

# "Experimental Studies on Congenital Malformations" (1959), by James G. Wilson

The article "Experimental Studies on Congenital Malformations" was published in the *Journal of Chronic Diseases* in 1959. The author, James G. Wilson, studied embryos and birth defects at the University of Florida Medical School in Gainesville, Florida. In his article, Wilson reviewed experiments on birds and mammals from the previous forty years to provide general principles and guidelines in the study of birth defects and teratogens, which are things that cause birth defects. Those principles included what species are convenient for conducting teratological research, what principles act in human embryological and fetal development, and what agents impact those processes. Wilson's article was one of the first attempts in the twentieth century to synthesize basic research conducted in the field of teratology. The article helped to establish teratology as a field in medicine during the twentieth century.

Prior to the twentieth century, few regarded teratology as a field of science. Earlier studies primarily catalogued, categorized, and described birth defects. At the turn of the twentieth century, researchers conducted experiments to explain birth defects as the results of abnormal human development and to identify teratogenic mechanisms. Wilson's "Experimental Studies on Congenital Malformations" was the first review article of its kind to collect and synthesize the findings from those early to mid twentieth-century studies of teratogens.

Wilson's article has four main sections titled "Types of Agents Used," "Factors that Failed to Cause Malformations," "General Principles of Experimental Teratology," and "Mechanisms of Teratogenic Action." Each section surveys and analyzes experiments done prior to the article's publication in 1959 and provides general but concise summaries of consistent results, such as agents that had been proven to cause congenital defects in rats. Additionally, each section illustrates the principles of human developmental and reproductive processes that Wilson and others had distilled from previous experiments.

In the section "Types of Agents Used," Wilson discusses a variety of agents that researchers used in teratology experiments. He organizes this section into the most commonly-used categories of tested agents: physical factors, maternal nutritional deficiencies, growth inhibitors and specific antagonists, infectious agents, hormone injections and endocrine states, and miscellaneous drugs and chemicals. Physical factors include x-rays, hypothermia, hypoxia, elevated carbon dioxide, and amniotic sac punctures. Of these, only x-rays caused human malformations in experimental studies. Among the most commonly tested maternal nutritional deficiencies, Wilson includes vitamin A, riboflavin, folic acid, pantothenic acid, vitamin B12, thiamine, biotin, vitamin D, vitamin E, and general inanition. Wilson notes that with such nutritional deficiencies, researchers struggle to determine exactly the right degree of deficiency that will cause a malformation, as the teratogenic zone between normal development and complete reproductive failure is narrow.

Wilson describes, among other agents responsible for birth defects, growth inhibitors and specific antagonists. These chemicals inhibit growth, cancer, and metabolic actions because they all interfere with growth, which can result in malformations or embryonic deaths. A few of the chemicals Wilson lists include nitrogen mustard and thiadiazole. Next, Wilson discusses infectious agents and claims that although many have been tested, only few have experimentally produced malformations, such as the influenza A virus, rubella virus, toxoplasma, hog cholera virus, and the Newcastle virus. Additionally, Wilson addresses hormone injections, including androgens, estrogens, insulin, cortisone, vasopressin, adrenalin, and alloxan diabetes, as causing birth defects. Finally, Wilson discusses miscellaneous chemicals and drugs that result in birth defects, such as trypan blue, ex-

cess vitamin A, excess nicotinic acid, sugars, thallium, sulfanilamide, antibiotics, and salicylates among others.

In the section "Factors that Failed to Cause Malformations," Wilson provides a list of agents for which, as of 1959, there was not evidence that they could produce congenital malformations. Those agents included, but were not limited to: the mumps virus, copper, vitamin C deficiency, and amino acid deficiencies. Wilson presents his list of agents by the species in which each agent was found unable to produce malformations.

In the section "General Principles of Experimental Teratology," Wilson presents five basic principles of teratology that describe the susceptibility of embryos to teratogens. Wilson states that he derived those principles from a number of experiments and existing literature. Wilson later developed and articulated those teratogenic principles in his 1973 book *Environment and Birth Defects*.

The first principle states that an embryo's susceptibility to an external agent depends on the embryo's developmental stage at the time when that agent interferes with it. Wilson discusses how teratogenic agents are most effective in creating congenital malformations when applied during early stages of organogenesis, the processes in which organs are formed. Susceptible periods vary from organ to organ, but are generally within the first few days of differentiation.

The second principle states that each teratogenic agent has particular effects on a specific aspect of cellular metabolism. This principle implies that every agent produces a particular, though not necessarily unique, type or pattern of malformations when applied to a certain species at a certain time. Wilson supports this principle by providing a table of congenital defect patterns induced in the rat through different teratogenic agents. Additionally, Wilson describes the research results of Walter Landauer, who worked at the University of Connecticut in Storrs, Connecticut. Landauer compared the effects of six different agents (sulfanilamide, eserine, thallium, insulin, boric acid, and pilocarpine) on developing chicks on their fourth days of incubation. The six agents produced skeletal defects, and the pattern indicated two different pathways of teratogenic action, and that a teratogenic agent could affect multiple metabolic pathways at one or more times during development.

Wilson's third principle states that the genotype of the test animal plays a role in how the animal reacts to the teratogenic agent. Wilson provides evidence to support this principle with many case studies. He describes experiments that different teams conducted, which demonstrate that a particular species or strain may be genetically susceptible to certain teratogenic effects. For instance, Wilson reports an experiment in which pregnant female mice were starved for twenty-four hours. This experiment demonstrated that when starved on the ninth day of pregnancy, twenty-two percent of the mice's offspring were born with cranial or rib defects. However, when the pregnant mice were on a regular diet, only two percent of offspring were born with such defects. Similarly, Landauer's experiment showed that injecting insulin into incubating chick eggs caused numerous birth defects that otherwise would have been rare.

The fourth principle states that any agent capable of producing malformations also causes an increase in embryonic mortality. Wilson states that abnormal development and death are probably different degrees of reaction to teratogenic agents, and he discusses the teratogenic zone, which is a range of dosage in which permanent changes occur. A slight increase in dose above this narrow teratogenic zone often results in mortality.

Wilson's fifth and final principle states that a teratogen might not harm the maternal organism. Wilson cites the rubella virus as an example. Pregnant women with the virus may not experience any discomfort or adverse reaction to the virus, but her conceptus may be affected. Wilson notes that often, the teratogenic agent does not negatively affect the pregnant female as much as the embryo, and that no standard relationship exists between the pregnant female's reaction and the embryo's reaction.

In the article's last section, "Mechanisms of Teratogenic Action," Wilson explains the ways in which a teratogen can affect an embryo using two categories: cell death and alteration in the rate of cell growth. When abnormal cell death occurs, there is a reduction in the normal amount of tissue or organ in which all cells had died. When cell growth is altered, slowed, or stopped, the effects are

the same as when cell death occurs. Accelerated cell growth, however, displaces a tissue or organ from its normal growth schedule. This phenomenon may result in congenital malformations such as spina bifida. Wilson also describes how a teratogen interferes with a growing embryo during any of the three major stages of differentiation: chemical, cellular and tissue, or organ and functional.

Wilson concludes his article by stating that there have been approximately sixty ways in which congenital malformations occurred in laboratory animals. These are categorized into nutritional deficiencies, infectious agents, endocrine states, metabolic and growth inhibitors, physical agents, and chemicals and drugs. Wilson summarizes his five principles of teratology and states that the end result of all teratogens appears to be either cell death or altered rate of cell growth.

"Experimental Studies on Congenital Malformations" was the first article that surveyed teratogen studies from the beginning of the twentieth century until 1959. Wilson's article is a comprehensive review that synthesizes data on previous teratology experiments into a list of five principles to explain how some agents induce particular teratogenic responses. Prior to Wilson's five principles, studies had lacked a cohesive synthesis. In 1973, in his book *Environment and Birth Defects*, Wilson added a sixth principle to his original five principles. The sixth principle holds that abnormal development occurs when dosage of the teratogenic agent increases. In the twentieth century, teratology became organized into a field of science based on empirical evidence that explains normal and abnormal developmental and reproductive processes. Into the early decades of the twenty-first century, researchers maintained Wilson's six principles as the standard theory of teratology.

## Sources

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