Environment and Birth Defects (1973), by James G. Wilson

By: Aston, S. Alexandra Keywords: congenital malformations, abnormal development, James G. Wilson

*Environment and Birth Defects* by James Graves Wilson was published in 1973 in the US. The book summarized information on the causes of malformations in newborns and aimed to acquaint policy makers with Wilson's suggestions for predicting the risks of environmental causes of birth defects, called teratogens. Wilson also provided six principles for researching teratogens, a framework revised from his 1959 article "Experimental Studies on Congenital Malformations." The book has ten chapters. The body of the text is followed by three appendices that contain reference material and photographs of laboratory animals, and reproductive and embryological information.

Throughout the 1920s and 1930s, scientists began to document the detrimental effects of things such as drugs, chemicals, and irradiation on unborn human fetuses. A rubella outbreak in the 1940s as well as the use of chemotherapy in the 1950s also alerted scientists to the chance that external factors played a bigger role in abnormal development than they had anticipated. In the 1960s, researchers began to use experiments to discern the causes of teratogens. Wilson summarized much of that work in his 1973 book.

In the book, Wilson identifies two areas of special concern within teratology: mutagenesis and teratogenesis. He emphasizes that he wrote *Environment and Birth Defects* for policy makers instead of for the general public or for the scientific community. Wilson provides background information on genetics, embryology, and toxicology to those who would otherwise be unfamiliar with it. During editing, Wilson broadened the text to encompass teratology, and consequently, *Environment and Birth Defects* evolved to become an introduction to the field.

Chapter one, "Is the Unborn Child at Risk in the Environment?" presents two scenarios concerning the transmission of environmental agents to the unborn: total protection and total vulnerability. Wilson states that risks to developing embryos and fetuses lies somewhere between the two scenarios. Wilson asserts that humans have altered their environment at a faster rate than they are able to adapt to the changes. Additionally, Wilson says that our ability to predict the safety of chemicals and drugs may be impossible due to variation in susceptibility across people and populations.

Prior studies in teratology described and classified deformities. But the fact that researchers could link many anomalies to items in the environments of pregnant women did not reveal cause-and-effect relationships. Wilson notes that environmental influences can lead to hereditary defects, non-hereditary defects, affect only certain species, or they can cause dissimilar defects in different species. Wilson claims that there is evidence that the presence of an environmental agent such as radiation cannot alone cause deformities, rather, those agents fit with a succession of responses to affected cells in a fetus to cause the fetus to develop abnormally.

Next, Wilson notes that there are nine major categories of causes known to mammals and of those, only four are teratogenic in humans: ionizing radiations, chemicals in the form of drugs or pollutants, infectious agents, and endocrine and metabolic imbalances. Mechanisms, such as altered energy sources or enzyme inhibition, are the middle steps between the first response to a teratogen and the development of a malformation. Wilson states that there are four kinds of manifestations of teratogenic effects: death, malformation, growth retardation, and functional deficit. Though there is no general name for all four manifestations across all developmental stages, Wilson suggests the use of developmental toxicity as a general term.

Wilson concludes chapter one with the history of teratology and recounts what he says are the major scientific advances in the field from early theories such as the theory of maternal impression, which held that by simply looking at something, the mother could affect her conceptus' development, to more recent research on teratogens, such as Norman McAlister Gregg's 1940 study on rubella in Melbourne, Australia.

Chapter two, "Principles of Teratology," lists Wilson's six principles of teratology. Originally published as five principles in his 1959 article, "Experimental Studies on Congenital Malformations," Wilson adds a sixth in this monograph. The first principle states that certain species respond to particular teratogens while others do not, or at least not to the same extent. Principle two chronologically illustrates the stages of development in humans from the early refractory period to post-birth. Wilson demonstrates the susceptibility of embryos within each stage to the effects of teratogens. Principle three states that specific
teratogenic agents produce distinctive malformation patterns. Principle four divides agents into two categories, physical agents and chemical agents.

Wilson's fifth principle divides into sections dedicated to each of the four manifestations of deviant development. Wilson argues that a harmful influence at any point during development has the ability to produce one or more of these manifestations, but that some manifestations are more likely to occur during specific stages of development. The sixth and final principle elucidates the concept of teratogen thresholds, and introduces the response curve, a curve that depicts how rapidly the effect of a teratogenic agent can change with varying dosages and stage of embryonic development.

Chapter three, "Causes of Developmental Abnormality," expands on the categories of causes mentioned in chapter one. In this chapter, Wilson distinguishes mutagenic agents from teratogenic agents. Teratogenic agents are detrimental to development, while the same cannot be said for all mutagenic agents. Wilson also discusses the effects on developing fetuses of combination interactions between two or more simultaneously-acting environmental agents. The combination of multiple agents individually below low-threshold levels could, through interaction, cause deformities. Wilson states that complex interactions between genes [13] and environmental factors are possible.

Wilson subcategorizes causes such as infections, maternal metabolic imbalances, and drugs. The section on drugs is the lengthiest and covers an entire spectrum of drug types. Drugs such as thalidomide, steroid hormones [14], and folic acid [15] antagonists are confirmed teratogens. Drugs suspected to be teratogens are listed with discussion on the controversy surrounding them. In the last paragraph of this section, Wilson explains that although links between drugs and deformities exist, use of drugs with teratogenic potential does not immediately predispose an embryo to abnormal development.

Four major chemical substances: methyl mercury, industrial solvents, pesticides, and cigarette smoke, along with their effects, are discussed in the environmental chemical section. Lastly, Wilson mentions the debate on whether or not perinatal nutritional deficiencies such as low caloric intake and scarcity of essential nutrients can damage developing fetuses.

Chapter four, "Mechanisms of Teratogenesis," details the mechanism Wilson introduced in chapter one. Using his definition of mechanism—the events between the introduction of the causative agent and its final manifestation—he demonstrates how mechanisms instigate and establish the direction of pathogenesis.

Wilson the describes nine mechanisms: 1. mutation, 2. chromosomal breaks or nondisjunction, 3. miotic interference, 4. altered nucleic acid integrity or function, 5. lack of precursors, substrates, etc., 6. altered energy sources, 7. enzyme inhibition, 8. fluid-osmolyte imbalance, and 9. changed membrane characteristics. These mechanisms are not always initiated by the same cause in each case; the resulting mutation depends on what type of cell was affected. Wilson concludes with a section on how scientists can anticipate risks of teratogenic agents if they study the mechanisms by which those agents work. Furthermore, doctors can use those mechanisms, instead of screenings, to identify teratogenic agents in affected organisms.

In chapter five, "Manifestations of Abnormal Development," Wilson describes two ways to characterize abnormal development. With the first way, pathogenesis, researchers follow the path of succeeding events. The second way describes qualitative or quantitative features of the final anomaly. Doctors can use pathogenesis after one or more of the mechanisms discussed in chapter four begin. The six modes of abnormal embryogenesis [16] involved in the pathogenesis of developmental defects are: 1. excessive cell death, 2. changed rate of cell proliferation, a reduced rate of proliferation being most detrimental, 3. failed cell interactions, meaning a lack of contact or proximity of cells that would work in cooperation in normal development, 4. impeded morphogenetic movement, such as decreased mobility of typically migratory cells or the aggregation of typically stationary cells, 5. reduced biosynthesis, or a total or partial inhibition of DNA or RNA synthesis, and 6. mechanical disruption. These modes often overlap or work together to generate abnormalities.

Wilson next notes the ambiguity and controversy surrounding what constitutes a developmental defect. Some researchers considered all manifestations (death, malformation, growth retardation [11], and functional disorders) together, while others emphasized structural defects over functional ones. Wilson argues that any attempt to classify malformations as major or minor, even when considering lethality, introduces subjective bias and offers little if any practical or theoretical advantage. Other variables such as frequency within populations, geographic location, biological sex, and maternal age also influence incidence. Despite the many confounding factors, Wilson contends that birth defects [8] are associated with or are directly responsible for roughly twenty percent of infant deaths within the first year of life.

Chapter six, titled "Access of Environmental Factors to Developing Tissues," covers vulnerability of the embryo to environmental agents, as well as defenses, both maternal and embryonic, particularly those of placental mammals. Maternal defenses against harmful environmental agents include absorption of the agent, the effectiveness of which varies depending on the concentration of the agent and the duration of exposure, and dispersal of chemical agents away from plasma. The embryonic defenses are excretion, storage, protein and tissue binding, and catabolism/detoxication. Catabolism degrades a chemical agent enzymatically
to convert it into a less toxic form that is easier to excrete. These processes take place primarily in the kidneys, though the liver, digestive tract, skin, and lungs also participate. The placenta\(^{[17]}\) is another buffer between the environment and the fetus\(^{[10]}\). While it is not an impenetrable barrier, it still protects the fetus\(^{[10]}\) against harmful foreign substances. The placenta\(^{[17]}\) also detoxifies blood in a similar manner as the liver. Furthermore, fluids within the amnion\(^{[18]}\) and chorion\(^{[19]}\) could perform minor protective roles in instances of mechanical trauma to the maternal abdomen, but there is minimal evidence to support that their protective abilities extend beyond that.

In chapter seven, "Normal Development and Susceptible Periods," the concept of critical periods is discussed. Wilson says that the concept of critical stages can mislead people if one describes an abnormality as only able to arise during a specific period of embryogenesis\(^{[16]}\). Wilson presents a summary of human embryology\(^{[7]}\) from fertilization\(^{[20]}\) through organogenesis\(^{[21]}\), complete with a table of height and weight data for human offspring, twenty-five plates depicting the different stages of human embryogenesis\(^{[16]}\), and a table that presents data on the gestational timeline of numerous species from hamsters to humans\(^{[6]}\). Wilson notes that in many species of lab animals, researchers struggle to identify precise times for the beginning and end of organogenesis\(^{[21]}\) due not only to variation in animals strains within one species, but due to controversy about which events should mark the beginning and end of those processes.

Chapter eight, "The Assessment of Teratologic Risk," concludes that despite advances in the field of teratology\(^{[6]}\), widespread malformations due to items like thalidomide are still possible. Total prevention may not be attainable, but risk can always be further reduced for environmental agents like drugs and chemicals. Early detection of unexpected harmful effects, along with more reliable preclinical testing, are the two major ways to reduce risks of birth defects\(^{[5]}\). When considering early detection, other variables that need to be considered are individual sensitivity, as well as the risk-benefit judgments when the mother’s health is in danger. Sometimes, these effects are only detected via epidemiological surveys, and effects can occasionally only be studied within a single population. Overall, Wilson calls for better reporting of adverse effects and requests that more attention be paid to case studies within medical literature until more reliable systematic reporting is in effect. Additionally, Wilson argues for surveillance of human populations, such as industrial workers, who are exposed to certain conditions or higher doses of agents that are potentially harmful. He lists requirements for laboratory animal tests and lists, for teratology\(^{[6]}\) research, advantages and disadvantages for eleven common laboratory animals, including rodents, ungulates, and nonhuman primates.

After chapter 8, the next two chapters and three appendices are directed towards those who want to conduct research in experimental teratology\(^{[6]}\). Wilson provides protocols for the collection and interpretation of observations for experimental teratology\(^{[6]}\) studies. Here, Wilson introduces the concept of litter effect, the litter-to-litter variation in teratogenesis between litters of the same mother. In chapter ten, Wilson states that there is not one particular animal species that is best suited for experimental teratology\(^{[6]}\) because of the variations that contribute to the ultimate presentation of a malformation or lack thereof. Therefore, multiple species should continue to be used in experimentation and a greater focus should be placed on examining offspring across generations.

Appendix one lists references on embryology\(^{[7]}\) and the reproduction of laboratory animals. Included are listings for the mouse\(^{[22]}\), hamster, rat\(^{[23]}\), rabbit\(^{[24]}\), pig\(^{[25]}\), sheep\(^{[26]}\), ferret, cat, dog\(^{[27]}\), rhesus monkey\(^{[28]}\), and baboon. In appendix two, Wilson presents three hand-drawn plates and a timeline for rat\(^{[23]}\) embryology\(^{[7]}\) alongside descriptions of these stages in development, from fertilization\(^{[20]}\) through day twelve. Appendix three present fifteen, 1-millimeter freehand sections of near term, or born near the normal length of pregnancy\(^{[29]}\), rats produced by Wilson.

Sources

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