Prenatal Opioid Exposure and the Problem of Causal Inference

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Descriptions in the medical literature of human neonates undergoing withdrawal following maternal opioid drug abuse during pregnancy date to the latter part of the 19th century. Because of an extremely high mortality rate among infants showing severe symptoms, the major concern through the 1960s was with diagnosis, treatment, and management of the passively addicted newborn. In the United States, the opioid most commonly abused then, as now, was heroin.

Methadone was first synthesized by the Germans during World War II, and, following favorable preliminary findings of Dole and Nyswander in 1965 of its effectiveness in the treatment of the heroin addict, it was made available for wide-scale use In drug treatment programs. By 1975, there were some 70,000 to 80,000 heroin addicts in methadone maintenance programs throughout the country and a significant proportion were women of childbearing age. At the time, it was estimated that in New York City metropolitan area alone, 10,000 to 12,000 such women were enrolled in methadone programs, yet little was known of possible risk to the fetus and newborn. With the advent of methadone maintenance as an experimental treatment for heroin addiction in the early 1970s, attention turned to the question of reproductive hazard and developmental toxicity. The problem shifted from one of managing an infant whose mother abused heroin during pregnancy to concern over both the possible short- and long—term neurobehavioral effects in infants whose mothers were administered methadone as a medical treatment.

The clinical literature of the early 1970s consisted largely of the description of methadone effects in the neonate. Controversy subsequently emerged over reported differences between heroin and methadone. Some workers reported that methadone appeared to be less toxic to the newborn than heroin, whereas others found that it produced a neonatal withdrawal syndrome that was more severe, prolonged, and difficult to control chemotherapeutically. Methadone also appeared to be associated with a higher frequency of seizures and incidence of jaundice. (For review, see Householder et al. 1982.) A major obstacle to drawing meaningful conclusions from these observations has been the nature of the population under

study. Reviews of the literature have emphasized the difficulty of attributing, with any degree of confidence, later sequelae among the exposed offspring solely to prenatal opioid exposure (Householder et al. 1984). A large proportion of the women are from low socioeconomic levels and have had a long history of drug abuse with associated medical complications. Many have poor diets, are heavy smokers, and currently use marijuana, cocaine, barbiturates, tranquilizers, or alcohol—often in a pattern of polydrug abuse. Adding to the list of confounding variables, neonates undergoing withdrawal, depending on the severity, type, and duration of symptoms, may be administered paregoric, diazepam, chlorpromazine, or phenobarbital for several days to weeks after birth.

One consequence of these interpretive problems was that the mid— 1970s also saw several laboratories attempt to develop animal models of prenatal methadone exposure, The hope was that animal experiments would yield less ambiguous data on the developmental toxicity of methadone, independent of the myriad uncontrolled variables that muddied the clinical observations. (For a recent review of the animal and clinical literature, see Hutchings and Fifer, in press.)

Before turning to some of the methodologic and interpretive problems of animal tests of methadone, it may be useful to examine some terms and theoretical considerations that are important for understanding the effects of chemicals on developing organisms.

TERMINOLOGY AND THEORETICAL CONSIDERATIONS

The appendix appearing at the end of this chapter contains definitions of several common terms as well as a synopsis of pharmaceutical compounds known or suspected of being developmentally toxic in humans. These are divided into two categories: 1) agents that produce gross structural malformations such as thalidomide and alcohol; and 2) agents that produce toxic effects but not gross structural malformations. All of the opioids fall into this latter category. Although problems of nomenclature persist, the term “developmental toxicology” is sometimes used to refer to the general scientific discipline that is concerned with chemically induced perturbations in development, with teratogenesis or altered morphogenesis being a special case of toxic effects on the embryo. However, as a scientific discipline, teratology is concerned not only with malformations induced by exogenous agents but also with those that arise spontaneously or are of genetic origin. Therefore, the field of teratology cannot simply fall under the general umbrella of toxicology.

There are a few important points that need to be emphasized here, especially for those not well acquainted with the principles of teratology and developmental toxicology. Essential to an understanding of a developmental toxic effect is to appreciate that for a given class of compounds, such as ethanol or thalidomide, adverse effects are produced in the embryo by a mechanism that is qualitatively different from its pharmacological activity in the adult.

For example, the well-documented effects of ethanol in the adult— central nervous system (CNS) depression, tolerance, and physical dependence—are produced by ethanol per Se. Ethanol readily crosses the placenta and may indeed be the embryotoxic culprit. Alternatively, a host of other biochemical events are likely involved. For example, acetaldehyde—the major metabolite of ethanol—may be embryotoxic; or transport mechanisms of the placenta might be affected by acetaldehyde, alcohol, or both. The nutritional status of the mother, folic acid levels, blood pressure, and oxygen transfer may also be altered. Together, these would make up a complex sequence of pathogenic events that converge on a final common pathway of adverse outcome. Such a scheme of hypothetical mechanisms is shown in table 1.

Implicit in this scheme is the assumption that exogenous compounds that produce embryotoxicity do so by affecting some cells and not others—in other words the effects are selective. The vulnerable cells are considered to be endowed with a special sensitivity so that they are targeted by a particular compound, whereas other cells are resistant and remain unaffected (Skalko 1981). One of the major features of this differential endowment of resistance and sensitivity in the embryo is that these characteristics change, moment by moment, as the process of development continues.

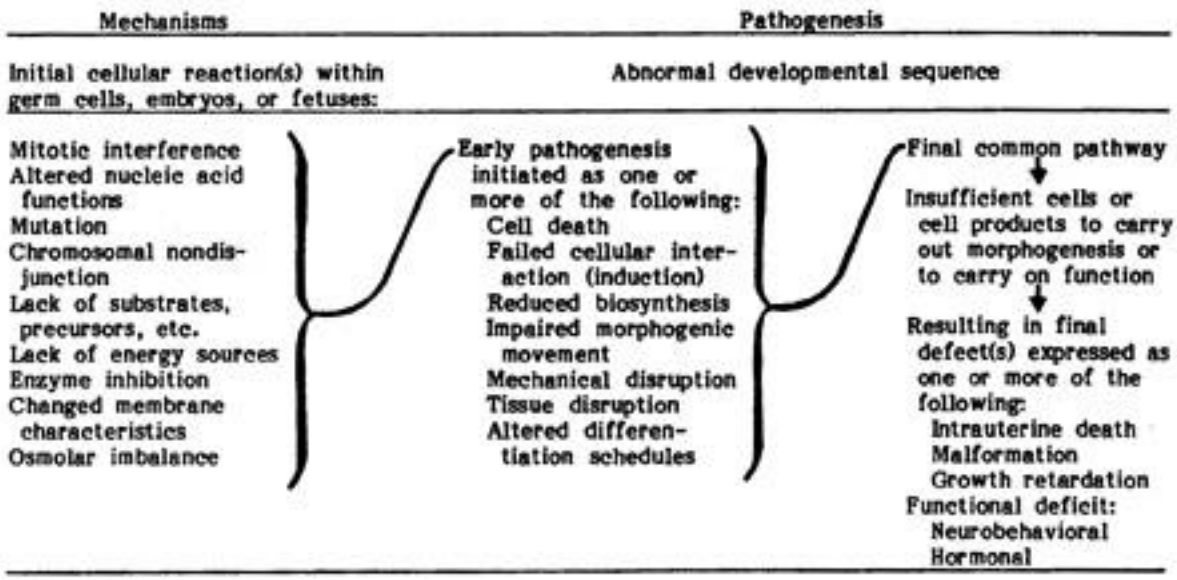
However, if it is shown that a compound crosses the placenta and enters embryonic circulation—and nearly every compound does—that fact tells us only that, and nothing more; its mere presence in the embryo does not mean that it is producing a toxic effect. Generally, there must be a special vulnerability before that substance can have an embryotoxic effect. Therefore, it is misleading to portray the embryo as having a kind of gossamer fragility that will be silently ravaged by all alien invaders. Rather, the evidence supports the view that the embryo has multiple lines of defense, is a feisty combatant, and, even if knocked down and out, has enormous powers of recuperation and repair. Without belaboring this point, let me simply point out that despite a colossal increase in industrial chemicals, environmental pollutants, and pharmaceuticals since World War II, the frequency of birth defects appears to have remained relatively stable.

DOSE-RESPONSE RELATIONSHIPS

Though dose—response relationships are one of the most critical issues in developmental toxicology, they are too often misunderstood, oversimplified, or simply neglected. Because studies of developmental toxicology involve two mutually interacting biological systems—the mother and fetoplacental unit—dose—response relationships are exquisitely complex and involve interactive, pharmacological, and toxic effects in the mother and offspring. An appreciation of the problem may be developed with a few examples. For this purpose, the term “toxicity” will be used here in the generic sense; a more detailed description would require a far more precise specification of response selectivity, target tissues, target organ systems, functional impairment, etc.

TABLE 1

Schematic Summary of Initial Cellular Reactions and Different Types of Pathogenesis into a Final Common Pathway.



Before discussing dose-response interactions in the maternal/ fetoplacental unit, two points should be made about variations in response in the dam and offspring. First, a phenomenon frequently overlooked in developmental toxicology studies is that in the rodent, the physiological state of pregnancy itself can cause a significant shift in the dose response of the mother. For example, with methadone, the acute LD—50 dose is dramatically lowered during pregnancy as compared with the nonpregnant animal—an effect that appears to be related to reduced metabolism in maternal liver. The result is that doses easily handled by the nonpregnant animal may be lethal in the pregnant animal. Clearly, when one is first establishing a dose range for study in a developmental toxicology experiment, the values must be selected on the basis of the response of the pregnant animal.

The second point to make is that below a dose level that is lethal to the embryo, there may be two embryotoxic responses, each with their respective thresholds. This is depicted in figure 1, showing that as dose increases above the "no observable effect level" (NOEL), the first embryotoxic response is an impairment in function, followed by a second threshold after which gross structural malformations are produced. Both vitamin A and salicylate in the rat are good examples of teratogens that produce functional effects at a lower dose range and dysmorphogenesis at a higher dose range (For review, see Hutchings 1983.)

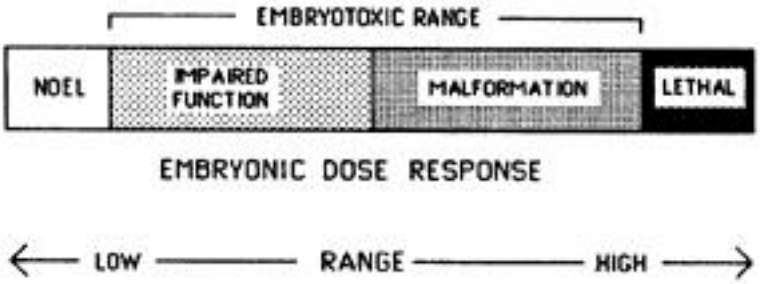


FIGURE 1
Dose-Response Profile of Toxic Effects in Embryos as Dosage of a Toxic Compound Increases

To illustrate dose-response effects in the maternal/fetoplacental unit, let us examine a few hypothetical dose-response profiles. These attempt to illustrate different types of relationships and interactions between the dose response of the mother and embryo. The general scheme, as shown in figure 2, depicts a maternal dose—response function in the lower bar; as dose is increased from subpharmaco-logical levels through the pharmacological range of the compound, there is a corresponding increase in toxicity culminating in death.

The top bar depicts the embryonic dose—response, ranging from the NOEL to embryolethality, as a function of maternal dose response.

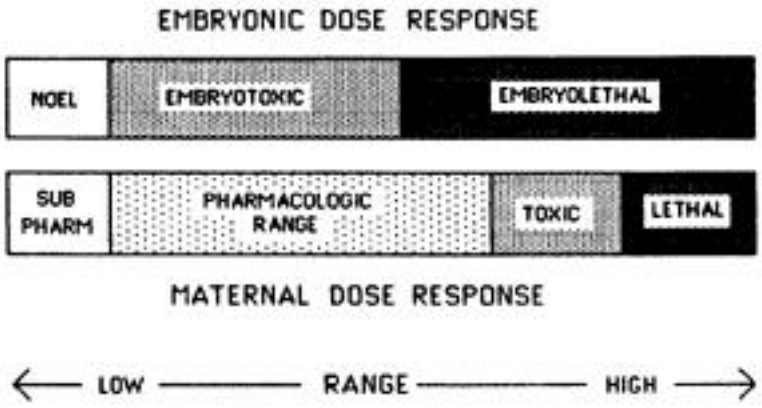


FIGURE 2
Dose-Response Profile of Toxic Effects in Maternal Organisms and Embryos as Dosage of a Toxic Compound Increases—Profile A

The hypothetical profile shown in figure 2 depicts a compound similar to thalidomide in humans. This shows that subpharmacologic maternal levels correspond to the NOEL in the embryo. However, at subtoxic, pharmacological levels in the mother, the compound is highly embryotoxic. In the case of thalidomide, the embryotoxic response is the occurrence of altered morphogenesis. Another compound with the same sort of profile and embryotoxic response in humans is the vitamin A derivative, isotretinoin. However, such compounds are far more the exception than the rule in animal studies of developmental toxicity. And to add to the complexity, thalidomide is not teratogenic in the rat, but vitamin A is. With both compounds, however, humans appear to be the most sensitive species.

A common type of profile encountered in animal studies is shown in figure 3. This shows that within the pharmacological range of the compound, and at levels that are not toxic to the mother, there is no embryotoxic response. Embryotoxicity is only seen at levels that produce maternal toxicity. One example in the rat is phencyclidine (PCP), which has been shown to be teratogenic, but only at doses that are highly toxic to the dam. In the case of PCP, we administered two doses that were pharmacologically potent as measured by behavioral effects in the dam (5 or 10 mg/kg) but of relatively low maternal toxicity based on maternal weight gain. Yet, we observed normal birth weights and not postnatal behavioral effects on two independent measures (Hutchings et al. 1984).

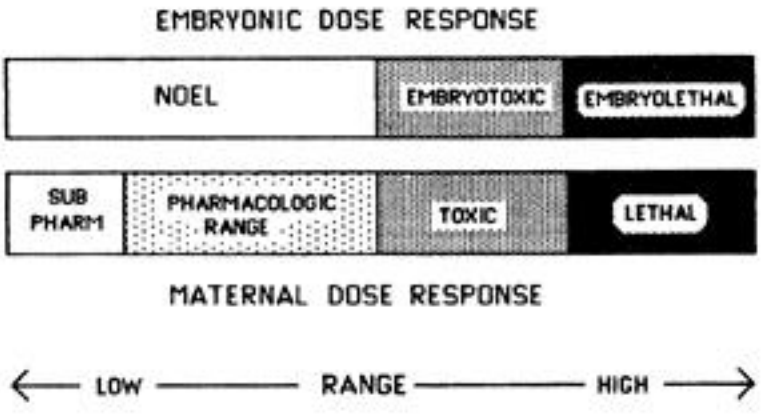


FIGURE 3
Dose–Response Profile of Toxic Effects in Maternal Organisms and Embryos as Dosage of a Toxic Compound Increases—Profile B

PRIMARY VERSUS SECONDARY EFFECTS

What should be eminently clear from these profiles is that dose-response relationships, though complex, are critical for a meaningful description and understanding of effects. Moreover, it is essential that every study include some measure of maternal dose response. This is of particular importance when embryotoxicity is found only at doses that produce maternal toxicity. Under these circumstances, it is important to determine whether the effects produced in the offspring are primary effects of the compound or secondary to maternal toxicity. For example, CNS depressants can suppress maternal breathing and in turn produce fetal anoxia and brain damage; other compounds produce reduced food intake and/or decrease fluid intake with subsequent undernutrition or dehydration and electrolyte imbalance. In short, if we are to make any sense of the embryotoxic effects of a particular compound, it is important to know if these effects are produced only at doses that make the mother sick or also at doses that show no maternal toxicity. This is the first step in trying to make some judgment about the reproductive hazard of the compound.

PRENATAL METHADONE—PROBLEMS OF PHARMACOKINETICS

The problem of maternal and offspring dose response applies equally to the opioid compounds, but these are further complicated with the phenomena both in the mother and in the offspring of tolerance, physical dependence, and abstinence. These properties present serious problems of management for the clinician working with opioid-dependent mothers, but pose for the scientist studying animal models intractable problems of methodology and interpretation. One result has been a rather heated debate among researchers as to

what constitutes an adequate perinatal animal model (see Sparber 1983 and accompanying critiques).

When we first started our work in 1972, we were unable to find any reliable data on animals and, instead, utilized the available human observations. It was clear from the Dole and Nyswander studies of the late 1960s that the 80 to 120 mg/day dose of methadone easily "held" their patients until the next day's dose and the current estimate of the half—life of methadone in humans is about 24 hours. In the literature of the early 1970s, and before levo-alpha-acetylmethadol (LAAM) came on the scene with any prominence, methadone was always compared with morphine and characterized as having a much longer duration of action. When we began administering methadone to pregnant rats, we were impressed not only with its relative potency as compared to morphine but also with our finding that it took twice as long for the animal to develop tolerance to it. To give some idea of the difference, Davis and Ling (1972) administered an initial dose of 15 mg/kg of morphine subcutaneous early in gestation, followed by 5 mg/kg increments every 2 days, achieving a final dose of 45 mg/kg by late pregnancy. This regimen produced tolerance and no maternal deaths. With methadone, we found that an initial oral dose of 10 to 15 mg/kg exceeded the LD 50 and it was necessary not only to lower the Initial dose but also to allow more time for the pregnant dam to develop tolerance. To achieve the same result with methadone that Davis and Ling did with morphine, we had to start with an initial dose of only 5 mg/kg and increase the dose by only 2.5 mg/kg every 4 days. With this regimen, we achieved a final maintenance dose of 10 mg/kg without death or significant maternal toxicity.

In collaboration with Dr. Tove Rosen, we had determined a dose-response methadone blood level in the mothers and offspring 60 minutes after their last dose, just prior to parturition (Hutchings et al. 1976). At the time, we assumed that the compound was persisting at tissue levels that produced physical dependence in the mothers. We based this on the report of Misra et al. (1973) who found that the half-life was about 1.4 hours for tolerant animals. However, they also found that measurable quantities of methadone persisted in brain and other tissues up to 3 weeks or longer, even though no measurable amounts of drug were present in plasma after 24 hours.

We would come to appreciate, particularly after the discovery of opiate receptors, that these findings of persistent quantities of methadone derived from whole brain must be interpreted with great caution; that It is important to distinguish concentrations that are nonspecifically tissue bound and not necessarily producing any pharmacological effects from concentrations that are, in fact, acting on receptors.

Thus, it appears that our dosing regimen, while clearly producing tolerance in the dam, probably did not maintain a state of physical dependence over 24 hours. Given the longer duration of action of methadone in the pregnant animal, it is reasonable to assume a half-

life of 3 to 5 hours. Sparber (1983) makes an important point in stressing that if future animal models of perinatal opioid exposure are to include the feature of physical dependence, they will have to employ a method of drug administration that maintains sufficient blood levels. One caveat, however, is that if such blood levels are maintained, the tradeoff may be a high neonatal mortality. And if the researcher has to administer an opioid or other drugs to reduce fetal infant withdrawal symptoms in rats, as clinicians must treat passively addicted babies with life-threatening symptoms, there may not be much gained by studying an animal model.

On the other hand, perhaps physical dependence is not necessary to produce some sort of embryotoxic response. For example, except for the tolerance and physical dependence that might be produced by a single dose of ethanol, these conditions do not appear necessary to produce teratogenic effects in the mouse. Randall and Anton (1984) produced both limb and kidney defects with only one acute dose of ethanol during embryogenesis. Again, the questions of mechanism and what is necessary and sufficient to produce a particular offspring effect remain. Are sustained tissue levels necessary or will a single or a few daily pulses of the compound during a sensitive period be sufficient to cross some threshold or perturbate a developmental pathway?

For example, a feature of methadone—exposed human infants of interest to us is the prolonged abstinence found to persist in some infants until around 4 months of age. Characterized by CNS arousal and sleep disturbance, it had been suggested that this may have resulted from the slow clearance of the compound by the neonate. We developed a behavioral sleep paradigm for the preweanling rat and showed that prenatal methadone exposure—using the dosing regimen described above—severely disrupted the rats' sleep pattern during the second and third postnatal week of life. As in humans, the effects were transitory and disappeared by 30 days of age (Hutchings et al. 1979). Given our rat mothers were probably not physically dependent, we tentatively concluded that this sort of exposure is sufficient to produce an opioid—induced rebound hyperexcitability in the offspring. Moreover, a radioactive tag study indicated that the compound did not persist in any significant amounts in offspring brain beyond the first several days after birth (Levitt et al. 1982). Further, the administration of naloxone failed to elicit any detectable withdrawal symptoms. So, we produced under experimental conditions a rat model of what may be occurring in human infants and concluded that this sort of effect persists long after the compound is cleared from tissue.

CONCLUSION

The combined human and animal data lead to the unequivocal conclusion that a variety of compounds can produce extremely subtle to severe damage in the developing CNS, with functional effects ranging from minor impairments of attention, impulse control, and activity to frank mental retardation. As with birth defects, these deficits may also be of genetic origin or arise spontaneously.

Therefore, in the clinical situation, one must take care to distinguish the primary toxic effects of a compound from secondary environmental—interactive effects and, in addition, consider that a genetic disorder might also contribute to long—term clinical outcome.

For example, there is no question that the opioids produce neonatal abstinence characterized by increased CNS arousal. Clinical observations suggest that this altered state results in a newborn that is less alert and less attentive with the result that the mother— infant interaction is compromised. This, in turn, may lead to secondary impairments of both cognitive and emotional development that emerge during the first year of life. (For a detailed discussion of possible effects on mother-infant interaction, see Hutchings and Fifer, in press.) Additionally, if a genetically transmitted behavior disorder of minimal brain dysfunction is associated with or contributed to a mother becoming a drug abuser in the first place, the clinical picture in her offspring may be even more complex. This could include a mixture of neonatal abstinence effects and the postnatal sequelae described above, and a genetically transmitted behavior disorder of attention deficit and impulse disorder giving rise to school failure in middle childhood, and drug abuse emerging in adolescence. And on it goes to the next generation.

It is these sorts of complex multifactorial effects that we must appreciate and that animal studies might help sort out. What must first occur, however, is the development of more precise animal research techniques and, with respect to drugs of abuse, several laboratories will have to study the same compounds from a basic research perspective in order to generate a reliable database and consensus of effects. Most important, the animal findings must be compared with the clinical observations. This mutual tradeoff cross-validates both the human and animal findings in a way that is impossible when the same observations are made independently and in isolation. The result could be a powerful and meaningful set of comparative observations that relate prenatal drug effects to a general set of embryotoxic and behavioral principles.

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APPENDIX

ADVERSE EFFECTS OF DRUGS DURING PREGNANCY: OUTLINE OF COMPOUNDS THAT ARE DEVELOPMENTALLY TOXIC IN MAN

Developmental Toxicology—the study of chemically induced alterations in the normal sequence of developmental processes.

Teratology—the study of the causes, mechanisms, and sequelae of perturbed developmental events in organisms that undergo ontogenesis. Traditionally, the study of abnormal morphogenesis.

Congenital Malformations—structural abnormalities of prenatal origin that are present at birth and that seriously interfere with viability or physical well—being.

Behavioral Teratology—an integration of developmental toxicology and teratology with experimental psychology—is primarily concerned with the study of neurobehavioral changes that result from exposure of germ cells, embryos, fetuses, and immature postnatal individuals to a variety of environmental disturbances and events.

Approximately 50% of human conceptuses fail to reach term and perhaps as many as half of those lost are structurally abnormal. Approximately 3% of newborns have one or more significant congenital malformations at birth and, by the end of the first postnatal year, an additional 3% are found to have developmental abnormalities. An additional group, whose size cannot be estimated, is born with functional abnormalities of the nervous, respiratory, gastrointestinal, and immunologic systems. Some unknown proportion of all these effects may be due to environmental insult during prenatal life.

Causes

Little is known of specific causes. Estimated that 10% to 15% of all human congenital malformations are due to environmental agents and another 10% to 15% to hereditary factors, such as gene mutations and chromosomal aberrations. The remainder are considered to result from unknown causes and complex interactions between multi-factorially determined hereditary susceptibilities and environmental factors that precipitate abnormal developmental sequences within the conceptus and its associated membranes.

Drugs/Chemicals Producing Malformations In Man

Thalidomide—one of the most potent teratogens known to man. Produces array of birth defects; most dramatic and debilitating is severe limb reduction or phocomelia.

Ethanol—in amounts consumed alcoholically (approximately 6 ounces pure ethanol/day). Produces fetal alcohol syndrome (FAS) characterized by pre— and post-natal growth retardation, developmental delay, craniofacial anomalies, joint defects, and mild to severe mental retardation. Of mothers consuming these large amounts of ethanol, only about 10% to 15% give birth to infants with frank symptoms of the FAS.

Aminopterin—folic acid antagonist used illegally as an abortifacient. Produces embryonic and fetal death and varied malformations in survivors.

Diethylstilbestrol—a synthetic nonsteroidal estrogen. Produces vaginal cancer in female offspring during teen years. Possible effects on gender—related behavior.

Vitamin A—compounds in the vitamin A family, including palmitate and retinoic acid, are potent teratogens in high doses. One form— isotretinoin—marketed as “Accutane,” a prescription drug for the treatment of cystic acne, has been documented as a human teratogen. Exposure causes CNS malformations and defects of the external ear. It was marketed with clear and explicit warning to physicians and consumers of its teratogenicity.

Hydantoin—anticonvulsant; strongly suspected of causing a fetal hydantoin syndrome characterized by mild to moderate growth deficiency, reduced brain size, short nose with anteverted nostrils, long philtrum and bowed upper lip, and small distal digits with unusually small nails. Data from relatively small numbers suggest mild to moderate mental retardation.

Trimethadione—anticonvulsant; suspected of causing a fetal trimethadione syndrome characterized by developmental delay, speech difficulty, V-shaped eyebrows, low-set ears with anteriorly folded helix, palatal anomaly, and irregular teeth. Of few cases reported, mild mental retardation suggested as component of syndrome.

Lithium—some evidence of increased risk of cardiovascular malformations. Data still being collected in the Register of Lithium Babies.

Drugs/Chemicals Producing Neurobehavioral Effects In The Absence Of Gross Structural Malformations

Several classes of compounds—tranquilizers, stimulants, hypnotics, analgesics—are generally not teratogenic in animals or man, but may produce long-term neurobehavioral effects. The mechanism of their embryotoxicity remains unknown, but early pathogenesis and the final common pathway probably involve biochemical, rather than gross morphological, effects. Few of these are well documented in man.

Barbiturates—used as an anticonvulsant or may be abused. Produce a neonatal withdrawal syndrome characterized by hyperactivity, restlessness, disturbed sleep, tremors, sneezing, hiccuping, vasomotor instability, hyperphagia, vomiting, and diarrhea. Some infants symptomatic for up to 6 months—no long—term follow-up.

Opioids—Heroin, Methadone—high frequency of abuse. Methadone used to treat heroin addiction. Neonatal withdrawal syndrome similar to that described for barbiturates. Symptoms characterized by CNS excitability may persist until 4 to 6 months of age. Follow-up to 5 years suggests risk of Attention Deficit Disorder.

Amphetamine—diet control, abuse. Suspected of producing neurobehavioral effects based on animal studies. No human data available.

Phencyclidine—drug of abuse (angel dust). Suspected of producing adverse effects based only on case study reports. Animal data inconclusive.

Marijuana—drug of abuse. No evidence of teratogenicity in man. In heavy users, some neonatal irritability around the time of birth; symptoms disappear by 30 days of age. Long-term follow-up did not find any persistent effects detectable during preschool years.

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