Teratology Primer
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PREFACE

What is teratology? Would I like to be a teratologist? This book is meant to answer both questions. The book was written by scientists who want to share their fascination for the development of complex organisms from a couple of microscopic cells, and for why, and how things don’t always go right in the process. Being a teratologist is having a front row seat for the most exciting and mysterious performances known to this planet. We hope in a few short pages to give you a sense of what this field is and why it turns us on.

Teratology has its share of controversies. We have tried to give a balanced presentation of different views. Not every scientist whose name is listed as a contributor to this book will agree with every statement made in the book, but disagreement in science is a good thing—it keeps us looking for the answers. We have tried to present a broad array of topics, but this field is large in scope and we have undoubtedly left out some important topics. We apologize for our omissions, but take some comfort in knowing that a book that included all of the richness of teratology would never be finished.

If you find yourself drawn to a topic and you want to learn more, we hope you will contact us. You are the future of this field, and we would be pleased to put you in touch with a teratologist who can answer your questions and get you started in making your own important discoveries. Our email address is teratology@teratology.org.

The Teratology Society, June 2005
What Is Teratology?

“What a piece of work is an embryo!” as Hamlet might have said. In form and moving how express and admirable! In complexity how infinite! It starts as a single cell, which by repeated divisions gives rise to many, genetically identical cells. These cells receive signals from their surroundings and from one another as to where they are in this ball of cells - front or back, right or left, headwards or tailwards, and what they are destined to become. Each commits itself to being one of many types; they migrate, combine into tissues, or die at predetermined times and places. The tissues signal one another to take their own pathways, they migrate, bend, twist, and form organs. An organism emerges. This wondrous transformation from single celled simplicity to myriad celled complexity is programmed by genes that, in the greatest mystery of all, are turned on and off at specified times and places to coordinate the process. It is a wonder that this marvellously emergent process, where there are so many opportunities for mistake, ever produces a well-formed and functional organism.

It sometimes doesn’t. Mistakes occur. Defective genes may disturb development in ways that lead to death or to malformations. Extrinsic factors may do the same:

“Teratogenic” refers to factors that cause malformations, whether they be genes or environmental agents. In common usage it applies to environmental factors. The word comes from the Greek “teras”, for “monster”, a term applied in ancient times to babies with severe malformations, which were considered portents or, in the Latin, “monstra”.

Malformations can happen in many ways. For example, when the neural plate rolls itself up to form the neural tube it may not close completely, resulting in a neural tube defect – anencephaly if the opening is in the head region, or spina bifida if it is lower down. The embryonic processes that form the face may fail to fuse, resulting in a cleft lip. Later, the shelves that will form the palate may fail to move from the vertical to the horizontal, where they should meet in the midline and fuse, resulting in a cleft palate. Or they may meet, but fail to fuse, with the same result. The forebrain may fail to induce the overlying ectoderm to form the eye, so there is no eye (anophthalmia). The web between the toes may fail to break down as it should, and the toes remain webbed.

Experimental teratology flourished in the 19th century, and embryologists knew well that the development of avian and amphibian embryos could be deranged by environmental “insults”, such as lack of oxygen. But the mammalian uterus was thought to be an impregnable barrier (except for sperm of course) that would protect the embryo from such threats. By exclusion, mammalian malformations must be genetic, it was thought.

In the early 1940s, several events changed this view. In Australia an astute ophthalmologist, Norman Gregg, established a connection between rubella (German measles) and the triad of congenital cataracts, heart malformations, and deafness. In Cincinnati, Josef Warkany, an Austrian pediatrician, showed that depriving female rats of riboflavin could cause malformations in their offspring. Warkany was trying to produce congenital cretinism by putting the rats on an iodine deficient diet. The diet did indeed cause malformations, but not because of the iodine deficiency; depriving the diet of iodine had also depleted it of riboflavin!

Shortly, several other teratogens were found in experimental animals, including nitrogen mustard (an anticancer drug), tryptophan blue (a dye), and hypoxia (lack of oxygen). The pendulum was swinging back; it seemed that malformations were not genetically, but environmentally caused.

In Montreal, in the early 1950s, Clarke Fraser’s group wanted to bring genetics back into the picture. They had found that treating pregnant mice with cortisone caused cleft palate in the offspring, and showed that the frequency was high in some strains and low in other strains. The only difference was in the genes. So began teratogenetics, the study of how genes influence the embryo’s susceptibility to teratogens.

The McGill group went on to develop the idea that an embryo’s genetically determined, normal, patterns of development could influence its susceptibility to a teratogen – the multifactorial threshold concept. For instance, an embryo must move its palate shelves from vertical to horizontal before a certain critical point or they will not meet and fuse. A teratogen that causes cleft palate by delaying shelf movement beyond this point is more likely to do so in an embryo whose genes normally move its shelves late.

As the work progressed, patterns began to appear, and the principles of teratology were developed. Those stated, in summary, that the probability of a malformation being produced by a teratogen depends on the dose of the agent, the stage at which the embryo is exposed, and the genotype of the embryo and mother.

The number of mammalian teratogens grew, and those who worked with them began to meet from time to time, to talk about what they were finding, leading, in 1960, to the formation of the Teratology Society.

There were, of course, controversies about whether these experimental teratogens would be a threat to human embryos, but it was thought that they were all “sledgehammer blows”, that would be teratogenic in people only at doses far above those to which human embryos would be exposed. So not to worry. Then came thalidomide, a totally unexpected catastrophe.

The discovery that the ordinary doses of this supposedly harmless sleeping pill and antinauseant could cause severe malformations in human babies galvanized teratology. Scientists who had been quietly working in their laboratories suddenly found themselves spending much of their time in conferences and workshops, sitting on advisory committees, acting as consultants for pharmaceutical companies, regulatory agencies, and lawyers, and redesigning their research plans. The field of experimental developmental toxicology expanded rapidly. The following pages will show how far we have come, and how many important questions still remain to be answered.

A lot of effort was put into developing ways to predict whether a particular experimental teratogen would be hazardous to the human embryo (Chapters 14-20). It was recognized that animal studies could never prove a drug was “safe” for the human embryo (chapter 16). In spite of great pressure from legislators and the public to do so, since species vary greatly in their teratologic responses. It is difficult to produce malformations in many animal species with thalidomide, whereas several agents (e.g. aspirin, vitamin A) that are highly teratogenic in experimental animals are not teratogenic in people, at ordinary doses. A number of human teratogens have been identified, and some suspected of teratogenicity have been exonerated - at least of a detectable risk (chapters 21-26).
Regulations for testing drugs before market release have greatly improved (chapter 15) - though criteria for approving release are still problematic. Incredible millions of dollars have been spent in lawsuits launched by parents of malformed children, including those related to the most clearly established non-teratogen, Bendectin (chapter 30). Progress has been made not only in the use of animal studies to predict human risks, but also to illumine how, and under what circumstances, teratogens act to produce malformations (chapters 1-11). These studies have contributed greatly to our knowledge of abnormal, and also normal, development. Now we are beginning to see exactly when and where the genes turn on and off in the embryo, to appreciate how they guide development and to gain exciting new insights into how genes and teratogens interact. The prospects for progress in the war on birth defects were never brighter.

Suggested reading

