FACTORS DETERMINING THE TERATOGENICITY OF DRUGS

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Because knowledge of this subject has expanded tremendously in the past several years, it is no longer possible to do more than outline it in a review of this length. The main objective, therefore, is to enumerate the aspects of the subject that are now recognized as important determinants; however, certain areas where concepts are currently undergoing change are reviewed in detail. The considerations presently known to be involved in determining whether a drug will be teratogenic are listed in Table 1. Before discussing these individually it should be emphasized that the term teratogenicity is used here in the broad sense of developmental toxicity, encompassing all deviations in developmental processes originating between fertilization and postnatal maturity, including death, malformation, growth retardation, and functional deficiency.

Table 1 Factors determining teratogenicity of drugs

1. Type of drug (chemical and pharmacological properties)
2. Level and duration of dosage
3. Maternal modulation of dosage
4. Access to the conceptus
5. Developmental stage at time of dosage
6. Disposition within the conceptus
7. Susceptibility of species and individual

TYPES OF DRUGS

The types of drugs shown to be teratogenic in laboratory mammals number in the hundreds and cannot be listed, although some impression of their variety is given

in Table 2. In most of the experimental situations in which such compounds have been shown to be embryotoxic, the doses used were much larger than those recommended for human therapeutic use or, in the case of environmental chemicals, than likely exposure levels to human populations. More extensive but by no means exhaustive lists have been compiled elsewhere (1–5). The multitude of substances thus implicated suggests that all chemical agents are teratogenic. In fact, most investigators in the field accept as a working hypothesis the principle that all chemicals are capable of producing some embryotoxic effect under the right conditions of dosage, developmental stage, and species selection (6, 7). It may be difficult to demonstrate embryotoxicity, however, when high maternal toxicity intercedes.

Table 2 Types of drugs and environmental chemicals shown to be teratogenic[a] in one or more species of mammals[b]

Salicylates (e.g. aspirin, oil of wintergreen)
Certain alkaloids (e.g. caffeine, nicotine, colchicine)
Tranquilizers (e.g. meprobamate, chlorpromazine, reserpine)
Antihistamines (e.g. buclizine, meclizine, cyclizine)
Antibiotics (e.g. chloramphenicol, streptonigrin, penicillin)
Hypoglycemics (e.g. carbutamide, tolbutamide, hypoglycins)
Corticoids (e.g. triamcinolone, cortisone)
Alkylating agents (e.g. busulfan, chlorambucil, cyclophosphamide, TEM)
Antimalarials (e.g. chloroquine, quinacrine, pyrimethamine)
Anesthetics (e.g. halothane, urethan, nitrous oxide, pentobarbital)
Antimetabolities (e.g. folic acid, purine and pyrimidine analogues)
Solvents (e.g. benzene, dimethylsulfoxide, propylene glycol)
Pesticides (e.g. 2,4,5-T, carbaryl, captan, folpet)
Industrial effluents (e.g. some compounds of Hg, Pb, As, Li, Cd)
Miscellaneous (e.g. trypan blue, triparanol, diamox, etc.)

[a]Teratogenic effects were usually seen only at doses well above therapeutic levels for the drugs, or above likely exposure levels for the environmental chemicals.

[b]From Wilson, J.G. 1972. Environmental effects on development—teratology. In *Pathophysiology of Gestation,* ed. N. S. Assali, Vol. 2. New York: Academic; 1973. *Environment and Birth Defects.* New York: Academic.

There is not always close correlation between the chemical structure or pharmacological action of a drug and its teratogenic potential. A few classes such as the polyfunctional alkylating agents have been found to be teratogenic in every instance in which they have been adequately tested. By the nature of their biological effects, antibiotics also would be expected to interfere with embryonic development, and many have been shown to do so. Those bacteriocidal agents that act by interference

with protein biosynthesis, however, seem to be exceptional, for they have not been found to cause malformations per se (unpublished data), probably owing to the essentiality of protein synthesis in all aspects of development, although they do cause early embryonic death. The diazo dyes, of which trypan blue is the best-known example, show highly variable teratogenicity despite being closely related in chemical structure (8, 9); a similar situation holds for the substances related to meclizine (10) and thalidomide (11). Although acetazolamide is highly teratogenic in several rodent species, other carbonic anhydrase inhibitors and related sulfonamides are much less effective (12, 13).

Even though drugs are usually if not universally teratogenic when tested at high dosage at known times of high embryonic vulnerability in susceptible species, it is surprising that so few drugs are known or suspected to be teratogenic in man, particularly considering their extensive use during human pregnancy (14). The teratogenicity of specific drugs has recently been reviewed in some detail (15, 16) and is only briefly
implicated in man: androgenic hormones, thalidomide, and the folic acid antagonists. To produce persistent developmental alterations in the genital organs of genetic females, male hormones must be administered prior to the twelfth week of gestation when the normal differentiation of these organs is completed. The thalidomide syndrome is so well known as to require no further characterization. The folate antagonists are more embryolethal than teratogenic, in the sense of causing irreversible structural or functional defects, but about 30% of surviving infants show a variety of anatomic or physiologic abnormalities. It now seems likely that another group of drugs will be added to these established as human teratogens, as indicated below.

A second category of drugs included those only suspected of some teratogenic potential in man. Although the percentage of total cases is small, the persistence of associations between the taking of these drugs during early pregnancy and reports of prenatal death or the birth of defective infants suggests the possibility of causal relationship. Most noteworthy in this group are the anticonvulsant drugs used in the treatment of epilepsy (15, 16). Since the earlier reviews, a spate of additional reports have left little doubt that a higher percentage of defective infants are born to epileptic women on anticonvulsant therapy during the first trimester of pregnancy than would be expected from births in the general population (17–31). Several important questions must be answered, however, before this effect can be attributed to the drugs used. The case reports and surveys have involved use of several different anticonvulsants and, of course, many of the women were on more than one of these drugs during all or part of their pregnancies. Furthermore, there has been no clear segregation of the effects of taking the drugs and of the physiologic imbalances that accompany and follow convulsive seizures occurring during pregnancy. Finally, whichever genetic factors may predispose to epilepsy may introduce an additional element of instability into embryonic development. Until these questions are nearer resolution, it seems more prudent to leave the anticonvulsant drugs in the "probable" category than to move them to the "proven" category as regards teratogenesis in man. Of incidental interest are the observations that diphenylhydantoin appears

to have a low level of embryotoxicity in rhesus monkeys (32) and is unquestionably teratogenic in rodents (33–36).

There is less compelling evidence that certain neurotropic anorexogenic drugs, oral hypoglycemics, and perhaps all alkylating agents should also be suspected of some degree of teratogenic potential in man (15, 16).

A third category consists of drugs thought to have teratogenic potential under some conditions because of infrequently reported associations between their use during human pregnancy and the birth of defective children and/or of demonstrated teratogenicity in laboratory mammals (15, 16). This list includes the following: (*a*) aspirin and other salicylates, none of which has been directly implicated in man, are known to be embryotoxic at high dosage in rhesus monkeys and laboratory rodents; (*b*) antibiotics, some of which have been questionably associated with increased rates of abortion, stillbirth, and the birth of defective children and others of which have been clearly shown to be teratogenic in rodents; (*c*) antituberculous drugs about which the reports are meager and conflicting;
in high doses as an abortifacient in man, may have been responsible for a few visual and auditory defects but which in animals has mainly caused death and growth retardation; and (*e*) insulin as used in psychiatric therapy which, if applied during pregnancy, may occasionally lead to death in utero or to the birth of defective children. Imipramine, reported early in 1972 to have been associated with the birth of infants with reduction defects of the limbs (37), now seems very doubtful as a human teratogen. The earlier claims were not substantiated in more than 220 subsequent case reports in which only six malformed children were found, none with reduction defects of the limbs.

Until very recently, female sex hormones applied during pregnancy have rarely been associated with human developmental abnormality (38). A few cases of malformed newborns were attributed to maternal treatment with large doses of estrogen early in pregnancy (39), but no instances of feminization of genetic males with estrogenic steroids is known. In the last three years, however, smaller doses of combined estrogen and progestins have raised some questions. Unsuccessful attempts to induce abortion by taking a number of contraceptive pills containing synthetic progestins and estrogen have been associated with the birth of defective infants in a few instances (40, 41), but arguments against such causation have also been presented (42). Questions have been raised about the possibility of teratogenic effects following use of hormonal pregnancy tests involving pills containing estrogenic and progestational hormones, although two well-controlled studies have found no significant association between such tests and specific malformations (43, 44). However, other recent reports of uses of female hormones during pregnancy have noted some associations with the birth of a number of defective infants (45–48). One study on reduction deformities of the limbs found a higher than expected number of contraceptive pill failures and of the birth of twins among the mothers of the deformed babies, but the authors (49) tended to relate both occurrences to maternal endocrine dysfunction. The teratogenic status of these hormones will depend upon the collection of further data, but their widespread use would suggest that if any appreciable teratogenic potential existed, it would already have been detected.

A puzzling reaction to maternal treatment with the nonsteroidal estrogenic substance, diethylstilbestrol, during pregnancy has been noted. Approximately 100 girls and young women between ages 8 and 25 years have been diagnosed as having vaginal or cervical adenocarcinoma, and a majority of the histories revealed that their mothers had been given stilbestrol, related drugs, or unidentified drugs for bleeding during pregnancy (50–52). Although these neoplasms do not appear to represent deviations of normal developmental processes, and accordingly are not strictly teratic in origin, they seem to have been induced during early differentiation of the mullerian ducts, possibly as a somatic mutation. In any event, they raise interesting questions about the relationship between carcinogenesis and teratogenesis.

As already noted, there is some basis for assuming that all drugs are embryotoxic if given under optimal conditions to laboratory animals. Nevertheless, there is ample reason to regard some drugs as safe for use during human pregnancy at recommended therapeutic levels. This opinion is supported by the fact that many drugs have been widely used during pregnancy and have not been associated with adverse effects on the conceptus. A few drugs have for one reason or another at some time been suspect, but have been found after further investigation to pose little risk for therapeutic or other use during pregnancy. This group includes LSD, sulfonamides, meclizine, adrenocortical steroids, and tranquilizers and antiemetics generally (15, 16). The possibility that these and other seemingly safe drugs may have undesirable effects during pregnancy under conditions of overdosage, individual sensitivity, or potentiative interaction with other drugs or environmental factors cannot be ruled out.

Before leaving the subject of the types of drug and causation of embryotoxicity, it should be recalled that chemical composition is the major factor in determining mechanisms of action, whether teratologic or pharmacologic. Mechanisms of teratogenic action are as yet poorly understood, although attempts have been made to enumerate several that appear to be supported by experimental evidence or logical presumption (15). As will be noted below, the type of drug also determines the rate and manner in which it is absorbed, metabolized, excreted, and transferred to the conceptus.

LEVEL AND DURATION OF EXPOSURE

That the level of dosage determines the degree and type of response above the no-effect level is as firmly established in teratology as in other aspects of toxicology. The existence of a threshold below which no embryotoxic effects can be demonstrated for a given substance has on occasion been questioned, probably because of uncertainties about thresholds as regards mutagenic and carcinogenic effects. Actually most teratologists accept the concept of threshold, owing to the vast accumulation of experimental studies on multiple dosage levels in which one or more doses caused no developmental deviations greater than those seen in controls. Nevertheless, the argument can be raised that because the lower end of the dose-response curve may be extremely flat, very large numbers of offspring would be necessary to rule out a low level of embryotoxicity at low dosage. This argument has logical

validity, but in practice two facts mitigate against it, in addition to the large volume of contrary data: (*a*) the dose-response curve for embryotoxic effects tends to have a steep slope, and (*b*) highly integrated systems such as embryos are well known to have appreciable regulatory and regenerative powers. The latter fact is significant because it would permit recovery from effects such as a slowed proliferative rate or a modest amount of cell death, assuming that these occurred at small doses. Until such time as experiments involving thousands of animals are able to demonstrate otherwise, it seems justifiable on pragmatic grounds to accept the existence of a threshold for teratogenic effects (15).

The period of time over which drug treatment is given can influence embryotoxicity under two conditions: (*a*) when the drug is capable of inducing or inhibiting its own enzymatic metabolism, and (*b*) when continued use of the drug would interfere with the function of the maternal liver, kidneys, or other organs essential for homeostasis, including the elimination of other potentially embryotoxic substances. Because of such considerations, single doses are sometimes more effective than multiple doses of equivalent or greater total amount. Using a number of pesticides, Robens (53) provided an experimental example of the fact that repeated dosage may produce different embryotoxic results than a single treatment. Groups of pregnant hamsters were treated on days 6 through 10 with the test compounds, while other groups were treated with smaller total amounts of the same compounds as a single dose on gestation day 7 or 8. Multiple treatments caused few developmental defects even at high doses but did cause some resorption and maternal death. The single treatments produced numerous defects in liveborn young. A similar phenomenon was observed by King et al (10) who gave chlorcyclizine to pregnant rats at 50 mg/kg/day from days 10 to 15 of gestation and produced a high incidence of cleft palate. However, when other rats were given the same daily dosage from days 1 through 15 of gestation, malformations were greatly reduced. The possible explanation in both instances is that repeated treatments induced metabolizing enzymes that were able to lower maternal plasma levels of the test substance before the embryo's most sensitive period was reached. In this and several other ways (Table 3) a potential embryotoxic effect could be masked by repeated dosage prior to the peak of the susceptible period of the embryo. These possibilities are of obvious importance in teratogenicity testing.

MATERNAL MODULATION OF DOSAGE

The dosage of a drug reaching the embryo or fetus in part depends on maternal plasma levels, particularly of free drug and metabolites. Concentration in maternal blood is the differential between rate of absorption and rate of dispersal by the maternal homeostatic and other factors that tend to reduce the plasma level. Dispersal is used here in the collective sense of all factors that reduce concentration: placental transfer as well as metabolism, excretion, storage, etc. Aside from the role of the placenta, which is discussed below, the subject of removal of drugs from the maternal blood stream is generally the same in the pregnant as in the nonpregnant individual and needs no particular consideration here. Figure 1 is a diagrammatic

Table 3 Ways in which repeated treatment prior to the peak susceptible period of the embryo may produce misleading results[a]

Time of treatment	Primary effect	Secondary effect capable of altering test results
1. Before implantation	Interference with implantation	No issue
2. Early organogenesis	Early embryonic death	No issue
3. Before peak susceptibility	Induction of catabolizing enzymes	Reduced blood level during susceptible period
4. Before peak susceptibility	Inhibition of catabolizing enzymes	Increased blood level during susceptible period
5. Before peak susceptibility	Liver pathology or reduced function	Increased blood level during susceptible period
6. Before peak susceptibility	Kidney pathology or reduced function[b]	Increased blood level during susceptible period
7. Before peak susceptibility	Saturation of protein binding sites[b]	Increased blood level during susceptible period

[a]From Wilson, J. G. 1973. *Environment and Birth Defects*. New York: Academic.

[b]These effects have not been demonstrated in experimental teratology but their existence in other toxicological situations makes their applicability to teratology likely.

representation of the fact that plasma concentration and secondarily embryo dose are influenced by the several maternal homeostatic functions that tend to reduce them.

ACCESS TO THE CONCEPTUS

Aside from being trite, the term "placental barrier," is inaccurate in the sense that the placenta probably does not totally exclude any chemical present in more than negligible amounts in maternal plasma. Certainly this applies to drugs, most of which have molecular weights of less than 600 (53). There is now abundant evidence that a variety of chemicals cross the placenta and are present in the conceptus in measurable amounts in both man (54–58) and in laboratory animals (59–61). Aside from the protein-type hormones such as glucagon (62), reports of failure of therapeutic agents to traverse the placenta in some fraction of maternal plasma concentration are virtually unknown; even some immune proteins are known to reach the conceptus in effective amounts. Thus the critical question would seem to be not whether, but at what rate, drugs taken by pregnant women reach their concepti.

Much remains to be learned about the dynamics of placental transfer, particularly at developmental stages that correspond to times of high teratogenic susceptiblity in the early embryo. Most studies to date have been done on rodent or near-term human placentas. Although human material obtained at surgical abortion is being used increasingly to study placental transfer (63–65), the substances studied to date

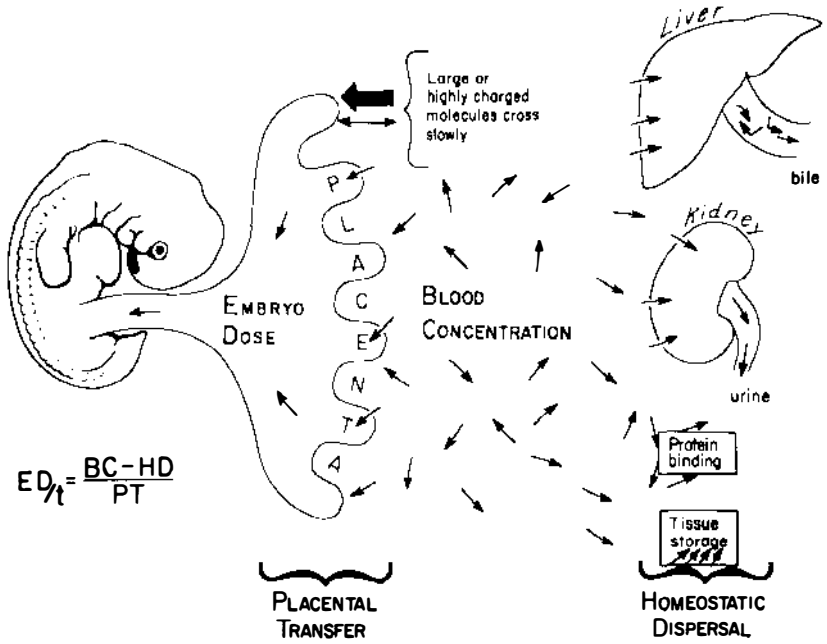

Figure 1 Diagram of the factors that influence embryo dose of a foreign chemical present in the maternal blood stream. The maternal blood concentration under usual conditions of exposure is subject to considerable change, representing as it does the differential between maternal absorption and the several routes for dispersal, including the maternal homeostatic processes of metabolism, excretion, protein binding, and tissue storage, as well as passage across the placenta to the embryo. These various biological processes are all functions of time; therefore the embryo dose depends on the duration as well as the level of a chemical in maternal blood. Embryo dose is proportional to maternal blood concentration, however, only for substances that traverse the placenta by simple diffusion. Otherwise the placenta imposes various rates of transfer depending on the nature of the substance being transferred. The formulation $ED/t = BC - HD/PT$ is in no sense a precise mathematical one, but does attempt to state the basic fact that embryo dose (ED) over a given period of time (t) depends on the maternal blood concentration (BC) which tends constantly to be reduced by homeostatic dispersal (HD) and by placental transfer (PT). From Wilson, J. G. 1973. *Environment and Birth Defects.* New York: Academic.

have been largely medications of therapeutic benefit to the mother that were given after the period of highest embryonic susceptibility, estimated to occur between 3 to 7 weeks of gestation. Both the thickness and the area of the membrane across which transfer occurs are known to vary markedly during development (59, 66, 67), conditions that would inevitably influence rate of transfer. Studies using rodents and rabbits to investigate placental transfer functions in relation to teratogenicity are of doubtful significance for man because the atypical yolk sac placenta, on which these

animals depend during early organogenesis, is thought to transfer many chemicals differently from that seen in higher mammals (68–71). A concentration gradient, with fetal tissues and fluid compartments having lower levels than maternal plasma, have usually been observed during middle and late pregnancy in animals and man (61, 63, 65, 72). This could be attributed to any of three factors postulated to reduce the amount of foreign chemicals that reach and are retained by the conceptus. The first has to do with the dynamics of simple diffusion, by which most drugs are thought to be transferred, and relates to the probability that concentration in maternal plasma would begin to fall as a result of homeostatic dispersal before fetal concentration would have time to reach equilibrium. The second possibility is that the placenta, by biotransformation of foreign chemicals, can catabolize a part of the dosage during transfer or conjugate them so that the rate of transfer would be slowed, as is discussed below. A third possibility is that a part of the dose reaching the conceptus would be metabolized in situ, thereby reducing the likelihood of appreciable concentration in the embryo or fetus, as will also be discussed below. Before considering the evidence concerning the latter two possibilities, however, it should be noted that embryonic or fetal concentration is not always less than that in maternal plasma. For example, hydroxyurea level in the 12-day rat embryo became and remained higher than the level in maternal plasma for several hours after ip dosage of the pregnant female (73), probably as a result of binding within the embryo. Incorporation of pyrimidine analogs in appreciable amounts into the DNA and RNA of rapidly growing rodent embryos has been repeatedly demonstrated (74, 75).

Much interest has recently centered on the possibility that the placenta may afford some protection to the embryo or fetus by metabolizing foreign chemicals before they are transferred to the intrauterine occupant. There is no longer any doubt that the placenta at term contains the enzymatic equipment to transform chemicals by all of the standard metabolic pathways, oxidation, reduction, hydrolysis, and conjugation (76–78). Some of these reactions have also been demonstrated in homogenates of fetal placentas from early in the second trimester (79) but, regardless of the gestational age when examined, such metabolic activity in vitro does not necessarily reflect activity in the intact placenta in vivo. In fact there seems little reason to believe that the placenta of any age contains more catabolizing enzymes than are needed in support of its own maintenance and extensive biosynthetic activities. Certainly there is no reason to regard the placenta as capable of protecting the embryo or fetus from exposure to drugs by virtue of its ability to degrade them metabolically.

DEVELOPMENTAL STAGE WHEN EXPOSURE OCCURS

That the degree and type of reaction shown by a developing organism depend on the stage in development when exposure to an adverse influence occurs is one of the most basic principles of teratology. The subject has been extensively discussed elsewhere (80), and the present purpose only requires a brief summary. Susceptibility to developmental deviation in man is thought to be low from fertilization until

the embryonic germ layers begin differentiation on about day 17; it then abruptly rises during early organogenesis and probably reaches a peak between days 25 and 35. It gradually subsides during later organogenesis and throughout the fetal period, and continues at a low level in certain tissues (nervous and endocrine systems) until about puberty. The time of exposure not only governs the severity of the reaction but also the type of developmental toxicity, i.e. death, malformation, growth retardation, or functional deficiency. During the embryonic period when proliferation and differentiation of tissues and organs is predominant, gross malformation or embryonic death is the usual response to an adequate dosage. During the fetal period when overall growth and functional maturation are in progress, adverse influences are more likely to result in growth retardation or functional deficiency, although high dosage may still lead to abnormal histogenesis or even to death. After birth only those organs which remain functionally incomplete, mainly brain and some endocrine glands, are likely to be vulnerable to impairment of final functional maturation, although unfavorable factors can still interfere with overall growth to mature stature.

DISPOSITION OF DRUGS WITHIN THE CONCEPTUS

This subject has recently been the focus of considerable attention. Data are virtually nonexistent on the capacity of the early mammalian embryo to carry out any type of catabolic metabolism of foreign chemicals. It is a safe assumption that embryos do not metabolize drugs until such organs as the liver, lungs, and kidneys have completed organogenesis, or at least have accumulated some parenchymatous tissue with a degree of functional competence resembling that in postnatal animals. This degree of organ maturation does not occur in rodents and rabbits until approximately term, and the situation may be only moderately more advanced in carnivores and ungulates at birth. It is not surprising, therefore, that newborn animals of these types generally have little or no capacity to metabolize drugs (81–84). In contrast, the histogenesis of the human liver is relatively advanced at birth. An appreciable accumulation of agranular endoplasmic reticulum (microsomes) is apparent by electron microscopy as early as the third month of gestation (85). The liver of the human newborn is able to carry out several enzymatic biotransformations (58), although the possibility exists that some of the necessary enzymes were induced by maternal drug therapy a few days before delivery, and some induction may even occur before surgical abortion at midpregnancy (86). Limited capacity to carry out certain drug metabolizing reactions has been repeatedly shown by the liver and other organs of fetuses removed at abortion during the second trimester (63, 64, 87, 88), but these have been quite weak and altogether lacking in some pathways, e.g. conjugation, as compared with adult liver (89, 90).

Whole-body autoradiography after treatment of pregnant mice with radiolabeled drugs has generally shown concentrations in fetal organs to be much lower than in maternal organs (61, 72) with the exception of such substances as steroids, vitamin B_{12}, and iron. The observation of appreciable amounts of labeled compounds in the uterine lumen has led one investigator (61) to suggest that the inverted yolk sac epithelium may be able to concentrate and excrete drugs directly into the lumen of

the genital tract where they could be eliminated directly without passage back across the chorioallantoic placenta to the maternal blood stream. This is an interesting possibility but it is so far supported only by circumstantial evidence. In any event, it would only apply to drug elimination in rodents and rabbits, the principal mammals possessing this unique accessory placental structure.

In sum the drug-metabolizing capacity of the embryo, except for incorporation of certain analogs in biosynthesis, is thought to be negligible for want of parenchymatous tissue with any degree of functional maturity, in the postnatal sense. This is the time that major teratogenesis has its inception; therefore, it is highly unlikely that the embryo has intrinsic defenses against foreign chemicals at the time they are most needed. This period of presumed high vulnerability extends only through the seventh or eighth week of human gestation; however, it occupies a much greater proportion of intrauterine development in rodents, in which tissue maturation is not appreciable until near term. The considerably longer fetal period of man is undoubtedly associated with significantly more functional development in such organs as liver, lungs, and kidneys; indeed, these organs have been shown to possess some capacity for enzymatic transformation of drugs as early as midgestation. Whether this capacity has significance in protecting against an adverse effect of drugs, however, can be questioned on two bases. First, the enzymatic activity in these fetal organs has generally been found to be quite low by postnatal standards; second, by the time appreciable drug-metabolizing competence is achieved by fetal tissues, most organs have reached advanced developmental stages that would render them immune from most structural and many functional deviations. Exceptions may be the brain and some endocrine glands.

SUSCEPTIBILITY OF THE SPECIES (AND INDIVIDUAL)

This subject has received much attention in experimental teratology and has been extensively reviewed elsewhere (15, 91). Of particular interest here are the factors that determine susceptibility to teratogenesis and their relation to the extrapolation of safety evaluation data from animal to man. As indicated in the foregoing discussions, the ultimate reaction of the conceptus to a given drug or foreign chemical in the maternal blood stream depends on three questions: 1. Can maternal homeostatic functions reduce the plasma level soon enough to avert an embryotoxic dose to the conceptus? 2. Are the structural and functional characteristics of the placenta such as to favor or impede transfer of an embryotoxic dose? 3. To what extent is the embryo or fetus inherently vulnerable to the chemical in question? The answers to these questions are in large measure determined by the genetic makeup of both the mother and the conceptus and, of course, in a broader sense to the genetic makeup of the species. Interspecies differences in the conditions that relate to all of these questions, possibly excepting the third, are now known, but they must be much more fully understood before test results in an animal species can be applied to safety predictions in man with a high degree of assurance. Thus, the preclinical evaluation of drugs for teratogenic potential in man will remain largely empirical until much more data have accumulated on the mechanisms of actions of drugs in the conceptus, the dynamics of their placental transport, and the factors governing their disposition in the maternal organism, both in man and the test species.

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