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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