REPRODUCTIVE TOXICOLOGY AND INFERTILITY

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To Sergio

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PREFACE

This multiauthored book is directed at clinicians needing an understanding of ways in which drugs and other potential toxicants may alter male and female reproductive competence. The audience includes physicians and scientists with an interest in clinical infertility problems and the book, therefore, has a major clinical orientation. At the same time, work derived from animal and in vitro models that is important in understanding reproductive toxicology is introduced and placed in the appropriate clinical context.

The first section of the book provides background information necessary for an understanding of the reproductive process in mammals. Male and female reproductive systems are separately reviewed. Because loss of the conceptus at or prior to implantation presents as infertility, this important portion of early embryology is also discussed.

The second section builds on this background with descriptions of the ways in which normal reproduction may become deranged. Clinical disease states are considered as examples of the kinds of disorders encountered, but particular emphasis is given to those disorders known to be, or theoretically likely to be, associated with toxicant exposure.

The third and final section describes methods by which fertility can be monitored and by which reproductive toxicity might be identified. Animal methods are described but most of the section will consider clinical and epidemiologic methods that are currently in use or under consideration.

INTRODUCTION

The fitness of a species depends on the ability of its members to reproduce. It is surprising, then, that the human species, which dominates the earth, has so much reproductive failure among its members. Perhaps as many as 15 percent of couples have difficulty achieving a clinical pregnancy, and, once conceived, at least 20 percent of these clinical pregnancies will end without the birth of a child. Preclinical losses (occult pregnancies) may represent an even greater proportion of pregnancy failures.

Fertility doctors have long known that a certain amount of reproductive failure is built into the system; the per-cycle fecundity of couples is only 25 percent under the best of circumstances. Nonconceptive menstrual cycles are a part of normal reproductive physiology. Physicians cannot change that, but they can attempt to identify and treat the conditions that increase the rate of nonconceptive cycles. It is, for this purpose, instructive to study physiology, that is, to learn why things go right in order to be better prepared to fix them when they go wrong.

Many of the scientists who tell us the most about normal reproductive function are toxicologists rather than physiologists. The role of reproductive toxicology as an aid to clinicians is not immediately evident and needs some explanation. A historical perspective is helpful in this regard.

Scholars in antiquity had all manner of explanations for the generation of the young of animals. These amuse us now but were seriously considered in their day. It was during the nineteenth century that reproductive physiology advanced as a modern science, with contributors such as Enrico Sertoli and Franz von Leydig. Among the investigators of that era was Gregor Mendel, whose work in genetics was rediscovered at the beginning of the twentieth century. Partly a result of a genetic-based determinism, and partly because the placenta was considered an effective barrier to bad influences, reproductive difficulties were considered failures of the fitness of the individuals afflicted with them rather than as dysfunction of specific organ systems.

In the 1930s, Fred Hale, a worker at the Texas Agricultural Experimental Station, ran a series of experiments in pigs that revolutionized our thinking about reproductive problems. Hale administered a vitamin A–deficient diet to pregnant sows in an attempt to disrupt normal reproductive physiology. The resultant piglets had anomalies of orbit development, showing the success of this manipulation. Hale's experiment followed decades of work with chick and avian

eggs. It had long been known in the poultry industry that abnormal development and other reproductive disasters could be induced by varying the temperature and other conditions of incubation, because chicks have no placenta and limited homeostatic mechanisms. Thus, the Hale experiment made an impression on those who viewed mammalian reproduction as privileged. There followed a series of experiments in other laboratories, using a number of manipulations to disrupt normal developmental events.

In 1941, an Australian ophthalmologist, Norman Gregg, described congenital cataracts in a child whose mother had contracted German measles during pregnancy. Twenty years later, German physicians called attention to limb reduction defects in children with antenatal exposure to the sedative thalidomide. These two episodes made the world aware that chemical and other agents can produce developmental abnormalities and have stimulated scientific and regulatory interest in the prevention of such abnormalities. A decade after thalidomide, the wives of men on a company softball team noted that they were having trouble conceiving. The husbands had in common, besides an interest in softball, exposure to 1,2-dibromo-3-chloroproprane (DBCP), a pesticide used to kill worms. Follow-up studies on this group showed DBCP exposure to be associated with oligospermia and male infertility.

These episodes made clinically relevant the relationship between toxicologists and physiologists because human "experiments" such as these clearly showed a toxicant-induced disruption in reproductive physiology. There arose from these episodes a renewed interest in identifying mechanisms by which normal physiologic events go awry. Herein lies the purpose of this book. *Mechanisms* has become the catchword of the modern era; if we can understand mechanisms of disease, we can develop therapies or even strategies for prevention.

For this reason we have organized a reproductive physiology book with a toxicology accent, because we believe that toxicology studies are likely to provide the basis for understanding reproductive disorders and perhaps for identifying disorders associated with environmental exposures. In fact, we devote our final section to the issue of monitoring for environmentally induced reproductive failure. At present, monitoring is inconsistently performed in workplaces and other environments that are considered to impose risks to reproduction. It is not clear how much reproductive failure will be shown to be due to such environmental exposures; however, it is evident that we will need to monitor for such toxicity if we hope to identify it when it occurs. One of the limitations in this effort is the inherent variability in normal measures of reproductive competence, such as menstrual cyclicity and semen analysis parameters. It is gratifying that current research is being directed to the characterization of the normal range and interindividual reproducibility of reproductive endpoints. This is not a text on the diagnosis and treatment of infertility, nor is it a catalog of genetic causes of gonadal failure, but nonetheless we expect it will be useful to physicians and geneticists who take care of infertile couples. It will also be helpful for investigators in the biological sciences to put into clinical perspective the basic physiology research that is described here. Finally, we envision that students of

the reproductive sciences will benefit from the approach we have adopted. Students are a wonderful audience; they have needs and requirements of a text that put authors and editors to the test. We believe students will benefit from the presentation of physiology as an applied science, rather than as a strictly bench science. It is our hope that all our readers, physicians, scientists, and students, will gain new insights into mechanisms of reproductive success and failure that are becoming so useful in clinical work.

Production of this book has been made more enjoyable by the participation of our contributors, who are among the best and the busiest in the field. We tip our hats to these scientists and clinicians who have done so much to bring this important area of research up to full speed.

ANTHONY R. SCIALLI, M.D.

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PART

I

THE BASIS OF FERTILITY

CHAPTER 1

Male Reproduction: An Overview

David Vantman

The human male reproductive system can be divided into the endocrine and the canalicular compartment. The endocrine compartment, which includes the brain, the hypothalamus, the anterior pituitary gland, and the testes is responsible for the development and maintenance of the secondary sexual characteristics as well as stimulation of spermatozoa development. The canalicular compartment, which includes the seminiferous tubules and adnexal glands under the regulation of the endocrine system, produces and stimulates the maturation of the spermatozoa. The regulatory mechanisms of interaction between both compartments is extremely sensitive to environmental changes; accordingly, many substances are capable of altering this equilibrium.

The knowledge of the physiologic events that regulate both compartments will allow us to understand the possible mechanisms of toxicity of different substances and therefore the appropriate treatment that may be developed.

PHYSIOLOGY OF TESTICULAR FUNCTION

The testis is regulated by two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are synthesized and released in the pituitary under the regulation of the hypothalamic peptide luteinizing hormone–releasing hormone (LHRH or GnRH).

The hypothalamus is anatomically linked to the pituitary both by a portal vascular system and by neural pathways (Green and Harris, 1949). The portal vascular system provides a mechanism for the delivery of releasing hormones from the brain to the pituitary and thus provides the major pathway by which the brain controls anterior pituitary function. Reverse flow through this hypophyseal–portal circulation may also allow pituitary hormones to reach the brain by a direct pathway rather than through the general circulation (Oliver et al, 1977). LHRH, a decapeptide, is synthesized in the hypothala-