

Teratology Primer, 3rd Edition

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What is Teratology? (Foreword from first edition of Teratology Primer)

F. Clarke Fraser, 1920-2014, was one of the founders of the Teratology Society. This original foreword is included for historical perspective.

“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 cell commits itself to being one of many types; the cells migrate, combine into tissues, or get out of the way by dying at predetermined times and places. The tissues signal one another to take their own pathways; they 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 marvelously emergent operation, where there are so many opportunities for mistakes, ever produces a well-formed and functional organism.

And sometimes it 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. 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 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 tissue to form the eye, so there is no eye (anophthalmia). The tissues between the toes may fail to break down as they should, and the toes remain webbed.

Experimental teratology flourished in the 19th century, and embryologists knew well that the development of bird and frog embryos could be deranged by environmental “insults”, such as lack of oxygen (hypoxia). But the mammalian uterus was thought to be an impregnable barrier 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 maternal rubella (German measles) and the triad of cataracts, heart malformations, and deafness. In Cincinnati Josef Warkany, an Austrian pediatrician, showed that depriving female rats of vitamin B (riboflavin) could cause malformations in their offspring – one of the early experimental demonstrations of a teratogen. 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; depleting the diet of iodine had also depleted it of riboflavin!

Several other teratogens were found in experimental animals, including nitrogen mustard (an anti cancer drug), trypan 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 others. 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, pattern 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 studies of the basis for abnormal development progressed, patterns began to appear, and the principles of teratology were developed. These 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, concerns about whether these experimental teratogens would be a threat to human embryos, but it was thought, by me at least, 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, or so we thought.

Then came thalidomide, a totally unexpected catastrophe. The discovery that ordinary doses of this supposedly "harmless" sleeping pill and anti-nauseant could cause severe malformations in human babies galvanized this new field of 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, as well as redesigning their research plans.

The field of teratology and 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 has gone into developing ways to predict how much of a hazard a particular experimental teratogen would be to the human embryo. It was recognized that animal studies might not prove a drug was "safe" for the human embryo (in spite of great pressure from legislators and the public to do so), since species can vary in their responses to teratogenic exposures. A number of human teratogens have been identified, and some, suspected of teratogenicity, have been exonerated – at least of a detectable risk. Regulations for testing drugs before market release have greatly improved. Other chapters deal with how much such things as population studies, post- marketing surveillance, and systems biology add to our understanding. And, in a major advance, the maternal role of folate in preventing neural tube defects and other birth defects is being exploited. Encouraging women to

take folic acid supplements and adding folate to flour have produced dramatic falls in the frequency of neural tube defects in many parts of the world.

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. 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

Fraser FC. Evolution of a palatable multifactorial model. *Am J Hum genetics* 1980; 32: 796-813.

Fraser FC. Thalidomide Retrospective: What did we learn? *Teratology* 1988:201-222.

Wilson JG. Current Status of Teratology - General Principles and Mechanisms Derived from Animal Studies. In: Wilson JG, Fraser FC, eds., *Handbook of Teratology*. Vol. 1. General Principles and Etiology. New York: Plenum Press, 1977: 47-74.