TOXIC SUBSTANCES AND CONGENITAL MALFORMATIONS

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The thalidomide catastrophe made the general public aware of the fact that a pregnant woman's exposure to a toxic substance could endanger her unborn child. The shock produced by this event resulted in reactions which were partly healthy and partly unjustified, emotional and unscientific.

Let me put into historical perspective the question of embryonic and fetal injury by adverse environmental conditions. There are old reports on women working in industry and mines exposed to lead and mercury who suffered sterility and repeated abortions. The medical literature of the 19th century that deals with congenital malformations is replete with statements which blame children's defects on the father's or mother's alcoholism, tuberculosis or syphilis, etc. Many of these correlations were accidental and not causative, they could not stand critical analysis in later years. In the 1930's it seemed more "scientific" to consider most, if not all congenital malformations, as genetic and hereditary. One reason for this was that there was no experimental proof that the mammalian embryo can be deformed by adverse conditions of the mother. Such proof became available from the 1930's and 1940's and is now known under the name of experimental teratology, a very well developed science.

There is also ample proof by now that adverse environmental factors can deform human embryos and fetuses. These proven factors are not numerous and they are very heterogeneous. Environmental teratogens in man include iodine deficiency (which caused endemic cretinism), carbon monoxide, X-rays, toxoplasmosis, rubella, and organic mercury, which caused Minamata disease. Other proven environmental teratogens in man are cytomegalic inclusion disease, aminopterin, virilizing progesterones, thalidomide, chronic alcoholism, anticonvulsants, and warfaring.

And now to my topic: teratologic animal experiments. During the 19th century, countless teratologic experiments were done with eggs of chickens, amphibians, and fishes. Although many of these tests were of great scientific value they were not applicable to human conditions. It was thought that the human embryo and fetus were so well protected by the mother within the uterus that they could not be deformed by environmental factors. Aside from radiation, the first mammalian congenital malformations were produced by dietary deficiencies of pregnant animals. The following list describes some of the well established deficiencies that can result in typical malformations if strict experimental conditions are observed:

TERATOGENIC DEFICIENCIES

1933/45	VITAMIN A	RAT
1954/56	VITAMIN A	RABBIT
1940/44	RIBOFLAVIN	RAT
1946/56	FOLIC ACID	RAT, MOUSE
1948/57	PANTOTHENIC ACID	RAT
1950/57	OXYGEN	MOUSE
1953/57	VITAMIN E	RAT
1934/38	COPPER	SHEEP
1966/72	ZINC	RAT
1954/56	FASTING	MOUSE

These experiments were (and are) of great theoretical interest. They proved once and for all that environmental hardships imposed on pregnant females could cause structural malformations in the young. They showed that such hardships could induce syndromes of malformations, an effect which before was thought to be exclusively due to gene anomalies. And, being ultimately attributable to enzyme deficiencies, they imitated gene effects in many respects. Most important, they alerted physicians, epiedmiologists and geneticists to the possibility that congenital malformations in children could also be caused by environmental adverse conditions. The list of factors teratogenic in humans that I described before was in part made possible by the animal experiments I have just listed.

And yet, as far as I know, none of these remarkable nutritional experiments has been simulated by human conditions. None of the deficiencies listed has been shown to produce malformations in man. And, vice versa, iodine deficiency which was such an important teratogen in man, has not been simulated in animal experiments. This taught us early that greatest caution is necessary in extrapolation of experiments to human situations. Early teratologists were fine scientists and neither propagandists nor alarmists.

I turn now from deficiencies to "positive" teratogens. So many substances and procedures have been used by now in teratologic experiments that it would take hours to read you the names of them. Instead I'd like to list some teratogenic substances which were found to be effective early, and which are used frequently for various reasons as research tools. To begin with, sex hormones can change secondary sex characteristics and virilize females and interfere with virilization of males.

Nitrogen mustard is a chemical compound which was a forerunner of many alkylating agents employed for production of severe malformations in rodents.

Trypan blue proved to be an excellent teratologic research tool which permitted production of exencephaly, hydrocephaly, spina bifida and other malformations. Its mode of action is still not

fully understood but it seems to interfere with the proper function of the yolk sac placenta of rodents. It has, of course, no direct importance for human malformations.

Many antimetabolites and antitumor drugs are good teratogens. Some of them have in rare cases caused congenital malformations in humans. I mentioned aminopterin before. Methotrexate, myleran, cyclophosphamide and chlorambucile were responsible for a few cases of malformations in children.

Some antibiotics are good teratogens in animals. We have used one, streptonigrin; it yielded most interesting malformations in rats which had not been produced by other teratogens before.

Cortisone played an important role in experimental teratology because it produces cleft palate in very high incidences in certain strains of mice and not in others. It was used to demonstrate the combination of genetic with environmental factors in the expression of a specific congenital malformation. It is still widely used in cleft palate experiments.

Oral hypoglycemics and insulin have been teratogenic in rodents.

Hypervitaminosis A is an excellent teratogen in rats and mice. It results in exencephaly in many specimens, and has been used a great deal in research on anencephaly. A special form of vitamin A, retinoic acid, is quickly excreted and removed from the organism after producing malformations. For this reason, it was used in hamsters for exact timing of exposure and subsequent registration of malformations.

As early as 1953 and 1955, it was shown that vaginal application of phenylmercuric acetate in pregnant rats caused malformations in the young, and after the recognition of Minamata disease additional experiments have been done along this line.

Nicotine and caffeine have mild teratogenic effects in mice.

Among the most interesting teratogens are salicylates, including aspirin. These wonderful drugs, which are used by almost everyone and available in lethal amounts in every drug store, proved to our surprise to be teratogenic. In rats, aspirin is such a reliable teratogen that we use it as a standard procedure to test modifying factors. Although it is well known that salicylates taken by pregnant women in large amounts for suicidal purposes can result in fetal death, I do not know of a case that ended in congenital malformations of the child.

Thalidomide is the best known teratogen in man. In our context it is of interest because its teratogenicity in animals was demonstrated after the fact. In rabbits and in monkeys malforma-

tions have been produced a few months or years after the epidemia in human beings was over. Teratogenic effects described in rats and mice may not be due to the chemical properties of the drug. The malformations observed in these rodents do not resemble the thalidomide syndrome in man.

At the end of the list is sodium chloride which under certain experimental conditions can induce congenital malformations in mice. You can draw your own conclusions concerning regulatory procedures based on this animal experiment. Other teratogenic agents that are not defined chemically include X-irradiation in rats, mice, and rabbits; viruses in sheep, swine, rats, and hamsters; mechanical agents in the rat and the mouse; and antisera in the rat.

My discussion was limited to mammals and limited in the choice of teratogens. There are much more complete lists available (Cahen, Wilson) and there is the special Catalog of Teratogenic Agents by Shepard which discussed critically observations in man and animals.

From the choice of my examples of animal models you will conclude that I am opposed to uncritical application of results obtained in experimental animals to man. To show on television one deformed animal, or to publish in a newspaper results of teratologic experiments with the suggestion of stopping fabrication or consumption of the inducing substance, is not the way to proceed. Remember sodium chloride! In spite of this admonition, I consider animal experiments as very important. However, they must be interpreted with caution, with knowledge of the experimental conditions, and with rationality. If one finds a chemical compound teratogenic in animals, it should alert us to vigilance in human conditions. Experiments can show <u>how</u> environmental agents can deform an embryo or fetus. They may even contribute to prevention of certain adverse effects. But they must not be equated with human teratogenicity.

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