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In Vivo Assessment of the Teratogenic Potential of Drugs in Humans

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The difficulties in assessing the teratogenic potential of drugs used during pregnancy have been made evident by experiences with thalidomide and diethylstilbestrol (DES). In the case of thalidomide, the drug's ability to cause phocomelia tended to be species specific, and thus animal studies were unreliable indicators of teratogenicity in humans. With DES, the delayed appearance of injury, almost a generation after birth, indicates that short-term studies may fail to reveal serious effects. In both cases only the otherwise rare occurrence of the condition led to the suspicion of a cause-and-effect relationship. Although widespread use of drugs such as LSD, heroin, and marijuana has necessitated assessment of their teratogenic potential, a controlled investigation of their effects has so far been impossible to conduct. Both tobacco and alcohol have been associated with adverse effects on the fetus and neonate, but the precise mechanisms by which these effects occur are as yet unclear. There is also reason for concern about the teratogenic potential of environmental pollutants such as organic mercury compounds, lead, and radiation. Furthermore, the fetus may potentially be harmed if a particular drug is not administered (eg, insulin for diabetes during pregnancy). In the final analysis, any potential benefits of therapy for the mother must be weighed against known and unknown risks to the infant. Rational management requires an understanding of the physiologic and pharmacologic principles involved in each case and careful and judicious selection of drug therapy. *(Obstet Gynecol 58:3S, 1981)*

Models of Human Teratogenicity

Thalidomide embryopathy, first suspected in 1961 by McBride[1] in Australia and Lenz[2] in Germany as the cause of phocomelia, provides a number of lessons in our approach to the teratogenic potential of drugs. The extent to which a similar tragedy can be avoided in the future may depend upon how well these lessons have been learned and assimilated.

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Thalidomide was introduced in the late 1950s in West Germany, England, and several other countries as a tranquilizing agent and hypnotic. It was effective, seemed remarkably nontoxic, and apparently had no aftereffects similar to the "morning-after hangover" attributed to other such drugs. Recovery from massive ingestion taken for suicidal intent indicated that there was a large difference between the therapeutic dose and the amount required to produce fatal overdosage, thus providing additional support and enthusiasm for the drug's effectiveness and its use. Although a typical therapeutic dose was about 100 mg, recovery from ingestion of as much as 14 g was noted. Around 1960 some scattered reports indicated that patients receiving this drug for prolonged periods sometimes developed neurologic disturbances, mostly peripheral neuropathy; the demonstration of the drug's destructive effects on the dorsal root ganglia in tissue culture later confirmed this finding. Because of its perceived therapeutic properties and advantages, the drug was marketed, and pregnant women comprised 1 of the selected target populations for distribution. It seemed safe and guaranteed tranquility and uncomplicated sedation for the anxiety produced by pregnancy. Shortly after its introduction, however, there was an increase in the number of infants born with phocomelia, a shortening or complete absence of the limbs. An initial small cluster of cases was reported from Australia, but the University Pediatric Clinic in Hamburg provided the major source of material as it observed a sudden rise in the incidence of a previously almost unheard-of malformation. Thus, although not a single case of phocomelia was seen between 1949 and 1959, 1 case was reported in 1959, 30 cases in 1960, and 154 cases in 1961. Comparable increases in the frequency of the anomaly occurred simultaneously in many parts of the world where thalidomide was used and led to the suspected association between phocomelia and the ingestion of thalidomide by the pregnant mother.

Both the previous rarity and sudden increase in incidence of phocomelia (the stated spontaneous occur-

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rence was approximately 1 in 500,000) combined to focus attention on the possibility of a de novo externally induced malformation. Subsequent investigation indicated that in virtually every case of phocomelia the mother had taken thalidomide between the third and eighth weeks of pregnancy. Sometimes only a few doses during this critical period sufficed.

The critical period for each kind of malformation produced in the human fetus has been established by careful retrospective analysis.[3] When thalidomide was taken 35 to 36 days after the last menstrual period (approximately 21 to 22 days' gestation), absence of the external ears and paralysis of the cranial nerves resulted. Ingestion 3 to 5 days later (about 24 to 27 days' gestation) produced the maximal phocomelia effect, affecting principally the arms. A day or 2 later, a similar defect of the legs occurred. The sensitive period terminated 48 to 50 days after the last menstrual period (34 to 36 days' gestation) with the production of hypoplastic thumbs and anorectal stenosis.

The now well-known predictive failure of animal testing before human use is worthy of reconsideration. As has been shown for other teratogenic agents, thalidomide displays a strong species specificity. No abnormalities were at first produced in rats. In selected strains of white rabbits, administration of the drug between 8 and 16 days' gestation resulted in the typical limb malformations.[4] Subsequent rat studies showed that the species was sensitive after all, but only at 12 days' gestation.[5] Eventually a syndrome of thalidomide-induced malformations similar to that seen in humans was produced in monkeys.[6] In the resultant uproar about the failure of animal testing, it remained an abject reply that the human fetus is not a rat, rabbit, or monkey, and that in the final analysis only humans are the true reliable model.

It seems likely that variations in metabolic pathways are a major cause of the species differences, as well as of the difference in sensitivity among humans. Thalidomide is metabolized extensively, and it is believed that 1 or more of the metabolites, rather than thalidomide itself, is the proximate teratogenic agent.[7] Hydrolysis of amide bonds and ring hydroxylation alone could account for more than 100 metabolites, of which only a dozen or so have been identified in vivo.[8] When the piperidine ring is opened, a glutamic acid derivative (pthalyl-L-glutamic acid) is formed. Decarboxylation of pthalyl-L-glutamic acid yields a monocarboxylic acid, which is the most abundant metabolite. Early studies showed that none of the metabolites was teratogenic when injected into pregnant rabbits under the same conditions in which thalidomide showed its effects. It was discovered, however, that this was due to the inability of the metabolites to pass from maternal plasma into the fetus in appreciable quantity; by contrast, when thalidomide itself was administered, it was all converted to the monocarboxylic acid in the fetus. With the use of radioactive thalidomide, samples of the plasma and allantoic fluid could be analyzed by paper electrophoresis. Localization of the radioactivity peaks showed that, after 4 hours, thalidomide, the monocarboxylic acid, and a dicarboxylic acid were all present in plasma, but only the monocarboxylic acid could be found in the allantoic fluid.[7] This finding, together with the previously demonstrated inability of the carboxylic acid metabolites to pass the placental barrier in the rabbit, shows that thalidomide was metabolized in the fetus or, at least, on the fetal side of the placenta. Without knowledge of the teratogenic potency of the monocarboxylic and dicarboxylic acid metabolites, however, it was impossible to conclude which, if either, was the proximate teratogen. Subsequent studies suggested that the dicarboxylic acid (pthalyl-L-glutamic acid) is teratogenic when given to the pregnant mouse at 7 to 9 days' gestation.[9] The D isomer appears to be inactive, as are various products of further metabolism. It thus seems likely that pthalyl-L-glutamic acid is a proximate teratogen in thalidomide teratogenesis. An analogue of thalidomide in which 1 of the CO groups in the pthalyl moiety has been reduced to CH_2 is also a potent teratogen[10] in at least 3 different animal species.

It must rank as a great misfortune that this knowledge became apparent only after an effect of epidemic proportions that may have afflicted as many as 10,000 infants worldwide. The difficulties of preventing such an occurrence again, however, are still with us.

Besides the problems of species and strain specificity and differences in critical timing per agent, the variation in the teratogenic:lethal effect ratio must be considered. Thus, aminopterin at a dose that kills most rat fetuses is not teratogenic for survivors, yet, in the human, if it fails to produce abortion, it results in fetal malformation. What role drugs may play in the overall problem of fetal wastage is difficult to detect in the absence of a teratogenic marker, but that such a relationship may exist seems likely in the absence of a malformed but living fetus or at the level of spontaneous abortion or unexplained death in utero. Moreover, the fact that the 2 best-known human teratogens (thalidomide and rubella) have no serious effect on the mother may not be universally true in animal testing. For most animal teratogens, the teratogenic dose is close to the maternal LD_{50}, so possibly a teratogenic effect will be missed if the experiment is abrogated early due to a high degree of maternal mortality in the species under study.

An untoward drug effect is not limited to the classic first-trimester teratogenic period. Thus, both the chlorthiazides[11] and tolbutamide[12] can induce throm-

Figure 1. Newborn infant showing typical upper-limb malformation of phocomelia.

bocytopenia apparent at birth when administered to the mother during the third trimester of pregnancy. Similarly, the capacity of maternal antithyroid medication to produce both goiter and hyperthyroidism in the newborn is well known.

Gauging the teratogenic effect by focusing only on the immediate perinatal period has been proved inadequate by the demonstration that the administration of DES to pregnant women is statistically related to the appearance of adenocarcinoma of the vagina in daughters in their early twenties.[13] Such an occurrence raises the frightening possibility of effects a generation or more after the administration of the offending agent if a permanent mutation occurs. It is not a pleasant prospect to consider.

These concerns raise the question of a proper risk : benefit ratio for both mother and fetus for the administration of any drug to the pregnant woman. For example, in the case of toxicity to the fetus from administration of diphenylhydantoin to the mother,[14] the maternal indications for administration may outweigh the fetal risk. Conversely, the wholesale administration of agents to banish every minor symptom from both the body and psyche of the pregnant woman seems not only inappropriate but potentially disastrous. It should not be forgotten that thalidomide was originally offered as a sedative particularly suitable to allow a good night's sleep to the pregnant woman.

Clinical Implications of Teratogenic Events

Phocomelia is derived from the Greek phoke (seal) + melos (limb). The words describe the condition (Figure 1) in which the upper or lower limbs or both are reduced to a "seal flipper" appearance. In strictest terms, the anomaly is characterized by the absence of the proximal portion of a limb or limbs: the hands or feet are attached to the trunk of the body by a single small irregularly shaped bone. Recognition of its possible "epidemic" occurrence and the relatively easy association with a specific teratogen were possible only because of its previously extraordinarily rare spontaneous occurrence. In contrast, diphenylhydantoin (Dilantin) teratogenicity was more difficult to recognize because its major manifestation, cleft palate, is a relatively common congenital malformation in both humans and experimental animals. Had the teratogenic manifestation of thalidomide been similarly common, its identification might have been delayed or difficult to establish.

That thalidomide was responsible for the outbreak of phocomelia is beyond reasonable doubt. But it is still uncertain what degree of risk was attached to the ingestion of this drug by a pregnant woman. The percentage of pregnant women given thalidomide during the critical period who had malformed or affected infants is not known. There are those who believe that all infants would have been affected if exposed at the

appropriate time, as it was difficult to find well-authenticated instances of thalidomide ingestion followed by the birth of a normal infant. Others, however, have placed the risk as well as the incidence much lower, believing that retrospective investigation exaggerates such an association extremely.[15] Women with malformed children could readily recall taking any agent during pregnancy, particularly one so publicized and with specific and otherwise rare effects. In contrast, a woman with a normal child who may or may not have taken this or another drug during pregnancy has no particular interest in recalling her drug history.

Thalidomide was withdrawn from the market at the end of 1961, and the outbreak of phocomelia subsided promptly. In the United States the drug had not been approved by the Food and Drug Administration primarily because of the concern for its potential neurotoxic effects. Although the reasons were unrelated to the teratogenic hazards of the agent, the serendipitous delay in approval prevented an outbreak that could conceivably have been proportionally greater than that observed in Germany and other European countries. In contrast, the drug had been approved for use in Canada, and its availability both there and to Canadian military personnel stationed in Western Europe at that time resulted in an appreciable incidence of the disorder.

Identifying a drug as a teratogen may often be related to the degree of usage in a specific condition. Thus, the teratogenic potential of phenytoin suggests the possibility of teratogenicity for other anticonvulsant agents. Phenobarbitone administration, more common in Europe, has been reported as resulting in the same cluster of malformations, both with and without phenytoin in the therapeutic regimen,[16] and a spectrum of malformations has been attributed to the diones (paramethadione and trimethadione) used in the treatment of petit mal epilepsy.[17] It thus appears that the anticonvulsants as a class, rather than a particular agent, are potentially teratogenic during pregnancy. Focusing on a specific drug may in essence reflect different patterns of usage rather than a quantitative or qualitative difference in the teratogenic potential between the agents. Also to be considered is the role played by the underlying disease (eg, maternal convulsive disorder) for which the drug was administered in the final pathogenesis of such untoward events.

Masculinization of the female fetus by administration of androgens or synthetic progestogens and estrogens to the mother for the treatment of habitual or threatened abortion had been reported by the late 1950s.[18] The 1971 report by Herbst et al[13] recorded the occurrence of adenocarcinoma of the vagina in 7 girls between the ages of 15 and 22 years whose mothers had received DES during pregnancy for prolonged vaginal bleeding. The analogy to the thalidomide report is once again apparent. Adenocarcinoma of the vagina is not common at any age, but its occurrence in girls and young women is rarer still. The unusually young age at which adenocarcinoma occurred led more easily to its identification as a specific drug-related effect than would have been the case with either a more common reproductive tract malignancy or its appearance in an older, more appropriate age group. Further studies have confirmed findings of genitourinary abnormalities and reduced sperm counts in male offspring of mothers treated with DES, suggesting that both sexes may be affected, although in strikingly different ways.[19] As the findings in males are neither as dramatic or rare as those in females, it is doubtful whether the effect of DES on male offspring would have been identified either easily or at all in the absence of the female teratogenic effect initially reported. Moreover, the delayed appearance of the injury in both sexes has introduced a new concern, ie, the necessity for long-term evaluation of any medication in pregnancy before a final clearance can be granted for agents administered during gestation.

Drugs and Congenital Malformations

There is a general concern regarding the liberal administration of drugs during pregnancy and the overall incidence of congenital malformations. Figures from a single service at the CHU La Grave in Toulouse, France, at 2 periods show a disconcerting trend toward a more-than-chance relationship between drug usage during pregnancy and congenital malformations (Table 1). Thus, between 1941 and 1950, during the war and the immediate postwar years, few if any drugs were given to pregnant women largely because they were not available. In contrast, the period between 1956 and 1965 was a more affluent time with virtually uncontrolled availability of drugs. Whereas the twofold increase in stillbirths parallels the increase in total live births, there is a greater than fivefold increase in the number of malformations recorded for the second as compared with first period analyzed. Such studies suffer the defects of retrospective as opposed to pro-

Table 1. Incidence of Congenital Malformations*

Period	Live births	Still-births	Malformations		
			Live-born	Still-born	Total
1941–1950	5905	97	17	3	20
1956–1965	10,584	200	93	17	110

* From Monrozies et al (Toulouse), 1967.

spective analysis but do suggest an overall trend worthy of consideration and further investigation.

Environmental and Other Hazards

The teratogenicity of commonly used agents is a subject of increasing concern. Widespread use of D-lysergic acid diethylamide (LSD) beginning in the 1960s has led to increased concern about chemical teratogenesis, and early studies with mammalian cells in culture as well as in experimental animals suggested that LSD, at least in high concentrations, could lead to chromosomal breakage.[20] A report of 9 children exposed to LSD in utero showed a significant increase in breakages in their somatic cells, but with no associated abnormalities.[21] There have been scattered reports of birth defects in infants born to women who admitted to the use of LSD in pregnancy. However, proper investigation of the effect of the drug in humans may be impossible. Prospective experiments with deliberate administration of LSD are not possible, and retrospective studies of people who use LSD illicitly are difficult to evaluate because of multiple drug use; uncertain purity of the LSD; unknown dosage and timing; inadequate nutritional status of many drug abusers, particularly in the adolescent age group; and the biases associated with retrospective studies in general. Thus, although no convincing evidence implicates LSD as a teratogen in humans, the possibility cannot be excluded. The situation with respect to marijuana (cannabis) is similarly unclear, although the use of this agent is even more widespread than that of LSD, particularly among teenagers and even preteen children. Heroin (diacetylmorphine) and its synthetic congener, methadone, are known to result in a high incidence of small-for-date intrauterine growth-retarded infants when taken regularly by the mother during pregnancy. How much of the growth retardation is attributable to the drugs and how much to the adverse social and nutritional circumstances that surround such drug abusers is open to question. However, it is of importance that heroin is capable of inducing both an acceleration of lung maturation and growth retardation in fetal rabbits.[22] As arrest of DNA replication is an anticipated accompaniment of accelerated maturation, the 2 effects seem related and appear likely to result, at least in the experimental animal study, from a drug rather than an environmental effect.

Until recently, tobacco smoking has been studied more in its relationship to adult disease than in the effects of maternal smoking on the fetus. The clinical suggestion of a distinct relationship between smoking during pregnancy and low birth weight of the infant[23] has been confirmed in an interesting experimental study in which cigarette smoke blown into animal cages induced growth retardation in rats, whereas smoke from burning lettuce leaves did not,[24] thus suggesting that smoke itself is not responsible for the result. The mechanism of this effect is unknown, but a direct effect on the umbilical vessels has been suggested.[25] There is also evidence that cigarette smoke has a stimulating effect on a number of placental enzymes, suggesting that the effect may also be mediated by enhancement of potentially undesirable placental metabolic functions.[26]

Exposure to environmental and occupational pollutants, in particular to a variety of herbicides and defoliants used for both agricultural and military purposes, is an ongoing concern. The human teratogenicity of organic mercurials is tragically reflected in the Japanese Minamata disease that resulted from industrial waste pollution with methyl mercury.[27]

Exposure to lead, via either industrial pollution and inhalation or drinking water conducted through lead pipes, represents a potential teratogenic hazard in view of the reports of an overall increased incidence of mental retardation and lower developmental quotients in infants born in circumstances of chronic lead exposure.[28] The possibility that milk, either de novo or through storage in lead-containing containers, may provide an additional route of exposure[29] warrants tighter controls of the composition and stability of the lead complexes involved.

Study of radiation injury either from background sources or for therapeutic purposes has primarily focused on genetic and chromosomal effects. In a prospective study of 972 children, significantly more children with trisomy were identified after maternal abdominal radiation exposure[30]; this suggests the possibility of both disorganization of division and disjunction, and enhanced chromosomal breakage.

Although excessive ingestion of alcohol has long been considered detrimental to maternal health during pregnancy, the systematized descriptive specific delineation of a dysmorphic fetal alcohol syndrome is relatively recent.[31] In this connection, the birth of such "monstrous" children has been mentioned sporadically in social and historic descriptions of life among the poor as early as 2 centuries ago, but the effects had been linked to defects in maternal function and/or a form of punishment for "sinful" behavior, rather than to a direct effect of alcohol on the fetus.

Implications for Therapy

It seems clear that reliable predictability of human teratogenic potential and/or safety of any agent is not possible other than by long-term assessment following the use of the agent in humans. The appropriate as-

sessment of a risk:benefit ratio for drugs given to pregnant women must therefore balance both known and unknown potential risks against the use of a drug that may benefit the mother but will not benefit the fetus except indirectly via the maintenance of maternal health during pregnancy. An excellent example of such a dilemma lies in the use of anticonvulsants during pregnancy. The risks to the fetus are known, but there is also significant danger to both mother and fetus if a serious convulsive disorder is inadequately controlled. Under these circumstances, both the problem and the approach to it must be individualized, rather than set or specific rules for management dictated.

Rational usage demands a basic understanding of physiologic and pharmacologic principles and their application. Thus, although insulin is known to be teratogenic to the fetus when given directly to the embryo, insulin administered to manage a diabetic pregnancy is unlikely to be teratogenic, as insulin does not cross the placenta. In this situation, the uncontrolled maternal hyperglycemia secondary to the inadequately treated diabetic state provokes an endogenous fetal insulin response resulting from the ready placental transfer of glucose. Thus, whereas insulin may indeed be the major teratogenic agent in the known higher incidence of congenital malformations in infants of diabetic mothers, it is not insulin administered to the mother but parenthetically the failure to administer it that is implicated in its pathogenesis.

Teratogenicity due to drugs given in pregnancy is an example of an iatrogenic occurrence. Iatrogenic disease is to be avoided or its risk at least minimized in any patient. This is doubly important for the pregnant woman.

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