

Teratogens

Teratogens are substances that may produce physical or functional defects in the human embryo or fetus after the pregnant woman is exposed to the substance. Alcohol and cocaine are examples of such substances. Exposure to the teratogen affects the fetus or embryo in a variety of ways, such as the duration of exposure, the amount of teratogenic substance, and the stage of development the embryo or fetus is in during the exposure. Teratogens may affect the embryo or fetus in a number of ways, causing physical malformations, problems in the behavioral or emotional development of the child, and decreased intellectual quotient (IQ) in the child. Additionally, teratogens may also affect pregnancies and cause complications such as preterm labors, spontaneous abortions, or miscarriages. Teratogens are classified into four types: physical agents, metabolic conditions, infection, and finally, drugs and chemicals.

The word teratogen originates from the Greek word for monster, *teratos*. Isidore Geoffroy Saint-Hilaire, a physician from Paris, France, defined it in 1832 in *Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux* (General and Particular History of Structural Monstrosities in Man and Animals). People had sought explanations for abnormal human and animal development, however, for centuries, and they had developed different theories about the causes for the abnormalities. In Babylon, many said that infants with congenital malformations, or structural abnormalities present at birth, were constellations in human forms as well as fortune-tellers. Many early Hebrews said that abnormal development resulted from the deformed person's association with the devil. Aristotle, who lived in Athens, Greece in the fourth century, B.C., deemed birth defects as disturbances in reproduction rather than supernatural occurrences. Aristotle and Hippocrates, a physician who practiced in Greece in the fifth century B.C., claimed that a pregnant woman's experiences or emotions, which became called maternal impressions, can affect the formation of the fetus. The theory of maternal impressions persisted until the early 1900s, despite evidence to the contrary by John Hunter, a surgeon in Scotland in the late eighteenth century.

At the beginning of the 19th century, Johann Friedrich Meckel, the Younger, an anatomist from Halle, Germany, asserted that deviations from the normal developmental process caused malformations. Meckel wrote his doctoral thesis on an anatomical study of heart disease in 1802 and founded a journal dedicated to teratology, *Journal für anatomische Varietäten, feinere und pathologische Anatomie* (Journal of Anatomical Varieties, Finer and Pathological Anatomy). Meckel examined anatomical defects and their causes. Because he asserted that to understand abnormal development, one must first understand normal development, he documented his observations of normal embryological development of mammals in a sequence of forms. Meckel also categorized abnormal development into four basic types: reduced or absent body parts (insufficient generative energy), enlarged or multiple body parts (excessive energy), aberration of form and of position, and hermaphroditism, which included deformities such as ambiguous genitalia.

Following Meckel, scientists in the nineteenth century began experimental studies to detect teratogens. Etienne Geoffroy Saint-Hilaire in Paris, France, experimented on chick eggs by subjecting them to pricking, inversion, jarring, and abnormally high or low temperatures to study the resulting malformations; he believed that certain manipulations could invoke specific deformations. Although deformities materialized, Saint-Hilaire didn't identify their exact causes. His son Isidore then reported the results of the experiments between the years of 1832 and 1837 in his three-volume *Traité de Tératologie* (Treatise on Teratology). Other scientists following Saint-Hilaire also experimented with teratogens, notably Camille Dareste in France, who successfully produced abnormalities in chick embryos during twenty-two years of experiments until his death in 1899.

Scientists in the twentieth century classified teratogens into four categories, physical, chemical, or infectious agents and maternal conditions. Physical agents include ionizing radiation or other agents that contribute to hyperthermia, or elevated body temperature. Ionizing radiation is radiation composed of particles, X-rays, or gamma rays that carry adequate energy to free an electron from an atom or molecule, resulting in electrically charged ions in matter. In the 1920s reports surfaced of abnormalities in the children of women who were X-rayed while pregnant. The common anomalies were small head circumference, or microcephaly, and small eyes, or microphthalmia. Douglas P. Murphy, from the University of Pennsylvania in Philadelphia, Pennsylvania, surveyed gynecologists and radiologists across the US between 1928 and 1929, and found that of the seventy-four children reported to have been exposed to radiation in utero, twenty-five were malformed.

Agents that cause hyperthermia are also physical teratogens. These could be saunas, hot tubs, or infections that raise a pregnant woman's body temperature to 102 degrees Fahrenheit or higher. Scientists have shown that hyperthermia-causing agents acted as teratogens in both animals and humans. Experiments on animals, such as guinea pigs, hamsters, rats, mice, rabbits, sheep, pigs, and monkeys from the early 1970s to the early 1990s demonstrated that hyperthermia causes central nervous system malformations, microcephaly, abdominal wall defects, defects of the eye and palate, and limb reduction defects. David L. Cockroft and Denis Alan Trevor New in the UK reported in the 1970s that heating explanted rat embryos caused microcephaly, enlarged hearts, and skeletal deformities. In the 1980s, scientists used other agents to cause hyperthermia in pregnant females, such as ultrasound and electromagnetic radiation, to test the agent's capacity to cause birth defects in offspring. In humans, hyperthermia is associated with neural tube defects, spontaneous abortions, and various cardiovascular abnormalities. Physicians and scientists gathered evidence in the early 1990s which supported their theories that there was an association between the high fevers of pregnant women and congenital abnormalities, such as cardiac defects, abdominal wall defects, or a disruption of the innervation of the large intestine called Hirschsprung disease, in their offspring.

Metabolic conditions affecting pregnant females such as malnutrition, diabetes, and thyroid disorders are a second category of teratogens. Metabolic conditions are abnormalities in the chemical process of producing energy from food, and thereby affect the development and function of the body. If a pregnant woman is malnourished, then her fetus likely lacks the nutrients essential for its development. In the case of diabetes, low blood sugar, or hypoglycemia, may cause fetal malformations. Hypoglycemia interferes with some proteins in the developing fetal heart by increasing the expression of proteins which are regulated by glucose. Excessive blood sugar, also seen with diabetes, may cause neural tube defects, or birth defects of the brain and spinal cord, and may also induce the release of free radicals, or damaged cells that are missing an essential molecule, which disrupt fetal development. In the 2000s, The Society of Obstetricians and Gynaecologists of Canada reviewed reports from 1990 to 2005 on the risk of congenital anomalies in pregnancies caused by pre-existing or gestational diabetes. They found that the risk of major malformations increases from four to ten percent in infants of diabetic mothers. This statistic was two to three times higher than that in general populations.

Thyroid disorders include disorders in which the thyroid gland malfunctions, thereby producing abnormal amounts of the thyroid hormones, thyroxine and triiodothyronine, which regulate metabolism. Thyroid disorders can cause a number of teratogenic effects to a developing fetus, as well as adverse effects on pregnancy such as miscarriage, premature separation of the placenta from the uterine wall (placental abruption), preterm labor, and lower IQ scores in the children. In the 1940s, pediatrician Josef Warkany and colleagues in Cincinnati, Ohio raised female rats on a diet high in substances which interfere with thyroid function or goitrogens. As a result of this diet, the pregnant females developed enlarged thyroid glands and their offspring had skeletal malformations such as abnormally short jaw bones and tails, shortened or absent lower leg bones, and fusion of the ribs.

Infections such as those caused by rubella virus, herpes simplex virus, and syphilis, are a third kind of teratogen. In 1941, ophthalmologist Norman McAlister Gregg at the Royal Alexandra Hospital for Children in Sydney, Australia witnessed cataracts in seventy-eight children whose mothers were infected with the rubella virus during either the first or second months of pregnancy. The connec-

tion Gregg made between the virus and congenital malformations contributed to one of the first discoveries of a teratogen that wasn't a manufactured chemical. In addition to rubella, herpes simplex virus, and cytomegalovirus—one of the herpes viruses that passes through direct contact with body fluids, congenital abnormalities can be caused by infections of *Toxoplasma gondii*, a parasite often obtained by eating contaminated meat, drinking contaminated water, or coming into contact with infected cat feces, and *Treponema pallidum*, the bacterium that causes syphilis.

The fourth kind of teratogen includes drugs and chemicals the pregnant female ingests such as alcohol, cocaine, thalidomide, Agent Orange, and vitamin A and its derivatives, called retinoids. In 1933, Fred Hale at the Texas Agricultural Experiment Station in College Station, Texas, fed pregnant female pigs a diet severely deficient in vitamin A and found that the offspring had various congenital malformations such as anophthalmia, which is the absence of one or both eyes, and cleft palate. Over the next four years, Hale experimented with pigs and vitamin A deficiency and found other defects such as cleft lip and malformed hind legs. Hale's experiments established that an absence or deficiency of a nutrient could produce severe congenital malformations in mammalian embryos. In 1953, pediatrician Sidney Q. Cohan in New York City, New York, reported that large doses of vitamin A caused congenital malformations of the central nervous system and other systems in rats. That announcement led to decades of experimentation with vitamin A and its derivatives, retinoids.

In the 1960s, thalidomide provided one of the first instances when governments enacted regulations regarding the risk of teratogens to the developing fetus. Thalidomide had been patented in 1954 and was approved for use in Europe as a sedative and anti-nausea medicine for pregnant women. After several years on the market, physicians noted that women who had taken thalidomide while pregnant gave birth to a increased number of infants with severe malformations such as shortened, absent, or extra limbs (dysmelia), incomplete development or a below average number of cells (bone hypoplasticity), and a variety of ear, heart, and internal organ defects. In 1961, physician Widukind Lenz in Hamburg, Germany reported his observations on thalidomide's teratogenicity and the drug was soon taken off the market. Physician and pharmacologist Frances Kelsey of the US Food and Drug Administration (FDA), headquartered in Washington D.C., never approved the sale of thalidomide in the US. Kelsey requested more clinical test results after she received reports of the adverse effects of thalidomide in Europe. Approximately 10,000 babies worldwide were born with defects due to thalidomide. After the thalidomide incident, in August 1962, the American Pharmaceutical Manufacturers Association implored the US pharmaceutical industry to establish a Commission on Drug Safety to develop ways of improving animal teratogenicity tests. In 1966, the FDA issued Guidelines for Reproductive Studies for Safety Evaluation of Drugs for Human Use, which created a standard for evaluating teratogenicity and was issued in many countries.

In 1977, James G. Wilson at the University of Florida Medical School in Gainesville, Florida, refined the principles of teratology he had first introduced in 1959 at a conference on congenital malformations. Wilson's six principles of teratology state verbatim:

1. Sensitivity to teratogen-induced malformation depends on the genotype (species) of the conceptus.
2. Sensitivity to teratogen-induced malformation varies during different developmental stages at the time of exposure, where there are critical periods of sensitivity to agents and organ systems.
3. Teratogens act via a specific mechanism on developing cells and tissues to initiate a cascade of altered developmental events.
4. Teratogenic effects are dependent on the nature of the teratogen, including chemical properties of the chemical, route of exposure, maternal/fetal bioactivation, placental transport, etc.
5. Teratogens produce a consistent deviation from normal development. Deviation can include: (1) death, (2) malformation, (3) growth retardation, or (4) functional defect.
6. Teratogen-induced malformations occur in a dose-dependent manner, ranging from no observable defects to total lethality.

Alcohol, which also falls under the fourth category of teratogen, can cause Fetal Alcohol Syndrome (FAS) in children born to women who drank too much alcohol while pregnant. FAS can cause defects

such as minor facial abnormalities and damage to the brain, which consequently leads to learning, behavioral, and cognitive abnormalities. In the US, pediatricians David W. Smith and Kenneth L. Jones examined a group of children at the University of Washington's Harborview Medical Center in Seattle, Washington in 1973. Of the eight children observed, four had similar deficiencies in growth and cognitive development. This observation led Smith and Jones to investigate alcohol as a teratogen and over the next few years, the duo collected case studies of children born to alcoholic mothers to enumerate morphological anomalies and growth deficiencies associated with FAS.

Today, the FDA monitors teratogen exposures to pregnant women in the US with a number of regulations and risk management programs. For example, the retinoic acid isotretinoin which is commonly used for acne treatment cannot be given to any patient unless they are enrolled in iPLEDGE, a risk management program designed to prevent fetal exposure to isotretinoin.

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