

GOALS IN MALE REPRODUCTIVE RESEARCH

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FOREWORD

Robert S. Hotchkiss

A scant fifty years ago, the sum total of articles in the English language relating to the male reproductive system numbered only a few hundred. An investigator had a reasonable opportunity to acquaint himself with the then current literature involving both fundamental and clinical aspects of the reproductive processes. During the subsequent years, there has occurred a veritable explosion of interest in the development of knowledge in the intricacies of reproduction and a voluminous literature now confronts both basic scientists and clinicians. This body of information is now so vast that any one individual lacks the capacity to be fully acquainted with all details. New scientific societies addressed to the study of reproduction have been established both here and abroad. New books, journals and periodicals have appeared dealing with various aspects of the subject so that the former paucity of knowledge of the behavior of the spermatogenic cells, the spermatozoon, the endocrines and the function of the male reproductive organs has now been replaced in a formidable manner. The literature is so vast that a dichotomy has developed according to the main interests of the investigators. The basic scientists have penetrated areas involving biochemical behaviorisms including cellular surface transfers, ultrastructure mechanisms for motility of the spermatozoon, influences of the endocrines, and factors dealing with capacitation, to mention only a few. Their work has largely been with laboratory animals and fish. The clinician, on the other hand, has encountered the task of digesting an increasing volume of reports on human subjects, especially in regard to hormones, antigens, evaluation of new drugs and the application of new surgical techniques for infertility and contraception. It is reasonable to suspect that there would be great mutual advantages if closer cooperation between the scientist and clinician could be achieved. The consequent exchange of information might very well alert the clinician to apply certain laboratory findings to human subjects that might otherwise remain of academic interest only.

One of the principle topics of discussion at this workshop revolved upon how this community of interests and research activities could be accomplished. The answer probably lies in encouraging and supporting projects that have the conjoint participation of basic scientists and clinicians. The expertise of each would be mutually stimulating and may effect a salvage of information that would benefit mankind.

This publication hopefully may not only gain the attention of prospective participants, but also reach those who direct departmental activities and are acquainted with the potentialities for activation of such interdepartmental programs within their institutions.

PREFACE

This book is based on the proceedings of a workshop on "Future Goals of Male Reproductive Medicine and Surgery" which was held on September 20, 1979 in Bethesda, Maryland, U.S.A. The workshop was designed to promote dialogue between scientists, clinicians and representatives of government and funding agencies who are interested in this field. The aim was to define directions and opportunities for further studies relative to male reproduction and to explore funding possibilities. The formal presentations and edited discussions are presented so that others may benefit from these recommendations.

The first part of this book contains manuscripts by selected scientists and educators who represent the fields of Biochemistry, Endocrinology, Molecular Biology, Pharmacology, Sexology, Toxicology and Urology as well as the legal and regulatory aspects of male reproduction. These individuals were given the difficult task of forecasting the areas of their expertise.

The second part contains the contributions of representatives from Congress and various funding agencies. The Congressional input was obtained at a luncheon seminar and discussion session. Invitations to participate in a panel discussion were sent to the major funding agencies and organizations who have previously supported research in this area. They were asked to contribute an insight into the mechanisms, trends, priorities and future goals in funding investigations related to male reproductive medicine and surgery. The interest and involvement of those who accepted the invitation are best judged by their respective chapters and the discussion that followed. On a disheartening note, several of those who rejected the invitation expressed the belief that population control was hopeless and noted that their monies would be better spent pursuing other endeavors.

The last part of this book contains the results of a questionnaire that the participants completed after the meeting. This was included to obtain a consensus of the "state of the art" and its needs. Anonymous comments were solicited on whatever might be appropriate to the workshop. Several participants also supplied brief evaluations of specific areas of opportunity. The summation highlights each contribution to focus possible goals for male reproductive medicine and surgery. These goals and recommendations are discussed in the epilogue.

K.L.P.
S.B.

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INTRODUCTION*

Kenneth L. Polakoski

It is an honor for me to welcome such a distinguished group this morning. I want to thank you for coming here to share our common interest in the Future Goals of Male Reproductive Medicine and Surgery.

As we are entering the 1980s, it seems appropriate to evaluate where we are and decide where we are going. We anticipate that today will be spent emphasizing the importance of our field, encouraging communication between our various disciplines and focusing on what our future goals should be.

Even though interest in male reproduction has a long history dating back at least to Aristotle, it has been overshadowed by the successes achieved in the regulation of female fertility. With the recognition that both partners share responsibility for fertility regulation, a dramatic upsurge of interest has occurred in this field within the last decade.

There is urgent need for communication between the scientists, clinicians and granting agencies involved in this area. Collaboration is required; a multidisciplinary approach appears to be the most effective means of defining present and future problems for attack.

We must also decide what direction this collaboration will take. We have a unique opportunity and a serious responsibility to help establish guidelines for furthering our mutual goals. Although it is not necessary to always agree, it is necessary to try to work together.

*Opening statement given at the workshop

CONTENTS

INVITED SPEAKERS AND PARTICIPANTS	xi
INTRODUCTION	xv
THE FUTURE OF MALE REPRODUCTIVE RESEARCH IN UROLOGY Saul Boyarsky	1
PRESENT QUANDARIES AND DIRECTIONS OF THE LABORATORY SCIENTIST IN REPRODUCTIVE BIOLOGY Kenneth L. Polakoski	9
FUTURE TRENDS IN CELL BIOLOGICAL RESEARCH ON THE MALE REPRODUCTIVE SYSTEM David W. Hamilton	19
DIRECTIONS IN ENDOCRINOLOGY AND INFERTILITY Philip Troen	29
FUTURE GOALS FOR PHARMACOLOGY AND TOXICOLOGY IN MALE REPRODUCTION Joanne M. Killinger	37
TOMORROW'S LEGAL ASPECTS OF ANDROLOGY AND UROLOGY Jules B. Gerard	47
MALE SEXUALITY IN 1990 John Money	53
RED (TAPE), WHITE (SHEETS) AND BLUE (CROSS), AN AMERICAN DILEMMA Edward T. Foote	61
FORTHCOMING CONGRESSIONAL ASPECTS Martin F. Kagnoff	71
RESEARCH ON MALE REPRODUCTION Sheldon J. Segal	81

FORD FOUNDATION ACTIVITIES IN SUPPORT OF MALE REPRODUCTIVE RESEARCH Linda E. Atkinson	83
PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION Gerald Zatuchni	85
FUNDING PROCEDURES AT THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT Summarized by Saul Boyarsky and Kenneth Polakoski	89
GENERAL DISCUSSION	93
ADDITIONAL COMMENTS	
Potential Goals of Urological Research Fletcher Derrick	103
Medical Students and Research Careers Frank Hinman, Jr.	105
Joint Appointments: A First Stage Robert S. Hotchkiss	107
The Role of Urology in Sexual and Reproductive Biology Research Colin A. Markland	109
A Practicing Urologist as a Researcher Stanwood Schmidt	113
Approaches for Preserving Reproductive Integrity Jerome K. Sherman	115
QUESTIONNAIRE	119
SUMMARY	125
EPILOGUE	129
INDEX	133

THE FUTURE OF REPRODUCTIVE RESEARCH IN UROLOGY

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ABSTRACT

The Urologic surgeon and leader for the 1990's will need to combine a University Residency type training with an M.D.-Ph.D. type laboratory training to graduate into a social medicine niche in his medical community where his talents can meet a public health need through his creative leadership example. But he needs a commitment from Society to match his personal dedication, a commitment of resources and support in research in reproductive surgery. This area of research is a frontier in American Science.

KEYWORDS

Urological research; Urological training; impotent male; infertile male; genital tract surgery; Urodynamics; education; leadership; semen analyses; penile prosthesis; role in Society; center; interdisciplinary.

INTRODUCTION

This conference points to three targets for the year 1995; the Urologic scientist in his role as one of society's leaders, the infertile male as a patient and the impotent male as a patient. The Urological scientist may be a clinical, academic, or basic scientist (Table 1).

TABLE 1 Focus of Workshop

Infertile male (couple).
Impotent Male (sexually dysfunctional couple).
Urology leader of 1995.

A-most important fact about reproductive research and the one which concerns us the most here is the disparity between progress in the reproductive process in the female as contrasted with progress in the reproductive process in the male. Most of the work has been devoted to the female. A corps of workers in reproductive

research have concentrated upon the female, while only a platoon has researched the male.

This Workshop aims to redress the balance. Possibly, the imbalance in part can be ascribed to the cultural stereotype of female responsibility for family, and popularized through erroneous assignment of responsibility for infertility to the female. Men are equal partners in the reproductive process and in the final result. The role of the male and the role of the Urologist as surgeon of the male reproductive tract are essential ones. The Urologist's insights and experience will always be unique in the final mix of sciences.

For Urologic surgery, Genito-Urinary surgery and its basic sciences, our goals are as follows:

1. To consider the social responsibilities of the Urologic surgeon.
2. To stimulate research in Reproductive Biology among Urologists.
3. To meet the challenges confronting Andrology.
4. To point out opportunities in research in surgery of the male genital tract and associated diseases and to point out opportunities for young academic Urologists to lead their profession.
5. To meet the needs of Gynecologists, Endocrinologists and other medical colleagues.
6. To adapt progress from other fields into Urology, particularly from Veterinary Medicine, Gynecology, Andrology, Endocrinology and Molecular Biology.
7. To meet further needs of patients and the public.
8. To diminish the lag between the laboratory and the clinic.
9. To develop clinical investigators in Urology as translators and catalysts.
10. To develop a comprehensive theory of all the reproductive sciences, biological, behavioral, social or normative.

This is a large task but we expect to address it, not to complete it. For this audience, there is no need to justify these purposes.

LESSONS FROM HISTORY

Historically, it has always proven necessary to recognize error and ignorance before any progress can begin (Table 2).

TABLE 2 Barriers to Progress

It's not what we don't know, so much.
It's what we do know that ain't so.

We have been fortunate in our life times to have experienced many successful medical revolutions which have led to great progress. Kuhn has perceptively described the structure of a scientific revolution where there is a tendency to

clinging to old beliefs until their inadequacy has been questioned by many, and until a paradigm experiment is performed to convince the scientific community of the validity of the new theory embodied by the paradigm. Even then, there remain some who continue to cling to the old beliefs, methods and theories. The beginnings of a revolution may reach far back into history.

For instance, the stage was set for the antibiotic and chemotherapeutic revolution of the 1930's and 1940's, according to Thomas, by the skepticism of the 1800's: Appreciation that patients with typhoid and typhus fever could recover spontaneously without therapy in 1876 led to the art of meticulous objective, clinical observation in medicine. This produced more accurate diagnoses and prognoses. Supportive therapy became part of careful clinical medicine.

The development of Bacteriology, Virology, the taxonomy of infectious diseases and the search for the tubercle bacillus laid the groundwork for the successes of sulfanilamide, penicillin, streptomycin and active and passive immunization and the like. This careful and long continued spade work was done with only the barest hope that a penicillin or streptomycin could be found.

Until one understands the underlying mechanisms of disease and pathogenic agents, one has not set the stage for the discovery of miracle drugs. Once the basic science has developed to a full enough extent, then serendipity and chance discoveries can result. It is our experience as well as our faith that biomedical research is one of the best investments for mankind, no matter what problems it stirs up along the way. The future of the human race requires more basic scientific research, not less. If our culture lacks the wisdom to handle powerful, technologic weapons, then we have a problem, but this is hardly a mandate for a research moratorium. Mankind has solved problems of fire, gun powder, bacterial warfare, the automobile, the wheel and the airplane without a research moratorium and has survived.

We need to break down the barriers to progress by first recognizing the barrier of ignorance and error and secondly by encouraging dialogue between would-be and should-be collaborators.

Urology cannot be a tight little island to itself. It will not survive without an influx of fresh ideas and methodologies from other fields. Physics of the 1890's was a tight little island, well codified and neatly understood by its practitioners and theoreticians. Albert Einstein scrambled its neat compartments and reassembled them in a more creative way. Only then did the science of physics become capable of predicting atomic power, a practical art which never would have arisen from the physical sciences of the 1890's. In a like manner, the technique of transplantation of the kidney was described by Alexis Carrel shortly after 1890 but it was not until the advances in biology of tissue compatibility and immunology that renal transplantation became feasible through immunosuppression.

The human reproductive sciences are young. Their worth will be the capabilities of their practitioners. But those capabilities require an adequate science to improve the art.

NEEDS

Let us turn to the leaders in Urology of 1995. Who will be the pacesetters for the profession? What can we expect and hope for in terms of genital tract surgery?

It takes only a cursory survey of current Urologic practice to list the multiple roles which a Urologist fills at present:

1. Urologic surgeon.
2. Physician. (Urology is proud of being both a medical and surgical specialty).
3. Counselor.
4. Educator, particularly a sex-educator.
5. A referral source, particularly to the family practitioner, psychotherapist, sex-therapist.
6. A first line psychotherapist and diagnostician.
7. Consultant.
8. Public policy advisor.

THE INFERTILE MALE

We participants in this Workshop share a dissatisfaction with the state of Urologic research in Andrology and especially in infertility, not in a destructive manner, but in a constructive manner. We hope to see it flourish. If progress in science requires that we clear out errors, an idea which has outlived its usefulness must be discarded.

Some cardinal assumptions in the infertility field fall into this class:

1. The current definition of male fertility.
2. Clinical studies of the infertile male.
3. Semen analysis as a measure of fertility.
4. Quantitation of male fertility.
5. The results of therapy.

1. The definition of male infertility is defined as the inability to produce a conception after one year of unprotected intercourse. But failure to produce conception can be due to failure of the female, failure of both partners, or to their incompatibility as well as failure of the male. These distinctions have not always been respected in published reports.

Even if they were, many couples are infertile because they do not know how or when to have adequate intercourse. Many couples do not protect their sexual and reproductive health from alcohol, other drugs, from necessary medications, from environmental and occupational hazards. Many couples have impaired copulatory effectiveness because of emotional disturbances. Large questions still exist about the deleterious effects of infection of the male and female genital tracts and of antibodies to seminal components on fertility.

It is not clear what part of infertility is due to diseases of the sperm or ovum and their passages, and what part is due to the previously mentioned factors, which are frankly behavioral.

Infertility is a chapter heading and a diagnostic wastebasket for many syndromes and diseases of different etiologies. It is time to sharpen our diagnostic classification by basing it in modern reproductive science. A proper diagnosis must include the sexual physiology and morphology of both partners and their combination. It must range from the molecular biological and biochemical levels through

cellular physiology, organ physiology, psychologic, and sociologic levels of human function, and must not ignore the cultural and anthropological ramifications.

2. Studies of the infertile male are necessarily taken out of the context of the infertile couple, as I noted. But even if lip service is paid to this principle, the assumption that marital and female factors have remained constant is not tenable. A reported success or failure of conception may have been due to a shift of female fertility or in the compatibility factor rather than to the therapy given the male. As a result, the male therapy may look deceptively effective.

3. The semen analysis is a poor measure of male fertility. It requires five days abstinence and six repetitions to provide a statistically valid measure. It is susceptible to technical error and to immediate and delayed biological and pathologic suppression. Lower and lower counts have been shown to be associated with successful impregnation.

The semen analysis represents only the product of ejaculation observed in vitro. It does not tell enough about what came before or what may happen after ejaculation in the female tract enroute to fertilize the ovum. It is a brief, explosive segment of half of that couple's reproductive physiology, the male half, studied in the wrong environment, the dish or slide.

The criticisms which have been registered against the use of the semen analysis for the quantitation of fertility should not be misunderstood. The semen analysis currently and historically has been of tremendous value in the workup of the infertile patient. Unless the presence of azospermia is ruled out or ruled in, the Urologist may be stymied in the management of his case. The presence or absence of azospermia must be demonstrated in order to determine whether the patient is completely sterile or to determine whether there is a functional block to the passage of otherwise viable or acceptable sperm into the ejaculate.

The demonstration of normal semen quality is necessary in order to proceed with the investigation of other factors, such as the purely female factors or the incompatibility factors rendering the couple infertile.

Therefore, it would be a mistake to draw the conclusion that semen analysis is dispensable or otherwise unnecessary to the workup merely because of the criticisms which have been levied against its misuse or misinterpretation.

4. Quantitation of male infertility is a morass. Few workers have separated out cases of primary from secondary infertility, the aged from the young patient, the categories of female partners paired with the males, nor have they separated the purely male infertility factors from female and combined factors.

Quantitation fails when the starting point of therapy is not specified. The starting point may have been the first visit, the time of diagnosis, the cessation of last therapy, the start of a new therapy, the addition of a second or third therapy to the first, or a post-operative adjunctive therapy.

The end point of therapy may be defined as an arbitrary point in time, another semen analysis, a conception, a pregnancy up to 20 months, or a live birth. These are all different measures.

A statistically attractive approach to surmount these difficulties is suggested by Cramer, Walker and Schiff as cumulative fecundity measuring cumulative opportunities for exposure along the model of current survival tables.

5. Few skeptics will accept current claims of therapeutic success in the infertility field.