toxicology of the male and female reproductive systems

Peter K. Working

chemical industry institute of toxicology series

TOXICOLOGY OF THE MALE AND FEMALE REPRODUCTIVE SYSTEMS

Edited by

Peter K. Working

Chemical Industry Institute of Toxicology

HEMISPHERE PUBLISHING CORPORATION
A member of the Taylor & Francis Group

New York Washington Philadelphia London

TOXICOLOGY OF THE MALE AND FEMALE REPRODUCTIVE SYSTEMS

1 2 3 4 5 6 7 8 9 0 BCBC 8 9 8 7 6 5 4 3 2 1 0 9

This book was set in Times Roman by Mid-Atlantic Photocomposition. The editors were Diane Stuart and Allison Brown. Cover design by Sharon Martin DePass.

Library of Congress Cataloging-in-Publication Data

Toxicology of the male and female reproductive systems/edited by Peter K. Working.
p. cm.—(Chemical Industry Institute of Toxicology series)
Based on the Ninth Chemical Industry Institute of Toxicology Conference on Toxicology held in Raleigh, N.C., Sept. 30–Oct. 1, 1987.
Includes bibliographies and index.
1. Reproductive toxicology—Congresses. 2. Genetic toxicology—Congresses. I. Working, Peter K. II. Chemical Industry Institute of Toxicology. Conference (9th:1987:Raleigh, N.C.)
III. Series.
[DNLM: 1. Mutagenicity Tests—methods—congresses. 2. Reproduction—drug effects—congresses. 3. Toxicology—methods—congresses. WQ 205 T755 1987]
RA1224.2.T69 1989
616.6'507—dc19
DNLM/DLC
for Library of Congress
ISBN 0-89116-583-5
ISSN 0278-6265

88-36986
CIP

Contributors

WILLIAM F. BLAZAK[1]
Cytogenics and Reproductive Biology Program
Toxicology Laboratory
SRI International
Menlo Park, CA
U.S.A.

ROBERT E. CHAPIN
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

GARY J. CHELLMAN
Syntex Research-ITS
Palo Alto, CA 94303
U.S.A.

RALPH L. COOPER
Reproductive Toxicology Branch
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
U.S.A.

EDWARD M. EDDY
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

[1]Dr. Blazak's current affiliation is the Department of Toxicology, Sterling Research Group, Rensselaer, NY 12144-3493.

PAUL M. D. FOSTER
I.C.I. Central Toxicology Laboratory
Alderly Park, Macclesfield
Chesire SK10 4TJ
England

JEROME M. GOLDMAN[2]
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
U.S.A.

MARK E. HURTT
Haskell Laboratory
E.I. du Pont de Nemours & Co.
Newark, DE 19714
U.S.A.

JAANA LÄHDETIE
Department of Anatomy
University of Turku
Turku SF-20502
Finland

JAMES C. LAMB, IV[3]
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Washington, DC 20460
U.S.A.

RICHARD J. LEVINE
Chemical Industry Institute of Toxicology
Research Triangle Park, NC 27709
U.S.A.

DONALD R. MATTISON
Department of Obstetrics and Gynecology
University of Arkansas for Medical Sciences
Little Rock, AR 72205
U.S.A.

JOHN A. McLACHLAN
Laboratory of Reproductive and Developmental Toxicology
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

MARVIN L. MEISTRICH
Department of Experimental Radiotherapy
University of Texas M. D. Anderson Hospital and Tumor Institute
Houston, TX 77030
U.S.A.

RICHARD E. MORRISSEY
National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

R. R. NEWBOLD
Laboratory of Reproductive and Developmental Toxicology
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

DEBORAH A. O'BRIEN
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709
U.S.A.

LEENA-MAIJA PARVINEN
Department of Anatomy
University of Turku
Turku SF-20502
Finland

[2]Dr. Goldman's current affiliation is with NSI Technology Services, Environmental Sciences, Research Triangle Park, NC 27709.

[3]Dr. Lamb's current affiliation is with Jellinek, Schwartz, Connolly & Freshman, Inc., Washington, DC 20005.

MARTTI PARVINEN
Department of Anatomy
University of Turku
Turku SF-20502
Finland

SALLY D. PERREAULT
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
U.S.A.

LIISA PYLKKÄNEN
Department of Anatomy
University of Turku
Turku SF-20502
Finland

GEORGIA L. REHNBERG
Reproductive Toxicology Branch
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
U.S.A.

RISTO SANTTI
Department of Anatomy
University of Turku
Turku SF-20502
Finland

PETER J. THOMFORD
University of Arkansas for Medical Sciences
Little Rock, AR 72205
U.S.A.

JORMA TOPPARI
Department of Anatomy
University of Turku
Turku SF-20502
Finland

PETER K. WORKING
Chemical Industry Institute of Toxicology
Research Triangle Park, NC 27709
U.S.A.

HAROLD ZENICK
U.S. Environmental Protection Agency
Washington, DC 20460
U.S.A.

Preface

This volume is the outcome of the Ninth Chemical Industry Institute of Toxicology (CIIT) Conference on Toxicology, held in Raleigh, North Carolina, September 30 to October 1, 1987. These conferences have been organized by CIIT since 1978 to encourage and promote exchanges of information on topics of special interest in toxicology. This Ninth CIIT Conference included over 150 attendees from academia, the chemical and pharmaceutical industries, and various governmental agencies, such as the National Toxicology Program, the U.S. Environmental Protection Agency, and the Food & Drug Administration. The sessions produced spirited and active interchanges of ideas and opinions, open interactions which, hopefully, will continue.

The goals of this volume are to provide the reader with a firm grounding in basic male and female reproductive physiology—including aspects of gametogenesis, postgonadal gamete maturation and transport, and fertilization—and then to relate this information to the practice of reproductive toxicology. Successive chapters present discussions of the mechanisms and modes of action of reproductive toxicants, the design and use of multigeneration-type breeding studies to identify potential toxicants, the quantitation of toxic effects using specific cellular end points in both males and females, the efficacy of these end

points as predictors of fertility changes, in vitro methods in reproductive toxicology, and the evaluation of genotoxic and mutagenic effects in germ cells. Finally, the extrapolation of findings in animal studies to the human is discussed, including the use of specific human end points, epidemiological methods, and the role of risk analysis in the assessment of human reproductive risk. I hope that the material in this book will allow the toxicologist reader to gain some insight on the complexity of the reproductive processes and that it will allow the biologist reader to appreciate the difficulties of accurately assessing toxic effects on the reproductive system.

Appreciation is expressed to Linda Smith and Sadie Leak for their invaluable organizational and secretarial support before, during, and after the meeting. Thanks also go to the speakers and authors of the chapters in this volume for providing such stimulating and inclusive coverage of reproductive biology and toxicology in the male and female.

Peter K. Working

Contents

Chapter 1

Testicular Structure and Physiology: A Toxicologist's View

Paul M. D. Foster

BACKGROUND

A cursory glance at the literature would reveal a bewildering array of chemicals capable of producing injury to the male reproductive system of experimental animals. Indeed the list of chemical classes possessing members that can cause adverse effects is a formidable one, ranging from synthetic steroids and therapeutic agents to metals. In contrast, there is a paucity of information on the pathogenesis of chemically induced injury to the male reproductive system and even less information on the biochemical mechanisms underlying injury. In addition, the number of compounds known unequivocally to have produced deleterious changes in man is exceedingly small, consisting of information relating to a few pesticides (notably Dibromochloropropane—Whorton et al., 1977; Reel and Lamb, 1985), agents used in cancer chemotherapy (cyclophosphamide and adriamycin—Meistrich et al., 1982), and some potential male contraceptives (e.g., gossypol—National Coordinating Group on Male Anti-Fertility Agents, 1978).

Toxicity associated with reproduction is likely to lead to an emotive response, and the notion exists among toxicologists, regulatory authorities, and

trade unions that reproductive effects are likely to be a major concern in toxicology in the next decade. There is therefore an obvious need to approach the subject area in a more logical, scientific manner and redress the balance regarding the limited information available, so as to develop new concepts in society's attitude and approach to the study of reproductive toxicants. The requirement to approach male reproductive toxicity in a more "mechanistic" manner so as to interpret hazard more accurately (and thereby produce a better estimate of risk) is very much dependent on the utilization of the strides made in male reproductive physiology in recent years. However, unlike many other organs, our data base on metabolic systems and cellular functions in this target organ is not large. Thus, our understanding of how a compound may influence the biochemistry of an organ is very largely dependent on our knowledge of the normal biochemistry of the organ. The study of male reproductive toxicants requires an integrated approach covering the various scientific disciplines associated with the male system, essential for normal function. Such techniques would range from detailed histopathology of the testis, through biochemical changes in appropriate in vitro systems, to studies on fertilization and reproductive outcome.

The objectives of the present paper are (1) to detail the basic structure and compartmentation within the rat testis, (2) to briefly review the process of spermatogenesis and its control, (3) to emphasize the key role of the somatic Sertoli cell, and (4) to present a rationale for an approach to the study of testicular toxicants leading to a more informed hazard assessment. The rat has been chosen to exemplify the male reproductive system for two major reasons: first, it is the species in which most of our toxicological, including reproductive, information is generated and necessarily where most toxicants have been described, and second, it is the species in which our knowledge of normal testicular structure and physiology is the greatest.

If one considers that the prime function of the male reproductive system is to produce a gamete capable of fertilizing an oocyte to produce a viable offspring, then there are a large number of potential target sites that could be envisaged where a compound effect would lead to a deficit in function (see Fig. 1). These would incorporate the hypothalamic-pituitary-testicular axis, extratesticular sites, and processes involved with sperm maturation and fertilization. Many of these potential targets will be taken up in later chapters. Examples of compounds thus exist that produce their reproductive effects via the central nervous system, for example, cannabinoids, the pituitary secretion of gonadotrophic hormones (e.g., estrogens) and directly on spermatogenesis (e.g., phthalate esters), whereas cadmium will disrupt the testicular vasculature. Other compounds may mediate their effects by indirect means by interference, for example, with normal steroid metabolism in the liver, or with seasonal breeders, on the pineal gland.

When sperm leave the testis, they are both nonmotile and nonfertile, and during maturation, compounds may also exert their effects (e.g., chlorosugars).

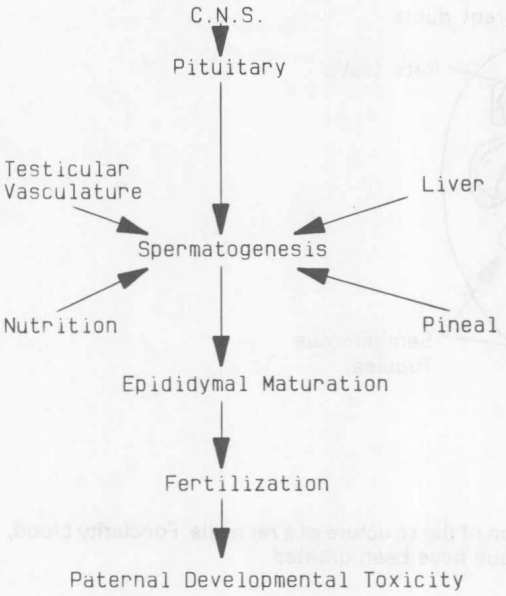

Figure 1 Potential target sites in the male reproductive system to toxicant attack.

An effect on the process of fertilization is certainly a potential target for toxicant action, as is the concept of paternally mediated developmental toxicity, but examples of effects at these targets are not well described. It is fair, however, to state that the vast majority of toxicants thus far described appear to exert their effects directly on the process of spermatogenesis.

TESTICULAR STRUCTURE AND COMPARTMENTS

The parenchymal tissue of the testis is enclosed within a tunica and consists of numerous seminiferous tubules, which are long, convoluted structures connected at both ends to the rete testis (Fig. 2). Spermatogenesis takes place within these tubules, and sperm are channeled from the rete testis via efferent ducts into the epididymis (see Chapter 3). Surrounding these tubules is a vascularized interstitial tissue that contains Leydig cells, macrophages, and mast cells. The relationship of the interstitial tissue to the seminiferous tubules is shown diagrammatically in Fig. 3. The boundary tissue of the seminiferous tubule consists of a number of layers of cells including myoepithelial peritubular cells, thought to be involved in the passage of released sperm along the tubule, possibly in response to oxytocin secretion by Leydig cells (Wathes, 1984); more recent investigations would indicate that they also have a role more closely associated with the Sertoli cell and the process of spermatogenesis (Skinner and Fritz, 1985).