

# **Immunology of the Male Reproductive System**

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**PIERLUIGI E. BIGAZZI**

# Immunology of the Male Reproductive System

edited by

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## Series Introduction

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One of the most intriguing areas of modern medical research is the interdigitation of the immunological and reproductive systems. We see two-way interactions at many levels: Peptide hormones of the pituitary act upon the thymus, which regulates the immune response; similarly, the immune response can alter the function of the testes and ovary, while steroid hormones affect lymphocyte levels. Pregnancy requires suspension of the usual laws of allo-rejection and, in turn, significantly alters the course of immunological diseases.

These interactions between the reproductive and immunological systems have attracted the interest of many investigators. A number of books have appeared recently to deal with the effects of pregnancy on the immune response and the immunology of the female reproductive system. It is ironic, therefore, that there has not been sufficient attention to the male reproductive system from an immunological viewpoint. The deficiency is particularly striking because of the historical connection between studies of the testes and the immune response, as described by Professor



Voisin in the foreword. It is, therefore, especially appropriate that Dr. Bigazzi and his colleagues have assembled an up-to-date and comprehensive review of this important field. A review of the table of contents emphasizes the broad spectrum of topics encompassed, ranging from the unique antigenic structures of the testes and genital tract, to the role of antibodies in regulating fertility, and the immunology of testicular and prostatic tumors. This book will fill a serious void in the immunological library and will attract many new investigators to this challenging field.

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Gamete immunology—more particularly male antigens and the immune response built up against them by males and females—seems to have been relatively neglected these past few years; however, it is a major field of reproduction immunology and bears on several important consequences, both practical and theoretical.

From a practical point of view, we are concerned with the diagnosis and treatment of immunologic forms of infertility in males and females, as well as with aspects of immunologic control of fertility in human beings. (The sharply rising population of the world is expected to reach 10 billion by the year 2100.) A related aspect of great interest is the necessity to increase cattle production and to detect infertile animals, as stressed by the late Kyri.

## Foreword

The immunology of the male reproductive tract was, by more than 50 years, the first of several fields presently embraced by the growing domain of the immunology of reproduction. Actually, investigations were begun by Metchnikoff in 1899 (spermatotoxins = spermatotoxic antibodies) and Metalnikoff in 1900 (autospematotoxins = spermatotoxic autoantibodies). Then, several experimenters and clinicians injected females with sperm in order to control fertility by this type of antibodies, but it was not before half a century had passed that immunopathology—a word we coined first in 1952 to name our laboratory, one year after having described guinea pig autoimmune aspermatogenic orchitis—of the male system was first investigated. Since then there has been growing interest regarding autoimmune reactions to spermatozoa and various antigens of the reproductive tract and, for females, isoimmune reactions to spermatozoa and seminal plasma antigens.

Other aspects of the immunology of reproduction (materno-fetal immune relationship, fertility-related hormone immunology, and breast-feeding-related immunologic events) have been, for the most part, covered during recent meetings and in several books.

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From a practical point of view, we are concerned with the diagnosis and treatment of immunologic forms of infertility in males and females, as well as with aspects of immunologic control of fertility in human beings. (The sharply rising population of the world is expected to reach 10 billion by the year 2100.) A related aspect of great interest is the necessity to increase cattle production and to detect infertile animals, as stressed by the late Kyril Bratanov. The techniques and problems encountered with farm animals are closely related to those described for humans. Fertilization in vitro and embryo transplantation have immunologic aspects in that they may evoke immune responses or be used to bypass a fertility problem.

From a theoretical point of view, male tract immunology, especially of spermatozoa and testis, has far-reaching implications, touching on several domains: autoantigens and autoimmune diseases due to the induction of the autoimmune reaction (induced experimentally or by vasectomy); the effector pathways of organ-specific autoimmune damage; and the reasons autoimmune reactions, which are among the most physiological of phenomena (simply consider the idiotypic/anti-idiotypic network), sometimes become highly pathologic. Male tract immunology also involves problems in self-recognition and self-tolerance. These are far from having been solved for autologous substances. Clonal elimination for antiself-reactive clones certainly does not apply to spermatozoal autoantigens in spite of the high probability that—like thyroglobulin—highly soluble and diffusible acrosomal autoantigens diffuse systemically. The local immune response in the genital tract demonstrates an aspect of the relative compartmentalization of the immune reaction, at variance with homogeneous test tube mixtures. The fields of tumor immunology and differentiation themselves will benefit from studies of testicular tumors

with their embryonal antigens and the still mysterious F9 shared by spermatozoa and early embryo. This book therefore comes in time to respond to a need.

*Guy André Voisin, M.D. Sci.D.*  
President  
The International Society for the  
Immunology of Reproduction

## Preface

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Investigation of spermatozoal antigens was initiated at the end of the last century by Landsteiner and Metchnikoff. In the years following those landmark studies, the literature on reproductive immunology grew at such a rapid pace that it is now difficult to present in a single book an in-depth review of the immunology of the male reproductive system together with that of pregnancy and the female reproductive tract. These considerations led to the preparation of the present book, aiming at comprehensive coverage of the immunology and immunopathology of the male reproductive system, in order to provide a more extensive analysis than is currently available in other publications on reproductive immunology.

The opening chapter is focused on the numerous antigens of the testis and the excurrent tract, an area that is also addressed in many of the following chapters because of its importance and the rapid expansion of data through the use of monoclonal antibodies, SDS-PAGE, Western blotting, and other technologic advances. The various methods to detect antisperm antibodies are explained at length in the second chapter, also covering the choices among the techniques currently available, as well as the

problems still unsolved. This is followed by a review of the immunologic regulation of fertility with spermatozoal antigens, stressing the development of synthetic peptides that may eventually be used as vaccines for birth control. The role of autoimmune responses to testicular antigens in male infertility is discussed in the next chapter, on the basis of experimental data and clinical observations. A review of the immunologic effects of vasectomy in men, including the useful lessons derived from the study of the autoimmune consequences of this sterilization procedure, is presented in the following chapter. The histopathology of immunologic lesions observed in testicular biopsies from infertile men is illustrated in the next section, together with an outline of the staging of human immune-complex orchitis. In logical sequence this is followed by a summary of the various treatments of immunologic infertility in men, a topic of obvious practical importance. The numerous animal models of testis autoimmunity, experimentally induced or naturally occurring, are then examined in detail, in an attempt to elucidate both the pathogenesis and etiology of autoimmune disorders of the male reproductive system. A subject not often covered in books on reproductive immunology, i.e., the immunobiology of testicular tumors as it relates to host-tumor interactions, is dealt with in the next chapter. Finally, two separate reviews elucidate the antigens of the normal prostatic gland as well as the immunology of prostatic tumors.

In all these chapters, a certain degree of overlap was unavoidable and perhaps to be encouraged, since it helps provide different perspectives on some issues, primarily the purification of antigens of spermatozoa and other constituents of the male reproductive tract, a field where we are anticipating rapid progress. Overall, the present book provides extensive coverage of male reproductive immunology and will stimulate interest and additional investigations in this field.

I thank all the contributing authors for their excellent collaboration and great patience during the long gestation of this book.

In addition, I wish to thank Dr. Noel R. Rose and Dr. Giuseppe A. Andres for their generous help and advice during my studies on autoimmunity of the testis.

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