

BASIC AND CLINICAL ENDOCRINOLOGY/7

MALE REPRODUCTIVE DYSFUNCTION

DIAGNOSIS AND MANAGEMENT OF
HYPOGONADISM, INFERTILITY,
AND IMPOTENCE

edited by
Richard J. Santen
Ronald S. Swerdloff

Male Reproductive Dysfunction

Diagnosis and Management of Hypogonadism,
Infertility, and Impotence

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Preface

Until approximately two decades ago, advancement of knowledge regarding male reproductive function proceeded in a stepwise and logical but limited fashion. With the development of a wide range of new methodologies—sensitive hormonal assays, monoclonal immunological techniques, isoelectric focusing and HPLC for protein purification, receptor methodology, photoaffinity labeling, and in vitro fertilization, among others—a nearly logarithmic acceleration in progress began. The scientific and clinical disciplines of reproductive biology and medicine became attractive to investigators and physicians from a wide range of backgrounds. New data emanated from departments and divisions of anatomy, biochemistry, physiology, reproductive biology, urology, endocrinology, gynecology, and psychiatry. The multidisciplinary nature of these studies resulted in the dissemination of this work in highly specialized journals and national meetings. This fragmentation of information has limited the ability of the clinician or basic investigator to attain in-depth knowledge beyond his own area of expertise.

In planning *Male Reproductive Dysfunction*, the editors attempted to consolidate accumulated knowledge from multiple disciplines into one comprehensive volume. Since the intended readership encompasses individuals of various types of specialized training, individual chapters were written with a view toward presentation of highly technical material at an easily understandable level.

The breadth of expertise represented in this book reflects a major current trend in the field, the attempt to draw from multiple sources to form a new specialty called andrology. The content of *Male Reproductive Dysfunction*, then, encompasses the data base most useful to clinicians, including internists, endocrinologists, urologists, and gynecologists, who see patients with disorders of male reproductive function. In addition, selected chapters, especially those outside of their specialized areas of expertise, should be highly useful for basic investigators working in the field of reproductive medicine.

The editors planned that *Male Reproductive Dysfunction* would provide critical reviews of important data rather than an encyclopedic presentation of all existing information. With this goal in mind, chapters covering basic concepts of testicular anatomy and physiology were written by investigators who have made major contributions to their field of expertise. Authors reviewing clinical topics were chosen because of their extensive personal supervision and study of patients with the problems described in their chapter. Ch. 16, by Baker, Burger, de Kretser, and Hudson, provides an example. The Infertility Clinic at Prince Henry Hospital in Melbourne, Australia, has enrolled and prospectively studied over 1000 men with oligospermia. Baker and colleagues present primary information from the Melbourne studies and compare this to data analyzed from a comprehensive literature review. Because of this approach, the chapters in *Male Reproductive Dysfunction* contain information presented for the first time. The extensive experience of each author provides a perspective for the critical assessment of recent advances by others in the field.

The editors' selection of contributors to this volume has resulted in a book with an international authorship. This approach facilitates a more comprehensive presentation of newer pharmacological research and adds balance to certain opinions that have a strong and national bias. Success in meeting this goal is reflected by the representation of the United Kingdom, Belgium, Scandinavia, Australia, and the United States among the contributors.

Male Reproductive Dysfunction is organized broadly into parts describing normal anatomy and physiology, Leydig cell dysfunction, abnormalities of spermatogenesis and sperm function, sexual disorders, and new perspectives.

In the first chapter, de Kretser integrates the light and electron microscopic features of the testis with functional characteristics of Sertoli cell function, spermiogenesis, and spermiation. Overstreet then reviews a body of recently advanced data regarding sperm maturation in the epididymis, capacitation, and ova penetration. He draws upon his own published and as yet unpublished studies regarding the factors required for penetration of human spermatozoa into ova. In the next few years, this important field of study should allow insight into many, as yet, unexplained causes of infertility. In Ch. 3, Vermeulen, who has worked in the field of Leydig cell physiology since the advent of sensitive testosterone assays, provides a broad perspective in reviewing androgen physiology. Having conducted and published a wide range of studies, he is in a unique position to review recent developments.

Until recently, the study of Sertoli cell function was largely descriptive and not amenable to quantitative measurements. With the discovery of androgen-binding protein and specific radioimmunoassays for it, one can systematically quantify the effects of various manipulations on Sertoli cell function, for example, the effects of hypophysectomy, radiation therapy, genetic defects, anti-LH antisera, fetal maturation, and puberty. Further tools for precise assessment are rapidly being developed, and Sertoli cells can be grown successfully in culture. Ch. 4, by Musto, Cheng, Gunsalus, Escobar, and Bardin, details the rapidity of progress in this area of andrological research and provides perspectives for currently evolving clinical tools. The chapter by Franchimont, Demoulin, and Bourguignon on the regulation of gonadotropin secretion provides interesting new insights through synthesis of a wide body of data. Of special interest is the intrinsic tendency of the pituitary to secrete FSH when exposed to minimal amounts of gonadotropin-releasing hormone. These authors put into perspective the potential roles of inhibin, testosterone, and the pituitary itself in FSH secretion. As a final part of this general section of the book, George and Griffin review their elegant studies regarding androgen actions on sexual differentiation during fetal life.

The chapters on Leydig cell dysfunction cover a relatively well-understood area of testicular physiology. Effective treatments exist for several of the clinical disorders encountered. Emphasis in this section is based on the clinical manifestations of disordered physiology. One longstanding clinical tool has been the use of testicular biopsy. This method is now being used with decreasing frequency, and recently trained clinicians have limited experience in its use. Few excellently prepared color photomicrographs have been published to serve as a data base for those with no opportunity to review testicular biopsies. For this reason, Paulsen, Bremner, and de Kretser prepared for this volume a representation of their extensive experience with testicular biopsy.

The chapters authored by Spratt, Santen, Nieschlag, and their respective collaborators critically review existing clinical data on Leydig cell dysfunction and present major new findings. For example, the data of Spratt, Hoffman, and Crowley and those of Santen and Kulin further document the extreme degree of heterogeneity found among patients with hypogonadotropic hypogonadism. Similarly, Nieschlag precisely documents the degree of testicular dysfunction in aging men. Since several effective treatments are now available for men with hypogonadism, two chapters (Chs. 10 and 11) are devoted to this topic. Sokol and Swerdloff describe available formulations and adverse effects of the various testosterone preparations available for the treatment of androgen deficiency. Spratt et al. describe their experiences using GnRH to induce spermatogenesis in men with hypogonadotropic hypogonadism; they compare the advantages of GnRH therapy to that of gonadotropin therapy. The authors of these two chapters have collected extensive information during the treatment of their own patients with hypogonadism and, through this perspective, critically review a wide body of published information.

The next group of chapters covers germ cell dysfunction. Contained here are two comprehensive discussions of topics that have always been difficult for clinicians to assess, namely, infectious and immunological causes of infertility. Berger, a urologist, and Holmes, an infectious disease specialist, combine forces to review their own and other data. They rightly point out the limitations of existing data and the need to reserve judgment regarding the uncontrolled studies previously published. In a similar vein, Haas presents a large data base of immunological information obtained on subfertile men and also concludes that the implications of test results are not yet certain. In contrast to the controversial implications of the role of infection and immunological factors in infertility, the genetic data presented by Chandley provide a clear insight into the frequency and etiological significance of various genetic disorders involving the testis.

Several chapters in the germ cell dysfunction part provide approaches to the precise quantitation of physiological defects. Clark and Sherins, in their chapter on semen analysis, and Winters, Nankin, and Troen, in discussing hormonal analyses, outline practical guidelines for evaluation of oligospermic men. Assessment of fertilization potential of male partners of infertile couples has until recently been limited to the standard semen analysis and serum hormone parameters. The search for a test of sperm ability to penetrate ova has led to the widespread use of the heterologous sperm-ova penetration test. Aitken is uniquely qualified to give a perspective on the usefulness of this test and describe its success in prediction of ultimate fertility. Another highlight of this section is the description of microsurgical techniques for correcting obstructive azoospermia. This represents an area where an improvement in methodology has resulted in a markedly better prognosis for the patient. In his chapter, Silber provides an elegant demonstration of the utility of precise surgical technique and new insights into the reasons for postvasovasostomy functional failures.

The next part of *Male Reproductive Dysfunction* reviews perhaps the most common reproductive dysfunction involving adult men, namely, impotence. Extensive quantitative techniques are now available to distinguish organic from psychogenic impotence. Karacan and Moore fully detail studies that are generally available for diagnosis of impotent men, and Hampson provides his perspective on the identification and treatment of men with nonorganic (psychogenic) etiology.

The insertion of penile implants for impotence is by nature a highly specialized procedure. The description of the available appliances and techniques by Krane puts this field clearly into perspective for those caring for patients with organic impotence. Finally, the chapter by Hampson presents the psychiatric aspects of impotence from a clear and objective point of view.

As in any rapidly evolving field, a number of concepts, treatment regimens, and etiological entities are controversial. In this book, several areas of controversy are discussed and deserve highlighting here. The most important is the efficacy of various treatments for oligospermia, such as exogenous gonadotropins, clomiphene,

gonadotropin-releasing hormone, and aromatase inhibitors. As discussed extensively by Steinberger, randomized controlled trials of various treatments of oligospermia have been infrequent. Only with such studies, now ongoing in several centers, will definitive answers be obtained. Notwithstanding, certain therapies such as varicocele repair have been widely accepted. Ch. 18, by Comhaire, reflects the fact that nearly all prior studies suggest the efficacy of this treatment. On the other hand, Baker et al. and Steinberger, drawing on data from their own clinics, believe that further randomized trials are required to determine the precise efficacy of varicocele repair. Another area of controversy is the etiological significance of the finding of antisperm antibodies in the presence of unexplained infertility. The editors believe, as does Haas in Ch. 20, that proper caution must be exercised in the interpretation of this area until controlled, prospective studies become available.

Another area of controversy is the degree to which testicular dysfunction is associated with aging. The editors believe that illness associated with, but not caused by, aging is the major confounding factor in the interpretation of studies of testicular function in aging men. Very healthy older men retain normal testicular and sperm concentrations, albeit with elevated gonadotropin levels. Those with impaired health often have low testosterone concentrations and even higher gonadotropin levels. This general concept probably explains the wide range of findings recorded in prior studies.

Another area of potential controversy is the application of highly developed diagnostic and therapeutic tools. For example, it is unclear whether cost and logistical considerations will limit the extent of highly specialized testing of the erectile function by nocturnal penile tumescence and rigiscan devices in an unselected group of men with impotence. It is the editors' belief that the cost-effective approach for the evaluation of such patients will remain controversial until intensive prospective studies reveal the relative value of each of the various diagnostic tests.

On a final note, *Male Reproductive Dysfunction* closes with a discussion by Bhasin and Swerdloff regarding the development of a male contraceptive. Their experience in male contraception stems from their own investigations in the U.S. and other countries throughout the world. They observe that contraception for men has lagged behind approaches for women and suggest that progress depends to a great extent on a clear understanding of the physiology of spermatogenesis and sperm function. The authors have summarized the state of the art of male contraceptive development and explore present and future directions of research in this area.

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Male Reproductive Dysfunction

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