

James G. Wilson's Six Principles of Teratology

James Graves Wilson's six principles of teratology, published in 1959, guide research on teratogenic agents and their effects on developing organisms. Wilson's six principles were inspired by Gabriel Madeleine Camille Dareste's five principles of experimental teratology published in 1877. Teratology is the study of birth defects, and a teratogen is something that either induces or amplifies abnormal embryonic or fetal development and causes birth defects. Detailed in his 1973 monograph, *Environment and Birth Defects*, Wilson's principles helped scientists research teratogens experimentally.

Between the 1860s and 1900, Gabriel Madeleine Camille Dareste, who studied embryology and zoology in Paris, France, relied on the early works of father and son duo of Etienne Geoffroy and Isidore Geoffroy Saint-Hilaire. In the early half of the nineteenth century in Paris, France, Etienne experimented on chick eggs by subjecting them to various physical manipulations, such as pricking, inversion, abnormally high and low temperatures, etc. and he studied the resulting malformations. He argued that certain abuses could invoke specific deformations. While deformations indeed materialized, Saint-Hilaire didn't identify their exact causes. His son Isidore then continued the work and reported Etienne's results between the years of 1832 and 1837 in *Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux* [General History and Specific Abnormalities of the Organization in Humans and Animals]. Building on the Hilaires' work, Dareste manipulated the temperatures, shook, and chemically treated chick embryos. He found that the most severe abnormalities occurred when he manipulated the embryos early in development. Dareste contended that his experiments delayed or completely arrested the developmental process. Dareste developed a set of five principles of teratology, which he detailed in his 1891 text *Recherches sur la production artificielle des monstruosités: ou, Essais de tératogénie expérimentale* [Research on the Artificial Production of Monstrosities, or Experimental Teratogenicity Testing.]

James G. Wilson, who had studied embryology at the University of Rochester Medical School in Rochester, New York in 1942, expanded Dareste's five principles in his 1959 article "Experimental Studies on Congenital Malformations". Wilson further revised these five principles and added a sixth generalization about dosage effects in his 1973 monograph *Environment and Birth Defects*.

The first principle described in Wilson's 1959 work, labeled "Susceptibility to Teratogenesis Depends on the Genotype of the Conceptus and a Manner in which this Interacts with Adverse Environmental Factors," has four sections. In Section A, "Species Differences," Wilson says that certain species respond to particular teratogens where others do not, or at least not to the same extent. For example, humans and other primates are extremely vulnerable to thalidomide, a sedative used in the 1950s to treat morning sickness. If exposed to thalidomide during embryonic development, fetuses develop limb and facial malformations. Other mammals, including rats and mice, however, are resistant to thalidomide. In section B, "Strain and Intralitter Differences," Wilson notes that animals of the same species with different genetic backgrounds can differ in the frequency and intensity of abnormalities caused by teratogens, because some lineages are more resistant to teratogens than are others. Section C, "Interaction of Genome and Environment," underscores the interplay between environment and genetics that results in different abnormalities between organisms with the same genome raised in different environments, and between organisms with different genomes raised in the same environment. Maternal characteristics, such as the ability of a pregnant female to metabolize teratogens, partly determine whether or not a fetus will develop abnormalities. In Section D, "Multifactorial Causation," Wilson argues that interactions between genes and environments involving more than one gene and/or more than one environmental factor can influence the severity of a birth defect caused by a teratogen.

Principle two, "Susceptibility to Teratogenesis Varies with the Developmental Stage at the Time of Exposure to an Adverse Influence," has into six sections. Starting with introductory section A, "Subdivisions of the Developmental Span," principle two chronologically illustrates the stages of development from the early refractory period to birth and afterward. Next, Wilson describes embryos' susceptibilities to teratogens within each stage of development. Entitled the "Highly Susceptible Period of Organogenesis," section C resulted from Wilson's studies of teratogens, and it depicts the process of organogenesis, the development of organs within an organism, along with the increased incidence of malformations caused by teratogens due to the abrupt differentiation of the conceptus' tissue. The last section, F. "What About Germ Cells?" Wilson says that factors such as environment, drugs, and dietary deficiency could damage germ cells and the germ layers from which they arise; however, when Wilson published his principles, researchers hadn't determined whether or not teratogens could impact certain stages of gametogenesis, or the formation of gametes.

Principle three, "Teratogenic Agents Act in Specific Ways (Mechanisms) on Developing Cells and Tissues to Initiate Sequences of Abnormal Developmental Events (Pathogenesis)," has two sections: A. "Mechanisms of Teratogenesis," and B. "Pathogenesis of the Defect." In these sections, Wilson asserts that specific teratogenic agents produce distinctive malformation patterns. Through this third principle, Wilson indicated that people may be able to take supplements to protect against particular teratogenic agents.

Principle four, "The Access of Adverse Influences to Developing Tissues Depends on the Nature of the Influence (Agent)," divides teratogenic agents into A. "Physical Agents," and B. "Chemical Agents." The body of a pregnant female protects the developing tissues of germ cells, embryos, and fetuses, and Wilson contends that in placental mammals, many physical agents such as low-energy radiation do not much affect developing fetuses. However, Wilson treated ionizing radiations as an exception among physical agents due to its ability to reach developing tissues. Thus, one of the first environmental agents classified as a teratogen was x-radiation. Unlike physical agents, however, chemical agents almost always reach developing tissues, usually via the maternal bloodstream. Due to factors of maternal metabolization, absorption, and elimination, the concentration of a chemical agent varies by the time the agent reaches the fetus, variation that affects the extent of abnormal development. A chemical that may be teratogenic in vitro, or to an embryo in a test tube, doesn't necessarily imply that same chemical will be a teratogenic agent in vivo, an embryo within its normal biological environment such as within the womb.

Wilson's fifth principle, "The Four Manifestations of Deviant Development are Death, Malformation, Growth Retardation and Functional Deficit," has sections about each of the listed manifestations within the principle's title. Wilson argues that encounters with teratogenic agents at any point during development have the ability to produce one or more of these manifestations, and that some manifestations are more likely to occur during certain stages of development. After an embryo implants in a uterus's wall, but before its cells differentiate, the most common manifestation of deviant development is the embryo's death. Additionally, organisms sensitive to teratogens are more susceptible to having their embryos die than they are to having those embryos develop with abnormalities; the converse holds for lineages of organisms somewhat resistant to teratogens.

The sixth and final principle listed by Wilson, "Manifestations of Deviant Development Increase in Frequency and Degree as Dosage Increases, from No-effect to the Totally Lethal Level," has five sections. In section A. "Thresholds in Teratogenesis," Wilson describes the concept of teratogen thresholds and explains that while studies may indicate that organisms may have a threshold to teratogens, or that pregnant females may interact with specific teratogens and have offspring that show no evidence of any defect, a large sample of test animals is still needed to definitively establish the existence of a no-effect level. Sections B to D are about the embryotoxicity and maternal toxicity and the dose-response curve. The dose-response curve depicts how rapidly a developmental effect can change depending on the dosage of a teratogenic agent and stage of embryonic development. Section E. "Dosage Level and Degree of Response," describes the range of toxicity from no effect to completely lethal. It also describes accessory effects such as lengthened gestation during the developmental period in which a defect forms. Also, an increase in a teratogen dosage may cause a particular malformation to arise across multiple developmental stages.

Close to three percent of infants exhibit significant morphologic anomalies, and developmental de-

fects account for about twenty-five percent of newborn deaths, making it the leading cause of infant mortality. Scientists investigate the mechanisms by which teratogens act, Wilson's six principles ground their work.

Sources

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