Behavioral Outcomes in Preschool and School-Age Children Exposed Prenatally to Marijuana: A Review and Speculative Interpretation

Peter A. Fried

INTRODUCTION

In considering the relationship between marijuana use during pregnancy and the impact of such use upon the behavioral outcome of the young children of these pregnancies, the paucity of objective information is striking and, from one point of view, quite surprising. Marijuana is far from being the "new kid on the block," with references to its use in civilizations thousands of years ago (Abel 1980), and, in fact, has had a role in pregnancy folklore for many centuries.

The very limited number of contemporary scientific studies that focus upon marijuana's potential long-term effect on the developing fetus becomes a major concern when one considers the number of women of reproductive age who use this drug. In some cases, marijuana may be the only potentially teratogenic substance used; in other cases, it may be used with other legal, potentially teratogenic agents (e.g., alcohol and tobacco); while in further instances marijuana may be combined with other illegal substances that are under extensive investigation for their possible role in affecting the unborn child. As one example, the majority of the studies using samples in which the long-term consequences of in utero exposure to cocaine are being determined report that the use of that substance is highly correlated with marijuana use (Chasnoff et al. 1992; Frank et al. 1988). Although it is sometimes possible to control, to a certain extent, marijuana's impact by statistical means, knowing the role of cannabis upon the dependent variable in question is clearly of great importance in interpreting the nature of the contribution of other substances.

Although overshadowed in both the public media and scientific publications by the current concern with crack cocaine, marijuana remains the most commonly used illicit drug among women of childbearing age. In the National Institute on Drug Abuse's (NIDA's) recently completed National Pregnancy and Health Survey (NIDA 1994), which provides

national estimates of prevalence and patterns of substance use among women delivering live-born infants in the United States between October 1992 and August 1993, self-reported marijuana use during pregnancy was 2.9 percent compared with 1.1 percent cocaine (0.9 percent crack). In the past few years, marijuana use appeared to be increasing among women in their reproductive years. In NIDA's Monitoring the Future Study (Johnston et al. 1994*a*) 1993 data, 10.4 percent of 19- to 32-year-old women reported using marijuana in the past month. Further, among U.S. high school seniors, the annual use of marijuana increased between 1992 and 1993 from 21.9 percent to 26.0 percent (sexes not differentiated), reversing a previous declining trend seen since the early 1980s (Johnston et al. 1994*b*).

A number of studies have examined the extent of use of marijuana during pregnancy, but in many instances the prevalence rates may not be representative of marijuana use in the general population, as sampling procedures involved populations selectively biased towards drug use. On the basis of either interviews or urine screens conducted prenatally or postpartum, a rate of 27 percent was reported among a high-risk, predominantly nonwhite, Boston inner-city sample (Zuckerman et al. 1989). In another high-risk sample in Pittsburgh (Day and Richardson 1991), a random sampling of women from an outpatient prenatal clinic found a 30 percent rate. In a relatively low-risk sample at the Yale New Haven Hospital, the rate at any time during pregnancy was found to be 10 percent (Hatch and Bracken 1986) and among another low-risk population in the Seattle area, the rate was 17 percent (Streissguth et al. 1989). In a comparison between Florida public health clinics and private obstetrical offices, the rate based on urine screens was quite similar, with 12.4 percent in the former and 11.3 percent in the latter group (Chasnoff et al. 1990). In contrast, in Chicago (MacGregor et al. 1990), based on urine screens at the time of admission into the labor-and-delivery unit, a marked difference for marijuana rates was noted between clinic patients (32 percent) and private patients (7.5 percent).

In the author's work in Ottawa, Canada (described below), among predominantly middle-class volunteers (Fried et al. 1984, 1985) in the year before pregnancy, 80 percent did not use any marijuana, 12 percent used the drug irregularly, 3 percent smoked two to five joints per week, and 5 percent smoked more than that amount. After the recognition of pregnancy, usage declined significantly, although during each of the three trimesters the percentages remained relatively constant. Approximately 6 percent reported irregular use, 1 percent reported smoking two to five

joints per week, and 3 percent continued to smoke a greater amount. The heaviest users were the most likely to reestablish prepregnancy levels of consumption in the year following the birth of the baby.

In spite of the fact that marijuana is the illicit drug most used by pregnant women (see above), there is a notable lack of information about its long-term consequences. The major reasons for this state of affairs lie in the ethical and practical difficulties surrounding quasi-experimental research (Kilbey and Asghar 1992). Obviously, drugs cannot be administered to gravid women and so exact doses or amounts utilized and the timing of such use are not quantifiable. Further, potentially confounding factors (such as other drug use or socioeconomic factors) cannot be controlled by random assignment to groups. Human studies, particularly those investigating the long-term effects of in utero exposure, have to be based on volunteer samples and reports of drug use gathered either before (prospectively) or after (retrospectively) birth. These limitations are severe. Although a degree of control can be attained with statistical procedures, the interpretation and conclusions drawn from the research must be placed in the proper context.

Aside from one or two studies, all of the information pertaining to the behavioral effect of prenatal exposure to marijuana in children beyond the toddler stage is limited to the reports coming from the Ottawa Prenatal Prospective Study (OPPS) (Fried et al. 1980). The protocol and the limitations of this Canadian work are described below in some detail. Additional information can be found elsewhere (Fried et al. 1980).

THE OTTAWA PRENATAL PROSPECTIVE STUDY

As recently as 1980, the only information pertaining to the effect marijuana may have upon the pregnant user and her offspring was limited to two polydrug case reports. This lack of information, the results of animal work (reviewed in Dalterio and Fried 1992; Fried 1984), the extent of usage among women of reproductive age, and the cooperation of the teaching hospitals in the Ottawa area combined to set the climate and the opportunity for the inception of the OPPS in 1978.

Data have been and continue to be collected in a prospective fashion from approximately 700 women residing in the Ottawa, Canada, region. Pregnant women volunteered after being informed of the study by a variety of means including via their physicians, by notices located in the waiting rooms of obstetricians, or by notices located in the reception

rooms of prenatal clinics in the major Ottawa hospitals. The information that was disseminated at this juncture did not mention marijuana but rather discussed, in general terms, how lifestyle habits during pregnancy may influence the developing fetus. Upon contacting the research facility, the potential subject was given further details about the particular habits of interest—use of marijuana, alcohol, and cigarettes. It was emphasized that, for purposes of comparison, the researchers wished to recruit women who used any of these substances to a very small degree or not at all. After volunteering and signing an informed consent, the mother-to-be was interviewed once during each of the trimesters remaining in her pregnancy by a trained female interviewer.

This procedure of recruiting volunteers has both strengths and weaknesses that pervade the entire OPPS. The self-selection procedure limits the extent to which generalizations can be made in terms of epidemiological informa-tion collected, the possibility of selection bias being obvious. However, as noted elsewhere (Fried et al. 1980, 1984), on several key demographic variables including parity, age, and family income, the OPPS volunteer sample is quite similar to nonparticipating women living in the Ottawa area who give birth in the hospitals taking part in the study.

The recruitment procedure used has the advantage of increasing the likelihood of the reliability of self-report (elaborated below) and of increasing the probability of a long-term commitment to the study. Aside from subjects who have moved from the Ottawa area (about a third), a retention rate of over 95 percent has been maintained over the past decade.

During each of the prenatal interviews information was collected on such variables as socioeconomic status, mother's health (both current and before pregnancy), the health history of the father, obstetrical history of previous pregnancies, a 24-hour dietary recall (including an assessment of caffeine intake), as well as past and present drug use patterns. Detailed information is gathered with respect to marijuana, cigarettes, and alcohol use. To establish the use patterns of these three drugs, information was gathered both for the year preceding the pregnancy and for each trimester of the pregnancy. Further details of the interview and the categorization of the various drugs have been described previously (Fried et al. 1980).

There was an extensive range of marijuana use in the sample and the drug was not used by a similar proportion of subjects. As a result of these factors, for descriptive and statistical purposes, the marijuana use data

were treated categorically. Volunteers were classified as nonusers, irregular users (one joint or less per week), moderate users (two to five joints per week), and heavy users (more than five joints per week).

The women who smoked marijuana regularly during their pregnancy differed from the nonusers and irregular users on a number of factors that have the potential of influencing offspring development. These factors were dealt with by various statistical procedures. These possible confound-ing factors included lower socioeconomic level, less formal education, and increased cigarette smoking. Although no difference in parity was noted, the heavy users were 3.2 years younger than the nonusers. There were no differences among the four groups in terms of nutritional adequacy and weight gain during pregnancy.

The self-report procedure used in the OPPS to assess drug habits raises the critical issues of validity and reliability. Despite the obvious shortcomings of this mode of assessing drug use, at the time of the collection of data (primarily between 1979 and 1983) no practical alternative was available. Today, laboratory tests can measure the presence of metabolites of mari-juana up to 1 to 2 weeks after the time of use. The uses of both the inter-view and biological assessment approaches are critically discussed in a well-reasoned paper by Day and Richardson (1991).

In the OPPS, procedures were undertaken to enhance the likelihood of accurate data collection. A congenial relationship between the interviewer and the individual being interviewed in a comfortable environment (typi-cally the mother's home) had been part of the protocol of the OPPS, and the same female interviewer followed the mother-to-be during her entire pregnancy. A second procedure designed to enhance the accuracy of the self-reports involved the number of times the same drug-related questions are asked. The questionnaire was administered once during each trimester; during each of these interviews, the questions pertaining to drug use during the preceding trimester and the 12 months before the pregnancy were repeated, permitting a test-retest reliability measure.

Neurobehavioral Observations

Although the focus of this chapter is on preschool children and beyond, it is relevant to highlight some of the observations (and lack of observations) noted at earlier ages. The literature pertaining to the behavioral effects of prenatal marijuana exposure is relatively sparse and,

although provocative, is far from definitive. The first report in 1980 examined 4-day-old babies born to 12 regular users in the OPPS (Fried 1980), and the findings were replicated in a subsequent, much larger study using the Ottawa sample (Fried and Makin 1987). Prenatal exposure to marijuana was associated with decreased rates of visual habituation and increased tremors, fre-quently accompanied by exaggerated startle responses that were both spontaneous and in response to minimal, external stimulation. Similar observations were noted at 9 and 30 days of age using the Prechtl neuro-logic assessment (Fried et al. 1987). Further, at 9 days, increased hand-to-mouth behavior was found among the babies born to the marijuana users.

These possible indicants of impairments in nervous system state regulation and/or mild withdrawal were noted by some others (Chasnoff 1990) but not by all (Richardson et al. 1989; Tennes et al. 1985). Other signs of alterations in nervous system integrity have also been associated with in utero marijuana exposure. Sleep cycling and motility in newborns differed between marijuana-exposed and nonexposed babies (Scher et al. 1988) and disturbed sleep patterns were still associated with prenatal exposure when the offspring were 3 years of age (Dahl et al. 1988). The observations of the OPPS sample in the newborn period are briefly described above as they were the only significant associations noted with prenatal marijuana exposure for a number of years as the children were followed.

When the children in the OPPS were examined at 1 year of age (Fried and Watkinson 1988) using the Bayley Scales (Bayley 1969), no adverse effects of prenatal marijuana exposure were noted. The Bayley Scales consist of three components. The Mental Developmental Index (MDI) assesses sensory perceptual abilities, early acquisition of object constancy, memory, problemsolving, vocalization, and the onset of words. The Psychomotor Developmental Index (PDI) assesses gross and fine motor movement. The Infant Behavior Record (IBR) evaluates the infant's attitudes, interests, and temperament. The failure to find a relationship between the infant's behavior and maternal marijuana use is consistent with other reports assessing the children at the same age (Astley and Little 1990; Tennes et al. 1985).

At 24 months, prenatal marijuana exposure was not negatively correlated with overall scores on the Bayley Scales (Fried and Watkinson 1988). Using the Reynell Developmental Language Scale (Reynell 1977), a negative association with a measure of language comprehension, but not

language expression (Fried and Watkinson 1988), was observed. This association did not persist after statistically adjusting for other variables, especially ratings of the home environment.

At 3 years of age, children in the Ottawa sample (Fried and Watkinson 1990) were administered the Reynell test of language expression and comprehension as well as the McCarthy Scales of Children's Abilities (McCarthy 1972). This latter instrument is based upon six scales: verbal, perceptual, quantitative, general cognitive (a composite of the three previous scales), memory, and motor. As found when the children were a year younger, after controlling for potentially confounding variables, prenatal marijuana exposure was not significantly associated with any of the outcome variables.

At 4 years of age the same sample was given the test battery that was administered a year earlier plus the Peabody Test of receptive vocabulary and a series of motor tests (Fried and Watkinson 1990). General, global intellectual measures were not related to prenatal cannabis exposure, congruent with the findings of another study in which marijuana was not the primary drug of interest (Streissguth et al. 1989). However, on tests of verbal ability (both the McCarthy subscale and the Peabody) and memory, the children of regular marijuana users were significantly inferior to other children. This relationship persisted after statistically controlling for a host of potentially confounding factors including the home environment. This negative relationship was the first reported association beyond the neonatal stage. The observation of a significant neurobehavioral effect at this age (and not earlier) may indicate that the degree and type of deficits noted can be identified only when normal neurological development has proceeded to a certain level of maturity and when complex behavior can be examined at a more specific, rather than global, level. This maturation hypothesis reflects the notion that the effects of prenatal exposure to marijuana are subtle and that their consequences on complex behavior are not manifested and/or cannot be tested before 4 years. This line of thinking is elaborated below.

The difficulty in unraveling the long-term consequences of in utero marijuana exposure becomes very apparent when one examines the data gleaned from the cognitive and language assessment of the 5- and 6-year-old OPPS participants (Fried et al. 1992). These children were given the same battery as when they were 4 but, unlike the findings at 48 months, statistical analysis found no relationship at either 5 or 6 years of age

between any of the subscales of the McCarthy or the Peabody tests and maternal marijuana use.

The reason for the disparity of observations is not at all clear. One possibility may be the increasing effect of environmental variables. As the children get older, they are exposed to an increasing similarity of postnatal influences that bear on cognitive development. For example, by 5 years of age, 89 percent of the nonexposed children and 87 percent of the exposed children had a year of formal schooling. Could it be that this common feature would tend to overwhelm some of the quite subtle differences in memory and verbal abilities noted at an earlier age?

Possible indirect evidence of the influence of ubiquitous, relevant environ-mental factors may be seen in the catching up scores of the marijuana-exposed children. The McCarthy verbal and memory scores at 4 and 5 years of age were essentially unchanged for the nonexposed children, being 1 to 1.5 standard deviations (SD) above age norms at both 4 and 5 years of age. On the same subscales, the marijuana-exposed children improved their scores by approximately half an SD between the ages of 4 and 5, to 1 SD above the age norm at 60 months. Thus, the postnatal influence of school may have served to overcome the marijuana-associated observations noted at 4 years.

Instruments that provide a general description of cognitive abilities may not be capable of identifying nuances in neurobehavior that may discriminate between the marijuana-exposed and nonexposed children. However, tests that examine specific characteristics that may underlie cognitive performance may be more appropriate and successful. This approach to assessing the consequences of prenatal marijuana exposure was examined in a recent study (Fried et al. 1992) in which impulse control and sustained attention were examined in 6 year olds.

The children were assessed using two forms of a computerized vigilance task with a one-button solid-state console (McClure and Gordon 1983). In order to examine the child's ability to withhold responding, a 6-second differential reinforcement of low rate responding (DRL) schedule was employed. Under this regimen, reinforcement (points displayed on a screen) would be obtained when a button press occurred 6 seconds after the emission of a previous response. Responses that occurred prior to the end of this 6-second period were not reinforced and served to reset the timer so that 6 seconds of no button pressing would have to elapse before the next button press would result in a reinforcement. Thus, on this DRL

6-second schedule, a child would receive reinforcement for every button press emitted after an interval of 6 seconds.

Three sets of data were obtained: the absolute number of responses, the total number of rewarded responses, and an efficiency ratio (ER) that was obtained by dividing the number of rewarded responses by the total number of responses.

The same apparatus was used to examine sustained attention. A series of single-digit numbers was shown on the screen at a rate of one per second. They were displayed for 200 milliseconds (ms) with an 800-ms interval between each signal. Each subject was asked to press a button whenever the target stimulus appeared on the display screen among a series of randomly presented numbers. The scores were the number of correct responses, the number of omissions (missed target stimuli), and the number of commissions (button press to nontarget stimuli). The scores were computed for each of three 3-minute blocks and then totaled for the overall 9-minute trial.

As an additional facet of this work, parents assessed their child's impulsivity/inattention at home by using portions of the Conners' Parent Rating Scale-48 (Conners 1989). This 48-item behavioral symptom check-list was completed by the child's mother at the time of testing using a four-point rating system. The scale yields six behavioral clusters, one of which—the Impulsive-Hyperactive Scale—was used for this assessment. The four items that enter into this scale include excitable/impulsive; restless or "squirmy"; wants to run things; and restless, always on the go.

The results suggested that prenatal marijuana exposure was not associated with poorer impulse control, as the children of the heavy marijuana users were not deficient in the delay task in either the number of rewards or the efficiency ratio. In the vigilance task, the commission errors were very similar among all three marijuana-exposed groups (again suggesting no impairment in impulse control), but the omission errors and the number correct were differentiated, in a dose-related fashion, among the children of the various marijuana-exposure groups. Further, across temporal epochs within the vigilance task, only the children in the heavy marijuana exposure category increased their omission errors. The overall increase in omission errors and the greater number towards the end of the vigilance task may reflect a deficit in sustained attention.

There was a significant tendency for the women who used marijuana heavily during pregnancy to rate their children as being more impulsive/ hyperactive. The nature of the scale emphasizes overall activity rather than attention behavior. Although consistent with the more objective measurements, there is a difficulty in interpreting these results. The fact that women in the heavy marijuana use group tended to identify their children as more problematic in this domain may be an accurate reflection of the child's behavior, or it may represent the mother's perception and attitude toward this behavior. Do the present observations indicate a true behavioral difference in the attention-related domain or is there a lowered parental tolerance? Ratings by other observers such as teachers and additional assessments of maternal parenting attitudes and expectations might help to clarify this issue.

In a recent preliminary report, O'Connell and Fried (1991) examined the school-aged (6 to 9 years of age) offspring of regular marijuana users and matched (in terms of alcohol and cigarette use during pregnancy) controls participating in the OPPS on a battery of neurobehavioral tests. These included assessment of intellectual abilities, visual perceptual skills, distractibility, memory, language comprehension, academic achievement, visual motor skills, and parental rating of behavior.

Measures that discriminated between the study groups and on which the children of the marijuana users scored more poorly included parental behavior ratings (particularly conduct problems), visual perceptual and visual memory tasks, language comprehension, and distractibility. It is striking that these are behaviors that have cropped up in work with these children at earlier ages. On the other hand, the data from this work are not without interpretative complications. For the measures of visual memory and language comprehension, the mother's age at the child's birth potentiated the effect of cannabis use to produce lowered scores for children of young, cannabis-using mothers relative to children of young, nonusing mothers. Further, when controlling for the influence of the mother's age at delivery, mother's self-rated personality (the marijuana-using cohort being higher on neuroticism and lower on agreeableness and conscientiousness), and the home environment (greater aggression and less supervision were present in the marijuana-using homes), the discriminating variables were no longer statistically significant.

Whether the inclusion of the personality and home environment variables as statistical controls is appropriate is a difficult issue that has been discussed elsewhere (Fried and Watkinson 1988; O'Connell and Fried

1991), and also is considered below. Briefly, the important question is whether this inclusion results in a conservative approach to the data analysis. The finding of differing personality and home environment ratings between the users and nonusers of marijuana may well be viewed in a transactional framework (Sameroff and Chandler 1975). This model states that the developmental outcomes are the product of both maternal and child characteristics and the relationship between the mother and child characteristics is a reciprocal one. Thus home environment measures and personality characteristics may be outcomes in themselves, arising from interactions with a behaviorally altered child.

Interpretative Issues

It is quite apparent that the data available to date make it very difficult to come to any definitive conclusion about the long-term implications of marijuana use during pregnancy. This difficulty arises for a number of reasons—some of which are generic to virtually all longitudinal, prospective teratogenic studies and others that are particular issues with marijuana. It is appropriate to include a brief discussion of these interpretative caveats in this chapter.

At a general level, separating the in utero effects from postnatal effects becomes more and more problematic as the child gets older. As discussed in detail elsewhere (Fried 1993; Kilbey and Asghar 1992) consequences of drug exposure noted in the offspring may be caused not only by the drug in question, but also by the lifestyle and parent-child interaction that often are related to a particular drug habit. Attempting to parcel out the statistically unique contribution of a drug, after controlling for so-called confounding factors, may obscure the reality of the drug effect(s). If there are effects of marijuana use, clearly they are very subtle. As discussed above, there is the real potential for a transactional state of affairs; thus this possible over-control becomes even more of an interpretative issue.

In other publications (e.g., Fried and Watkinson 1988) arising from the OPPS, it has been argued that it is more likely that the drug's real association with the behavioral outcomes in question may lie between the drug's unique contribution (after potential confounds are considered) and its zero-order correlation (with no potential confounds considered). In the latter approach, variance attributable to drugs may be as high as 12 percent, whereas, as stated earlier, the unique contribution is often in the region of 1 or 2 percent. The likely contribution or influence of the drug may well fall between these two figures.

Related to the above discussion is the fact that the amount of outcome variability in question that may be attributed to almost any prenatally used drug is relatively small compared with other factors and diminishes as the child gets older. In the author's work, spanning more than a decade, nondrug lifestyle habits account for up to 35 percent of the cognitive outcome variability (Fried and Watkinson 1988), but the behavioral effects uniquely associated with maternal drug use (tobacco or alcohol or marijuana) range only from 1.5 to 8 percent after the variance due to other potentially confounding factors is parceled out. In other laboratories with higher risk samples, the figure is frequently less. This low proportion of unique, explained variance should not be interpreted as indicating that maternal drug use is of little significance. Not only are there real, measurable effects as described above, drug use is also one of the few variables that can realistically be modified—more so than other lifestyle factors such as socioeconomic status that impinge on the mother and child. Furthermore, rarely does a drug act in isolation or in a statis-tically unique fashion. It interacts with a host of factors including other drugs and other environmental and genetic risk factors.

However, the small proportion of unique variance attributable to maternal drug use does lead to a variety of interpretative problems and emphasizes the importance of longitudinal investigations in which suspected drug effects from maternal drug usage can be examined across many ages. If one notes effects in the very young infant along particular dimensions of behavior and continues to see effects in related spheres as the offspring gets older, more confidence can exist in attributing some of the findings to the in utero exposure.

Two additional points have to be kept in mind in interpreting the findings with respect to prenatal marijuana exposure described in this chapter. The women in the Ottawa work represent a very low-risk sample. There is a considerable body of literature (animal and human) to suggest that the drug's effect is potentiated in a higher risk environment (reviewed in Fried 1993) and thus one must be very cautious in extrapolating the present observations to other marijuana-using populations. There is also the concern that the potency of marijuana preparations, in terms of tetrahydrocannabinol content, has increased several fold (Elsohly and Elsohly 1989) since the entrance of pregnant women into the Ottawa study in the late 1970s and early 1980s. This increase in drug potency heightens the importance of interpreting the present results as representing conservative observations.

ATTEMPT AT A SYNTHESIS

What can one conclude from the material described up to this point, bearing in mind the interpretative issues just raised? On the surface it appears that the only definitive statement would be that, if there are long-term consequences of prenatal exposure to marijuana, such effects are very subtle. However, the data may allow conclusions that go somewhat beyond this level.

The marijuana findings may be summarized in the following manner. In the newborn and neonate, although far from definitive, there appears to be an association between nervous system state regulation and prenatal exposure to marijuana. However, between 6 months and 3 years of age no neurobehavioral consequences of marijuana have been reported in the OPPS children, although, at 2 years of age, language comprehension was lower among the children of cannabis users prior to statistical control for the home environment. At 4 years, tests of verbal ability and memory statistically discriminated between the offspring of regular marijuana users and the remainder of the children in the OPPS sample. At 5 and 6 years of age, prenatal marijuana exposure was not associated with global tests of cognition and language after statistically controlling for potentially confounding data. However, at approximately these ages and slightly older, tests that examined more specific aspects of behavior did appear to suggest a relationship between performance and in utero exposure to marijuana. In school-aged children, a deficit in sustained attention was noted on a task that differentiated between impulsivity and vigilance. Further, parental ratings of behavior indicated greater problems (particularly in the area of inattention and conduct) among the children of cannabis users. Finally, visual perception, visual memory, language comprehension, and distractibility discriminated between the 6- to 9-year-old offspring of marijuana users and nonusers. The latter findings did not remain statistically significant upon the inclusion of maternal personality and home environment conditions as potential confounds, although this statistical control (as discussed above) may be inappropriate.

Two issues that arise from these data are the seeming absence of prenatal cognitive effects of marijuana at 4 years of age and the question of whether there is any common theme among the effects and trends noted at 4 years and beyond.

Dealing with the latter issue first, the areas of vulnerability that have emerged over the course of the OPPS are quite consistent with the

cognitive construct that several authors have termed “executive function” (Duncan 1986; Luria 1966; Welsh and Pennington 1988). This function is defined as the ability to maintain an appropriate problemsolving set for attainment of a future goal and involves the integration of cognitive processes. The executive function behaviors noted to be negatively associated with prenatal marijuana exposure include those that involve self-regulatory abilities (the dysfunction possibly manifesting itself in the form of behavioral problems), the ability to maintain attention (noted as impairments in vigilance and distractibility), and the ability to act on accumulated knowledge (poorer performance on facets of language and memory).

Executive function is thought to serve as a marker of prefrontal lobe function, and thus this part of the central nervous system (CNS) may be particularly vulnerable to prenatal marijuana exposure. Frontal lobe development is not an all-or-none phenomenon but appears to be a multistage process, as is executive functioning (Welsh and Pennington 1988). Although aspects of executive functioning are present in infants and toddlers (e.g., object permanence behavior), certain aspects of pre-frontal functioning are not apparent or are difficult to test (e.g., self-control, strategies to enhance problemsolving such as the generation and maintenance of goal-oriented sets involving memory and self-monitoring) until children approach or reach school age. This would certainly be very congruent with the results reported in this chapter.

An important further property of executive functioning is that it is disassociated from measures of global intelligence. This is consistent with the observation of the sparing of intelligence quotient (IQ) after frontal lobe damage (Damasio 1979) and may reflect the fact that traditional, global intelligence tests evaluate overlearned information and established cognitive sets. One of the consistent findings noted among the children in the OPPS was that prenatal marijuana exposure was not associated with a lowering of general IQ.

Recent observations from diverse fields within the marijuana research literature also implicate the frontal lobes in that drug's effects. The dis-covery of receptors for cannabinoid substances in the mammalian brain (including humans) provides very convincing evidence for the possibility of direct action of marijuana on mental processes (e.g., Herkenham et al. 1990, 1991; Matsuda et al. 1990). In long-term, chronic adult users, that action includes fragmentation of thought; difficulty in short-term memory tasks; and disturbances in attention, concentration, and judgment—tasks that are associated with frontal lobe functioning. In the rat, within

different regions of the cortex, the frontal area has been reported to contain the highest density of binding sites (Herkenham et al. 1991). In nine chronic adult marijuana users, Tunving and colleagues (1986) reported reduced blood flow throughout the cerebral cortex. Intriguingly, only two of the users were not polydrug users and in these cases the prefrontal area was the most affected (Lundqvist, personal communication, July 1993). Finally, Struve and coworkers (1989, 1993) have recently reported that chronic, daily use of marijuana results in a marked alteration in alpha activity, primarily in the frontal region, even after prolonged cessation of use.

Together, then, a suggestive (although at this stage, highly speculative) picture is beginning to emerge. The behavioral evidence gathered primarily from the children participating in the OPPS over the past years, the temporal sequence of the observed effects, and the recent findings linking altered frontal lobe functioning with chronic marijuana exposure are certainly compatible with the notion that prenatal marijuana exposure may result in altered frontal lobe functioning in the offspring. One of the next steps in this research is to examine the children in the OPPS in tasks that are thought to be particularly sensitive to frontal lobe dysfunction. These include tests of problemsolving that require cognitive flexibility, route finding tasks, measures of distractibility and attention, and working memory. These assessments are presently underway.

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ACKNOWLEDGMENTS

The OPPS has been supported in the past by grants from the National Research Council of Canada and National Health and Welfare, Canada. In recent years and presently the work is supported by National Institute on Drug Abuse grant DA-04874. The thoughful, insightful, and stimulating comments pertaining to frontal lobe functioning and clinical observations of chronic marijuana users by Drs. Dan Ericsson and Thomas Lundqvist of Lund, Sweden, at the International Cannabis Research Society meeting in June, 1993 in Toronto, Canada, are gratefully acknowledged. The work described could not have been carried out without the continuing and ongoing assistance of long-time associates over the years, including B. Watkinson, H. Linttell, and R. Gray, and the enduring patience of the mothers and their children during the past decade.

AUTHOR

Peter A. Fried, Ph.D.
Professor of Psychology
Department of Psychology
Carleton University
Ottawa, Ontario K1S 5B6
Canada

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