

REPRODUCTIVE AND DEVELOPMENTAL
TOXICOLOGY

This book is dedicated to my wife Denise, daughter Rekha, and parents the late Chandra and Triveni Gupta.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Edited by

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Foreword

This book, *Reproductive and Development Toxicology*, presents one of the most comprehensive and thorough treatments of the complex discipline of toxicological phenomena in reproducing and developing organisms available. The focus is obviously often on human species, which is quite understandable, but the book also covers other species, from organisms used for toxicology testing to related aspects of wildlife species. The book surveys a large number of different chemicals, from pharmaceuticals to environmental pollutants, and various experimental systems at all levels of biological organization. We anticipate that this book will be heavily used as a handbook for critically evaluated information which may be not so easily available from other sources.

There are several reasons why such a wide and thorough collection of authoritative reviews and surveys is useful, even imperative. The first reason is the very extraordinary nature of the subject: the developing organism and its creation. Adults of reproducing age “get the ball rolling”, so to speak, but by no means is the new organism a small adult. It could even be said that there is no such thing as a developing organism, but an organism that is constantly and often rapidly changing, with various and variable characteristics at each point in time. It is a moving target for research and the dimension of time has always to be taken into consideration.

Development is manifest at all levels of inquiry: expression of genetic programs at specified stages, consequent changes in the patterns of nucleic acid messages, proteins, enzyme activities, signal transduction systems and so on, as well as formation and modification of anatomical structures and physiological functions. And ultimately, this finely tuned marvel of creation of a new individual could be disrupted at any stage of development, in various ways and by various forces, by physical, chemical and biological insults. The grand goal of the research on reproductive and developmental toxicology is to understand the interplay between exogenous, potentially harmful factors and endogenous, intrinsic molecular, physiological and anatomical determinants, which may ultimately result in derangements in reproduction and development. The epitome of such a deranged

development was the thalidomide catastrophe about 50 years ago, which had and still has far-reaching consequences in basic research, drug development and regulatory pharmacology and toxicology.

As toxicologists and pharmacologists, we used to think that chemicals most often cause their effects via specific target molecules, receptors, enzymes, regulatory factors and so on. However, the appearance of such targets in the developing organism depends on developmental programs, which dictate appearance and disappearance of specific molecular effectors and modifiers. Consequently, if a specific target is still “sleeping” at a certain stage in development, a chemical affecting that specific target does not cause an effect. Toxicity mechanisms elucidated in adults do not necessarily apply in developing organisms.

A developing organism does not exist on its own; it is dependent on its mother, and there are unique structures such as yolk sac and placenta taking care of certain functions during pregnancy. The placenta both connects and separates mother and fetus, and after birth its function has been fulfilled. From a toxicological point of view, the placenta has a central function: it controls the movement and access of chemicals from mother to fetus. Although we know now that the placenta is not a barrier in the old meaning of the word, we still use this misnomer. It is imperative to understand the role of the placenta in the kinetics and dynamics of chemicals, because only then we can fully assess potential hazards and risks to a developing organism.

Up to this day many, perhaps most, reproductive and developmental toxicants have been detected after human exposures. However, the best way to avoid such tragedies should be prevention: to detect potential developmental toxicity in animals before human exposures. Since the thalidomide tragedy, drugs and many other chemicals with intended or unintended human exposures have had to be screened in animal experiments. Recently also a few *in vitro* testing systems have been validated for the same purposes. Animal experiments have their own drawbacks, including sometimes very large and partially unknown or unexplained

interspecies differences, and increasingly influential ethical issues. The main problem of *in vitro* testing systems is that they can never represent the whole complex organism, only some rather limited processes, and thus they need extensive validation to be reliable indicators for developmental hazards and risks. A significant way to avoid difficulties inherent in animal or *in vitro* studies is the thorough characterization of physiological and pathological development and the identification of rate-limiting processes and mechanisms via which toxicants may affect normal development.

The most important humane reason to emphasize the significance of continuous research in reproductive and developmental toxicity is the simple fact that damage in early life, if permanent, will be with the affected individual for the rest

of their life. This is also the principal reason why research efforts have to be directed towards preventive, anticipatory tools and actions. The ultimate goal is to prevent the exposure of reproducing adults and developing individuals to potentially harmful toxicants by reliable and predictive toxicity testing, which employs the most modern *in silico*, *in vitro*, *ex vivo* (and *in vivo*, if possible and necessary) tools in an integrated framework of hazard identification and risk assessment.

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