

## **Introduction**

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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<sup>5</sup>—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- ophthalmological 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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