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EDITORIAL

Teratogen?

It is an honor to have been asked to guest edit this issue of *Birth Defects Research*, devoted to Teratogen Updates by some of our most distinguished scientists and clinicians. In this era of turning our back on the historical term, Teratology, it is time to raise the question of whether the word, teratogen, has outlived its usefulness. The perfectly fine word, Teratology, was rejected by the journal some years ago. The Teratology Society not long ago rejected the name of the professional organization founded by Wilson, Warkany, and Frasier, among others, because the name was poorly understood or believed not to represent the subject we are studying. Is the word, teratogen, any more clear or specific than the word, Teratology?

The definition of teratogen often includes "an agent that causes birth defects." There are two problems with this definition:

1. Most of us think we also are studying growth problems, decreased viability, and functional abnormalities as well as structural malformations. Any definition that might be limited to structural malformations does not work for us;
2. Everything causes developmental effects at some exposure level, and everything fails to cause developmental effects at some other dose level.

The first problem can be handled by replacing teratogen with developmental toxicant, not a difficult trick. Indeed, James Wilson solved this issue as early as 1977 with one of his Principles of Teratology (Wilson, 1977), repeated from an earlier set of principles as, "The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder." However, "developmental toxicant" does not really get us out of the soup, at least not if a toxicant is understood to be a chemical. Toxoplasmosis, zika, and rubella are not toxicants, zinc and iodine deficiency are not toxicants, maternal systemic lupus erythematosus (SLE) is not a toxicant. We can stretch and posit that some chemical made by women with SLE must be poisoning the fetal cardiac conduction system, but no amount of stretching will make a chemical agent out of a deficiency of a nutrient, will it?

The second issue is based on the observation that developmental toxicity is contextual, depending on exposure level, timing, species, and so on. This problem was also solved by one of our forebears, David Karnosky, the fifth president of the Teratology Society, who wrote, "any drug administered at the proper dosage, at the proper stage of development to embryos of the proper species—and these include both vertebrates and invertebrates—will be effective in causing disturbances in embryonic development." (Karnofsky, 1965). Doctor Karnofsky was a physician, an oncologist, in search of medications to treat cancer patients. He and other teratologists gave candidate medications to pregnant laboratory animals, believing the conceptus, parasite as it is, to be a good model of a malignancy. The goal was to find a treatment that would destroy the embryo without destroying the mother.

What has sometimes been called Karnofsky's law is exemplified by caffeine. As reviewed by Bob Brent, our ninth president, and others, caffeine does not increase malformations in human pregnancy, and a decrease in embryo viability is questionable (Brent, Christian, & Diener, 2011). A daily intake of caffeine of about 200 mg/day (about 4 mg/kg) appears to be beyond reproach in pregnant women. Yet administration to pregnant rats results in ectrodactyly at 100 mg/kg daily but not at 25 mg/kg/day four times daily (Smith, McElhatton, & Sullivan, 1987). So is caffeine a teratogen or not? Is it even a rat teratogen?

"The dose makes the poison" was attributed to Paracelsus, who worked 500 years ago and sadly was not a president of the Teratology Society, but the idea was taken up more recently by four past presidents, a President-elect, and their colleagues. They devised a list of teratogenic *exposures* for which exposure levels, presented generally as peak blood concentrations in the rat, were considered positive or negative, rather than specific compounds being positive or negative for developmental toxicity (Daston et al., 2010; Daston et al., 2014, with refinements by Wise, 2016). Those of us in clinical medicine have been spoiled by the rather narrow prescribed dose range of the chemicals we ask people to take, so when we get sloppy and say that a medication is teratogenic, we understand that we are talking about conditions of therapy. But we can still get into trouble.

Take, for example, the first woman I counseled on an exposure during pregnancy. She had been to the emergency department for a fractured arm, and without

knowing she was pregnant, she had a couple of unshielded X-rays. I calculated the approximate embryo dose to be zero, which reassured her, and she asked me if I would take care of her during pregnancy. Her doctor had told her not to come back if she continued the pregnancy, because X-ray is a teratogen.

Once we label an agent as a teratogen, there can be all sorts of consequences. Some regulators will take adverse actions on permitting the agent to come into commerce. Some putative experts will opine that if an agent causes any developmental effects, it can thereby cause them all in virtually any circumstance. But even the famous "teratogen" thalidomide does not cause every kind of adverse developmental outcome, every kind of congenital malformation, or even every type of limb malformation (Newman, 1985).

I am fine with keeping the name, "Teratogen Update," just as I was fine with keeping the name, "Teratology Society," because these names have historical underpinnings. The names tie us to the 60 years of forebears who launched us into this amazing field of study. And so, with pride, I introduce you to our most recent group of Teratogen Updates. Just do not ask me what a teratogen is.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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