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Predictiveness and Limitations of Test Methods in Teratology: Overview

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Compounds intended for marketing by the pharmaceutical industry are tested for possible effects on reproductive processes in much the same way today as was carried out even before November 1961, when the drug thalidomide was related to human malformations. At that time, effects on male and female fertility were sought, but generally only for agents considered likely to alter the endocrinologic status of the patient or that were designed primarily for use by young women. The test species was usually the rat.

When it became evident that this system did not detect the teratogenic potential of thalidomide, it was realized that a model that would detect this type of activity was needed. Thalidomide was under study in my laboratory at the William S. Merrell Company (*1*) within three days of Lenz's announcement of the relationship between thalidomide and human malformations. Hence, routine testing was being conducted in at least one industrial laboratory when the FDA guidelines were circulated in 1966. These guidelines and the principles published by WHO in 1967 have been followed by private industry, which has conducted most of the routine testing carried out to date to determine the teratogenic potential of agents. These test results on prospective therapeutic agents now represent most of the information available on the teratogenic potential of chemicals. With the increased commitment of resources currently available for the testing of additional components of our environment, it is necessary to determine whether such test procedures are doing the job.

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We have come to realize that the teratogenicity of thalidomide represented the exception rather than the rule for most tranquillizers and for drugs in general. Today chemicals are known to be responsible for no more than 5% of the structural malformations seen in man. Less than 25 chemicals are known teratogens in man, yet more than 800 are identified as being teratogenic in laboratory animals. Is this because man is more resistant, or is this difference merely a reflection of the difficulties encountered in determination of positive teratogenicity in man? Of the human malformations seen, 60% are still of unknown etiology, in spite of continued testing. Does this mean the value of the test system is in question, that we have not tested the human teratogens yet, or that most of the unidentified etiology involve combinations of genetic and environmental factors that are not present in test animals? Does the high incidence of apparent false positives in animal testing render the results of this testing worthless? Are there alternative approaches available now? Are potentially promising techniques under investigation?

The presentations by the speakers of this session were most interesting and provocative. Palmer discussed the procedures routinely conducted in test animals for determining teratogenic potential and pointed out the value of these tests. He emphasized the need for more dedication to proper execution of the tests to enhance predictive capability and to minimize limitations. As viable alternatives to the *in vivo* approach still are not available, he stressed the need to apply information gained through testing for toxicity, reproduction, and mutagenicity after the evaluation of teratogenic investigations in or-

der to optimize assessment of potential hazard to the human.

An example of the progress being made in new method development was presented by New, who described the technique premitting extension of the period of successful culture *in vitro* of the post implantation rat embryo. This technique is amenable to short-term investigations of the type described, but as a test for teratogenic potential more extensive application is dependent upon the creation of an artificial placenta such that continued development of fetuses will be possible after experimentation. Several other methods are being investigated that permit direct application of test agent to the developing conceptus both *in vitro* and *in vivo*, but unfortunately time did not permit presentations or discussion of these techniques.

Detection of functional deficits in animal offspring after intrauterine exposure to environmental agents is an aspect of teratology that has received only peripheral attention to date. Hence, the current thinking of enzymologists regarding the potential for detecting alterations in enzyme function of offspring and the significance of the alterations detected is of particular importance. Andrew's presentation provided us with the approaches being contemplated and the realization that enzyme markers are still a long way from providing a major contribution to our test methodology.

The monitoring of human births for changes in background incidence of malformations and deficits is of major importance. In this regard, not only do we have the experience of the thalidomide episode, and several additional incidents that involved fewer individuals, but the realization that our exposure to potentially hazardous agents has never been greater than it is today. Flynt has provided us with a lucid overview of the role played by epidemiologists, the approaches available to them, and the limitation of each, and has given us an appreciation of the extent of monitoring and surveillance that is being carried out in the U.S. The system described are likely to detect the most severe or prevalent human teratogens missed through application of animal models but it is unfortunate that this information comes to light only after children are affected. It is hoped that animal model development someday will prevent such human suffering.

REFERENCES

1. Staples, R. E., and Holtkamp, D. E. Effects of parental thalidomide treatment on gestation and fetal development, J. Exptl. Med. Pathol. (Suppl. 2) 81 (1963).
2. Food and Drug Administration. Guidelines for reproduction studies for safety evaluation of drugs for human use. 1966.
3. World Health Organization. Principles for the testing of drugs for teratogenicity. Technical Report Series, No. 364, Geneva, 1967.