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THEORETICAL REVIEW

Behavioral Teratogenesis: A Critical Evaluation[1]

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COYLE, I., M. J. WAYNER AND G. SINGER. *Behavioral teratogenesis: A critical evaluation.* PHARMAC. BIOCHEM. BEHAV. 4(2) 191–200, 1976. – A critical review of some relevant literature concerning the effects of prenatal administration of drugs and several other substances on postnatal behavior. Significant variables and problems in the adequate design of experiments to assess these effects are discussed. Although the evidence concerning prenatal drug effects on behavior is equivocal, sufficient data exist to indicate that this will continue to be a viable and important area of research in the future. Present results demonstrate the complexity of drug interactions with other variables.

Teratology Behavioral pharmacology Behavioral teratogenesis Prenatal drug effects Tranquilizers
Vitamin A Amphetamine Sedatives Methylmercury

TERATOLOGY is the study of abnormalities arising during prenatal development [15]. For many years studies have been restricted mainly to the investigation of morphological abnormalities particularly those involving the skeletal system. In the past decade it has become evident that other organismic systems display teratogenic effects which might affect behavior. Consequently, the term teratology has taken on a much broader meaning and will be used in this review to describe morphological, physiological, biochemical and behavioral abnormalities. Specifically, the term behavioral teratology will be used to describe deleterious changes in the behavior of animals attributed to teratogenic agents administered during prenatal development [83].

Although a variety of extrinsic factors such as X-rays [32] and rubella [34] have been implicated in the production of congenital abnormalities, it was not until the thalidomide tragedy that chemical agents were shown to be teratogenic in humans [51,72]. The observation [51] that ingestion of thalidomide during pregnancy could result in severe deformaties in the offspring created considerable interest. As a result, the teratogenic effects of many pharmocological agents and a wide variety of other chemicals have been studied. The abnormalities induced by many chemical teratogens are not as obvious as the limb deformities caused by thalidomide. For example, administration of halothane or nitrous oxide to gravid rats results in relatively minor abnormalities of the vertebrae and ribs that are not externally visible [7,30]. Similarly, growth retardation has been reported in the offspring of female rats treated with morphine prior to conception without any other directly observable physiological changes [31]. Physical teratogenic effects can be extremely subtle and it has been suggested that dermatoglyphic changes, the intricate pattern of ridges in the skin of the hands and feet, might be sensitive indicators of teratogenicity in man [42].

There are several obvious ways drugs might interfere with normal prenatal development [87] which are summarized in Table 1. Any drug which produced any one of these effects should be considered to be teratogenic.

Growing awareness of subtle teratogenic effects without obvious morphological changes has stimulated considerable research. Teratogenic defects are not necessarily structural [48] and biochemically related behavioral changes might be a more sensitive indicator. The administration of methylmercury in rats during pregnancy can produce enduring behavioral deficits without any observable morphological changes [61, 70, 71]. At present few drugs can be classified as behavioral teratogens since most commonly used drugs have not been tested for possible prenatal effects on behavior. Unfortunately, psychoactive or mood altering drugs seem to be implicated in certain congenital abnormalities and are commonly used by pregnant women or those of childbearing age [54]. Many of the studies concerned with prenatal drug effects on behavior have not been designed adequately from the point of view of

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TABLE 1

POSSIBLE TYPES OF DRUG INDUCED INTERFERENCE WITH PRENATAL DEVELOPMENT*

Failure of ovulation	Secondary to endocrine or metabolic imbalance
Prevention of fertilization	By reducing fertilizing capacity of the germ cells
Interfering with migration	Interference with the ovum or early embryo in the female tract
Faulty or no implantation	Due to damage blastocytes or improper uterine condition
Indirect damage to the embryo or fetus	As a result of altered placental function or maternal metabolism
Direct damage to the embryo or fetus	Increased fetal mortality and morphological or behavioral anomalies

*Adopted from Wilson [85].

teratogenic testing. Therefore, it is necessary to consider the problems involved in the assessment of prenatal drug effects before evaluating the current literature on behavioral teratology.

ASSESSMENT OF PRENATAL DRUG EFFECTS

Problems involved in teratogenic testing have been reviewed in some detail [15, 46, 50, 87, 88]; however, the application of teratological principles to the study of abnormalities in behavior arising during embryonic development requires further elaboration. In mamals the teratogenic effects of any drug are determined primarily by the following factors: chemical nature of the teratogenic action; access of the drug to the embryo or fetus; mode of drug administration; stage of development of the organism at the time of drug administration; and the susceptibility of the species and individual sensitivity [87]. Postnatal variables can also interfer with the expression of behavioral abnormalities. Even though these variables are not independent, for the purpose of convenience they will be considered separately.

Nature of the Teratogenic Action

Congenital abnormalities are the result of certain pathological changes which are either transmitted at inception or which occur during earlier development. Previously suggested [89] factors are: mutation; chromosomal aberrations; interference with mitosis; altered nucleic acid synthesis and function; deficiencies of precursors, substrates, enzymes and other substances necessary for normal cell metabolism; enzyme inhibition; altered energy sources, osmotic imbalance; and changes in cell membrane characteristics. Drug induced behavioral deficits can result from any one or a combination of these factors. Since the teratogenic action of most drugs is unknown and possibly unrelated to expected pharmacological effects, it might be best to consider all chemical agents potentially harmful in this context. It seems reasonable to assume that drugs which affect the central nervous system are more likely to cause congenital behavioral anomalies. Most behavioral teratogens also affect the central nervous system in mature animals. However, the brain of a developing organism is not simply a small adult brain and drugs which affect the adult central nervous system might have a different effect or no effect at all in the immature animal [50].

Access of the Drug to the Embryo

The notion that the placenta acts as a filter to protect the developing organism from harmful agents in the maternal blood stream is not supported by the evidence [79,91]. Although drugs which are non-lipid soluble, ionized at tissue pH, or have a molecular weight greater than 600 cross less readily, all substances dissolved in the maternal plasma pass through the placental barrier [79]. The main protection afforded by the placenta is to slow the transfer of the substance which thereby provides more time for the maternal organism to metabolize and excrete the substance before the concentration in the embryo or fetus becomes injurious. The results of several studies indicate that this might not be the case with psychoactive drugs. Equilibrium between the mother and fetal rat is established within 3 minutes of an intramuscular injection of moderate dose, 10 mg/kg, of imipramine [28]. Placental transfer of nortriptyline and chlorpromazine appears to be rapid in humans [37, 65, 66]. These results of tests with tranquilizers and tricyclic antidepressants indicate that placental transfer of drugs might be similar to that of the blood brain barrier, an idea expressed earlier by others [55,91]. Consequently, it seems reasonable to assume that many, if not all, psychoactive drugs will cross the placenta.

Mode of Drug Administration

In teratogenic studies with animals the mode of drug administration is important. Clinically, most drugs are given orally and the use of a different route can significantly affect absorption, fate, and eventual excretion of the substance or its metabolites. However, it cannot be argued that teratogenic investigations should only utilize oral administration. For example, even though there might be more rapid absorption of imipramine with subcutaneous or intraperitoneal injections [2], the metabolic patterns following intraperitoneal and oral administration are similar [17]. Also, the variability in absorption rates for both oral and intraperitoneal administration is very large [9,17]. Therefore, although the oral route might be preferred because of clinical applications, other methods might be applicable in animal studies.

Duration of Drug Administration

Some drugs prevent or terminate pregnancy and therefore would not be considered potential teratogens. Consequently, short-term exposure of an embryo or fetus to a relatively low dose of a drug could produce a teratogenic effect; whereas, chronic treatment might prevent pregnancy and/or cause death. Also, accumulation of metabolites as a result of chronic drug administration could be teratogenic even though the substances are inactive in the mother. There might not be a relation between the teratogenic action of a drug and its effects in the fully developed animal. The concentration of metabolites in the embryo or fetus could be higher than in the maternal organism as a result of interference with the transport of waste products across the placenta. Apparently, the human fetus can metabolize and excrete tricyclic antidepressants and some

other drugs [29,66]. However, this ability is probably not present early in embryogenesis when the developing organism is most susceptible to some teratogenic effects and in this respect the human fetus is similar to other animals which tend to have poor drug metabolizing capacities at birth [29]. Since most studies on teratology have employed only acute drug administration, it would be advisable to utilize both acute and chronic techniques in the future.

Drug Dose

Selection of doses in studies on behavioral teratogenesis is complex and for a time will have to be determined empirically. Four discriminable ranges have been suggested [87] for potential teratogenic substances which include: (a) low doses without measurable effects; (b) teratogenic doses; (c) fetal lethal doses and (d) maternal lethal doses. The extent and overlap between teratogenic and fetal lethal doses must be determined. Some drugs are capable of producing a spectrum of teratogenic effects from subtle behavioral dysfunctions to gross physical abnormalities. High doses of methylmercury or vitamin A produce severe physical abnormalities, particularly of the central nervous system [47], whereas lower doses result in behavioral anomalies [12, 43, 44, 61, 70, 71]. Other drugs do not have as wide a range of teratogenic effects. Chlorpromazine is not a teratogen in the classical sense [8] but it does induce behavioral anomalies in offspring of rats exposed to the drug during pregnancy [33]. Similarly, attempts with delta-nine-tetrahydrocannabinol to produce congenital abnormalities even with doses toxic to the maternal organism [10,58] have failed even though prenatal administration of delta-nine-tetrahydrocannabinol can delay physical maturation and behavioral development [11].

Any drug capable of producing morphological abnormalities should be tested at lower doses to determine its effects on behavior. It would seem appropriate to use a dose just below the minimum required to produce a physical deformity. If the clinical efficacy of the drug is being evaluated, then it would also be necessary to use a dose corresponding to the highest therapeutic dose. With drugs that do not induce morphological anomalies the situation is more complex since there is no readily determined upper dosage limit. Some authors have argued that the highest dose should be determined in terms of toxicity. Some prenatal drug effects might be due to maternal and/or fetal toxicity rather than a direct teratogenic effect [11]. Dosages should be selected lower than those required to produce signs of overt toxicity in the maternal organism or fetus. The upper dose should not be toxic to the maternal organism since any developing effects on the fetus would be concealed by preventing or terminating pregancy [46].

Developmental Stage of the Organism at the Time of Drug Administration

Although any interference with prenatal life can be considered potentially teratogenic [46,87], the embryo is generally resistant prior to implantation and after organogenesis. The period of development most susceptible in terms of morpholgical changes is from the formation of germ layer cells, early differentiation, through organogenesis. In mammals, the central nervous system has the longest period of development. The most vulnerable period with respect to behavioral dysfunctions has not been determined.

Results of studies which have reported behavioral defects following prenatal drug administration are summarized in Tables 2 and 3. In most of these studies no attempt was made to vary the period of drug administration. In those which did, the data are inconclusive. Several investigators [49, 81, 82, 84] reported that the period in which a drug was administered, early, mid or late pregnancy, had no differential effects on the behavior of the offspring. Conversely, where chlorpromazine is administered in early pregnancy maze learning is impaired [41,56] but it has no observable effects when applied late. These results are difficult to reconcile since the doses and developmental period of administration were identical in all the studies. Similar contradictory results have been obtained with meprobamate and reserpine [41, 49, 56, 82, 84]. Since none of these aforementioned experiments utilized fostering procedures, it is not clear if the behavioral effects were due to prenatal or postnatal influences. Unfortunately, the majority of studies which employed fostering procedures [11, 12, 33, 43, 44, 57, 70] were not concerned with differential behavioral effects due to the developmental period of drug administration.

Since the previously mentioned studies have shown that some drugs administered during organogenesis induce behavioral anomalies in the offspring it seems reasonable to search for effects after organogenesis is completed. Vitamin A, for example, administered after organogenesis is complete can produce behavioral deficits in the offspring [44]. There is considerable evidence that the developing brain remains vulnerable to deleterious environmental influences during the neonatal period. Neurological impairment caused by dietary inadequacy during pregnancy or weaning is well known [4,67]. Neonatal exposure to halothane, an established teratogen [7], produces enduring learning deficits and cerebral synaptic malformation [59]. Behavioral teratogens might therefore produce specific anomalies dependent upon the developmental stage at the time of drug administration. Although the effects of vitamin A on discrimination learning seem to depend upon the period of development, the results are not entirely consistent. Animals which receive vitamin A late in gestation respond at a lower rate as compared to controls. Animals which receive vitamin A on the 14 and 15th day of gestation perform at normal rates. On the other hand, animals exposed to vitamin A early in gestation are impaired in their ability to acquire and perform an auditory discrimination whereas animals exposed late in gestation display no such impairment [43,44]. Considering these results, it seems apparent that probably behavioral teratogens should be administered at various periods during fetal development and chronically throughout pregnancy.

Susceptibility of the Species and Individual Sensitivity

Species and individual sensitivity to teratogens vary considerably [15,18]. Although genetic factors are primarily responsible for determining embryonic reactivity to environmental stimuli, genetic and environmental interactions are complex and the maternal genotype can also influence reactions of the developing organisms to teratogens [18]. Individual differences in drug absorption and metabolism in the maternal organism can determine in part

TABLE 2

PRENATAL DRUG EFFECTS ON BEHAVIOR AS A FUNCTION OF DEVELOPMENTAL STAGE DURING ADMINISTRATION

Drug		Period of Administration Days Post Conception	Effects on Behavior	Reference
Isocarboxazid Iproniazid	Rat	5–8, 11–14, 17–20	Yes	80
Chlorpromazine Meprobamate Reserpine	Rat	5–8, 11–14, 17–20	Yes	41
Chlorpromazine Meprobamate Phenobarbital Reserpine	Rat	5–8, 17–20	Yes	56
Chlorpromazine Meprobamate Reserpine	Rat	5–8, 11–14, 17–20	No	82
Chlorpromazine Meprobamate Reserpine	Rat	5–8, 11–14, 17–20	No	84
Meprobamate	Rat	5–8, 11–14, 17–20	No	49
Sodium Bromide	Rat	3–20	No	35, 36, 38
Sodium Barbital Pentobarbital	Rat	19–parturition	NA	6
5-Hydroxy-tryptophan 1-benzyl-2-methyl 5-methoxytryptamine Reserpine	Rat	8–14	NA	81
Chlorpromazine Reserpine	Rat	4–7	NA	45
Chlorpromazine	Mouse	6–parturition	NA	57
Chlorpromazine d-Amphetamine-sulphate	Rat	12–15	NA	14
Chlorpromazine	Rat	5–8	NA	33
Methylmercury	Mouse	7–9	NA	70
Methylmercury	Mouse	7 or 9	Not stated	71
Delta-9-Tetra-Hydrocannabinol	Rat	10–12	NA	11
Vitamin A	Rat	8–10	NA	12
Vitamin A	Rat	14–15	See text	43
Vitamin A	Rat	17–18	See text	44

Days post conception: Day 1 is the day sperm was found.
NA: not applicable.

embryonic reactivity. In the absence of an ideal experimental species to substitute for man, it has been suggested [87] that the species selected should have (a) a relatively short gestation period and high reproductive capacity, (b) a drug metabolism similar to man and (c) a well documented reproductive physiology, embryology and genetics. Species specific metabolic sensitivity is particularly important. For example, administration of imipramine to pregnant rabbits causes gross physical deformities of the central nervous system in developing fetuses [60]. However, the metabolism of impramine in rats is more similar to man [9, 17, 27] and studies on rats have failed to produce the teratogenic effects reported in rabbits [2,60].

Postnatal Variables

Before it can be established that prenatal drug administration deleteriously affects the behavior of offspring, other factors which operate between conception and behavioral testing must be considered. Any treatment which produces prenatal effects on the behavior of offspring might be capable of affecting the behavior of the treated female after the cessation of treatment. The behavior of adult rats can be influenced by the differential handling of mothers or grandmothers during infancy [22,23]. Since fostering procedures were employed, it was shown that both natural and foster mothers affected the behavior of the young. These observations have been confirmed [20,46] and it is clear that behavioral effects are mediated both through the prenatal mother-fetus relationship and the postnatal mother-offspring interaction.

Litter size is also an important variable in determining behavioral effects and physical development in both the fetus and neonate [5, 64, 77, 78], probably by influencing nutrient and oxygen transfer to the fetus and offspring. Changes in the mother's milk due to prenatal drug administration might influence the behavior of the offspring after cessation of treatment. Postnatal transmission of a drug administered prenatally might affect the behavior of the neonate [57,65]. The rate of metabolism and excretion of some drugs can be prolonged [3] and significant amounts administered late in pregnancy can be transmitted to the offspring during lactation [57]. Significant amounts of the drug administered throughout gestation or late in pregnancy can be present in the offspring at birth [57]. If so, then any behavioral anomalies in the drug exposed offspring might be due to a direct drug action rather than a teratogenic effect. In humans, the neonate has considerable drug metabolizing capacity [29] and it is likely that any behavioral effect caused by residual drug concentration and/or postnatal transmission during lactation, if breast fed, would be transient. These transient effects on behavior could be confounded with teratogenic changes. In other species, neonates usually have a poor drug metabolizing capacity and toxic concentrations might accumulate which could produce behavioral effects difficult to distinguish from teratogenic changes.

Even though some behavioral effects induced by prenatal drug administration are not influenced by fostering methods, such procedures are always necessary in the determination of prenatal or postnatal origin of such effects in the offspring of drug treated animals. When drugs are administered late in pregnancy or if the rate of metabolism and excretion is prolonged, then the extent to which residual drug concentrations affect the behavior of prenatally exposed offspring must also be determined.

TABLE 3
A SUMMARY OF PRENATAL DRUG EFFECTS ON BEHAVIOR

Drug and Dose	Behavioral Measure	Fostering	Ref.
Reserpine 0.1 mg/kg	Inclined plane Open field 4-Unit T-maze Shock avoidance Audiogenic seizures*	No	81
Reserpine 0.1 mg/kg	Inclined plane* Open field* Audiogenic seizures*	No	82
Reserpine 0.1 mg/kg	Lashley III maze	No	84
Reserpine 0.1 mg/kg	Lashley III maze	No	41
Reserpine 0.1 mg/kg	Activity Wheel Audiogenic seizures	No	45
Reserpine 0.1 mg/kg	Activity wheel Hebb-Williams maze Electroshock seizures	No	56
Chlorpromazine 6 mg/kg	Activity wheel Audiogenic seizures*	No	45
Chlorpromazine 6 mg/kg	Inclined plane Open field Audiogenic seizures*	No	82
Chlorpromazine 6 mg/kg	Lashley III maze	No	84
Chlorpromazine 6 mg/kg	Lashley III maze*	No	41
Chlorpromazine 6 mg/kg	Activity Wheel Hebb-Williams maze* Electroshock seizures	No	56
Chlorpromazine 1 mg/kg	Open field* T-maze Operant conditioning	No	14
Chlorpromazine 6 mg/kg, 16 mg/kg	Open field* Shock avoidance* Activity wheel*	Yes	57
Chlorpromazine 4 mg/kg	Flurothyl seizures* Shock avoidance*	Yes	33
Meprobamate 60 mg/kg	Inclined plane* Open field* Audiogenic seizures*	No	82
Meprobamate 60 mg/kg	Lashley III maze*	No	84
Meprobamate 60 mg/kg	Inclined plane Open field Lashley III maze	No	49
Meprobamate 60 mg/kg	Lashley maze	No	41
Meprobamate 60 mg/kg	Activity wheel* Hebb-Williams maze* Electroshock seizures*	No	56

TABLE 3 (cont.)

Drug and Dose	Behavioral Measure	Fostering	Ref.
Pentobarbital 6 mg/kg	Hanawalt maze* Maier-type maze*	No	6
Sodium Bromide 40 mg/kg 80 mg/kg 120 mg/kg	5-Unit T-maze Maiers table test* Open field* Water wading test* Audiogenic seizures*	No	35, 36, 38
Phenobarbital	Activity wheel Hebb-Williams maze* Electroshock seizures*	No	56
Sodium Barbital	Hanawalt-maze Maier-maze	No	6
Iproniazid 2 mg/kg 4 mg/kg 8 mg/kg	Audiogenic seizures*	No	80
Isocarboxazid 2 mg/kg 4 mg/kg 8 mg/kg	Audiogenic seizures*	No	80
Vitamin A 100,000 iu/kg	Swimming-maze*	Yes	12
Vitamin A 60,000 USP	Auditory discrimination	Yes	43
Vitamin A 90,000 USP	Auditory discrimination	Yes	44
d-Amphetamine-sulphate 1 mg/kg	Open field* T-maze* Operant conditioning	No	14
Methylmercury 8 mg/kg	Open field*	Yes	70
Methylmercury 8 mg/kg	Open field* Swimming ability*	No	71
Methylmercury 0.05 mg/kg 0.5 mg/kg 5.0 mg/kg	Open field Detour learning*	NA	61
5-Hydroxy-tryptophan 50 mg/kg 100 mg/kg	Inclined plane* Open field* 4-Unit T-maze Shock avoidance Audiogenic seizures	No	81
1-benzyl-2-methyl-5-meth-oxytryptamine 100 mg/kg	Inclined plane* 4-Unit T-maze* Open field* Shock avoidance Audiogenic seizures	No	81
Delta-nine-Tetra-hydro-cannabinol	Open field* Reflex ontogenesis*	Yes	11

*Significant results.

The time which elapses between weaning and behavioral testing is important. Even routine laboratory procedures during this period can interact with prenatal drug effects in the determination of behavior. Some investigators [90] consider the drug-environment interaction to be the most crucial experimental variable. Obviously, behavior is elicited by stimulation and environmental conditions are of the utmost importance at any stage of postnatal development. Rats raised in an enriched environment display distinct changes in brain chemistry and anatomy when compared to animals reared in isolation [25, 26, 53, 62]. Enriched experiences in early life resulted in better problem solving behavior in adulthood [24]. Similar enrichment during infancy reduces emotionality and increases activity in an open field [19,20]. The degree of environmental enrichment during development can modify a variety of behavioral characteristics [20]. Normal laboratory conditions can also obscure some possible experimental effects. Certain genetic induced changes in behavior of mice do not appear under normal laboratory conditions [39]. Although neonatal treatment with para-chlorophenylalanine improved active-avoidance responding when animals were reared in an enriched environment, there was no difference between treated and control animals when both groups were reared in isolation [63]. These results are interesting because they indicate that possible teratogenic effects on behavior might be obscured by so-called normal laboratory rearing procedures. Consequently, normal and isolated and enriched environmental laboratory conditions must be compared in the assessment of any possible drug effects on behavior.

BEHAVIORAL MEASURES OF PRENATAL DRUG EFFECTS

Even though a detailed examination of physical development is being emphasized in the current literature [31,42], considerable evidence exists which indicates that morphological observations alone are insufficient measures of teratogenesis. Behavioral changes can be a more sensitive indicator of teratogenic action [11, 12, 33, 43, 44, 61] and have become a necessary adjunct to morphological examination and even biochemical assays. In measuring behavior, questions concerning validity and reliability arise which must be considered. Testing procedures which have been utilized in the evaluation of behavioral teratogenic effects are summarized in Table 3. Apart from the ubiquitous open field [11, 35, 49, 57, 70, 71, 81, 82], the only other tests which have been frequently used are the Lashley III maze [41, 49, 84] and susceptibility to audiogenic seizures [35, 45, 80, 81, 82]. Considerably more data is required on a variety of different tasks in the development of a set of adequate criteria for the assessment of behavioral teratogenic effects.

Determination of Transient and Permanent Effects

The problems of distinguishing between transient and permanent effects of behavioral teratogens must also be considered. Behavioral deficits which persist into adulthood appear to be the most serious. Delays in the development of certain kinds of behavior could be more sensitive indicators of behavioral teratogenic effects than tests of adult behavior [11, 67, 76]. In the determination of permanent effects on behavior, one approach has been to use a test-retest procedure [35,57]. Another method involves testing on a variety of tasks over a prolonged period of time [6, 11, 49, 56, 81, 82]. Both can lead to incorrect conclusions. With a test-retest procedure, baseline performance on the dependent variables cannot vary with age. For example, defecation and urination in the open field vary with age [13] and any effect of the teratogenic treatment on these variables would produce a confounding and equivocal interaction. Exploration in an open field also varies with age and the observation that prenatal treatment with chlorpromazine decreases such activity [57] is also questionable. The major difficulty in administering a battery of tests is the differential sensitivity of the subjects at different ages to the various tests. Specificity of the behavioral effects and cross-validation between different tests and drugs must also be established.

BEHAVIORAL TERATOGENS

Results of animal studies on teratogenesis are not always applicable to humans [29] and any cross-species comparison must be evaluated carefully [40]. For obvious reasons most experimentation with potential teratogens cannot be justified and carried out with humans. Even then possible human experimentation is fraught with difficulties. Many of the mothers who received thalidomide and had deformed children could not remember having taken the drug [69]. The human postnatal environment is extremely complex, fostering procedures are impossible, and factors such as parental influences and education are impossible to control and, for example, the effects of minimal brain damage could easily be imperceptible [75]. Considering the difficulties involved it is not surprising that few human studies have been conducted on behavioral teratogenesis. Consequently, animal experimentation will continue to present almost the only source for testing drug effects in the future.

In a review of the literature on prenatal drug effects on behavior [46] serious methodological inadequacies were described. Some of the problems are unique and others are typically associated with psychopharmacological research. Most of the studies on prenatal drug effects on behavior have been concerned with tranquillizers such as chlorpromazine, reserpine and meprobamate. Results are equivocal.

Chlorpromazine

Prenatal administration of chlorpromazine has been reported to decrease the duration of audiogenic seizures [82] and to increase susceptibility to them [45]. With respect to activity, two studies [56,82] report no effects and a third reports [45] a decrease. Differences can probably be attributed to the different methods utilized to measure activity. In another study [14], offspring of chlorpromazine treated mothers were less active in an open field on the 13th day after birth and more active on the 18th day as compared to control animals. By weaning and at 40 and 60 days of age the differences had disappeared. In addition to the differences in testing procedures and the type of activity measured, doses, the period of drug administration, and the age at testing were also different as indicated in Table 2. Possible teratogenic effects of chlorpromazine on learning are uncertain. Contradictory results have been reported when the offspring were tested in a Lashley III maze [41,84] and a Hebb-Williams maze [56]. No differences were reported in T-maze habit acquisition [14]; however, offspring of chlorpromazine treated mothers made more errors in acquiring a bar pressing

response. In addition to the criticisms mentioned in the preceding paragraph, housing conditions between at least two of the studies were not the same [14,41]. The most serious difficulty in these studies was the failure to control for postnatal variables and it is impossible to attribute the behavioral effects reported to prenatal or postnatal influences. For the same reason, it is impossible to reconcile contradictory results. Relatively few studies have utilized adequate fostering procedures. In one such study on mice [57], prenatal treatment of mothers with chlorpromazine produced offspring which were less active both in an open field and in running wheels and made fewer avoidances in shock elicited escape avoidance learning. Two doses were used and the larger one resulted in greater behavioral deficits. Unfortunately, housing conditions were not reported, long-term effects were not determined, and the presence of radioactive labeled chlorpromazine and metabolites in the liver and brain homogenates of drug offspring indicate the possibility of a direct effect of the drug on the behavior of the offspring. The impaired shock avoidance performance supports recent results of a rat study which also utilized fostering procedures [33]. Chlorpromazine administered during gestation increased offspring susceptibility to flurothyl-induced convulsions, impaired shock avoidance learning, and increased intertrial responding. Chlorpromazine does seem to have some behavioral teratogenic effects.

Reserpine and Meprobamate

Since reserpine and meprobamate were used in most of these studies on chlorpromazine, results on these drugs are difficult to interpret for the same reasons. Although reserpine did not affect the learning of several tasks, the effects on susceptibility to audiogenic seizures and activity are equivocal. Offspring from meprobamate treated mothers were less active in an open field, were slow in climbing an inclined plane, and displayed shorter duration audiogenic seizures [82]. These results were not confirmed in a so-called "exact replication" [49]. It seems useless to continue the controversy because questions concerning dose, housing conditions and statistical treatment of the data can be raised in addition to the important fact that, since none of the studies utilized fostering procedures, any change in behavior could be due to postnatal factors. Only the results of more adequately conducted experiments in the future will resolve the inconsistencies of the present data. Significant differences in methodology make any further comparisons seem pointless.

Sedatives

A similar situation exists for the possible behavioral teratogenic effects of sedatives. Sodium pentobarbital and sodium barbital administered prenatally had adverse effects on offspring maze performance and on a reasoning task [6]. All the drug treated groups for the two drugs and different doses were combined for statistical analysis and no fostering procedures were employed. Apart from the logical difficulties in such an analysis of data, other technical details were not reported. Although sodium bromide administered to pregnant females decreased defecation of the offspring in an open field, increased defecation in a water wading test, and increased susceptibility to audiogenic seizures [35, 36, 38], the falure to control for postnatal variables and other methodological difficulties make these results difficult to attribute to the drug. Handling of the pregnant females might have been the most significant variable in this study [1, 23, 73]. Phenobarbital offspring also display a different pattern of shock induced seizures and impaired performance on a Hebb-Williams maze [56] but the differences cannot be attributed clearly to a behavioral teratogenic effect.

Antidepressants

Possible teratogenic effects of antidepressants on behavior have also been investigated. Iproniazid and isocarboxazid treated females produced offspring less susceptible to audiogenic seizures [80]. However, the results are subject to many of the same criticisms which have been made of other drug studies reviewed in this article. In addition, 1-benzyl-2-methyl-methoxytryptamine, an analogue of serotonin, and 5-hydroxytryptophan, the precursor of serotonin, when administered to pregnant females increased the activity of offspring in an open field and prolonged the time required to climb an inclined plane [81]. There were no differences on learning tasks but animals from 5-hydroxytryptophan treated females were more susceptible to audiogenic seizures. Apart from the issues already discussed, these data deserve some additional discussion. As a result of maternal deaths, the dose of 5-hydroxytryptophan was reduced from 100 mg/kg to 50 mg/kg; however, neonatal mortality was still high enough to necessitate the use of all survivors at weaning. Since the offspring in the other groups were selected non-systematically, it is possible that there were important differences in the genetic constitution of the 5-hydroxytryptophan group and the other drug and control groups. This point is relevant to the previous discussion [39] that genetic factors can be confounded with treatment effects in behavioral research.

Amphetamine and Delta-Nine Tetrahydrocannabinol

Although the amphetamines have been studied extensively, it is surprising that little is known concerning the effects of their prenatal administration on the behavior of offspring. Prenatal administration of d-amphetamine sulphate resulted in offspring less active at 21 days of age but normal at 13, 18 and 60 days [14]. Although there was no drug induced differences in rate of acquisition, performance level or rate of extinction on an operant conditioning task involving bar pressing at 27 days of age, performance in a T-maze with the mothers as a goal was enhanced by amphetamine at 16–18 days of age. Results are difficult to interpret because fostering procedures were not employed. Apart from chlorpromazine, the only other psychoactive drug of which the behavioral effects of prenatal administration have been adequately evaluated is delta-nine tetrahydrocannabinol [11]. The development of cliff-avoidance and visual placing was retarded in the offspring of treated mothers. No other reflexes seemed to be affected. At 9 days of age progeny of drug treated females were hyperactive in an open field. By 13 days, rearing, grooming and time to reach the periphery of the field had increased, and by 21 days, at weaning, the hyperactivity had disappeared. Cross fostering procedures had no effect on reflex ontogeny or behavior in an open field and indicate that the behavioral deficits might be related to prenatal drug treatment and not postnatal

factors. Since the rate of metabolism and excretion of delta-nine tetrahydrocannabinol in the adult rat might be prolonged and the metabolizing capacity of the neonatal rat is low [29], it is possible that these behavioral effects resulted from a direct action of the drug still present in the neonate. The decrease in drug induced effects with increasing age tends to support such an hypothesis.

Vitamin A

Vitamin A apparently has behavioral teratogenic effects [12]. Fostering procedures were utilized and the offspring of pretreated mothers exhibited poor performance in a swimming maze. Since swimming ability was not affected the poor performance was attributed to a learning impairment mediated prenatally. Unfortunately, observations were limited to 50–53 days of age and the duration of the deficit is unknown. Vitamin A also produces in the offspring of pretreated mothers an inability to inhibit responding on non-reinforced trials in an auditory discrimination learning task [43]. In a subsequent experiment [44] using a larger dose of vitamin A administered 3 days later during gestation, Days 17–18 instead of Days 14–15, experimental rats performed the auditory discrimination task as well as controls but exhibited slower rates of responding which was interpreted as a subtle motor impairment rather than a learning deficit.

Methylmercury

As a result of a growing concern over the effects of environmental pollutants, several recent studies have investigated the behavioral changes of prenatal exposure to methylmercury. Offspring of mothers treated with methylmercury during pregnancy have longer exploration latencies, defecate and urinate more, and show a greater incidence of backward locomotion in an open field and signs of neuromuscular impairment while swimming [71]. Although fostering procedures were not utilized in this experiment, some behavioral effects of prenatally administered methylmercury can be partially reversed by fostering drug exposed neonate mice to saline injected control mothers [70] which indicates that some of the deficits were due to postnatal influences. In an analogous experiment in chicks [61], methylmercury had no significant effects on open field activity and motor performance but did impair learning ability.

CONCLUDING REMARKS ON BEHAVIORAL TERATOGENS

Teratology was defined at the beginning of this review as the study of abnormalities arising during prenatal development. According to this broader concept of teratology, behavioral dysfunctions can arise from impairment at any stage of development and behavioral teratogenic deficits might thereby be induced by smaller doses of a drug than those necessary to produce morphological abnormalities. The results of several studies of the behavioral effects of prenatal exposure to methylmercury support such a notion. Methylmercury crosses the placenta and is concentrated in fetal tissue, particularly the central nervous system. The behavioral consequences of such action is clearly demonstrated by the mentally retarded children in the Minamata Bay area of Japan whose mothers ingested the fish contaminated with methylmercury during pregnancy [52,68]. In view of the results of animal studies [61,70], it seems likely that many people with minor symptoms or subclinical damage have gone undetected. Even large doses of methylmercury which affect the central nervous system do not cause overt signs of morphological teratogenesis. Similarly, chlorpromazine and delta-nine tetrahydrocannabinol do not produce morphological abnormalities in the developing organism although they produce behavioral deficits [11, 33, 57]. The only substance which produces behavioral deficits at low doses and overt morphological defects at higher doses is vitamin A [12, 16, 43, 44, 47]. While it seems clear that substances capable of producing central nervous system defects might only induce behavioral anomalies at lower doses, it has not been demonstrated that behavioral teratogens cause morphological abnormalities at high doses. For example, chlorpromazine does not produce morphological abnormalities with doses that are toxic to the fetus. Recent evidence indicates that prenatal and neonatal administration of chlorpromazine

TABLE 4

VARIABLES INFLUENCING PRENATAL DRUG EFFECTS ON BEHAVIOR

Variables	Comments
Drug type	Psychoactive agents are more likely to produce teratogenic effects on behavior. No available direct evidence.
Drug dosage	Multiple dose effects must be determined and the lethal dose must be considered in the determination of dose-effect relations.
Duration of drug administration	Chronic and acute drug treatments should be studied.
Developmental period of drug administration	A drug might have an effect at only some dose or doses and at some one or more critical periods in prenatal development.
Species and individual susceptibility	Individual and species differences in drug sensitivity vary considerably. Until test procedures are standardized, drugs with known pharmacological action should be studied in the most frequently utilized test species.
Fostering procedures	Unless fostering procedures are employed, effects of prenatal and postnatal variables are confounded.
Rearing conditions	Drug effects and environmental variables interact and must be considered in the experimental design.
Other laboratory routines	Age at weaning, diet, handling, various ambient stimulation and other differences in environmental stimulation can interact in the prenatal determination of effects on behavior. No available direct evidence.

affects turnover rates and concentrations of brain noradrenaline [74]. The possibility that substances which interfere with neurotransmitters and affect the metabolism of neurochemicals will produce behavioral teratogenic effects is very attractive. Although there is considerable face validity in such an assumption, there is little evidence to support such an hypothesis. Of the three substances, chlorpromazine, vitamin A and methylmercury, which produce teratogenic effects, only chlorpromazine is considered to be a psychoactive drug.

Although the evidence concerning prenatal drug effects on behavior is equivocal, sufficient data exist to indicate that this will continue to be a viable and significant area of research in the future. Present results demonstrate the complexity of the drug interactions with other variables. Table 4 summarizes the major variables and some of the interactions involved and is an indication of the possible direction of future research.

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