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Current Research on the Consequences of Maternal Drug Abuse

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Introduction

Theodore M. Pinkert, M.D., J.D.

The study of the consequences of maternal drug abuse represents one of the most compelling areas of research in the drug abuse field. The potential victims of this problem have no say in the maternal behaviors, which may place them at risk. Therefore, it is incumbent upon the research community to attempt to delineate the potential hazards to the fetus, the newborn, the infant, and the child, so that deficits may be identified in sufficient time to compensate, where possible, with specific treatment interventions.

The purpose of this volume is to focus attention on recent studies of the effects of maternal substance abuse on offspring. The material presented includes reviews of animal data, as well as the results of large interdisciplinary clinical studies, which were originally presented on September 24th and 25th, 1984, at a National Institute on Drug Abuse Technical Review sponsored by the Divisions of Preclinical and Clinical Research. (The papers presented in the preclinical portion of this meeting will be published in a separate volume, entitled Prenatal Drug Exposure: Kinetics and Dynamics.)

In the opening chapter of this monograph, Dr. Donald Hutchings defines the field of study known as behavioral teratology and provides a conceptual and historical framework that facilitates an understanding of what inferences may reasonably be drawn from both the animal and clinical literature. His studies in behavioral teratology integrate developmental toxicology and teratology with developmental psychology and focus on a variety of neurobehavioral changes that are crucial to the development and maturation of the individual.

The next chapter, by Dr. Ernest Abel, elaborates on the difficulties inherent in attempting to understand the interactive nature of the maternal and fetoplacental units. Through a careful review of his own work, and that of others, he provides important insights into the limitations and strengths of both

epidemiological and clinical studies. He also points out the value of animal studies in providing the methodological rigor necessary (in combination with the human studies) to establish the most convincing demonstration of causality when adverse pregnancy outcomes are suspected from one or more chemical agents. Then he reviews the effects of marijuana (A^5—THC) on pregnant animals and their offspring and discusses both the results and the methodological pitfalls to be avoided in these studies.

In the following chapter, Dr. Nancy Day and her colleagues analyze the problems faced by clinical researchers in obtaining reliable and valid results using the instruments and techniques currently employed in prenatal research. The two major challenges identified are: (1) When questionnaire formats are used, do subjects understand the questions and report accurately? and (2) How does one obtain accurate measures of complex and changing events (substance abuse patterns) for specific time periods which coincide with different stages of fetal vulnerability, so that the prediction of biological effects can be made with a high degree of probability?

In the same chapter, the authors suggest techniques for eliciting accurate patterns of maternal drug intake and describe how these techniques are implemented in their current research on the effects of maternal marijuana and alcohol use during pregnancy. The value of the assessment instruments they have developed is that they measure both the quantity and frequency of drug intake in a manner that more closely resembles the way subjects naturally organize their own memory of substance use——in terms of both language and sequence.

The authors also elaborate other techniques which are designed to overcome accuracy problems created either by the patient’s deliberate misrepresentation of past drug intake or by their flawed recall of remote events. These techniques include the bogus pipeline, which attempts to overcome misrepresentation of drug use, and the breakdown of prepregnancy and first trimester events into specific time intervals to aid in more accurate recall of the quantity and frequency of drug use.

The next chapter, by Katherine Tennes and colleagues, describes the results of a large clinical study on the effects of prenatal marijuana exposure. Participating women responded to structured questionnaires about themselves, their habits (substance abuse, nutritional, etc.), and the habits of the father, if known. After delivery, infants were examined for birth measurements, physical anomalies, and muscle tone, and the Brazelton Neonatal Behavioral Assessment Scale was administered. At 1 year of age, the infant's physical parameters were reexamined and they were evaluated on the Bayley Infant Scale of Mental and Motor Development and Behavior Checklist.

One finding of this study is that maternal marijuana use

decreased from previous levels of consumption as the pregnancy advanced. At delivery, no significant differences in 12 indices of obstetrical complications were detected that could not be attributed to parity, or to the amount of pain—relieving medication administered (although users of marijuana required more pain—relieving medication than nonusers). Heavy marijuana use was found to be associated with an increase in male over female offspring, but with a decrease in infant length at birth. No increase in teratogenicity, or decrease in APGAR or Brazelton scores, was associated with prenatal marijuana use. No significant differences were detected in physical measurements or Bayley scores at 1 year.

The authors point out that some of their outcome data are in disagreement with previous clinical studies, and they explore possible reasons for the difference in results. In addition, the authors caution that studies examining the effects of maternal marijuana use on more complex cognitive functioning in offspring have yet to be performed.

In the next chapter, Dr. Peter Fried reports on another major clinical study of maternal marijuana use, but in a population with significantly different demographics than the previous study. Among his findings were that gestation was shortened by maternal marijuana use and that there were neurobehavioral effects, as measured by altered visual responses and changes in state regulation (heightened tremors and startles), in the newborn. Although not yet completed, studies employing neuro- opthalmological and electrophysiological testing suggested that prenatal exposure to marijuana might delay maturation of the visual system.

In agreement with the Tennes study, there were no differences in rates of miscarriage, obstetrical complications. APGAR scores, or teratological effects between the marijuana—using population and the comparison group. (Studies of both animal and human populations which suggest different results are presented and discussed.) In addition, data collected from developmental tests administered to the infants at 6—month intervals after birth failed to discriminate infants of marijuana—using mothers from either matched controls or the general population. Dr. Fried cautions that it is not at all clear whether neurological findings present at birth are transient, or compensated for by maturation. He suggests the possibility that the tests currently used to measure developmental neurological disturbances in the newborn and neonate may not have sufficient discriminatory sensitivity to detect subtle differences that may remain in the older, marijuana—exposed infant or child.

In the next chapter, Drs. Rosen and Johnson review their findings on the prenatal effects and postnatal consequences to the offspring of methadone—maintained mothers. Their results include analyses of methadone’s effects upon the neonatal and infant periods of development, and they present recent data from their

oldest cohorts of children, who are now in the 4— to 7—year—old age range.

Among the effects on offspring of methadone—maintained mothers was a higher incidence of small—for—gestational—age infants, and infants below the third percentile in head circumference. In addition, the maternal methadone dose and the length of time on methadone had a positive correlation with a higher incidence of obstetrical complications, decreased birth weight, and decreased infant performance on certain Brazelton measures. Neurological and developmental testing continued to reveal significant differences between methadone—exposed children and a comparison group through the 36—month evaluations. These differences included an increased incidence of abnormal reflexes, nystagmus, infections, abnormal muscle tone, and delayed developmental milestones among the methadone—exposed infants.

As the children reached school age, those who did poorly neuro— developmentally at earlier evaluations continued to do poorly. A trend toward lower scores in receptive language evaluations was evident among the methadone—exposed children. Their neurological evaluations demonstrated a higher prevalence of abnormalities of fine and gross motor coordination, poor balance, decreased attention span, hyperactivity, and speech and language delays. There was also a higher incidence of referrals for behavioral and academic problems. However, as the comparison group of children (a population selected from women in a low socioeconomic status similar to that of the methadone—maintained mothers) approached school age, they too began to show poor performance in testing. This raises important questions about the interaction between prenatal environments and the socioeconomic status of the child in the postnatal environment.

In the following chapter, Dr. Ira Chasnoff compares the effects on offspring of the maternal use of narcotic versus nonnarcotic substances. Unique in this group of reports, his study is an attempt to distinguish the in utero effects of narcotic use (methadone and pentazocine/tripelennamine groups), from non— narcotic drug use (including a small group of women whose primary drug of abuse was phencyclidine EPCPJ, and another group with mixed sedative/hypnotic exposure, including marijuana).

Although the number of subjects in each group was small, infants exposed in utero to narcotic substances showed fairly consistent decreases in birth weight, length, and head circumference from both the sedative/hypnotic group and the comparison group. The methadone—exposed group of neonates also demonstrated deficits in auditory orientation and motor maturity. Infants exposed to both narcotic and nonnarcotic drugs showed decrements in state regulation, and infants exposed to PCP showed increased state liability and poor consolability when compared to all other drug—exposed groups. As was manifested in the preceding Rosen and Johnson material, the scores of the comparison group of

infants began to fall away from the normal range toward that of the drug—exposed infants by 24 months of age.

In the last chapter, Dr. Barry Zuckerman reviews the developmental consequences of maternal drug use. He describes the features compatible with the fetal alcohol syndrome and discusses research which suggests that these features may reflect a final common pathway of numerous agents (Including drugs of abuse), rather than a specific teratogenic effect of alcohol.

In addition, the author stresses the importance to developmental outcome studies of repeated assessments over time, and he suggests the application of newer physiologic techniques such as evoked responses, Brain Electrical Activity Mapping (BEAM), Positron Emission Tomography (PET Scan), and Nuclear Magnetic Resonance (NMR), to enhance our understanding of the effects of prenatal drug exposure.

In summary, much remains to be learned about the specific developmental effects of a variety of commonly used and abused drugs. The research community has not yet exhausted the potential for the development and application of new testing techniques and Instruments that will help us to identify the scope of subtle cognitive and motor effects caused by prenatal drug exposure. Beyond these refinements lies the possibility of understanding the particular mechanisms through which these drugs exert their effects. It is the hope of those who participated in the conference that what lies herein will stimulate research into the many unanswered questions In this area.

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Prenatal Opioid Exposure and the Problem of Causal Inference

Donald E. Hutchings, Ph.D.

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.

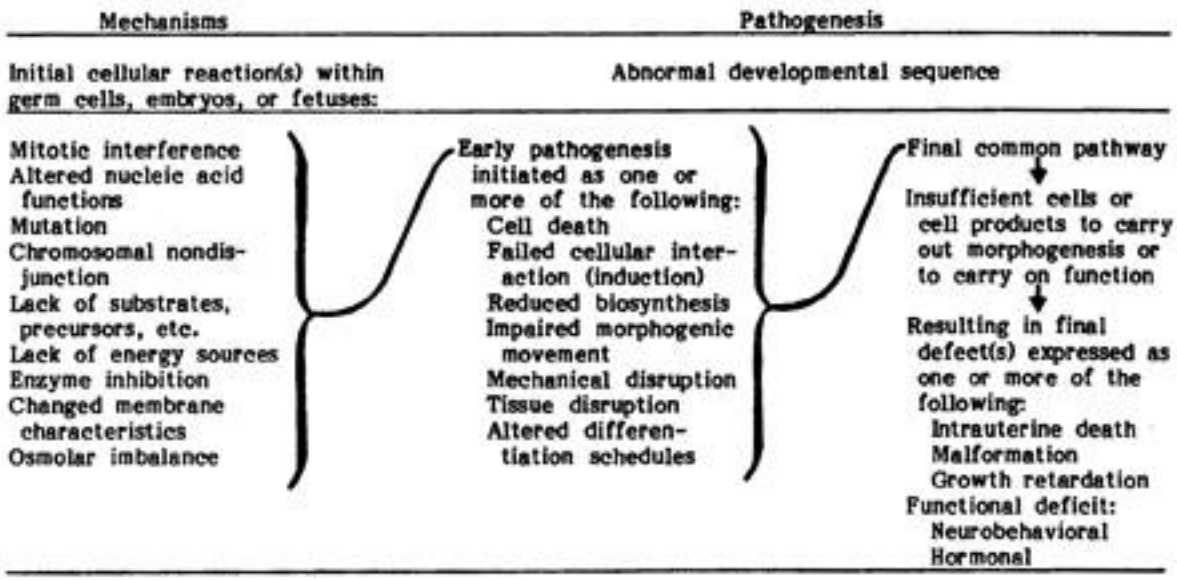
However, if it is shown that a compound crosses the placenta and enters embryonic circulation—and nearly every compound does—that fact tells us only that, and nothing more; its mere presence in the embryo does not mean that it is producing a toxic effect. Generally, there must be a special vulnerability 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.)

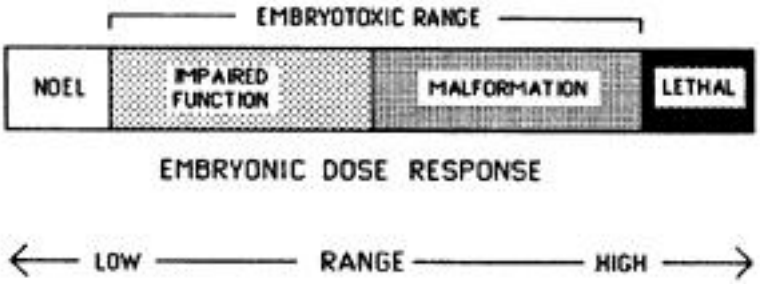


FIGURE 1
Dose-Response Profile of Toxic Effects in Embryos as Dosage of a Toxic Compound Increases

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.

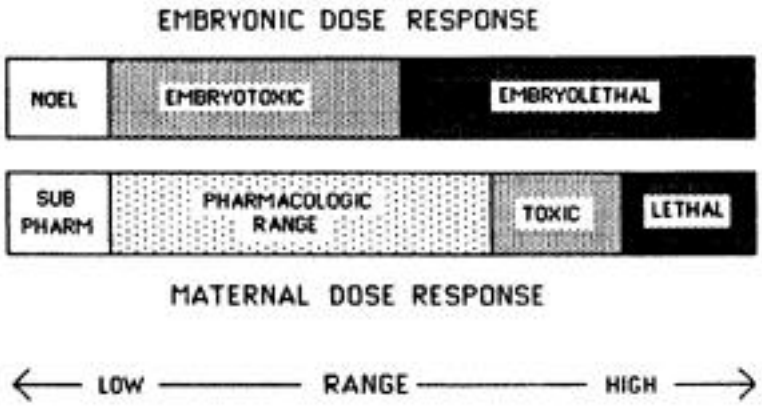


FIGURE 2
Dose-Response Profile of Toxic Effects in Maternal Organisms and Embryos as Dosage of a Toxic Compound Increases—Profile A

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).

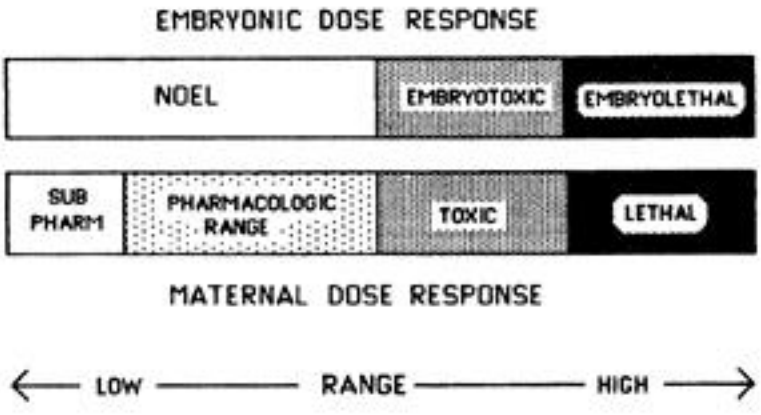


FIGURE 3
Dose–Response Profile of Toxic Effects in Maternal Organisms and Embryos as Dosage of a Toxic Compound Increases—Profile B

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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Effects of Prenatal Exposure to Cannabinoids

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Marijuana is among the most widely used psychoactive substances in the Western world. In the United States, about 255 of Americans 18 to 25 years of age use it to some degree (U.S. Department of Health, Education, and Welfare 1980). Considerable marijuana use also appears to be occurring among pregnant women (Sokol et al. 1980; Hingson et al. 1982; Linn et al. 1983; Fried et al. 1984; Gibson et al. 1983). It is only in the last few years, however, that critical attention has been focused on the possibility that these substances can cause birth defects and postnatal behavioral aberrations, although delta—9—tetrahydrocannabinol (6^9—THC), the principal psychoactive ingredient in marijuana, is known to cross the placenta (Abel 1983). Before examining the data relevant to this issue, the first part of this review will examine some of the general methodological considerations which should be kept in mind in evaluating research in this area.

CLINICAL AND EPIDEMIOLOGICAL STUDIES

Since experimental administration of drugs to pregnant women is unethical, evaluation of potential teratogens is limited to clinical observations or epidemiological investigations. Although clinical reports can be of considerable importance in alerting physicians and health care providers to possible agents causing abnormal development, they are often difficult to evaluate. For example, two early clinical reports of malformations in children born to marijuana users (Hecht et al. 1968; Carakushansky et al. 1969) were inconclusive since the mothers of these children were users of other drugs as well.

When clinical reports are followed by epidemiological studies involving larger numbers of patients, a better appreciation of incidence and causation is possible. Such epidemiological studies can be divided into two types, retrospective and prospective, each of which has its own strengths and shortcomings.

In most retrospective studies, information from large numbers of' cases is obtained from hospital records. However, such records are often inadequate or incomplete, thoroughness of reporting varies widely, and criteria for assessment of anomalies may also vary. In contrast to retrospective studies, prospective studies carefully establish criteria and protocols for maternal histories and examination of infants in prenatal health clinics. However, women who are usually most seriously at risk for giving birth to infants with drug—related anomalies may not attend prenatal health care facilities and, therefore, do not participate in prospective studies, resulting in underestimation of whatever problem is being investigated. Because prospective studies are so rigid in their design, they also are less flexible in allowing for changes to be incorporated as new information is obtained. Also, prospective studies cannot anticipate knowledge. For example, in the U.S. Collaborative Perinatal Project (Heinonen et al. 1977) which prospectively evaluated 55,000 consecutive births, no information was obtained with respect to maternal marijuana consumption because, at the time of the original protocol, marijuana was not a suspected teratogen.

In addition to these general problems, epidemiological studies are limited to the observations evident at the time of examination.

Even when diagnostic criteria have been standardized so that statistical evaluation is possible, the number of cases may be too few to derive any "significant" results. Diagnoses also may not be "blind" to the history of drug use, resulting in a higher than normal likelihood of some association simply because it is being actively searched for. A third possibility in epidemiological investigations is confounding." Any specific drug ingested by a pregnant women is but one of a multitude of possible pregnancy risks (cofactors) along with the use of other drugs, general health, age, and exposure to environmental pollutants. While complex statistical procedures may be used to "control" or "adjust" for various known factors to support suspected links between agent and outcome, there are limitations to such procedures and many risks are still unknown. Consequently, confounding is always a possibility.

Epidemiological studies may document associations between suspected teratogens and adverse pregnancy outcomes, but they cannot demonstrate causality convincingly. To demonstrate causality, there is a need for better control and isolation of potential factors resulting in anomalies. At present, the best means of achieving such methodological rigor is through studies in animals, although such studies carry with them their own intrinsic problems.

STUDIES IN ANIMALS

Considerable attention has been devoted to “animal models” for duplicating various defects allegedly resulting from prenatal exposure to particular drugs. Such studies can be of special interest because they allow manipulation of variables that would otherwise be impossible to control in humans.

A major advantage of animal studies is the ability to perform dose—response evaluations. A given dose of a drug may or may not be teratogenic. If the dose does not produce observable defects, one cannot conclude that it is not teratogenic, since the tests may have been too insensitive or the dose may simply have been too low to produce an effect.

It is also advantageous to determine drug levels actually in the blood. In some cases, drugs such as alcohol are readily absorbed from the intestine or areas of injection. Other drugs such as marijuana are water—insoluble and except for inhalation are poorly absorbed from sites of administration. Thus, some doses may produce little or no effect because they do not achieve levels in the blood required for an effect to occur. If levels of drug in the blood are known, there is also the advantage of being able to extrapolate to humans somewhat more heuristically than is the case when extrapolating on the basis of dose per body weight. At present, blood alcohol levels are relatively easy to determine, whereas blood levels of 6^{9}—THC, the principal psychoactive ingredient in marijuana, cannot be determined in most laboratories because of lack of equipment and sophistication.

ROUTE AND METHOD OF ADMINISTRATION

A basic issue involving administration of cannabinoids into the body is route of administration. In humans, the principal route by which marijuana is taken into the body is via the lungs in the form of smoke. In such cases, only about 50%to 75% of the A^{9}—THC present in the smoke is absorbed (Manno et al. 1970; Mikes and Waser 1971) and various transformations of cannabinoids occur due to heat—induced carboxylation (Kuppers et al. 1975). The other route by which marijuana is taken into the body by humans is by mouth. About 3 times as much of the drug has to be consumed in this way to have an effect comparable to that obtained via smoking (Isbell et al. 1967).

In animals, cannabinoid compounds can also be administered by inhalation (Charlebois and Fried 1980). However, very little Δ^{9}—THC is absorbed by animals in this way. Exposure to “smoking machines” also means that only a few animals can be treated at any time.

Intraperitoneal administration is sometimes used to administer cannabinoids to animals, but is inadvisable because of the possibility of piercing the amniotic sac, injecting fetuses

directly, and because of the possibility of peritonitis if injections are repeated (Manning et al. 1971). Abdominal discomfort can also be observed in animals injected in this way (Carlini et al. 1970). Subcutaneous injection is another route but can result in abscesses at the site of injection. The more preferable route for administration of cannabinoids to pregnant animals is the oral route. However, this requires frequent handling of animals and, therefore, introduces the possibility of additional stress. Furthermore, after oral administration the rate of absorption is relatively slow and levels of drug in the blood remain considerably below those encountered with other routes of administration. These differences are apparent from studies of ^{9}—THC—induced toxicity in animals. In rodents, Δ—THC is 2.5 times more toxic when inhaled compared to when given intravenously (Rosenkrantz and Braude 1971), 10 times more toxic when given intravenously compared to intraperitoneally and twice as toxic when given intravenously compared to orally (Phillips et al. 1971).

Although animals are typically given considerably greater amounts of Δ—THC than would ever be taken by humans, comparison of drug effects on the basis of administered dose is misleading. Many factors contribute to quantitative differences in the amount of a drug that is necessary to produce various effects in each species, e.g., higher metabolic rate of animals, distribution, excretion, route of administration, etc.

PLACENTAL TRANSPORT

Although cannabinoids are able to cross the placenta, the placenta in some species of rodents provides a barrier for complete transmission to the fetus (Abel 1983) and may also provide such a barrier in humans.

NUTRITIONAL FACTORS

An important methodological problem encountered with respect to administration of cannabinoids in animals is that these compounds depress food and water consumption (Abel l975a). As a result, there is the possibility of “confounding” between drug exposure and drug—related undernutrition.

One approach to this problem is to use a “pair—feeding” technique by which one group of animals is alloted only the food and water consumed the previous day by cannabinoid—treated animals. In this way, animals can be equated for food and for water intake, and the only difference is drug exposure. A second control consists of a group given ad lib food and water, to assess the role of decreased food and water intake per se. Comparisons can then be made between drug—treated animals and both pair—fed and ad lib fed animals. If drug—treated animals differ from ad lib fed animals but not pair—fed animals, the result could likely be due to drug—related undernutrition rather than direct pharmacological

factors. However, if drug—related animals also differ from pair—fed animals, the result could be attributed to the drug's pharmacological effects.

Table 1 illustrates the importance of inclusion of the pair—feeding procedure when cannabinoids are administered to animals. In this study, pregnant rats were treated with 10 or 150 9 mg/kg Δ—THC and their food and water intake and weight gain during pregnancy were compared to ad lib fed animals. As indicated by the table, drug—treated animals ate less food, drank less water, and gained less weight during pregnancy, underscoring the need to control for these factors.

TABLE 1

Effects of Oral Administration of Marijuana Extract on Food and Water Consumption and Weight Gain During Pregnancy in Rats

	Dosage		
	10 mg/kg day	150 mg/kg	Ad lib
Total food consumption(g)	323	255	480
Total water consumption(ml)	5514	442	824
Weight gain(g)	101	72	149

Pair—feeding is a deceptive process however. There is no point in pair—feeding animals that weigh 1400 g with those weighing 200 g, for instance. Even if animals weigh the same, there is still the possibility of differences in metabolic rate. Furthermore, drugs such as the cannabinoids may affect utilization of nutrients through reducing nutrient transmission across the gut or placenta.

For example, Abel (1983) intubated pregnant rats which were treated with marijuana (100 mg/kg), alcohol (2 g/kg), or vehicle. Another group was not treated. The untreated animals were fed ad lib. The marijuana—, alcohol—, and vehicle—treated animals all received the same amount of food and water. Despite receiving the same food and water allotment, alcohol—treated animals gained less weight than vehicle—treated animals, and marijuana—treated animals gained less weight than alcohol—treated animals.

POSTNATAL FACTORS

Another important methodological issue concerns how offspring are cared for after birth. Since considerable development occurs postnatally in rats and mice, postnatal factors have the potential for affecting development independent of prenatal insult. In the case of marijuana, there may be residual effects of drug exposure during pregnancy on postnatal maternal behavior or lactational performance (Singh et al. 1981). Such residual effects could arise because cannabinoids are stored in body fat (Kreuz and Axelrod 1973) and cam be secreted back into the blood after drug treatment has stopped. Since cannabinoids are also secreted into milk (Jakubovic et al. 1973), they could be ingested postnatally by nursing pups, thus confounding pre— and post—natal exposure. Marijuana has also been shown to affect maternal behavior adversely (Abel 1972, 1975b; Frischknecht at al. 1980; Kaplan 1979).

To study the possibility of residual maternal effects, rat pups born to nontreated dams were placed with marijuana—treated dams that had just given birth and had had their own offspring removed (Abel et al. 1979). These latter dams had been treated with marijuana only during pregnancy. Another group had been treated with vehicle and had been pair—fed. A third group had been nontreated and was fed ad lib. There was no postnatal drug exposure, yet offspring raised by animals exposed to marijuana during pregnancy did not grow at the same rate as control offspring. When these offspring were tested in the open field, offspring raised by drug—exposed dams also reared significantly less often than control offspring.

To deal with this problem of residual effects, we remove offspring as soon as possible from their biological mothers and place them with nondrug—treated surrogate mothers that have also just given birth. While removal of their own litters and discovery of a new litter may introduce some stress to the surrogate mothers which could affect their maternal behavior, such stress is more than compensated for by removal of the potential for residual effects noted above.

RESORPTION RATE

Both marijuana extract and Δ^9—THC increase resorption rate in pregnant mice, regardless of route of administration. Studies relating to this point are summarized in table 2.

TABLE 2

Effects of Cannabinoids on Resorption Rate in Mice

Compound	Route	Effect	Reference
cannabis extract	smoke inhalation	+	Rosenkrantz et al. 1978
cannabis extract	i.p.	+	Persaud & Ellington 1967
cannabis extract	p.o.	+	Kostellow et al. 1978
Δ^9—THC	i.p.	+	Harbison & Mantilla—Plata 1972
Δ^9—THC	i.v.	+	Joneja 1976
Δ^9—THC	p.o.	+	Fleischman et al. 1980

In rats, this increased resorption rate produced by both marijuana extract and A^9—THC is less robust (Persaud and Ellington 1968; Rosenkrantz et al. 1978; Banerjee et al., 1975; Wright et al., 1976). Furthermore, the absence of controls for cannabinoid—related undernutrition leaves open the possibility that this effect is due to maternal undernutrition, rather than to the direct effects of the cannabinoids on pregnancy.

Studies of “sensitive periods” for this effect have identified gestation day 8 as the most critical time for cannabinoid—related resorptions (Joneja 1976; Mantilla—Plata et al. 1975; Fleischman et al. 1980).

MALFORMATIONS

Except for two previously mentioned reports in which mothers used marijuana in addition to other drugs, there are no reports of malformations in children born to women who smoked marijuana during pregnancy (Fried 1982; Gibson et al. 1983). Reports of teratogenic effects of cannabinoids in animals are inconsistent and have rarely controlled for drug—induced maternal undernutrition. The mouse appears to be the most sensitive species for these effects (Abel 1980), but within this species there are important differences in susceptibilities of strains of mice (Joneja 1976).

INTRAUTERINE GROWTH RETARDATION

Epidemiological Studies

Fried (1980, 1982) reported that marijuana use prior to or during pregnancy did not affect birth weight, birth length, or head circumference in children born to marijuana takers when corrected for gestation length. In these studies, pregnant women were divided into irregular users (less than one marijuana cigarette per week), moderate users (two to five marijuana cigarettes per week), and heavy users (more than five marijuana cigarettes per week). There were only 21 “moderate” and “heavy” users in this study (Fried 1982), so their results should be considered tentative. Gibson et al. (1983) found a significant decrease in birth weight in children born to women who smoked marijuana, but this decrease was no longer significant when corrected for gestation length. Greenland and co—workers (1982), on the other hand, did not observe a significant effect of maternal marijuana use on birth weight or gestation length.

Intrauterine growth retardation is one of the most reliable effects of prenatal exposure to cannabinoids in animals (Abel et al. 1980; Abel et al. 1981; Fried and Charlebois 1979; Persaud and Ellington 1967; Wright et al. 1976; Pace et al. 1971; Geber and Schramm 1969; Cozens et al. 1980).

Our studies on intrauterine growth retardation in rats resulting from in utero exposure to cannabinoids (Abel 1979, 1982; Abel et al. 1980; Greizerstein and Abel 1981; Abel et al. 1981) were designed to evaluate drug—related effects under controlled conditions to permit distinctions to be made between the combined effects of cannabinoid exposure and undernutrition, and the effects of undernutrition alone. This was accomplished using the previously described “pair—feeding” control procedure whereby one group of pregnant animals was drug treated and allowed ad libitum access to food and water, whereas other drug— and vehicle—treated groups were only given food and water equal to that consumed by the first group.

Using this control procedure, our studies have shown that crude marijuana extract and Δ^{9}—THC produce dose—related decreases in the weight of rat offspring at birth and also increase postnatal mortality. We have also shown that this effect is probably not due to the secondary effects of drug—related maternal undernutrition. Even though the food and water consumption of drug—treated and control dams was equalized, drug—exposed offspring still weighed less at birth.

Although we employed pair—feeding control measures, rats treated with marijuana still gained less weight than pair—fed controls. This suggests that maternal undernutrition cannot be dismissed as a possible factor contributing to the effects of prenatal cannabinoid exposure. In this regard, Charlebois and Fried (1980)

reported that supplementation of regular laboratory diet with protein attenuated the efforts of marijuana—induced intrauterine growth retardation. A comparable effect of increased dietary protein has also been reported in conjunction with the effects of prenatal alcohol exposure in rats (Weiner et al. 1981).

Other studies from our laboratory have examined "critical periods" during development for the growth—retarding effects of cannabinoids (Abel et al. 1981). These studies have shown that the most sensitive period for marijuana's effects on intrauterine growth retardation is during the third trimester of pregnancy. This is also the most sensitive period for the increase in postnatal mortality produced by marijuana in the rat.

Related studies from our laboratory examined the effects of prenatal exposure to cannabinoids on newborn rat body composition (Greizerstein and Abel 1981). Such exposure resulted in decreased lipid body content and higher sodium and lower calcium body levels compared to pair—fed offspring. These aberrations suggest cannabinoid—induced delay of in utero maturational processes.

LONG LASTING EFFECTS ON GROWTH RETARDATION

Few studies have examined whether the reduction in birth weight associated with prenatal marijuana exposure persists after birth. As noted above, such studies must control for residual drug effects on maternal behavior to minimize confounding of pre— and post—natal factors.

Our studies examining this issue have been inconsistent. In our first study (Abel et al. 1980), rats born to mothers receiving 150 mg/kg/day weighed less than pair—fed controls at 21 days of age but, at 11 weeks of age, only female offspring weighed less than controls. In a subsequent study (Abel et al. 1981), in which mothers received 200 mg/kg/day cannabis extract, offspring did not weigh less than pair—fed controls at 2 days of age. In a third study (Abel 19814) offspring whose mothers received 50 mg/kg/day of Δ^9—THC weighed less at 7, but not at 21, days of age, compared to pair—fed controls.

BEHAVIORAL EFFECTS

Epidemiological Studies

Fried (1980) reported that children born to women who were "moderate" or "heavy" marijuana smokers (see above for criteria) responded less to light stimuli, habituated less to such stimuli, and "self quieted" themselves less than other infants. In a subsequent report (Fried 1982), such children also had heightened tremor and startle responses. Also of interest was the occurrence

of high pitched cries (cri du chat) among one—third of the children born to marijuana users.

When these children were tested at 30 days of age using the Prechtl neurological exam, previously observed differences in response to visual stimuli were no longer evident, nor did children differ in tremor incidence at this age. At 12 months of age, children born to marijuana users also did not differ from controls on the mental, motor, or behavioral scales of the Hayley Scale of Infant Development, or on any physical measurements of growth.

Studies in Animals

There have been relatively few studies of the long—term behavioral consequences of prenatal alcohol exposure in animals. Most of the studies that have been conducted in this area have not controlled for drug—related maternal undernutrition or postnatal maternally mediated residual effects (see above). When such controls have been included, there have been very few instances of significant long—term sequelae which can be attributed to prenatal cannabinoid exposure.

ACTIVITY

Prenatal exposure to cannabinoids has been reported to increase activity in offspring (Borgen et al. 1973), but there are also reports of decreased activity (Charlebois and Fried 1980; Kawash et al. 1980; Uyeno 1973) as well as no changes in activity (Abel 1979; Vardaris et al. 1976). With the exception of the study by Abel et al. (1979), drug—related maternal undernutrition was not taken into account, and only Abel et al. C 1979) and Borgen et al. (1973) took residual effects of cannabinoids on maternal behavior into account.

MOTOR ACTIVITY

In our first study (Abel 1979), we reported that rats prenatally exposed to cannabis extract were unable to remain on a Rotarod as long as pair—fed controls. However, we have not been able to replicate this observation using cannabis extract (Abel et al. 1980) or A^9—THC (Abel 19814).

LEARNING/MEMORY

Effects of prenatal exposure to cannabinoids on learning/memory function in animals are as inconsistent as effects on activity and motor function.

Using a water—maze to assess behavior, Abel (1979) and Charlebois and Fried C 1980) did not observe any effects on learning, whereas Kawash et al. (1980) reported that rats prenatally exposed to cannabinoids were unable to learn this problem as well as controls (not pair-fed).

Uyeno (1973) did not observe any effect of prenatal cannabinoid exposure in learning a two—channel maze. Likewise, Abel (1981, 19814) could not detect differences between rats prenatally exposed to cannabis extract or Δ^9—THC and pair—fed controls in active shock avoidance learning or brightness discrimination learning. Gianutsos and Abbatiello (1972), on the other hand, did find that female offspring prenatally exposed to cannabis did not perform as well as controls (not pair—fed) on Lashley maze learning.

PERSEVERATION BEHAVIOR

Abel (1979, 19814) tested animals for their perseverative behavior in a T—maze. Typically, rats placed in such mazes alternate their entry into different areas of the maze on each trial. Failure to alternate indicates perseverative behavior. In this test, cannabinoid—exposed rats did not differ from pair—fed controls.

VISUAL ATTENTION

Golub et al. (1981) administered Δ—THC (2.14 mg/kg) to monkeys during pregnancy and lactation. At 12 and 214 months of age, offspring of these animals were presented with pairs of stimuli—— a blank slide or a picture of toys. Cannabinoid—exposed offspring spent more time looking at both slides than controls, a result interpreted as “a failure to inhibit the response to stimuli.” In a subsequent study (Golub et al. 1982), stimuli of varying complexity and novelty were presented to determine which properties of the stimuli affected attention. Complexity did not affect duration of attention in drug—treated offspring, but novelty did prolong attention. This effect of visual stimuli in monkeys prenatally exposed to marijuana is especially interesting, since Fried (1982) likewise reported changes in response to visual stimuli in children born to marijuana smokers.

SEXUAL BEHAVIOR

The only aspect of behavior in which there appears to be a consistent effect of perinatal marijuana exposure involves sexual activity. Dalterio and Bartke (1979) reported that perinatal exposure to Δ^9—THC resulted in decreased sexual responsiveness (increased latency to mount and number of mounts) in male mice. Testosterone levels in these mice were not decreased. In a subsequent study (Dalterio 1980), copulating behavior in male mice was again suppressed relative to controls. Testes weights were also reduced, but testosterone levels did not differ significantly from controls. Likewise, Hatoum et al. (1981) observed decreased sexual responsiveness in male mice when mothers received Δ^9—THC prior to parturition and for the first 5 days after parturition. Fried and Charlebois C 1979) reported that the F_1 generation of rats prenatally exposed to marijuana took longer to mate than controls. (In this latter study, offspring were cross—fostered after birth.)

Summary and Conclusions

Prenatal exposure to cannabinoids does not produce gross malformations in humans and only does so with any consistency in mice following exposure to relatively high doses and following the intraperitoneal route of administration. Resorption rates are reliably increased in mice but not rats following in utero cannabinoid exposure. There is also a reliable decrease in maternal food and water consumption and weight gain during pregnancy associated with maternal cannabinoid administration. This effect may account for many of the effects associated with prenatal exposure to cannabinoids, e.g., increased resorption rate.

Prenatal exposure to cannabinoids produces a reliable decrease in birth weight in animals, but this is the only postnatal effect on offspring that has been reliably documented. Studies examining long—term postnatal effects are generally inconsistent. This inconsistency may be due to methodological flaws in experimental design, such as absence of controls for drug—related undernutrition and residual effects of maternal cannabinoid exposure during postnatal nursing. When such controls have been implemented, postnatal effects of prenatal cannabinoid exposure have not been reliably observed.

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Measurement of Substance Use During Pregnancy: Methodologic Issues

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This paper discusses some methodologic issues in the measurement of substance use, particularly the more complex issue of measuring substance use during pregnancy. Two specific questions are addressed in this presentation:
(1) Whether the questions on use result in accurate assessment of use, and (2) Whether respondents report use accurately. Some of these methodological issues are illustrated with data from our ongoing research on substance use during pregnancy and its effect on outcome.

The assessment of substance use is complicated because there are as many patterns of use as there are users. These patterns, however, can be described by the frequency, quantity, and type of substance. The combination of these three variables defines the pattern of use. Measurement of these parameters will be discussed specifically with reference to marijuana use.

The first descriptor, frequency, is generally considered to be a measure of how much the substance is part of one's life (Room 1977). Clearly, marijuana is a more important part of the life of women who smoke daily compared to women who use marijuana monthly or even less often. This more frequent use has biological implications in terms of exposure, and also has social implications, in that the frequency of substance use correlates very highly with other behaviors, including the use of other substances prior to and during pregnancy (Alpert et al. 1981).

The standard method of collecting data on frequency has been to present the subject with an ordinal ranking of frequencies. There are several problematic issues that need to be considered, however, with this type of assessment. First, from a simple mechanistic viewpoint, the fineness or crudeness of the groupings is an important element in accuracy of assessment. Global categorizations such as daily, often, rarely, or never are so broad as to be meaningless. In addition, qualitative terms such as often and rarely may mean quite different things to different respondents.

At the opposite end of the spectrum, some researchers simply ask how many times the subject has smoked marijuana in a given time period (Greenland et al. 1983). While the specificity of this latter query seems more satisfactory, it too has serious drawbacks. This measure is a rather curious mixture of frequency and quantity and misses the pattern of use.

This kind of metric can be adapted as a time—line follow— back (Sobell et al. 1980; Tennes and Blackard 1980). In this assessment, subjects are asked to recall specific incidents of use for each day over a given time period. Using this technique, it is possible to obtain patterns of use as well as amounts of use because the quantity is measured for each incident of use. However, because this technique asks for recall over a specific period of time, care must be taken to ascertain whether it reflects a usual or aberrant pattern for that subject, as well as whether the subject's recall is accurate. Another variant of this method of data collection is the diary method where respondents are requested to write down all use as it occurs. While this theoretically corrects for some of the memory problems of the time—line technique, it requires a high level of motivation from the subject.

More commonly, researchers have asked subjects to report frequency of use in terms of incidents per day, week, or month. While these data are easy to organize, there are some problems inherent in this method. The issue of grouping is again germane, as the broadness or fineness of the categories can seriously bias estimates. This becomes a problem not so much with the ordinal ranking of subjects, assuming the groupings are not too broad, but with attempts to accurately assess the biological effects of certain doses. The inaccuracies of grouping are also propagated by the need to code data for analysis and to create scales. In most cases, for example, a woman who reports a use level of 1 to 2 times a day will be coded as 1.5 times a day even though she may use only once a day, or she may use twice a day, double the former amount. Due to the need for data reduction, however, these women would be scored as equivalent,

The value of simple frequency assessments is further limited in that the reported frequency will be the usual frequency for that time period. Researchers tend to regard frequency as a constant and seldom allow for variability. This conflicts with reality, since we can document seasonal and situational changes in frequency of substance use. Again, in the assessment of biological, or in the case of pregnancy, teratogenic effects, the "ripples" in the system may have major effects and yet may be missed because of the form of questioning. Practically, even if a respondent volunteers that she used marijuana at a much more frequent rate for a period of time within the time frame considered,

it is very difficult to incorporate this information into the data analysis because of the analytic need for a single, preferably continuous, measure of use.

Quantity, the other major descriptor of patterns of use, is similarly difficult to assess. We ask about the number of joints smoked per incident, for example, and this serves in some respects as a measure of dose, and also as a reflection of whether a subject uses the substance to the point of intoxication, or in more moderate amounts (Room 1977). Thus, it represents a style of use as well as an estimate of the dose received.

Quantity, like frequency, varies. In the measurement of drug use, however, most assessments have been of the usual quantity used, e.g., “How much (how many joints) do you usually smoke?” (National Institute on Drug Abuse 1981). The answers then represent ~ usual pattern, often one that the respondent considers to be more socially appropriate. All use that differs from the usual quantity will be missed in the assessment. Thus, any use greater than the usual, or less than the usual, is not considered.

Another major problem with quantity lies in the estimation of the actual amount consumed. One joint can be of varying sizes and/or varying strengths. In marijuana, unlike alcohol, there is no standardized “proof” of content, and again, unlike alcohol, different methods of consumption yield different degrees of exposure (Nahas 1979; Abel 1980). Additionally, the availability of other substances, such as hashish and sinsemilla, makes the measurement of quantity, or dose, problematic. We also found in our pilot testing that women would report smoking, for example, six or seven joints on an occasion; but, on further questioning, it would turn out that these joints were shared among several friends. Therefore, since marijuana use, unlike the use of many other substances, is a social behavior, it is essential to determine whether the reported quantities were shared or used alone.

Biological assessments are useful measures of the recency of use, and have been used successfully in studies during pregnancy (Greenland et al. 1982) . These tests, however, have some of the same drawbacks as the interview data. It is not possible to determine pattern of use from a laboratory test because it only measures exposure at the time the user is tested. Furthermore, there is only a short period of time following marijuana consumption in which laboratory tests can detect or measure levels of cannabinoids in biological fluids of users. This creates a problem for research when we want to cover, for example, the span of a trimester. The researcher must choose between the option of monitoring the women very frequently, i.e., at about 2—week intervals, or less frequently, and having blank spots in the time spanned by

the biological assessment. The first method of frequent assessment could interfere directly with the behavior of the study population. The second method could result in misleading or incomplete data. In addition, laboratory testing of illicit substances will increase both refusal and noncompliance rates, especially in the user groups.

There is a major analytic need for scales that represent the use patterns reported by the subjects. This process is, of course, a necessary step in data reduction. It is highly problematic, however, to take two measures, frequency and quantity, that in themselves are not particularly accurate, and combine them in an algorithm that may just compound the inaccuracy. The most commonly used scale is the usual—quantity/usual—frequency measure.

In our own data, we can illustrate the inaccuracy resulting from asking only about usual quantity and frequency of use. Among the first 290 women in our study who used marijuana, average daily use was calculated to be .7 joints per day, or approximately 5 joints per week. Eliciting maximum quantity increased our estimates of use by 30%, and the addition of questions about use of quantities less than the usual quantity contributed an additional 5.5% to the total reported use. Thus, the usual quantity that our subjects reported represented only 64% of the amount of use reported when we added questions about quantities greater than and less than the usual reported amount. For the first trimester, usual quantity and frequency represented only 57% of the total use.

Among those women who reported using quantities greater than their usual prepregnancy quantity, the mean quantity reported was 3.6 joints. Clearly this represents fairly heavy use and thus greater single dose exposure. On the average, marijuana users who increased their quantity did so about once a week. Quantities less than usual are consumed even more frequently (0.2 per day or about 1.4 times per week). Though occurring more frequently, the relatively small quantities consumed (mean quantity = .9 joints per occasion) do not contribute as much to the overall average daily use.

When measuring the teratogenic effect of drug use during pregnancy, this level of inaccuracy becomes unacceptable because we are misestimating the dose as well as the pattern of delivery of the dose. That is, it is quite possible that a larger exposure at a critical point in the fetal development could have a greater impact than the same dosage spread out over a longer time period. For this reason, it is critical to select measures of quantity and frequency that will allow the data to reflect the variance from the mean as well as the mean experience.

One type of measure that has been used in various forms in fetal alcohol research is the volume variability scale, developed originally by Cahalan et al. (1969). This series of questions ascertains frequency and then asks the subject to indicate for each drinking time whether she drank various numbers of drinks (5 or more, 3—4, 1—2) “nearly every time, more than half of the time, less than half the time, once in a while, or never.” The proportion of drinking incidents spent at each volume level is then calculated to yield a volume—variability score that reflects the variability in quantity.

The Khavari Alcohol Test or KAT scale (Khavari and Farber 1978) is a variant of this technique, though simplified. It asks overall frequency of use and usual quantity. Maximum quantity and frequency of maximum quantity are then ascertained.

These measures also allow one to create different scales that can reflect differing concerns. Calculation of average daily use gives an overall average estimate of use during the time period. With data on variable quantities, it is also possible to look at the frequency with which a woman uses, for example, five or more joints to assess the frequency of use of higher amounts.

There are, of course, a number of other ways to combine the data once they are gathered. But the important point to be made is that each scale highlights one aspect of drug use while suppressing others. A measure of frequent heavy use will reflect those who, for example, use five or more joints when they smoke, but not those who smoke an equivalent amount in more frequent, smaller doses. These different attributes can be compared analytically to explore the relative contributions of the individual scales, as they reflect patterns of use, to the explanation of the variance in the outcome.

Because of the importance of obtaining accurate measures of both marijuana and alcohol use, we conducted an extensive pilot test in our study to develop these assessments. Several variants of traditional questions were pretested using usual quantity and frequency and several scales from alcohol research including the volume variability (VV) scale and the KAT scale discussed above.

Our population is a lower class population of women 18 to 30 years of age who attend the outpatient prenatal clinic at Magee—Womens Hospital in Pittsburgh. sixty percent have graduated from high school, *50%* are married, 40% are minorities, predominantly black.

We found that our population initially had problems with the format of the questions. First, they had difficulty because the standard method of assessment asks women to give an overall, total frequency of use, and then to partition that use into the proportion of time she might spend using various quantities. This requires fairly complex mathematical thinking that may not result in accurate measurement under the time and social pressures of the interview. Second, particularly with respect to the marijuana use, it is not clear that women think in terms of frequency first. There has been very little research on how subjects cognitively organize their own assessments of use, but it seemed to be easier for our subjects to think first of quantity and then to describe frequency.

In recognition of this fact, we designed our use assessments to respond to the way our subjects seemed to be organizing their patterns of use. In our study, we first ask questions about quantity, e.g., "When you smoke marijuana, how many joints do you usually smoke?" and then questions about frequency, such as "How often do you smoke this amount?" After this, the respondent is asked "Do you smoke more than this amount?" . . . "How many joints?"

> "How often?" . . . and further, "Do you smoke less?" and again, "How many joints?" and "How often?" With

few exceptions, our pilot test subjects felt that these questions were easy to answer and described their use accurately. From these questions, it is possible to develop scales that reflect variability in both quantity and frequency, measures of the frequency of heavy use, and measures of average daily use.

We conducted validity tests on these measures comparing our instruments to the VV scale, the KAT scale, and the usual quantity—frequency. There were no significant differences in the rank order of subjects on our measures compared to the other scales. However, the overall average daily use obtained was significantly higher.

Complementary to concern about the validity of the method of assessment is an equally important issue of whether the subjects' answers are accurate. Two major reasons for inaccuracy are deliberate misrepresentation and errors in r e cal 1.

Deliberate misreporting is an important issue when measuring an illicit substance or a substance whose use might be licit but is negatively labeled at particular times, such as alcohol use during pregnancy. We have tried several techniques to increase reporting accuracy. The first was simply to lead into the marijuana questions in a nonthreatening manner. They are imbedded in a section on social supports and drug use by friends.

We have also employed the bogus pipeline technique (Jones and Sigall 1971). This is a method of convincing the subject that you have a laboratory assessment of use when in fact you do not. Interestingly, while the use of the bogus pipeline did significantly increase reporting of other illicit drugs, it did not significantly increase marijuana reporting, leading us to the conclusion that our marijuana assessments were relatively accurate. Further, we discovered during our pilot phase that most women were reluctant to report using any substance currently. However, when asked about use last month or some time in the past, they would respond. As a result, we changed our study design to interview in the fourth month about use during the first trimester, in the seventh month about use during the second trimester, and at delivery we assess the third trimester.

Errors in recall are also important. In the pilot study, we interviewed all clinic women about their use, regardless of month of pregnancy. Women in late pregnancy reported approximately half of the first trimester use that women early in their pregnancy reported. Since there is no reason to believe that these women differed in any way, this represents the problem of accurately recalling actual use during the first trimester, some 6 months earlier. In our study 82% of the women who used marijuana prior to their pregnancy reported a decrease in use during the first trimester. Remembering and accurately reporting a behavior that is changing is difficult, especially many months later.

An accurate assessment of first trimester use is crucial, however, when we are looking for teratogenic effects. The first trimester of pregnancy is the most vulnerable time for the developing fetus. It is the time of major organ and systems development, and the time that major birth defects occur. Also, because of the sequential timing of developmental events during this time period, the same dose of a substance at different time points during organogenesis will have different effects. Thus, it is questionable whether data that average use estimates over the first trimester are sufficiently specific to reflect the relationship between exposure and effect.

A further difficulty with assessment of first trimester use is that though researchers may count conception as the beginning of the pregnancy, it is not clear whether pregnant women really think back to that point when asked to report events during the first trimester.

We have developed a technique to assess the use of marijuana during the first trimester that allows us to circumvent this problem. Early in the interview, women are asked to indicate on a calendar the month and part of the month (beginning, middle, or end) when they: (a) got

pregnant; (b) recognized their pregnancy; and (c) had their pregnancy confirmed by a pregnancy test. Later in the interview, we ascertain marijuana use prior to pregnancy and in the first trimester of pregnancy. Immediately after these questions, the interviewer returns to the calendar and asks the subject whether for the time period between conception and recognition of pregnancy, her marijuana use was more like that which she reported prior to pregnancy or more like the rate she reported for her first trimester. After this, we ask the same set of questions about the time period from recognition to diagnosis. The dates of conception, recognition, and diagnosis and the rates of marijuana use prior to and during pregnancy are used to calculate a month—by—month rate of marijuana use and a weighted estimate of the average daily use for the first trimester.

Sixty—six percent of all marijuana users reported that from conception to recognition of pregnancy, their use was similar to their prepregnancy pattern and 33% reported that from recognition to diagnosis, they were still using marijuana at their prepregnancy rate.

When we looked only at women who had an average daily use of two or more joints prior to pregnancy, 83% said that from conception to recognition their use was similar to their prepregnancy pattern, and 52% reported that from recognition to diagnosis their use was similar to their prepregnancy pattern.

On the average, there were 30.5 days from conception to recognition for the total population, 31.2 days for all marijuana users and 33.2 days for women who smoked two or more joints per day prior to pregnancy. The time span from recognition to diagnosis was also lengthened for these heavier smokers, who had a mean of 22.1 days compared to 20.1 days for all marijuana users and 19.3 days for the total population. Therefore, the heavier users were more likely to continue to use marijuana at their prepregnancy rate, and they used marijuana at this higher rate for a greater part of the first trimester.

The reported and calculated estimates of the average daily use of marijuana are given in table 1. A total of 11.6% of our subjects reported smoking two or more joints per day before their pregnancy, although only 3.4% of the women reported using two or more joints per day during the first trimester of pregnancy, an apparent decrease of two—thirds. However, when we calculated the average daily use as described above, 5.5% of the subjects actually used an average of two or more joints per day during the first trimester. In other words, only about two—thirds of the women who were calculated as using at least two joints per day reported doing so; a sensitivity rate of 63%. The sensitivity rate for those calculated as using one joint

TABLE 1

Reported and Calculated Marijuana Usage, N=644*

Average Daily Use	Pre-pregnancy Reported Use	Calculated Usage: Month 1	Month 2	Month 3	Average	First Trimester Reported Use
≥ 2 per day	11.6	8.1	5.5	3.8	5.5	3.4
1 per day	4.2	3.7	2.8	1.7	3.4	2.0
1-6 per day	15.5	12.0	9.0	7.0	12.5	6.4
Less than weekly	13.7	8.7	11.2	9.7	11.6	7.6
None	55.0	66.9	71.0	77.8	67.0	80.6

*Values given in percent of total.

per day was 60% and for those calculated to have a rate of one to six per week, 51%. This reflects the pattern of misreporting downward. Overall, we found that 56% of the subjects underreported their use when we compared the calculated rate to the actual reported rate. This means that studies that use the more global assessment of first trimester use underestimate the actual amount of exposure in more than half of the cases.

Since the teratogenic effect of any drug can be specific to certain time periods, we calculated rates separately for each month of the first trimester. This allowed us to determine whether the effect is a direct function of extended use over a period of time as long as 3 months, or whether it is the result of exposure over a shorter more specific time period. In table 1 the calculated average daily use is shown for each month of the first trimester. During the first month of pregnancy, 8.1% of the subjects had a calculated use of two or more joints per day. That is, 70% of the women who used marijuana at this rate prior to pregnancy continued at that rate through the first month of pregnancy. However, only 42% of these women reported using that amount for the first trimester, Of those women who we calculated as having used marijuana at the rate of two or more joints per day during the first month but who did not report this rate, 58% actually reported no first trimester use at all.

Thus, the rate that women report for first trimester use is particularly inaccurate during the early part of the

first trimester. In fact, in the absence of estimates of first month use, it is quite clear that the prior—to— pregnancy rate is a better estimator of use during this time period than is the reported first trimester use. This is especially true for estimates of use among heavy users.

The other end of the scale is also problematic in terms of misclassification of subjects. Eighty percent of our subjects reported using no marijuana during the first trimester. However, on closer questioning, only 67% used none during the first trimester. That is, about one out of every five women who reported no marijuana use during the first trimester was actually a user.

We began this paper by pointing out that the measurement of substance use is a complicated issue. We have attempted to highlight some of the areas of difficulty. In particular, it is essential that we work to develop valid instruments to measure substance use and that, particularly for studies of use during pregnancy, these questions be designed to give us information about pattern of use in addition to average use.

An additional serious problem lies in the accuracy of subject's reports about their use, particularly during the first trimester. Our data clearly demonstrate that reports of first trimester use really only represent late first trimester use, the most recent memory. This is not surprising since drug use decreases during the first trimester for most women, and accurate recall is difficult. This means, however, that previous studies using reports of first trimester use underestimated the exposure and seriously underestimated the exposure during the first month of pregnancy.

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Marijuana: Prenatal and Postnatal Exposure in the Human

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Recent studies of prenatal exposure to marijuana have produced presumptive evidence that marijuana has an adverse effect on growth and development of the fetus. Two investigators (Linn et al. 1983; Gibson et al. 1983) reported a decrease in birth weight and an increase in malformations in marijuana— exposed infants, but differences between marijuana users and nonusers were not statistically significant when confounding factors were taken into account. Hingson et al. (1982) reported that woman who used marijuana during pregnancy delivered infants with a mean birth weight 105 grams lighter than infants of nonusers, and the infants were five times mere likely than infants of nonusers to have features compatible with Fetal Alcohol Syndrome. Although confounding factors were controlled statistically, the investigators cautioned that marijuana use might identify a group of women at higher pregnancy risk due to unexplored maternal factors, rather than identifying a specific agent causing abnormal fetal development. In a preliminary report from an ongoing prospective study in Canada, Fried (1980, 1982) found no difference in birth weight between marijuana users and nonusers, but infants of heavy users had shorter gestations and signs of neurobehavioral immaturity as compared with matched controls.

Some protection from potentially harmful effects of cannabis on fetal development may be due to the partial restriction of cannabis compounds by the placenta. In a recent study of placental transfer of Δ—9—'IHC and the principal metalxilite, 9—carboxy—THC (Blackard and Tennes 1984), levels of the cannabinoids were found to be two—and—a—half to seven times higher in maternal plasma than in fetal cord plasma at delivery in 10 women who used marijuana daily. Although these results may not apply to placental transfer at periods of gestation other than delivery, or to peak plasma concentrations immediately after smoking, the findings are in agreement with animal studies that have indicated that the fetus is exposed to appreciably less cannabis than is ingested by the mother (Reviews: Bloch et al. 1978; Abel 1980).

Because of the limited number of studies and the complexity of factors that need to be controlled in human clinical research of illicit drug use, it has been difficult to estimate the seriousness of risks associated with marijuana use during pregnancy.

This paper reports our study of the effects of marijuana in a population of pregnant women known to include a relatively high proportion of marijuana users (Tennes and Blackard 1980). The purpose of the study was to investigate effects of exposure to marijuana on fetal growth and development at birth and at 1 year of age.

Method

Population and Data Collection

During a 12—month period beginning in November 1981, 1,032 pregnant women were approached at the prenatal—care clinics of Denver General and University Hospitals during the women's regular clinic visits. The population served by these clinics is predominantly of lower-middle to lower—class socioeconomic status. The subjects selected were at least 24 weeks pregnant. Vietnamese and Hispanic women who did not speak English were excluded.

Of those approached, 865 women gave informed consent and were interviewed by one of three experienced interviewers. A structured questionnaire developed in a previous study (Tennes and Blackard 1980) was used to obtain information on demographics, illnesses, and medications, as well as use of caffeine, nicotine, alcohol, marijuana, and other illicit drugs. Specific details about kind, potency, aid physiologic effects of marijuana, as well as use by the child's father, were obtained. After delivery, the women were interviewed a second time to cover drug use in the interval between the initial interview and delivery. An attrition rate of 16% between the initial approach and delivery was due to 8% who refused to participate and 8% who moved away or delivered at a different hospital.

Infants of the 756 participating women were scheduled between 24 and 72 hours of age for an examination by one of four examiners who were blind to all information about the mother. we developed a systematic examination procedure which included measurement of length, head circumference, and palpebral fissures; the Brazelton Neonatal Behavioral Assessment Scale (Brazelton 1973), a scale of muscle tone derived from Parmalee (Howard 1976); and a checklist of 34 minor physical anomalies prepared by Blackard and Tennes (1981). All examiners had been certified for administration of the Brazelton prior to this research.

Birth weight, the Dubowitz score for gestational age (Dubowitz et al. 1970), Apgar scores and neonatal clinical data were obtained from the infants' hospital charts. Antepartum and intrapartum clinical data on the women were obtained from their medical records. Women with diabetes, renal, or collagen disease were excluded.

At 1 year of age, infants of a selected sample of marijuana users and controls were seen for measurements and examination with the Bayley Infant Scale of Mental and Motor Development and Behavior Checklist (1969). After the examination, the mothers were interviewed regarding the child's health, routine care, behavioral traits, and special problem during the first year. Women who had breastfed completed a questionnaire regarding drug use during breastfeeding. Two investigators were present at all examinations, one acting as examiner aid the other as observer, and all scales were scored independently by each. Correlation coefficients between examiners' aid observers' scores of mental and motor development were .95 and .97.

RESULTS

Thirty—four percent of the 756 women in the sample reported using marijuana during pregnancy. Marijuana users were significantly different from nonusers (p (.001) in age, marital status, number of prior live births, and frequency of induced abortions (table 1). No significant differences were found between users and nonusers in race, socioeconomic status, spontaneous abortions, or previous stillbirths. Alcohol, nicotine, and other illicit drugs (hash, cocaine, amphetamines, LSD, barbiturates, PCP, or psilocybin) were sore frequently used by marijuana smokers than by nonsmokers.

TABLE 1

Significant Differences (p < .001) in Demographics
Between Marijuana Users and Nonusers.

Demographics	Nonusers	Users
	N=498	N=258
Mean age (mean years)	23.0 years	21.8 years
Marital status: Married	58%	42%
Single or Cohabiting	32%	51%
Prior live births	57%	37%
Elective abortions	20%	32%
Nicotine use	30%	40%
Alcohol use	30%	70%
Other illicit drugs	4%	31%

Levels of Exposure

To estimate the dose—response relationships between drugs and outcome variables, the number of times the women used the drug was totaled for each week of the pregnancy, and the weekly amounts were summed to estimate the exposure for the entire pregnancy or for each trimester separately. The unit of measure for alcohol was number of drinks of beer, wine, or liquor; for nicotine, packs per day; for marijuana, the number of joints; for the other illicit drugs, the number of occasions the drug was used.

There was a significant linear dose—relationship between the women's use of marijuana aid alcohol (r=.45, p<.Ol), but not between marijuana and nicotine (r=.07, n.s.).

There was a high correlation between amounts of marijuana smoked by trimesters (r = .71 and .73), but the amounts smoked decreased during pregnancy. To examine change in marijuana use during pregnancy, estimates of marijuana were converted to an approximate weekly average and the women were categorized as nonusers, light (one time only to once a week), moderate (more than one a week but less than daily), and heavy (once or more daily). The categories were established for each trimester.

The proportion of women in each category shifted during the course of pregnancy (table 2). Nonusers increased from 68% in the first trimester to 84% in the third, aid the number of daily users declined from 10% in the first trimester to 2% in the third. The women who continued to smoke daily throughout pregnancy decreased from a mean of 4.5 (S.D.=4.5) per day in the first trimester to a mean of one a day (S.D.=1.1) in the third.

TABLE 2

Changes in Reported Marijuana Use During Pregnancy

	First Trimester	Second Trimester	Third Trimester
Level of Use			
Nonuser	519 (68%)	601 (79%)	633 (84%)
Light	87 (12%)	73 (10%)	67 (9%)
Moderate	89 (10%)	49 (6%)	42 (5%)
Heavy	72 (10%)	33 (4%)	14 (2%)

Pregnancy and Delivery Complications

We compared the frequency of medical complications among nonusers and marijuana groups. No dose—response relationship was found for a specific complication nor for the total number of complications incurred by each woman. The only differences found in medical histories was that marijuana users gained significantly more weight during pregnancy than nonusers (mean gain by users 36.25 lbs., nonusers 32.0 lbs.).

We compared marijuana users and nonusers on 12 indices of complications at delivery, namely: precipitous labor, prolonged labor, need for oxytocin, chorioamnionitis, abnormal presentation, fetal distress, meconiun staining, placental abruption, assisted vaginal delivery, cesarean section, pain relief requirements, and narcotics used in labor. The only significant difference between users and nonusers was an increased requirement for pain—relieving medication during labor (users 67%, nonusers 57%, p (.01). In multiple—variant analysis of factors contributing to narcotic dose and to administration of analgesics, only parity and delivery complications were significant determinants. Since more marijuana users than nonusers were primiparous, the difference in pain—relieving medication may be attributed to parity rather than marijuana.

Infant Outcomes

Heavy marijuana use was found to be associated with an increase in male over female offspring, a finding previously reported by Fried (1982). Women who reported smoking marijuana three times a week or more throughout pregnancy (N = 31) gave birth to 61% males and 38% females as compared with 50% males and 49% females among nonusers (N = 498). Among fathers who were reported to be chronic smokers of more than one ‘joint” a day, the ratio was 67% males to 33% females (table 3).

Table 3

Ratio of Male to Female Births for Fathers Using Marijuana

Frequency of Marijuana Use

	No Data	Nonuser	One A Day Or Less	More Than One A Day
Females	96 (52%)	158 (47%)	71 (55%)	35 (33%)
Males	87 (48%)	181 (53%)	58 (45%)	70 (67%)

Chi square = 13.29, p=.004

Intrauterine Growth

Multivariate analyses of the impact of marijuana on three measures of fetal growth—birth weight, length aid head circumference—did not yield uniform results.

Infant length was the only measure influenced by marijuana when confounding variables were taken into account. Of eight variables, accounting for 22% of the variance in length, marijuana (total amount used during the first trimester) entered the regression on the fourth step (table 4). Other confounding variables considered in the regression that did not reach significance were: mother's age, parity, Hispanic race, socioeconomic status, caffeine, alcohol, hash, amphetamines, aid cocaine. As calculated from the unstandardized p—coefficients, the reduction of .55 centimeters in length, attributable to smoking an average of three joints a day during the first trimester, was roughly comparable to the reduction of .48 centimeters attributable to smoking one—and—a—half packs per day of cigarettes.

When the analysis was repeated for second and third trimester use of drugs, or for the total amount smoked during pregnancy, marijuana did not have a significant impact on infant length.

TABLE 4

Step—wise Multiple Regressions on Infant Length at Birth

Dependent Variable: Length Mean = 49.8 cm., S.D. = 2.23

Variables	Significance	r^2 change	Beta
Gestational age (weeks)	.000	.100	.29
Infant Sex	.000	.035	.19
Nicotine (packs per day)	.000	.019	—.13
Marijuana, first trimester	.001	.015	—.07
Weight gain during pregnancy	.001	.014	.13
Ponderal Index	.001	.015	.12
Mother's Height	.007	.009	.11
Black Race	.009	.008	—.09

N=659 R=.47 R^2=.22

In contrast to the findings on length, no independent effect of marijuana on birth weight or head circumference was found when marijuana was considered either by trimesters or by the total amount smoked.

We also analyzed multiple drug Lee, not as an assessment of the synergistic effect of several drugs, but rather as a surrogate variable representing lifestyle attributes of women who used one or more illicit drugs other than marijuana. This measure of the

number of different kinds of other illicit drugs, regardless of frequency, was found to have a significant but marginal impact on the regression on birth weight ($p < .01$, r^2 change = .006, p= —.07). The calculated reduction in birth weight associated with exposure to four different illicit drugs other than marijuana was 199 grass. Thus, infants of women who use multiple illicit drugs, regardless of kind or amount, appear to be at an increased risk for a significant reduction in birth weight.

Gestational Age

The total amount of marijuana used during pregnancy was positively correlated with the infant's gestational age at birth (r = .10). Three indices of gestational age that had been recorded were the woman' s reported last menstrual period, the Dobowitz examination of the infant, and the obstetrician's estimate given in the medical record. The mean or mode of the three was used as the estimate. In a multiple regression analysis, five variables accounted for 4 percent of the variance in gestational age (table 5). Two of the significant variables, pregnancy complications and black race, are known to be associated with preterm deliveries (Berkowitz et al. 1982). The three other significant variables, weight gain, ponderal index, and marijuana, were associated with prolongation of gestation. Additional noncontributing variables entered in the regression were Hispanic race, mother's age aid height, infant sex, socioeconomic status, parity, and abortions (yes and no). None of 31 women who smoked an average of three times or more a week throughout pregnancy gave birth preterm (before 37 weeks), as compared with 7% of nonusers.

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TABLE 5

Step-wise Multiple Regression of Gestational Age Dependent Variable: Gestational Age Mean=39.88 weeks,

S.D.1 .65

Variables	Significance	r^2 change	ß-coefficient
Ponderal Index	.01	.01	.14
Pregnancy complications	.01	.009	—.09
Weight gain	.01	.009	.11
Marijuana	.03	.006	.09
Black race	.04	.005	—.08

N=719 MultipleR= .23 R^2 .04

Postnatal Outcomes

No associations were observed between exposure to marijuana and assessments of the infants' postnatal course in the nursery period. Apgar scores of less than seven were not more frequent among nonusers (23%) than users (light 13%, moderate 13%, heavy 22%). Nursery complications as measured by time in high—risk nursery, time in isolette, jaundice, peripheral hematocrit, Dextrostex, weight change, presence of hypothermia, or feeding problems were no different in exposed than in nonexposed infants.

We found no evidence of a teratogenic effect associated with marijuana nor with the other illicit drugs. Of 39 infants with major malformations recorded in the infants' medical records, 12 (31%) were children of marijuana users, which is the expected percentage for the population. Likewise, no disproportionate increase in any of 34 minor anomalies observed by the investigators, or pattern of these anomalies, was evident in either dose—response relationships to the drugs or time during gestation of the exposure. Furthermore, there was no increase in the total number of anomalies per infant in the exposed subjects.

None of the variance in infants' responses to individual items on the Brazelton scale, nor to scores on clusters of the Brazelton items (adopted from factor analysis of the scale by Lester' et al. 1982) was accounted for by exposure to marijuana, alcohol, nicotine, or other illicit drugs.

Three variables—black race, nicotine, and gestational age—made significant contributions to the prediction of variance in muscle tone (Multiple R = .16, p<.O1). However, exposure to marijuana was not associated with either hyper— or hypotonicity.

Fried (1980) reported that infants of heavy marijuana users, as compared with matched controls, had heightened tremulousness and startles. To examine this relationship, in addition to the assessment of these behaviors on the Brazelton, 46 infants whose mothers reported using marijuana within 48 hours of delivery were compared with nonexposed infants. No increase in startles, tremors, or other neurobehavioral measures was apparent in these infants.

Evaluation of One—Year-Old Infants

Seventy—nine women who had reported smoking marijuana an average of seven times a week or more for one or more trimesters of pregnancy were selected for the follow-up study when the children were 1 year of age. Eighty women who had reported smoking less

than an average of seven times a week, and 80 women who were nonusers were selected randomly from each of these groups as controls.

Sixty percent of those selected were located and agreed to participate in the examination. Although 10% fewer users than nonusers were located, the difference in attrition was not statistically different among groups ($X^2 = 2.42$, $p<.10$). Additional cases were lost from the analysis by delays beyond 2 weeks from the child's birthday in arranging the appointments. The final data base consisted of infants of 38 heavy users, 44 light or moderate users, and 47 nonusers. There were significantly more first—born infants among the marijuana users (73%) than nonusers (32%), ($X^2 = 19.2$, $p<.001$) and also a higher percentage of males (table 6).

TABLE 6

Growth and Development of One—Year-Old Infants Selected for Level of Prenatal Exposure to Marijuana

			Means			
Marijuana Category	N	Males%	Weight (kgs)	Height (cms)	Mental Score	Motor Score
Nonusers	47	55	8.9	72.3	104.6	98.3
Light and Moderate	44	50	9.3	73.0	101.8	103.3
Heavy	38	63	9.1	72.8	104.8	98.2

No significant differences in infant outcome measures were observed among the groups (table 6). Multiple regression analysis on total amount of marijuana use reported during pregnancy, controlling for sex and parity, revealed no independent association of prenatal exposure to marijuana on growth or development scores. No significant differences attributable to marijuana were found in infant temperament, as assessed by the Bayley Behavior Checklist, or by the mothers' reports of illnesses, eating or sleeping problems, or personality characteristics during the first year.

Exposure to Marijuana During Breastfeeding

Sixty—two of the infants seen at 1 year of age had been breast— fed. Of these, 27 of the mothers reported using marijuana during breastfeeding; 12 of them smoked once a month or less, 9 weekly, and 6 daily.

No significant difference was found between users and nonusers in the age infants were weaned, suggesting that marijuana did not interfere with lactation.

Comparison of infant outcomes on growth, or on mental and motor development, revealed no apparent effects of postnatal marijuana exposure. Since statistical analyses were limited due to the small numbers and lack of comparability among cases for duration or dose, raw data for growth and development of the infants of six women who reported using marijuana daily during breast— feeding are given in table 7.

TABLE 7

Individual Data for Six One—Year-Old Infants Exposed
Daily to Marijuana Prenatally and Through Breastfeeding

	Subjects					
Infant Characteristics	1	2	3	4	5	6
Number of weeks breastfed	52	52	28	12	12	12
Prenatal exposure (av. per day)	1	2	1	3.6	2	2
Infamtsex	M	M	F	N	F	M
Height (cns)	76	72	69	74	73	75
Weight (kgs)	12.1	9.0	10.9	7.7	9.0	9.0
Mental Score	112	109	122	84	89	93
Motor Score	105	98	63	98	98	111

DISCUSSION

The findings in this investigation are consistent with other studies that have reported a trend toward or a significant reduction in fetal growth associated with exposure to marijuana during gestation (Hingson et al. 1982: Linn et al. 1983; Gibson et al. 1983). The previous studies found an impact on birth weight, whereas in the present study the impact was on length. This discrepancy may be related to different smoking habits in the populations sampled. In the present study an effect on birth weight may have been prevented by the marked reduction in number of women smoking and in amounts of marijuana consumed in the third trimester, which is the crucial period for fetal weight gain, and by the better—than—average weight gain during pregnancy by the marijuana users. Similarly, the effect on length may have been detected because of the high proportion of women ingesting relatively large doses of marijuana in the first trimester, when growth of cells may be affected (Miller and Merritt 1979; Redmond 1979). Further research comparing different populations and habit patterns is needed to clarify these discrepancies.

The finding of a positive correlation between length of gestation aid marijuana exposure is in conflict with reports of an inverse relationship between gestation and marijuana by two investigators (Fried 1982; Gibson et al. 1983). In one animal study, gestation was found to be prolonged by 1 to 2 days in

rats exposed to A—9—TSC throughout pregnancy (Borgen et al. 1971). The evidence of prolonged gestation in the human from the present study is weak in terms of the magnitude of the effect calculated from the equation, which was an average of two days delay associated with daily marijuana exposure throughout pregnancy. Research using animal models to investigate marijuana effects on maintenance of pregnancy or initiation of delivery may be required to resolve this controversy.

To our knowledge, no other study of humans has reported a significant increase in male births associated with father's marijuana use. In two animal studies, an increase in male offspring was observed in rats and in chimpanzees sired by males exposed to marijuana prior to mating (Fried and Charlebois 1979; Grilley et al. 1974). - In the present study, the assumption that marijuana is the sole determinant of the altered ratio is subject to question, since no information about the father's use of other drugs was obtained. If the finding is confirmed in other human studies, it would be of interest to determine the mechanisms involved in the reduction of female births.

Although there was no apparent increase in malformations among marijuana—exposed infants, the results of this study cannot be considered as providing firm evidence that marijuana or the other illicit drugs used by the women are not teratogens. Since the subjects in the study were selected after 6 months gestation, we could not investigate the possibility that exposure to marijuana early in gestation is associated with lethality for severely malformed fetuses. Our examination included inspection for minor physical anomalies compatible with Fetal Alcohol Syndrome which Hingson et al. (1982) had reported to be increased among marijuana users. Failure to replicate Hingson'5 findings may have been due to differences in criteria used to make the subtle clinical judgments required to discriminate a unique pattern of anomalies. Nonetheless, the findings from this study are compatible with experimental animal studies that report an absence of malformations associated with Δ—9—THC administered orally in doses equivalent to heavy human use (Wright et al. 1976).

The results of examinations of development and behavior in the neonate and at 1 year of age do not suggest that fetal or postnatal exposure to marijuana is associated with marked deficits in central nervous system functioning. Discrepancies between the present study and Fried's observation of poor habituation to a visual stimulus, increased tremors, and a peculiar cry as characteristics of marijuana—exposed neonates (1980) may be due to unknown differences in the two samples or differences in methodology.

Fried (1982), in agreement with the present study, reported no negative effects associated with prenatal marijuana use in a small number of infants examined at one year of age. In the present study, the evaluation of effects at 1 year of age may

have been biased ~y the self—selection of women who participated in the 1—year follow-up. However, there were no differences in refusal rates between marijuana users and controls to suggest that more marijuana users than controls failed to participate if the infant was developing poorly.

Although evidence of effects on central nervous system functioning in the neonate are inconclusive and no convincing evidence of effects lasting until 1 year of age have been produced, the possibility of effects on more complex cognitive functioning which develops after infancy, particularly the acquisition of verbal learning, have not been addressed to date.

In conclusion, several additional areas of research are needed to estimate the health risk associated with prenatal exposure to marijuana. Investigations of pregnant women are appropriate to establish the dose level of cannabis that may be related to adverse effects on fetal growth. Comparative studies with different species might clarify the effects of cannabis on duration of pregnancy. Additional longitudinal studies of children are needed to determine if there are long—term health risks associated with prenatal exposure.

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Postnatal Consequences of Maternal Marijuana Use

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Interest in marijuana's effects on various aspects of reproduction has a surprisingly long history. In his absorbing account of cannabis, Abel (1980) describes how Eastern European folk medicine has proclaimed for several centuries that marijuana could be used to hasten delivery. Reports from India that circulated widely in Europe discussed marijuana as both a sexual stimulant and a sexual inhibitor and, in the mid 1800s, the U.S. Dispensory (the widely read pharmacopea of the time) reiterated what the Arabs had been saying in the 16th century--that marijuana possessed aphrodisiac properties.

More contemporary reports that link marijuana with increased sexual pleasure have been plagued by the difficulty of separating the drug's effect from the drug user's overall lifestyle and the value placed on sexual activity (Abel 1981).

Moving from the realm of anecdotal reports to more objective reproductive measurements, one comes across a number of studies that have explored the relationship between maternal marijuana ingestion and fetal outcome in a variety of nonhuman species. A review of the data and an interpretation of these works is described by Abel (this volume). With respect to the human fetus, however, we are still very much at the frontier of knowledge.

Cannabis constituents can cross the placenta and be stored in the amniotic fluid (Harbison and Mantilla-Plata 1972; ldanpaun-Heikkila et al. 1969). Transfer of marijuana constituents from mother to infant can also occur via the milk as animal studies have shown (Jakubovic et al. 1974). This method of potential exposure of the neonate takes on considerable importance in the human as central nervous system (particularly glial and myelin growth) develops extensively postnatally.

The combination of the absence of information with respect to humans, the animal work from our own laboratory as well as others, the prevalence of marijuana use by women of reproductive age, and the cooperation of a number of hospitals in the Ottawa area led to what

we have called the Ottawa Prenatal Prospective Study. Since 1978, data has been collected from approximately 700 pregnant women in the Ottawa area for this study. Mothers-to-be are informed of the study by their obstetricians or by notices in waiting rooms of prenatal clinics in the four largest area hospitals. Upon volunteering to participate, each subject is interviewed once during each of the trimesters remaining in her pregnancy. The volunteer method of subject recruitment, dictated mainly by ethical considerations, serves to increase the reliability of self-report (discussed below) and to increase the likelihood of a long-term commitment to the study by the participants. Aside from the subjects who have moved from the Ottawa region (29%), we have maintained a retention rate of over 98% during the past 4 years.

During each of the interviews, typically conducted in the home of the mother-to-be, information is collected concerning socio-demographic status, mother's health (both currently and prior to the pregnancy), father's health history, obstetrical history of previous pregnancies, a 24-hour dietary recall, and past and present drug use, with particular emphasis on marijuana, alcohol, and cigarette use. For the drug histories, information is gathered pertaining to the year before pregnancy and each trimester of pregnancy.

The details of the interview and the categorization of the various drugs have been described earlier (Fried et al. 1980). Because the range of marijuana use in the sample was quite broad and bimodal in distribution, the drug data were usually not treated as a continuous variable, but rather as an interval variable. Four levels of use have been developed (Fried et al. 1980; Fried 1982): nonuser; irregular user (one joint or less per week or exposure to the exhaled smoke of others); moderate user (two to five joints per week); and heavy user (more than five joints per week). If hashish use was reported, the number of joints was multiplied by five to take into account the estimated greater concentration of tetrahydrocannabinol (THC) in hashish (the major psychoactive ingredient in cannabis) (Lerner and Zeffert 1968).

The method of using interviews to assess such variables as nutrition and drug habits raises critical issues of both validity and reliability. Several factors are relevant. Despite the potential shortcomings of self-reporting questionnaires, there is no practical alternative method of establishing the information needed for this type of investigation. A number of procedures to enhance the probability of an accurate self-report have been utilized in the present research. First, in order to develop a relaxed rapport, the same female interviewer "followed" the mother-to-be during her entire pregnancy. Second, the questionnaire was administered once during each trimester and, during each of these interviews, the questions pertaining to drug use for each trimester were repeated, permitting a test-retest reliability measure. With marijuana, the consistency of self-report was very high, with fewer than 7% of the women inconsistently reporting their marijuana usage. When an inconsistency was reported, the higher figure was utilized.

The demographic details and the extent of drug use during pregnancy among the first 407 subjects in the study have recently been published (Fried et al. 1984), as has a comparison of drug use before, during, and after pregnancy (Fried et al., in press). In the present sample, 80% stated that they did not use any marijuana in the year before pregnancy, 12% used it irregularly, 3% smoked 2 to *5* joints per week, and *5%* smoked 6 or more joints per week. Upon becoming pregnant, usage declined significantly, but during each of the trimesters the percentages remained relatively constant with 90% reporting no use, 6% reporting irregular use, 1% smoking 2 to *5* joints, and 3% reporting 6 or more joints per week.

Many, but not all, of the women who smoked marijuana regularly during pregnancy differed from the remainder of the sample on a number of factors that could be associated with adverse effects on the course of pregnancy and on the development of the offspring. These potential confounding factors included lower socioeconomic level, less formal education, and increased cigarette smoking. Increased alcohol consumption was also associated with heavy marijuana use, although not as strongly as was cigarette smoking. With respect to age, the heavy marijuana users were a significant 3.2 years younger than the remainder of the sample. However, no differences in parity were noted. Further, nutritional adequacy did not differ among the four categories of marijuana use.

A variety of variables have been examined during the course of the ongoing Ottawa Prenatal Prospective Study. The work that has been carried out and the work that is presently underway are described in table I.

One aspect that we have considered is the course of pregnancy (Fried et al. 1983). In our work, no differences have been found between the marijuana users and their matched controls (matched in terms of alcohol use, cigarette use, and family income) in terms of rate of miscarriage, type of presentation at birth, Apgar status, and the frequency of complications or major anomalies at birth.

In a recent report, Greenland et al. (1982) described the results of the effects of marijuana use in 35 pregnancies. The women included in the investigation reported not using other illicit drugs and were recruited from two California prenatal clinics. Compared to control subjects, significant differences in duration of labor (both protracted and prolonged) were observed, as well as an increased incidence of meconium staining among the infants born to marijuana users. A subsequent study (Greenland et al. 1983), which was designed to replicate the first, did not find that these adverse outcomes reached statistical significance. One of the principal differences in the two studies was a general higher level of health and living conditions among the women who participated in the second study. The sample in the latter report was more similar in terms of ethnicity, education, and general health to the Ottawa subjects than were the women in Greenland’s first report.

TABLE 1

Protocol of the Ottawa Prenatal Prospective Study

Birth

Labour-anaesthetics and analgesics
General birth measurements
Cord blood assay
Apgar
Postpartum medications
Birth Anomalies

Neonatal Perception Inventory
(Day 2 and 30)

Mother's perception of how her child compares to the "average" child with respect to crying, feeding etc.

Visual and Auditory Sensory Assessment
(one test at 3 - 5 years)

Ophthalmological examination
Visual and auditory cortical evoked potentials

Pegboard fine motor coordination test
(48,60 months)

Fine motor

Physical Anomaly Assessment
(one examination between 18 months and 4 years)

Anomalies of the face, head, hands and feet

Brazelton Neonatal Assessment Scale
(Day 4)

Visual and auditory responsiveness and habituation
Temperament
Tremors
Startles
Reflexes
Gross motor
Physical assessment

Bayley Scales of Infant Development
(6,12,18,24 months)

Temperament
Physical Assessment
Fine motor
Gross motor
Cognitive skills
Language comprehension and expression

Reynell Expressive Language and Verbal Comprehension Scale
(18,24,36,48,60 months)

Language comprehension and expression

Tactile Form Recognition Test
(48,60 months)

Fine motor
Sensory interaction

Postnatal Questionnaire
(one after child's first birthday)

General health of child
Age of walking
Onset of speech
Mother's use of alcohol nicotine, cannabis and caffeine during first year postpartum
Feeding decisions and pattern during first year postpartum
Socio-economic status
Family make-up
Childcare arrangements

Prechtl Neurolological Test
(Day 9 and 30)

Motor activity
Physical state and facial configuration
Reflexes
Visual and Auditory responsiveness and habituation
Physical assessment
Temperament
Nervous System symmetry

HOME Inventory
(24 months)

Assesses child's environment - both animate and inanimate

McCarthy Scales of Children's Abilities
(48,60,72 months)

Fine and gross motor
Cognitive skills
Language comprehension and expression

Peabody Picture Vocabulary Test
(48, 60 months)

Language comprehension

Neuropsychological Battery
(60,72,84,96 months)

Fine and gross motor
Sensory
Visual-motor
Spatial
Language and abstract reasoning abilities
Behavioural Rating Scale

In one animal study (Charlebois and Fried 1980), the interaction of marijuana with other pregnancy risk factors has been demonstrated and is consistent with Greenland's observations. In Charlebois and Fried's study, rats were exposed to either cannabis smoke, placebo smoke, or no smoke while concurrently consuming one of three diets differing in protein concentration. Both the diet and drug treatments were administered 20 days prior to and throughout gestation. A number of dependent variables, including stillbirths, litter destruction, and postnatal deaths, were potentiated by a combination of a low protein diet and cannabis smoke. Interestingly, some physiological and developmental milestones that were delayed in the normal-protein-diet/cannabis-smoke condition were attenuated in the high-protein-diet/cannabis-smoke condition.

An additional pregnancy variable that was noted in the Ottawa study was an inverse dose-response relationship between marijuana use and the length of gestation (Fried et al. 1984). An average use of marijuana six or more times per week during pregnancy was associated with a significant reduction in length of gestation of 1.1 weeks after statistically adjusting for nicotine, alcohol, parity, mother's prepregnancy weight, and the child's sex. With similar adjustments, no reduction in birth weight was noted once gestational age was taken into account. The association between marijuana use and shortened gestation is consistent with historical anecdotes that have, over the past centuries, described how cannabis has been used as a method to increase the vigor of contractions and shorten labor (Abel 1980).

Animal work has indicated that cannabis constituents can alter a wide range of pituitary-ovarian and adrenal hormones (Dalterio and Bartke 1979; Harclerode 1980; Smith 1980). Harclerode's study provides indirect evidence that THC can affect steroid production by the placenta. Although the underlying physiological nature of the shortened gestation length associated with heavy marijuana use can only be speculated upon at this stage of research, a likely candidate for the mechanism of action is marijuana's influence upon the reproductive hormonal system.

As part of the Ottawa Prenatal Prospective Study, we have examined the relationship between marijuana and minor physical anomalies (MPA) (O'Connell and Fried, in press). The offspring of 25 cannabis using women and the offspring of 25 matched controls were examined for the presence of a large number of anomalies. None of the anomalies noted occurred more frequently among the offspring of cannabis users, nor were the number of anomalies present in an individual correlated with maternal cannabis use. Although a pattern of anomalies was not detected among the offspring of cannabis users, two anomalies--true ocular hypertelorism and severe epicanthus--were found only among children of heavy users of cannabis.

The lack of a definite relationship between minor physical anomalies and prenatal cannabis exposure is compatible with several other reports in the recent literature (Linn et al. 1983; Rosett et al. 1983). Apparent exceptions are one large generally prospective study (Hingson

et al. 1982) and two reports based on five Individual cases (Qazi et al. 1982; Qazi et al. 1983). All of these studies examined neonatal outcome in relation to maternal alcohol or marijuana consumption in large, racially mixed, inner-city samples.

Rosett et al. (1983) found that the risk of congenital anomaly was greater among offspring of women who drank heavily throughout pregnancy as compared to those of women who stopped drinking, but the risk was not increased by the use of cigarettes or marijuana.

Linn et al. (1983) found crude associations between marijuana use and lowered birth weight, prematurity, and major malformations, which disappeared when demographic characteristics, other drug use, and medical history were controlled for.

The reports of congenital anomalies related to maternal cannabis use have dealt with those anomalies which are part of the diagnostic criteria of the fetal alcohol syndrome (FAS). Flingson et al. (1982) found that women who smoked marijuana during pregnancy were five times more likely than nonusers to deliver a child with features considered compatible with the fetal alcohol syndrome (CFAS).

In the case reports, Qazi et al. (1982; 1983) suggested a link between prenatal cannabis exposure and FAS-type features because, in four of the five cases reported, the mothers were regular users of cannabis, but denied use of alcohol or any other psychoactive drugs during pregnancy. However, little demographic information or medical history was given in the reports, and no matching to control potentially confounding variables was undertaken.

The lack of statistically significant CFAS features in the Ottawa sample may be due to at least three factors: sample size, age of the subjects, and the relative “risk status” of the women in the Study.

First, the sample size in the Ottawa Prenatal Prospective Study hindered the finding of significant relations among the variables studied. This difficulty has been encountered by other researchers in similar studies (Greenland et al. 1982). If the 2% rate of occurrence of CFAS found in Hingson’s study could be considered accurate and was applied to the present sample, only one child would be expected to meet the diagnosis.

The subject of the Hingson et al. (1982) study were all examined during the first week of extra-uterine life. The mean age of the subjects in the present study was 28.8 months. This difference is an important one considering that some MPA’s are transient, being seen only in the neonatal period, or gradually changing as development proceeds through infancy, e.g., epicanthal folds (Smith 1974). Evidence suggests that features indicative of fetal alcohol effects may normalize with age, thus suggesting a delay, rather than a deficit, in development (Majewski 1981).

As maternal nutrition interacts with cannabis consumption during pregnancy to influence fetal outcome (Charlebois and Fried 1980), it is not surprising that definite physical effects have been reported only in a sample where poor nutrition (as evidenced by low weight gain) and poor prenatal care are common. The influence of cannabis may be one of potentiation of the maternal factors which have a direct effect on fetal outcome. This interaction was not evident in the sample, which appeared, overall, to be better nourished than those of Hingson et al. (1982). The mean weight gain of the present sample was 16.02 kilograms compared to 13.64 kilograms in the Hingson sample. Several maternal factors combined to place the children of the Ottawa Prenatal Prospective Study at a low risk for environmentally induced congenital anomalies. The mothers lacked any chronic or debilitating diseases; received prenatal care; had an improved nutritional status; and had a higher socioeconomic status (i.e., 18% of the Hingson sample had a yearly income of less than $6,000, but only 2% of the present sample did).

Published data pertaining to the issue of the potential behavioral teratological effects of in utero marijuana exposure are limited to the work arising from the Ottawa Prenatal Prospective Study. The widely used Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Brazelton 1973) is utilized in an effort to quantify the newborn's response to external stimuli, motor organization, and ability to regulate alertness (table 1). In the Ottawa Prenatal Prospective Study, the examination is conducted at 60 to 80 hours postpartum, midway between feedings in a warm quiet room free from sudden extraneous noises, and located close to the hospital nursery. Observed behaviors include consolability, self—quieting, irritability, tremulousness, startles, alertness, orientation to animate and inanimate visual and auditory stimuli, habituation to stimuli in various modalities, hand-to-mouth movements, pull-to-sit muscle tone, Moro reflex, and liability of states. Assessment is carried out by two trained raters who are not aware of the mother's drug history.

A number of group differences have emerged using the Brazelton Scale (Fried 1980; Fried 1982). Smoking marijuana regularly during pregnancy was correlated with a marked decrease in the likelihood of the offspring responding to a light repeatedly directed at their eyes. Among infants born to women categorized as heavy users, 46% did not respond to the light in contrast to 16% of the babies born to matched nonusers ($X^2 = 4.282$, $p < .04$). Among the babies of the heavy users that did respond to the light, 33% failed to habituate compared to 7% of the matched controls. In the auditory modality, there were no differences between the marijuana offspring and the matched controls.

The apparent association between in utero marijuana exposure and visual functioning has been reported in previously published nonhuman primate work. Golub et al. (1981) examined the behavior of offspring of monkeys who had received daily treatment of tetrahydrocannabinol prior to and during pregnancy and throughout lactation. The types of behavior that were examined at I and 2 years of age included regulation of activity level, environmental responsiveness, problem solving, and social interaction. The category of behavior that

distinguished cannabis offspring from control offspring was visual attentiveness. In comparison to the offspring of untreated animals, the experimental babies failed to habituate visually to novel visual stimuli. It may also be noteworthy that Lodge (1977) and Finnegan (1981) observed that babies born to methadone-using mothers also responded poorly to visual stimuli, but were not abnormal in their responsiveness to auditory stimulation.

The most consistent and visible consequences of regular heavy marijuana consumption were significantly heightened tremors and startles. Among those offspring born to heavy marijuana users, 73% displayed marked tremors (a score of 7 or higher on the Brazelton Scale) contrasted to 30% of matched controls ($X^2 = 6.744$, $p < .009$). Startles (spontaneous and elicited) were also more pronounced among the offspring of heavy marijuana users ($X^2 = 5.287$, $p < .03$). These, together with the altered visual responsiveness, may reflect neurological dysfunction, possibly in the form of nervous system immaturity or a manifestation of drug withdrawal. However, unlike infants going through narcotic withdrawal, the marijuana babies were not more irritable than controls and were readily consolable. Finally, at this age, in our study, no association was observed between the degree of activity or of alertness and maternal marijuana use.

The Prechtl and Beintema neurological examination (1969) is given at 9 and 30 days of age (table 1). By using standardized techniques to elicit a comprehensive selection of reflexes and responses, this neurological inventory is designed to measure subtle qualitative and quantitative differences in behavior. Results from this test indicate that the altered responsiveness of the visual system noted above persisted in those infants whose mothers smoked marijuana six or more times per week during their pregnancy. The consistency was rather striking. Of the offspring of the heavy marijuana users who failed to respond to the visual stimuli at 3 days of age, 71% were not responsive at 9 days and *50%* continued to be unresponsive at 30 days. In contrast, all of the babies of heavy users that did respond to the visual stimulus during the Brazelton test continued to respond on the Prechtl test at 9 days of age. Among the matched controls who did not respond on the Brazelton, all did respond at 9 days, and all but one at 30 days when tested on the Prechtl.

As part of the Prechtl test, various extraocular movements were also examined, and some abnormalities among the marijuana infants were noted. In order to pursue these “soft” visual signs of the potential effect of intrauterine exposure to marijuana, a series of neuro-ophthalmological and electrophysiological tests are presently being conducted jointly with Drs. B. W. Tansley (sensory psychologist) and H.
T. J. Mount (neuro-ophthalmologist). Included in this neuro-ophthalmological battery are pupillary responses, gaze preponderance, tracking capability, optokinetic reflexes, and visual-evoked potentials to a patterned stimuli.

The preliminary results are quite striking. The dimension of interest in the pattern-evoked cortical response are the latencies of various

components of the waveform, with particular emphasis on the major positive component, P100, which occurs at approximately 100 milliseconds after the stimulus onset in adults. This component tends to be later in children and begins to approximate the adult waveform by 10 years of age.

Twenty children born to mothers who used marijuana prenatally were matched with 15 control children on the basis of child's age (3 to 6 years) and mothers' prenatal use of alcohol and nicotine. Findings showed that the P100 latency is consistently delayed in both left and right eye monocular condition. This is consistent with the notion that prenatal exposure to marijuana may delay the maturation of the visual system.

The ophthalmological examination has also demonstrated differences among the marijuana subjects and their controls in terms of myopia, strabismus, abnormal oculomotor functioning, and unusual discs. The neuro-ophthalmologist, examining the children without knowledge of their prenatal history, noted that *35%* of the marijuana subjects had more than one of the above problems, as compared to only 6% of the controls ($z = 2.43$, $p < .008$).

The Prechtl examinations also revealed some motor differences among the babies born to the heavy marijuana users. Most prominent were the marked tremors which at 9 days were observed in 43% of the babies contrasted with 12% of the matched controls ($X^2 = 9.362$, p (.003), and at 30 days were still present in 25% of the heavy marijuana offspring and only 8% of the controls ($X^2 = 3.806$, $p < .06$). The tremors among the babies born to the heavy marijuana users were significantly more likely to be low frequency, high amplitude in nature compared to the controls. Other motor differences observed among the infants of heavy marijuana users included an exaggerated Moro reflex, increased occurrence of athetoid movements and disinhibition in a number of motor tests. Like some of the observations made soon after birth, many of these behaviors are similar to those observed in infants undergoing narcotic withdrawal (Finnegan 1981).

In the Ottawa study, children are administered the Bayley Scale of Infant Development (Bayley 1969) at 6, 12, 18, and 24 months of age (table 1). The mental portion of this test assesses sensory perceptual abilities, early acquisition of object constancy, problem solving, and the onset of vocalization. The motor portion is directed at assessing both gross and fine motor abilities. A temperament portion measures more clinical aspects of behavior, evaluating various general aspects of the child's functioning rather than assessing particular skills. At 18, 24, 36, and 48 months of age, the Reynell Expressive Language and Verbal Comprehension Scale (Reynell 1969) is administered and, at 36 and 48 months, the McCarthy Scales of Children's Abilities (McCarthy 1972) is given. Table I outlines the tests administered to the infants and children at the various ages.

Group data collected from the tests administered at 6 and 12 months of age failed to discriminate between those babies born to heavy

marijuana users and either those born to matched controls or normative scores based on the general population. However, among the offspring of the heavy marijuana users, two subgroups were identified. Although the number of subjects that fulfill the criteria for inclusion within the subgroups is small, the results are quite pronounced. Among those babies who demonstrated a consistent decrease in visual responsiveness on all three neonatal tests and for whom the two Bayley scores are available (N = 6), the mean Mental Developmental Index (MDI) was 82 (range 60 - 92) at 6 months, and 96 (range *75* - ill) at 12 months. Among the few children who did not show the neonatal decreased visual responsivity, but who were born to mothers with similar heavy marijuana habits (N = 7), the mean MDI at 6 months was 118 (range 106 - 129), and at 12 months was 106 (range 98 - 120). Among the matched controls, the mean MDI at 6 months was 102 and at 12 months, 101. At 18 and 24 months, no differences were noted on the MDI between the offspring of the heavy marijuana users who were consistently visually less responsive as neonates and those who had normal visual responses.

An examination of both the overall motor portion of the Bayley Psychomotor Developmental Index (PDI) and the fine and gross motor clusters at 6, 12, 18, and 24 months failed to reveal any differences between the offspring of marijuana users and matched controls. Further, subdividing the babies born to mothers who used marijuana heavily into those who showed marked tremors on the neonatal tests and those who did not failed to distinguish the babies on the Bayley motor tests.

The picture that has emerged to date is that there are a number of neonatal neurobehavioral variables that are correlated with in utero marijuana exposure that persist after controlling for nonmarijuana drug habits, the history of previous pregnancies, socioeconomic status, and nutritional (including caffeine) intake.

Finally, the general observation that the neonatal nervous system alterations seen in the offspring of regular maternal marijuana users seemingly does not express itself in poorer performance on cognitive and motor tests at U and 2 years of age must be interpreted cautiously. It is not at all clear whether this is the true state of affairs arising because neurological disturbances present at birth are truly transient and are overcome, or compensated for with maturity, or whether the tests used at the Ii and 2 year ages might have a decreased discriminatory sensitivity to subtle cognitive differences that actually may exist.

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Long-Term Effects of Prenatal Methadone Maintenance

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Methadone maintenance has been the treatment of choice for heroin addiction for several years. The prenatal and early neonatal effects have been described in several reports (Kandall et al. 1979; Finnegan 1983). However, there have been few reports on the long-term effects of methadone maintenance during pregnancy on the child's somatic and neurobehavioral development. Some investigators have described mild neurobehavioral abnormalities, while others have found none (Finnegan 1983: Wilson et al. 1981; Lifschitz et al. 1983; Strauss et al. 1979).

Since 1977, we have followed a group of children born to mothers on methadone maintenance during pregnancy and a matched group of children born to drug-free mothers. The children are now between 3j and 7 years old. This report covers in some detail our findings from the neonatal period through 36 months. The trends in the data that have been collected thus far on the children who have reached ages 4, 5, 6, and 7 years will then be discussed.

METHODS

Fifty-seven mothers on methadone maintenance were enrolled in the study during pregnancy. After delivery, their children were enrolled in the follow-up study. The 31 comparison mothers and their neonates were enrolled within 24 hours after birth and were matched to the methadone subjects for maternal race, socioeconomic status (SES), sex, birth weight, and gestational age. A total of 61 infants (30 females and 31 males) of methadone maintained mothers and 32 infants (15 females and 17 males) of comparison mothers were enrolled in the follow-up study. There were 4 sibling pairs in the methadone group and 1 sibling pair in the comparison group. By the time the child reached
36 months of age, the attrition rate was 36% in the methadone group and 28% in the comparison group. At the present time, in the 7th year of the study, the attrition rate is 43% for both groups. Comparisons were made between the lost and continuing subjects, and no significant differences were found in the prenatal and neonatal characteristics. Table 1 is a summary of the maternal and neonatal data at intake. Although the comparison mothers are significantly younger than the methadone mothers, both groups are well within optimal childbearing age. Another significant finding is that

methadone mothers smoke more than one pack of cigarettes/day with higher frequency than the comparison mothers. In the methadone group, maternal urines were analyzed during pregnancy for drugs of abuse, using the homogeneous enzyme immunoassay procedure (EMIT) (SYVA Palo Alto, Calif) and thin-layer chromatography. Multidrug abuse of such drugs as diazepines, opiates, cocaine, barbiturates, and tricyclics was evident in 56% of the methadone mothers. Fifteen percent were also moderate to severe alcohol abusers, as evaluated by frequent history taking. By 36 months, 10% of the mothers on methadone maintenance had discontinued their methadone use. Also, significantly more comparison mothers than methadone mothers were working and off welfare by 36 months (p<.O2).

TABLE 1

Maternal and Neonatal Data at Intake

Maternal Data	Methadone	Comparison
Age	26.8+5*	22+.9*
Race (%)		
White	7.3	3.6
Black	78.2	78.6
Hispanic	14.5	17.9
Obstetrical complications (%)	22.2	14.3
Methadone dose (mg/day)	42+3	
Months on methadone	43+3	—-
Multidrug abuse (%)	56	0
Tobacco (1 pack/day)	90*	28.6*
Neonatal Data		
Birth weight (gin)	3129+192	3037+101
Premature rate (%)	15.4	11
SGA (%)	13	3
Apgar score 1	7.4+.3	8.1+.l
Apgar score 5	8.5+.2	9.0+.1
Sex (n)		
Males	31	17
Females	30	15
Withdrawal syndrome (%)	75.1	—-
Severe (%)	23.3	
Moderate (%)	51.8	——
Mild (%)	24.9	——

* $p<.^{05}$

NEONATAL PERIOD

Procedures

All neonates had a physical and neurological evaluation within 48 hours of birth. Gestational age was determined by the estimated date of conception (EDC) when known and/or using Dubowitz criteria (1970). Severity of narcotic abstinence syndrome was evaluated using a withdrawal scoring system modified from one used by Finnegan et al. (1975) daily until discharge. In addition, Brazelton's Neonatal Behavioral Assessment Scale was administered to each infant between 48 and 96 hours after birth (Brazelton 1973).

Results

As illustrated in table 1, there was a higher incidence of small for gestational age infants and head circumferences below the third percentile in the methadone group ($p<.05$). These findings were not associated with alcohol intake or tobacco smoking. The incidence of narcotic withdrawal was 75%, with 75% of these cases exhibiting moderate to severe symptoms. In early infancy, at approximately 2 weeks of age, 20 infants of mothers on methadone maintenance developed elevated systolic blood pressure as measured using the Doppler. The mean systolic blood pressure was 95, with a range of 59 to 132 mm/Hg. This occurred irrespective of the severity of narcotic abstinence syndrome, and lasted for about 12 weeks. This systolic hypertension may be secondary to autonomic nervous system dysfunction as a result of in utero narcotic drug exposure (Rosen and Johnson
1982).

Correlations were run between prenatal and neonatal variables. Methadone dose and length of methadone maintenance correlated positively with the presence of obstetrical complications and the severity of narcotic abstinence syndrome ($p<.01$). Maternal methadone dose also correlated positively with birth weight ($p<.05$). The Brazelton Behavioral Assessments, done at 48 to 72 hours of life, revealed several differences between the methadone group and comparison group infants. The methadone neonates were less responsive to rattle decrement, less responsive to inanimate visual orientation, less alert, less cuddly, and less consolable. They also demonstrated increased tone, less motor maturity, increased pull-to-sit, and more tremulousness. Many of these findings were most likely related to the infants' experiencing narcotic abstinence syndrome.

FOLLOWUP: 2 TO 36 MONTHS

Procedures

After birth, the infants were seen at the follow-up clinic at 2, 4, 6, 8, 10, and 12 months of age and then every 6 months. Each follow-up visit included physical, neurological, and behavioral evaluations, as well as routine well baby care. Emergency medical care and social service assistance also were provided when necessary.

In general, the physical and neurological examination covered growth parameters, cranial nerves, tone, gross and fine motor coordination, normal and abnormal reflexes, and developmental milestones. In addition, hospital and clinical charts were reviewed for emergency room/clinic visits and number and type of infections and referrals. The behavioral evaluation included the Bayley Scales of Infant Development, which was given at 6, 12, 18, and 24 months of age, and the Merrill-Palmer Scale of mental tests at 36 months. At 30 and 36 months, a 30-minute mother—infant interaction session, including both free play and structured task situation, was videotaped. Spontaneous language production in these tapes was analyzed, using Brown's (1973) procedures for computing length of utterance.

Results

During the first 36 months follow-up there were no significant differences in somatic growth among the two groups. There was a consistently higher incidence of head circumferences below the third percentile in the methadone group of children. Many of these children demonstrated eye disorders, such as strabismus and/or nystagmus. With respect to the rate of infections during the first 24 months of life, the methadone children had significantly more episodes of acute and chronic otitis media ($p<.OOl$). These episodes may have been due either to therapeutic noncompliance or to an early immune deficit. The neurological evaluations, summarized in table 2, showed a significantly higher incidence of abnormalities in the methadone children. These abnormalities included hypotonia or hypertonia, poor fine motor coordination, delays in attaining developmental milestones, and poor language development. The Bayley Scales scores are summarized in table 3. All mean scores were within the range for normal performance. However, the methadone group scored significantly lower on both the Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 12 and 18 months, and on the PDI at 24 months ($p<.05$). To determine if there were differences in score distribution, the frequency of Bayley scores below 85 was examined in each group at both 12 and 24 months. Methadone children had disproportionately more low scores at 12 months in both MDI and PDI scales ($p<.O5$). Further analysis of the components of the Bayley Scales revealed that responsiveness to verbal requests from others by 12 months of age was only present in 18% of the methadone children as compared to 50% of the comparison children. The ability to express wants, usually present by 18 months, was evident in only 28% of methadone versus 47% of comparison children at this age (Rosen and Johnson 1982).

To evaluate consistency of neurobehavioral performance across measures and across time, correlations between Bayley MDI and PDI scores and neurological assessments were run for each subject group. In the methadone group, there were strong correlations between Bayley scores at different time points, as well as between the neurological evaluations and Bayley scores at both 12 and 24 months ($p<.05$ for all correlations).

TABLE 2 Neurological Evaluations (6-36 months)

Age (mo.)	Suspect to Abnormal (%) Methadone	Comparison
6	(n~45)	(n=25)
	44.3	36
12	(n~46)	(n=22)
	22*	4.5
18	(n=38)	(n~23)
	18.3*	4.3
24	(n=39)	(n=21)
	20.6*	43*
36	(n=39)	(n=23)
	32	13

TABLE 3
Developmental Evaluations

I. Bayley Scales of Infant Development

	Methadone	Comparison
6 months	(n=41)	(n=23)
MDI	95+2.5	100.7+4.2
PDI	lOT.0+2.8	105.1+2.9
12 months	(n=41)	(n=22)
MDI	98.4+2.7	107.0+2.8*
PDI	94.9+2.5	102.8+2.3*
85 (MDI)	20%	
(PDI)	20%	
18 months	(n=38)	(n=23)
MDI	96+2.3	.106.4+3.6*
PDI	92.6+2.4	105.3+2.2*
24 months	(n=34)	(n=22)
MDI	90.4+2.6	96.9+3.1
PDI	99.1+2.7	108.is2.7*
85 (MDI)	39	15*
(PDI)	17	5

II. Merrill-Palmer Scale

36 months	(n=39)	(n=21)
NIPS	44.6+2.1	46.3+2.3
SPP	55.7+4.4	63.1+5.1
25%	18%	4%

* p ~•.05

The relationship between various prenatal and neonatal characteristics and developmental outcome was further examined at 18 and 24 months. Perinatal variables included maternal age, length of methadone maintenance, methadone dose, multidrug abuse, obstetrical complications, Apgar score at 5 minutes, and severity of narcotic abstinence syndrome. There were no significant correlations between these perinatal variables and developmental outcome (Rosen and Johnson 1982; Johnson et al. 1984). An analysis of covariance in a regression mode indicated that treatment group (methadone vs. comparison) and sex (male vs. female) were the only factors related to poor developmental outcome (Rosen and Johnson 1982; Johnson et al. 1984). The scores of the Brazelton Neonatal Assessment Scale did not correlate with the 18 months neurodevelopmental outcome.

At 36 months there were no differences in the mean Merrill—Palmer scores and percentiles, although lower scores were more prevalent in the methadone group. Measurement of head circumference and the neurological evaluation correlated with the Merrill—Palmer scores.

Using the videotapes, an analysis of spontaneous language production with mean lengths of utterances (MLU) was performed at 36 months. The MLU was based on 50, rather than 100, utterances due to only 30 minutes of videotaping. However, even with this lower utterance requirement it was necessary to drop 5 methadone and 6 comparison children from the analysis. The mean MLU for the methadone children was 2.71 $\pm$ .66 and 3.14 $\pm$ .66 ($p<.O7$) for the comparison children. These MLU samples are lower than those reported for middle-class samples (Brown 1973).

Cluster analysis was used to determine whether the study population was comprised of homogeneous groups having distinct patterns of developmental outcome (Hartigan 1975). In this analysis, developmental outcome was defined by four variables: percentile head circumference, neurological examination, Merrill—Palmer Scales scores, and number of referrals for educational and/or developmental problems. The mean scores are illustrated in table 4. Cluster III, the group showing the weakest developmental status, consisted overwhelmingly of methadone children (85%) 5:1 ratio. This suggests that some children born to mothers on methadone maintenance demonstrate no long-term effects, while for others, their outcome is guarded. The factors that distinguish one group from the other are not yet known. We found no differences in Clusters I and Ill as far as prenatal and neonatal factors were concerned. At present, we are further examining the environmental and early experiences of these infants.

FOLLOWUP: 37 TO 84 MONTHS

Procedures

Children are seen for routine follow-up evaluations every 6 months, although the project continues to provide emergency medical care and social service assistance when needed. The focus of the physical and neurological evaluations remains on growth parameters, tone, motor coordination, and developmental milestones.

TABLE 4

Summary of Variable Means for 3-Cluster Analysis of

Continuing Subjects at 36 Months

Cluster	I	II	III
Head circumference (%)	61.5+13.7	32.5+7.1	6.0+5.2
Neurological evaluation @	l.4+.6	l.2+.5	1.4+.?
Merrill-Palmer score ~	52.1+14.7	45.1±9.4	41.0+9.7
Referral for Special Services @	0		
Number of methadone subjects (n=36)	9	10	17
Number of comparison subjects (n=18)	4	11	3

@ M±SD

The behavioral evaluations have concentrated on language and perceptual development. Between 42 and 60 months, children receive verbal and comprehension tests and the Perceptual Integration Test. At 66 and 78 months, the children receive three standardized measures of emerging skills. The first, the Boehm Test of basic concepts. measures mastering of basic relational concepts. The Boehm Test is widely used and has been standardized for inner-city children. The second measure is the Motor—Free Visual Perception Test (MVPT), which yields a perceptual quotient relating the child's perceptual development to his age. The third measure is the Northwestern Syntax Screening Test, which yields separate scores for receptive and expressive language skills. In addition, children receive the McCarthy Scales of Children's Abilities at 72 months, and the Wechsler Intelligence Scale for Children-Revised at 84 months.

Results

Because not all of the children have reached 84 months, results are preliminary. Again, there are no differences in height and weight between the methadone and comparison children. These children are generally healthy. There are three children with generalized lymphadenopathy of unknown etiology which, thus far, have yielded negative workups. Neurological evaluations, summarized in table 5, show a higher prevalence of abnormalities of fine and gross motor coordination, poor balance, hyperactivity, decreased attention span, and speech and language delays in the methadone children.
Significance

was not determined as the numbers are still incomplete in each group. Table 6 is a summary of the behavioral evaluations. As the children approach school age, it appears that the differences between the two groups are diminishing. There is a trend toward lower scores in the Northwestern receptive language evaluations among the methadone children. There is also a higher incidence of referrals among the methadone children for behavioral and academic problems. Those children who showed poor neurological development at 18 to 36 months continue to do poorly at 37 to 84 months. As the comparison group children approach school age they have begun to show poor performance in testing. This has been reported by others in children from low socioeconomic class. There is no significant difference in the McCarthy Scales between the two groups. Further preliminary analysis of the McCarthy scores, in relation to the three clusters created, reveal the following: Cluster I means the GCI score was 100.7+4; Cluster II score was 83.6+3; and Cluster III score was 85.4+3. Those children in Cluster III continued to perform poorly. The children in Cluster II showed poor performance on the McCarthy Scales. This most likely reflects the deteriorating performance of the comparison children..

TABLE 5

Neurological Evaluations (48-72 months)

	Suspect to Abnormal (%)	
Age (mo.)	Methadone	Comparison
48	(n=36)	(n=19)
	44	32
60	(n=31)	(n=15)
	42	33
72	(n=20)	(n=9)
	50	11.1

DISCUSSION

The data from our study reveal no uniform long-term effects of prenatal methadone maintenance. In the first 36 months of life, however, children in the methadone group do exhibit a higher incidence of minor neurological abnormalities and lower scores on developmental evaluations. While the comparison children seem to do better during the first 36 months of age, their performance deteriorates as they approach school age. The methadone children show very little flexibility in developmental course. Children in the methadone group seem to continue early patterns of performance and developmental status without a change. Thus, despite exposure to similar prenatal as well as postnatal environmental stresses, some methadone children do well initially and throughout early childhood, while others do poorly

initially, and then continue to show poorer development. At the same time, however, various prenatal variables (e.g., use of other drugs, obstetrical history, and neonatal course) did not correlate with neurodevelopmental outcome. The methadone-exposed babies, born at high risk, have special needs which place extra demands on their mothers. However, many of these mothers themselves have many special needs and problems which make it very difficult for them to adjust to their infants' needs. Consequently, inconsistent mothering and unstable environments may further accentuate the effects of early infant characteristics (Thomas and Chess 1977). In examining further the characteristics of the children who did well on the Merrill-Palmer at 36 months, two factors emerged: maternal education and family stability. Other researchers have also reported on children who were born at risk, but who were able to overcome their handicaps because they were reared in stable environments with parents responsive to their needs (Sameroff 1975; Werner et al. 1968).

TABLE 6

Developmental Evaluations (66-78 months)

		Methadone		Comparison
MVPT PQ	66 mo. (n=13)	85.08+3.72	(n=6)	96.8+ 3.9
	78 mo. (n=12)	95.8+ 3.7	(n=7)	98.4+ 7.3
Boehm %	66 mo. (n=12)	62.9+ 8.3	(n=6)	82.5+10.6
	78 mo. (n=12)	31.5+ 6.9	(n=7)	39.3+10.4
NW Rec %	66 mo.(n=l0)	40.2+10.9	(n=5)	58.0+14.8
	78 mo. (n=12)	41.9+ 7.2	(n=7)	28.4+ 7.9
NW exp %	66 mo. (n=10)	25.9+ 7.9	(n=5)	31.6+15.2
	78 mo.			
MGCI	72 mo. (n=18)	89.22+3.4	(n=l0)	88.9+ 3.2

(M± SE)

In our study, as the children got older, the differences in mean scores between the groups have become smaller. This phenomenon has already been noted at 36 months on the Merrill-Palmer Scales and at 72 months on the McCarthy scores. This type of decline in scores has been shown in low SES children by others after 24 months (Bradley and Caldwell 1976). In analyzing individual tasks, however, the methadone children seem to have particular difficulty with tasks which are highly structured or involve verbal instruction. In summary, a child born to a mother on methadone maintenance is not only exposed to a drug or drugs in utero, but is also exposed to the continued emotional, familial, and environmental instability associated with the drug culture. This places the child at even greater risk for long—term developmental difficulties.

An examination of the interaction between prenatal factors, early experience, and environment should be used to plan intervention and treatment programs to enhance the subsequent development of these children.

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Effects of Maternal Narcotic vs. Nonnarcotic Addiction on Neonatal Neurobehavior and Infant Development

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There is no question that the number of women using and abusing nonnarcotic drugs far exceeds the number who are addicted to narcotics (Chambers and Hart 1977). Current data show that 63% to 93.5% of women use analgesics during pregnancy and that sedative drug use ranges from 22% to 28% (Doering and Stewart 1978; Forfar and Nelson 1973; Hill 1973). However, until recently, little attention has been given to pregnancies complicated by the maternal use of drugs other than heroin and methadone.

At the Perinatal Addiction Project of Northwestern Memorial Hospital, the last 5 years have seen a rapid increase in the proportion of women enrolling in our program who are using and abusing non-narcotic substances during pregnancy. Screening of all women presenting to Prentice Women's Hospital and Maternity Center for prenatal care during a 6-month period in 1982 revealed that 3% of these women had evidence of sedative-hypnotics in their urine at the time of admission to the general maternity clinic (Chasnoff et al., in press). Reflecting the increasing popularity of phencyclidine hydrochloride (PCP) in the United States (Showalter and Thorton 1977), a number of pregnant women who abuse PCP have entered the Perinatal Addiction Project. The present report will review the intrauterine growth, neonatal behavior, and growth and development of infants whose mothers used nonnarcotic substances during pregnancy. These infants will be compared to infants born to mothers who used narcotics during pregnancy and to infants delivered to women with no history or evidence of substance abuse.

SUBJECTS AND METHODS

Data are available on 95 infants born to mothers enrolled in the Perinatal Addiction Project between December 1976 and December 1982. All of the women were enrolled in the first or early second trimester of pregnancy and completed a course of intensive prenatal care. Maternal urine samples were obtained regularly to screen for illicit drug use. For neonatal assessment, the 95 infants were divided according to the type of primary maternal addiction:
heroin/methadone (N=5l), Group I; mixed sedative/stimulant (N=22),

Group II; pentazocine/tripelennamine (N=13), Group III; and PCP (N=9), Group IV.

Mothers in Group I conceived while on heroin. Forty-seven of these women were abusing heroin only. Four women abused an additional one or two nonnarcotic drugs. Upon admission to the program, each woman was placed on a variable initial daily dose of methadone. This dosage was steadily decreased to the lowest level which would prevent craving or withdrawal in the mother. By the beginning of the third trimester, each woman was on a maintenance dose of methadone, ranging from 5 to 40 mg daily (mean=15.9, S.D.=1O.4). This dose was held at the same level for the rest of the pregnancy, and no woman was completely withdrawn during pregnancy. Daily urine screens indicated that all but three of the women remained clean of narcotic and non narcotic drugs, other than the prescribed methadone.

Mothers in Group II were addicted to multiple licit and/or illicit nonnarcotic drugs. Each woman used two to five of the following drugs in various combinations before and during pregnancy: phenobarbital, diazepam, marijuana, alcohol, and cocaine. These women received the same regimen of prenatal care as Group I except that they did not receive methadone. Although abstinence was the objective for this group, only five of the women remained clean of drug use throughout the third trimester of pregnancy.

Thirteen infants were delivered to women who abused a combination of pentazocine and tripelennamine (T's and blues, respectively) during pregnancy (Group III). All of the women in this group sporadically used other, nonnarcotic drugs, but T's and blues were the only drugs consistently used throughout pregnancy. Although abstinence was the objective of the program, none remained clean of T's and blues during the third trimester of pregnancy.

Group IV infants were delivered to nine women whose primary drug of abuse throughout pregnancy was PCP. All of the women had positive urine screens which demonstrated sporadic use of other nonnarcotic drugs in addition to the PCP, which was the only substance used heavily (at least 5 days per week) throughout the third trimester.

Three of the Group II women sporadically used T's and blues or PCP during pregnancy, but this use was very limited and did not occur in the third trimester. Hence, these three women were included in Group II based on their primary abuse of various sedatives and stimulants throughout pregnancy.

For comparison, infants of a group of drug-free mothers (Group V, N27) were selected for neonatal assessment in the order the women presented for prenatal care to the clinic of Prentice Women's Hospital and Maternity Center. These women had no history or evidence of drug or alcohol abuse, and management of prenatal care and nutrition was similar to the four drug-abusing groups of women.

All groups were evaluated for maternal factors which might affect neonatal outcome: race, maternal age, education, gravidity, prenatal care, nutrition, cigarette smoking, and drug use. Analysis of variance and chi—square analysis were utilized for statistical analysis of these parameters. All neonates were examined at birth, and weight, crown-to-heel length, and fronto—occipital head circumference were recorded. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) (Brazelton 1976) was administered at 2 days of age by trained examiners who were blind to the infants' prenatal history. Results of neonatal data were analyzed utilizing analysis of variance. For those items which reached statistical significance ((.05), the Fischer's LSD (Kirk 1968) was utilized to identify homogenous subsets.

For long-term follow-up, the opiate-exposed infants (Groups I and III) were combined into Group A, and nonopiate-exposed infants (Groups II and IV) were combined into Group B. The previous group of control infants (Group V) was expanded to include a total of 35 infants to serve as controls for long-term assessment (Group C). The Bayley Scales of Infant Development (Bayley 1969) were administered to all infants at 3, 6, 12, and 24 months of age. The infants were examined at these same time intervals, and weight, fronto-occipital head circumference, and crown—to—heel length were recorded. Differences between control and each drug—exposed group of infants at each interval for all parameters of growth and development were analyzed through use of the two—tailed t test.

RESULTS

Neonatal Assessment

Demographic data (age, gravidity, education) for the women in Groups I through V were similar, as was the frequency of cigarette smoking in each of the groups. However, racial distribution varied between the groups (table 1). Thus, for analysis of neonatal data, race was controlled through covariate analysis when each drug-using group was compared to the Group V mothers and infants.

All infants were delivered at term gestation as determined by the criteria of Ballard et al. (1977). There was an even distribution of infants by sex in each group. Apgar scores in the five groups were similar, and no significant perinatal complications occurred in any group. Twelve infants in Group I required therapy for significant withdrawal, based on clinical criteria of marked irritability, poor feeding, and/or excessive weight loss. No infants in the other drug groups required therapy for withdrawal.

Somatic Measures

Infants delivered to mothers in Group I and in Group III had a significantly lower weight and length than control (Group V) infants (table 2). In addition, these Group I and Group III infants had significantly smaller head circumference than both the control infants and those in Groups II and IV. These differences remained when

TABLE 1

Racial Distribution of Neonates

	I Heroin/ Methadone		II Sedative/ Stimulant		III T & B		IV PCP		V Drug-free	
	N	%	N	%	N	%	N	%	N	%
White	33	65	10	45	1	8	8	89	7	26
Black	16	32	11	50	12	92	1	11	12	44
Hispanic	2	3	1	5	0	-	0	-	7	26
Oriental	0	-	0	-	0	-	0	-	1	4

TABLE 2

Neonatal Growth Parameters

	I Heroin/ Methadone		II Sedative Stimulant		III T & B		IV PCP		V Drug free	
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.
Weight (gm)	2840*	600	3165	560	2799*	430	3201	440	3479	623
Length (cm)	48.2*	3.5	50.0	3.1	48.1*	1.8	49.3	2.6	51.1	2.8
Head circumference (cm)	32.2*†	2.4	33.9	1.5	32.9*†	1.2	33.7	2.0	34.7	1.7

*ANOVA (Specific Drug Group x Group V), $p<.01$

†Significant difference from Groups II and IV (Multiple Range Test)

race was statistically controlled. The birth weights, lengths, and head circumferences of the sedative/stimulant- and PCP-exposed infants were not significantly different from those of the control infants.

Neonatal Behavior

Means and standard deviations for those BNBAS items for which statistically significant differences were obtained are listed in table
3. Significant differences were obtained in items related to interactive ability, motor maturity, and state control. Items related to visual and auditory orientation and motor maturity differentiated the methadone-dependent group from both the control and all other drug groups (Fischer's LSD). All four groups of drug-exposed neonates showed deficits in state control with an abnormal predominant state, an increased lability of state, and poor consolability. In addition, PCP-exposed infants (Group IV) showed significantly increased lability of states and poor consolability when compared to all other drug groups (Fischer's LSD).

Infant Assessment: Two-Year Follow-up

In this portion of the study, demographic data for the two drug-exposed groups of infants and the control group of infants were again similar. In addition, upon combining Groups I and III (opiate-exposed infants) into Group A and Groups II and IV (nonopiate—exposed infants) into Group B, racial distribution was similar for the two study groups and the control group (C): 53% white, 43% black, 4% Hispanic in Group A; 58% white, 39% black, 3% Hispanic in Group B; 52% white, 40% black, 6% Hispanic, 2% Oriental in Group C.

Somatic Growth

Infants in Group A had significantly lower weight and length than the Group C drug-free infants at both 3 and 6 months (t test) (table 4). By 12 months of age, Group A infants had caught up in weight and length to the control infants. [lead circumference measurements for the opiate-exposed Group A infants did not exhibit such catch—up growth, however, and head circumference for these infants remained significantly smaller than that of the control infants throughout the 2-year follow-up. Polydrug-exposed infants in Group B exhibited normal growth patterns throughout the 2-year period for all parameters, except that head growth had slowed by 18 months, and mean head circumferences at 18 and 24 months were significantly smaller than those of the control infants. Growth parameters for PCP-exposed infants were almost identical to those of the polydrug-exposed infants, so that separate analysis was not performed.

Infant Development

Mean scores of the three groups of infants on the Bayley Scales of Infant Development are shown in table 5. Group A infants had significantly lower Mental Developmental Index (MDI) scores from

TABLE 3

BNBAS Items Which Discriminated Between The Neonatal Groups

	I Heroin/ Methadone		II Sedative/ Stimulant		III T & B		IV PCP		V Drug-free	
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.
Interactive										
Inanimate Visual Orientation	3.3*	2.2	5.7	2.1	5.2	2.7	6.0	2.0	5.6	1.9
Inanimate Auditory Orientation	3.4*	1.2	5.6	1.4	5.4	1.7	4.3	2.0	5.3	2.3
Animate Visual Orientation	3.9*	1.7	4.9	2.1	4.5	1.9	4.5	1.3	5.7	1.9
Animate Auditory Orientation	3.9*	1.6	5.2	1.6	4.3	.5	4.5	1.0	5.2	2.4
Consolability	4.4*	2.4	3.7*	2.2	4.2*	2.2	2.5*	1.0	6.3	1.5
Motoric										
Motor Maturity	3.3*	1.4	4.5	1.4	4.7	2.4	5.0	2.2	4.8	1.6
Organization, State										
Predominant State	4.1*	1.4	4.8*	.4	4.5*	1.9	4.8*	.5	3.9	1.0
Lability of State	3.2*	1.6	3.7*	1.9	3.3*	1.5	5.0*	1.9	1.6	1.1

*ANOVA (Specific Drug Group x Group V), $p<.01$

TABLE 4

Mean Growth Parameters, Ages 3 Months to 2 Years

Age (mos.)	A Narcotic $\bar{X}$	A Narcotic S.D.	A Narcotic N	B Nonnarcotic $\bar{X}$	B Nonnarcotic S.D.	B Nonnarcotic N	C Controls $\bar{X}$	C Controls S.D.	C Controls N
				Weight (gm)					
3	5,485*	854	40	5,865	931	24	5,904	708	35
6	7,261*	922	37	7,753	904	18	7,579	807	35
12	9,588	1102	25	9,541	1250	13	9,729	1036	35
18	11,247	1266	20	11,092	1557	11	11,133	1201	35
24	12,341	1833	16	12,544	1852	9	12,199	1275	35
				Length					
3	59.5*	3.0	40	61.4	3.0	24	62.3	2.6	35
6	67.0*	3.5	37	68.7	2.7	18	69.3	2.6	35
12	76.1	2.6	25	74.3	4.9	13	77.5	2.9	35
18	83.7	3.0	20	82.8	5.0	11	84.5	3.2	35
24	89.0	3.1	16	89.1	4.2	9	90.2	4.3	35
				Head Circumference					
3	39.1*	1.2	40	39.6	1.4	24	40.6	1.6	35
6	42.0*	1.6	37	42.9	1.9	18	43.3	1.7	35
12	45.3*	1.7	25	45.9	3.2	13	46.8	1.7	35
18	46.7*	1.3	20	46.9*	1.5	11	47.8	1.6	35
24	47.7*	1.6	16	47.2*	2.0	9	48.8	1.6	35

*$p < .05$

TABLE 5

Mean Scores on the Bayley Scales of Infant Development

Age (mos.)		A Narcotic			B Nonnarcotic			C Controls		
		$\bar{X}$	S.D.	N	$\bar{X}$	S.D.	N	$\bar{X}$	S.D.	N
3	MDI	104.2	11.1	36	99.0	13.6	22	99.2	9.0	34
	PDI	104.3	11.8	36	97.6*	9.8	22	102.8	7.0	34
6	MDI	103.6*	13.5	26	99.9	12.7	17	111.0	12.3	29
	PDI	102.2	11.9	26	103.2	8.8	17	107.6	15.1	29
12	MDI	99.6*	10.6	20	103.5	8.1	12	105.8	8.1	27
	PDI	104.4	11.9	20	98.1	12.3	12	103.8	12.5	27
24	MDI	98.7	16.0	16	104.8	15.1	9	96.2	15.9	14
	PDI	100.3	14.2	16	97.9	10.1	9	98.2	8.9	14

Controls at 6 and 12 months (t test). Group B infants had a significantly lower MDI at 6 months and Psychomotor Developmental Index (PDI) at 3 months. If PCP infants were considered separately, their scores were almost identical to the polydrug-exposed infants. In general, scores for both Groups A and B and for the control group of infants were in the normal range, but exhibited a downward trend by 24 months of age.

DISCUSSION

The extensive literature devoted to the effects of intrauterine exposure to heroin and methadone on the fetus and neonate has recently been reviewed (Householder et al. 1982). However, information regarding the outcome of nonnarcotic-exposed neonates is sparse. In the present study, newborns delivered to women whose primary substance of abuse was sedative/stimulants or PCP were found to demonstrate marked deficits in neonatal behavior. These two groups of infants showed significantly poorer state organization and consolability than the drug-free controls. In addition, when internal comparisons were made, the PCP-exposed neonates were found to demonstrate more lability of state and poorer consolability than all other groups of drug-exposed neonates. The unique neurobehavioral changes of the PCP-exposed infants during the neonatal period clearly differentiated them from the other drug-exposed newborns (Chasnoff et al. 1983). The low threshold of stimulation and rapid changes in state are similar to behavior reported in children and adults intoxicated with PCP (Showalter and Thorton 1977; Welch and Correa 1980).

Sedative/stimulant- and PCP-exposed neonates did not manifest significant differences from normals in somatic growth measures at birth, orientation, or motor maturity responses. Deficits in intrauterine growth appeared mainly in narcotic-exposed infants, especially in relation to head growth. Similar to methadone-exposed neonates, neonates exposed to T's and blues showed significantly lower somatic growth rates and poorer state control than the drug-free controls, although the methadone-addicted neonates could be further differentiated by poorer visual and auditory orientation responses and poorer motor control. The similarities between the methadone-exposed and the T's and blues-exposed neonates may be related to the mixed opiate agonist-antagonist properties of pentazocine (Chasnoff et al. 1983).

There are no previous studies evaluating long-term patterns of growth and development in nonnarcotic-exposed infants, although preliminary developmental data have been examined (Chasnoff et al. • in press). The nonnarcotic-exposed infants in the present study demonstrated normal growth patterns in weight and length throughout the 2-year follow-up period. The narcotic-exposed infants, on the other hand, demonstrated early deficits in growth at 3 and 6 months and subsequently caught up to normals by 12 months of age. This same early stunting of growth during the period of subacute withdrawal for the narcotic-exposed infants is similar to the early growth patterns of methadone—addicted infants reported by our group in 1982 (Chasnoff et al.).

The early depression of growth could be due to the direct effect of methadone on the hypothalamic-hypophyseal axis of the newborn (Friedler and Cochin 1972). With the slow excretion of the methadone by the newborn, plasma and tissue drug levels fall, the endocrinological effect of the drug subsides, and growth recovers.

The mean head circumference of the narcotic-addicted newborns was significantly smaller than controls at birth and remained so throughout the 2-year follow-up period. The inhibitory effects of heroin on fetal growth include effects on brain growth (Chasnoff et al. 1982; Naeye et al. 1973). The mean head circumference of the nonnarcotic-exposed infants was normal at birth and continued so until 12 months. By 18 months of age, however, head growth had slowed and the mean head circumference for these infants had fallen to a significantly lower level. Small head size in young infants has been reported to be predictive of poor developmental outcome (Gross et al. 1983) and may be another indicator of the high-risk status of all drug-exposed infants.

Two-year developmental follow-up showed that the drug-exposed infants' development, as measured on the Bayley Scales of Infant Development, was comparable to that of the drug-free infants. The isolated instances in which mean MDI or mean PDI fell to a low level are probably not clinically significant in that all scores were within the normal range, as defined for the Bayley Scales (100±S.D. 10). Of greater concern is the fact that all three groups of infants, including controls, demonstrated a downward trend in mean developmental scores by 2 years of age. From the present data, it appears that the infants' environment and subsequent lack of stimulation had a more direct influence on 2-year development than maternal drug use during pregnancy.

The problems involved in evaluating the effects of maternal substance abuse on the developing fetus and infant are multiple, not the least of which are the difficulties involved in following these infants over a long period of time. The chaotic and transient nature of the drug-seeking environment impairs the early intervention and intensive follow-up necessary to insure each infant's maximum development. In addition, most women from substance-abusing backgrounds lack a proper model for parenting. These factors, compounded by the early neurobehavioral deficits of the drug-exposed newborns, earmark these infants to be at high risk for developmental and school problems. Maternal and perinatal addiction programs should be aimed at not only helping the mothers to deal with their addiction but teaching them the parenting skills necessary for proper infant stimulation and subsequent development. Future programs must develop methods to ensure adequate follow-up of all infants born to substance-abusing women.

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Developmental Consequences of Maternal Drug Use During Pregnancy

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The consumption of psychoactive substances during pregnancy has a negative impact on fetal growth. Heroin, methadone, and heavy alcohol consumption during pregnancy are associated with lower birth weight and central nervous system (C NS) dysfunction. Recent evidence suggests that marijuana use also may be associated with lower birth weight No information documents the impact of cocaine use on fetal outcome.

This paper will primarily present information pertaining to the identification of the major independent variables associated with developmental outcome for infants exposed prenatally to a variety of drugs Information regarding developmental assessment will also be presented.

STRUCTURAL TERATOGENICITY-FEATURES COMPATIBLE WITH FETAL ALCOHOL SYNDROME

In addition to lower birth weight, infants of mothers who consume large amounts of alcohol during pregnancy may exhibit a pattern of physical anomalies referred to as the Fetal Alcohol Syndrome (FAS). Because the reported incidence of the syndrome is rare (between 1 and 2 per 1000 live births), criteria developed by Hansen et al (1978) are used to classify infants as having features compatible with the fetal alcohol syndrome (CFAS). This classification is an attempt to identify an association between lower levels of drinking and less extensive fetal involvement. Each infant is rated according to the following criteria: 1) small size for gestational age (weight, length, or both, less than the third percentile); 2) microcephaly (head circumferences less than the third percentile); 3) short palpebral fissures Class than 1.8 cm wide in infants >36 weeks' gestational age); and 4) multiple dysmorphic features, judged by clinical observation, including: broad low nasal bridge, epicanthic folds, thin upper lip, hypoplastic philtrum, small nails, limitation of joint movement, large hemangiomas, altered palmar crease patterns, cardiac murmurs, and ear anomalies. Infants are classified as having features compatible with the fetal alcohol syndrome if rated abnormal on at least two of the four criteria. One of the two criteria must be either short palpebral fissures or multiple dysmorphic features.

CFAS features may not be specific to alcohol. Of 1,384 infants examined in a study (Hingson et al. 1982) of the effect of alcohol on fetal development, conducted at Boston City Hospita1 (BCH), 31 (2.3%) had features compatible with the fetal alcohol syndrome. Women who smoked marijuana during pregnancy were five times more likely than nonusers to deliver a child with CFAS features (p<.00l). Women who gained less than 5 pounds during pregnancy were 2.6 tines more likely to deliver a CFAS child than women who exhibited the mean weight gain in the sample (p<.00l). The relative risk for women who were expc8ed to roentgenograms was 2.8 compared with women who were not exposed (p<.02). In contrast, the relative risk for women who averaged two or more drinks daily compared with nondrinkers was 0.6 and not significant. This is the only study that the author is aware of that attempts to identify a possible association between factors other than alcohol and CFAS.

Features compatible with FAS may reflect a final common pathway of numerous agents or combination of agents rather than a specific teratogenic effect of alcohol. This may be more true with fetal alcohol effects, which are identified when two of three areas (growth, dysmorphology, and C NS related development) demonstrate abnormality. while some investigators consider the facial dysmorphology the most unique aspect of FAS, a recent report demonstrates the similarity between the facial appearance in FAS and the face of children born to mothers with phenylketonuria (Lipson et a]. 1981). In reviewing her work and other studies regarding craniofacial dysmorphogenosis, Sulik (1984) also concludes that the creation of the FAS phenotype may not be unique to alcohol. Animal studies suggest that teratogen exposure, such as might be seen with high levels of alcohol during the gastrulation (primitive streak) stage of development, results in the interference with the formation of the prechordal mesoderm. At this stage of development, teratogens must get to the embryo by diffusion, since the placenta is not yet formed. A teratogenic process at this stage of development will result in the craniofacial, brain, and eye defects noted in severe forms of FAS which is on the mild end of the spectrum of malformations which extends to holoprosencephaly (failure of cleavage of the prosencephalon, a primary brain vesicle in the embryo, with a deficit in midline facial development). Other agents, such as other drugs or radiation, or a combination of agents, may also interfere with embryogenosis at this stage. The commonly accepted association between alcohol and this constellation of dysmorphic features known as FAS may be because alcohol is the teratogen to which humans expose themselves most frequently. In summary, there is epidemiologic and animal data to suggest that alcohol may not be specific to either end of the spectrum of malformations associated with FAS.

VALIDITY OF SELF-REPORTED DRUG USE

The unreliability of self-reported drug use may explain the inconsistent association of the use of some drugs and fetal growth in the research literature to date. The association between low birth weight and certain substances, such as cigarettes, heroin, and methadone, is fairly consistent across studies. The association of low birth weight and other substances, however, such as the moderate use of alcohol and marijuana, differs from investigation to investigation.

A pilot study conducted at Boston City Hospita1 (Zuckerman et al, in press) raises questions about the validity of self-reported drug use. Seventy-five pregnant women were interviewed about their consumption of marijuana and other drugs. In addition, a urine sample was analyzed for the presence of marijuana metabolites. The urine assay technique used detects marijuana metabolites 5 to 7 days after smoking one marijuana cigarette. Eighteen women (24%) had urine samples positive for the presence of marijuana metabolites. Eight of these women (12.5%) reported not having smoked marijuana in the previous week. While all eight women reported having used marijuana at some point, four of them reported using marijuana prior to, but not during, their pregnancy. The other four acknowledged using marijuana during their pregnancy, but not during the week before the interview. Had we relied on self-reporting alone, we would have missed 15% (4 of 27) of the women who used marijuana during pregnancy. The misclassification of 15% of women who did consume marijuana during pregnancy might result in an underestimation of an association between marijuana use and neonatal growth.

This B C H study also found a greater percentage of pregnant women reporting marijuana use, smoking cigarettes, and drinking alcohol during pregnancy than did a 1977-79 study (Hingson et al. 1982) at BCH (table
1). There are four possible, not necessarily mutually exclusive, explanations for the discrepancy between these findings 1) Awareness that their self-report might be confirmed by urine assay may have prompted more women to report their substance use accurately in the 1983 sample, compared to the earlier study: 2) Demographic differences between the two study populations may account for the different patterns of substance use identified; 3) Health habits during pregnancy may be determined more accurately by prenatal rather than postpartum interview, because there is less risk of recall bias; and 4) True changes in drug use during pregnancy from the late 1970s to the early 1980s may be reflected in this data.

The first explanation is consistent with the bogus pipeline paradigm (Jones and Sigall 1971) that involves connecting subjects to a fictitious lie detector type device. Subjects are then asked to report their feelings and attitudes toward topics likely to alicit highly socially desirable responses. Various studies demonstrate that participants in the bogus pipeline condition give more truthful responses to questions subject to high social desirability bias than those asked to answer without a lie detection type device (Quigley-Fernandez and Tedeschi 1978). The higher rate of reported drug use in our recent study may be due to women’s knowledge that their urine was to be assayed. Correspondingly, the lower rate of drug use in our previous study may be due to underreporting because of social stigma attached to the illegal status of some of the drugs. Pregnant women, particularly, may feel pressure to underreport certain health habits if they believe thc6e habits will damage their unborn infant.

One could speculate that in the absence of urine samples, people might systematically underreport drug use. The effects of underreported factors may be underestimated or incorrectly attributed to other habits. Specifically, if Illicit substances such as marijuana or cocaine are more

TABLE 1

Self-Reported Substance Use Any Time During Pregnancy

	Boston City Hospital Pilot Project Study	June 1983+
Substance Use During Pregnancy Feb. 1977-Oct. 1979*		
	N=1690	N=75
Marijuana	14%	31%
Cigarettes	48%	60%
Psychoactive Drugs	1%	11%
Alcohol	38%	64%

* Hingson et aLl982
\+ Zuckerman ~ al, in press

often underreported than legal substances, such as alcohol or cigarettes, researchers may misattribute the effects of illicit psychoactive substances to alcohol and cigarettes. This may help explain the reported consistency in the association between cigarette smoking and lower birth weight. and the lack of consistency in findings concerning the effects of other either illicit or socially undesirable substances upon birth weight The accurate determination of such substance use is critical to the interpretation of our ongoing study and all previous work in the field. We are conducting a methodological trial to assess the impact of urine testing upon the reporting of cigarette, marijuana, alcohol, cocaine, and other psychoactive drug use during pregnancy. Our hypotheses are 1) More pregnant women will report drug use when they know their urine will be tented; and 2) the impact of the urine assay will be greater for drugs that are illegal or considered l~ socially desirable. Use of illicit drugs, such as marijuana and cocaine, will be underreported more often than alcohol consumption or cigarette smoking when urine tests are not obtained.

BEHAVIORAL TERATOGENICITY-NEUROBEHAVIORAL ASSESSMENT OF THE NEONATE

The Neonatal Behavioral Assessment Scale (NBAS) developed by Brazelton (1973) is the most commonly used assessment of neonatal neurobehavioral functioning. The scale assess 20 reflexes and 26 behavioral items, such as the ability of the neonate to habituate to stimuli; to orient to social and nonsocial stimuli to regulate states of arousal, vasomotor functioning, and activity level4 and to exhibit social behaviors, such as smiling or cuddling. A newborn’s neurobehavioral

functioning is a reflection of genetic endowment coupled with intrauterine exposures and experiences. The scale has been extensively used in the fo1lo wing types of studies: 1) to evaluate the effect of prenatal and intrapartum effects on newborn behavior; 2) to relate newborn behavior to maternal responsivity; 3) to compare different clinical populations of infants; and 4) to determine the predictive validity of the scale to later developmental outcome. An important consideration in the use of the scale is the magnitude of decrements in performance. Behaviors are assessed on a nine-point scale. Differences in performance of l~ than one point may not be clinically significant. This is a special problem when large numbers of subjects are assessed, and statistically significant differences in behavioral functioning may not be clinically significant.

The behavioral teratogenicity of prenatal opiate ingestion is described in terms of a withdrawal syndrome. Specific behavioral characteristics of opiate addicted newborns identified by the NBAS include numerous state changes, tremors, motor in maturity, decreased alertness, decreased ability to habituate to stimuli, and decreased auditory and visual orientation. (Soule et al. 1974; Strauss et al 1976; Chasnoff et al. 1982).

Alcohol consumption during pregnancy is associated with infants who have poorer ability to habituate and have a lowered level of arousal (Streissguth et al 1983). Using a special pressurized mattress, neonates of mothers who were heavy alcohol users during pregnancy demonstrate poorer state regulation as manifested by a decrease in total amount of sleep and an increase in the fragmentation of sleep periods (Rosette et al 1979). Fried (1980) demonstrated that infants of mothers who used marijuana during pregnancy were less likely to respond to and habituate to repeated visual stimuli than infants of mothers who did not use marijuana during pregnancy. The infants exposed to marijuana in utero also demonstrated more tremors and startles. Finally, in a study of the effects of prenatal exposure to smoking, caffeine, and small amounts of alcohol, Jacoteen (in press) demonstrated independent effects on behavior by alcohol and caffeine, but not cigarette smoking. The obvious withdrawal symptoms of opiate-exposed newborns and these studies which control for confounding variables suggest a behavioral teratogenetic effect of prenatal drug exposure of the specified agents. The independent effect of marijuana remains to be conclusively demonstrated.

It cannot be ascertained from these findings whether the observed behavioral differences reflect permanent CNS damage, or a transient drug or withdrawal effect on CNS functioning. Even if the behavioral dysfunction is transient. it may have an indirect effect on later childhood functioning via mother-infant interaction. For example, a decreased ability for an infant to habituate may result in a more irritable infant. Excessive crying is reported as the reason for battering by 80% of the abusing parents whose infants are less than 1 year old (Weston 1968). Infants with poor arousal may not elicit sufficient care-taking (stimulation and nutrition) from their mothers, which may contribute to a cycle of failure to thrive. This cycle may be compounded when a mother is less sensitive to her infant’s signals because of her own drug use.

CONSEDERATIONS REGARDING DEVELOPMENTAL ASSESSMENTS

Developmental outcome studies should include repeated assessments over time. An assessment at any one point in time can only demonstrate a dysfunction at that time; one cannot assume that a particular symptom, delay, or dysfunction will endure over time. For example, the Bayley Test of Infant Development only becomes modestly predictive of early school age LQ. at 18 months. The study of children asphyxiated at birth demonstrates this point (Corah et al 1965). Compared to nonasphyxiated children, children suffering from asphyxia had more neurobehavioral signs at birth, and, at 3 years of age, scored lower on all tests of cognitive function and had more positive neurologic findings. However, when reassessed at age 7, significant LQ. differences had disappeared between the anoxic group and control population. Similar findings are reported between children with neonatal hyperbilirubinemia compared to controls. Children with hyperbilirubinemia had decreased motor development at 8 months and increased evidence of neurologic abnormalities at 1 year. However, there was no difference in LQ. scores and neurologic examination between groups at age 4 and 7 years (Ruben et al. 1979). These findings emphasize the value of repeated assessments and suggest plasticity of the central nervous system.

In addition to repeated assessments, numerous skills should be assessed to best understand a child's central nervous system functioning. A false conclusion about an adverse effect of an in utero exposure might be made if only I. Q. scores are used. I. Q. scores reflect a summation of numerous skills. Children with learning disabilities may have significant deficits in their perceptual or language functioning, but have an average LQ.. In utero exposure to a drug may result in a significant CNS deficit in one area of functioning, which is balanced by a strength in another area. Multiple areas of functioning should be assessed. Developmental assessment should include age appropriate assessment of perceptual$_1$ cognitive, and motor skills; speech and language abilities; and behavior (especially attentional abilities). Laboratory assessments of attention in young children may be a more sensitive indicator of future cognitive or memory functioning than developmental testing.

In addition to these clinical assessments, newer physiologic techniques such as evoked responses (somatosensory, visual, and train stem auditory), Electroencephalogram (EEG), Brain Electrical Activity Mapping (BEAM), Positron Emission Tomography (PET Scanner), and Nuclear Magnetic Resonance (NM R), may prove to be important adjuncts in assessing central nervous system functioning more objectively and with greater sensitivity in both neonates and older children. Neonatal assessments are especially important because postnatal. factors are less likely to confound the results. These electrophysiologic techniques have an added advantage of being able to be used in the neonatal period.

MULTIFACTORIAL MODEL FOR DEVELOPMENTAL OUTCOME

Outcomes measured in the neonatal period can be ascribed best to intrauterine events. Low birth weight is the major adverse outcome described for numerous substances, such as cigarettes, alcohol, heroin,

and marijuana, used during pregnancy. The significance of low birth weight is its association with increased infant mortality and morbidity. The Select Panel for the Promotion of Child Health (1981) reported that very low birth weight is among the most significant predictors of later developmental deficits. However, correlations between birth weight and developmental outcome demonstrate conflicting findings due in part to methodologic differences among studies (Kiely and Paneth 1981).

Few studies have assessed the relationship between substance use during pregnancy and developmental outcome. At 18 months of age, children born to methadone-maintained mothers had more neuralgic signs and significantly lower scores on the Bayley Test of Infant Development (Rosen and Johnson 1982). Retrospective studies have associated alcohol consumption during pregnancy with lower LQ. scores (Streissguth et al 1978) and learning disorders or hyperactivity (Shaywitz et al 1980). A prospective study of children exposed to alcohol in utero demonstrates a small but statistically significant decrease in their scores at 8 months on the Bayley Scales of Infant Development (Streissguth et al 1980).

Research in the past 20 years on the outcome of newborns with perinatal complications and low birth weight provides an important source of information to understand better the developmental consequences of drug exposure during pregnancy. Pasamanick and Knobloch (1966) coined the term “continuum of reproductive causality’ to describe the relationship between perinatal factors, such as anoxia, low birth weight. and delivery complications, to deviant development, such as cerebral palsy, epilepsy, mental retardation, and learning disorder. They demonstrated in a retrospective study that children having more serious conditions, such as cerebral palsy, had more obstetrical complications than children who had mild disorders, such as a learning problem. They proposed that the greater the perinatal insult$_1$ the greater the brain damage, and the worse the clinical condition. Subsequent prospective studies on anoxia and low birth weight do not completely support this entirely biologic explanation of outcome. For instance, infants with low Apgars (<5) at 5 minutes, demonstrate a four-fold increase in neurologic abnormalities at 1 year compared to infants with higher Apgar scores. However, 96% of the infants with low Apgars did not demonstrate any gross neurologic abnormality (Drage et al 1968). While hypoxic insult contributes to poor outcome for some children, the vast majority of children appear to do well$_1$ and individual prediction is limited. Other studies of low birth weight (Drillien 1964) and perinatal complications (Werner et al 1971) suggest that poor outcome is most likely to occur when the adverse condition is associated with low socioeconomic status of the family.

Perinatal complications can be considered somewhat analogous to prenatal drug exposure because both of these events can result in C NS damage. Perinatal asphyxia is associated with hypoxic-ischemic injury of the brain. Animal research has clearly documented an adverse impact of methadone (Zagon and McLaughlin 1978) and alcohol (Abel et al. 1983) on the developing brain. Animal research has also directly assessed the plasticity of the developing brain. When experimental lesions are induced in selected areas of adult monkey’s brain, the associated function is permanently lost. However, when these same lesions are

experimentally induced prenatally, the monkeys perform as well as normal animals (Goldman-Rakic and Galkin 1978). By injecting tritiated amino acids, Goldman-Rakic (1978) demonstrated the reorganization of CNS connections following a specific experimentally induced brain lesion. The process of C NS reorganization and four other possible pathways for recovery of function in infants with known CNS insult are reviewed by Saint James-Roberts (1979).

Sameroff and Chandler (1975) propose a transactional model of development to explain the perinatal risk research findings. This model states that developmental and behavioral outcome are due to ongoing reciprocal interactions between the organism and the environment. This model goes beyond a unitary model, which explains outcome either entirely by biologic or environmental factors. Research in the past 10 years has furthered the understanding of the developmental process by defining characteristics of the child, such as temperament and behavior, and the child's environment. including maternal depression, social supports, surrogate child care, and quality of the home environment. A recent study demonstrates that responsive caregiving is the most important factor associated with developmental competence at 5 years of age for low birth weight infants (Cohen et al 1982). Neonatal problems per se did not contribute to the developmental vulnerability of these infants.

One study directly controlled for the caretaking environment of drug using mothers by comparing four groups of children: a heroin-exposed group, a drug environment comparison group (children who lived with addicts or whose parents used heroin after the birth of the child), and two groups matched for perinatal complications and socioeconomic status. There were few differences between the in utero exposed children compared to the children exposed to the social environment of drug using caretakers (Wilson et a]. 1979).

To best understand the developmental consequences of prenatal drug exposure, one must understand both the in utero environmental effect (teratogenic effect on the brain) and the postnatal environmental effect (drug using caretakers). The effect of the social environment in research models must go beyond the measurement of socioeconomic status. More specific aspects of the caretaking environment. such as mother-infant interaction, social supports, etc., need to be included. Characteristics such as depression may be very important because there is a known association between depression and heroin-methadone, and marijuana use. Children of drug users may be subject to a double jeopardy. They may suffer in utero effects on their central nervous system associated with drug abuse and then suffer from poor environmental circumstances due to non-optimal parenting associated with a drug user's lifestyle. From a public health perspective, injuries are the leading cause of childhood morbidity and mortality. It has never been adequately studied whether children of drug-using mothers sustain more injuries. Do drug—using mothers provide the same level of supervision and compliance with safety guidelines as nondrug using mothers?

In summary, developmental outcome is the result of a complex interaction of a variety of factors. In utero exposure to certain

substances, best documented by studies using excessive amounts of heroin, methadone, and alcohol, represents a significant source of biological vulnerability. The valid identification of specific drugs associated with a behavioral or structural teratogenic effect on the fetus remain a source of methodologic concern. These drugs may interact synergistically, as well as with poor nutrition or health, to further impair optimal in utero growth. Many conditions associated with poor developmental outcome are more prevalent among people living in poverty, which further confounds the effect of prenatal drug exposure. These conditions include drug exposure, increased perinatal complications, congenital infections, and postnatal health factors such as lead exposure and malnutrition; social factors like maternal depression; lower maternal education; and less optimal caretaking environments. Studies that assess the developmental consequences of in utero drug exposure need to assess the variables that are associated with childhood outcomes, especially those variables that are more likely to be found among mothers whose lifestyles involve excessive drug use.

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