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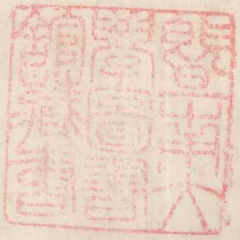

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Reviews

An Overview of Research Approaches to the Control of Male Fertility

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The purpose of this paper is to discuss the following questions:

1. What are the most appropriate objectives of research on male fertility?
2. What is the status of current research efforts?
3. What new approaches are needed and what research strategy should be pursued?

No attempt will be made to pursue these issues in depth; rather the intent is to provide an overview.

OBJECTIVES OF MALE FERTILITY CONTROL RESEARCH

Research to control, i.e., decrease or eliminate, male fertility is currently pursuing a number of objectives. The relative importance one places on various research objectives is, of course, related to judgment and point of view. For example, some may consider questions of safety paramount and therefore wish to focus research on side effects of vasectomy. The major interest of the authors is in developing improved technology for the control of male fertility for use in developing countries. Therefore, this discussion will emphasize research goals that meet the needs of these countries.

Fundamental questions that must be answered relate to the willingness of men to use fertility control and furthermore to the relative acceptability, cost and availability of a particular technique. The first important point to be

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made is that men are willing to share the responsibility for contraception. In 1970 among couples in the United States practicing contraception, one-quarter used a male method: condom, 14.2%; male sterilization, 7.8%; and withdrawal, 2.1% (179). Male methods predominate in much of Europe and Japan (28). Rough estimates suggest that of the approximate 154 million users of contraceptives in developing countries, 57 million or about 37% employ male methods: 15 million sterilization, 18 million condom and 24 million withdrawal (158, 163). Male willingness to accept responsibility for fertility control is further evidenced by the recent worldwide increase in demand for vasectomy (158). In the United States perhaps half a million men were sterilized in 1973 (73). Although a male contraceptive pill of injection is not yet available, a survey of 438 males indicates that 70% of those interviewed would accept such a method (149). It would seem, therefore, that improving male fertility control technology is a useful objective.

RESEARCH ON RELATIVELY IRREVERSIBLE TECHNIQUES

Although permanent sterilization is not offered in many family planning programs, available evidence suggests that it is acceptable to many individuals. 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 (90, 129, 130, 159, 164). Survey research in many countries also reveals a great potential demand for sterilization and a satisfaction with results among the sterilized (55, 57, 130, 131, 158, 179). 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 (90, 130, 136, 161). Although special centers for reversing sterilizations were established in India, Pakistan and South Korea, few requests for reversals are received (157). In Korea and the United States about one or two per thousand of those receiving a vasectomy request a reversal (94, 139).

The initial cost for sterilization programs in the developing countries may be high. However, there may be an ultimate programmatic advantage in that the need for maintaining a continuing service program to provide reversible contraceptives would not be needed, especially if nonclinical distribution of the contraceptive were not possible (158). Therefore development of improved irreversible techniques for male sterilization would appear to be an important and valid research objective. Research along these lines has included attempts to develop a transcutaneous vasectomy, modifications of standard techniques, e.g., use of cautery and clips, and use of various flushing solutions to decrease the duration of postvasectomy fecundity. In the formu-

lation of research objectives it should be borne in mind that procedures requiring costly and difficult-to-maintain equipment or undue technical skill may prove to be impractical in developing countries. The ability of country programs to provide the method safely, effectively and inexpensively must be considered. Desirable characteristics of a method include: 1) out-patient in preference to in-patient procedure; 2) provision by paramedical or nonmedical personnel, with minimum of training and minimum follow-up care or supervision required; 3) no sacrifice of the virtues of currently available methods, particularly with respect to safety, efficacy, cost and user acceptability.

RESEARCH TO IMPROVE REVERSIBILITY

If sterilization were reversible, it is conceivable it would be more widely accepted by individuals in both the developing countries and the developed countries.

In the United States the success of centers offering semen preservation and the enthusiasm of volunteers for experimental, possibly more reversible male sterilization procedures and apparent willingness to receive a pill or injection suggest that availability of more reversible methods will broaden the appeal of male fertility control. A delay in return of fertility following use of a reversible male method could have some influence on acceptability of such a method. However, until such a method is actually made available, the question remains speculative. In the last analysis it is impossible to judge the importance of this research objective since we have no valid way of measuring its impact a priori. What little evidence there is suggests that improved reversibility would enhance use of what is currently a demographically important method and therefore is an important research objective.

RESEARCH ON SAFETY OF CURRENT MALE TECHNIQUES, i.e., VASECTOMY

Safety of any medical procedure is important, especially when applied to millions of otherwise healthy individuals. Clear evidence of safety could also enhance the appeal of the method or at least allow a valid assessment of risk versus benefit. However, in the absence of any compelling evidence of serious risk of vasectomy, this research objective would seem to be of somewhat lower priority.

CONDOM RESEARCH

The condom is a very prevalent and effective means to control male fertility. Research to improve condoms might be accorded a moderately high priority.

BASIC RESEARCH ON MALE REPRODUCTION

A number of the objectives noted above could be pursued more rationally, if greater knowledge of reproductive physiology were available. This area should also be accorded a moderately high priority.

CURRENT AND NEEDED RESEARCH ON MALE FERTILITY

OVERVIEW OF RESEARCH SUPPORT

Excellent data on United States federal support of population research are prepared on an annual basis by the Interagency Committee on Population Research (74, 75, 126, 168, 169). Data from private sources including foundations and drug companies are not nearly so accessible. However, an analysis of the federal data is hindered by inability to determine if male or female research is involved, or the proportion of a grant or contract devoted to the male or the proportion devoted to animal or human species. The reader should therefore recognize the limitations of this analysis and consider all figures to be approximations.

A review of federally supported research on reproductive processes over the past several years reveals that funding for projects related to the male has lagged substantially behind those for the female. Perhaps reflecting some increase in interest in male reproductive physiology and the control of male fertility, the ratio of dollar support for federal research reported on male anatomical sites versus female anatomical sites increased from 1:4 in fiscal year 1972 ($5,768,000: $22,873,000) (74) to 1:3 in fiscal year 1973 ($5,648,000: $18,387,000) (75). However, the proportion of funds committed to male studies relative to all federal biomedical fertility research has changed little between fiscal years 1970 and 1973.

Approximate federal funding of male fertility research for fiscal years 1969–1973 is shown in Table 1. Between 12 and 17% of total funds have been devoted to male studies. Most of the support provided goes to rather fundamental studies under the categories of male fertility, fertilization, steroid hormones and other reproductive processes. Only a very small proportion of support is provided to applied research on male contraception. A recent development is the provision of a relatively large amount of funds to support studies on side effects of vasectomy (8).

A more detailed breakdown of the category "Male fertility" in Table 1 is provided in Table 2. This category of federally supported research is fundamental in nature. The 61 studies supported in fiscal year 1973 can be classified into scientific disciplines as follows: 26 biochemical, involving research on macromolecular (DNA, RNA, protein) metabolism and function; 11 tissue

TABLE 1. Approximate Federal Support of Biologic Male Fertility Research by Category and Fiscal Year*

Research Category	Fiscal Year (thousands of dollars)					1973 Funds for Human Studies	
	1969	1970	1971	1972	1973	Amount	%
Male fertility	519	1722	2457	3022	2724	483	18
Fertilization†	714	1262	1393	1224	1090	143	13
Steroid hormones (androgens) and reproductive processes	219	235	453	674	603	77	13
Contraceptive development	75	61	744	815	324	68	21
Side effects of vasectomy	0	0	0	819	1462	720	49
Total‡	1527	3219	5047	6554	6203	1491	24
% Total Biologic Fertility Research	12	12	17	15	15		

* From (74, 75, 126, 168, 169).

† Fertilization research relates to both male and female reproduction.

‡ May not include all male fertility research since titles are not always adequately descriptive and some projects are listed under multiple categories; also female fertilization projects are included.

TABLE 2. Details of the $2.7 Million of Federal Research Support Listed as Male Fertility in Fiscal 1973*

Scientific Discipline	No.	Experimental Animals Used	No.	Anatomic Site and Body System	No.
Biochemistry	20	Rodents and rabbits	33	Sperm and semen	29
Physiology	11	Others (including birds, invertebrates and		Testis, epididymis and vas deferens	28
Anatomy	10	multiple species)	12	Other	4
Endocrinology	7	Domestic animals	8		
Cell and molecular studies	6	Humans and other primates	8		
Genetics	3				
Immunology	3				
Biophysics	1				
Total	61		61		61

* See Table 1. Data provided by the Interagency Committee on Population Research.

metabolism; 7 endocrinology; 10 microscopic anatomy; 3 immunology; 1 biophysics; and 3 genetics (73a). In this category, as in the others noted in Table 1, only a small proportion of the research involves humans.

Between fiscal years 1967 and 1974 the Agency for International Development has obligated $35.8 million for fertility research; of this amount, $1.7 million or 5% has been allocated for male contraceptive development (124).

On an international basis perhaps 40% of contraceptive development and reproductive biological research funds are provided by the United States federal government. The remainder of funds is from scattered sources, the most important being other governments, private foundations and pharmaceutical

firms (161). The effort of these organizations does not appear to be large in male fertility. For example, in fiscal year 1969, the most recent year in which data are available for private United States funding of male fertility research, only 11 of 74 projects received funds from nonfederal sources (125). The World Health Organization's Programme of Research in Human Reproduction expended $7.4 million in 1972; of this amount $408,500 or 6% was specifically allocated for research on male fertility regulation (181).

RESEARCH ON PERMANENT METHODS

Vasectomy

Many surgical techniques of vasectomy are practiced, and there have been too few comparable series using standardized surgical procedures to allow firm conclusions as to which techniques are superior. A growing number of investigators are of the opinion that cautery or fulguration is more effective than ligation, with better obstruction and fewer complications resulting from sperm granuloma or hematoma formation (141, 142, 180). Interposition of fascia between the cut ends may further reduce the incidence of granuloma formation and recanalization (160).

The Battelle Memorial Institute has recently developed a portable battery powered, electrocautery unit (shown in Fig. 1), which will be suitable for large-scale sterilization programs in the developing countries (25, 44, 160). A desirable feature of this unit is its concentric bipolar needle electrode, which

reduces the coagulating power and limits the lesion by concentrating the current in the immediate area of the mucosa of the vas.

Transcutaneous Interruption of the Vas

The use of bipolar electrocautery may make vasectomy feasible as a transcutaneous procedure. The vas would be palpated beneath the skin, and under local anesthesia the bipolar needle would be inserted through the skin into or near the vas lumen and the current applied to fulgurize a small section (160). The vas of dogs has been successfully occluded using needles heated in a diathermy field (180).

Transcutaneous localization of the vas lumen could also allow application of vas-occlusive substances for sterilization. Freeman and Coffey (47) have reported that 50 ul of absolute ethanol injected directly in the lumen of the vas deferens in rats and dogs resulted in sterility throughout a 6 month post-treatment observation period. Recently, Coffey and Freeman (15) have reported the successful vasectomy of 10 men by transcutaneous injection of ethanol into the vas.

Many investigators feel that a technique requiring transcutaneous localization of the vas lumen would prove too difficult or hazardous for general use. However, Coffey and Freeman (15) have suggested that periluminal injection of a substance might suffice, and Schmidt (140) believes that paramedics can be trained to consistently locate the vas transcutaneously and that with electrocautery, even in the event of a near miss to the actual vas lumen, a 95% success rate in terms of infertility might reasonably be expected.

Clips for Vasectomy

Clips are also being evaluated for vas occlusion in conjunction with vasectomy. Moss (110) and Leader et al. (93) have recently completed series of vasectomies applying a pair of tantalum clips to each of the divided ends of the vas (eight per operation). They believe this technique may reduce failures and complications. The clips are both hemostatic and vas-occlusive, and their use further simplifies and speeds the operation (70, 110). Additional studies are needed to establish the efficacy of this approach to vasectomy and to determine the extent of necrosis of the wall of the vas and whether the clips will migrate.

Complications of Vasectomy

One aspect of improving irreversible techniques relates to research to evaluate and decrease the complications of vasectomy. This area of research is relatively well funded, particularly studies of the immunologic consequences of vasectomy. 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 (160). It is believed that recanalization through sperm granulomas can occur, which may account for some of the spontaneous restoration of fertility observed (24, 121, 142, 143). Sperm granulomas are thought to be inflammatory responses to sperm leakage from the reproductive tract into surrounding tissue (180). Electrocoagulation of the vas may lessen the occurrence of sperm granulomas and recanalization by creating a firm scar at each end of the vas.

There is no evidence to date that vasectomy in any significant way affects the endocrine status of the human male (12, 24, 70, 155, 177). Pituitary-gonadal function measured prior to vasectomy and at the time of azoospermia during the follow-up period reveals that no significant short-term changes in pituitary gonadotropin (FSH-LH) or meaningful change in testosterone levels occur following vasectomy (70, 155, 177). There is no indication of any effects on sexual behavior, except as may be psychologically induced (24, 70).

Several studies have shown increases in the proportion of men with both spermagglutinins and sperm-immobilizing antibodies postvasectomy. The proportion of men with such antibodies in serum may increase from a few percent to over 50% 1 yr postvasectomy (4, 5, 11, 152, 180). The persistence and significance of these antibodies to general health is unknown. As yet no pathology has been detected. Reports on links between these antibody changes and long-term clinical consequences are not confirmed (1, 6, 8, 23, 111, 133, 134). A report of changes in human lymphocyte antibody following vasectomy involved only 12 patients and was not substantiated in a subsequent study (68, 78a).

Irrigation for Immediate Postvasectomy Sterility

The time needed for semen to become azoospermic following vasectomy is a programmatic limitation. Craft and McQueen (20) found that irrigation with sterile water into the distal cut end of the vas prior to ligation reduced postvasectomy sperm counts. Ethacrine (175), potassium permanganate (98), nitrofuran (172) and other compounds (94) have also been used. The possibility of local inflammatory reactions or an increased risk of infection should be weighed in the use of such a procedure.

Pharmacologic and Other Agents

Preliminary studies injecting a gelatin-resorcinol-formaldehyde (GRF) tissue glue into the vas to provoke an appropriate inflammatory response and tissue ingrowth to occlude the vas have not seemed promising (39a). Quinacrine has been investigated for occlusion of the vas in rats (148).

Very little, if any, systematic research to develop an easily administered

drug for permanent male sterilization has been carried out (34). Known chemicals such as cadmium or agents such as x rays have toxicity and side effects that rule out their use. The potential advantages of a nonsurgical permanent male method in family planning programs should not be ignored.

Immunologic Approaches

Although it may be possible to develop a reversible method of male fertility control based on immune mechanisms, e.g., passive immunization, it is probably most appropriate to consider such methods as permanent.

Shulman (150, 151) and Katsh and Katsh (83) have reviewed the attempts to bring about infertility in males using immune mechanisms. The findings of autoimmunity in some infertile men (9, 137a) 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 from testis, seminal vesicle, prostate, sperm cell, seminal plasma and the gonadotropins FSH and LH that might cause infertility following an antigen–antibody reaction. Furthermore it is likely that some of these antigens, particularly those associated with spermatozoa, will be highly specific, so that immunization against these antigens would not cause systemic autoimmune disease (107, 167).

Even so, it would seem that there is little prospect for early 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 sufficient intensity and specificity, without cross-reaction with other tissues (160).

Although considerable basic research must be carried out before sterilization by vaccination can become a reality, the field would benefit from the application of the most recent advances in immunology to the problem of reproduction and fertility control.

RESEARCH ON REVERSIBLE METHODS

Two basic approaches are being pursued: 1) improvements in surgical techniques using prostheses, valves, etc., to improve reversibility and 2) research to develop reversible pharmacologic means of fertility control.

Improvements in Surgical Techniques

Vasovasostomy. While numerous procedures for vasovasostomy have been reported, successful anatomic reanastomosis with reappearance of sperm in the ejaculate has been achieved in only 50–80% of the patients (30, 48, 71, 99,

103, 104, 117, 122, 135). Of these successes possibly 20–25% result in semen of quality suitable for impregnation (24, 27). Factors that may influence success of reversibility include: a) preoperative semen quality, b) vasectomy technique, c) vasectomy to reanastomosis interval, d) vasovasostomy technique and e) fertility of the sex partner (70).

The chance for success of subsequent surgical reanastomosis is diminished if a large segment of vas is removed at vasectomy (70, 144). When fulgurization is used and no segment of the vas is removed, vas patency (not necessarily sperm flow) can be restored in most cases (140).

Numerous techniques of vasovasostomy have been described (41, 122, 138, 144). High success rates have been reported with microsurgical techniques utilizing stereooptical surgical microscopes (70). Splinting (138) and nonsplinting (27, 41) methods have both been described as advantageous. Recent data suggest that for most clinicians use of a temporary nylon pullout stent results in more frequent successful vasovasostomy (27). Nuwayser (116a) has developed an absorbable stent made from a copolymer of lactic and glycolic acid, which seems promising in early animal studies.

Intravasal Plugs. The search for a satisfactory reversible method of male sterilization has led to experimentation with different methods of vas obstruction. Preliminary reports of obstruction with injected silicone rubber, plastic threads and tapered tubes are often optimistic.

Freund (49) has described a reversible vas device consisting of a string of Silastic balls, which are 2.0 mm in diameter and 3.0 mm apart. The device is stretched to decrease the diameter of the balls and inserted through a small longitudinal incision; the ends of the device are then brought together and tied. Although this method is successful in guinea pigs, no human work has been initiated.

Moon and Bunge (108) have studied a polyethylene tubing device in dogs and a few humans. The device is 7 cm long with the midportion occluding the vas lumen about 3 cm in length. The ends are left protruding from the vas and are clamped with silver clips to stabilize the device. Work has been discontinued because of pain and semen leakage encountered in human studies (11a).

Long-term studies of vas plugs accompanied by breeding tests show generally unsatisfactory results (60, 69, 91, 92, 96, 160). They range from degeneration after several months (29, 53), to reappearance of sperm either because of expulsion or displacement of the plugs (92) or because of recanalization between the inserted material and the vas wall (70), to difficult removal because of local tissue reaction resulting in permanent vasal stenosis in the area of insertion or injection making return of fertility highly unlikely (69). Recent reports of experience with the Brodie reversible intravas device showed no success with reversibility (26).

From these studies it is apparent that, if a substance or device is to be ef-

TABLE 3. Current or Recent Research on Reversible Intravasal Devices*

Institution (Principal Investigators)	*Funding Agency*	*Concept and Status*
New York Medical College School of Medicine Bionyx Co., New York, N.Y. (M. Freund and J. Davis)	NIH	Gold and stainless steel stopcock installed in the sectioned vas with gold mesh for ingrowth; works in on and off position in guinea pigs; human work initiated.†
Ortho Corp., Raritan, N.J. (J. Loe)	Ortho	Metal device with magnetic valve for nonsurgical reversal; discontinued research after 1 yr biologic studies in rabbit and dog.†
Illinois Institute of Technology Research Institute, Chicago, Ill. (E. E. Brueschke)	NIH	Porous ceramic and etched stainless steel device with valve; second generation device of Silastic; dog experiments show tissue ingrowth and near normal sperm passage.
Abcor, Inc. Cambridge, Mass. (E. W. Nuwayser)	NIH	Hollow fiber tube with bonded flock and removable center pin made of steel, vitallium or plastic; Quinacrine used to promote tissue ingrowth.†
Tecna Corp. Emeryville, Calif. (T. C. Robinson)	NIH	Plastic tubes with microporous polyurethane surface for tissue ingrowth; rabbit experiments show good tissue ingrowth and near normal sperm passage.
University of Missouri Columbia, Mo. (E. C. Mather)	NIH	Reversible vasectomy prosthesis of Silastic with Dacron sheath; tissue ingrowth achieved on transected bull's vas; work discontinued.†
Medical Engineering Foundation, Inc. Little Rock, Ark. (J. T. Turley)	?	Ball valve device made of fluoro-plastic material; flexible stems install through a slit in the unsectioned vas by means of a special inverted V clamp; valve kept in place by rolled plastic clip; ball valve has slotted head.
Battelle-Pacific Northwest Laboratories Richland, Wash. (M. J. Free)	AID	Flexible plastic device with textured surface installed into the unsectioned vas in two halves; halves are joined around a plastic plug and uncoupled and rejoined around open tube for reversal.
Southwest Foundation for Research and Development San Antonio, Tex. (D. C. Kraemer)	NIH	Nonocclusive device with copper coils inside a tube for spermicidal action; copper caused semen coagulation and occlusion; now seeking new spermicides.†
Massachusetts General Hospital Boston, Mass.	The Population Council	Removable Silastic obturator.
Carolina Population Center University of North Carolina Chapel Hill (J. Hulka)	AID	Polypropylene tube with Teflon velour, also a proplast sponge; work discontinued.