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The Principles of Teratology: Are They Still True?

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Received 23 March 2010; Revised 8 May 2010; Accepted 12 May 2010

James Wilson originally proposed a set of ''Principles of Teratology'' in 1959, the year before he helped to found the Teratology Society. By 1977, when these Principles were presented in a more definitive form in Wilson and Fraser's *Handbook of Teratology*, they had become a standard formulation of the basic tenets of the field. Wilson's Principles have continued to guide scientific research in teratology, and they are widely used in teaching. Recent advances in our knowledge of the molecular and cellular bases of embryogenesis serve only to provide a deeper understanding of the fundamental developmental mechanisms that underlie Wilson's Principles of Teratology. *Birth Defects Research (Part A) 88:766–768, 2010.* © 2010 Wiley-Liss, Inc.

Key words: Principles of Teratology, James Wilson, history of teratology

A remarkable conference was held on April 5, 1959. Because of the recent successful development of a vaccine against polio virus, the National Foundation, which up to that point had supported research only on poliomyelitis, decided to broaden its focus. The organization, the predecessor of today's March of Dimes Foundation, began working to understand and prevent congenital anomalies. Consequently, a conference was held to review the current state of knowledge in the field for the Foundation's medical advisory committees (Rivers, 1959).

This conference on ''congenital malformations'' (''birth defects'' had not yet been adopted as the descriptor of choice) brought together recognized leaders in the field. Their talks, which were published in the *Journal of Chronic Diseases* later that year (Table 1), provide insight into the scientific thinking of the founders of the Teratology Society at the time it was being organized. Moreover, the paper presented by James Wilson includes the first formulation of his Principles of Teratology (Table 2), which he put forward very tentatively: ''After careful deliberation, and no little vacillation, as many as five generalities emerge which seem to be applicable to most teratologic situations. It is certainly premature to formulate these as universal laws of teratology. They are presented here only as points of reference for thinking and planning and as hypotheses yet to be put to the final test'' (Wilson, 1959).

Like any good scientist, Wilson revised his ''hypotheses'' as more data became available, and the Principles of Teratology matured as the field did. They were discussed in a revised form in his 1973 monograph *Environment and Birth Defects* (Wilson, 1973), but the definitive version, which many of us have used in our teaching ever since, appeared in 1977 in Wilson and Fraser's magisterial four-volume *Handbook of Teratology* (Table 3).

At a distance of more than 30 years, there are two ways we could look at the Principles presented in Table 3: We could be very impressed at how well Wilson understood teratology in 1977 (Wilson, 1977) and gratified that almost all of the research done since then supports the ideas he put forward at that time. Alternatively, we could be disappointed that our understanding of teratology has not changed very much over the last generation.

I prefer the former interpretation because the latter overlooks a subtle but profound difference in our understanding of Wilson's third principle: Although we can agree with Wilson that the chief manifestations of teratogenesis observed at the level of the whole organism are death, malformation, growth retardation, and functional disorder, our knowledge regarding the mechanisms that produce these abnormalities in response to a teratogenic exposure has improved dramatically.

Wilson used the term ''mechanisms'' in a very specific manner to mean the earliest, if not the first, event in the pathogenic pathway between a cause (in this instance, the teratogenic exposure) and its effect. He explained that later events in the pathogenic process might be expressed as one or more of a few higher-level effects. He listed excessive or reduced cell death, abnormal cellular interactions, reduced biosynthesis of important products, aberrant morphogenic movement, and mechanical disruption of tissues as examples, and suggested that

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Published online 12 Augsut 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/bdra.20697

Table 1
The National Foundation Conference on Congenital Malformations as reported in the *Journal of Chronic Diseases* 10(2):83–151, 1959

Thomas M. Rivers:[a]	Introduction to the National Foundation Conference on Congenital Malformations
Josef Warkany:	Congenital Malformations in the Past
F. Clarke Fraser:	Causes of Congenital Malformations in Human Beings
James G. Wilson:	Experimental Studies on Congenital Malformations
Donald D. Matson:	Surgical Treatment of Birth Defects Involving the Central Nervous System
Rustin McIntosh:[b]	The Problem of Congenital Malformations: General Consideration

[a]Dr. Thomas Rivers was a distinguished microbiologist who, as chairman of the National Foundation's Committee on Research, oversaw clinical trials of the Salk vaccine.
[b]Dr. Rustin McIntosh was the Carpentier Professor of Pediatrics at Columbia University and Director of the Pediatrics Service at Babies Hospital in New York City from 1931 to 1960.

Table 2
The Original (1959) Formulation of Wilson's Principles of Teratology (Wilson, 1959)

1.	The susceptibility of an embryo depends upon the developmental stage at which an agent is applied.
2.	Each teratogenic agent acts in a specific way on a particular aspect of cellular metabolism.
3.	The genotype influences to a greater or lesser degree an animal's reaction to a teratogenic agent.
4.	An agent capable of causing malformations also causes an increase in embryonic mortality.
5.	A teratogenic agent need not be deleterious to the maternal organism.

Table 3
Wilson's Six Principles of Teratology as Presented in the Wilson and Fraser *Handbook of Teratology* (Wilson, 1977)

1.	Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.
2.	Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.
3.	Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).
4.	The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.
5.	The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).
6.	Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.

these higher-level effects might, in turn, result in a few final common pathways of abnormal development.

Wilson explicitly recognized that little was then known about the earliest teratogenic mechanisms, and he pointed out that, because they operated at the molecular level, they were difficult or impossible to study experimentally with the techniques available at that time (Wilson, 1977). Nevertheless, he stressed the fundamental importance of these primary developmental mechanisms and devoted extended discussions to them in his later presentations of the Principles of Teratology (Wilson, 1973, 1977).

Table 4 lists nine early mechanisms of teratogenesis that Wilson discussed in the *Handbook of Teratology*. One is immediately struck by the absence from this list of several mechanisms that have been intensively studied over the past few years and are now known to be important in embryonic development. These include the following:

- Epigenetic control of gene expression (Corry et al., 2009; Hemberger et al., 2009; Shi and Wu, 2009; Geiman and Muegge, 2010)
- The effects of small regulatory RNAs (Lee et al., 2006; Amaral and Mattick, 2008; Stefani and Slack, 2008)
- The imbalance of gene products resulting from submicroscopic alterations of genomic structure such as copy number changes (Zhang et al., 2009; Carvalho et al. 2010)
- Alterations of the cytoskeleton (Li and Gundersen, 2008; Johnson, 2009)
- Perturbations of the extracellular matrix (Holmbeck and Szabova, 2006; Daley et al., 2008)
- Effects of mechanical forces on embryogenesis (Patwari and Lee, 2008; Davidson et al., 2009; Nelson, 2009)

Table 4
Mechanisms of Teratogenesis as Presented in the Wilson and Fraser *Handbook of Teratology* (Wilson, 1977)

- Mutation
- Chromosomal nondisjunction and breaks
- Mitotic interference
- Altered nucleic acid integrity or function
- Lack of precursors and substrates needed for biosynthesis
- Altered energy sources
- Enzyme inhibitions
- Osmolar imbalance
- Altered membrane characteristics

- Disturbances of intracellular or intercellular signaling (Kovacic and Pozos, 2006; Arnold and Robertson, 2009; Zeller et al., 2009)
- Dysfunction of molecular chaperones (Akerfelt et al., 2007; Ni and Lee, 2007)
- Effects on the distribution of molecules into subcellular compartments (Olkkonen and Ikonen, 2006; Gissen and Maher, 2007) and
- Alterations of the integrity of intracellular organelles (Steinberg et al., 2006; Zeviani and Carelli, 2007; Thoms et al., 2009).

This list is not exhaustive, but it illustrates the breadth of the advances that have been made in our molecular understanding of teratogenic mechanisms since Wilson emphasized the fundamental importance of these primary developmental events. It also demonstrates the validity of another concept that was implicit in the way that Wilson, as an experimental teratologist, thought: the idea that basic developmental mechanisms are shared among species. The insight that teratology studies in one species, such as mice, can inform our understanding of developmental processes that occur in another species, such as humans, has been critical to our progress (National Research Council Committee on Developmental Toxicology, 2000).

Wilson would have been pleased to learn that the knowledge we have gained over the last 33 years has strengthened the scientific basis for his Principles of Teratology and that they remain central in our teaching of the field that he helped to establish.

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