability and potential role of sterilization as a means of fertility control. It then becomes possible to examine barriers to the full provision and acceptance of sterilization, particularly in the family planning programs of developing countries, and to formulate research objectives to improve sterilization technology which will result in improved utilization of this fertility control method. This paper will therefore define objectives and priorities for research and then discuss approaches to these objectives.

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Family planning strategists have sought to determine the role of fertility control technology in the success of fertility control efforts. An examination of family planning practices and programs in many cultures and locations has led to the conclusion that the nature of the available fertility control technology has profound implications for the success and efficiency of family planning programs.^{1,2,3,4} Programs offering a variety of methods (particularly oral contraceptives, termination of pregnancy, and sterilization) are the most successful.

Conclusions of previous reviews of the role of sterilization in family planning are summarized below:

1. *Prevalence* Although sterilization is common (perhaps 25 million protected couples throughout the world), until recently its use in developing countries has been limited. It has only been a major component of family planning programs in India, Bangladesh, Pakistan, and South Korea. However, Ceylon, Fiji, Hong Kong, Malaysia, Nepal, Singapore, Thailand, Tunisia, and the People's Republic of China now offer sterilization.^{5,6,7}

2. *Acceptability* Although sterilization is not considered as acceptable by society as reversible contraception and it is not always considered a valid part of family planning programs, available evidence suggests that the acceptability of sterilization to many individuals is great. Large numbers of men and women will take advantage of this method of fertility control when the necessary clinical services exist, the providers of the clinical services are favorably inclined, and the administrative requirements for eligibility to receive a sterilization are not unduly restrictive.^{5,6,8,9,10} Survey research in many countries also reveals a great potential demand for sterilization and a satisfaction with results among the sterilized.^{5,11-15}

3. *Administrative and organization feasibility* Because sterilization is still a medical operative procedure, particularly in developing countries, availability of medical care infrastructure may be an important, limiting factor in the provision of sterilization procedures. This is especially true for female sterilization.⁶ The permanence of sterilization does allow an organizational approach to provision of fertility control services which does not require an ongoing relationship with the target population. Therein, use of "campaign" strategies and acceptor incentives to increase motivation becomes more practical and need for concern over dropouts is eliminated.¹⁵

4. *Demographic impact* Low contraceptive failure rates for both vasectomy and tubal ligation and the obviation of need for continuing motivation and application of the technique suggest a very high potential demographic impact. At present, this is limited by the high age and parity of acceptors. However, experience in the U.S. and Puerto Rico suggests that removal of administrative barriers and provisions of services will greatly increase use of sterilization among those of low age and parity.^{6,9,11,12}

RESEARCH PRIORITIES

There are at least two general objectives for improvement of sterilization technolo-

gy: (a) to make the technique more acceptable to individuals and (b) to make it easier to provide sterilization services. Of course, an advance in sterilization technology may contribute to the achievement of both of these objectives.

From the available data, summarized briefly above, it would appear that user acceptability of current sterilization technology is greater than the ability of many countries or programs to provide such services. Therefore, particularly for female sterilization, techniques which obviate the need for scarce and expensive medical care personnel and facilities are desirable. In formulating research priorities for male sterilization techniques, it may be advantageous to place relatively increased emphasis on user acceptability.

Desirable characteristics for improved sterilization technology are:

1. The method can be applied outside of hospitals or other medical care facilities; at a minimum, outpatient procedures are preferable to inpatient procedures.
2. The method can be carried out by paramedical or nonmedical personnel with a minimum of training; methods usable by a physician or surgeon with average skill and training are preferable to more difficult techniques.
3. The method does not sacrifice the virtues of current techniques, particularly with respect to contraceptive effectiveness, safety, and the requirement for a single procedure.
4. The method should be more acceptable to individuals; this implies the technique should offer increased safety, an increased potential for reversibility, avoidance of a surgical procedure, or if it is necessary, decreased internal and visible scarring, decreased discomfort, and a short convalescence following the procedure.

Of great theoretical interest is the impact of improved reversibility, and considerable research effort is being directed towards more reversible male sterilization techniques. However, it should be noted that present, relatively irreversible techniques seem acceptable to both men and women of low enough age and parity to have a significant demographic impact.^{4,5,7,10} In the U.S. the success of centers offering semen preservation and the enthusiasm of volunteers for experimental, possibly more reversible male sterilization procedures suggests that availability of more reversible sterilization procedures will broaden the appeal of this means of fertility control.

Although development of non-clinical means of sterilization may have the greatest potential for impact on fertility control programs, incremental improvements in currently used means are also desirable.

EVALUATIVE TECHNIQUES

Most of the currently used techniques of surgical sterilization have been evaluated through isolated clinical series using non-comparable techniques. For example, pregnancy rates resulting from various techniques of tubal ligation are not well established.^{16,17} The frequency and nature of events with less precise definition, such as complications resulting from various procedures or reversibility of procedures, are even less well established.⁵

In order to seek accurate performance data on sterilization techniques, the establishment of collaborative clinical research programs for carrying out multiple clinic field trials on carefully standardized techniques is important. These programs, such as the Population Council's Combined Statistical Program, Pathfinder's International IUD Program, and the International Fertility Research Program at the University of North Carolina, have been most successful in the rigorous evaluation of IUDs.^{18,19,20} A similar evaluation of clinical requirements, pregnancy rates, and major and minor complications of currently used and new sterilization techniques is needed. Such studies must establish series of adequate size using standardized techniques so that results of (sometimes subtle) variation of techniques can be established with statistical validity.

RESEARCH APPROACHES TO IMPROVED FEMALE STERILIZATION TECHNOLOGY

A review of this subject has been facilitated by the 1972 publication of the proceedings of two conferences held to assess current status and research needs relating to sterilization: a Conference on Human Sterilization held in Cherry Hill, N.J., October, 1969²¹ and a Conference on Female Sterilization held at Airlie House, Airlie, Va., December, 1971.^{22,23} A brief discussion of research needs and approaches relating to various techniques of female sterilization follows:

1. *Sterilization by laparotomy and colpotomy*

These traditional techniques of surgical sterilization can be improved by the development of simplified anesthetic techniques and by the design of simplified and specialized surgical equipment to make the procedures less difficult technically.²⁴ New times of use of these procedures may increase their value, such as post-partum when sterilization by laparotomy is particularly easy, post-abortion^{25,26} or during pregnancy (carried out without incident in a few cases in India).²⁷

A recent conference in India concluded that interval sterilization by posterior colpotomy, carried out under spinal, epidural, or local anesthesia, is the preferred technique for female sterilization in developing countries. The simplicity of this approach is a great advantage and only a few instruments are necessary. It has been suggested that in some patient populations the relatively deeper vaginal vault will make this procedure technically difficult.^{24,28,29}

Elective hysterectomy has been advocated as a sterilization procedure, although it is debatable whether hysterectomy for the single indication of sterilization is a justifiable procedure. Recently, there have been great increases in this operation in the U.S., and many physicians consider the prevention of potential neoplasia sufficient indication for its use on an elective basis.^{30,31}

As noted above, careful clinical evaluation of existing variations of surgical technique, including elective hysterectomy, is desirable. For example, solid data comparing morbidity and mortality of elective hysterectomies to tubectomies is not available.

2. Endoscopic sterilization

a. Laparoscopy Although it requires complex and expensive equipment, laparoscopic sterilization offers the important advantage of being a procedure that often can be carried out on an outpatient basis under local anesthesia. It causes minimal abdominal scarring and, of all the endoscopic sterilization procedures, it seems relatively easy to learn.

Recent reviews have described its use mainly in sophisticated medical settings.^{16,32-37} Even so, significant morbidity relating to current techniques has been apparent.

A report in 1972 from the Complications Committee of the American Association of Gynecologic Laparoscopists reviewed the experience of society members in 1971-1972 with over 12,000 laparoscopies, about 7,000 of which were carried out for sterilization. The following approximate rates were reported: minor complications 10‰, major complications 6‰, pregnancy after surgery 0.2‰, and deaths 0.3‰. Major complications related to anesthesia, insufflation and electrocoagulation.³⁸

Research has therefore been focused on elimination of the most serious side effects: thermal trauma to bowel and other internal structures following cautery, and hemorrhage after cautery and division of the tubes. Additional morbidity is caused by distension of organs and subcutaneous tissues or gas emboli following improper placement of the pneumoperitoneum needle, perforation of bowel with trocars and instruments, anesthesia accidents, etc.^{16,32-36,39-42}

To avoid the hazards of cautery and to minimize the problems of hemorrhage resulting from avulsion of tube and mesosalpinx, various clips and laparoscopic applicators are being developed to occlude the fallopian tube.⁴³

Over a decade ago, Neumann, Frick, and Hayashi used clips of tantalum and other materials for tubal occlusion.^{44,45} These initial efforts were hindered by technical difficulties in application, postoperative complications, and pregnancy failures. More recently, Haskins with puerperal abdominal and interval vaginal operations, Wheelless with laparoscopy, and Gutierrez with culdoscopy, have established clinical series using the tantalum hemoclip (Weck[®]). Careful application is necessary, since Gutierrez noted that as small as a 0.25 mm opening allowed pregnancy in one case. Wheelless is applying two clips in an attempt to lower the pregnancy rate, which Haskins and Gutierrez have found to be somewhat higher than with traditional surgical techniques.⁴⁶⁻⁴⁸ Trying to eliminate tissue regression and recanalization, Hulka, working with Clemens, has developed a clip which maintains pressure on the tube (Clewe has a similar design). Hulka's spring clip, which is made of metal and polycarbonate plastic (Lexan[®]), is just being introduced into human clinical trials (Fig. 1).⁴³

An additional possible advantage of the use of clips is that they cause relatively limited tubal trauma, and therefore, such procedures may be simpler to reverse. Gutierrez has removed several which were applied via culdoscopic procedures but no pregnancies have resulted.⁴⁶

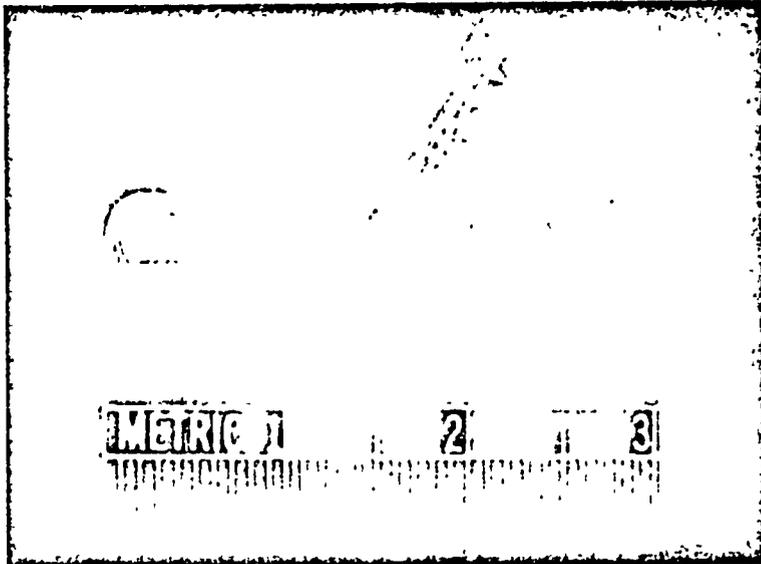


Fig. 1. Experimental clip for laparoscopic tubal sterilization developed at the University of North Carolina.

In addition to research to reduce patient risk, equipment and procedures are being developed to make laparoscopic sterilization less complex, easier to carry out, and the equipment less costly. These research approaches include: (1) further refinement of the single puncture technique and the elimination of general anesthesia;^{32,37} (2) Siegler's work on a combined alligator biopsy and cautery probe;⁴⁰ (3) Hulka's development of a simple "controlling tenaculum" to manipulate the uterus;⁴⁹ and (4) efforts by Wheelless, Hulka, and various equipment manufacturers to develop lighter, less bulky, and less costly equipment for light sources and gas insufflation.³⁷ Prototypes of simplified and portable equipment of "attache case" size have been developed.³⁷

b. Culdoscopy Although probably more difficult technically than laparoscopy, culdoscopy is easier to do under local anesthesia, eliminates the need for gas insufflation, and does not require tubal cautery.^{50,51} Tubal clips can replace the somewhat technically difficult steps of traditional ligation procedures. Comments relating to clips made above also apply to culdoscopy.⁴⁶

Hysteroscopy is discussed in the following section.

3. Transcervical approaches to female sterilization

a. Mechanical or thermal trauma of the uterotubal junction or oviduct Recent advances in hysteroscopy techniques and instrumentation have renewed interest in the transcervical approach to the uterotubal junction and the fallopian tube. A review of the past experience with uterotubal cautery techniques in humans reveals

a variable, but high incidence of subsequent pregnancies (reflecting the excellent regenerative power of the uterotubal junction) and high complication rates including intraperitoneal trauma, hemorrhage, and infection.^{40,52-56}

Lindemann's recent report of 100 women with 100% tubal occlusion on hysterosalpingographic examination 8 weeks post-cautery is encouraging, but longer term follow up is necessary to determine efficacy of this technique.^{56a}

Evaluation of experimental cautery techniques in animal systems has likewise been discouraging; however, it should be noted that satisfactory animal models have not been found for use in assessment of clip or chemical tubal occlusive procedures either. Improved clinical results may be possible with lesions produced by electrocoagulation, at controlled current and time duration, when introduced by direct visualization, using only a paracervical block for anesthesia.^{57,58} Halbrecht has initiated studies using laser beams, introduced either by laparoscopy or hysteroscopy and directing the beam to the precise point of interest, for tubal occlusion.

A research project being carried out by the IIT Research Institute is seeking a steerable hysteroscope, for use both as a diagnostic instrument and as a means of implanting a (as yet undeveloped) reversible tubal occlusion device.⁵⁹

b. Chemical tubal occlusive agents There is a long history of investigation of chemical agents for tubal occlusion, beginning in 1849 with the infusion of silver nitrate into the uterine cornua.⁶⁰ If an agent were discovered which is highly effective and if its administration were simple, it would come close to fulfilling the criteria for an ideal sterilization technique outlined in the introduction. Chemical occlusive agents were not investigated seriously until Corfman et al. blocked the utero-tubal junction with methyl-2-cyanoacrylate. They successfully blocked the oviducts of a number of rabbits by infusing the adhesive through fine gauge polyethylene catheters.⁶¹ Later, the same authors described an instrument developed for the transcervical administration of chemical agents. It consisted of a curved uterine sound with a small syringe on its distal end and a balloon to assist the tip of the sound into the cornua.⁶² Longer chained butyl and octyl monomers were proposed to be more effective, in light of their improved ability to cover irregular tissue surfaces.⁶³

Further work on delivery of chemicals to the oviduct was performed by Thompson et al. These investigators infused cyanoacrylates and sotradecyl into the oviducts of rabbits. Although able to locate the tubal orifices, they were unable to achieve permanent tubal occlusion.^{76,77} In similar studies, neither isobutyl cyanoacrylate nor 2-methyl-cyanoacrylate produced permanent intrauterine adhesions following lavage of rabbit uteri, which was undertaken in an attempt to experimentally induce synechia and an associated sterility.⁷⁸ The latter compound also had no lasting effect on human endometrium. Stevenson and Taylor observed, in this study, that the tubal epithelium was lost and the tubal lumen obliterated for up to 12 weeks following transcervical injection of 1 ml of methyl-2-cyanoacrylate into the fundal region of the uterine cavity.⁷⁹

Richart et al. infused scarifying and necrosing agents, such as zinc, chloride, phenol, silver nitrate, salicylic acid, strong acid and bases, atabrine, sodium mor-

rhuate, and cyanoacrylate esters, by intubation of the fallopian tubes. Of significance was the observation that the fallopian tube had a remarkable ability to regenerate, suggesting, perhaps, that a sustained release of an epitheliotoxic substance might be required to produce permanent blockage.^{64,65}

Beginning in 1968, Zipper and colleagues published a series of optimistic reports on tubal occlusive agents. They used a variety of chemical occluding agents which were introduced into the uterine cavity by a small catheter. They found Quinacrine acts as an effective tubal occlusive agent, disrupting the epithelium of the intramural region of the human oviduct, without altering the histology of the endometrium. The principal limitation of this non-surgical sterilization technique is that two instillations of Quinacrine are required to achieve 90% tubal obstruction. Four years of clinical experience indicate that pregnancy and recanalization rates are very low after successful occlusion.⁶⁶⁻⁷⁰

Dafoc et al. are assessing the effects of paraformaldehyde administered as a suspension in absolute ethanol. This vehicle was selected with the objective of prolonging the retention of formaldehyde at the site of injection. 90% of monkeys injected in the cornual area of the uterus evidenced acute and chronic myometrial lesions; however, tubal occlusions did not occur. They cite the discrepancies previously noted between animal and human results, thus offering reason to anticipate that clinical studies presently in progress may prove effective.⁷¹

Rakshit studied the blockage of fallopian tubes by injection of silicone rubber plugs, with successful results in a number of experimental animals. In this work, 4 to 6 ml of room temperature vulcanizing polymer were injected into the uterine cavity. No attempt was made to find the uterotubal junction.^{64,65,72-74} More recently, Erb et al. reported that 38 of 40 rabbit oviducts into which liquid silicone elastomer was injected, remained occluded throughout a 56-day observation period. Fertility, although impaired, was observed in treated rabbits after the plugs were subsequently removed.^{58a}

Hulka and Omran inserted dacron-felt plugs into the uterotubal junction of experimental animals and demonstrated an overall lower rate of fertility. Their studies were complicated, however, by a high incidence of infection and adhesions involving the tubes and uteri.^{52,75}

Positive findings in experimental animals with the use of tissue adhesives for a nonsurgical blockage of the tubes were reported by Grode et al.⁵⁰ and by Falb et al.⁹¹ They described a gelatin resorcinol-formaldehyde (GRF) adhesive system. Originally developed for cardio-vascular applications, GRF forms strong flexible tissue bonds in the presence of body fluids, is non-toxic, and is compatible with tissue growth.^{42,43} The GRF adhesive system forms covalent bonds with amine and hydroxyl groups of protein providing a bonding strength far in excess of other tissue adhesives. It provokes tissue ingrowth to form a permanent tissue block, the adhesive biodegrading over a period of 3 to 6 months.

The efficacy of the adhesive systems was evaluated in several series of rabbits by surgically exposing the uterus and placing the adhesive in only one uterine horn of each rabbit.

Efficacy of the adhesive was evaluated by either breeding the rabbits and observing impregnation or by determining patency of the tubes with a dye solution. 90% blockage of conception has been achieved in this species which is noted for its resistance to the sclerosing effects of Quinacrine. Additional studies are underway assessing efficacy of a variety of GRF formulations, including some containing Quinacrine and chelating agents.

Further development of hysteroscopy may be warranted as a means for precise introduction of agents or devices into the uterotubal junction. Chemical tubal sterilization procedures would be greatly facilitated, however, by instrumentation which would permit the "blind" application of GRF and other tubal occluding agents to the region of the uterotubal junction by a non-invasive route.

In order to meet the requirements for an effective fertility control method which can be administered to a large number of women, a rapid and simple method of delivery of the chemical to the uterotubal junction must be available. This method should allow transcervical administration of the adhesive by paramedical personnel, with maximum safety and a high degree of effectiveness.

Since the GRF adhesive is a two-part formulation, the delivery system requires a mixing apparatus and a cannula mechanism to both locate the uterotubal junction and deliver the adhesive to that site. Prototype equipment developed at the Battelle Memorial Institute includes: (1) a mixing apparatus incorporating two syringes, driven by a worm gear, which feed the two components into a static flow mixing chamber, and (2) a cannula mechanism that is of small enough diameter to be inserted through the cervix without dilation. The tip of the device contains a spring-loaded linkage mechanism for locating the junction blindly, and a silicone rubber tip to provide a seal at the fundal region when the adhesive is delivered. An alternate

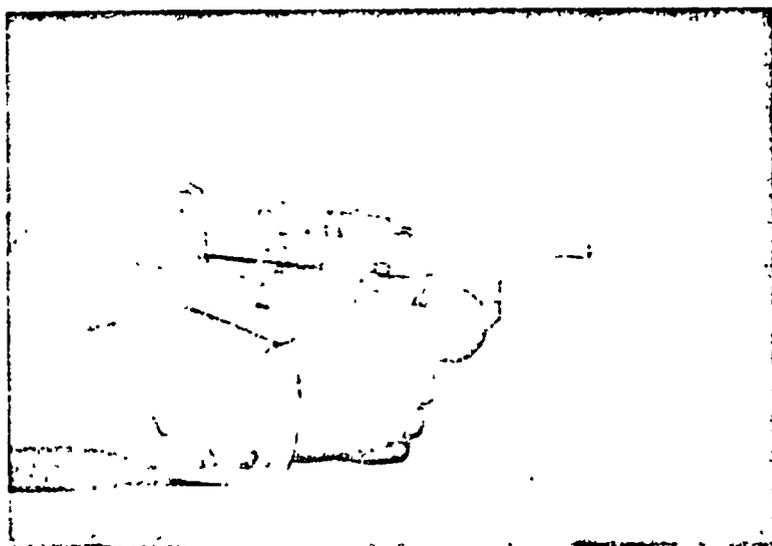


Fig. 2. Infusion/mixer device for GRF developed by the Battelle Memorial Institute.

method of delivery based on the cannulated intrauterine balloons (design of Moulding and Thompson) is also being evaluated. When inflated, these balloons protect most of the endometrium and expose only a small area at the uterotubal junction to the occlusive chemicals (Figs. 2, 3a, b, 4).⁷⁶

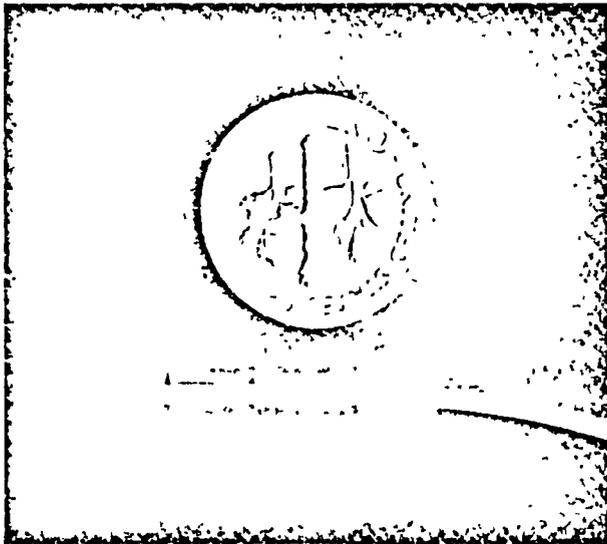


Fig. 3a. Prototype of device for finding the utero tubal junction developed by the Battelle Memorial Institute.

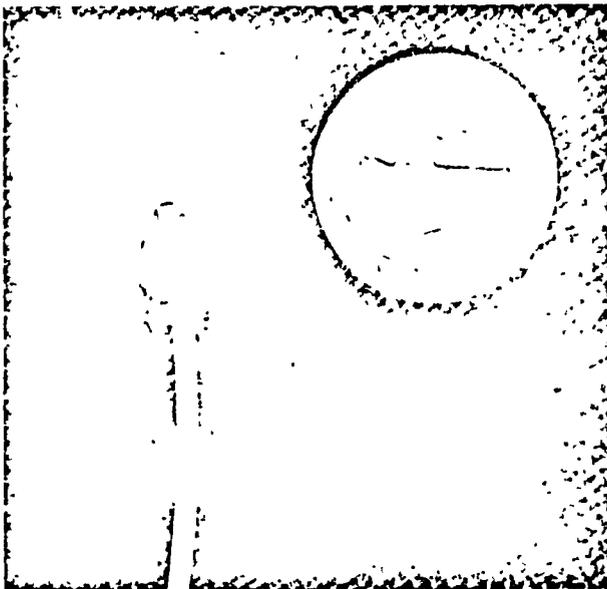


Fig. 3b. Expanded in utero geometry of UTJ finder/delivery system.

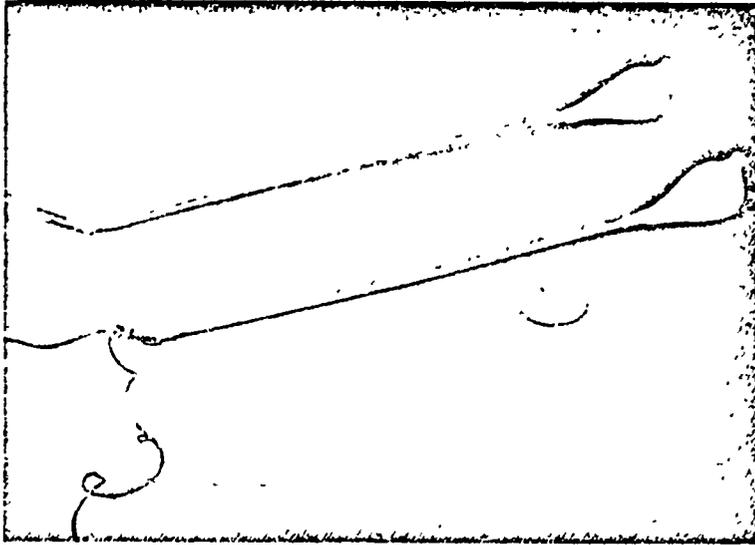


Fig. 4. Double and triple lumen occluding balloons developed by Moulding and Thompson.

The development of a means for replacing the required multiple Quinacrine administration with an equally effective single transcervical treatment would greatly enhance its projected role in sterilization programs. To achieve 100% obstruction with a single instillation, Dr. Zipper suggested two approaches: (1) identifying specific potentiating agents as an adjunct to Quinacrine treatment; and, (2) using utero-relaxing agents to reduce the incidence and severity of tubal spasms associated with transcervical instillations.⁶⁶

An alternative approach is utilization of a delivery system which provides retention of the Quinacrine in the tubal lumen long enough so that a single treatment is effective. Combining Quinacrine with GRF affords one such system. Other systems include aqueous suspensions, gels, and microcapsule formulations, which are suitable for Quinacrine as well as other sclerosing agents such as chloroquine, silver nitrate, formaldehyde, etc., some of which have significantly different mechanisms of action from Quinacrine (Fig. 5).

A number of techniques exist for the production of microcapsules in a wide range of sizes (1 to 1,000 μ) and of widely varying drug permeability. It should therefore be possible to produce microcapsules of the occluding agent in the appropriate size to release the occluding agent in amounts and at rates necessary for effective tubal blockage.

c. Endometrial ablation Surgical or chemical ablation of the endometrium is a possible approach to sterilization by causing "end organ failure." Because the depth of tissue damage can be precisely controlled with freezing, cryosurgery is an attractive approach to endometrial ablation.

With paramedical personnel presently inserting intrauterine devices, it would be easy to train such personnel to perform cryosurgical sterilization. The flexible

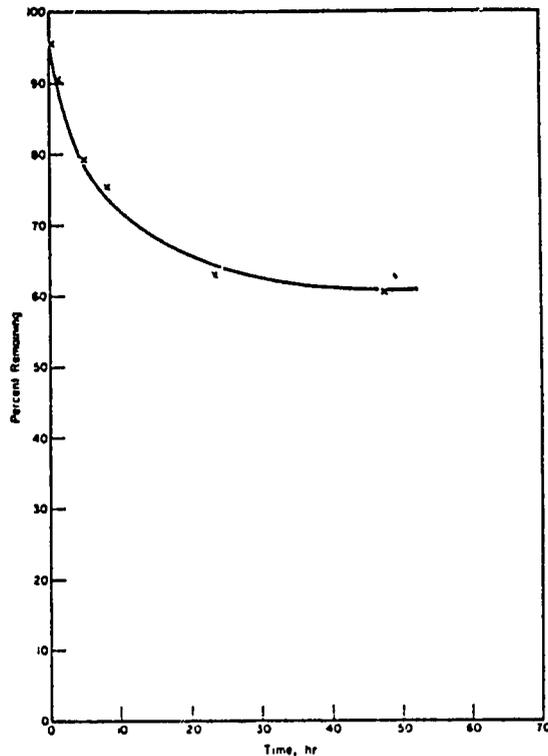


Fig. 5. Extraction of Quinacrine from GRF.

and inflatable balloon through which the freezing medium circulates, would be as easy to insert as a large intrauterine device. A cryosurgical delivery system could have a single on/off control dial and, therefore, the only variable for the technician would be the length of the freeze-thaw cycle. The low morbidity, lack of a surgical incision, and combination of amenorrhea and sterility, are attractive features for patient acceptance.

With the exception of a few oncologists who have treated selected cases of endometrial carcinoma with cryonecrosis using metal cryoprobes, apparently only Droegenmueller and co-workers, who have developed a balloon technique for cryo-ablation of the endometrial lining, are pursuing work along these lines.

Droegenmueller's group has had considerable experience over the past 2 years. They have described the histological changes in the endometrium produced by cryosurgery,⁵⁴ shown that cryosurgery can be performed under local anesthesia with minimal morbidity,⁵⁵ and demonstrated that all the patients were amenorrheic for the 6 to 8 week interval between cryosurgery and subsequent hysterectomy.⁵⁶ Since the nerve endings which transmit pain are particularly susceptible to cold, minimal or no anesthesia is required for the procedure.

Approximately 25% of cryosurgery patients complain of moderate lower ab-

dominal pain within the first 12 hours following the procedure. This has been relieved by mild oral analgesic preparations. All patients develop a serosanguineous vaginal discharge which persists from 10 to 20 days postoperatively, but no patients have had evidence of pyometra at subsequent hysterectomy. A long range study of morbidity and results of intrauterine cryosurgery involving over 30 patients with a follow-up of 16 to 23 months post-cryosurgery is in progress. In total, over 80 patients have undergone intrauterine cryosurgery with negligible morbidity.

Current work is being directed towards: (1) *in vitro* testing of the expandable cryoprobe; (2) sub-human primate studies to determine the safety of the system; (3) determination of an adequate necrotic isotherm using the system; (4) determination of long-term morbidity and regenerative capacity of the endometrium; and (5) determination of success and failure rates as a sterilization procedure, including the incidence of ectopic pregnancies.

4. *Systemic and other approaches to female sterilization*

Transabdominal radiation can be used, with up to 1500–2000R in divided doses required; however, hormonal disruption, the potential of carcinogenesis, pregnancy failures, and possible mutagenic damage to offspring when recovery does occur, render this approach unwise. Intrauterine application of radium has been abandoned for similar reasons.¹⁷

A possible approach to ovarian destruction involves use of focused ultrasound. Although it would likely have the drawbacks of castration, it is theoretically possible to use ultrasonic holography to visualize and locate the ovary and then use focused ultrasound as a destructive energy source.⁵⁷

Immunologic approaches to sterilization are attractive on a theoretical basis in that the woman could be immunized against a unique tissue antigen occurring only in embryonic or placental tissues, e.g., embryonin or trophoblast, or in semen, e.g., sperm cell antigens. Each pregnancy, or each intercourse in the case of anti-semen immunizations, could then act as a booster dose serving to keep antibody titers high.⁵⁸⁻⁶⁰

Behrman and others are pursuing such studies; however, success is hindered by the lack of a suitable adjuvant for use in humans to achieve high antibody titers and also by the difficulties in isolating both specific antigens and antigens which are unique to non-maternal tissues so that cross reaction and difficulties with autoimmunity do not develop.⁹⁰⁻⁹² Hulka has shown that local cervical secretion of anti-sperm antibodies can be induced. The initial bovine studies suggest that some decrease in fertility is possible with this approach.⁹⁶

Another theoretical approach being studied by Laurence et al. involves immunization against hormones, preferably only those associated with pregnancy, such as human chorionic gonadotrophin.⁹³⁻⁹⁵

An easily administered drug with specific toxicity to the germinal elements of the ovary would be desirable and could completely eliminate the need for clinical programs for female sterilization. Menopausal symptoms and cessation of menses have

been reported in women to whom the immunosuppressive drug cyclophosphamide was given for various nephritides and collagen diseases^{97,98}; however, systemic side effects and inconsistent activity render use of this drug impractical.

5. Reversible techniques of female sterilization

In a recent review, Garcia discussed the success of attempts to re-establish tubal patency and achieve pregnancy in women who had previously undergone tubectomy with no attempts having been made to enhance reversibility at the time of the procedure. As might be expected, the removal or destruction of large segments of the oviduct and the presence of adhesions decrease the success of reversing operations.⁹⁹ Although not proven, some surgeons feel that microsurgical techniques improve the likelihood of success.

Numerous surgical techniques have been proposed for temporary female sterilization. Those which involve burying the tube or covering the tube with silastic caps have resulted in blurring of the delicate fimbrial anatomy and frequent formation of adhesions. Burying the ovary beneath the peritoneum has not proven successful because of adhesion formation and herniation of the ovary through the peritoneum. Covering the ovary with a silastic sheet, "ovariotexy," may enhance the success of this procedure.^{100,101}

Meeker has suggested ligation around a notched intratubal plug. Preliminary studies in baboons and rabbits are promising with respect to effectiveness and reversibility.¹⁰² The silicone rubber plugs of Erb, mentioned earlier, are designed to allow their removal transcervically.^{98a} There seem to be considerable species differences in tolerance of oviduct plugs, and Hulka's experience with pigs was unsatisfactory since displacement, adhesions, and infection were frequent.

As noted above, the relatively short segment of trauma resulting from some clips may enhance reversibility potential, but what minimal experience is available suggests that more than a simple removal of the clips will be necessary.

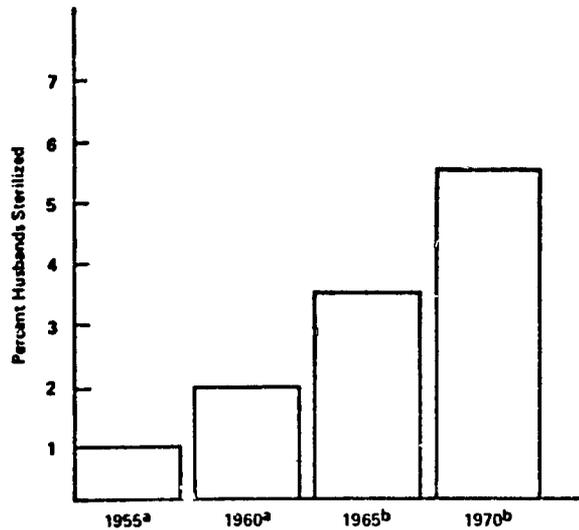
All of these procedures require extensive clinical evaluation, including assessment of the potential for ectopic pregnancies.

RESEARCH APPROACHES TO IMPROVED MALE STERILIZATION TECHNOLOGY

There exists an important potential role for male sterilization in population programs of all countries, including the developing countries. Recent dramatic increases in vasectomy in the U.S. are testimony to the demand and popularity of male sterilization, as shown in Figure 6.¹⁵

1. Vasectomy

a. Improvements in permanent techniques This section, describing techniques and modifications, draws upon a recent workshop¹⁰³ and a review by Hulka and Davis.¹⁰⁴



Sources

^a Wives age 18-39, data from: Ryder N. L. and Westoff C. F. *Reproduction in the United States 1965* Princeton University Press, Princeton, New Jersey 1971, p 151

^b Wives age 18-44 data from Westoff C. F. "The Modernization of U. S. Contraceptive Practice" *Family Planning Perspectives* Vol 4 No 3, July 1972 pp 9-12

Fig. 6. Use of vasectomy as a means of contraception by white married couples in the U.S. 1955-1970. Reproduced from J. J. Spedel (1973): Male sterilization and its contribution to solution of population problems. Presented at the New York Section of the American Urological Association, October 23, 1973, Montreal, Canada. *Urology*, 1, 277.

Bilateral vasectomy is usually an outpatient procedure performed under local anesthesia via a bilateral or single midline scrotal incision. Most surgeons prefer to cut the vas high in the scrotum where it is straight, rather than in the convoluted portion, since any subsequent attempt at reanastomosis will be simpler and more likely to be successful. A $1/4$ - $1/2$ inch segment is usually removed.

There is much variety in techniques and there have been few comparable clinical series to allow firm judgments as to which techniques are superior. Some surgeons merely ligate the stump, others fold back the proximal vas onto itself for double ligature, and others do both. Some surgeons use a non-absorbable suture, while others use chromic suture material.

Simply ligating the vas in continuity by means of sutures or clips does not suffice for permanent vas occlusion, since crushing leaves islands of epithelium which frequently join and re-establish continuity. Although widely practiced, Hanley has stated that simple division and ligation, even with removal of a piece of the vas, is not an adequate surgical technique to ensure permanence, since any apposition of mucosa may result in persistent fistula formation.¹⁰⁵

A number of investigators believe that cautery or fulguration may be a more ef-

fective procedure than ligation, with better obstruction and fewer complications due to granuloma or hematoma formation.^{103,106,107} The interposition of fascia between the cut ends may further reduce the chance of sperm granuloma formation and recanalization. McRoberts found virtually no granuloma complications following fulguration versus 10% following ligation.¹⁰³

Schmidt recently reported a series of more than 1000 consecutive vasectomies in which no segment of the vas was excised but the proximal vas was fulgurated with a needle electrode introduced approximately 4 mm into the vas lumen, using coagulating current at the same setting as used for fulgurating skin bleeders. As the current was turned on, the needle was withdrawn so that the full thickness of the vas was not destroyed until its cut surface was reached. Blanching of the muscle and destruction of the surface blood vessels were avoided; the distal vas was fulgurated on the cut surface only and the sheath of the vas was closed over it with a single suture; and no ligatures were used. With the distal vas under the vas sheath and the proximal vas exterior to it, the ends are therefore separated by a layer of fascia.¹⁰⁷ It is interesting that this procedure is remarkably similar to that described by Uchida for tubectomy which is thought to be the tubectomy technique with the lowest pregnancy rate.¹⁷

Research to develop simple instruments for cautery is underway. For many years, the technical advancement of electrocautery instruments has been limited to refinements of the original spark-gap diathermy units first introduced in 1928. Since the report of a solid state electrocautery instrument in 1968 by Petty et al.,¹⁰⁸ many modern solid state instruments have become available. Although these solid state instruments are smaller than the older spark-gap instruments, they are not fully portable; and they all require a 110 volt AC power source. The versatility of these instruments, necessary for a surgical electrocautery, adds an expense and complexity, both unnecessary and undesirable, in an electrocautery unit limited to vasectomies only.

Based on this report and on medical and technical advice from Schmidt, the Battelle Memorial Institute has designed a solid state battery powered electrocautery instrument specifically for fulguration of the vas during vasectomy (this equipment is depicted in Figure 7). The development of a concentric bipolar needle electrode reduced the coagulating power by concentrating the current in the immediate area of the mucosa of the vas. Furthermore, the extent of the lesion formed by this electrode arrangement is self-limiting, due to the concentrating of power in a small area; this overcomes the objection to previously available instruments, which required a very subjective control of the lesion by adjusting the withdrawal rate of the electrode from the vas lumen. The instrument is inexpensive, simple to use, and battery powered, making it suitable for use in extensive male sterilization programs in less developed countries.¹⁰⁹

In addition, the bipolar concentric electrode of this cautery unit may make it possible to simplify the vasectomy to a nonsurgical, "transdermal" procedure. The vas deferens can be easily palpated beneath the skin, high in the scrotum. Under local anesthesia, the bipolar needle would be inserted through the skin into the

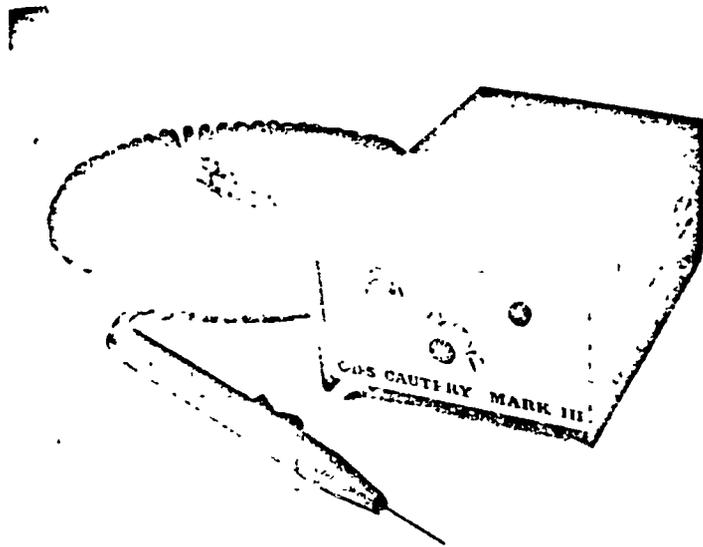


Fig. 7. Cautery equipment for vas occlusion developed by the Battelle Memorial Institute.

lumen of the vas and the current applied to fulgurize a small section. This "transdermal" technique relies on the theory that sufficient scar tissue would be formed in the intact vas to permanently block sperm flow. Schmidt reported on the successful transcutaneous use of needles heated in a diathermy field to occlude the vas of dogs.¹⁰³ In this procedure, the needle is inserted blindly, using resistance to determine when the lumen is reached.

Schmidt's technique for localization of the lumen might be used for the introduction of many types of potential vas-occlusive substances. Freeman and Coffey have reported that 50 μ l of absolute ethanol injected directly into the lumen of the vas deferens in rats and dogs resulted in sterility throughout a 6 month post-treatment observation period.^{103,4} Many investigators feel that a technique requiring transcutaneous localization of the vas lumen would prove too difficult or hazardous for general use; however, Coffey has suggested that periluminal injection of a substance might suffice.

Clips are also being evaluated for vas occlusion use. Recently, Moss reported on a simple method of bilateral vasectomy using a 3 mm single midline scrotal incision and 2 tantalum clips on each of the divided ends of the vas. A series of 400 consecutive vasectomies was performed, using tantalum clips, without any failures or other complications.¹¹⁰ Hulka and Davis also utilized tantalum clips for vasectomy, applying 2 clips to each end of the vas and removing a $1/4$ - $1/2$ inch segment.¹⁰⁴ Leader has a series of over 400 vasectomies using 2 hemoclips on each end of the cut vas (8 per operation) which has reduced complications. The clips are both hemostatic and vas occlusive, and their use further simplifies and speeds the operation.^{104,110} Questions remain as to the extent of necrosis of the wall of the vas

produced by the clip, and as to whether the clip will migrate as the vas wall becomes necrotic under its pressure. Jhaver et al.'s animal and human studies suggest that this may be a problem.¹¹¹ Additional studies are needed to demonstrate the efficacy of this promising procedure for vasectomy.

One limitation of vasectomy is the time taken for the semen to become azoospermic. Craft and McQueen studied two groups of men undergoing vasectomy. In half the men, 20 ml of sterile water was injected under pressure along the distal cut ends of the vas before ligation. Positive sperm counts were found 15 weeks post-operatively in 25% of the men who underwent simple vasectomy and in 6% of the men after vasectomy and irrigation. Studying the effect of irrigating with a spermicidal preparation was suggested, with the caution that this might result in local inflammatory reactions of the seminal vesicle and prostate, complications so far not encountered with sterile water.¹¹² Injection of a 1/1000 solution of ethacrine at the time of vasectomy is reported to dissolve spermatozoa in the vas deferens and seminal vesicles.¹¹³ Use of potassium permanganate injections to devitalize spermatozoa has also been reported.¹¹⁴

b. Complications Research regarding complications is necessary, in order to seek improved techniques and to fully identify hazards of vasectomy and other means of vas occlusion.

Mortality Presser has reviewed the literature on mortality from vasectomies and has found no deaths reported.⁵ However, several deaths from tetanus were reported from Ernakulam style vasectomy camps in India in 1971. Even so, vasectomy is one of the safest means of fertility control available.^{6,115}

Morbidity Morbidity following vasectomies is usually minor, but there is occasionally some difficulty from hemorrhage, infection, and sperm granulomas.

Sperm granuloma formation is a controversial subject, and no definitive understanding of its etiology is available. It is believed that recanalization through sperm granulomas can occur, which may account for some of the spontaneous restoration of fertility observed.^{106,116-118} Sperm granulomas are thought to be inflammatory responses to sperm leakage from the reproductive tract into surrounding tissue.¹⁰¹ While many granulomas represent simply a local foreign body reaction, others may result in a major abscess; the resultant scar tissue formation possibly precluding subsequent re-anastomosis. The extent, duration, and magnitude of sperm leakage and/or other conditions required to induce granuloma formation in man is unknown. Research on this problem – and on many of the other questions which arise regarding vasectomy – is complicated by the failure to have identified an animal model whose testicular, epididymal, hormonal, and immunologic reactions to vasectomy resemble those encountered in man.

The subject of recanalization has been reviewed by Schmidt.¹⁰⁶ He believes recanalization occurs in the following manner: fluid pressure builds up in the proximal vas after obstruction by ligation. Tissue beneath the ligatures becomes necrotic, and occasionally the ligatures cut into the lumen of both cut ends of the vas. Spermatozoa then leak into the area between the ends of the vas, and a sperm granuloma results. When the lumen of the distal vas is open and is involved in the granuloma, the

spermatozoa will drain out through the distal vas. One or more tracts develop within the granuloma. These become lined with epithelium originating from both ends of the vas, and patency is restored. If fascia is interposed between the cut ends of the vas, Schmidt believes recanalization cannot occur even if a sperm granuloma should arise. Similarly, electrocoagulation of the vas may lessen the occurrence of sperm granuloma of the vas (and thereby recanalization) by creating a firm scar at each end of the vas.

There is no evidence to date that vasectomy in any way affects the endocrine status of the human male.^{104,118-120} Pituitary-gonadal function measured prior to vasectomy and at the time of azoospermia during the follow-up period reveals no significant short-term changes in pituitary gonadotrophin (FSH-LH) or testosterone levels occurring following vasectomy.^{104,120} There is no regression of secondary sex characteristics, nor any change in composition or quantity of prostatic or seminal vesicle secretion. Ejaculatory volume, lactic dehydrogenase, glucose phosphate isomerase activity, and protein and fructose levels are unchanged.^{119,121-124} There is no indication of any effects on sexual behavior except as may be psychologically induced.^{104,118}

Several studies have shown increases in the proportion of men with spermagglutinins post-vasectomy. The proportion of men with such antibodies in serum may increase from a few percent to over 50% a year post-vasectomy.^{103,125-127} The persistence and significance of these antibodies to general health is unknown. As yet no pathology has been detected, although Roberts¹²⁸ and Henry have suggested the possibility of delayed thrombophlebitis and other systemic complications following vasectomy. The absence of consistent or convincing reports following the millions of vasectomies performed favors the view that the operation is safe.

Several studies of long range effects of vasectomy have recently been funded by the U.S. Government, and it is hoped results will be available in 3-5 years.

2. Reversible vas occlusion

a. Theoretical considerations Because restoration of fertility cannot always be achieved after anatomical reconstruction of the vas, the possibility of irreversible damage to the testes or other components of the male genital tract has been raised.

The increase in proportion of men with spermagglutinins may have no health significance but may contribute to post-vasovasostomy infertility.^{103,127} It is unknown whether sperm antibody titers decline after vas occlusion is reversed or following healing of the local trauma and sperm spillage at the time of vasectomy.

The extent to which normal spermatogenesis persists and the fate of those sperm which are produced are not yet adequately resolved. In the rhesus monkey, spermatozoa become agglutinated in the lumen of the ductuli where they are ingested by macrophages and it has been suggested that long term vasectomy results in an autoimmune response to spermatozoa which may aid in the disposal of spermatozoa still being produced by the testes.¹³⁰ Examining testicular biopsies from a group of 58 men, Heller reported spermatogenesis continued in an apparently normal con-

dition for up to 17 years after vasectomy.¹⁰³ Expanded prospective studies are required to determine how universally these limited findings apply. Phagocytosis of sperm by monocytes and polymorphs occurs in the epididymis. This reabsorption may not occur until the epithelium of the ducts ruptures. At that time sperm are exposed to immunologically competent cells and leukocytic infiltration occurs.^{103,117}

The physiology of sperm transport in the vas is poorly understood. Relatively little is known about the muscle activity and pressure phenomenon in the lumen of the vas deferens. Information on smooth muscle activity and control in the isolated rat and guinea pig vas deferens in vitro suggests a role for the sympathetic nervous system¹³¹ and a responsiveness to serotonin,¹³² electrical stimulation,¹³³ and prostaglandins.^{134,135} Activity of this organ in vivo in the resting, sexually active or vasectomized animal is relatively unknown, although spontaneous contractions, which may be under hormonal control,¹³⁶ have been observed in the rabbit.¹³⁷ Ventura et al.¹³⁸ have recently demonstrated spontaneous motility of the human vas in vitro and presented evidence that the motility of the human vas in vivo is probably under the control of the sympathetic nervous system.

Researchers working on the development of a valve device for reversible sterilization in the male are focusing more attention on these parameters, especially on their quantitative description in the proximal segment of an occluded vas. Proper valve design requires a knowledge of muscle activity and pressure changes following occlusion of the vas deferens. At present, a limiting factor in the application of devices which lend themselves to reversible male sterilization is the development of an effective device-tissue interface. The apparent increases of pressure in the proximal vas due to continued spermatogenesis and the secretory activity of the seminiferous tubules and related tubular systems, as well as the pressure changes associated with the ejaculatory response, are important to the design of a device which can be retained in the vas and which does not alter the integrity of the proximal vas segment. The quantification of the dynamics of this relationship will assist in the design and development of devices.

The magnitude of vas dilation following vasectomy is not known, nor is it known whether it is due to hydrostatic pressure, or denervation, or both. It is also not known whether the contractility and the tonus of the vas are restored after re-anastomosis.

Animal models There has been extensive discussion of the utility of animal models for the assessment of vasectomy sequelae and for the development of vas occlusive devices. The major drawback to the use of animals for testing new approaches is the marked species differences that make it difficult to transpose data to the human. For example, Bedford has studied the long-term effects of vasectomy in the rabbit, hamster, rat, and rhesus monkey. Marked distension of the vas occurred in the rabbit, rat, and hamster and progressed to the cauda epididymis and eventually to the corpus, at which time lesions, ruptures, and scars could be seen in the caput and/or cauda epididymis.¹⁰³ Depression of spermatogenesis and decreases in androgen production and testicular weight are observed after vasectomy in rodents.

In distinct contrast, a far less marked response to vasectomy is observed in the rhesus monkey. There are morphological and functional changes in the epididymis and particularly in the ductuli efferentes. Epididymal and vas distension are less pronounced, partly due to the presence of a large amount of interstitial tissue. The ductuli enlarge as much as 4 times in diameter, and the epithelial basal lamina thickens considerably. The number of ciliated cells is greatly reduced and, in those remaining, the characteristic lipid complexes are absent. Spermatozoa become agglutinated in the lumen of the ductuli where they are ingested by macrophages. Fluorescein-labeled antibody and electron microscopy show the thickened basal lamina to be the site of antigen-antibody complexing.^{103,130}

The situation in the human is apparently similar to that in the rhesus (whose epididymal architecture is somewhat similar to man's), as most patients show only temporary enlargement of the epididymis after vasectomy.¹⁰³ Destructive changes with suppression of testicular function, such as described in the rabbit, rat, and hamster, following vasectomy have not been reported in the human.^{103,104,119,120}

For development of vas occlusive devices it is desirable to use an experimental animal with a vas similar in size and anatomy to that of the human. Freund has suggested that the guinea pig vas has an intraluminal diameter similar to that of a human vas.¹³⁹

While a great deal of information from animal studies is not transferable to the human, animal models may be suitable for such studies as biocompatibility and optimization of surface treatment to induce tissue ingrowth. Selection of the appropriate animal models for study of vasocclusive techniques is difficult, and promising approaches developed in animal research should have fairly early extension into ethical human studies. Since the physiology and anatomy of the human vas are unique, direct observation should be initiated as soon as preliminary animal studies warrant it.¹⁰⁴ It bears note that medical devices may soon come under stricter regulation by the Food and Drug Administration in the United States, and that preliminary safety and materials testing may be required in animals before human studies are initiated.¹⁴⁰

b. Vasovasostomy Reversibility of surgical vasectomy is under intense investigation. While numerous procedures for vasovasostomy have been reported, successful anatomic reanastomoses with reappearance of sperm in the ejaculate have been accomplished in only 50–80% of the patients.^{141–149} Of these successes, possibly only 20–25% result in sperm of quality suitable for impregnation, and the resulting conception rates have been low.¹¹⁸ To ascertain the success of vasovasostomy adequate follow-up is required; however, follow-up rates of less than 50% have been observed in several small series of reanastomoses.¹⁰⁴ Table 1, taken from Hulka and Davis, summarizes reported vasovasostomies and success rates.¹⁰⁴

Hulka and Davis have recently described possible factors influencing the success of reversibility: (1) the quality of semen at the time of vasectomy, (2) the technique of vasectomy, (3) the interval between vasectomy and attempted reanastomosis, (4) the technique of vasovasostomy, and (5) the fertility of the sex partner.¹⁰⁴

The original technique of vasectomy is an important factor in the chance for

TABLE 1 Reported vasovasostomies with success rates*

Author	Country	Year	No. of cases reported	Criteria for success		Pregnancies		Interval between vasectomy and repair
				Cases with reappearance of sperm No.	%	No.	%	
Strode	U.S.A.	1937	2	1	50	?	1	8 mth - 7 yr
Humphreys and Hotchkins	U.S.A.	1939	4	3	75			4-8 mth
O'Connor	U.S.A.	1948	14**	9	64			5-18 yr
			420***	?191	45	?		
Massey and Nation	U.S.A.	1949	4	3	75	1	25	
Mauritzen	Denmark	1952	1	1				11 yr
Dorsey	U.S.A.	1953	6	5	83			3-13 yr
		1964-67	100	80	85			14 yr
Schmidt	U.S.A.	1956	5	4	80	3	60	
		1959	(1)	?				21 yr
Rosenblum	U.S.A.	1956	8	3	37	1	12.5	
Belt	U.S.A.	1960	24	22	92	11	46	
Roland	U.S.A.	1961	9	7	78	1	11	1-16 yr
Waller and Turner	U.S.A.	1962	10†	6	60	1	10	
Phadke and Phadke	India	1967	76	63	83	42	55	1-5 yr (50c.) 6-10 yr (17c.) 11-15 yr (6c.) 16 yr (3c.)
Mehta and Ramar	India	1970	22	20	91			3 mth - 4 yr
<i>Totals:</i>								
All reported cases			705	423	60			
Series reporting pregnancies			136			60	44	

*Reproduced from: Hulka, J. F., and Davis, J. E. (1972): Vasectomy and reversible vas occlusion. *Fertil. and Steril.*, 23, 683.

**His own series since 1920.

***His questionnaire to 750 urologists.

†Operated on since 1920.

success of subsequent surgical reanastomosis. If the vasectomy is performed with the intent of preventing spontaneous recanalization, e.g. removing 3–4 cm of vas and folding back the stumps and double ligating them, subsequent vasovasostomy is more difficult, since reanastomosis must deal with considerable scar tissue and with the requirement for traction on the proximal and distal portion of the vas.^{104,150} The new surgical techniques of vasectomy previously described may improve the chances for subsequent successful surgical reanastomosis.

“Successful” reanastomoses have been reported as long as 21 years after vasectomy.¹⁵¹ Previous infection and improper hemostasis, with resultant scarring at the site of surgery, may be more important factors in reversibility than the time between vasectomy and reanastomosis.¹⁴⁵ However, since there are so few subsequent pregnancies reported in the world’s literature, it seems fair to say that it is not known whether or not prolonged vas occlusion leads to permanent testicular failure. In evaluating reports of the reversibility of vasectomy, the interval between occlusion and reanastomosis must be considered.

Numerous techniques of vasovasostomy have been described.^{145,150,152,153} Most recently, high success rates have been reported with microsurgical techniques utilizing stereo-optical surgical microscopes.¹⁰⁴ Splinting¹⁵² and non-splinting¹⁵³ methods have both been described as advantageous. Schmidt¹⁵² has inserted polyethylene tubing, as a permanent endosplint, at the time of vasovasostomy to promote healing and reversibility. Although some pregnancies resulted, he discontinued the method because of the unreliability of the technique. The feasibility of using prosthetic devices to minimize the tension between the proximal and distal stumps in the reanastomosis attempts and the feasibility of using grafts of vein rather than artificial material to provide a channel for such reanastomoses have been suggested.¹⁰⁴

As noted above, very little is known about the mechanisms regulating sperm transport in the male reproductive tract. Ventura et al.¹³⁸ have shown that the human vas deferens has spontaneous motility *in vitro* and that it responds to the administration of norepinephrine with a series of powerful contractions. They propose that *in vivo* intrinsic rhythmicity of the human vas deferens is dependent upon the local concentration of norepinephrine, while the powerful and coordinated series of contractions that propel the sperm from the epididymis to the urethra during ejaculation are initiated and controlled by the release of substantial amounts of norepinephrine from sympathetic nerve endings. This suggests that an intact sympathetic nerve supply may be vital to the transport of sperm from the epididymis at the time of ejaculation. The question of whether this sympathetic nerve supply is adequate or will regenerate following a vasovasostomy performed 5, 10 or more years after vasectomy remains unanswered.

Bedford suggested that failure of the nerve supply to regenerate after reanastomosis may result in semi-functional muscle tissue.¹⁰³ Approximately 70% of the sperm in a normal individual comes from the region proximal to the point where vasectomy is performed, and movement of sperm during ejaculation requires a powerful series of coordinated contractions. Sperm counts after reanastomosis tend to be low, and it may be that sperm are simply pushed out under pressure rather than as a result

of contraction. Division of the inferior spermatic nerve should be followed by re-innervation, but damage to or removal of the nerve stump and presence of scar tissue may make this impossible. A major question that must be answered is whether normal or near normal function can return without this nerve supply.

It is thought that use of a small longitudinal incision in the vas sheath at the time of the original operation is the best technique to preserve the nerves and blood vessels which ramify to the vas from the vas sheath. Winer feels that the high success rate that can be obtained when both the original vasectomy and the subsequent re-anastomosis are carefully performed indicates that impairment of the blood and nerve supply can be avoided.¹⁰³

With an increased understanding of the mechanisms controlling vas motility and of the effects of vasectomy on the innervation of the vas, a scientific basis may be provided for the development of a standard vasectomy operation and for an improvement in the vasovasostomy success rate.¹³⁸

Many of the considerations for reversibility of surgical vasectomy also apply to reversibility following use of a vasocclusive device.

Transplantation of the vas The authors wish to suggest a new, and to our knowledge as yet untried, surgical technique for sterilization: transplantation of the vas into the bladder. This would have the disadvantage of requiring intra-abdominal surgery, and the effects of increased pressure of urine on coughing and at micturition would have to be assessed. Potential advantages include minimal disruption of sperm transport and vas physiology. Reversibility might be accomplished by either (a) re-establishing normal anatomy or (b) removal by catheter of semen from a previously saline filled bladder after ejaculation for artificial insemination.

This latter procedure has been successfully used to effect conception in cases of retrograde ejaculation. It is recognized that this suggested procedure may prove to be impractical but it is one example of the many innovative surgical approaches for male sterilization which deserve consideration.

c. Intravasal plugs The search for a satisfactory reversible method of male sterilization has led to experimentation with different methods of vasal obstruction. Preliminary reports of obstruction with injected silicone, plastic threads, tapered tubes, and silver clips are often optimistic. However, long-term studies accompanied by breeding tests are needed, and the relevance of these studies to humans may be questionable.^{111,154-157}

The availability of medical grade elastomers prompted investigation of such substances for temporary occlusion of the vas deferens by plugging the vas from within.¹⁵⁸ In the 1960's, injections of silicone rubber and other non-reactive synthetic materials were attempted in animals and man.¹⁰⁴ Hardlicka et al. reported complete vas blockage by injection of silicone rubber, and a normospermic condition followed after its removal by vasotomy.¹⁵⁵ Zinsser, investigating silicone plugs in dogs and pigs, found signs of degeneration after 8 to 9 months, although sperm leakage did not occur.^{159,160} Zinsser, as well as some groups in India, have been experimenting with a 1.5 mm silicone thread; but it has been difficult to insert, and long-term follow-up has been discouraging.¹⁵⁹

Laurence injected medical grade liquid silicone rubber into the vasa of rats, guinea pigs, and rabbits. Azoospermia lasted only a few months. Then, sperm reappeared and pregnancies ensued due to the expulsion or displacement of the silicone plugs.¹⁵⁸ The sperm usually reappeared around a channel of recanalization between the foreign body and a side of the wall of the vas in which it had been placed.¹⁰⁴

Hooker and Gilmore found that injection of 0.15 ml of Silastic Medical Adhesive (Silicone Type "A" – a non-flowing soft silicone paste) into the vas deferens of rats was an effective method of sterilization. An observation period of only 21 days precluded an assessment of the long term efficacy of this approach. Fertility apparently could not be restored by simple removal of the obstructing plug, because local tissue reaction caused permanent vasal stenosis in the area of injection. In addition, spermatoceles had frequently formed in the epididymal region, indicating tubal rupture; and it was considered most unlikely fertility would have returned. Similar results occurred in rabbits, except for the absence of spermatocele formation.¹⁵⁴

From the studies described above, it is apparent that the elastomers can only be effective in occluding the vas if they can be fixed in place with no movement within the lumen.¹⁵⁸ Any substance used to block the vas deferens must also compensate for dilatation of the vas and for channel formation around the material. The substance should adhere well to, and therefore probably require ingrowth from, the wall of the vas so that permanence and total impenetrability to sperm are insured.¹⁰³ In order to provide reversible sterilization, adhesion should be great enough to prevent sperm passage, but should not be so great that removal causes extensive tissue damage.

For this reason, experimental studies are now going on to evolve materials which will effectively occlude the vas and prevent recanalization by provoking an appropriate tissue response, resulting in attachment of the vas to the prosthetic device.¹⁰⁴ Possibilities for prosthetic devices designed to block the vas deferens, which were discussed at a recent workshop,¹⁰³ include: (1) porous core materials, (2) a porous core filled and coated with a hydrogel, (3) a hollow fiber with the proper negative charge, possibly coated with hydrogel, and (4) a solid or porous core coated with flocculated fibrils. The criteria used for the selection of biomaterials include: (1) they must have the required physical properties, (2) they must be easy to purify, fabricate, and sterilize, (3) they must maintain their physical properties and function over the desired time period, and (4) they must not produce any undesirable side reactions. Biomaterials may be plastics, metals or ceramics; and they are used in the form of fibers, films, foams, tubes, rods, etc. The possibility of using Dacron or Teflon to establish contact between plastic or metal and tissue has been suggested.¹⁵⁹

An alternative materials approach may be the use of the GRF preparation, previously described for sterilization of the female, to provoke an appropriate inflammatory response and tissue ingrowth which will effectively occlude the vas. Whereas it is yet too early to assess the effectiveness of GRF for vas occlusion,

Quinacrine can be used to occlude the vas. Setty et al. found that a single intraluminal injection of 1–2 mg Quinacrine dihydrochloride in aqueous carboxymethylcellulose (CMC) suspension effectively occluded the vas in 15/18 rats tested. CMC appeared a suitable carrier for localizing the Quinacrine for a sufficient period of time to permit granulomatous tissue formation in the desired sector of the vas.¹⁶¹

Moon and Bunge have reported use of a plastic device made of polyethylene tubing. The device is 7 cm in length, with the midportion occluding the lumen about 3 cm in length. The ends, which are left protruding from the vas, are clamped with silver clips to prevent mobilization of the device and to serve as a mark of identification for subsequent removal of the tubing. This procedure has been carried out on 13 dogs. Consistent azoospermia was observed in 12/13 dogs at 2, 3 and 4 weeks after insertion. At 4 weeks, the devices were removed from the 12 dogs with successful occlusion, and by 4 weeks, post-removal sperm motility and number were grossly normal and histological changes in the vas were minimal. Breeding studies were not conducted.¹⁶² It should be noted that the experimental time period in this study was short and more extended periods of observation are needed to evaluate several uncertain factors, such as tissue reaction, quality of semen, and improved material for the device.

d. Intravasal devices Work on intravasal devices which is somewhat distinct from plugs and valves has proceeded on two bases: (1) on devices which completely block passage of sperm, and (2) on the possibility of interfering with the function of the vas or damaging the sperm, without interfering with sperm flow, by chemically or mechanically disrupting the maturation process, or otherwise traumatizing the sperm as they travel through the vas. It is possible that sperm are vulnerable to the altered environment which would result from the presence of a foreign body inside the vas. Thus, sperm would continue to be produced in the testis and to appear in the ejaculate but would be incapable of fertilization. Hulka and Davis have suggested that sperm may sustain slight enzymatic damage while traveling through the segment of vas containing the intravasal device.¹⁶⁴

A number of investigators have studied the effects of silk or nylon thread,¹⁶³⁻¹⁶⁵ thick nylon wire or other synthetic material¹⁶⁶ devices that partially occlude the vas and are anchored to its exterior surface. Subsequent ejaculates are either azoospermic or contain a high percentage of disrupted spermatozoa. The effect in man is short-lived, so that restoration of high sperm counts is not infrequent.¹⁶⁴

Lee placed an intravasal thread of either surgical nylon or silk into the vasa of 216 men. Sperm passage was inhibited in 90% as long as the thread remained in place, while sperm reappeared in the ejaculates of 10% (21/216) with the thread still in situ, due to dilatation of the vas, possibly resulting from increased intravasal pressure caused by continued spermatogenesis. Eight subjects were studied for reversibility 8 months after the thread had been inserted, and 7 exhibited reappearance of sperm.¹⁶⁵

More recently, Lee has investigated an intravasal thread device which is 3 cm long, is made of non-absorbable nylon and silicone, and is flocculated to permit tissue ingrowth. It is held in place by a filiform thread tied around the vas. The device

has a diameter of 0.8 mm (the average vas diameter of Korean men is 0.3 mm). Sperm content dropped below 7 million ($\frac{2}{3}$ of these to zero) in 408 cases, but it increased later in 30. In the latter cases, the device had been extruded from the vas due to its stiffness. A local foreign body reaction has been found in the region of the device. Only 1–2 pregnancies have resulted from those patients having a sperm count below 7 million. Insertion of the device can be performed under local anesthesia requiring 15–20 minutes, compared to 5–10 minutes for the standard ligation procedure. Complications are minimal, with only minor inguinal discomfort and some tissue firmness.¹⁰³

The problem of sperm escaping through the dilated vas lumen around the intravasal thread device must be overcome before the procedure will be acceptable as a means of contraception.¹⁶⁵ Reversibility after removal of the device should be confirmed by actual conception.

Freund is currently investigating a reversible vas device consisting of a string of silastic balls which are 2.0 mm in diameter and 3.0 mm apart. The needle of the device is inserted through the wall of the vas and into the lumen. A small longitudinal incision is made into the wall and the device is stretched to decrease the diameter of the balls and to permit their passage into the vas. The ends of the device are brought together and tied, and the small longitudinal flap incision is closed with a single suture. The device has been inserted in 24 guinea pigs and, during 3 months of observation, sperm blockage has been complete when the device has been properly inserted. No irreversible damage to the vas has been observed. As yet the device has not been removed to test for reversibility. The device is currently being tested in human cadaver material to determine compatibility with respect to size and to refine the insertion technique.¹⁶⁷

e. Clips Another approach to temporary occlusion of the vas is the placement of external clips around the vas. The initial attraction of this approach was its ease of applicability and the hope that it would be reversible by simply removing the clips.

In preliminary studies by Jhaver et al. the use of tantalum clips for reversible vasocclusion was tested in 13 dogs. 25% of the clips applied were dislodged during the course of the study (presumably due to muscular contractions of the vas) and application of 2 clips per vas was required to effect aspermia (still with a projected 6% failure rate). Simple removal of the clip, alone, to accomplish reversal of sterility was not supported by the study. Although fine dissection requiring considerable surgical skill was needed to expose and remove the clips in some cases, it was judged that the relative absence of scar tissue in the majority of vasa occluded by the tantalum clips was less than following conventional vasectomy, thus rendering subsequent reanastomosis technically easier. However, in the 4 dogs in whom reanastomoses were attempted after successful vasocclusion, sperm reappeared in the ejaculates of only 2.¹¹¹ While the observed formation of less scar tissue may offer a theoretical advantage for reversibility, any optimism for the use of tantalum clips for reversible sterilization of the male – in light of this preliminary study showing high failure rates and questionable reversibility – should be guarded.

f. Vas valves An intravas device equipped with a valve would have the advantage

of allowing the sperm either to go through the device or not, according to the wishes of the man.

Davis and Freund are developing a T-shaped device called the Bionyx Phaser, which is permanently implanted into the vas, with a valve which can be turned "on" and "off" to permit flow of sperm as desired. The device, made of gold with a stainless steel stem, is covered with a mesh designed to promote tissue ingrowth so that a permanent attachment to the vas is formed. The vas is transected high in the straight portion, the mucosa is cored out, and the device is inserted 1 cm into each side. The valve stem is placed perpendicular to the vas in the "off" position. In preliminary clinical tests, 9 of 10 volunteer subjects became azoospermic and resembled normal vasectomized patients. In the 10th patient, the valve was found to be improperly positioned, and he became azoospermic when the valve was correctly placed in the "off" position. Valves placed in the vas in the "on" position have caused no reduction in sperm counts. In future studies, the valves will be turned to the "on" position to see whether sperm counts and motility return to normal.^{103,160}

Davis reports that the device has been inserted in approximately 40 men; and when properly in place, the flow of sperm can be controlled. Extrusion of the device has been a problem, and modification in device size, valve design, and surgical insertion technique are currently being investigated. (At present, insertion is a 1 hour procedure, performed under general instead of local anesthesia.) It has been demonstrated in both guinea pigs and humans that tissue ingrowth has been achieved. Safety studies with the device have been favorable.

The IIT Research Institute is engaged in developmental work on vas valve devices using the dog as an experimental animal.⁵³

Similar studies are underway at the Battelle Memorial Institute. A Battelle designed valve device requiring transection of the vas for insertion is shown in Figure 8. Adherence of the vas mucosa to the valve tubing remains a key problem.

The tubing must have an adequate inside diameter to minimize resistance to fluid flow, while it must meet the necessary limitations on outside diameter imposed by the vas cross-sectional diameter. Most velours or mesh coatings prove too bulky or are too difficult to insert into the vas without causing undue trauma. An alternative

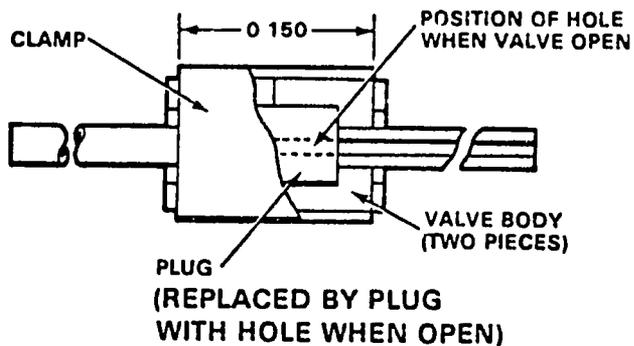


Fig. 8. Vas valve.

Table 2. Male antifertility agents – pharmacologic activity.
(pp. 418–429)

approach being studied is the use of micro-tubing with 100 micron pores on its exterior surface and a relatively impermeable core. Neither of these designs resolves the problem of increased pressure in the vas following occlusion.

It is possible that high (but as yet unmeasured) pressure following vasectomy may dislodge the valve before ingrowth can secure it or before fibrous ingrowth can form a perfect seal. Since the vas is easy to manipulate through the scrotum, a manual valve could be installed in the open position and closed after healing had occurred. An alternative way to avoid pressure build-up is through use of a vented valve. In view of the evidence in the literature concerning the fate of spermatozoa in the obstructed male tract, which appears to involve the eventual disruption of the epithelial lining of epididymis or proximal vas, it may well be meaningful to consider venting sperm into the tunica cavity. If spermatozoa are not absorbed in the intact tract, the argument can be made that they have to be dealt with eventually by the reticuloendothelial system. It might improve the reversibility of the procedure if these mechanisms were permitted to deal with the sperm at a steady and constant rate (with no damage to the tract) rather than as a relatively sudden and massive invasion following epithelial rupture with associated pressure damage to epididymis, peripheral vas, and possibly other more remote structures, such as vasa efferentia or testis. The valve shown in Figure 8 can be modified to include a vent.¹⁰⁹ Of course, sperm granulomas and spermatoceles could be a problem with this approach, and not enough data are available at present to judge its practicality.

3. *Chemical approaches to male sterilization*

Although discussion of a reversible chemical male contraceptive is not an objective of this paper, some attention to agents which cause short term reversible infertility is necessary since they might be useful in a prolonged release delivery system as male chemosterilants.

Research efforts on pharmacologic control of male fertility have been far less than studies on the female. To date, not a single acceptable chemical method for the male has evolved. Considerably more research, involving a fuller understanding of the normal reproductive physiology of the human male, is needed to permit a rational search for agents to control fertility in the male. In addition to agents which cause reversible interruption of fertility, consideration should also be given to agents which produce permanent sterility and could be used as an alternative to permanent surgical sterilization.

Many types of agents affect the germinal epithelium adversely. Most research in this area has focused on inhibition of testicular function, either by direct action of an agent on one or more of the stages of germ cell multiplication and differentiation, without affecting the endocrine system, or secondarily by suppression of gonadotrophic hormones.

In addition to the chemical inhibition of events occurring within the seminiferous tubules, the alteration of rete, epididymal or vasal function, or of the spermatozoa within these structures, affords another approach to male sterilization. Advantages

to the interruption of post-testicular events are the more rapid onset of effectiveness following initiation of treatment and the potential provision for a more rapid onset of reversibility. Also, since there is less likelihood of altering Leydig cell steroidogenic processes, libido should not be altered.

As Jackson pointed out, very simple molecules like methylmethanesulphonate, hexamethylphosphoramide, trimethylphosphate, and α -chlorohydrin can exert striking selective actions on the spermatogenic process. With the range of chemicals now available, it is time that serious efforts be made to evaluate the possible consequences in the male of long-term suppression of fertility by interference with different stages of the spermatogenic process. A combination of agents, incorporating a functional action along with testicular inhibition, might eventually lead to an acceptable combination.¹⁶⁹

A general limitation to the chemical approach is the necessity of an agent that would prevent the appearance of any sperm cells in the ejaculate. This is evidenced by the fact that a man normally produces over 100,000,000/ml sperm cells a day, but that a sperm output of as low as 10,000,000/ml may cause pregnancy.¹⁷⁰ A further important reason for suppressing the appearance of sperm completely is the risk of releasing genetically damaged sperm that can still fertilize. This must also be considered during the recovery phase in the case of a reversible chemosterilant. Breeding studies in animals carried out over several generations are required to rule out the possibility of genetic damage. The question of genetic damage, occurring as a consequence of altering any of these events, has no doubt inhibited the enthusiasm for developing chemosterilants which affect spermatogenesis or mature sperm. It is perhaps unwise to assume that this damage is inevitable. The question may indeed be useful in directing subsequent safety studies, but it should not be arbitrarily employed to preclude the characterization of interesting chemical leads.

Patanelli has recently prepared a comprehensive summary of chemical agents affecting fertility in the male, and much of our presentation of the subject is taken from this work.¹⁷¹ There are a great number of compounds which affect male fertility, and most are not suitable for long term male fertility control because of toxicity or side effects. Representative compounds are presented in Table 2.

4. Delivery systems for male antifertility agents

With the availability of suitable drug delivery systems, a number of compounds become candidates for use as chemosterilants including those for which antifertility properties are already well established. Ewing et al.¹⁷² and Stratton et al.¹⁷³ reported that testosterone-filled polydimethylsiloxane capsules implanted subcutaneously into rabbits induced azoospermia without any significant alteration in either plasma testosterone concentration, libido, or the weight or secretory activity of accessory sex glands. Apparently, the testosterone released from these subcutaneous implants was sufficient to block gonadotrophin release from the pituitary and to maintain accessory organ function, but was insufficient to support – by direct stimulation of the seminiferous tubules¹⁷⁴ – spermatogenesis. It remains to be determined

whether the potential hepatotoxicity and the perhaps theoretical concerns of prostatic hypertrophy, prostatic carcinoma or other neoplasia, and atherosclerosis which have precluded serious consideration of androgens for induction of azoospermia previously, can be avoided by selection of the proper androgen and dosage level.¹⁷³⁻¹⁸⁰

Subcutaneous polydimethylsiloxane implants, containing cyproterone acetate, render rats sterile without inhibiting spermatogenesis, libido or accessory organ secretory activity. This effect persists throughout the 6-month-period for which the implants are left in place. In contrast to the androgen-induced inhibition of spermatogenesis, this response is due to the antiandrogenic properties of cyproterone acetate which cause a loss of motility and viability of the sperm. This reportedly is a result of alterations in the post-testicular environment of the sperm.^{181,182} These effects have not been corroborated using implants of either cyproterone acetate or norgestrel.^{182a}

Should either of these subcutaneous systems prove effective in man, a number of steroid hormones and hormonal antagonists could be envisioned as candidates for inclusion in the delivery device.

The recent report of Free et al.,¹⁸³ describing a testosterone concentrating mechanism for the testes, provides renewed emphasis for the development of a scrotal delivery system for the localized administration of pharmacologic sterilants. Following infusion of tritiated testosterone into the testicular vein, they found the level of labeled testosterone in the testicular artery to be many times higher than that in the femoral artery. Thus, the testes apparently recirculate hormones produced locally. This phenomenon, coupled with the normal diffusion of drugs through tissues and the extensive collateral links in the scrotal/testicular circulation, suggests that certain drugs released in the scrotum will be provided to the testes and associated structures at levels which are substantially in excess of their level in the general circulation. Selected antifertility compounds readily pass the blood-testes barrier and presumably have reasonably free access to the germinal epithelium and the lumen of epididymis.^{184,185}

Substances inhibiting spermatogenesis or subsequent sperm maturation and function may be effectively concentrated by this system, thereby producing antifertility effects at dosages significantly below the pharmacological doses presently required. A number of compounds which have well-established contraceptive properties, dependent upon regional effects on the male reproductive tract, but which also have an unacceptable spectrum of side effects, are now potential candidates for contraceptive studies. Classes of male antifertility drugs which would benefit from recirculation and diffusion effects are: (1) those suppressing primary spermatocyte maturation, exemplified by the heterocyclic compounds nitrofurans, dinitropyrrroles thiophenes, the dichlorodiacetyldiamines, and the nitroimidazoles; (2) those affecting spermatogonium development, as exemplified by the alkalating agents; (3) those affecting secondary spermatocytes and spermatids, as exemplified by fluoroacetamide; (4) those affecting the epididymis such as α -chlorohydrin and the antiandrogens, cyproterone acetate, and 4-nitro-3-trifluoromethylisobutyranilide; and (5) non-steroidal hormonal antagonists such as the polysiloxanes.

Gonadotrophic hormones, locally administered, are likewise candidates for inclusion in scrotal delivery systems. Building upon an earlier observation of Murphy¹⁸⁶ that intratesticular injections of follicle stimulating hormones (FSH) in the immature hypophysectomized rat caused depletion of germinal cells, Cervantes and Lyons¹⁸⁷ have shown that intratesticular injections of relatively low doses of FSH caused an inhibition of spermatogenesis and desquamation of mature germ cells, resulting in infertility in mature rats. The effect was reversible within 3 weeks of discontinuing treatment. The mechanism involved in this response and the uniqueness of FSH for its induction remain to be established.

As with any implant system, a scrotal delivery system must be comprised of an inert, biocompatible material which can contain a sufficient amount of drug to provide a uniform release for the desired – or at least acceptable – time interval. These conditions are now technically well within the realm of possibility.¹⁸⁸

5. Other methods of male sterilization

Various physical insults can stop sperm production. Heat and X-ray have been studied, and diathermy, ultrasonic waves, and laser beams have been suggested, but none of these has been tested to any real extent.¹⁸⁹ X-ray and possibly heat have the drawbacks of possible mutagenicity and carcinogenicity discussed earlier in this paper.

6. Immunological approaches to male sterilization

Shulman,^{88,89} and Katsh and Katsh⁹⁰ have reviewed the status of attempts to bring about infertility in males using immune mechanisms. The findings of autoimmunity in some infertile human males and the (inconsistently) successful attempts to cause infertility in laboratory animals by immunization with antigens from various sites in the male genital tract suggest that there is some potential to this approach. Antigens have been identified in many sites and tissues which might cause infertility following an antigen-antibody reaction. These include the testis, seminal vesicle, prostate, sperm cell, seminal plasma, and the gonadotrophins FSH and LH.^{190,191}

It would seem that there is no early prospect for success because of two problems: (1) the unavailability of suitable adjuvants for human use which could ensure a sustained and consistent immune response without local tissue damage at the injection site, and (2) the failure to isolate adequately specific and pure antigens to ensure an antibody response of adequate intensity and specificity, without cross reaction with other tissues.

Therefore, considerable basic research must be carried out before sterilization by vaccination can become a reality.

7. Semen storage

A potential approach to ensuring fertility of a vasectomized man is to preserve his

donated semen by freezing in a so-called "sperm bank." Pregnancy rates in the human can be quite high following frozen storage but are usually lower than with fresh semen. A 10–60% decrease in motility can be expected with current techniques of storage. This has been thought to be a function of the freeze thawing cycle and not a function of duration of storage; however, recent studies by Smith and Steinberger suggest that motility loss also occurs with time (20% in 5 years).^{103,102,103} Frozen semen has been used with success after 3–4 years and, in a few cases, with storage of 5–8 years.^{104,118} Additional evidence of the deleterious effect of freezing on fertilizing capacity was reported by Steinberger who found a mean sperm count of semen which successfully induced pregnancy to be about 50% higher in fresh than in frozen semen.¹⁰³

Although offspring born from artificial insemination with frozen semen appear to be normal, their numbers are still too small (less than 1000) to state with assurance that some adverse effects will not appear. So far, miscarriages and congenital defects do not appear to be increased.

A number of studies need to be carried out to seek the best possible freezing and thawing techniques, to determine long term survival and fertilizing capability of frozen semen, and to ensure no deleterious effects on the offspring resulting from insemination with frozen semen.

Freund has suggested the importance of establishing foolproof means of positively identifying frozen semen and has emphasized the importance of developing techniques to work with diluted human semen. Dilution allows preparation of many samples from a single donated semen specimen. This would facilitate conduct of controlled and replicable studies and, if such semen is effective for artificial insemination, it could increase fertilization rates by allowing several attempts at fertilization with a single donated specimen.¹¹⁴

At present, it would not seem wise to offer semen storage as a means of preserving fertility after vasectomy since, for any individual, surety and duration of maintenance of fertility are not known.

Summary and conclusions

This paper has attempted an overview of current research approaches to improved sterilization technology. It has also offered commentary concerning needed basic research to provide knowledge of reproductive physiology, which can then be exploited to develop improved means of sterilization technology.

Until recently, research efforts to develop new and improved means of fertility control have by and large focused on reversible contraceptives. The annual surveys of U.S. Federal Support for research on fertility control technology reveal that only a minute fraction of this support goes for sterilization research. Growing recognition of the important role and popularity of sterilization has stimulated increased funding and efforts in sterilization research in recent years. There appear to be promising research approaches to improved sterilization technology, which it is hoped will make practical the further extension and utilization of this means of fertility control.

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