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This conclusion should be brought to the attention of the public, in view of the widespread use of marihuana among child bearing women and prospective fathers. Blackard (1984) reports in The New England Journal of Medicine, the presence of THC or of its metabolite in maternal plasma and umbilical cord blood sampled from ten women who delivered their babies in two Denver general hospitals and admitted having smoked marihuana daily during the third trimester of pregnancy.

Furthermore, systematic epidemiological studies should be undertaken to determine, in man, the extent of incidence of neonatal and postnatal morphological, neurological and behavioral anomalies associated with prenatal marihuana exposure.

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Marihuana Use by Pregnant Women and Effects on Offspring: An Update

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FRIED, P. A. *Marihuana use by pregnant women and effects on offspring: An update.* NEUROBEHAV. TOXICOL. TERATOL. 4(4) 451–454, 1982.—This report is based on a previously described sample of 291 mothers-to-be and on an additional 129 subjects. Among these 420 predominantly middle class pregnant women, approximately 3 percent used marihuana regularly during pregnancy. For assessing the effect of marihuana on pregnancy variables and the offspring, the mothers-to-be were matched in terms of nicotine and alcohol use. Marihuana use was associated with a shorter gestation period and a decreased maternal weight gain. No effect on birth weight, length of labor or difficulty in birth were observed. Consistent with the earlier report, babies born to women who smoked more than five joints per week during pregnancy demonstrated marked tremors and startles and altered visual responsiveness at 2–4 days of age. These symptoms had attenuated by 30 days and no developmental impairments were observed in any of seven babies who had reached one year of age born to women who had smoked 2 joints or more per week during pregnancy.

Marihuana Pregnancy Development Neurobehavior

THE present report is a brief update of aspects of an ongoing study started in 1978 involving the department of Psychology of Carleton University and the Ottawa Civic and Ottawa General hospitals. The purpose of the investigation is to examine, in a prospective fashion, the pattern of use of social levels of alcohol, cigarettes and marihuana during pregnancy and the effects of these drugs on the offspring. Details of the procedure and epidemiological information on approximately 200 subjects have been presented previously [4] and birth data and the results of behavioral testing of babies up to 4 days of age born to the marihuana users among 291 subjects in the Ottawa study have also been described elsewhere [3].

METHOD

The present report is based on a sample consisting of 420 subjects and includes several more infants born to marihuana users. As both the demographic data on the mothers and the results of the newborn are essentially the same as those found in the original cohort [3], the data will be described very briefly. Since the original report, a number of offspring of the marihuana users have been followed up and been examined using the Prechtl neurological examination [5] at nine (±1) and 30 (±2) days and the Bayley Scale of Infant Development [1] at 12 months. Although it is obvious, it must be emphasized that the sample size is small and these longitudinal results have to be viewed as quite preliminary.

Mothers-to-be were informed of the study by their obstetrician or notices in the public media and upon volunteering to participate were interviewed one during each of the trimesters remaining in their pregnancy. Information obtained included the volume and variability of alcohol consumption, cigarette smoking habits and marihuana intake for the year before pregnancy and each trimester of pregnancy. In addition to this "soft" drug report a general health history, previous pregnancy details, a 24-hour dietary recall and socio-demographic data were obtained.

The categorization for marihuana use for each of the four time periods (year before pregnancy and each of the trimesters) was: non-user; 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.

RESULTS

The socio-demographic characteristics of the new sample is essentially the same as that of the cohort described previously [4] and therefore will not be dealt with separately. Among the total sample of 420 women the average family income was $29,250±$13,050 and the average age and parity was 29±4 and 0.7±0.9, respectively. The economic profile was very similar to that of the general population of the Ottawa area reported by Statistics Canada and the age and parity figures were consistant with all the women giving birth in 1979 in the participating hospitals. Ninety-four percent of the women had at least a high school diploma and 63 percent had continued their education beyond high school.

In Table 1 the marihuana habits of the original 291 subjects [3] are compared to the additional 129 subjects making up the 420 subjects described in this report. As can be seen,

TABLE I

PROPORTION OF WOMEN IN DIFFERENT CATEGORIES OF MARIHUANA USE BEFORE AND DURING PREGNANCY IN TWO PHASES OF STUDY

Marihuana category (joints/week)	Pre-pregnancy (%)		First trimester (%)		Second trimester (%)		Third trimester (%)	
	Phase 1 n=291	Phase 2 n=129	Phase 1 n=291	Phase 2 n=129	Phase 1 n=291	Phase 2 n=129	Phase 1 n=291	Phase 2 n=129
Non-user	80	84	90	92	91	92	91	95
Light (<1)	14	11	6	6	6	7	6	4
Moderate (2–5)	2	2	1	1	1	0	1	0
Heavy (>5)	4	3	2	2	3	1	3	1

the percentages during pre-pregnancy and during each trimester for the two sub-samples are quite consistent. Among the overall 420 subjects, during the year before pregnancy 82% of the women reported that they did not use any marihuana, 13% were irregular users, 2% were moderate users and 3% were heavy users. Of the 14 women in the latter category, 10 women smoked between 6 and 45 joints per week whereas the remaining four exceeded 100 joints per week. Of the 344 women who reported not using marijuana prior to pregnancy, three did report irregular use during pregnancy. Of the 54 women categorized as irregular users before pregnancy, approximately 58% became non-users in the first trimester and the proportion that changed their marihuana habit remained constant throughout pregnancy. Of the seven women categorized as moderate users prior to pregnancy, all became irregular users or abstainers in the first trimester and remained so throughout pregnancy. Of the 14 subjects categorized as heavy users before pregnancy, one abstained from marihuana throughout the pregnancy. Of the remaining 13, four became moderate users during the first trimester. In the second and third trimesters, nine women continued to be categorized as heavy users.

In both the sample described in the previous report and in the present subsample the women who smoked marihuana to either a moderate or heavy extent were different from the remainder of the sample in a number of ways that might have an adverse effect on the development of the offspring, e.g., lower socio-economic level, less formal education, and increased cigarette smoking. Alcohol was not statistically associated with categories of marihuana use although among the women categorized as heavy marihuana users, the average daily amount consumed was significantly greater than that consumed by the other subjects.

In terms of age, before pregnancy only 3 subjects of the 75, who reported any use of marihuana, were over 32 years and during pregnancy, whereas no moderate and only one heavy user was older than 32.

In order to examine pregnancy variables and the data of the offspring, a matched control procedure was utilized in which the mother-to-be who used marihuana to either a moderate or heavy extent was paired with a non-user with comparable nicotine and alcohol habits.

Marihuana users revealed no differences in rate of miscarriages, complications at birth, length of labour, medicated versus non-medicated type of birth. Among the women in the heavy category (the eight women who smoked more than five joints per week during all three trimesters) both maternal weight gain and length of gestation was less than matched controls in all but one case (Wilcoxon T; $p<0.02$ and $p<0.05$ respectively). Among the 8 heavy marihuana users, 4 had a weight gain of less than 10 kg, whereas none of the matched controls had weight gains of less than 11 kg. Whereas only one control mother had a gestation length of less than 40 weeks, 5 of the heavy marihuana users had gestation lengths of 39 weeks or less.

Taking into account gestational age, no effect of marihuana was seen in terms of the newborn's weight, length or head circumference. Interestingly, the four heaviest users (more than 40 joints a week before pregnancy and more than 10 joints per week during each trimester) all gave birth to males. Neither Apgar status nor haemglobin or hematocrit counts differed among the various groups of offspring.

The results of the assessment, 60–80 hours post-partun, of the newborn's capacity to interact and adjust to its environment (2) revealed group differences. Smoking marihuana regularly during pregnancy was associated with a marked decrease in the likelihood of the offspring responding to a light repeatedly directed at their eyes. Among the nine heaviest marihuana users, five failed to respond to the light and two who did respond failed to habituate. Thus seven of the nine offspring had an altered response. Data, although incomplete, on the matched controls tested so far revealed that, out of seven babies examined, only two failed to respond and all responders habituated.

In terms of general behavior using the matched controls for comparison, the finding described in the earlier report, i.e. of a tendency of the babies born to heavy marihuana users to be less successful at self-quieting than controls, was not confirmed. However, as reported previously, the infants were readily consoled and, in fact, even somewhat more cuddly than controls in the sense of grasping rather than resisting being held. The marihuana babies were not more irritable.

Tremors and startles were significantly heightened among the babies born to women who smoked marihuana regularly during pregnancy. These behaviours, frequently interpreted as symptomatic of nervous system immaturity, were the most consistent and visible consequences of regular heavy marihuana consumption. Interestingly, the babies of four subjects, who reduced their intake from heavy prior to pregnancy to lesser categories as the pregnancy progressed, all had babies that did no display the marked tremors.

Neither degrees of activity nor alertness differentiated among the different categories of users. The same lack of

effect was seen in laterality of handedness.

Finally, at this testing age, a high-pitched cry was noted among a third of the regular marihuana users and was not observed among the controls. This *cri de chat* [6] has been reported among neonates undergoing narcotic withdrawal [7].

The Prechtl [5] neurological examination given at 9 and 30 days was administered to 6 babies born to heavy users during pregnancy and to four babies born to women who were heavy users prior to pregnancy, two of whom became moderate users and two of whom became irregular users during pregnancy. The trend for diminished responsiveness to visual stimuli, seen at 4 days of age, persisted in half of the heavy users and one of the moderate users at 9 days but was not seen in any of the matched controls. However, at 30 days responsiveness was equal in both marihuana offspring and matched controls. Rate of habituation did not differ among any of the groups tested.

The tremors that were so marked during the first few days of life persisted in about half of the babies of the heavy users at nine days of age but were not different from controls at 30 days of age. The *cri de chat* was present in 3 babies; one was born to a woman categorized as a heavy user during pregnancy and the other two were born to women who were heavy users prior to pregnancy and had reduced their pregnancy intake to a moderate and irregular level. No *cri d chat* was heard among any of the matched controls. Analysis of the muscular components of the Prechtl examination is presently underway.

The Bayley Scale of Infant Development [1], consisting of mental, motor and behavioral scales, has been administered to the 12-month-old offspring of 4 heavy users and 3 moderate users. In comparison to both matched controls and normative scores, the data from these few babies did not suggest any negative effects associated with marihuana use during pregnancy. Among the offspring of the heavy users, the range of scores on the mental scale was from 98–120 and the range among the babies of the moderate users was from 97–122. On the motor scale the ranges were 99–120 and 98–111 among the heavy and moderate offspring, respectively. The Bayley Infant Behavior Record, which provided an evaluation of the babies' attitudes, interests and temperament, also failed to discriminate between the children of the marihuana users, matched controls or normative scores.

Physical measurements of growth taken at the time of this test did not differentiate the babies in any of the groups.

DISCUSSION

The demographic data obtained from the present updated sample is very consistant with that found in the initial reports [3,4]. The heavy and moderate marihuana users tended to be younger, have less formal education, a lower family income, a greater likelihood to smoke cigarettes and, on the average, drink more alcohol than irregular and non-users.

These data represent a two-edged sword. Although it is very important to know the characteristics of regular marihuana users who are pregnant many of these characteristics make the interpretation of the effects of marihuana quite difficult. Like virtually all observational studies in which membership in particular groups is defined by an attribute of subject rather than by random assignment, the role of background variables that may influence the dependent variables being considered is a major problem. Due to the extensive information collected during pregnancy, some attempt can be made to identify the influence of these "nuisance" variables in the present study.

The sample size of the marihuana groups prevents the use of such statistical procedures as multiple regression or canonical correlations for this purpose. What has been used in the present report as a preliminary step to focus in on the role of marihuana is to match the others in terms of nicotine and alcohol before and during pregnancy. Other approaches have been used in the previous report [3].

From the use of the matched-control procedure, two birth data results emerged that were not found in the original report; heavy marihuana use was associated with a shorter gestation period and a reduced maternal weight gain. However, as originally reported, no association between marihuana and birth weight, birth abnormalities or difficulties at birth were observed. The relationship reported previously between marihuana and aspects of neurological neonatal behavior such as increased tremors and startles and altered visual responsiveness remained a consistant finding in the 60–80 hour old babies.

However, based on a limited number of babies, these effects were less striking at nine days and by 30 days, no longer distinguished the offspring of the heavy marihuana users. Further, at one year of age no motor, mental or general behavioral attributes appeared to characterize the offspring of the marihuana users.

Thus the very preliminary results suggest that the measurable correlates in newborns of regular marihuana use during pregnancy diminishes with age. Whether this is because the neurologicgal abnormalities present at birth are overcome or compensated for with maturity, or whether the tests used and the later ages have a decreased discriminatory sensitivity to subtle differences that may exist can only be answered by increasing the sample size and further follow-up of the infants. Both of these steps are presently being taken.

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Cannabinoid Exposure: Effects on Development

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DALTERIO, S. L. *Cannabinoid exposure: Effects on development.* NEUROBEHAV TOXICOL TERATOL 8(4) 345–352, 1986.—The literature concerning the teratologic effects of cannabinoids is reviewed, and some methodological issues associated with perinatal cannabinoid exposure are discussed. The long-term consequences of perinatal cannabinoid exposure on brain, endocrine, immune, and hepatic functions are considered. In our studies, perinatal cannabinoid exposure affected the long-term development of body weight regulation, neuroendocrine function, and adult sexual behaviors. In addition, the immune system and [redacted] were also influenced in adult male mice perinatally-exposed to cannabinoids. It is hypothesized that these effects may be mediated by cannabinoid-induced alterations in the fetal and/or neonatal hormonal milieu. In addition, the possibility that perinatal cannabinoid administration affects the subsequent ability of the exposed offspring to adapt to the environment is discussed. Finally, possible mechanisms of cannabinoid action in altering development are evaluated. It is concluded that the evidence to date indicates that cannabinoids can be embryocidal, affect gestational length and labor, induce maturational delays, and that these substances affect a myriad of physiological processes in the developing offspring, including effects on behavioral parameters, not only in laboratory animals, but also in the human neonate. Consequences of perinatal cannabinoid exposure on development are described and possible mechanisms of action of cannabinoids are discussed.

Cannabinoids Δ⁹-Tetrahydrocannabinol Cannabinol Cannabidiol Developmental effects
Perinatal exposure Mammary gland development Fetal androgens Adaptation to the environment
Follicle-stimulating hormone Hepatic function Immune system Testosterone
Luteinizing hormone Brain amines Fertility Sexual behavior Maternal variables Neonatal effects

IN the adult, administration of marihuana, or its purified components has been shown to affect a myriad of physiological processes (review in [7]). It is not, therefore, entirely surprising that exposure of the fetus or neonate results in long-term consequences for subsequent development.

In 1975 Fleischman *et al.* [32] reviewed the teratologic evidence from experiments in which various cannabis products were administered during gestation. Several variables, such as species or strain used, route, timing and dosage, and the type of cannabis preparation, influenced results. These studies evaluating possible cannabis-induced congenital anomalies employed high doses of cannabinoids, and it is possible that the route by which these substances were administered, and the vehicles in which these highly lipophylic agents are suspended, may have also influenced the results.

In a 1978 review, Block *et al.* [7] concluded that the existing data was consistent with evidence of teratogenic effects of cannabinoids in mice, with the most frequently reported defects being cleft palate and exencephaly. However, the high doses required to elicit these effects largely blunted the impact of these earlier reports. The accumulation of evidence regarding the effects of cannabinoids on fetal development did appear consistent with the contention that cannabinoids were embryocidal [7,73].

While earlier studies focused largely on the immediate effects of maternal cannabinoid administration on the fetus or neonate, there has been increasing interest in the long-term consequences of these substances on offspring.

ISSUES IN PERINATAL DRUG STUDIES

Maternal Factors

Several variables need to be considered in evaluating experiments involving pregnant and/or lactating animals. Certainly, stress may accompany any procedure involving handling and drug administration. Drug treatment may also affect maternal endocrine function, behavior, or nutritional status [3, 29, 73, 74]. There have been reports that THC treatment increases cannabalism of pups in mice [1], and also affects other maternal behaviors, such as pup retrieval [2]. In studies in this laboratory, maternal exposure to THC, or to the non-psychoactive, cannabinol (CBN), on the day prior to parturition and the first six days post-partum, did not affect such indices of maternal behavior as, time spent on nest, pup retrieval or lactational performance [16]. Other investigators also did not observe effects of maternal cannabis exposure on time spent on the nest or in pup retrieval [10]. Certainly, there have been several reports of decreased milk production in THC-treated females [8, 51, 70], probably since THC decreases prolactin levels in lactating females and interferes with the prolactin release in response to suckling stimulus [70]. It is possible that the early culling of litters to male pups

only in our experiments may have masked any lactational deficiency. In a recent study, in which the lactating females received a single oral administration on day 1 post-partum (within 12 hr of parturition), we observed milk bands which appeared normal in size in the neonates. Furthermore, postnatal mortality, and weight at weaning were quite normal by colony standards. However, the adult body weights from cannabinoid-exposed males were decreased [25]. In another report, increased mortality was observed after maternal administration of THC, but not after THC and cannabichromene (CBC), or after CBC alone [43]. However, in this study, litters were not culled until 10 days of age [43], while in our study the mice had been culled within 24 hr of parturition [16]. In a report by Charlebois and Fried [10], effects of administration of cannabis prior to, and during, gestation were found to interact with the level of protein in the diet, but these nutritional factors did not totally account for the effects of cannabis on the developing rat. These authors also suggest that the interactive effects of nutrition and cannabis exposure may be the result of diet-related changes in the hepatic drug-metabolizing enzyme systems, since it has been shown that nutritional deficiency impairs drug elimination [9].

It is conceivable that rearing practices or strain differences could influence the acute effects of maternal cannabinoid exposure. In our experiments, mice were obtained from a random-bred stock of animals which routinely produce 10–14 pups, and in which cannabalism is rare. Indeed, the only cannabinoid-related difficulties in our studies, as evidenced by increased neonatal mortality, occurred after administration of crude marihuana extract (CME) (Dalterio, unpublished).

Cross-fostering has been suggested as a method of dealing with the confounding effects of drugs on maternal functions, including food or water intake, which may affect development in their offspring [3]. While such an approach may be indicated for studies of other drugs, research on cannabinoids possesses some methodological problems that do not exist with water-soluble and/or shorter-acting substances. It has been well-documented that cannabinoids accumulate in the fetus and neonate as a result of maternal transfer via the placenta [6, 33, 49, 80], or milk [16, 46, 47]. Thus, uni-directional transfer of cannabinoids from mother to fetus or neonate has been demonstrated. However, the possibility of bi-directional transfer of cannabinoids has not been considered. The pups themselves should eventually excrete cannabinoids via the urine and feces, as does the adult [76]. Maternal grooming patterns in most mammalian species strongly indicate that surrogate mothers (assumed to be drug free), will ingest waste material from their suckled pups. Indeed, in earlier studies using adult animals, we observed behavioral alterations consistent with cannabinoid intoxication in the non-treated partner of a mating pair (Dalterio, unpublished). Thus, it became apparent that the fecal reingestion characteristic of the mouse insured that untreated animals, housed in contact with the treated mice, would receive some degree of drug exposure.

Route of Administration

In studies conducted over the past nine years, repeated administration of cannabinoids by oral feeding, i.e., 20–25 μl drop in sesame oil which the mice readily ingest, has not produced a single mortality in our cannabinoid-treated animals. Indeed, in studies involving repeated administration in adult male mice (3× week for seven weeks at 50 mg/kg) there were no final differences in body weight between THC-treated and control animals, which had been initially matched by litter and body weight [16].

It is possible that the route of administration and vehicle strongly influence cannabinoid-induced decreases in food or water intake. In some studies, oral administration has been used to designate per os, intragastric or intubation procedures. Certainly, the latter can be stressful, and, after repeated treatments, this could also affect the animal's food or water intake. In contrast, we have demonstrated the oral feeding, as employed in our laboratory, does not produce significant stress on the animals as indicated by levels of stress-labile hormones [20]. In our experience, the vast

TABLE 1
DEVELOPMENTAL EFFECTS OF PERINATAL CANNABINOID EXPOSURE

Treatment	Species	Effects
prenatal THC	rat	↓ protein, nucleic acids & lipids in brain [56]
prenatal THC	rat	delayed reflex development
prenatal cannabis	rat	↓ open-field activity, retarded wt. gain, eye opening & incisor eruption [10, 34]
prenatal THC	rat	fluctuating dental asymmetry [75]
prenatal THC	rat	↓ passive avoidance response [80]
perinatal hashish	mice	↓ body weight gain [36]
perinatal THC	monkey	altered visual attention [39]
prenatal cannabis	human	attention deficits [33]. ↓ birth wt., length & head circumference [44]; meconium staining [33]
prenatal	rat	↓ fertility & body wt. [34]
pregestational	male mice	↓ fertility & chromosomal anomalies in F_1 [22]
perinatal THC	mice	↓ adult sex behavior; ↑ plasma LH [16]
perinatal CBN	mice	↓ adult sex behavior; ↓ plasma LH and T at puberty [16]
prenatal THC	mice	↑ hepatic cytochrome P-450 [27]
prenatal CBN	mice	↑ *in vitro* T production, testes & seminal vesicles wt.; ↓ brain DA; ↑ hypothalamic 5-HT post-castration; ↑ hepatic cytochrome P-450 [24,27]
prenatal CBD	mice	↓ brain DA, ↑ hypothalamic 5-HT post-castration; ↑ hepatic cytochrome P-450 [24,27]
postnatal THC	mice	↓ body wt.; ↑ pituitary wt., & LH production *in vitro*; ↓ plasma LH and FSH; ↑ hypothalamic LHRH; ↓ hepatic cytochrome P-450; ↓ fertility [25–27]
postnatal CBN	mice	↓ body wt.; ↑ pituitary wt., & LH production *in vitro*; ↓ hepatic P-450; ↓ albumin & ↑ γ-globulin, ↓ fertility [25–27]
postnatal CBD	mice	↓ testes wt., plasma LH & hepatic cytochrome P-450; ↓ fertility [25,27]

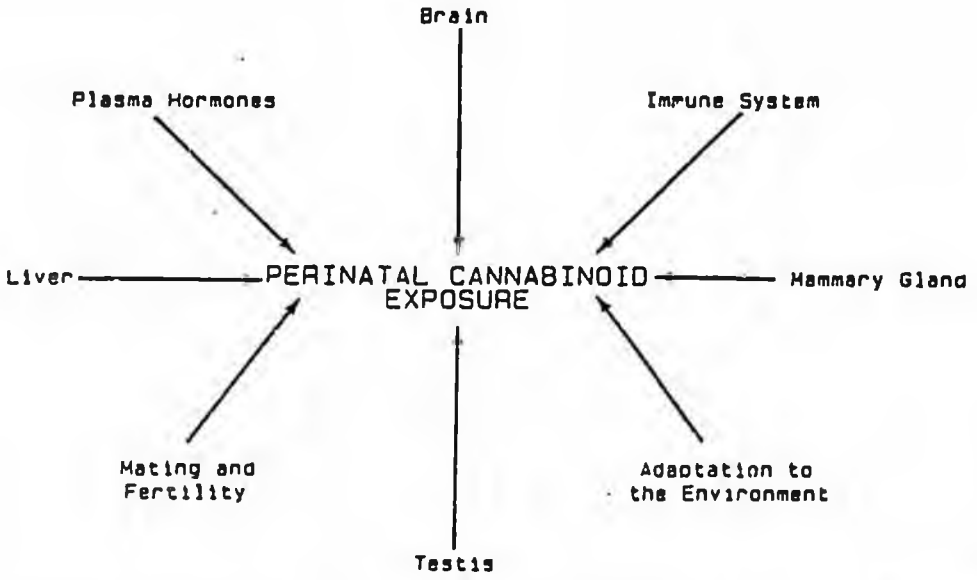

FIG. 1. Target areas whose functions may be altered as a result of perinatal cannabinoid exposure.

majority of mice receiving THC by the oral route show overt symptoms of behavioral intoxication within 15 min post-treatment (Dalterio, unpublished), and we have demonstrated that endocrine effects are already apparent at 5–10 min post-THC exposure in male mice [21].

MATURATIONAL EFFECTS

Delayed reflex development has been observed in rat pups exposed to THC on days 10–12 gestation [8]. Offspring also exhibited delayed incisor eruption and retarded development of cliff avoidance, and the visual placing reflex [8]. However, at 9 days post-partum, drug-exposed female offspring were more active in the open-field, but this effect was no longer apparent by weaning age [8]. Other investigators either found no effect [79], or decreased activity [35], after maternal cannabinoid treatment. In the Fried study [35] pups also presented evidence of retarded weight gain, eye opening and incisor eruption. Another study, which reported fluctuations in dental asymmetry in THC-exposed pups, suggested that this effect was related to THC "stressor" actions [75].

In another study in mice, Frischnecht *et al.* [36] reported that body weight gain was reduced in suckled mice during the entire lactation period, when mothers were given hashish. However, maternal weights and food intake were not affected [36].

Maternal cannabinoid exposure, therefore, affected dental development in different species, i.e., rats and mice, using PO, inhalation, or oral routes at different periods of gestation, with or without cross-fostering or pair-feeding, and in the absence of effects on maternal weights or food intake. It, thus, appears that maternal cannabinoid exposure affects at least this maturational index.

It is always difficult to explain differences between experimental results obtained in different laboratories. However, it is also difficult to ignore repeated evidence from several years experience in our own laboratory, indicating that effects on maternal behavior, general toxicity or stress effects do not appear to account for either cannabinoid-induced alterations in the reproductive system in the adult, or the long-term consequences on development in exposed offspring.

Perinatal cannabinoid exposure affects the development of a number of physiological systems (Fig. 1).

BRAIN BIOCHEMISTRY

Decreases in protein, nucleic acid and lipid synthesis have been observed in young rats exposed to maternal doses of 5–10 mg THC/kg [56]. In recent studies, we have reported that exposure on day 18 of gestation to CBN or CBD reduced the concentrations of norepinephrine (NE), and dopamine (DA) in hypothalamus, and in the remaining portion of the brain in adulthood [24]. In contrast, levels of serotonin (5-HT), and its metabolite, 5-HIAA, were elevated [25].

Adult mice exposed to THC on day 1 post-partum had significantly higher hypothalamic luteinizing hormone releasing hormone (LHRH) levels, and, in mice exposed postnatally to CBN, hypothalamic DA levels were significantly lower [25]. In addition, postnatal exposure to THC or CBN attenuated the depletion of catecholamines after α-methyl-p-tyrosine (α-MPT). Brain levels of 5-HT and 5-HIAA were also significantly higher in castrated, than in intact THC-exposed males. In CBN-exposed female offspring, hypothalamic levels of NE were lower, and the α-MPT-induced depletion of NE was attenuated in CBD-exposed females.

An interrelationship between gonadal steroids and the central nervous system biogenic amines has been reported [13, 28, 71]. It is, therefore, possible that cannabinoid-induced alterations in the biochemical function of these aminergic systems may be related to subsequent effects on endocrine functions.

BEHAVIORAL ALTERATIONS

It is difficult to determine whether any of the changes in brain biochemistry consequent to perinatal cannabinoid exposure is specifically related to long-term effects on behav-

ioral parameters. In our studies, we noted that perinatal cannabinoid exposure significantly affected adult male copulatory behavior [16]. In later studies, we observed an increase in brain 5-HT levels in adult males exposed postnatally to THC [25], and in mice exposed prenatally to CBN or CBD [25]. This latter group of males also had reduced levels of DA in brain [25]. It has been suggested that increased 5-HT may inhibit sexual behaviors, while the increased catecholamines appear to be facilatory [37]. Whether or not the alterations in visual attention observed in human infants [34], or in monkeys perinatally-exposed to cannabinoids has not been determined. In one study [39], administration of cannabis resin to pregnant rats affected subsequent learning behavior, body weight, brain weight and DNA ratio. At this point, any direct relationship between brain biochemical alterations induced by perinatal cannabinoid exposure, and the observed effects on open-field activity [8], reflex development [35], acquisition of the passive avoidance response [80], or any other cannabinoid-induced behavioral disruptions, remain to be established.

IMMUNE SYSTEM

Cannabinoid administration has been demonstrated to effect immune responses in laboratory animals [56, 63–65], and in man [14,67]. Recently, we have reported that postnatal exposure to CBN produces a concomitant decrease in plasma albumin, and an increase in γ-globulin concentrations in adult male mice [69]. At this point, it seems reasonable to suggest that cannabinoid-induced suppression of androgens could be related to this enhanced immunoglobulin level. Effects of the gonadal steroids on the development and function of the immune responses are well known [50, 55, 83]. Certainly, perinatal manipulation of the early steroid environment and/or administration of exogeneous androgens or estrogens during early development have been related to alterations in immunoresponsiveness [55,83].

NEONATAL EFFECTS

Rhesus monkey infants whose mothers received daily oral THC prior to, and during lactation, presented evidence of altered visual attention, which appeared to be characterized by sustained focus on a novel stimulus [39]. A significant increase in symptoms associated with nervous system abnormalities were also observed by Fried [34] in infants born to heavy regular marihuana users. Attention deficits, visual preference anomalities, tremors, and meconuim staining were also noted [34].

In a recent study by Hingson [44], women who smoked marihuana during pregnancy delivered infants with significantly reduced birth weights, length and head circumference. In addition, marihuana-exposed infants were 5 times more likely to exhibit features compatible with those of the fetal alcohol syndrome [44]. An association between maternal marihuana use and low Apgar scores in infants has also been observed [45].

ADAPTATION TO THE ENVIRONMENT

In our studies, we noted that, at puberty, male mice that had been perinatally-exposed to THC or CBN responded to individual housing with an immature female very differently than did the control males [16]. The THC- and CBN-exposed males housed with females, weighed significantly less than did animals which were housed in all male groups since weaning. In contrast, the control males gained weight as a result of female exposure [16]. In addition, in cannabinoid-exposed males, plasma corticosterone levels were increased one week after housing with an immature female (Dalterio, unpublished), suggesting that the housing arrangement was stressful for these males.

It is difficult to determine whether there is a common mechanism by which early cannabinoid exposure influenced the responses of these mice, or those of the human or nonhuman primates. It is conceivable that alterations in brain biochemistry may mediate these behavioral or perceptual alterations induced by perinatal cannabinoid exposure.

PLASMA HORMONES

Perinatal exposure to THC resulted in a marked elevation in plasma LH levels in pubertal and in adult mice [16]. In contrast, exposure to CBN during the same period resulted in a significant decrease in plasma LH concentrations at puberty, but with normal levels in adulthood [16]. Although plasma FSH levels tended to be reduced, they were not significantly different from those of the controls [16].

Prenatal CBN exposure significantly decreased plasma FSH levels [24], and tended to reduce LH, but this was not statistically significant. Prenatal THC exposure had no apparent effects on plasma gonadotropins in intact adult males [24].

In contrast, plasma LH concentrations were significantly lower in adult males exposed on day 1 post-partum, to THC, CBN, or CBD [25]. Although plasma FSH levels also tended to be lower, this was significant only in THC-exposed mice [25].

Plasma gonadotropin levels in response to castration were influenced by prior exposure to cannabinoids. Perinatal THC exposure resulted in a more marked elevation in plasma LH and FSH than those observed in the castrated controls [19]. In adult mice exposed to THC on day 18 of gestation, plasma LH and FSH levels were also higher than those observed post-castration in control males [24].

It is possible that cannabinoid exposure resulted in a differential sensitivity to the stress associated with castration. Or, perhaps, cannabinoid-induced alterations in neuroendocrine functions become more apparent when the neuroendocrine axis responded to the removal of steroid negative feedback. It does appear that cannabinoids affect the physiological reactions to events which disturb homeostatic conditions, or those that elicit endocrine responses.

MATING BEHAVIOR AND FERTILITY

In one study, the F_1 generation of rats exposed to cannabis smoke *in utero* took longer to mate and were less fertile than offspring of controls [35]. In addition, exposed females experienced more resorptions during pregnancy and offspring weighed significantly less at 1, 10, 11 and 30 days of age [35]. Recently, we observed that adult male mice exposed to cannabinoids on day 1 post-partum were less successful in mating, and produced fewer live offspring [26]. Pre-gestational exposure of the male parent also influences the subsequent fertility of the F_1 male offspring, and, indeed, results in congenital abnormalities in the F_2-generation [22].

Thus, maternal or paternal exposure to cannabinoids influences subsequent fertility in their offspring. This suggests that cannabinoids are either directly gametotoxic or mutagenic, or perhaps, that cannabinoid-induced endocrine alterations affect the subsequent production and/or integrity of gametes.

LIVER FUNCTION

Recently, we observed that prenatal exposure to THC, CBN or CBD significantly increased hepatic cytochrome P-450 concentrations, while levels of this enzyme are reduced in adult males exposed to these cannabinoids on day 1 post-partum [27]. These changes in hepatic enzyme activity may be related to the long-term effects of cannabinoids on plasma hormone concentrations, by affecting steroid metabolism or clearance. It is also possible that these long-term changes in enzymatic activity may be related to cannabinoid-induced alterations in perinatal androgen production. Certainly, the early hormonal milieu plays a critical organizational role in establishing sexual dimorphic hepatic functions [11, 30, 31]. This exerts an "imprinting" action on the liver, affecting subsequent sensitivity to the activational effects of steroids in adulthood [30,31]. However, in view of the effects of perinatal cannabinoid exposure on hepatic function in adulthood [5, 53, 54], it is possible that these substances may directly influence hepatic enzyme activity, possibly by interfering with macromolecular protein synthesis [65].

TESTES

Exposure to THC during the latter part of gestation and early post-partum resulted in a significant decrease in testicular weights at puberty [16], and also in adult male mice [16]. In one study, we observed that plasma T levels were significantly reduced [19], and, in another, in the low normal range [16].

Prenatal exposure to CBN did not affect testicular weights in adulthood, but did result in a reduction of testicular T concentration [24]. However, *in vitro* production of T was significantly increased after prenatal CBN exposure [24].

Testicular weights were increased in adult male mice exposed to CBD on day 18 of gestation [24], while these were significantly reduced in mice exposed to CBD on day 1 post-partum [25]. Interestingly, the *in vitro* responsiveness of testes obtained from these CBD-exposed mice to gonadotropic stimulation was enhanced [25].

These effects of early cannabinoid exposure on the testis may reflect long-term changes in the function of the hypothalamo-pituitary-gonadal (HPG) axis. In examining the diverse effects of perinatal cannabinoid exposure on hormone levels in adults, it is possible to conclude that cannabinoids disrupt the functional feedback regulation of the HPG system. Whether these disruptions reflect specific actions at a particular level of this system, or multiple actions, possibly by similar mechanisms, on HPG target sites, remains to be determined.

MAMMARY GLAND

We have demonstrated that exposure to THC or CBN during gestation suppresses androgen production in male fetuses [18]. Androgen exposure during gestation affects mammary gland development. In fetal male mice, within 36 hr of the initiation of fetal T production the mammary gland becomes sensitive to androgens, which results in separation of the epidermal bud from the mesenchyme, and ultimately, in necrosis [52]. This action of androgen occurs about day 13.5 of gestation, and androgen sensitivity of the mammary tissue is no longer apparent after day 15 [52]. It is, therefore, possible that the subsequent morphology and hormonal responsiveness of the mammary gland may be altered in the cannabinoid-exposed male. Since there have been reports of gynecomastia in human males who used marihuana [42], it is also conceivable that the cannabinoids can affect mammary development by direct actions on this tissue. Studies are presently underway to evaluate this possibility.

POSSIBLE MECHANISMS OF ACTION

It is possible that alterations in responsiveness to gonadotropins, either *in vivo* or *in vitro*, may reflect cannabinoid-induced alterations in gonadotropic action at the target tissue. It is also conceivable that cannabinoid exposure may have affected gonadal steroid feedback or pituitary gonadotropin release patterns. Cannabinoid-induced changes in the pulse frequencies, or duration [77,78], or perhaps, in the biological activity of LH, could have influenced the subsequent sensitivity of the testis to gonadotropic stimulation.

Cannabinoid influence on fetal and/or neonatal androgen production appears to be consistent with the observed effects of exposure to these substances. Certainly, it has been well-documented that the early hormonal milieu is critical for the establishment of sexual dimorphism in a number of physiological systems [41, 57, 58]. Hypothalamic nuclei regulating neuroendocrine and sexual functions are altered as a result of early gonadal steroid exposure [40, 41, 57, 58], and the reproductive structures are influenced, both in terms of morphology and function, by the fetal endocrine environment [12,84]. Androgen actions also affect the steroid and drug metabolizing enzymes in liver, and influence the development of immunoresponsiveness [11,50]. Obviously, if cannabinoids alter androgen production or actions during the masculinization of these systems, the long-term effects on hepatic and immune functions, such as those we have recently reported [26], are not surprising. Any long-term effects of cannabinoids on the pubertal and/or adult hormonal profile could also have an additional impact, by influencing the activational actions of the gonadal steroids on reproductive and non-reproductive systems [41, 57, 58].

The fact that estrous cyclicity (Dalterio, unpublished), and brain biogenic amines are also affected in female offspring perinatally-exposed to cannabinoids [25], does suggest that, either cannabinoids affect fetal or neonatal androgen production indirectly via interference with neuroendocrine functions, or, that these substances can directly affect several target areas independently, including the fetal and/or neonatal testis.

Certainly, there appears to be differences in the effects of cannabinoids, depending on the time of maternal exposure, and the particular cannabinoid administered. It may be that these differences represent cannabinoid-induced alterations in critical period phenomena during development, or perhaps, may be due to biphasic effects of these compounds on testicular steroidogenesis [17,23]. Thus, depending on the dose or timing of exposure, fetal and/or neonatal androgens may have been increased and/or decreased, as we have reported for adult mice [21].

In comparing these data from our laboratory with those of others investigating perinatal manipulations, certain similarities in the effects seem apparent. Protein malnutrition during prenatal periods reduced *in vitro* T production by neonatal rat testes [38], and maternal stress has been shown to reduce fetal T levels [82], as does THC and CBN [18], but did not affect subsequent testes weights [81]. In other studies, maternal stress has been associated with changes in

reproductive structures [15], and in brain catecholamines [62]. In addition, we reported that perinatal ethanol exposure decreased adult plasma T, as well as *in vitro* T production, and testicular weights [19].

CONCLUSIONS

Several lines of evidence suggest that the effects of perinatal cannabinoid exposure are most likely due to complex pharmacological actions, and not, simply, the result of stress, nutritional, toxic or behavioral factors. Differences between the long-term effects of the various cannabinoid products are apparent, and critical periods seem to exist for their developmental disruptions [24,25]. Strain differences in the behavioral responses to THC have been reported in adult mice [68], and pre-treatment with SKF-525A or phenobarbital, which influence THC metabolism, potentiated teratogenic effects in mice [59]. In another study, the long-term disruptions in reproductive functions in adult male mice perinatally exposed to THC could be prevented by concomitant CBC exposure [43]. These findings may indicate that CBC competitively interacts with an as yet unidentified receptor site or sites, or that CBC alters THC metabolism [43]. In our studies, the non-psychoactive CBN and CBD also produce long-term changes in reproductive functions in male and female offspring [16, 24, 25]. In addition, studies in adult male mice have suggested that there are differential effects among cannabinoids on testicular steroidogenesis [16,23]. It would be difficult to account for such findings without concluding that cannabinoids have specific effects on the development of biological systems.

Cannabinoid influences on maternal factors, including the uterine environment, nutritional intake, or maternal behaviors probably do interact with those directly attributable to the pharmacological effects of the cannabinoids themselves. Of course, it is important to determine, experimentally, the relative impact of such maternal factors in the overall actions of cannabinoids on development. However, it would seem that, if a drug affects maternal factors, that these must also be regarded as drug actions with possibly important consequences for fetal or later development. Thus, the relevance of maternal variables in the etiology of cannabinoid-induced teratogenesis, perhaps, need to be considered as possible mechanisms of cannabinoid action, not simply as extraneous variables, which need to be eliminated.

Cannabinoids represent a unique class of compounds. Their highly lipophylic property complicates drug administration procedures, as well as the determination of precise time courses or tissue concentrations at potential target sites. In addition, the insoluability of these substances in aqueous media has posed problems in the design and interpretation of data from *in vitro* experiments, the preparation of suspension vehicles, and in the determination of route of administration for *in vivo* studies. Cannabinoid effects can be biphasic, and dose effects are often absent. Nonetheless, the evidence to date strongly suggests that the cannabinoids, especially THC, are embryocidal, and that these substances affect the fetal endocrine environment. Maturational indices appear to be affected, and cannabinoid-induced alterations in brain biochemistry may mediate long-term effects on behavior, and possibly also neuroendocrine functions. While some of the consequences of perinatal cannabinoid exposure may be partly related to maternal effects, it seems probable that these substances also directly affect the developing fetus at a number of sites, and by several different mechanisms. Certainly, the review of the literature to date no longer confines effects of perinatal cannabinoid exposure to laboratory animals, but now also includes effects on the human neonate. Clearly, there are strong indications that perinatal cannabinoid exposure may also have long-term, perhaps subtle, effects on development in the human.

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angioedema, wheezing, laryngeal edema, or hypotension). Such patients do seem to be at increased risk of a similar reaction to cephalosporin. Most patients with penicillin allergy, however, have a rather vague history of rash, usually of the delayed variety. They are no more at risk of severe, IgE-mediated reactions than patients without such a history. Alternative antibiotics, such as vancomycin or erythromycin, should be used if there is any possibility of a history of an immediate-type allergic reaction to a penicillin.

Dr. Saxon has focused on our data on the teichoic acid antibody, which must indeed, although strongly suggestive, be viewed as preliminary evidence that a positive test is associated with metastatic seeding during bacteremic staphylococcal infections. Like all other tests, the teichoic acid–antibody assay needs to be used with its benefits and limitations kept clearly in mind. A prospective study of whether patients whose treatment is managed with the benefit of information yielded by the assay do better than those cared for without such information is definitely needed and is now feasible, since sufficient quantities of standardized antigen are commercially available.

Dr. Rahal's points are similarly cogent, and I would agree that there is no method by which a metastatic abscess secondary to *S. aureus* bacteremia can be absolutely excluded after two weeks of intravenous therapy. However, since some authorities suggest that a two-week course of therapy is enough for a clinically uncomplicated episode of staphylococcal bacteremia, a test that helps to distinguish between patients with and without metastatic complications should be considered an extremely useful adjunct to clinical decision making, unless proved otherwise. Again, a prospective study of the usefulness of the teichoic acid–antibody test in these patients is needed to assess the expense of the assays and outcome data and the expense (in this age of skyrocketing health costs) of arbitrarily treating all patients with bacteremia parenterally for four weeks. The suggestion that a course of oral therapy be continued in all patients who seem to have no complications at two weeks also needs study, but such a course may be a prudent approach until more data are available on these controversial questions.

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HUMAN PLACENTAL TRANSFER OF CANNABINOIDS

To the Editor: Cannabis and its derivatives have been shown to cross the placenta in pharmacologic studies of animals, but concentrations were found to be lower in fetal than in maternal tissues.[1-4] No comparable information has been available regarding fetal blood or tissue levels of cannabinoids associated with marijuana smoking by pregnant women. We studied women who reported heavy marijuana consumption at the end of pregnancy, in order to determine the relative levels of delta-9-tetrahydrocannabinol (Δ9-THC) and its principal metabolite, 11-nor-delta-9-carboxylic acid (9-carboxy-THC), in the mother and fetus.

Ten women who reported that they smoked marijuana daily in the third trimester of their pregnancy were identified by personal screening interviews in two Denver public hospitals. The highest consumption reported was five marijuana cigarettes per day.

At delivery, blood samples were drawn from the mother's arm, and cord-blood specimens were taken from the umbilical remnant before delivery of the placenta. The two specimens were collected within 10 to 20 minutes of one another and analyzed at the University of Utah for Δ9-THC and 9-carboxy-THC by gas chromatography–mass spectrometry according to the Foltz method.[5]

Six of the 10 women and 3 of their infants had detectable levels of Δ9-THC (Table 1). The level of Δ9-THC in maternal blood was 2½ to 6 times greater than in cord blood. All maternal and cord-blood samples had detectable levels of the metabolite 9-carboxy-THC. Maternal levels of the metabolite were from four to seven times higher than cord levels. The observation that levels of 9-carboxy-THC were higher than those of Δ9-THC was consistent with reports that concentrations of the metabolite were higher several hours after smoking.[6]

The findings indicate that cannabinoids are detectable in fetal cord blood at delivery when there are appreciable levels in the mother's plasma. The data from this study are limited to the difference in marijuana components in the infant at term and may not be applicable to other periods of gestation. Furthermore, they do not provide information about the maternal/fetal ratios that are present closer to the time of peak exposure (seven to eight minutes after beginning to smoke a marijuana cigarette[6]).

Table 1. Serum Levels of Tetrahydrocannabinol (Δ9-THC) and Its Metabolite (9-carboxy-THC) in Maternal Blood and Fetal Cord Blood.*

Case No.	Δ9-THC (ng/ml)		9-carboxy-THC (ng/ml)		Hours since Smoking
	Maternal	Fetal	Maternal	Fetal	
1	6	1.0	125	18	5
2	1.2	0.3	39	5.2	10
3	1.0	<0.2	31	7.2	12
4	0.8	0.3	19	3.5	19
5	0.4	<0.2	3.8	2.3	
6	<0.3	<0.2	14	1.8	12
7	<0.2	<0.2	18	7.1	17
8	<0.2	0.4 †	3.9	0.9	24
9	<0.2	<0.2	8.1	1.5	26
10	<0.2	<0.2	2.3	0.4	12

*The lower limit of sensitivity on gas chromatography–mass spectrometry was 0.2 ng per milliliter for Δ9-THC and 0.1 ng per milliliter for 9-carboxy-THC.

†The laboratory had reservations regarding the accuracy of this value.

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VITAMIN A TERATOGENICITY

To the Editor: I was pleased by the excellent review of vitamin A and retinoids by Goodman in the April 19 issue.[1] However, I was greatly distressed that the article did not mention the teratogenic nature of vitamin A or retinoids taken in therapeutic doses. Almost half the persons who take such doses are women of childbearing age.[2] Vitamin A in the form of isotretinoin (e.g., Accutane, or 13-*cis*-retinoic acid) has been clearly shown to be teratogenic in human beings.[2-4] The risk of spontaneous abortion or congenital malformations may be as high as 100 per cent if the drug is taken in therapeutic doses into the second month of gestation. Absence or hypoplasia of the external ears, central-nervous-system anomalies (including microcephaly and hydrocephaly), cortical blindness, and severe congenital heart disease have been reported singly and in combination.[2,3] These anomalies were predictable from animal studies,[3] and use of the drug during pregnancy is clearly contraindicated in the information for patients and prescribing information for physicians. I was surprised that this potentially devastating complication of vitamin A therapy was not brought to the attention of practitioners in such an excellent review article.

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Induction of sister-chromatid exchanges in heroin-cannabis, heroin and cannabis addicts

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Summary

The aim of this study was to determine the frequency of sister-chromatid exchanges (SCEs) in heroin-cannabis, heroin and cannabis addicts. The group of 84 subjects consisted of 42 controls, 16 heroin-cannabis addicts, 12 heroin addicts and 14 cannabis addicts.

The mean number of SCEs/cell was 12.95 in heroin-cannabis addicts, 12.05 in heroin addicts and 11.99 in cannabis addicts. These values are significantly ($P < 0.002$) higher than the mean values found in controls. This increase in SCEs may be related to reduced DNA repair in chronic drug addicts, which would allow the fixation or retention of a greater fraction of the DNA lesions caused by normal environmental exposure.

The cellular site of mutagens and carcinogens is thought to be nuclear DNA. It has been well established that many compounds which damage DNA induce SCEs (Faed and Mourelatos, 1978). Because of its sensitivity and ease of performance, the SCE assay is commonly used to assess the DNA-damaging potential of suspected mutagens. The purpose of this study is to demonstrate how the SCE analysis in human lymphocytes can serve as a rapid and sensitive genetic screening method in cases of chronic drug addiction.

This study refers to a group of 84 volunteers. Some of the subjects had received medically prescribed drugs and the addicted subjects had taken no drugs (of abuse), other than those indicated. The group consisted of 42 controls with a mean age of 26.5 years, 12 heroin addicts (8 males, 4 females) with a mean age of 28.33 years and a mean period of heroin addiction of 6.29 years, 14 cannabis addicts (11 males, 3 females) with a mean age of 28.91 years and a mean period of addiction to cannabis of 6.32 years and 16 heroin-cannabis addicts (15 males, 1 female) with a mean age of 27.68 years and a mean period of addiction to heroin and cannabis of 9.06 years.

The control subjects were divided into 3 groups, the numbers of males and females equalling those in the drug addict group to which they were being compared. Both controls and drug addicts groups include members with similar habits of tobacco, alcohol and coffee consumption.

The daily heroin dose varies from addict to

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dict within the range 30 mg (minimum) to 2 g aximum), while the daily cannabis dose ranges om 450 mg (minimum) to 6 g (maximum). We nnot be sure about the purity of heroin and nnabis taken by some participants during their ng period of addiction.

Lymphocyte cultures were prepared by adding drops of whole blood from each participant to 4 l of chromosome medium 1A (Gibco).

Air-dried preparations were made and stained y the FPG procedure (Perry and Wolff, 1974). he cultures were incubated for 72 h at 37°C and ietaphases collected during the last 2 h with olchicine at a concentration of 0.3 μg/ml. To emonstrate SCEs, 4 μg/ml 5-bromodeoxyuridine BrdUrd) was added during the last 48 h of culure. Throughout the experiment, all cultures were naintained in the dark to avoid photolysis of 3rdUrd. The chromosome analyses were performed blind.

For the statistical evaluation of the experimental data, the chi-square test was used for the cell-kinetic comparisons, whereas for the SCE-frequencies, Student's *t*-test was performed to determine whether any values deviated significantly ($P < 0.01$) from the appropriate controls.

Heroin addicts were found to have a mean of 12.05 SCEs/cell, cannabis addicts had a mean of 11.99 SCEs/cell, while heroin-cannabis addicts had a mean of 12.95 SCEs/cell. These values are significantly ($P < 0.002$) higher than the mean values of corresponding controls (Table 1). In spite of the significant ($P < 0.001$) increase in SCEs in cannabis addicts, compared with controls, the range of 3–24 SCEs per metaphase is considered to be very close to normal (Table 1). Ranges of 1–21 SCEs/cell are considered to be normal for human lymphocytes at BrdUrd concentrations of up to 10 μg/ml (Deknudt and Kamra, 1983). However, the findings concerning cannabis addicts may also seem to be biologically relevant, since a cell division delay, although non-significant ($P > 0.05$), was observed in cultures from heroin-cannabis, heroin and cannabis addicts compared with cultures from the corresponding controls (Table 1). Chemically induced cytotoxicity is clearly manifested as a change in the relative proportions of cells in their first, second and subsequent divisions (Morimoto and Wolff, 1980). Studies in search of a relationship between SCE induction and other expressions of genotoxicity have found a positive relationship between SCEs and alterations in cell

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TABLE 1

INDUCTION OF SISTER-CHROMATID EXCHANGES[a] IN HEROIN ADDICTS, CANNABIS ADDICTS AND HEROIN CANNABIS ADDICTS

	Subjects (*n*)	Mean age	Mean period of addiction (years ± S.E.M.)	Mean SCEs/cell ± S.E.M. (range)	*t*	*P*	PRI[b]
Heroin addicts	12	28.33	6.29 ± 1.92	12.05 ± 0.70 (3–30)	3.73	< 0.002	1.98
Controls	12	26.7		9.22 ± 0.28 (0–19)			2.13
Cannabis addicts	14	28.91	6.32 ± 1.43	11.99 ± 0.42 (3–24)	4.18	< 0.001	2.01
Controls	14	27.1		9.31 ± 0.47 (0–21)			2.12
Heroin and cannabis addicts	16	27.68	9.06 ± 1.50	12.95 ± 0.76 (3–38)	4.14	< 0.001	1.95
Controls	16	25.7		9.51 ± 0.32 (1–22)			2.11

[a] Each subject's SCE value was established as the mean of 30 counted metaphases (*n*).

[b] For proliferation Rate Index (PRI) 100 cells, at least, were scored. PRI was calculated as $(1M_1 + 2M_2 + 3M_{3-})/100$, where M_1 the percentage value of cells in the 1st, M_2 in the 2nd and M_{3-} in the 3rd and higher divisions.

cycle kinetics. These findings suggested that a common element, possibly a type of DNA damage, produced by certain agents was responsible for inducing SCEs and reducing cell growth (Morimoto and Wolff, 1980; Morris and Heflich, 1984).

To date, the available literature does not report any clastogenic effect produced by cannabis, with the exception of the report by Chiesara et al. (1983) who found increased chromosome aberrations in marijuana addicts. A clastogenic effect of heroin has been described in pregnant monkeys and their offspring by Fischman et al. (1983).

Since there is already some evidence that chronic opiate addicts have a reduced capacity for DNA repair (Shafer et al., 1983), and marijuana addicts an increased chance of chromosome damage (Chiesara et al., 1983), we propose that the increase in SCEs observed in this study may be related to the reduced DNA-repair capacity which such chronic drug addicts may have acquired. The genetic material is constantly attacked by various environmental factors and these premutation defects have to be continuously corrected by the natural repair system. Reduced DNA-repair capacity in chronic drug addicts, as in those currently studied, would allow the fixation or retention of a greater fraction of DNA lesions caused by normal environmental exposure. It has been proposed that the induction of SCEs may be related to the repairability of DNA lesions prior to or during the replication process (Shafer et al., 1983; Dozi-Vassiliades and Mourelatos, 1985).

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THE EFFECTS OF MARIJUANA SMOKE ON GAS EXCHANGE IN OVINE PREGNANCY

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Summary

The effects of marijuana smoke on maternal respiratory rate and gas exchange were examined in nine chronically instrumented, late gestation ewes carrying singletons. The magnitude of exposure was randomly varied producing peak plasma levels of delta-9-tetrahydrocannabinol (Δ-9-THC) ranging from 0 to 161 ng/ml. Δ-9-THC levels, respiratory rate and arterial blood gas tensions were monitored before and for two hours after inhalational exposure. When compared to placebo, marijuana smoke produced a dose dependent and sustained decrease in maternal respiratory rate and arterial oxygen tension without evidence of either systemic acidosis or carbon dioxide retention. A logarithmic relationship was observed between the blood level of Δ-9-THC and the change in respiratory rate. The change plateaued at 30% of control at levels above 80 ng/ml. However, the relationship between the blood level of Δ-9-THC and the change in arterial oxygen tension had a linear fit with a maximum decrease of 45% at a blood level of 160 ng/ml. No change was detected in minute ventilation. Fetal oxygen tension fell significantly and remained depressed after maternal values had returned to control levels. We conclude that, in this species, inhalational exposure to marijuana smoke induces a prolonged maternal ventilation/perfusion imbalance and limits fetal oxygen availability by one or more mechanisms.

The physiological changes which accompany marijuana smoking during pregnancy are of societal concern as little is known about the effects of repetitive exposure on fetal well-being (1, 12). The recent development of a simple system for reproducible inhalational exposure in large animals (2, 3) has allowed us to begin to assess the effects of both acute and chronic exposure on the maternal fetal unit using the chronically instrumented pregnant ewe animal model (2, 8). During our initial dose ranging studies, we monitored respiratory rate and arterial blood gas tensions in the mother and fetus, as initial studies using nonpregnant animals suggested that substantial effects on pulmonary gas exchange should be present. This communication reports our findings in nine late gestation animals randomly exposed to varying doses of marijuana smoke. The data indicate that maternal respiratory rate and arterial oxygen tension are valuable indicies of the intensity of exposure and that marijuana smoke exposure in late gestation impairs pulmonary gas exchange in this species.

Materials and Methods

Nine singleton pregnancies were surgically prepared for chronic study between the 105th and 130th day of gestation (term is 147 days). Details of the preparation appear elsewhere (2, 8). Briefly, polyvinyl sampling catheters were placed in the maternal and fetal inferior vena cava and distal aorta and a silastic T tube was implanted in the maternal trachea for smoke exposure. In addition, extradural stainless steel electrodes for monitoring electrocortical activity were placed over the fetal parietal cortex and either the umbilical or uterine circulation was instrumented to estimate flow. For this purpose a Dienco electromagnetic flow transducer was placed on the main uterine artery supplying the pregnant horn or alternately on the fetal common internal iliac artery. It is unlikely that the additional instrumentation had any systematic effect on the changes observed in either arterial blood gas tensions or maternal respiratory rate following maternal exposure to marijuana smoke.

After a 3 to 5 day recovery period, the animals were exposed every third day in random order to variable amounts of smoke from either a marijuana placebo cigarette or a marijuana cigarette containing 2.64% Δ-9-THC. The magnitude of exposure was controlled by varying the exposure time between 5 and 13 minutes. The cigarettes were prehumidified and burned in a small, hand-held cylinder which delivered fresh smoke through the tracheal T tube with each inspiration. This system produces an appearance and decay curve of Δ-9-THC in arterial plasma similar to that observed with human smoking while minimizing both irritative disturbances in respiratory pattern (coughing and/or breath holding) and the production of side stream (2, 3, 13). On each day of exposure, the animal's respiratory rate was monitored continuously with a pneumotachometer for at least 90 minutes before and 120 minutes after smoking with blood sampling at specified intervals. Samples for Δ-9-THC levels were obtained prior to, immediately after, and 2 hours post-smoke from the mother and prior to and 2 hours post-smoke from the fetus as earlier kinetic studies indicated peak and trough levels occurred in the two compartments at these times (3). Arterial samples for measurement of pH and gas tensions were obtained anaerobically from the mother 60, 30 and 2 minutes prior to smoking, immediately post-smoke, and at 15, 20, 25, 30, 40, 60 and 120 minutes after the initiation of smoking. Fetal samples were drawn 30 minutes before and 15 and 120 minutes after the initiation of smoking to assess the relative effect on fetal oxygenation of changes in maternal gas tension versus those of placental perfusion imbalance. Plasma levels of Δ-9-THC were measured by radioimmunoassay (9). Whole blood pH, pO_2, pCO_2 were measured immediately with a precalibrated Radiometer microblood gas analyzer at 38°C using Clark and Severinghaus electrodes. Regression, using the least squares method, was employed to assess dose-response relationships while the unpaired t test and repeated measures were used to detect between and within group differences over time. A significant difference was defined as a p value of < 0.01.

On six separate occasions three additional animals plus a single animal from the above experimental group were studied to assess the effects of exposure on minute ventilation which was estimated intermittently before and after smoking by measuring expiratory minute volume. This was accomplished using a low resistance, one-way valve and a 50 L Tissot spirometer which was attached to the side arm of the tracheal T tube after balloon occlusion of the proximal tracheal arm.

Results

The nine animals weighed between 50 and 61.4 kg (mean = 55.5±1.4 kg) at

the onset of study and maintained or increased their weight over time. Thirty-one studies were conducted between the 110th and 136th day of gestation (mean = 125±2 days). Based on magnitude of exposure they were divided into high (entire 2.64% cigarette), low (0.25-0.5 of a 2.64% cigarette), and placebo (0.25 to entire placebo cigarette) dose groups with 11, 11 and 9 studies in each of the three groups respectively. In the high exposure group, peak maternal blood levels of Δ-9-THC ranged between 62 and 161 ng/ml (mean = 100±11 ng/ml) while the range was 9 to 55 ng/ml (mean = 28±4 ng/ml) in the low exposure group. Values were consistently below the detection threshold after exposure to placebo smoke. There were no significant between group differences in either gestational age or maternal weight and the number of smoke exposures ranged between two and six per animal. The variability in the number of exposures was due in large part to an unanticipated high incidence of premature labor.

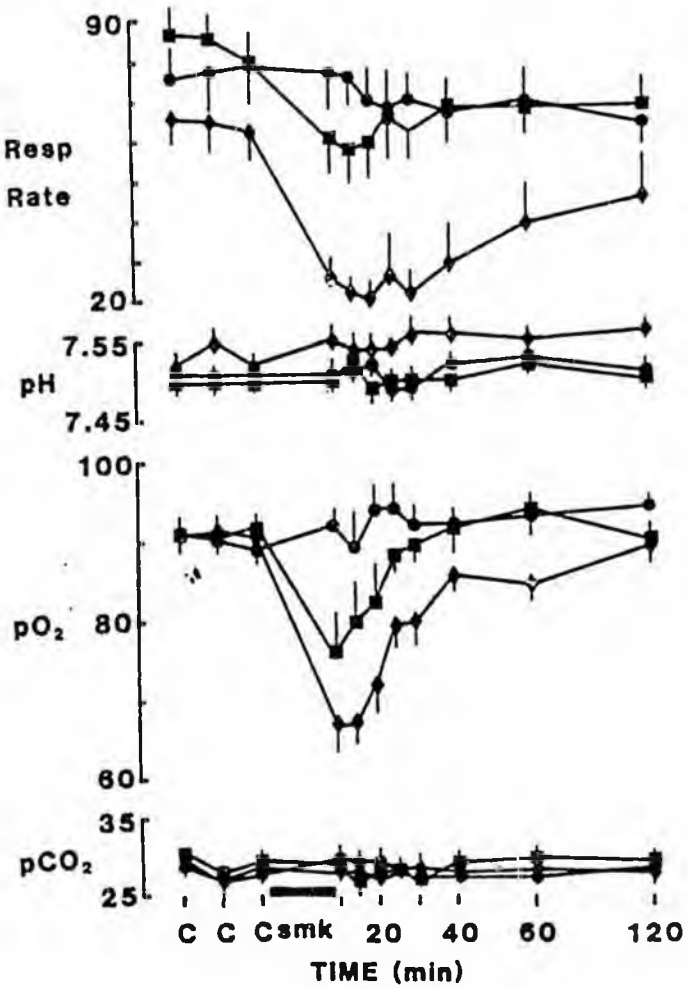

FIG. 1

The longitudinal changes observed in maternal respiratory rate, pH, pO_2 and pCO_2 with exposure to placebo (●), low dose (■), or high dose (◆) marijuana smoke. Data shown as mean ± s.e.m.

affects of cannabis extracts and constituents (bronchodilation and changes in respiratory rate) have been described in anesthetized experimental animals (6, 7, 10, 15), the specific issue of gas exchange has not been previously examined in detail and there are no data other than the preliminary report of Niederreither et al. (13) that deals with the effects of inhalational exposure on blood gases in an unanesthetized chronic model. In the human marijuana smoking has been reported to have either no effect or to increase minute ventilation without evidence of CO_2 retention and to decrease airway resistance (4, 5, 14, 16). However, its impact on ventilation/perfusion balance and oxygenation has not been assessed. Support for the possibility that marijuana smoking disrupts ventilation/perfusion balance in the human as well as the sheep is found in the pharmacokinetic studies of Perez-Reyes and associates (14). They noted that plasma levels of Δ-9-THC peaked in their volunteers before they finished smoking. While they felt that this probably was due to subtle changes in smoking technique for the latter half of a cigarette, they could not detect any differences in smoking technique. Although they did not consider the possibility, a disruption in ventilation/perfusion balance during the smoke would explain their findings as it would impair drug uptake during the remainder of the smoke. Therefore, peak levels would be reached during rather than at the end of the smoke. It is also of note that in the initial pharmacokinetic studies of Abrams et al. (3) Δ-9-THC levels peaked in at least three of their ewes before the end of smoke exposure. Thus, the ovine data coupled with evidence from human pharamacokinetic studies suggests that the issue of ventilation/perfusion imbalance following marijuana smoking deserves further evaluation in the human.

The data from the present study demonstrates a clear relationship between the magnitude of exposure, as measured by the plasma Δ-9-THC level at the end of smoking, and changes in the physiological parameters of maternal respiratory rate and arterial oxygen tension. Both relationships have high r values and appear to hold true both within and between animals. As one might anticipate, maternal weight did not affect the relationships and, with exposure every third day, there was no evidence of tolerance. Thus, if our initial experience is confirmed, the impact of intermittent inhalational exposure on one or both of these parameters can be used during experiments to assess the intensity of exposure and perhaps to standardize it both within and between animals. The same may be true for the induced inspiratory pause which has also been noted by others (11).

These dose ranging experiments also confirm that placental transfer of Δ-9-THC occurs in this species and that, despite its highly lipophilic nature, fetal levels only reached 0.3 of maternal levels at 2 hours. Despite the wide range in the magnitude of exposure in the present study, this value for the feto-maternal ratio is quite similar to the mean value of 0.298 achieved with standardized dosing in an earlier kinetic study (3).

Finally, these data indicate that, in this species, maternal inhalational exposure to marijuana smoke in late gestation limits fetal oxygen availability by at least one mechanism. Namely, by producing a significant and prolonged decrease in maternal arterial oxygen tension that is dose dependent and often lasts for more than 30 minutes. Although this decrease in maternal oxygen tension results in an average, dose dependent decrease of only 2-5 mmHg in fetal arterial oxygen tension, it is important to remember that at normal fetal oxygen tensions of 20-25 mmHg and with the high oxygen affinity of fetal hemoglobin, this decrease in fetal oxygen tension represents a decrease in oxygen contents of between 2 and 4 ml of oxygen per 100 ml of blood. Also of interest was the finding that fetal arterial oxygen tension remained depressed long after maternal arterial oxygen tensions had returned

to control levels. This cannot be explained by the data available and suggests that additional direct or indirect effects may also exist.

Acknowledgements

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EFFECT OF MARIJUANA USE IN PREGNANCY ON FETAL GROWTH

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Hatch, E. E., and M. B. Bracken (Yale U. School of Medicine, New Haven, CT 06510). Effect of marijuana use in pregnancy on fetal growth. *Am J Epidemiol* 1986;124:986–93.

In a prospective study of 3,857 pregnancies ending in singleton live births at Yale-New Haven Hospital, New Haven, Connecticut, in 1980–1982, 9.5% of mothers reported using marijuana (4.1% occasionally and 5.4% at least 2–3 times monthly). Among white women, regular use was associated with an increased risk of delivering a low birth weight (<2,500 gm) infant (odds ratio (OR) = 2.6, 95% confidence interval (CI) = 1.1–6.2) and small for gestational age infant (OR = 2.3, 95% CI = 1.3–4.1) after adjustment for other risk factors. Nonwhite marijuana users were not at further increased risk for delivering a low birth weight or small for gestational age infant beyond the elevated rates of these conditions already experienced by nonwhites in general. Marijuana use was also related to preterm delivery (gestational age <37 weeks from last menstrual period) in white women (OR = 1.9, 95% CI = 1.0–3.9) but not nonwhite women. Occasional use was unrelated to the risk of low birth weight, small for gestational age, or preterm delivery.

birth weight; delivery, preterm; infant, small for gestational age; marijuana; pregnancy

Studies of pregnant women (1–5) have found that at least 10 per cent report some marijuana use during pregnancy, however, the effects on pregnancy outcome are still uncertain. Delta-9-tetrahydro-cannabinol; a major component of marijuana, has been shown (6, 7) to cross the placenta in rats, mice, and dogs. Less of the drug is absorbed by the fetus than by the mother, but clearance is also slower. The cannabinoids from marijuana tend to be stored in fat and may be detected in body tissues for up to 30 days following administration of a single dose (8), indicating the potential for prolonged fetal exposure in regular marijuana users.

Reported developmental effects in animals include increases in fetal and embryonic mortality, fetal resorption, reduction in birth weight, growth retardation, and neurobehavioral abnormalities (6).

There have been a few case reports in humans which implicate marijuana as a teratogen (9–11), however, in each case the mothers had used multiple drugs during pregnancy. Several cases of a "fetal alcohol-like" syndrome were recently described (12, 13) in infants whose mothers used marijuana but denied alcohol use during pregnancy.

Results of epidemiologic studies are in-

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Abbreviations: CI, confidence interval; OR, odds ratio; RR, risk ratio.

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way by which it could affect fetal growth. Cannabinoids are also metabolized more slowly than components of cigarette smoke (7), which might explain why the effects on the fetus were found at lower levels of the drug than those seen for tobacco smoking.

It is of concern that nearly 10 per cent of the women in our study reported some marijuana use. Because the drug is not legal, this may be an underestimate of the true extent of marijuana use during pregnancy, although it is in close agreement with the 10–14 per cent marijuana use reported during pregnancy in similar populations (4, 5). Definitive conclusions about the effect of marijuana on pregnancy outcome cannot yet be reached. Further research should attempt to collect detailed information on marijuana use at several times during pregnancy, and, if possible, should verify self-reports with biochemical screens. The possibility that marijuana use may result in features similar to those seen in the fetal alcohol syndrome (4, 12) should also be explored.

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study (5), while another study (4) did find a reduction in mean birth weight, and yet another study (15) found an increased rate of preterm delivery but not low birth weight among marijuana users. There are several possible explanations for these inconsistent results. In the negative study by Linn et al. (5), marijuana use was treated as a dichotomous variable which may have obscured any effect in the regular users. The data from the present study were collected prospectively, shortly after the first prenatal visit, whereas the data in the study by Linn et al. (5) were collected after delivery. Animal studies have indicated that marijuana use during early pregnancy may have a greater effect on the developing fetus than later on (6). If this is true in humans, collection of data early in pregnancy may result in a more valid estimate of effect. Finally, an interaction between race and marijuana use was not considered in the study by Linn et al. (5).

Gibson et al. (15) found that heavy marijuana use increased the risk of preterm delivery but had no effect on birth weight after preterm infants were excluded from the analysis. Our analysis controlled for gestational age, instead of excluding preterm infants, which may account for the different results.

In summary, our study found an increased risk of delivering low birth weight, small for gestational age and preterm infants among white women who reported regular marijuana use during pregnancy. Certain limitations of our study should be noted in interpreting this finding. Of foremost concern is that the result may be due to unidentified confounding variables such as unreported psychoactive drug use, poor maternal health, an inadequate diet, or some other correlate of lower socioeconomic status. Other potential problems with the study include possible misclassification of both marijuana use and confounding variables such as cigarette smoking, and assessment of marijuana use at only one point in pregnancy. The overall rate of low birth weight in our sample is somewhat lower than the rates for the United States as a whole (21). This is presumably because our study is based upon women who seek prenatal care, whereas the US rates are based on all deliveries. However, this difference is unlikely to bias our assessment of the effect of marijuana use. It should also be noted that the outcomes of low birth weight, small for gestational age, and preterm births are not entirely independent. Low birth weight infants are a heterogeneous group, consisting of some who are low birth weight solely because of a premature delivery, and some who are delivered at term, but whose growth has been retarded in utero. In our study, among white infants classified as low birth weight (n = 88), 53.4 per cent were preterm, 35.2 per cent were small for gestational age, 10.2 per cent were both, and 1.1 per cent (n = 1) were neither. There were an additional 115 infants who fell above the 2,500 gm cutoff point but who were classified as small for gestational age. Among infants delivered prematurely (n = 126), 43.1 per cent fell into the low birth weight category, and 7.1 per cent were also classified as small for gestational age. Because these outcomes are not mutually exclusive, we attempted to determine if the effects that were found were due primarily to one of the outcomes. We saw no evidence for this in our data.

It is worth noting that in our study, the risk of having a small for gestational age and/or low birth weight infant was more strongly associated with regular marijuana use than with smoking 20 or more cigarettes daily, and that the marijuana effect was in addition to the effect of cigarette smoking, which is an established risk factor for those conditions. Since the effect of marijuana on fetal growth is occurring at much lower levels of use than the corresponding effects due to tobacco, it is probably not due to the carbon monoxide contained in smoke, which is often implicated as the causal agent in fetal growth retardation due to tobacco smoking (7). Marijuana use has been shown to alter hormonal levels (7), which may be an indirect path-

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TABLE 4

Odds ratios for variables significantly related to delivery of low birth weight and small for gestational age infants to white women at Yale-New Haven Hospital, 1980–1982*

Variable	Odds ratio	95% confidence interval
Low birth weight		
Frequency of marijuana use		
Occasional†	0.3	-2.8
Regular‡	2.6	1.1-6.2
20+ cigarettes/day vs. none	1.5	0.9–2.4
Nulliparity	1.8	1.1–3.1
Small for gestational age		
Frequency of marijuana use		
Occasional	1.3	0.6–2.9
Regular	2.3	1.3–4.1
20+ cigarettes/day	1.9	1.4–2.4

* Adjusted for other variables in the model.
† Occasional use = once per month or less.
‡ Regular use = 2–3 times per month or more.

ally variables which significantly predicted the occurrence of a preterm birth were race (for nonwhites vs. whites, OR = 1.8; 95 per cent CI = 1.3–2.5) and education, which was inversely related to the risk of preterm delivery (OR = 1.3 for a reduction of four years of education). The adjusted odds ratio for regular marijuana users from the final model was 1.5 (95 per cent CI = 0.9–2.5). The model was fitted separately for white women in further analyses, and the association of regular marijuana use and preterm delivery was of borderline significance (OR = 1.9, 95 per cent CI = 1.0–3.9).

Multiple linear regression was used to estimate the effect of marijuana use on mean birth weight, using all variables listed above in the full model. The interactions between marijuana use and tobacco and alcohol were not significant ($p > 0.50$) and were dropped from the model. The interaction with race was also not significant ($p = 0.10$) and was dropped. Other variables not significantly related to birthweight were history of induced abortion, alcohol consumption, education, and maternal age, whereas caffeine use was significantly related to a reduction in mean birth weight. Neither category of marijuana use was significantly related to mean birth weight in the final model (F ratio = 0.91, $p = 0.40$; for occasional users, $\beta = +1$ gm, and for regular users, $\beta = -44$ gm). However, when models were fitted separately for white women in exploratory analyses, regular marijuana use was related, although not quite significantly, to a reduction in mean birth weight (F ratio = 2.7, $p = 0.07$; for occasional users, $\beta = -24$ gm; for regular users, $\beta = -97$ gm).

DISCUSSION

The results of this study indicate that white women who reported regular marijuana use during pregnancy had a significantly higher risk of delivering a low birth weight or small for gestational age infant. The risk of delivering prematurely was also elevated in white marijuana users, although this relationship was of borderline statistical significance. Equivalent effects were not observed among nonwhite marijuana users. It is not known whether these differential effects by race could be due to innate biologic characteristics. It seems more likely that the reporting of marijuana use was less accurate in nonwhites than in whites, resulting in a greater degree of misclassification which could explain the lack of an effect in nonwhites. If underreporting in nonwhites had been associated with other risk factors for the outcomes which were analyzed, this would have led to a more dramatic reduction in the odds ratios than if the underreporting had been entirely random. Alternatively, nonwhites have a much higher risk of these adverse pregnancy outcomes, and perhaps the effect of marijuana use is difficult to detect in the presence of other strong risk factors.

These results conflict with those of one

TABLE 3

Mean birth weights and per cent of infants classified as low birth weight, small for gestational age, and preterm, by frequency of marijuana use during pregnancy and by race: infants delivered at Yale-New Haven Hospital, 1980–1982

	Frequency of marijuana use		
	None	Occasional*	Regular†
Whites	(n = 2,778)	(n = 105)	(n = 122)
Birth weight (gm)			
Mean	3,455.1	3,424.2	3,268.0
SD‡	495.9	548.6	589.2
% <2,500 gm	2.7	1.9	8.2
% Small for gestational age§	4.9 (n = 2,733)	7.1 (n = 99)	12.5 (n = 120)
% <37 weeks‖	4.0	3.8	8.2
Nonwhites	(n = 706)	(n = 53)	(n = 86)
Birth weight (gm)			
Mean	3,147.9	3,136.1	3,108.6
SD	563.9	483.4	535.4
% <2,500 gm	9.2	5.7	9.3
% Small for gestational age§	8.2 (n = 685)	7.6 (n = 53)	6.0 (n = 84)
% <37 weeks‖	8.8	11.3	10.5

* Occasional use = once per month or less.
† Regular use = 2–3 times per month or more.
‡ SD, standard deviation.
§ The number of infants considered in the analysis of small for gestational age is lower due to the exclusion of 76 infants with a recorded gestational age greater than 44 weeks.
‖ Calculated from first day of last menstrual period.

race and marijuana use was of borderline significance (p = 0.06), therefore separate logistic models were fit for whites and nonwhites, as well as for both races combined. Variables not significantly related to the risk of low birth weight in any of the models were history of induced abortion, alcohol and caffeine use, education, and maternal age. Maternal age was also entered into the model as trichotomous variable (<20, 20–34, 35+ years), and as a continuous variable with both first and second order terms but it still did not contribute significantly to the models. When whites and nonwhites were considered together, the adjusted odds ratio for low birth weight in regular marijuana users relative to nonusers was 1.5 (95 per cent confidence interval = 0.8–2.8).

The odds ratios and 95 per cent confidence intervals from the final model for whites are shown in table 4. The risk of delivering a low birth weight infant in regular marijuana users relative to nonusers was significantly elevated, an odds ratio of 2.6, after adjustment for parity, cigarette smoking, and gestational age. Occasional use was not associated with low birth weight. In nonwhites, no effect of either category of marijuana use was found (for occasional users, odds ratio (OR) = 0.4, 95 per cent CI = 0.1–1.5; for regular users, OR = 0.7, 95 per cent CI = 0.6–1.8). The final models were also run excluding eight women with a known history of drug abuse, but this did not change the results.

For analyzing the proportion of infants who were small for gestational age, the same variables listed above were included in the initial models, with the exception of parity because adjustments for parity were made in classifying an infant as small for gestational age. Again, the alcohol-marijuana and cigarette-marijuana interactions were not significant and were dropped from the model, whereas the race-marijuana interaction was significant (p = 0.01). The results of the final model for whites are shown in table 4. Regular marijuana users had a significantly increased risk (OR = 2.3) of delivering an infant who was small for gestational age. The only other variable significantly associated with this outcome was cigarette smoking. In nonwhites, regular marijuana use was not associated with adverse fetal growth, the odds ratio for regular marijuana users being 0.6 (95 per cent CI = 0.2–1.6).

Race did not appear to modify the effect of marijuana use on preterm delivery. The

TABLE 4

Odds ratios for variables significantly rel delivery of low birth weight and small for ge age infants to white women at Yale-New Hospital, 1980–1982*

Variable	Odds ratio	95 confidence
Low birth weight		
Frequency of marijuana use		
Occasional†	0.3	0.0-
Regular‡	2.6	1.1-
10+ cigarettes/day vs. none	1.5	0.9-
Nulliparity	1.8	1.1-
Small for gestational age		
Frequency of marijuana use		
Occasional	1.3	0.6-
Regular	2.3	1.3-
10+ cigarettes/day	1.9	1.4-

* Adjusted for other variables in the mod
† Occasional use = once per month or le
‡ Regular use = 2–3 times per month or

only variables which significantly p the occurrence of a preterm birth w for nonwhites vs. whites, OR = 1. first CI = 1.3–2.5) and educatio was inversely related to the risk of delivery (OR = 1.3 for a reductio years of education). The adjusted o for regular marijuana users from model was 1.5 (95 per cent CI = The model was fitted separately f women in further analyses, and th tion of regular marijuana use and delivery was of borderline significa 1.9, 95 per cent CI = 1.0–3.9).

Multiple linear regression was mate the effect of marijuana birth weight, using all variab were in the full model. The int between marijuana use and tob alcohol were not significant ($p >$ (were dropped from the model. T

marijuana and tobacco and marijuana interactions were also tested initially.

Logistic regression models were fit to the data to estimate the effect of marijuana use on the proportion of low birth weight, small for gestational age, and preterm infants, controlling for potential confounding variables. Variables included in the initial models of low birth weight were maternal age (<20 years versus 20+ years), race (white versus nonwhite), parity (0, 1+ births, completed years of education, marital status (currently married versus not), history of induced abortion, alcohol consumption (none, <0.25 oz (<7.1 ml), ≥0.25 oz (≥7.1 ml) of absolute alcohol/day), number of cigarettes smoked per day in the first month of pregnancy, caffeine intake in mg per day, gestational age of the infant, and two-way interactions between alcohol, cigarette smoking, and race and the categories of marijuana use. The interaction between

TABLE 1

Associations between frequency of marijuana use during pregnancy and other maternal characteristics: infants delivered at Yale-New Haven Hospital, 1980–1982

Maternal characteristic	Total	Frequency of marijuana use (%)*		
		None	Occasional†	Regular‡
Age (years)				
<20	380	80.5	6.8	12.6
20–34	3,273	91.1	4.0	4.9
35+	204	98.5	1.0	0.5
Parity				
Nulliparous	1,770	87.9	5.4	6.8
One or more	2,087	92.7	3.0	4.3
Race				
White	3,005	92.5	3.5	4.1
Nonwhite	845	83.6	6.3	10.2
Education				
Less than high school	523	83.4	5.2	11.5
High school graduate or more	3,334	91.6	3.9	4.5
Marital status				
Married	3,014	93.8	3.0	3.2
Not married	840	78.7	8.0	13.3
Cigarette smoking				
None	2,658	94.2	3.0	2.8
1–10/day	623	82.8	6.5	10.8
11+/day	566	81.6	6.7	11.7
Alcohol (oz/ml)/day)				
None	1,190	94.7	2.4	2.9
<0.25 (<7.1)	2,352	90.1	4.7	5.2
≥0.25 (≥7.1)	315	77.8	5.7	16.5
Caffeine (mg/day)				
None	895	90.8	3.8	5.4
1–150	1,896	91.6	3.7	4.7
151–300	737	88.6	5.8	5.6
301+	329	87.2	3.3	9.4
Previous induced abortion				
Yes	819	82.3	7.1	10.6
No	3,038	92.7	3.3	4.0

* All differences between subgroups are statistically significant, $p < 0.0001$.
† Occasional use = once per month or less.
‡ Regular use = 2–3 times per month or more.

TABLE 2

Mean birth weights, gestational ages, and the per cent of infants classified as low birth weight, small for gestational age, and preterm by frequency of marijuana use during pregnancy: infants delivered at Yale-New Haven Hospital, 1980–1982

	Frequency of marijuana use		
	None (n = 3,490)	Occasional* (n = 158)	Regular† (n = 209)
Birth weight (gm)			
Mean	3,392.8	3,327.6	3,206.4
SD‡	524.7	530.7	573.7
Gestational age (weeks)			
Mean	40.0	40.2	39.8
SD	2.3	2.6	2.5
% <2,500 gm	4.0	3.2	8.6
% Small for gestational age§	5.6 (n = 3,424)	7.2 (n = 152)	9.8 (n = 205)
% <37 weeks‖	5.0	6.3	9.4

* Occasional use = once per month or less.
† Regular use = 2–3 times per month or more.
‡ SD, standard deviation.
§ The number of infants considered in the analysis of small for gestational age is lower due to the exclusion of 76 infants with a recorded gestational age of greater than 44 weeks.
‖ Calculated from first day of last menstrual period.

occasional users (once per month or less), and 3) regular users (2–3 times per month or more). We hypothesized that occasional users would not be at greater risk for adverse outcomes than nonusers, because the majority of these had used marijuana only once since conception. The remaining women who reported regular marijuana use were considered together in order to provide adequate statistical power for the multivariable analyses.

Crude mean birth weights and gestational ages, and the per cent of infants who were low-birth weight, small for gestational age, or preterm were computed within the categories of marijuana usage. Potential confounding variables were identified by assessing their association with both outcome variables and the categories of marijuana usage by means of chi-square tests (18). Three-way stratified analyses between marijuana use, covariates, and the outcome variables were performed to identify potential interactions. Multivariable analyses were conducted using linear regression (19) and logistic regression (20). Other covariates which were assessed include maternal age, race, parity, education, marital status, history of stillbirth, spontaneous abortion, or induced abortion, cigarette smoking, and average daily alcohol and caffeine intake. Race was treated as a dichotomous variable (white vs. nonwhite), since the majority (84 per cent) of nonwhites were black, and since the numbers of Hispanics and other races were too small to allow meaningful analysis. To identify the final models in both linear and logistic regression analyses, backwards stepwise variable selection (19, 20) was used and, at each step, the parameter estimates were analyzed to ensure that deletion of the variable did not change the estimates of marijuana use.

Results

The majority of the sample (n = 3,490 or 90.5 per cent) reported no marijuana use between the estimated date of conception and the date of interview. There were 158 women (4.1 per cent) who reported occasional use of marijuana and 209 women (5.4 per cent) who reported that they used marijuana 2–3 times per month or more, of whom 43 reported daily use that ranged from 1–5 times per day.

The association of marijuana use with other maternal characteristics is shown in table 1. Women who use marijuana during pregnancy were more likely to be young, nonwhite, nulliparous, and have less than high school education. They were also significantly more likely to report cigarette smoking, alcohol, and high caffeine use. A history of induced abortion was more common in marijuana users, whereas a history of previous stillbirth or spontaneous abortion was unrelated to marijuana use.

Mean birth weights, gestational ages, and the per cent of low birth weight, small for gestational age, and preterm infants according to frequency of marijuana use are shown in table 2. Women who report occasional use of marijuana have a reduced but not statistically significant, risk of low birth weight infants relative to nonusers. Regular users have an elevated risk of delivering a low birth weight infant (risk ratio (RR) = 2.1, 95 per cent confidence interval (CI) = 1.3–3.4) and/or a small for gestational age infant (RR = 1.7, 95 per cent CI = 1.1–2.6) relative to nonusers. The risk of a preterm delivery is also elevated in regular marijuana users (RR = 1.8, 95 per cent CI = 1.2–2.9). Mean birth weights decreased across the categories of marijuana usage, whereas there are no major differences in mean gestational age.

Preliminary stratified analyses suggested a possible interaction between race and marijuana use on the outcomes of mean birth weight, low birth weight, preterm delivery, and small for gestational age. Although nonwhites were both more likely to use marijuana and to deliver an infant with these adverse outcomes, the risk was not further increased in nonwhite marijuana users (table 3). Therefore, an interaction term between race and marijuana use was included in all initial models. Alcohol and

marijuana and tobacco an
teractions were also tested
Logistic regression mode

TABLE 1

Associations between frequency during pregnancy and other mat infants delivered at Yale-New 1980–1982

Maternal characteristic	Total	Freq Non
Age (years)		
<20	380	80.5
20–34	3,273	91.1
35+	204	98.5
Parity		
Nulliparous	1,770	87.8
One or more	2,087	92.7
Race		
White	3,005	92.5
Nonwhite	845	83.1
Education		
Less than high school	523	83.4
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Marital status		
Married	3,014	93.4
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Cigarette smoking		
None	2,658	94.1
1–10/day	623	82.2
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Alcohol (oz(ml)/day)		
None	1,190	94.1
<0.25 (<7.1)	2,352	90.2
≥0.25 (≥7.1)	315	77.8
Caffeine (mg/day)		
None	895	90.4
1–150	1,896	91.1
151–300	737	88.2
301+	329	87.2
Previous induced abortion		
Yes	819	82.2
No	3,038	92.1

* All differences between sub
nificant, $p < 0.0001$.
† Occasional use = once per
‡ Regular use = 2–3 times p

conclusive. The majority have reported some adverse effects of marijuana use including precipitate labor and meconium passage (3, 14), altered visual, tremor, and startle responses in neonates (1, 2), lower birth weight (4), increased frequency of preterm delivery (15), and shorter infant length at eight months of age (16). However, other studies have found no effect on birth weight (5, 15) or preterm delivery (5).

The present study is part of a series of analyses on various exposures during pregnancy and pregnancy outcomes. The association between reported marijuana use and the outcomes of low birth weight, small for gestational age, preterm delivery, and mean birth weight and gestational age are analyzed.

Materials and Methods

The study population consisted of all women who made a first prenatal visit to a private obstetric or midwifery practice, health maintenance organization, or hospital clinic in the greater New Haven, Connecticut area between May 12, 1980 and March 12, 1982 and who intended to deliver at Yale-New Haven Hospital. A total of 4,219 women had the study introduced to them by their health care provider, and 3,331 (85.7 per cent) agreed to be contacted by a member of our research staff. Of this number, 405 women did not meet the eligibility criteria for the study because: 1) they planned to deliver somewhere other than Yale-New Haven Hospital; 2) they demonstrated poor English language comprehension; 3) they were not pregnant at the time that the study interview was to be conducted; or 4) they were familiar with the study. In all, 4,926 eligible subjects were contacted regarding the research, and valid interviews were completed on 4,186 (85 per cent) of those contacted. The majority of women (76 per cent) were interviewed before the 20th completed week of gestation. Of the original 4,186 women who were interviewed, 76 had moved or were lost to follow-up, 59 did not deliver at Yale-New Haven Hospital, 116 had spontaneous abortions or stillbirths (including three women who had an induced abortion, two with hydatidiform mole, and one who was not pregnant), 44 had multiple births, and 34 had missing information on birth weight and/or gestational age of the infant. This left a total of 3,857 singleton live births for analysis.

Women were interviewed within a few weeks of their first prenatal visit. The majority of interviews were conducted in the women's homes and consisted of questions on history of prior pregnancies, demographic characteristics, contraceptive practices, medical history, and exposure to possible risk factors, such as alcohol and tobacco. Women were asked whether they had used marijuana or hashish since they had become pregnant. If they responded positively, they were asked how frequently they had used the drug since pregnancy, and were shown a response card with answers which ranged from "less than once per month but once since pregnant" to "five or more times daily".

Information on outcome of each pregnancy was obtained from the medical records of the mother and infant. Low birth weight was defined as less than 2,500 gm. Gestational age was calculated from the first day of the last menstrual period, and preterm delivery was defined as a birth which occurred before 37 completed weeks of gestation. Birth weight standards developed by Brenner et al. (17), from a sample of 30,772 deliveries in Cleveland, Ohio, were used to define a population of infants who were small for their gestational age. Any infant whose birth weight was less than the tenth percentile for race, sex, mother's parity, and gestational age according to the standards of Brenner et al. was defined as small for gestational age. These standards were used in addition to low birth weight in order to separate out infants who were small for gestational age from those who were low birth weight because of shortened gestations.

Three categories of marijuana use during pregnancy were defined: 1) nonusers, 2)

Maternal Marijuana Use and Neonatal Outcome: Uncertainty Posed by Self-Reports

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Abstract: To assess the validity of self-reported marijuana use during pregnancy, this study randomly allocated pregnant women into a group who were told their urine would be tested for marijuana, alcohol, and other drugs and another group not so tested. Women told they would be tested reported more marijuana use during pregnancy than did untested women. Moreover, urine assays identified more women who used marijuana during pregnancy than were willing to admit it in the interview even after being told their urine would be tested. No differences in reported drinking or cigarette smoking during pregnancy were found between tested and untested women. (*Am J Public Health* 1986;76:667–669.)

Introduction

Research on maternal smoking and drinking during pregnancy has consistently revealed that women who smoke cigarettes during pregnancy on average deliver infants whose birthweight is 150–250 grams lower and experience a one to two day lower mean duration of gestation than nonsmoking women.[1] This association has held up through social classes, and over different age groups, ethnic groups, and geographic locations. In contrast, the relation of maternal drinking during pregnancy and low birthweight or pre-term delivery has been less consistently observed.[1]

Only four published studies of the effects of maternal marijuana use on fetal development have examined samples of at least 500 mother-child pairs and analytically controlled for potential confounding. Two studies in Boston interviewed mothers after delivery about their habits during pregnancy. One study of 12,718 mother-child pairs[2] found a suggestive association between maternal marijuana use during pregnancy and congenital malformations, but no association between maternal marijuana use and shorter gestation or lower infant birthweight. Another Boston study of 1,690 mother-child pairs[3] found an independent association between maternal marijuana use during pregnancy and lower infant birthweight. The mean reduction was 105 grams. Mothers who smoked marijuana during pregnancy delivered infants who were also more likely to have features compatible with the fetal alcohol syndrome. Both findings were observed after the effects of maternal cigarette smoking, drinking, weight gain, and illnesses were analytically controlled. An association with shorter duration of gestation, however, was not observed.

Prospective studies of 7,301 births[4] in Australia and 583 infants in Canada[5] both found independent associations between maternal marijuana intake during pregnancy and shorter gestation after cigarette use, alcohol use, and several other variables were controlled analytically. Only the Australian study noted an independent association with low birthweight, and neither identified an association with congenital malformation. Mothers in these two studies were interviewed prior to delivery about their habits during pregnancy.

A possible reason for the inconsistency in study results is the reliance by these studies on maternal self-report of marijuana use, smoking, and drinking with disproportionate underreporting by different study populations. Maternal marijuana use during pregnancy in particular may be underreported relative to cigarette and alcohol use because marijuana is illegal.[6]

This study explores whether self-reported maternal marijuana use is underreported relative to self-reported cigarette and alcohol use during pregnancy.

Methods

We undertook a study of pregnant women who spoke English or Spanish and who received prenatal care at Boston City Hospital between June and December 1984. Women were asked if they would be interviewed for 20 minutes about their nutrition, work, illnesses, and habits such as marijuana use, drinking, and cigarette smoking during pregnancy. The mothers were told these factors were being explored to assess what effects, if any, they might have on the development of the child they were carrying. Prior to the interview, these women were randomly divided into two groups. One group of women was told, "Urine samples are requested as part of standard prenatal care from you to examine sugar, protein, nutritional problems, and infections. As part of this study we would also like to recheck the sample for kidney function and presence of alcohol, marijuana, prescription, and non-prescription drugs." The other group of women was not told about urine testing and their urine was not tested for marijuana or other drugs. Approval to conduct this study was granted by the Boston City Hospital Human Subjects Committee in May 1984. A member of the study team other than the interviewer explained the urine testing to respondents.

Interviewers did not know which women were told their urines would be tested. In the interview women were asked if they had ever used marijuana and those responding affirmatively were asked if they had used it during the three months prior to pregnancy and if they used it since they became pregnant. The bogus pipeline paradigm[6,7] offers reason to expect higher self-reported marijuana use in the group given urine assays. Of 276 women asked to participate

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266 (96 per cent) agreed to be enrolled in the study. Of the ten refusals, four were originally assigned to the urine tested group, three to the nontested group, and three initial assignments were not recorded.

After the interview, the urine specimen provided by each subject in the first group of women was immediately labeled with subject identification number and refrigerated in the clinic. Within 24 hours, the urine samples were received in the Massachusetts State Laboratory and frozen at −20°C in plastic containers until analyses were performed. Use of cannibinoids was determined by a positive result from the EMIT d.a.u. Urine Cannabinoid Assay (EMIT) which is designed to detect 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-C●●H).[8] THC-COOH is the major urinary metabolite of delta-9-tetrahydrocannabinol (delta-9-THC). The assay also detects other delta-9-THC metabolites. When sufficient urine was available, samples that tested positive by EMIT assay were tested by High Pressure Liquid Chromatography (HPLC) to confirm the presence of THC-COOH.[9]

Levels of urinary metabolites are detectable within a few hours after exposure of marijuana[10] and can remain detectable seven to ten days after smoking.[11] Frequent users often have continually detectable baseline levels. Only as much as 50 per cent of an initial dose may be excreted within 72 hours.

One hundred twenty-nine samples were tested for cannabinoid use by EMIT. Eight women were unable to provide samples because of an inability to urinate during their clinic visit. Nineteen samples yielded a positive result. Sixteen of those samples were confirmed by HPLC. The remaining three samples were not tested because there was an insufficient amount of urine.

Results

Forty-five per cent of women in the urine assay group reported ever smoking marijuana, compared to 51 per cent in the non-assayed group (Table 1). There were no important differences between groups in race, religion, marital status, and trimester of pregnancy at the time of interview. No differences were observed in the proportions of respondents who had ever drank or smoked cigarettes, who drank or smoked cigarettes during pregnancy, or during the three months prior to pregnancy.

Subjects within the group that had ever smoked marijuana did not differ appreciably in age, race, marital status, education, religion, or trimester of pregnancy, nor did they differ in their reported use of cigarettes prior to pregnancy or during pregnancy, drinking either during the three months prior to pregnancy or the first three months during pregnancy. As shown in Table 2, women in the group that knew their urine would be assayed were more likely to report using marijuana during the three months prior to pregnancy (63 per cent vs 41 per cent) and more likely to report marijuana use during pregnancy (37 per cent vs 24 per cent). During pregnancy, women in the group told their urine would be assayed reported greater frequency (Table 3) and greater amounts of marijuana use during pregnancy (Table 4) than women in the non-assayed group. No differences in reported frequency or amount of either cigarette smoking or drinking were observed between the groups. This was also true when the two total groups (137 and 129) were compared.

In the urine assay group, 23 women acknowledged smoking marijuana during pregnancy. The urine test further identified five subjects whose urine was positive for marijuana but who did not report such use in the interview. By combining urine and self-report results, overall use during pregnancy was identified among 20 per cent in the assay group, compared to a reported level of 12 per cent in the group that were not told about urine testing (95 per cent confidence interval of difference: 1, 15).

TABLE 1—Characteristics of Pregnant Mothers in Urine Assay and No Urine Assay Groups

	Urine Assay	No Urine Assay
Ever Smoked Marijuana	45% (62/137)	51% (66/129)
	Of Respondents Who Ever Smoked Marijuana	
Characteristics	Assay (N = 62) %	No Assay (N = 66) %
Race		
White	18	20
Black	71	61
Other	11	20
Religion		
No Religion	13	8
Catholic	32	44
Protestant	34	36
Other	21	12
Education		
Elementary	8	6
Some High School	39	33
High School	37	42
College	16	18
Marital Status		
Single	60	57
Single, Living w/Father of child	23	12
Married	11	19
Separated, Divorced, Widowed	7	12
Mean Age	22.2	22.8
Trimester of Pregnancy at time of Interview		
1st	16	20
2nd	39	33
3rd	45	47

TABLE 2—Self-Reported Marijuana Use, Cigarette Smoking, and Drinking Prior to and during Pregnancy of Respondents in the Two Groups Who Ever Smoked Marijuana

Self-reported Use	Urine Assay (N = 62) %	No Urine Assay (N = 66) %	Difference (95% C.I.; one-tailed)
Smoked Cigarettes			
Prior to Pregnancy	65	59	6 (−9, 21)
During Pregnancy	50	53	−3 (−18, 12)
Drank			
Prior to Pregnancy	66	68	−2 (−16, 12)
During Pregnancy	55	49	6 (−8, 20)
Smoked Marijuana			
Prior to Pregnancy	63	41	22 (7, 37)
During Pregnancy	37	24	13 (0, 27)

Discussion

All of the epidemiologic studies of maternal marijuana use during pregnancy and fetal development have recognized that marijuana users also tend to smoke cigarettes, drink, and take more illicit psychoactive drugs. When the independent variables are so highly interrelated, measurement becomes a major concern. None of the published studies with large samples have attempted to verify maternal self-report with urine or blood testing. This comparison of interviews with

TABLE 3—Reported Frequency of Marijuana Use (%) in the Two Groups Prior to and during Pregnancy

Reported Frequency of Marijuana Use	Urine Assay (N = 62) %	No Urine Assay (N = 68) %
Prior to Pregnancy		
None	37	59
Monthly	21	20
Weekly	31	11
Daily	11	11
During Pregnancy		
None	63	76
Monthly	23	11
Weekly	10	14
Daily	5	0

TABLE 4—Usual Number of Marijuana Joints Reported Consumed on Days Respondents in the Two Groups Smoked Marijuana

Reported Joints Smoked	Urine Assay (N = 62) %	No Urine Assay (N = 68) %
Prior to Pregnancy		
None	37	59
1	21	19
2	19	6
3+	23	15
During Pregnancy		
None	63	76
1	24	11
2+	13	14

pregnant women told and not told that their urine would be tested for marijuana, alcohol, and other drugs indicates that women told their urine would be tested report more marijuana use during pregnancy than untested women. (We obtained similar results in our pilot study [12] conducted in our own clinic.) Little difference between groups in reported cigarette smoking or alcohol use during pregnancy was observed. Further, the urine test results revealed even more women who smoked marijuana during pregnancy than those willing to admit to it in an interview. Because this study was conducted at an inner-city hospital with a high proportion of unmarried subjects and of ethnic and racial minority groups, the study will need to be replicated with a sample more representative of the US population.

Nevertheless, these findings raise concern about conclusions that have been reached in studies on fetal outcome that rely entirely on maternal self-report of marijuana, alcohol, and cigarette use during pregnancy. If marijuana use is underreported relative to alcohol and cigarettes as this study suggests, it is possible the potentially adverse effects of marijuana may be inadvertently misattributed to alcohol or nicotine. It is also possible that potentially interactive effects of marijuana with alcohol, tobacco, or other drugs have not been adequately examined.

ACKNOWLEDGMENT

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Perinatal Cannabinoid Exposure: Effects on Hepatic Cytochrome P-450 and Plasma Protein Levels in Male Mice

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ABSTRACT Maternal exposure to the major psychoactive Δ^9-tetrahydrocannabinol (THC), or to the nonpsychoactive cannabinol (CBN) or cannabidiol (CBD) on day 12 of gestation, or on day 1 postpartum, affected the concentrations of hepatic cytochromes P-450 in adult male offspring. Levels of P-450 were significantly increased in adult males prenatally exposed to cannabinoids, but were reduced after postnatal exposure. The response to exogenous testosterone was also differentially affected by perinatal cannabinoid exposure, with reduced plasma androgen in males prenatally exposed to THC, but increased levels of hormone in mice exposed postnatally to THC or CBN. There was a concomitant decrease in plasma albumin and increased γ-globulin in adult males postnatally exposed to CBN. Beta-globulin levels were also significantly increased in adult males exposed to cannabichromine (CBC) on day 1 postpartum. Cannabinoid exposure during perinatal periods of development exert effects on hepatic function, plasma androgen levels, and on the immune system. These effects may reflect the ability of perinatal cannabinoid exposure to interfere with androgen-mediated processes of differentiation.

Perinatal cannabinoid exposure influences androgen-dependent sexual differentiation in male mice (Dalterio and Bartke, '79; Dalterio et al., '80; Dalterio et al., '84a,b). It is well documented that the early hormonal environment affects the subsequent development of nonreproductive functions, such as hepatic enzyme activity (Einarrsson et al., '73; Chung et al., '75) and immune responsiveness (Kenny and Gray, '71; Kalland, '80). Sex differences in hepatic enzyme activity have been demonstrated in laboratory rodents and in man (Vessel, '68; El Defrawy and Mannering, '74; Gustafsson and Stenberg, '76), and the mammalian liver has receptors for the gonadal steroids (Eisenfeld et al., '75). While hepatic enzymes appear to be androgen-regulated to maintain the male metabolic pattern, another group of enzymes is partially dependent on androgen, but castration does not induce a female pattern (Quinn et al., '58; Brown et al., '76; Al-Turk et al., '80). Androgens induce liver production of secretory proteins and are known to affect the rates of hepatic metabolism of certain drugs and steroids through effects on cytochrome-P-450-dependent monooxygenases (Rumbaugh et al., '84). It is also known that these sex differences in hepatic enzyme activity are a function of the neonatal and/or adult gonadal-steroid environment and are also influenced by factors of hypothalamic and pituitary origin (Denef '74; Gustafson et al., '76). Administration of cannabinoids has been reported to exert immunosuppressive effects in adult animals (Cushman et al., '76; Munson et al., '76; Zimmerman et al., '77). In mice, Δ^9-tetrahydrocannabinol (THC), the

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TABLE 2. Effect of postnatal cannabinoid exposure on plasma protein levels in male mice (values expressed as % for albumin and globulins; means ± SE)

	Sesame oil	CBD	THC	CBC
n	10	19	11	19
Albumin	31.50 ± 1.20	27.70 ± 0.80*	30.70 ± 1.00	27.30 ± 1.10
Globulins				
α-1	18.70 ± 1.20	17.20 ± 1.10	20.60 ± 1.00	18.10 ± 1.00
α-2	21.00 ± 1.20	21.60 ± 0.30	21.40 ± 1.60	20.80 ± 1.80
β	11.60 ± 0.60	12.80 ± 1.00	10.30 ± 0.40	19.00 ± 1.90
γ	7.50 ± 1.30	9.10 ± 0.90*	7.50 ± 1.30	8.60 ± 0.50
A/G ratio	0.46 ± 0.03	0.40 ± 0.02*	0.45 ± 0.02	0.38 ± 0.02*

*Significantly different from controls, ($P < .05$).

to CBD also exhibited polyclonal gammapathy.

Beta-globulin or heme-binding globulin was also significantly elevated in animals exposed to CBC during early postnatal life (Table 2).

DISCUSSION

Prenatal exposure to cannabinoids increased hepatic cytochrome P-450 levels and liver weights. In contrast, postnatal exposure decreased the concentrations of this enzyme in liver, but did not affect liver weights. Body weights were also increased in adult males exposed prenatally to CBN, or postnatally to THC. A concomitant decrease in plasma albumin and increased γ-globulin levels were also observed in adult males postnatally exposed to CBD. Exposure on day 1 postpartum to the nonpsychoactive CBC also increased the levels of β- or heme-binding globulin. Plasma testosterone concentrations after a measured dose of exogenous androgen were lower in adult males prenatally exposed to THC, but were increased in animals exposed on day 1 postpartum to THC or CBN.

The increased body weights observed in males postnatally exposed to THC was consistent with, but not as marked, as the increases observed with combined pre- and postnatal exposure (Dalterio and Bartke, '79). Certainly the fact that the liver weights were quite similar in control and postnatally exposed animals, together with the findings that body weights were either not affected, or were increased, would suggest that perinatal cannabinoid exposure was not producing general toxicity.

It has been shown that THC accumulates in the liver (Bloch et al., '78) and alters hepatic enzyme activity after administration in adult animals (Benowitz and Jones, '77). It has also been shown that THC competitively inhibits the 5-α reduction, as well as the hydroxylation of testosterone (Chan '78). In addition, THC and CBN I spectral changes, indicating the of an enzyme-substrate complex chrome P-450 (Kupfer et al., '72; '79).

In the present study the plasma one concentrations after exogenous administration were differentially prenatal and postnatal cannabi sure. In fact, the reduced levels of one in peripheral plasma in males THC on day 12 of gestation were with the increased levels of hepa chrome P-450s. Indeed, the increas androgen in animals exposed to THC postnatally also correlated with the hepatic cytochrome P-450 levels obs this group. Although the effects CBN, or CBD on hepatic cytochrom levels were more consistent than plasma androgen concentrations, factors may have influenced the pla netics of the injected testosterone. The natal CBD exposure also reduced albumin, which may have affected ity of these animals to transport low lar weight substances, including the steroids. It is also possible that the albumin levels may reflect the ac early cannabinoid exposure of the site of albumin production.

It is interesting to note that the cytochrome P-450 levels in the pren trol animals whose mothers received oil on day 12 of gestation were consi different that those whose mothers oil on day 1 postpartum. It is possi the difference between exposure thro centae or milk, even to small amo sesame oil, could have altered fetal natal hepatic functions, either dur possibly via changes in the endocrin ronment. Hepatic cytochrome P-450 le

trols were inversely correlated with sma androgen levels after exogenous T inistration, as was observed for canna-oid-exposed offspring. Thus, it appears t hepatic cytochrome P-450s are vulnera- to manipulations of the perinatal envi- ment; that such effects persist into ulthood; and t .at they are correlated with e fu.ctional ability of the liver to metabo- gonadol steroids.

It is possible that perinatal cannabinoid posure affects androgen metabolism. In a vious study, we reported that, in intact strous females injected with testosterone opionate (TP), concomitant exposure to C did not affect plasma testosterone, but ncentrations of the 5-α-reduced metabolite, hydrotestosterone, were markedly higher animals receiving TP and THC (Dalterio al., '83b). Although the metabolic clear- ce rate was not actually measured, these sults are compatible with the hypothesis t cannabinoids induce changes in adult patic function, with resultant effects on drogen metabolism or distribution (Con- et al., '65; MasKarinec, '78).

In adult rats, chronic administration of HC or CBD decreased levels of cytochrome 450s, and selectively stimulated the con- sion of gonadal steroids in hepatic micro- omes (List et al., '77). We have previously monstrated that, in adult, TP-treated cas- ated male mice, concomitant administra- n of THC increased plasma testosterone, while in intact TP-treated males, THC re- uced plasma testosterone levels (Dalterio et al., '81a). In fact, in this study, we also noted t THC modified the response of the pitui- ary to negative feedback inhibition, possibly ggesting THC-induced alterations in the tabolism of the exogenous androgen. Ef- cts of cannabinoids on hepatocytes could o be responsible for the increased produc- n of β-globulin. Indeed, certain drugs, in- ding some carcinogens, have been shown increase levels of this plasma protein ith et al., '84).

It is interesting that in the present studies male mice exposed perinatally to cannabi- oids appear to have hyperactive immune stems, at least as indicated by increased munoglobulin levels. We have previously monstrated that these male mice present ficiencies in androgen production or ac- n (Dalterio et al., '84a,b). Since it has n demonstrated that androgens suppress mune function (Sitteri et al., '80), it is pos- ible that the effects of perinatal cannabinoid exposure on the immune system are a result of decreased fetal and/or neonatal androgen production. Females, in general, have higher immune responses, but are more prone to autoimmune diseases (Siterii et al., '80). Therefore, the immune system, which is still developing during the perinatal period (Owen, '72), may be influenced by cannabinoid effects on the fetal and/or neonatal hormonal milieu. Thus, it is possible that cannabinoid exposure may have "feminized" the immune system in the male mice in the present study.

Maternal exposure to synthetic estrogen alters cell-mediated and humoral immune function (Luster et al., '78, '79; Steven and Snook, '75). Neonatal exposure to estradiol, progesterone, testosterone, cortisol, or to diethylstilbestrol (DES) produces an initial hyperstimulation in spleen cell response, followed by a decline in immune responsiveness as animals age (Ways et al., '80). It has also been suggested that the diminished antibody response induced by neonatal DES is due to a defect in the T lymphocyte populations (Kalland, '80). It has been shown that there is increased antibody responses in estrogen-treated male mice immunized with testosterone-independent antigens (Luster et al., '78), and administration of estrogens decreases thymic weights in mice (Greenman et al., '77).

Although the proposal that THC is estrogenic is highly controversial (Solomon et al., '77; Virgo, '79), certain similarities between the effects of estrogens and those of cannabinoids do exist. Cannabinoid exposure has also been reported to affect T lymphocytes and immune responses in humans and in laboratory animals (Nahas et al., '74; Luthra et al., '80; Peterson et al., '76; Baczynsky and Zimmerman, '83). Early cannabinoid exposure may represent a situation, like that with DES, in which exposed fetuses and newborns exhibit no apparent immediate effects. Indeed, early exposure to methyl-mercury has been demonstrated to have delayed teratogenic effects on hepatic cytochrome P-450s (Robbins et al., '78). Certainly, cannabinoid-induced alterations in the subsequent function of hepatic microsomal enzymes and immunoglobulins may affect susceptibility to environmental toxins, including carcinogens, and may therefore, represent a serious potential risk to the exposed individual.

It is clear from the present studies, as well as from previous reports from this laboratory, that a single maternal exposure to can-

nabinoids has long-term consequences for subsequent development of neuroendocrine and reproductive as well as hepatic and immune functions. It is evident from these studies that differences exist in the effects of cannabinoids, depending upon the time during development in which the animal is exposed. However, the effects of either psychoactive or nonpsychoactive cannabinoids appear to be long-lasting, with effects on reproductive and nonreproductive systems. While the mechanism(s) of action of perinatal cannabinoid exposure remains to be determined, there is mounting evidence that cannabinoid exposure is capable of affecting those processes of differentiation which are dependent on the fetal hormonal milieu, particularly those of the gonadal steroids. Certainly it is clear that the consequences of perinatal cannabinoid exposure are complex, involve several complementary processes, and may also compromise the ability of the exposed animal to develop normal physiological response mechanisms.

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Journal of Studies on Alcohol, Vol. 44, No. 3, [illegible]

The Effects of Alcohol, Marihuana and Their Combination on Driving Ability[1]

Lawrence R. Sutton, Ph.D.

SUMMARY. *The combination of marihuana and alcohol yielded significant impairment during a driving test but neither drug alone did.*

DESPITE data (2) which indicate that many teenagers of driving age report use of marihuana and laboratory studies using driving simulators (3–7) which show significant impairment of skills essential for driving under the influence of marihuana, law-enforcement officials acknowledge the lack of attention to problems of youth who combine drinking, drugs and driving. The Director of the Allegheny County Bureau of Public Protection wrote: "Somehow, I think it was believed that if the problem were ignored, it would go away."[2] A possible reason for the lack of attention to this problem is the absence of definitive guidelines regarding the effects of different levels of marihuana and of alcohol–marihuana combinations on driving ability.

[1] From the Institute for Driver Research and Substance Abuse, Inc., 237 Magnolia Place, Pittsburgh, Pennsylvania 15228. This article is based on a dissertation [illegible] in partial fulfillment of the requirements of the doctoral degree from the University of Pittsburgh. The Human Use Committee of the School of Medicine and the School of Education of the University of Pittsburgh gave approval for human subjects to participate in this study. Positive review and permission to conduct this study were granted by the following agencies: the National Institute on Drug Abuse, the Drug Enforcement Administration, the Food and Drug Administration, the Allegheny District Attorney's Office, and the Pennsylvania Department of Justice.

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...Williams, Dr. Cindy
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...nty Coroner's Office,
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Prior to this study, there have been only a few on-road studies which examined the effect of marihuana on driving. One of those driving studies (8) compared marihuana intoxication with alcohol intoxication, but none examined the joint consumption of marihuana and alcohol.

This study was undertaken to examine the effects of varying levels of alcohol and marihuana consumption and their combined effect on driving performance. Driving performance was measured in a controlled obstacle course which closely paralleled actual driving situations.

Method

Subjects

Nine male volunteer subjects, all graduate students at the University of Pittsburgh, were selected on the basis of self-reports of at least weekly use of alcohol and marihuana, and of having driven under the influence of both drugs. Subjects were matched in terms of driving ability (mean, seven years' experience), age (mean, 25.1), weight (mean, 164.7 lb) and health (blood pressure and pulse within normal range, absence of allergic reaction to medication and normal electrocardiogram).

Measures

Drug Levels. Blood alcohol concentration (BAC) and serum tetrahydrocannabinol (THC) level were drawn to verify levels of the drugs. Serum samples were drawn approximately 45 min after alcohol consumption and 15 min after marihuana consumption based on prior research experience showing that these time periods coincide with peak blood concentration of the two drugs.

Driving Performance. Driving performance was measured in two ways. The first was an evaluation of driving performance using Pennsylvania motor vehicle code Title 67, Chapter 153—Driver Examination Statutes. This evaluation was made independently by a safety manager from the American Automobile Association and by a high-school driver-education instructor. The second performance measure was an evaluation made by an off-duty patrol officer who followed each driver on the obstacle course in an unmarked automobile. The officer attempted to determine whether the driver was impaired enough to warrant his being stopped for further investigation. His evaluation criteria included: traffic violations, speed (used to show cautiousness or aggressiveness), slow or quick starting or stopping, weaving over the yellow center line, hugging the yellow center line, and leaving the driving course (Figure 1).

Self-Reports of Feeling "High." Self-reports of feeling "high," using a scale from 1 (not being high,) to 10 (being the highest they had ever been), were collected from the subjects prior to their driving under the influence of the drugs.

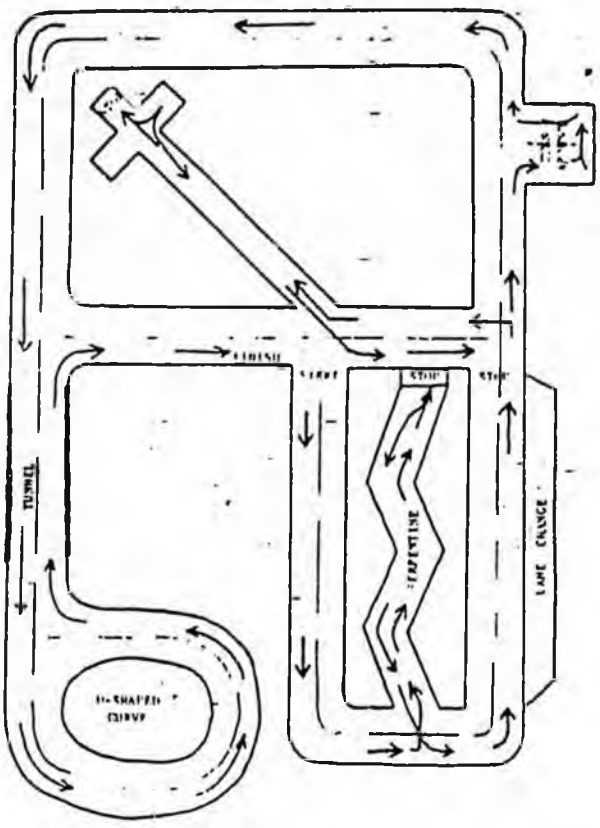


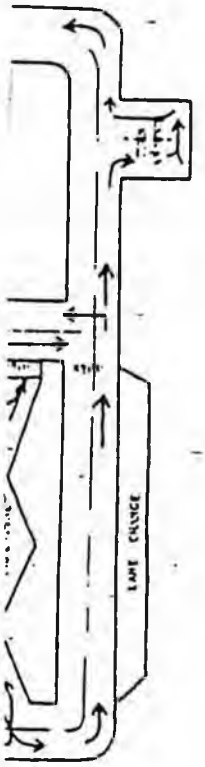
FIGURE 1.—*Experimental Driving Course Used by Subjects*

Procedure

Subjects were randomly assigned to one of four experimental groups. A repeated-measures design was used so that all subjects participated in each experimental condition.

Urine samples were taken from each subject at the beginning of each session to rule out the possibility that a drug other than those introduced during the study was responsible for driving impairment. Pulse rates were monitored before drugs were given and again after each experimental condition was completed.

Driving trials were conducted over a four-day period. During the first day, subjects were trained on the obstacle course through the use of a dual-controlled automobile. Subjects practiced until they were able to complete each maneuver in the course without error (mean, three trials). On each of the three following days, subjects completed the course one time as a reorientation measure prior to receiving any drug. Following practice trials each day, pulse rates were taken and subjects were then



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given alcohol (either a placebo or enough vodka to approximate a .06% BAC) and marihuana (either a placebo or 2% D-9-THC). To ensure that they were not aware of their conditions, all subjects received an equal amount of beverage (three glasses), and the placebo drinks were "misted" with a small quantity of vodka to create an odor of alcohol. The marihuana placebo consisted of a marihuana cigarette detoxified of all THC.[3] To achieve peak intoxication for both drugs simultaneously, subjects were given the marihuana-like cigarette 25 min after ingesting the desired alcohol dosage. The subjects were required to smoke the entire cigarette with cycles of inhaling, holding the smoke in the lungs for 15 sec and then exhaling (9). Two blood samples were drawn approximately 45 min after the subjects stopped drinking. It was at this time that the subjects were asked to rate how high they thought they were. Subjects then entered the dual-controlled automobiles with a driving instructor. The driving instructor answered any questions posed by the subject and then instructed the subject to drive through the obstacle course.

RESULTS

A one-way analysis of variance (ANOVA) to evaluate the effects of alcohol and marihuana on driving performance, as rated by the driving instructors, yielded a significant effect under the combination condition ($F = 4.00$, 3 df, $p < .05$). Neither alcohol alone nor marihuana alone resulted in significantly poorer driving performance when compared with the same subjects' performance under the placebo state.

A one-way ANOVA to compare the patrol officers' evaluation of driving impairment across the four conditions yielded a significant effect for the combination condition ($F = 11.70$, 3 df, $p < .01$). Using Scheffé post-hoc comparison, significant impairment was noted for the combination condition but not for the alcohol or marihuana conditions. The patrol officer indicated that he would have stopped drivers in a total of 15 trials, including all those in the combination condition. According to this measure, therefore, neither marihuana alone nor alcohol alone at the levels used in this study impaired driving performance to a significant degree, but use of both drugs simultaneously resulted in significant driving impairment.

Pulse rates taken before drug use and at the conclusion of driving were compared with a one-way ANOVA; significant differences were noted ($F = 34.62$, $p < .01$). A Scheffé post-hoc comparison showed the marihuana and combination conditions to be associated with

[3] Supplied by the National Institute on Drug Abuse.

significant increases in pulse rates ($p < .01$). The alcohol and placebo conditions were not significantly different from each other, nor were the combination and marihuana conditions. Mean increases in beats per minute were as follows: placebo, 6.89; alcohol, 9.22; marihuana, 35.67; combination, 38.78.

Subjects' ratings of feeling "high" were compared by a one-way ANOVA, yielding a significant overall effect ($F = 59.61$, $p < .01$). A post-hoc Scheffé comparison showed that subjects rated themselves as significantly more "high" in the combination and marihuana conditions than when under the placebo or alcohol conditions ($p < .01$). The alcohol condition resulted in a significantly greater "high" feeling than the placebo condition ($p < .05$). Mean ratings for each condition were as follows: placebo, 1.44; alcohol, 3.78; marihuana, 7.56; combination, 8.89.

Discussion

The combination of marihuana and alcohol, even at low levels of the drugs, proved to have a potentially dangerous effect on the driving task. The impairment created by the combination of the two drugs was much greater than that created by either drug separately.

The most practical dependent variable was the blinded evaluation of the patrol officer. It was most practical because this type of evaluation is used every day in the apprehension of alcohol-intoxicated drivers by patrol officers. The patrol officer stopped every driver under the combination condition. This is an important result with rather serious implications. The most serious implication is that, at the present time, Pennsylvania and almost every other state have no way of detecting or prosecuting drivers under this condition, because there is no simple or practical way to detect or measure marihuana intoxication. Under the conditions in this study, all drivers in the state of Pennsylvania, barring a traffic accident or fatality, would be cited with only a minor charge because their BACs would be significantly lower than the legal criterion for intoxication (.10%).

Marihuana alone did not significantly impair driving performance as measured in this study. This result is puzzling because of the elaborate efforts made in this study to maximize marihuana intoxication (9). Klonoff (10) and Le Dain (8) found serious impairment when marihuana was given at a dosage similar to that used in this study. Driving-simulator studies (3–7) found impair-

ment on numerous skills essential for driving at this level of intoxication. It is imperative to include maneuvers testing perception and attention in any study examining the effects of marihuana intoxication on driving performance. Unfortunately, the course used in the current study had very few such maneuvers and subjects consequently showed very little driving impairment under the influence of marihuana. Another reason that so little impairment was visible on the course may have been the experience of the subjects in the use of marihuana. Each subject smoked marihuana at least once a week and had driven an automobile on at least one occasion under the influence of marihuana. The results of the study would most likely have been different if subjects naive to marihuana use had been used.

The subjects used in this study were good representatives of the population that consumes marihuana and alcohol socially—they were relatively young and were often in situations where smoking marihuana and consuming alcohol are socially acceptable, e.g., at parties. As reported by Small and Rush (2), the age range of 20–34 reports the highest use of both marihuana and alcohol.

Because of the high potency of the drugs used, most subjects indicated that they could tell when they were smoking marihuana after only a few "hits" from the cigarettes. In other words, the usefulness of the placebo cigarettes was greatly limited and all future experiments must consider this. Effective ways of eliminating this problem in the future would be to use different subjects in each condition rather than repeating the same subjects through all conditions, or to have two marihuana conditions in addition to the placebo condition. For the most part, subjects indicated that the alcohol placebo was an adequate disguise.

The subjects also made several useful comments about the off-road course. Many of the subjects stated that they were too intoxicated to drive (in fact, some had difficulty walking to the automobiles), but once in the automobiles they stated that they "crawled" through the course at a much slower speed than in the training exercises in order to compensate for their intoxication. The subjects indicated that the most difficult parts of the course were the U-shaped curve, the tunnels and the "T" exercise. A few stated that they had to force themselves to keep their attention on the course. Many of the subjects stated that they had made a great effort to drive the best they could, apparently in an effort to show that the drug had no effect on their driving.

Of particular interest was the impairment demonstrated under the combination condition, which suggested a synergistic reaction between the two drugs. This would make the task of operating a motor vehicle much more difficult and dangerous, particularly for youth. In a recent survey[4] which examined marihuana and alcohol use and attitudes toward driving, high-school-aged students showed a high use of both drugs combined. Some even stated that, contrary to existing literature, the drugs acted in an antagonistic manner, thereby making the driving task easier. It is imperative that educators and psychologists properly educate this more vulnerable segment of our society.

The current research demonstrated a serious interaction effect between alcohol and marihuana and driving performance. With the growing combined use of alcohol and marihuana,[2,4] future research must be designed to examine the role of this combination on the operation of motor vehicles. Future research must (*1*) investigate further the effects of marihuana intoxication on driving performance using actual road studies, (*2*) investigate the combined effect of marihuana and alcohol on driving performance using actual road studies and driving simulators, and (*3*) develop legislation concerning marihuana intoxication while driving.

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The Effects of Marijuana and Alcohol on Actual Driving Performance

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OVERVIEW

Approximately 80 volunteer male marijuana and alcohol users received one of four experimental treatments: (1) marijuana, (2) alcohol, (3) marijuana and alcohol, or (4) double placebo. After consumption, each subject drove a vehicle over a test course which simulated a number of real-world driving conditions. Four post-drug runs were involved, separated by one-hour intervals. The subject's performance was rated by an in-car examiner, outside observers, and computerized vehicle measurements. Blood and urine specimens were extracted after each run to establish levels of tetrahydrocannabinol (THC), serum carboxy, and alcohol. A variety of multivariate statistical techniques were applied in evaluating treatment effects. Both marijuana and alcohol had significant effects on driving performance, and the effects were particularly detrimental under the both-drugs treatment. The effects of marijuana were more rapid than those of alcohol and somewhat less severe for most tasks.

INTRODUCTION

This paper summarizes Phase II of an effort to characterize and quantify the effects of marijuana use, alone and in combination with alcohol, on driving performance. An earlier study (Department of Justice [DOJ] Incidence Study) funded by the Office of Traffic Safety indicated that Δ^9-THC was present in a significant proportion of the submitted blood samples drawn from California drivers detained by Highway Patrol officers because of ostensibly impaired driving performance (Zimmerman et al., 1983). Phase I of this grant suggested that volunteers given ad lib doses of marijuana by inhalation were subsequently considered impaired when required to perform the standard field sobriety tests (Reeve et al., 1983). These impairment ratings persisted for up to three hours after smoking and were

Acknowledgement. This paper is a condensation of a technical monograph titled *Marijuana and Alcohol Performance Study* (Biasotti, Boland, Mallory, Peck and Reeve, California Department of Justice and California Department of Motor Vehicles, 1986). The research was supported by funding from the National Highway Traffic Safety Administration through a grant administered by the Office of Traffic Safety (#087902). The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of the State of California or the National Highway Traffic Safety Administration. The authors wish to acknowledge the contribution of Fe Arconado-Hignight, Seresa Hartwell, Debbie Difuntorum and Karri Yee in typing this manuscript under the pressures of a very tight time deadline.

associated with mean hemolyzed blood concentrations of Δ^9-THC measured from the subjects. One limitation of the Phase I study was the absence of experimental controls for placebo bias. Phase II is designed to extend this research to include actual driving performance within the confines of a rigorously controlled experimental design. Subjects received a standard dose of marijuana by inhalation, and a double blind control condition was included to minimize experimenter and subject bias. In addition, since alcohol was observed in a large number of cases in association with Δ^9-THC during the DOJ Incidence Study, the present study included alcohol and marijuana plus alcohol as additional experimental conditions.

The specific objectives of the study are listed below:

1. To determine the singular and combined effects of marijuana and alcohol on driving performance on a closed-course driving range.

2. To determine if there is a relationship between the ranges of Δ^9-THC in blood and/or alcohol in breath and measures of driving performance.

3. To determine if the various driving performance measures are differently affected by marijuana and alcohol ingestion.

4. To determine the relationship between the time following marijuana and/or alcohol ingestion and driving performance.

5. To determine the interrelationship among the performance factors affected by the marijuana and alcohol ingestion.

6. To determine whether marijuana, alone or in combination with alcohol, results in impairment that can be reliably detected through external observation of the driving and standard field sobriety tests.

It was beyond the scope of this study to establish a definitive relationship between performance decrements on the various driving range maneuvers and impaired driving ability on public streets. Instead, the study measured performance of various driving range maneuvers related to "real world" driving. One limitation of using a closed-course driving range is that some behavioral domains that are known to be critical to accident avoidance, such as risk taking and response to other vehicles, are not tapped. In spite of these limitations, the impairment of any skill component of a driving task has potential safety implications and is therefore deserving of serious scrutiny. In addition, some driver-behavior investigators, such as McPherson and McKnight (1981), suggest that deficiencies on the skill and motor components of the driving task may indirectly degrade accident avoidance components. Such an effect would be mediated by a reduction in the "spare capacity" for handling emergency situations that could occur in drivers whose low skill level requires use of large portions of their perceptual and attentional capacity to maneuver a vehicle through traffic.

The following results and methods sections present only a brief overview of the major findings and methodology, followed by a detailed discussion of the complete findings contained in the technical monograph (Biasotti et al., 1986). Readers interested in the complete results should refer to the latter report.

METHODS

Research Design

Subjects were randomly assigned to the four treatment combinations created by the following 2 x 2 factorial design:

(1) alcohol plus marijuana placebo;
(2) marijuana plus alcohol placebo;
(3) marijuana and alcohol; and
(4) double placebo.

BITE and CTT. The mean BITE and CTT scores by treatment groups and run are presented in Table 3. On each measure, higher scores indicate better performance.

TABLE 3

Treatment Means for BITE and CTT Measures

BITE

Run Number	Placebo	Marijuana	Alcohol	Both
Run 3	60.63	53.82	56.16	52.55
Run 4	62.52	56.47	58.95	53.43
Run 5	58.32	57.58	62.30	49.90
Run 6	57.45	53.93	52.33	57.40
Total	59.89	55.20	57.55	52.89

CTT

Run Number	Placebo	Marijuana	Alcohol	Both
Run 3	5.03	4.93	4.34	4.47
Run 4	4.89	4.94	4.21	4.16
Run 5	4.93	5.17	4.48	4.45
Run 6	5.04	5.20	4.63	4.67
Total	4.98	5.01	4.49	4.45

Although there was a definite trend on the BITE task for the placebo group to perform best, and the both-drugs group to perform most poorly, none of the analysis of variance tests produced a significant difference at $p<.05$. The results are nevertheless suggestive of impaired time estimation, particularly when both drugs are combined.

The results on the CTT measure show that the alcohol and both-drugs groups did significantly worse (lower means) than did the placebo and marijuana groups, indicating a clear-cut alcohol effect. The differences reached statistical significance ($p \leq .05$) at runs 4 and 5 and on the total composite (runs 3-6 combined). Somewhat surprisingly, there is not even a directional trend toward marijuana impairment on the CTT. The scores for the placebo do not change materially from run to run, whereas all three drug groups tended to improve. Thus, there is no evidence of residual practice effects but there is clear indication of reductions in impairment on the CTT over time.

DISCUSSION AND CONCLUSIONS

The Main and Interactive Effects of Alcohol and Marijuana—General Characteristics

The results of the univariate and multivariate analyses indicate that both substances affected driving performance. The MDF analyses resulted in two significant linear composites (functions) of the 12 performance measures which

were most consistently and uniquely impacted by the treatments. These two functions explained between 65% to 70% of the between-group variance on the 12 measures across the four posttreatment trials. Approximately 60% of the explained variance was attributed to the first function compared to 20% for the second function. The first function produced maximum discrimination between the placebo and the both-drugs groups, with marijuana alone and alcohol alone occupying intermediate positions between these two performance extremes. Inspection of the group means on the 12 variables which defined the function indicated the both-drug polarity was generally indicative of impaired performance.

The second function tended to separate the marijuana and alcohol groups from the placebo group, with the both-drugs group occupying an intermediate position.

An attempt was made to interpret the "meaning" of the two functions by inspection of the standardized discriminant function coefficients and structure loadings. Persons scoring higher (better) on the first function produced higher estimates of the speed at which they could drive the chicane and drove more quickly through it; drove at lower and more appropriate speeds when the speedometer was covered, as well as on most other parts of the course; drove more cautiously; made more accelerator reversals on the extended drive; performed better on the detour task; performed better on the field sobriety tests; were judged to be less impaired by the officer; rated their driving and field sobriety performance higher (less impaired); received higher overall ratings from the driver's license examiner (LRE); and made fewer driving errors on the drive course. This function clearly reflects between-group variations and performance decrements on a wide variety of measures: (1) subjective self ratings; (2) LRE ratings of speed control, overall performance, cautiousness and number of driving errors; (3) officer field sobriety and vehicle control ratings; (4) objective measures of performance (number of stanchions knocked down, accelerator reversal, urban driving speed; and (5) number of attempts on the risks task. Since this function produced maximum separation between the both-drugs and placebo groups with the latter falling at the positive end of the first function, higher scores on most of the preceding variables were associated with not being drugged, and lower scores with being exposed to alcohol and marijuana combined. The nature and range of variables affected indicate that exposure to the combined marijuana/alcohol condition resulted in impaired vehicular control and an accurate subjective awareness of the impaired performance.

Inspection of the second function indicated that higher scores on the function were associated with the marijuana and alcohol condition, and the structure loadings indicated that it is primarily a measure of impaired stopping. By far the highest loading on the function was on the variable POSTOP, which correlated +.69 with the function. This variable represents the LRE's rating of proper stopping position on all stopping maneuvers throughout the driving range. Since the variable was scaled so that low scores indicate proper stopping position (1=smooth stop, 2=abrupt or misjudged stop, and 3=rolling or no stop), the high positive correlation between the function and variable is indicative of a higher proportion of improper stop ratings among marijuana and alcohol subjects. Unfortunately, the method of scaling did not distinguish between stopping too soon or too late relative to the sign.

Four other stopping measures also had significant positive loadings on the second function: (1) SStop (stopping errors on the speedometer-covered segment of the course, (2) EStop (stopping errors on the extended drive), (3) Stops (total number of stopping errors on all segments of the course), and (4) BIPOST (bipolar rating of stop position cautiousness). A fifth stopping measure, BIStop, yielded a negative loading (-.31), indicating that stopping position caution on the speedometer-covered portion of the course was negatively associated with the function.

Taken together, the above results indicate that marijuana and alcohol affected stopping behavior but that the negative effects were reduced when both drugs were combined. The mechanism underlying what appears to be a suppressive interaction is not clear, and interpretation is further complicated by the above-mentioned scaling problems. One possibility is that the separate drugs produced different types of stopping errors (e.g., delayed vs. early stops) which cancelled out when both were combined.

The main and interactive multivariate effects of marijuana and alcohol on the 12 variable discriminant functions were evaluated through a series of canonical analyses, and an analysis of variance procedure was used to evaluate univariate effects. The canonical analyses indicated that both substances had highly significant multivariate main effects on all four posttreatment runs. The marijuana condition explained between 23.1% to 29.2% of the variance on the 12 most discriminating performance measures, averaging 25.1% for all four trials. The alcohol condition produced a somewhat larger effect, accounting for 29.9% to 32.3% of the performance variance, and yielding an average effect of 31.4% for all four trials. The multivariate effects were largely additive, although small but

significant interactions did occur on runs 3 and 6 where the respective explained-variance totals for the marijuana by alcohol interactions were 12.0% and 12.9%, respectively.

Factorial analyses of variance of univariate effects on each of the 12 discriminating variables (not shown) provided additional confirmation on the locus of treatment effects and on their interactions with variables that were considered to be the potential moderators of treatment effects (baseline performance on the 12 discriminating variables and five background characteristics representing prior alcohol/drug use and driving experience). These analyses indicated that marijuana had significant main effects on three measures: (1) COGNIT, (2) SMPH, and (3) ESTCHIC. A suggestive main effect also occurred on attempts (risk task). Inspection of the means indicated that the marijuana negatively affected performance on the cognitive factor of the field sobriety test; produced higher speed while the speedometer was covered; resulted in a lower self assessment of the fastest speed the subject could drive through the chicane; and required more attempts to complete the risk task. The alcohol condition produced a significant main effect on four measures: (1) BSPEED, (2) STOUCH, (3) CTT, and (4) SMPH. Suggestive main effects were also noted on attempts (risk task), COGNIT, and BISKILLS. Inspection of the means for these variables indicated that all of the effects were suggestive of impairment. No consistent evidence for a marijuana/alcohol interaction emerged from these analyses, or of an interaction with any of the baseline and background factors. Thus, these analyses support the conclusion that the effects of marijuana and alcohol are largely additive with each other and with the background and baseline performance characteristics of the subject sample.

The above conclusion of general additivity requires some qualification and further discussion. The detailed interaction analysis was limited to the 12 variables identified from the discriminant function analysis and was further limited to the total runs-composite (runs 3-6 combined). Since the effects of marijuana were most acute at run 3 and declined thereafter, the use of the composite measure could have masked some of the effects. In addition, interaction effects on variables other than "the best 12" were not evaluated.

There was, in fact, evidence of a small, but statistically significant, interaction between marijuana and alcohol at run 3, cited above in connection with canonical analyses of treatment effects. Further evidence of non-additivity also emerged in connection with the homogeneity of slopes test for the regression of baseline (run 2) performance on posttreatment performance (runs 3-6 combined). The slope differences were particularly dramatic for the CTT and ESTCHIC variables, suggesting that response to treatment varied as a function of subject's baseline level on these measures. The structure and substantive meaning of these interactions are not clear and seem in conflict with the failure to find significant treatment x baseline interactions in the analyses of variance. Two reasons can be advanced to explain the above paradox. First, the baseline measures were collapsed into dichotomous categorical factors for the analysis of variance test, whereas the slopes test treated each variable as a continuous measure. If relationships and interactions among the measures were approximately linear, the categorical approach would significantly reduce the sensitivity for detecting interactions. Second, the slopes test was based on a slightly smaller sample size (n=63) due to the deletion of cases with missing values on some of the measures.

The Main and Interactive Effects of Marijuana—Detailed Characteristics of Effects within Trials

The above discussion has primarily focused on the effects on all posttreatment trials combined into single composite measures. It has also been limited to the 12-variable core selected through the multiple discriminant function analysis (MDF).

A complete understanding of the results of the experiment requires interpretation of effects within and across trials and consideration of the many variables not included in the final MDF analyses.

The evaluation of treatment x trial interaction was achieved through a test of slope differences on the trial factor. Since the trials occurred at fixed points in time from a single drug ingestion, the trial slopes represent the effects of time, and the slope differences reflect temporal differences in each treatment group's performance gradient. These tests indicated significant slope differences on each of the 12 measures selected from the MDF analysis. A major source of the difference was marijuana's tendency to result in maximum impairment in the first posttreatment trial while alcohol's effect maximized at run 4 and did not decline as rapidly as the marijuana effect. The both-drugs group tended to show the impairment gradient that would be expected from the component drugs, evidencing maximum impairment at both runs 3 and 4 and consistently showing greater impairment than either marijuana or alcohol alone.

In addition, the combination of the two substances significantly lengthened the duration of effects, resulting in a rather remarkable increase in impairment from runs 5 to 6. The emergence of a synergistic marijuana-alcohol interaction at run 6 suggests an effect mediated by some residual mechanism occurring when the two substances are combined. An obvious intuitive explanation would be that marijuana and alcohol interact to produce greater fatigue and "hang over" effects.

Other results of interest are the findings on various peripheral measures, such as FALLCAR, field sobriety tests, self-rating and the CTT. In general, the subject self-rating of impairment was among the more sensitive indicators of treatment and tended to parallel the objective measures. The fact that the self-rating impairment indices closely mirror both the objective indicators and the overall LRE and officer rating provides confirmation for the reliability and validity of the results.

That the officers in the following-car (FALLCAR) were able to detect driving impairment with a significant degree of accuracy is notable. The FALLCAR results also clearly reveal the different time gradients for marijuana and alcohol. The marijuana subjects were detectable only at run 3, whereas alcohol peaked at run 4, and the both-drugs group was detected as impaired on all runs except 6.

The results on the CTT variable are surprising in that marijuana alone did not produce evidence of impairment, which is in conflict with prior research findings. This complex psychomotor task was originally devised to detect alcohol impairment. The fact that alcohol and marijuana plus alcohol combined did produce impairment would seem sufficient to dispel the hypothesis that the marijuana finding can be attributed to some type of error or procedural artifact. Some possible reasons for the findings are discussed below in connection with the review of relevant literature. Surprisingly, the marijuana-only condition resulted in fewer stanchions being knocked down at run 3—where the level of intoxication was actually greatest. However, it is important to note that persons receiving marijuana or marijuana and alcohol tended to drive more slowly through the chicane than did the placebo and alcohol-alone subjects. Speed through the chicane was measured by the vehicle line sensor, which produced the following elapsed times for the placebo, alcohol, marijuana, and both-drugs treatments, respectively: 16.7, 16.3, 17.3, and 18.4. Although the differences were not statistically significant (p=.22), it is instructive to note that other researchers have found that marijuana tends to cause persons to compensate for subjective impairment by reducing task difficulty through reduced vehicle speed.

Blood Levels

One of the objectives of the study was to assess the feasibility of developing an objective chemical index of marijuana impairment. Although the results did show that the quantitative levels of THC and carboxy combined resulted in some increase in the ability to explain performance variations, the practical and theoretical implications of the finding are not entirely clear. Experimental replication of the study and use of a wider range of marijuana-dose levels is needed before the feasibility of establishing a quantitative threshold can be fully evaluated. We are not optimistic about the prospects for development of quantitative thresholds for marijuana impairment.

Relationship to Prior Studies

There is a vast amount of empirical evidence documenting the effects of marijuana on a wide array of human performance measures—cognitive, psychomotor and affective. Although the literature has clearly established that marijuana affects all three domains and results in detriments in the ability to perform many psychomotor and cognitive tasks, the evidence is somewhat more equivocal on the question of actual driving skill and even more equivocal on the question of those aspects of driving skill that are *related to safety and accident avoidance*. Any attempts at formulating a comprehensive and coherent theory on the effects of cannabis on driving performance, or reconciling the various empirical outcomes of different studies are complicated by the differing circumstances unique to each investigation. Among the variables to be considered are: (1) the specific performance task; (2) the frequency of prior marijuana usage and the strength of the typical THC concentration of the marijuana; (3) previous experience driving after consuming marijuana; (4) the amount and strength of the experimental dosage; (5) mode of ingestion (oral or smoke); and (6) the type of research design employed in each study. The demonstration of behavioral change following ingestion, and the magnitude of the performance change, can obviously be affected by each of the above variables. Finally, there is the problem of equating change with detriment and then generalizing the inferred

detriment to real world accident avoidance behavior. With the above cautions in mind, we will attempt to show some tentative conclusions as to how the present findings articulate with the conclusions of other investigators.

Studies of marijuana's impact on driving performance can be grouped into five general categories:

(1) Laboratory studies.
(2) Simulator studies.
(3) Closed-course driving range studies.
(4) On-street driving studies.
(5) Epidemiological studies of accident-involved drivers and victims.

With the few exceptions discussed below, we believe that the measurement domains and research design of the present study are too dissimilar to warrant detailed comparison with the results of studies from areas 1 and 2. (The implications of study area 5 are discussed later in connection with traffic safety ramifications of marijuana and driving.) One area of conflict between the present and prior studies is the failure of marijuana alone to exhibit even a suggestive detrimental impact on the CTT measure. The critical tracking task was originally designed to detect alcohol impairment, and has been shown to be sensitive to relatively moderate levels of alcohol. Sharma and Moskowitz (1975) reported that a dose of 200 µg/kg THC resulted in significant impairment lasting throughout the four hours of a repeated measures test session. Remarkably, the impairment was almost as great in the fourth hour as in the first hour after ingestion. More recently, Barnett et al. (1985), using data from the above Sharma and Moskowitz (1975) study, reanalyzed the effects of the three dose levels of marijuana (100, 200, and 250 µg/kg) on divided attention, visual search and CTT performance. All three measures exhibited dose-related marijuana effects which, in the case of the CTT, lasted roughly 7.1 hours.

Given this evidence, the present authors would be inclined to dismiss the present result as an artifact were it not for the fact that both the alcohol and both-drugs groups did show the expected decrement. Any error or procedural artifact would be expected to have affected all groups, since assignment to the experimental conditions was random and was rigorously monitored.

Two explanations are proposed here for consideration. The first is the differences in experimental design between this and the above two studies. The present study utilized an independent-group design and also treated the trials condition as a collapsed factor for most of the analyses. In contrast, the studies by Sharma and Moskowitz, and Barnett et al. used repeated-measures designs in which each subject received all experimental conditions and were compared to their own baseline scores. Repeated-measures designs have greater sensitivity than do independent-group designs when the very strong mathematical assumptions on which the designs are based are satisfied. (These assumptions are often *not* satisfied in experiments on human subjects.) Although it is doubtful from the inspection of pre- and posttreatment means that creation of pre- vs. postdifference scores or use of analysis of covariance would have materially altered the results, one can always posit that the randomization did not completely control for idiosyncratic differences in drug response. There was also a slight trend in the data for marijuana subjects to achieve lower (worse) scores than the placebo at run 3, which is also the trial where marijuana intoxication was most intense. Any use of analysis of covariance or repeated measures differencing to increase the sensitivity of the run 3 contrast are complicated by the significant treatment by baseline CTT score interaction encountered in comparing regression slopes.

A more reasonable hypothesis is that the studies were not equivalent in terms of subjects' prior marijuana use (frequency and potency). There is reason to believe that persons accommodate, at least partially, to the effects of marijuana through acquired tolerance and/or experience in performing tasks while intoxicated. Even though learning new tasks is generally impeded by marijuana use, there is evidence to show that recall of material originally learned while intoxicated is greatest during subsequent periods of intoxication, i.e., "state dependent learning" (Darley et al., 1974). If one accepts the preceding evidence and line of reasoning, it seems clear that investigations of marijuana-induced performance decrement can produce conflicting results if based on subjects with different levels of tolerance and experience.

It appears that subjects in the present study were, in fact, heavier users than subjects in the Sharma and Moskowitz, and Barnett et al. data sets. The latter data were based on subjects whose current use frequency did not exceed three cigarettes per week and a minimum lifetime use of only ten episodes. The present study required subjects to be current users of 1-7 "joints" per week, to have been users for at least two years, and to have experience with marijuana that was "at least" as potent as that used in the study.

The average impairment/intoxication rating given at run 3 by the subjects in the marijuana-alone group was only 3.41 on a scale of 1-9. This, combined with the extremely high serum carboxy level of some of the subjects at baseline, suggests a chronic use of high potency marijuana that in many cases exceeded the self-reported use frequency. In any event it seems clear that the subjects of this study were heavier users than those used in the Sharma and Moskowitz, and Barnett et al. studies and many of the other studies cited in the literature. This speculation is also consistent with the prevalent availability and use of the high potency "sinsemilla" variety of marijuana grown in northern California.

Variations in acquired tolerance and accommodation could also explain conflicting results of other investigators. For example, most studies, including the present, have not produced psychomotor decrements approaching the magnitude, consistency and duration of those reported by Belgrave et al. (1979). These investigators used orally ingested THC on subjects whose use history appeared quite moderate. In addition, the oral ingestion of THC—a mode not normally encountered and which produces slower but more enduring effects—further confounds interpretation and any generalization as to what would be expected from smoking normative dose levels.

Several of the results obtained in the present study articulate quite well with those reported by other investigators. The ability of the police observers in the following car to detect impairment, particularly in subjects who received both marijuana and alcohol, is consistent with the results of Sutton (1983). However, neither alcohol nor marijuana alone could be detected in Sutton's study, which is in conflict with the present results.

The fact that marijuana and alcohol exerted a relatively additive effect on many driving behaviors is also consistent with prior research findings. The consistency of this effect and the range of the affected behaviors is notable. The emergence of a significant synergistic interaction between marijuana and alcohol in the fourth hour after ingestion is a novel finding. The mechanism underlying such an effect requires further study.

One limitation of the study was the lack of emergency response and accident avoidance tasks. A forced lane change (FLC) maneuver was included to tap the ability to respond to a choice reaction task, involving some of the same psychomotor components required to avoid accidents; it was not consistently affected by any of the drug conditions (other than a tendency for the drugged subjects to more often drive below the minimum speed threshold). Although across-study comparisons are tenuous, the failure to find a marijuana main effect on this task is consistent with the Stein et al. (1983) finding that even a substantial dosage of marijuana (200 µg/kg) had no effect on the ability to avoid accidents on a simulated driving task. However, Stein did find evidence of a marijuana-alcohol interaction on accident avoidance, with lower doses (100 µg/kg) of marijuana decreasing the negative effect of alcohol and larger doses (200 µg/kg) accentuating alcohol's negative effects.

An important limitation of the forced lane change task as a proxy for accident avoidance is that it was introduced as a discrete "off-line" task rather than integrated into the driving course. It, therefore, does not really measure vigilance and divided attention which are critical components of accident behavior and attributes which are more likely to be affected by marijuana (Sharma & Moskowitz, 1973; Moskowitz, 1976).

Since this study utilized a closed-course driving range, a detailed comparison with prior research using similar task modes is in order (one such study by Sutton was already alluded to above). Several other such studies have been reported in the literature (Klonoff, 1974; Attwood et al., 1981; Smiley, 1974; Casswell, 1979; and Hansteen et al., 1976).

Hansteen et al. found that marijuana (88 µg/kg THC) resulted in a significant increase in the number of cones overturned on the slalom portion of the course but did not lead to increased erratic vehicle handling as judged by raters, whereas alcohol impaired both measures. In contrast, the present study found that marijuana significantly reduced the number of cones knocked over in the chicane task but that the marijuana subjects tended to drive more slowly through the chicane. The both-drugs group also reduced their speed compared to the placebo but hit the same number of cones as the placebo. The alcohol-alone group tended to drive the fastest and also tended to hit the most cones.

Casswell found that marijuana alone decreased vehicle speed and course steering corrections. In contrast, alcohol, and marijuana plus alcohol, decreased fine steering reversals and increased variation in lateral placement of the vehicle. Casswell concluded that marijuana subjects tended to compensate for their perceived impairment by reducing vehicle speed, thereby reducing task difficulty and information processing demands. This conclusion is consistent with our finding, cited above, concerning marijuana's effect on the chicane task. However, marijuana did

not result in reduced speed on most parts of the course and was associated with increased speed when the speedometer was covered. This can easily be attributed to the fact that most parts of the course were of minimal difficulty and did not require compensation. Although there was little evidence from the present study to show impact on steering reversals, marijuana and alcohol did impair steering control as rated by the in-car observer. The failure of the vehicle steering reversal sensor to detect change in the present study could be due to the sensor defects and signal loss caused by equipment malfunction, and to the fact that the scores were limited to mean values of nondifference parameters (Biasotti et al., 1986).

The study by Smiley (1974) is one of the few examples of a marijuana-alcohol interaction in which marijuana appeared to reduce the negative effects of alcohol. Such an interaction occurred on stopping accuracy. In contrast, the present research showed that marijuana was associated with more stopping errors than alcohol but did show evidence of significant negative interaction (interference) in which the combination of alcohol and marijuana resulted in better stopping position than marijuana alone. Attwood et al. (1981) found no persuasive evidence of any univariate effects of marijuana and alcohol on driving range performance as measured by an instrumented vehicle. However, they did find significant multivariate effects. The strong tendency of multivariate methods to capitalize on chance relationships in small samples requires that the results of Attwood et al. be interpreted with caution until replicated.

The driving range portion of the study by Klonoff (1974) most resembles the present study in method and scope with respect to the driving course tasks. Klonoff found that the higher marijuana dose (one cigarette of 1.2% THC) resulted in an increase in the number of cones hit on a slalom task, risk task, a funnel task, two tunnel maneuvers, and total composite score. No effects occurred on the back-up and corner tasks. The low dose condition resulted in detriment on one of the tunnel tasks, the cornering task, and on the total composite score. Effects on braking distance were suggestive but equivocal. Klonoff also found evidence of marijuana-induced improvement on various in-car observer ratings of on-street performance. The largest effects occurred on ratings of judgment, care, and concentration (since these are highly subjective ratings, the possibility of some observer halo bias should be noted, particularly if the raters were able to accurately guess the treatment condition).

While the majority of Klonoff's subjects showed impairment due to marijuana, a substantial minority actually improved. Several variables were analyzed as potential moderators of treatment response, including prior experience driving while under the influence of marijuana, and none produced evidence of interaction. (The present study also found no evidence of interaction on similar background variables.)

The present study was not analyzed in a way which would permit direct comparison with Klonoff's conclusion that some subjects improved following marijuana ingestion. However, we do know from the discriminant function classification matrices (which were not presented) that a small number (n=2) of marijuana subjects could not be differentiated from placebo subjects at run 3 based on their discriminant function scores. This, of course, does *not* necessarily mean that the misclassified subjects were not impaired, because these analyses did not take into account performance at baseline. It is therefore possible that the misclassified marijuana subjects represent persons who possess an extraordinarily high degree of skill, which was reduced to an average level by the marijuana treatment. This hypothesis and its articulation with Klonoff's findings will require a more in-depth analysis of the present data.

Traffic Safety Implications

Authorities are not in agreement on the traffic safety threat posed by marijuana use (Warren & Simpson, 1980). In a recent series of papers, McBay and Owens (1980) and Mason and McBay (1984, 1985) concluded that marijuana is a relatively minor factor in traffic accidents and they questioned the feasibility of relating impairment to specific levels of THC. Although many of their criticisms of past studies are both astute and pertinent, we believe these same limitations prevent forming unqualified opinions in any direction about the role of marijuana in traffic accidents. Many of the conclusions formed by McBay and his associates are based on the failure to find a substantial incidence of THC in the blood or plasma levels of drivers killed in single vehicle accidents in North Carolina. Considerable caution is necessary in generalizing incidence data from North Carolina to a state like California. Not only are there likely to be large differences in marijuana usage, there may also be large differences in driving task complexity between such states and in the use of cannabis in conjunction with vehicle travel.

In addition, Moskowitz (1985) has recently pointed out that behavioral impairment and subjective intoxication are still manifest after THC has dissipated from the blood. This factor results in an unknown proportion of false

negative findings from analyses of accident victim blood specimens. Nevertheless, the point remains that the traffic safety implications of marijuana use must ultimately be based on direct evidence of its *causal* role in increasing accident risk. This necessitates establishing accurate "population-of-risk" baselines for: (1) the incidence at which persons drive under various levels of THC alone; (2) the same incidence in combination with alcohol; and (3) the same incidence in combination with other drugs. The fact that marijuana is so often detected in conjunction with alcohol makes it difficult to establish a case against marijuana since any increase in relative risk could be due to alcohol alone. Establishing incident rates for the above risk groups would facilitate interpretation of the respective incident rates among accident-involved drivers.

Probably the most consistent and important finding of this study was the demonstration of an additive marijuana/alcohol effect on a wide array of performance measures. If one accepts the thesis that marijuana in conjunction with alcohol makes people "drunker," then it follows that marijuana in this context increases accident risk. A public policy implication of such a thesis might be to reduce the illegal, *per se*, BAC level for persons detected with both substances in their blood.

The question of the traffic safety risk posed by marijuana alone is not as clear cut as the risk presented by marijuana and alcohol in combination. Although evidence of impairment was identified in both the present and numerous past studies, the translation of this evidence into inferences about *accident causation* presents numerous difficulties. Before explaining why, we offer a dissenting opinion from a recent comprehensive review of the literature by Moskowitz (1985):

> It should be clear from the above review that there is more than sufficient experimental evidence to conclude that marijuana seriously impairs psychomotor performance required for driving. Among the areas which exhibited overwhelming evidence for impairment were: A. coordination...; B. tracking; C. perception; D. vigilance; E. driving and flying performance measured by simulators; F. driving performance on the road....
>
> Clearly, marijuana is a substance which produces serious behavioral toxicological effects. Any situation in which safety both for self and others depends upon alertness and capability of control of man-machine interaction precludes the use of marijuana.

Based on the present study and past evidence, we agree that marijuana undoubtedly impairs psychomotor abilities that are functionally related to skillful driving and that driving skill itself may be impaired, particularly at high dose levels or among naive subjects. Given these facts alone, Moskowitz' implicit recommendation that people not drive after consuming marijuana should obviously be heeded. However, the extent to which marijuana-impaired driving causes accidents cannot be deduced from the present study, or from any of the studies cited by Moskowitz. Our more conservative posture in regard to this question is based on the following rationale:

(1) In their multidisciplinary investigation of traffic accidents, Treat et al. (1979) identified "improper lookout" and excessive speed as the two most frequent human factor causes of accidents. Harano, Peck and McBride (1975) evaluated a large array of psychomotor measures including divided attention, and concluded that none were important predictors of a driver's accident propensity.

Although improper lookout may involve some of the perceptual and information-processing components affected by marijuana, it is more closely related to the search and scan strategies utilized by drivers in anticipating and detecting potential conflicts. In the only study of marijuana's impact on traffic visual search behavior, Moskowitz et al. (1976) found no evidence of a negative effect on search and scan behavior. Excessive speed can be best viewed as a reflection of attitude toward risk, risk assessment and aggressiveness. Several investigators have reported that marijuana reduces risk-taking propensity and driving speed. Because of these compensating tendencies, it is presently not possible to assess the *net impact* of marijuana as a causal agent in traffic accidents. Although some increased accident risk appears likely, the magnitude of the risk remains obscure.

(2) Many of the laboratory marijuana studies which have shown the greatest psychomotor impairment have utilized tasks that are only abstractly related to driving. Although divided attention and tracking are required for driving, it does not necessarily follow that performance on a highly novel and complex laboratory task designed to magnify performance decrements is correlated with actual "real world" performance in a vehicle. The fact that attempts to measure response to simulated accident situations

have not consistently detected a marijuana-induced decrement, even at high dose levels, underscores the need for more research (Stein et al., 1983).

Future Research Needs

In addition to the need for improved epidemiological studies mentioned earlier, the relationship between marijuana consumption and driving behavior can be clarified by a research design possessing the following characteristics:

(1) A multi-method/multi-criterion approach in which subjects perform relevant psychomotor, driving simulator, and actual driving tasks. The utilization of different measurement domains will permit an assessment of the multivariate effects across domains, leading to more generalizable characterizations of the extent and locus of marijuana-induced impairment.

(2) At least three dose levels of marijuana should be used (none, moderate, and high) in order to obtain a greater range of THC variation for investigating dose-response relationships.

(3) Frequency of prior marijuana usage should be treated as an experimental factor by selecting subjects who vary substantially on use rate. At least three levels should be employed—light users, moderate users, and heavy users. Such a design would permit an evaluation of treatment x use frequency interaction, resulting in a better understanding of whether acquired tolerance and accommodation are important factors in influencing impairment.

(4) An independent-groups design with repeated measurement trials should be employed in preference to latin square designs in which each subject receives all treatments. Individual differences in drug response and experimental error could be reduced through matching and analysis of covariance procedures.

(5) The design should include some tasks under reduced illumination to simulate night-driving conditions. Serious accidents more often occur at night, and there is reason to suspect that marijuana-induced impairment would be greater under simulated night-driving conditions.

Further research is also needed to validate the relationship between tasks (or simulators) designed to detect drug impairment and actual driving behavior, as measured by driving performance tests and accident involvement rates.

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Epidemiology of Road Accidents Involving Marijuana

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INTRODUCTION

Overview

The point of departure for this paper is captured in the contrast afforded by two quotations that summarize the state of knowledge concerning marijuana and traffic safety in 1977:

> All these studies indicate that cannabis is, as should have been anticipated, a hazardous drug for the road user.... Judgement, perception, mood, coordination and attentiveness are all affected.... At this point in time marijuana and other cannabis intoxication effects would seem to be a very real hazard in our community, especially in terms of the road toll. (Milner, 1977, p. 2)

> At the present time there is no evidence that marijuana is a significant public safety problem or is about to become one. The effects of marijuana reported in these studies are such that it is unlikely that a person driving erratically and recklessly would do so because of the influence of the drug. (McBay, 1977, p. 97)

These disparate views illustrate that unanimity of opinion regarding the issue of marijuana and traffic safety had certainly not been achieved less than a decade ago. The present paper, which focuses principally on epidemiological research since that time, is intended to determine whether the burden of evidence now weighs more heavily in one or the other direction. The purpose of this review is, therefore, to identify what is known about the magnitude of the problem of marijuana in road crashes and the level of risk it poses for traffic safety, insofar as can be determined from epidemiological research.

Background

It is widely accepted that many drugs can have serious impairing effects that could contribute to traffic accidents. The purpose of experimental research is to determine the nature and extent of those effects; the purpose of epidemiology is to determine whether those effects are translated into real problems on the highway. For example, if a drug like marijuana is shown to increase distractability in controlled settings, it would still be necessary to demonstrate not only that people actually drove under the influence of the substance, but were in fact involved in

As in the previous investigations, results from the Williams et al. (1985) study showed that drinking drivers were more likely to be responsible for their crashes than were the drug-free drivers (92% vs. 71%). However, in contrast to the previous studies, Williams et al. (1985) found that drivers in whom only marijuana was detected were *less likely* to be responsible for the crashes (53% vs. 71%). Those who had used both alcohol and marijuana were slightly more likely to be seen as responsible than those with alcohol alone. These disparities within and between the studies cannot easily be reconciled. In summary, three studies suggest that marijuana contributed to the risk of collision, one study suggests it was unimportant (may have contributed to one out of 600 fatalities) and in one study marijuana-users were actually less likely to be judged responsible for the crash than drug-free drivers. To say the least, the results are mixed and inconclusive.

CONCLUSIONS

The epidemiological literature relevant to marijuana and driving is fragmented and relatively sparse. What does exist shows that people do drive after or during marijuana-use, not infrequently, and people involved in crashes (both injury producing and fatal) show evidence of marijuana use, often quite frequent use. But, the significance of those findings remains disputed and certainly is rendered no less equivocal to date by attempts to establish the contributory role of marijuana to collisions by culpability or responsibility analysis. Closure has not yet been attained. While this may appear distressing, progress in the past decade should be judged against that made in understanding the role of alcohol in road crashes. The indictment of this relatively simple substance has required decades of research and even given such research, fundamental questions about *how* alcohol-induced impairment contributes to road crashes and the extent of this contribution remain unanswered today. In this context, there is no need to apologize for the current, relatively pathetic state of knowledge regarding marijuana and traffic safety.

As a closing note, to illustrate the complexities in the field and to amplify the diversity of opinion that exists, it is interesting to trace an issue that has recently come full circle. Early work on the involvement of marijuana in road crashes was based on toxicologic tests performed on urine specimens. Such studies were soundly criticized, since cannabinoids in urine could be present for many days after use, so the significance of the findings for road safety were indeterminate. As a result, researchers began to rely on the incidence of THC in blood, which indicated more recent use and, therefore, could potentially have more relevance to the collision. But, detections in blood, *per se*, were also judged inadequate, since low concentrations were regarded a unlikely to affect driving performance. Even this was disputed because the dose-response data needed to state what levels result in impairment were unavailable. More recently, it has been suggested that preoccupation with findings in blood are unfortunate, since there is evidence that the behavioural effects of marijuana can be detected even when there is no longer evidence of the substance in blood. Accordingly, it has been argued that what is needed in addition to blood, is urine. And, the issue has come full circle.

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The Clinical Syndrome of Marijuana Dependence

By FOREST S. TENNANT, Jr. MD. DrPH

Dependence upon cannabis sativa was initially described in the United States about 40 years ago.[1] In 1944, 55 "confirmed marijuana addicts" were admitted to a military hospital and developed withdrawal symptoms. In the same decade, Fraser in India reported on soldiers who had been ganja smokers for some years and, after joining the army, exhibited severe withdrawal symptoms due to difficulty in obtaining cannabis products.[2] Since these initial reports, a number of studies clearly document that tolerance, dependence, and withdrawal symptoms may occur after chronic administration of cannabis.[1-7] Supporting data comes from clinical observations, animal studies, and a carefully controlled trial where humans were given known quantities of tetrahydrocannabinol (THC) and then observed for tolerance and withdrawal symptoms.[3-7]

There is little question that the need for clinical treatment of marijuana dependence will escalate. Many persons who have used marijuana for several years are now beginning to realize that they are dependent and will not be able to cease use without medical intervention.

Until very recently, cannabis dependence had not been a significant clinical concern in the United States. This is accounted for by two factors. First of all, the form of cannabis usually consumed in America is marijuana, and its THC content throughout the 1970s generally ranged from about 1% to 3%. This contrasts with other countries where the more potent forms of cannabis, including hashish, ganja, and dagga have been traditionally used, and where observation on cannabis withdrawal symptoms have frequently been made.[1] In the decade of the 1980s, however, potent forms of marijuana with a THC content of 5% to 15%, as well as hashish, have emerged as the usual forms for self-administration. This high THC content makes it relatively easy to consume over 180 mg per day, which was the daily dose given to human volunteers for 11 to 21 days by Jones and co-workers, and which showed an opioid-like withdrawal syndrome when it was abruptly discontinued under controlled conditions.[7] A second factor that has helped make cannabis dependence an increasingly common clinical entity in the United States is the recent development of low-cost, urine screening technology that can detect marijuana metabolites.[8] Wide-spread urine screening in the workplace, criminal justice system, and clinical settings are now identifying persons dependent upon marijuana. This practice has resulted in routine referrals for treatment in my ambulatory clinics located in West Covina, California (East Los Angeles County). This article reviews pertinent literature and summarizes some of my clinical experiences.

EVIDENCE OF DEPENDENCE

In 1971, Deneau and Kaymakcalan succeeded in producing self-administration of THC in monkeys.[5] When THC was abruptly discontinued,

TABLE 1
Commonly Observed Cannabis Withdrawal Symptoms*

Insomnia	Anorexia
Nausea	Photophobia
Myalgia	Cannabis craving
Anxiety	Depression
Restlessness	Mental confusion
Irritability	Yawning
Chills	Anergy

* *These symptoms have been reported in animal and human studies*

the monkeys exhibited a withdrawal syndrome that was not dissimilar to the opioid abstinence syndrome. Other investigators were able to repeat these experiments and make similar observations.[1] Self-administration has also been induced in rats following a forced injection period.[1] In early studies, rats given THC chronically also appeared to develop an opioid-type withdrawal syndrome when THC was abruptly discontinued.[1] These observations were confirmed when, in 1974, Hirschhorn and Rosecrans gave naloxone to rats treated with THC for five weeks and precipitated an opioid-like withdrawal syndrome.[5] Kaymakcalan duplicated this study and also found that naloxone produced withdrawal symptoms in THC-treated rats.[6] The most common withdrawal signs observed in both studies were diarrhea, teeth-chattering, wet-dog shakes, salivation, ptosis, piloerection, yawning, and increased activity.[1]

After the human observations of withdrawal in the 1940s, there were no reports of cannabis dependence and withdrawal symptoms in humans until the 1970s.[1] In a research project sponsored by the World Health Organization (WHO) in 1976, 50 long term cannabis users in India were compared with 25 non-user controls.[1] It was found that the majority of users (98%) felt uncomfortable if they were unable to obtain their daily supply or dose of cannabis, and in addition to a strong craving for the drugs (86%), the majority also showed mental irritability and feelings of anxiety (74%) as well as profound lethargy and physical weakness (60%). About 70% of the users reported some kind of physical discomfort in the absence of the drug. There are reports from other countries, including Greece and Egypt, where there is a relatively high hashish consumption. Tennant and Grossbeck observed dependence in American soldiers in West Germany who were able to obtain large amounts of hashish.[9] Bensusan described five young South Africans who had marijuana withdrawal symptoms for one to three days and who were able to relieve them by re-administering marijuana.[10] Teitel reported three cases of manic-depressive illness that followed withdrawal after prolonged use.[11] Other clinicians have reported that heavy marijuana users may develop tolerance rapidly, become dependent, and experience flu-like withdrawal symptoms following cessation of use.[1]

To substantiate whether withdrawal symptoms exist with chronic marijuana use in humans, controlled human studies have been done. Volunteers have been given bedtime dosages of THC and monitored in sleep laboratories. When THC is administered nightly for only four to 15 nights and then abruptly discontinued, there is insomnia and increase in REM sleep and eye movements that last for up to 12 days.[12] In addition to controlled sleep studies, Jones and co-workers gave oral THC to volunteers for 11 to 21 days and then substituted placebo. They observed a variety of withdrawal symptoms similar to those described in clinical reports and animal studies.[7]

Based on numerous reports and studies, it is clear that there is a cannabis withdrawal syndrome. I have frequently observed marijuana-dependent patients in withdrawal, and my observations support previous reports. In particular, my patients have reported insomnia, nausea, myalgia, restlessness, and irritability. Table 1 summarizes the common withdrawal symptoms that have been reported in human and animal studies. A major question is whether this syndrome is identical to the opioid withdrawal syndrome. To date there are no reports of naloxone challenges in cannabis-dependent humans. A recent animal study, however, shows that THC will deplete endogenous opioid peptides, so marijuana dependence and withdrawal may be at least partially mediated through the endogenous opioid system.[13] THC administration also has effects on the catecholamine system.[14] Another study suggests that marijuana withdrawal may be mediated through the serotonergic system.[15] Rats made dependent on THC were given chlorimipramine, which is a potent inhibitor of serotonin re-uptake. Following this challenge, they developed a clear and quantifiable withdrawal syndrome similar to that observed when naloxone was given.[3,6]

CLINICAL TYPES OF DEPENDENCE

Two types of marijuana dependence will con-

TABLE 2
Two Clinical Forms of Marijuana Dependence

	Frequency of Self-Administration	Likely Dependence Metabolite(s)	Usual Referral Route	Patient's Perceived Dependence	Usual Severity of Withdrawal Symptoms	Relapse Rate
Type One	Multiple times each day	THC 11 OH-THC	Voluntary: self referred	Significant	Moderate	High
Type Two	Every 24 to 48 hours	THC-C	Involuntary: Detected by mandatory screening	Minor to moderate	Mild	High

ront today's clinician (Table 2). Type One is an ndividual who will self-administer marijuana sev- ral times per day, usually at an interval of about vo to four hours unless asleep. This individual iay voluntarily present to the clinician with the omplaint that their daily dosage has escalated and iat they are unable to cease use without medical sistance. The patient may or may not relate men- l impairment primarily related to memory, otivation, time-keeping, abnormal thoughts, and ork or school performance. In addition, they may 'ate a number of withdrawal symptoms that :ur when they attempt abrupt cessation. The 'iety of symptoms generally resemble those :cribed in the controlled animal and human stud- (Table 1), although they may report others. The 'cise relapse rate following withdrawal is :nown, but it occurs.

SE REPORTS

Case 1: Marijuana Dependence: Voluntary Admission to Treatment

MV was a 25-year-old male who presented with ie complaint that he could not "stop marijuana by iyself." He was a 12-year user having begun mari- iana smoking at 13 years of age. He had used arijuana daily for about five years and was using :o to three joints per day at the time of admission outpatient treatment. The patient was married d held a regular job as a warehouse superinten- nt. He claimed he was having considerable con- :ts with his wife and employer. In addition, he d noticed in the two months just prior to admis- n that he occasionally heard voices that were t real, did not always have total "control over his id," and had some thoughts of suicide. He ied use of any other drug or excessive alcohol ike. His treatment admission breath alcohol negative, and his urine contained marijuana metabolite but no other abusable drug. The patient was administered desipramine, 25 mg, three times per day and was given weekly psychotherapy for approximately six months. During the first ten days of treatment, he reported insomnia, abdominal cramps, diaphoresis, tachycardia, and anxiety. These symptoms subsided, and he submitted a urine void of marijuana approximately 30 days after admission. Most of the thought disturbances noted above disappeared after about two to six weeks of treatment. He denied any marijuana use during the six months after entering treatment, and he submitted monthly urine tests that showed no marijuana.

Case 2: Volunteer with Unsuccessful Treatment

JS was an 18-year-old male who voluntarily presented because he "wanted to stop." Consumption of drugs consisted of about 3.5 grams of marijuana and hashish per day for one year prior to seeking treatment. He self-administered every one to four hours while awake and complained of chronic cough, anorexia, depression, and weight loss. When he had tried abruptly to cease marijuana by himself, he had hallucinations, depression, and anergy. Urinalysis testing revealed the presence of marijuana, but no other drugs. The patient entered a counseling program, but received no medications. Only one return appointment was kept, and he was lost to followup.

Type Two form of marijuana dependence is primarily being identified as a result of mandatory urine screening and treatment referral in the workplace. Seldom does a Type Two voluntarily present for treatment, although it may occur. In this form, the patient is usually self-administering marijuana every 24 to 36 hours and may give a history of carrying on this habit for several years. As in Type One, reported impairment relative to memory, motivation, time-keeping, and job performance is

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variable. In contrast to Type One, however, the patient may report few if any symptoms of withdrawal upon abrupt cessation. Relapse, however, is common.

Case 3: Mandatory Work-Site Detection and Referral

HS was a 37-year-old male salesperson. He was reported to the management of his company to be a marijuana user who also sold it to other employees while on company premises. A mandatory urine test revealed the presence of marijuana metabolite, and in order to retain employment he was required to undergo withdrawal and enter a periodic urine-testing program. Upon interview, he stated that he had used marijuana every evening for approximately 22 years. He believed this habit had not been injurious to himself until approximately three months prior to treatment when he began to notice some defects in his short term memory. Physical examination was normal. Plasma analysis showed there to be 148 ng/ml of 11-OH THC and 80 ng/ml of THC-C. He was administered desipramine, 25 mg, three times per day and tyrosine. During the first three weeks following cessation of marijuana, he reported mild insomnia, depression, anergy, and craving. Urine analysis showed no marijuana metabolite after about 30 days. After six weeks of abstinence, he reported improvement of short term memory and improved job performance.

METABOLIC BASIS FOR TWO FORMS OF DEPENDENCE

New data on the metabolism and pharmacokinetics of marijuana provide a sound rationale as to why two basic clinical forms of dependence appear to exist. When a marijuana cigarette is smoked, THC is converted to two major metabolites, 11-Hydroxy-THC (11-OH-THC) and 11-Nor-THC-9-Carboxylic Acid (THC-C). THC and 11-OH-THC both have psychoactive effects, and they remain in the plasma at concentrations above about 5 ng/ml to 10 ng/ml for only about two to six hours.[16-18] During this period they appear to produce a short-term characteristic "high" or euphoria. This time period correlates well with the self-administration frequency of Type One marijuana dependence. The THC-C metabolite remains in plasma at concentrations above 5 ng/ml to 10 ng/ml for at least 48 to 72 hours. Although this metabolite may produce little or no euphoria, it is likely the compound that sustains Type Two dependence. A similar phenomenon also exists with some benzodiazepines, such as diazepam, and with the opioid methadone. For example, methadone will provide analgesia and euphoria for about four to six hours, but it and its metabolites will remain in plasma for 24 hours and sustain dependence. A similar time course may be observed with

A number of studies clearly document that tolerance, dependence, and withdrawal symptoms may occur after chronic administration of cannabis.

diazepam, which also has long-lasting metabolites. For example, some withdrawal symptoms and even seizures may not appear for several days following cessation of diazepam dependence.[19] I have recently observed that withdrawal symptoms following abrupt cessation of marijuana dependence may not appear for several days.

The following is an illustrative case in which plasma concentration of THC-C was assessed at three intervals during the first week following abrupt cessation of Type Two marijuana dependence. Withdrawal symptoms did not occur until the eighth post-drug day at which time plasma concentration of THC-C was undetectable. The delay in withdrawal symptoms is undoubtedly related to slow clearance of plasma and tissues of marijuana metabolites, particularly THC-C.

Case 4: Delayed Withdrawal Symptoms

A 27-year-old male was admitted to a day-treatment program for marijuana dependence. He had been identified at work for being "under the influence" on more than one occasion and was, therefore, referred for treatment. Drug consumption consisted of intermittent cocaine use and daily use of about one marijuana joint. He perceived that he had been "addicted" to marijuana for about 15 years, and that he had skipped marijuana use on very few days during this time. A physical examination was normal except for mild nasal-septum inflammation and a swollen uvula. Urine analysis showed the presence of marijuana metabolite and marijuana plasma analysis by high performance liquid chromatography (HPLC) showed no 11-OH-THC and THC-C to be 8 ng/ml. A 24-hour urine specimen showed secretion of 2-methoxy-4-hydroxy-phenyglycol (MHPG) to be 143.0 MCG/24 hours (normal is 1164 to 2216). Since his continued employment was dependent upon attending the day-care program until his urine was void of all drugs, compliance with treatment and testing procedures was good. Withdrawal medication consisted of desipramine, 25 mg, administered three times per day, and the amino acid, tyrosine. On the third treatment day, his urine still contained metabolite, and his plasma contained 5 ng/ml of THC-C. On the eighth day of attendance, he complained of a flu-like illness consisting of nausea, vomiting, diaphoresis, chills, myalgia,

TABLE 3
Clinical Patients to Screen for Covert Marijuana Dependence

Psychiatric patients under age 35
Adolescents and young adults with recurrent respiratory ailments
Adolescents and young adults with recurrent accidents and unexplained somatic complaints
Patients under age 35 who abuse alcohol, cocaine, phencyclidine, hallucinogens, and amphetamines

anorexia, and insomnia. The patient did not relate these symptoms temporally to his marijuana use, since he had ceased use eight days previous. Plasma analysis showed no detectable presence of 11-OH-THC or THC-C, but marijuana metabolite was still present in urine at this time. The apparent withdrawal symptoms resolved within 48 hours. Marijuana metabolite remained in his urine until the 34th day of treatment.

SCREENING

There are some clear clinical indications to screen for marijuana dependence. Proper screening requires urine testing, physical examination, and history-taking relative to frequency of use (Table 3). Once detected, a treatment program can be developed. Patients who should particularly be screened by urine test are those who are under age 35 and who exhibit psychiatric symptoms, deviant behaviors, use cocaine, phencyclidine, or amphetamines, abuse alcohol, or have recurrent respiratory ailments. The association of various psychiatric symptoms and chronic cannabis use has often been described.[9] Although it is difficult, if not impossible, to always determine whether psychiatric symptoms pre-date or post-date the cannabis dependence, the association is so high that it is prudent to screen for it. In particular, chronic cannabis use has been associated with chronic thought disorders that are characterized by delusions, hallucinations, depersonalization, poor ability to perform at work or school, and inappropriate interpersonal relationships. Physical examination can often give clues to marijuana dependence. In particular, chronic marijuana smoking produces a swollen uvula and signs of chronic bronchitis. A generally unappreciated clinical candidate to screen for marijuana dependence is the adolescent or young adult who presents with apparent abuse of another drug or alcohol. For example, the underlying marijuana dependence may pharmacologically potentiate another drug, but remain unrecognized if a urine screen is not done.

Case 5: Marijuana Dependence Underlying Alcohol Abuse

A 17-year-old girl was arrested for being "drunk in public" on more than one occasion, and was referred for treatment. As part of a routine urine drug screen done for all persons under age 35 with substance abuse or psychiatric problems, she was found to have marijuana metabolite in her urine. Upon questioning, she stated that she drank alcohol only once or twice per week, but smoked marijuana daily. In addition, she questioned whether she could cease all marijuana use. Physical examination on admission to treatment revealed strabismus on the right and non-reactive pupils. She was administered desipramine, 25 mg, three times per day and tyrosine. She participated in outpatient counseling weekly. After approximately one week, the strabismus disappeared and pupils began to react. Marijuana metabolite could not be detected in urine after approximately two weeks of treatment. After three months of treatment, no known episodes of drunkenness occurred.

TREATMENT

At present there is no recognized medical withdrawal regimen for marijuana dependence. Outside of this review, the author cannot identify any reported use of a medical regimen for this purpose. Additionally, the use of the tricyclic antidepressant, desipramine, and tyrosine, a precursor of norepinephrine, as reported here, is not necessarily the optimal treatment. Recent studies of cannabis administration given to animals and humans indicate that it reduces noradrenergic activity and endogenous opioids.[13,14] For this reason desipramine, which is a potent blocker of the reuptake of norepinephrine, may be an effective withdrawal agent. For example, a case described here showed extremely low urinary excretion of MHPG, which is a metabolite of norepinephrine. Although this regimen appeared clinically effective in the cases reported here, plus others treated by me, only a double-blind, placebo-controlled study can prove true effectiveness. Regardless of pharmacologic effectiveness, I have observed that patients who present for treatment and who do not receive withdrawal medication for at least a few days tend to drop out of treatment just as did one of the illustrative cases described above. This appears to apply to both Type One and Type Two dependency.

Although there has been a scarcity of attempts at medical withdrawal, there are recent reports of hospitalization and withdrawal attempts.[20,21] Swatek found that many patients would drop out or fail to reduce marijuana use enough to ever clear

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their urine of marijuana metabolite.[20] This study points out the necessity to regularly monitor urine for marijuana metabolite as an indicator of successful treatment. I have found that assessment of the plasma concentration of 11-OH-THC and THC-C to be useful in determining whether the patient is ceasing self-administration of marijuana.

Regular psychotherapy to accompany urine monitoring and possible medication appears essential in most cases. Patients dependent upon marijuana tend to have a plethora of psychiatric symptoms and considerable problems with interpersonal relationships, motivation, and reality functioning.[9,11]

TRENDS AND RESEARCH NEEDS

There is little question that the need for clinical treatment of marijuana dependence will escalate. Many persons who have used marijuana for several years are now beginning to realize that they are dependent and will not be able to cease use without medical intervention. This realization is enhanced by the availability of more potent forms of cannabis that were not available just a few years ago. Some persons are probably becoming dependent as a result of these potent forms, where they might not have done so if their only consumption was the low potency forms that were formerly available. Perhaps the biggest impetus for dependency treatment will be the identification of dependent persons in mandatory urine screening programs operated by industry.

Research is needed to develop a medical withdrawal treatment for marijuana dependence. From a prevention perspective, we need information as to how frequently and for what length marijuana must be used to develop dependence. For example, I have clinically observed that withdrawal symptoms will occur in persons who use marijuana on a daily basis, but I am not clear as to whether they will occur in persons who use marijuana every second or third day. Since THC has long-acting metabolites whose pharmacologic activity is uncertain, our concepts of dependence must be refined. Lastly, there is almost no available data on relapse rates with marijuana dependence.

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Effects of Long Term Marijuana Use

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INTRODUCTION

While one or a few exposures to cannabis may occasionally result in untoward reactions (anxiety or panic states or accidents in connection with the intoxication), it is the consistent, heavy usage of the drug that concerns the public, the clinician and the researcher. A brief review of the impact of chronic cannabis use will be attempted here. Only selected organ systems will be mentioned since information on others remains incomplete or inconclusive.

Pulmonary Function

A few clinical studies have addressed the question of whether habitual marijuana smoking significantly increases the risk of developing lung disease. Although there have been reports of bronchitis after heavy or chronic smoking of marijuana, these are either anecdotal or based on uncontrolled clinical observations. For example, in India, Chopra (1973) observed an apparently high prevalence of asthma, bronchitis and nose and throat irritation among 124 selected cannabis users. In Jamaica, Hall (1975) noted that an emphysematous configuration of the chest was particularly common among frequent, heavy users of cannabis. However, neither of these authors systematically compared their observations in marijuana smokers with findings in a control group of subjects and both failed to take into account the variable of tobacco smoking since most Indians and Jamaicans who smoke marijuana also smoke tobacco.

In the study of Tashkin et al. (1980) in which the results of lung function tests in 74 young habitual marijuana smokers were compared with those in a control group, comparison was also made of responses to a detailed respiratory questionnaire incorporating questions relating to cough, phlegm production, shortness of breath and other respiratory symptoms. No differences were noted on comparing the symptoms reported by the marijuana smokers with those reported by the control subjects. However, in this study, the marijuana-smoking participants were carefully screened to exclude individuals with obvious respiratory disease, thereby tending to minimize the presence of respiratory symptoms in the marijuana-smoking group.

A more damaging case against cannabis was made by Tennant (1971) and Henderson (1972) and their colleagues from their observations in young U.S. servicemen in West Germany who smoked more than 50 grams of hashish per month and sought medical attention because of respiratory symptoms. Among these hashish smokers the authors found frequent, severe nose and throat inflammation, as well as X-ray findings of sinusitis and clinical and functional evidence of significant lower airway disease (bronchitis and asthma). Several of these patients with chronic cough underwent bronchoscopy and biopsy of the epithelial lining of the posterior wall of the trachea. On microscopic examination of these biopsy specimens, extensive cellular abnormalities were noted, including loss of cilia, basal epithelial cell proliferation and atypical cells, findings which have been associated with the later development of lung cancer and COPD (chronic obstructive pulmonary disease). Although most of these men also smoked tobacco along with hashish, they were in an age group in which such extensive microscopic abnormalities involving the larger airways are not generally noted among smokers of tobacco alone. In a follow-up study by the

same investigators (Tennant et al., 1980), bronchoscopy was performed in an additional group of 30 heavy hashish smokers (25-150 grams/month for 3–24 months) of whom seven did not smoke tobacco. In addition, three non-smoking control subjects and three tobacco smokers (average of 1.6 packs per day for 11.3 years) who did not smoke hashish, also underwent bronchoscopy. All of the smokers of both hashish and tobacco showed extensive abnormalities in their tracheal biopsies similar to those previously noted, whereas these abnormalities were found in only two of seven individuals who smoked hashish alone, in one of the three subjects who smoked tobacco alone and in none of the non-smokers. These findings suggest, therefore, that combined use of cannabis and tobacco may be more harmful than the use of either substance alone.

In contrast to the above observations, a Greek study (Boulougouris et al., 1976) failed to find a higher prevalence of bronchitis among 44 chronic hashish users (who also smoked tobacco) compared to tobacco-smoking controls, although cough and throat irritation were common complaints among the hashish smokers. In this study, tracheal biopsies were not obtained. The discrepancy between these findings and those in the U.S. soldiers could be due to differences in the design of the two studies: in the Greek study, subject selection forced exclusion of those with incapacitating illness, whereas the American study was conducted among individuals seeking treatment for respiratory complaints, thereby favoring the inclusion of those with more severe respiratory diseases. It is also possible that the discrepant results of these two studies were due to differences in the smoking techniques employed by the Greek and American hashish users: the rapid, deep and prolonged inhalation technique favored by Americans might lead to greater deposition of irritating particulates in the larger airways and greater exposure of the peripheral airways to the more deeply penetrating and longer-retained gaseous irritants in the smoke.

There are no data from human studies concerning the risk of death from lung cancer in relation to marijuana smoking. However, the presence of known carcinogens in marijuana smoke and the findings in the central airways of heavy hashish smokers of microscopic abnormalities that have been correlated with the subsequent development of lung cancer in long-term tobacco smokers raises the strong possibility that chronic heavy users of marijuana and hashish may be predisposed to the development of lung cancer, particularly if they also smoke tobacco. Although not a single case of lung cancer has yet been attributed to chronic marijuana smoking in this country, the possibility cannot be ignored that chronic, heavy marijuana smoking, like chronic tobacco smoking, may be a risk factor for the development of lung cancer and that the risks of developing lung cancer as the result of combined marijuana and tobacco smoking could be additive or even synergistic. With regard to the relative carcinogenic effects of marijuana and tobacco, one might conjecture that tobacco smoking poses a greater risk for the development of lung cancer than does marijuana smoking simply because many more tobacco cigarettes are generally smoked per day than marijuana joints. On the other hand, differences in the amounts of carcinogenic material deposited at certain sites in the airways (possibly related to different techniques of smoking) could magnify the carcinogenic potential of marijuana smoking compared with tobacco smoking.

Since marijuana smoking, at least in Asia and the Near East, is an older custom than tobacco smoking, it might be argued that if a real causal relationship between the development of lung cancer (and COPD) and marijuana smoking existed, it should have become apparent by now, as it has for tobacco. However, we must consider that the serious health consequences of tobacco were not well documented until the 1950s and 1960s, some four decades after the custom of regular daily smoking of moderate to heavy quantities of tobacco cigarettes was adopted by a substantial fraction of the population of the developed countries of the Western world where health is fairly closely monitored. Similarly, heavy consumption of marijuana on a regular daily basis is still relatively infrequent in our society and of more recent occurrence (past 10-20 years) than is the case with tobacco (past 60-65 years). Therefore, with respect to an appreciation of its health effects, marijuana may now be at the equivalent stage to that of tobacco cigarette smoking in the 1920s and 1930s, when the risks of tobacco smoking were not recognized due to the latency period before illness appears and the failure of diagnosticians to make the connection.

Extensive pulmonary macrophage infiltration of the lung has been documented in animals and by biopsy in humans. A recent investigation described autopsies of 13 known marijuana smokers who died suddenly from trauma. Morris (1985) reports moderate to severe infiltration of the pulmonary alveolar spaces with pigmented macrophages leading to a fibrous tissue response and ulceration. The pigmentation was due to deeply inhaled marijuana smoke. Tobacco smokers of similar age (15-41 years) show little macrophage infiltration, and they do not develop the fibrosis and inflammatory changes until after many years of smoking. This speaks for the development of chronic obstructive pulmonary disease in heavy users. One heavy marijuana smoker, 28 years old, had dyspnea on exertion due to alveoli completely filled with macrophages.

Central Nervous System

Brain wave changes from cannabis generally consist of an increase and slowing of alpha waves. This is consistent with a state of drowsiness. Although scalp electroencephalogram (EEG) records show minimal alterations, electrodes implanted in deep brain structures like the septum, a center for emotionality, obtain marked changes in electrical activity (Heath et al., 1979). In monkeys these abnormal tracings occur after smoking the equivalent of three marijuana cigarettes a day for three months and may persist for many months after discontinuance of the drug. Heath et al. (1979) reported ultra-structural changes in the septal area when monkeys received the equivalent of two cigarettes a day for six months, were withdrawn from marijuana for six months, and then autopsied. Controls did not manifest the alterations which included widening of the synaptic cleft (the space between nerve cells), clumping of the synaptic vesicles and other microscopic deviations from normal structure.

In an earlier study Campbell et al. (1971) reported cerebral atrophy in a series of young cannabis users, employing pneumoencephalography to obtain cerebral ventricular size. These subjects had used other drugs and alcohol so that the findings could not be considered definitive. In addition, two investigations utilizing computerized tomography (CT) scans could not confirm Campbell's work (Co et al., 1977; Keuhnle et al., 1977).

More recently, McGahan et al. (1984) using high resolution computerized tomography scanned three groups of monkeys. One was a control group, a second was given 2.4 mg/kg of the tetrahydrocannabinol (THC) a day by mouth for two to ten months, and a third group received a similar daily dose over a five-year period. The dosage was considered the equivalent of smoking one joint a day. The groups receiving THC were not studied until a year after discontinuing the drug. Statistically significant ventricle enlargement in the frontal and caudate areas of the brain in the five-year treated monkeys as compared to the control and short-term THC groups were found. This finding suggests that the frontal and caudate portions of the brain can atrophy after long-term administration of THC in amounts relevant to human exposure as measured by CT.

The findings revealed by the depth EEG, and the ultra-structural changes found in septal areas, are suggestive that long-term, heavy use of marijuana or THC may produce microscopic changes. The possibility of macroscopic changes in the form of cerebral atrophy remains open, and additional imaging studies must be done.

Weller and Halikas (1985) re-examined 97 regular marijuana users and 50 controls six to seven years after an original psychiatric evaluation. The members of the experimental group were not particularly heavy users with only 12% using the drug almost daily. High levels of depression and alcohol abuse were present in both groups during both examinations. The only impressive difference was an increase in diagnosable antisocial personality disorders in the marijuana group from 6% in the initial evaluation to 21% in the follow-up. The figures for the control group were 0% initially and 2% at follow-up. The authors make no attempt to explain the difference.

The possibility that cannabis interfered with antipsychotic medication was raised by Knudsen and Vilmar (1984). Ten schizophrenics controlled by depot antipsychotic drugs were acutely impaired functionally following cannabis use. The authors postulate that the cannabinoids may have an antagonistic effect upon antipsychotic medication.

Psychomotor Functioning. A wide range of intellectual performance impairment due to marijuana intoxication is known. Cognitive tasks, such as digit symbol substitution, complex reaction time, recent memory and serial subtractions, are all performed with an increased error rate as compared to the sober state. These abilities are all generally recognized to be necessary to perform skilled tasks. Marijuana interferes with the transfer of information from immediate to short-term storage. Less demanding tasks such as simple reaction time are performed as well as during the non-drug condition. A major unresolved question is whether long-term use produces irreversible effects.

In order to determine the role of alcohol and other drugs in fatal auto crashes, blood samples from deceased males between 15 and 34 years of age were obtained in four California counties. Driver responsibility for each fatal accident was determined. The blood was analyzed for 23 drugs or drug groups. The sample consisted of 440 drivers; slightly more than half were killed in single-vehicle accidents. In all, 88% of the 440 drivers were considered responsible for the crash. Only 19% had no drugs present in their blood; 81% were found to have one or more drugs present (Williams et al., 1985). Alcohol was detected in 70% of the drivers, cannabinoids in 37%, cocaine in 11%, diazepam and phencyclidine in 4%, and others in 3% or less. Fifty-two percent of those who had alcohol present, had blood alcohol concentrations (BACs) of 0.1 to 0.19%, and 30% had BACs of .2% or more. THC or its acid

metabolite were present in 0.2 to over 50 ng/ml concentrations in blood. THC was found alone in 12%, in combination with alcohol in 81%, and with other drugs in 7%.

Although alcohol is the prime cause of automotive accidents, marijuana and cocaine are currently being found frequently enough to constitute potentially significant problems. It is established that marijuana and alcohol have additive effects upon driving skills. Since marijuana metabolites were found in more than a third of the drivers, impairment due to marijuana is contributing to the problem.

The pure marijuana user is hard to find. When a small group of such individuals is identified in outpatient treatment centers, they are either quite young, or they turn out to be multiple drug users who have a primary complaint relating to their marijuana usage (Wish and Deren, 1985). Therefore, heavy marijuana users are either in a state of transition toward the use of other mind altering substances, or they are already multiple drug abusers who happen to believe that marijuana is producing difficulties that require treatment. The concerns are related to panicky feelings, especially about changes in time sense, difficulty in sensing how other people were responding to the individual, fear of losing control or inability to stop using.

Performance decrements are another source of complaints by some marijuana smokers. Low energy levels, impaired school or job performance and loss of interest in other activities are mentioned in surveys of high school seniors and others (Johnston, et al. 1986).

Weller et al. (1984) compared alcohol and marijuana use in 97 regular alcohol and marijuana users, a very common form of multiple drug use. Alcohol use preceded marijuana use by three years. Both drugs were used in social situations with about 10% meeting the criteria for alcoholism and the same number for marijuana abuse. Significant problems associated with alcohol included blackouts (20%) and self reports of overuse (27%). The significant complaints about marijuana were panic reactions (22%) and feeling addicted (14%). Of interest was the fact that only 6% of those interviewed reported traffic arrests while drinking compared to 15% while using marijuana.

A chronic cannabis syndrome sometimes follows heavy daily use, particularly in adolescents and young adults. Since it is so variable in presentation and importantly influenced by magnitude and premorbid psychopathology, its existence remains somewhat controversial. In some persons the drug is used as self-medication for a variety of dysphoric states. Chronic cannabis syndrome consists of loss of energy, reduced levels of drive and motivation, apathy, some degree of depression and agitation, and a withdrawal from previous interests. Lethargy, loss of ambition, and loss of goal directedness persist during the interval between marijuana intoxications. After months of abstinence, the anergic condition is reversed, although some clinicians insist that they have encountered permanent brain dysfunction.

In a five-year follow-up of regular marijuana users, it was found that the continued use of the drug was associated with a decrease in certain pleasurable effects (Weller & Halikas, 1984). Users who had earlier reported positive feelings of relaxation, peacefulness, enhanced sensitivity, floating sensations, self-confidence, subjective impressions of heightened mental power, and other sought-after effects now said that these effects had significantly diminished. The undesirable aspects of the experience, however, persisted essentially unchanged. It should not be assumed that the decreased pleasure over time leads to a discontinuance of cannabis use. The persistence of a well established conditioned response without particular positive rewards is also seen with regular use of other drugs such as cocaine, tobacco, phencyclidine, and heroin.

The effects of cannabis on pre-existing serious psychiatric conditions such as schizophrenia have been reviewed by J.C. Negrete (Arif & Archibald, 1981). Sufficient clinical experience is available to recommend abstinence from marijuana for schizophrenics in remission because of the possibility of precipitating a relapse. Although infrequent, other psychiatric problems can emerge. Acute anxiety and panic states from use of the drug are known, especially in persons who have never used marijuana before. Acute paranoid states will occur at times in experienced smokers who have previously used the drug without untoward reactions. Paranoid thinking tends to reverse itself upon discontinuance of the drug.

A shift in cerebral hemispheric dominance was postulated because of the dream-like, imagistic, nonlogical type of cognitive patterns induced by marijuana. It was speculated that the shift was determined to be caused by impaired left hemispheric functioning, with no alteration in right hemispheric performance (Hecht, 1980).

Learning ability during marijuana intoxication is diminished because of the perceptual changes and the fact that immediate recall is intermittently impaired. In addition, the lack of motivation to learn and the attenuation of logical thinking abilities make the acquisition of new information difficult. The incapacity to order sequences of events in time (temporal disorganization) (Tinklenberg et al., 1970), and the lack of rehearsal time associated with episodes of marijuana intoxication, tend to retard learning.

Gonads

It is now generally believed that the effects of cannabinoids on the hormones that modulate the reproductive process originate within the brain by changes in neurotransmitters like dopamine, norepinephrine and serotonin. These amines alter the secretion of the releasing hormone (Tyrey, 1984). A principal site of action of THC is in the hypothalamus where the gonadotropin releasing hormone is suppressed, which in turn inhibits the secretion of leutinizing hormone (LH), follicle stimulating hormone (SH) and prolactin in the pituitary (Smith & Asch, 1984). In turn these changes induce decreases in the female sex hormones, estrogen and progesterone, interfering with ovulation and other hormone-related functions. With discontinuation of cannabis use these effects are reversible. After chronic administration of the drug, tolerance to the reproductive effects of THC is observed. Therefore, the disruptive effects of the THC upon the non-human primate's reproductive functioning is only initially impaired. Its impact on human females requires further study.

Regular marijuana use during at least two phases of development can be detrimental: during fetal existence and during adolescence. The fetal risks will be discussed later. The endocrine events associated with puberty are strongly dependent upon a properly functioning hypothalamic-pituitary axis.

As indicated, many of the endocrine effects caused by the chronic treatment of animals with THC are reversible or demonstrate tolerance development. Still, many questions remain regarding the long-term consequences of use, for example, sperm formation, psychosexual maturation and sex organ function. Until these and other issues are resolved, it is questionable whether marijuana should be consumed by adolescents or males with marginal fertility (Harclerode, 1984).

Immune System

Although additional information regarding the reduction of immune responsibility has become available, the evidence that marijuana smoking in humans decreases resistance to infections remains inconclusive. The question is of particular importance since THC is used as a treatment for cancer chemotherapy side effects. The cancer chemotherapeutic chemicals, themselves, are severely immunosuppressive, and if THC adds to the depressed immune state, it would not be favorable. Another speculation is the possibility that certain drugs could be cofactors in producing Acquired Immune Deficiency Syndrome (AIDS). Marijuana use is often correlated with AIDS, but whether it contributes to its development is not known.

THC does decrease host resistance to herpes simplex virus, type 2, in the guinea pig. This occurs in a dose-related fashion in amounts equivalent to human consumption (Cabral et al., 1985). THC also appears to inhibit both B- and T-lymphocyte production, especially the former. Other preliminary reports suggest that THC modifies lymphocyte membranes and prostaglandin production *in vitro*. It should be recalled that AIDS is caused by a destruction of T4 lymphocytes. One *in vitro* study has shown that small doses of THC resulted in marked inhibition of macrophage spreading and phagocytosis (Lopez-Cepero et al., in press). If confirmed in animals or humans, a further mechanism of immune inhibition might be established.

Fetal Development

Additional information has accrued relating to the effects of maternal marijuana use upon fetal development. This is a complicated subject with many variables like nutrition; alcohol, tobacco, and other drug use; socioeconomic status; etc., impinging upon fetal health, and these variables must be equalized or controlled. Large numbers of mother/child pairs are necessary if infrequently occurring disorders are to be studied.

Three studies have examined samples of sufficient size to adequately parcel out the confounding effect. Hingston et al. (1982) studied 1,690 mother/child pairs. Marijuana in varying amounts was used by 234 mothers during the pregnancy. Marijuana use was found to be associated with lower infant birth weight and length compared to non-users. Women who used marijuana less than three times a week delivered infants who averaged 95 grams less, and those who used more than three times a week delivered babies 139 grams less than the non-using group. Maternal marijuana use was the strongest independent predictor of whether the infant had features compatible with the fetal *alcohol* syndrome (FAS). It was a better predictor of the FAS than alcohol use.

Gibson et al. (1983) sampled 7,301 births for abnormal infant characteristics. Maternal marijuana users were significantly more likely to deliver premature infants with low birth weight. The relationship of marijuana use to perinatal death did not achieve statistical significance, but it was suggestive (p=.12).

The largest study to date is that of Linn et al. (1983). Of 17,326 women who gave birth at the Boston Hospital for Women, 12,718 were interviewed to determine the impact of marijuana and other risk factors on the newborn. Of the 10 independent variables analyzed (which included tobacco and alcohol), marijuana use was the most highly predictive of a congenital malformation.

Hingston et al. (1984) noted that tobacco and marijuana smoking, alcohol and other drug abuse all tend to occur frequently in the same women. Therefore, some of the adverse consequences on fetal development attributed to maternal drinking or smoking may be due to an interaction with marijuana and other psychochemicals. It may be that when a number of these toxic substances are consumed together, their toxic effects on the fetus are additive.

From Downstate Medical Center in Brooklyn, Qazi et al. (1985) reported on five infants of mothers who had smoked two to 14 joints of marijuana a day prior to and during pregnancy. All denied the intake of alcohol or other psychoactive drugs except for one who had consumed a pint of rum a week. Three women smoked a pack or less of cigarettes a day during pregnancy. Each infant had a low birth weight, small head circumference, tremors at birth, abnormal epicanthic folds, posteriorly rotated ears, a long philtrum (the groove on the upper lip), a high arched palate and abnormal palm creases—all stigmata of the FAS. Why do not all heavy marijuana smoking pregnant women have abnormal offspring? Morishima's work (1984) indicates that about 5% of ova are damaged by THC exposure. It may be that a selective vulnerability to injury is present even in the same tissue.

Gross malformations in human infants due to prenatal exposure to cannabis are not yet completely proven. In mice, major malformations occur following exposure to THC, cannabinol and cannabidiol. Mice also have an increased fetal death following maternal cannabinoid administration. Prenatal effects of cannabinoids reliably decrease birth weight in most animal species. When factors like drug-related maternal malnutrition and the residual effects of cannabinoids during the nursing period are eliminated, the fetal weight loss is not large (Abel, 1985).

Infant rats given THC show damage to the hypothalamic cells that produce the gonadotropic releasing hormone. It is possible that this change is irreversible. Amounts of THC equivalent to 2.5 joints a day disrupt the processing of high energy sugars in the testes of young adult male rats.

Cannabinoid levels were found to be 2.5-6 times higher in maternal plasma than in umbilical cord plasma at time of delivery. Although the cannabinoids are certainly found in the human fetus, a partial protection may exist (Blackard & Tennes, 1984). In another investigation (Tennes, 1984), no particular effects upon the newborn were found except a decrease in length and an increase in male infants delivered in the marijuana group.

Fried (1985) found that newborn nervous system alterations in regular maternal marijuana users apparently are not manifested by poorer performance on cognitive and motor tests at one-and-one-half to two years of age. Whether this means that neurological disturbances present at birth are transient, or whether the tests used at one-and-one-half to two years of age have a decreased sensitivity, is unknown.

CONCLUSION

It is reasonable to conclude, as the Institute of Medicine report (1981) did that "what little we know for certain about the effects of marijuana on human health—and all we have reason to suspect—justifies serious national concern."

The following statements about the long-term effects of cannabis can be made.

1. Protracted use causes inflammatory changes of the upper airway and appears to play a role in chronic obstructive lung disease. The question of the carcinogenicity of marijuana must await further study.

2. An amotivational syndrome, especially among adolescents and young adults, is quite well established clinically. Whether chronic usage impairs psychomotor skills during the unintoxicated period has hardly been studied. Permanent macroscopic brain changes cannot be ruled out at this point. People with psychotic states, active or in remission, may do poorly with this drug.

3. The reproductive effects of marijuana are not yet firmly established, but indications of decreases in estrogen and follicle stimulating hormone are frequently reported. Testosterone levels in animal and some human studies show a decrement in most studies.

4. Although numerous reports of decreased immune responsivity are available *in vitro* and in small animal studies, the clinical significance of these findings remains to be established.

5. The teratogenicity of cannabis seems likely but its incidence and exact manifestations remain to be worked out in further investigations.

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The addictive potential of cannabis*

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ABSTRACT

The author reviews the literature on the dependence potential of cannabis. Case studies and experiments of tolerance to cannabis as well as psychological and physical dependence on cannabis are presented in man and in laboratory animals. Some effects common to both species are also recorded. Although the addictive potential of cannabis is often compared with the addictive potential of alcohol and tobacco, the author concludes that the characteristics of cannabis tolerance are similar to those of opiate dependence.

Introduction

Although cannabis as a psychoactive drug has been used by man for many centuries, its addictive potential has only recently been recognized. Eddy and others in 1965 described the main features of dependence for several drug types and their views on the characteristics of the cannabis-type dependence found general acceptance [1].

However, since 1965, new scientific knowledge has been acquired. The identification of Δ-9-tetrahydrocannabinol (Δ-9-THC) as the main active substance of cannabis and its synthesis [2, 3] contributed enormously to knowledge on the pharmacology of cannabis. Moreover, an explosive increase in cannabis consumption has stimulated laboratory, clinical and epidemiological research on cannabis in many countries.

The author of this paper reviewed tolerance to and dependence on cannabis some years ago [4], and this paper presents some additional information.

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Tolerance to cannabis

For a long time it was considered that cannabis did not produce tolerance. Lemberger and others in 1971, after injecting radioactively labelled (C^{14})-Δ-9-THC (0.5 mg) intravenously to chronic marijuana smokers and naive subjects, stated that non-smokers did not indicate any pharmacological effect. In contrast, all of the long-term marijuana smokers reported effects that lasted as long as 90 minutes [5]. They interpreted the results as chronic marijuana users having "reverse tolerance".

At present it is considered that so-called "reverse tolerance" is a misinterpretation [6]. However, there is evidence supporting the view that tolerance develops to many effects of cannabis both in laboratory animals and in man. The diverse effects of cannabis have been described in many species. Ataxia in the dog, ptosis of eyelids in the monkey and tachycardia in man are the most characteristic effects of cannabis use which lose their intensity after repeated administration indicating tolerance development. In most animal and human studies related to tolerance, marijuana (extract or smoke) or Δ-9-THC has generally been used. However, some investigators have also used other pharmacologically active cannabinoids such as DMPH (a dimethylheptyl homologue of Δ-6a(10a)-THC, Δ-8-THC, 11-OH-Δ-9-THC) and a few synthetic derivatives. In the following pages the term "cannabis" will, in addition to plant material, include all active cannabinoids.

Psychological dependence on cannabis

The indication of psychological dependence to any substance in man is a compulsive need to take the substance, or intensive craving for it. As is the case for many substances of abuse, psychological dependence is the basis of cannabis abuse. The continued self-administration of drugs by animals after a period of withdrawal provides evidence of psychological dependence [7]. In this context, in 1971, Deneau and Kaymakçalan [8] succeeded in producing self-administration of Δ-9-THC in monkeys. In 1972 Kaymakçalan, using cocaine, obtained self-administration of this substance in monkeys [9]. The results of these studies have been summarized in an earlier issue of the *Bulletin on Narcotics* [4].

Pickens and others in 1973 reported intravenous self-administration of Δ-9-THC in two monkeys which had previously been self-administering phencyclidine (PCP). After the substitution of Δ-9-THC, the animals continued to self-administer this latter drug [10]. In addition to intravenous self-injection, the same authors produced self-administration of cannabis smoke by inhalation, training two monkeys to smoke hashish from a tube [10].

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Van Ree and others, as well as Takahashi and Singer, were able to induce self-administration of Δ-9-THC in the rat [11, 12]. The former authors produced this effect by intravenous injection following a four-day forced injection period. At the highest dose level (0.3 mg/kg/injection) only 40 per cent of animals initiated self-administration of Δ-9-THC [11]. This percentage and the drug intake were low in comparison with self-administration of amphetamine and narcotics in the rat.

Physical dependence on cannabis

Physical dependence on cannabis in laboratory animals

Although there are reports of CNS hyper-excitability [13, 14] or increased aggressiveness in mice after abrupt withdrawal of Δ-9-THC [15], the most conclusive evidence on the physical dependence of animals to cannabis is obtained from studies of rats and monkeys.

Deneau and Kaymakçalan [8] and Kaymakçalan [9] in experiments in self-administration of Δ-9-THC in monkeys observed a typical abstinence syndrome which was not dissimilar from the opiate abstinence syndrome.

Other investigators also observed withdrawal changes in monkeys receiving either Δ-9-THC or cannabis smoke. Stadnicki and others reported the effects on behaviour and EEG in three rhesus monkeys following chronic oral administration of marijuana extract. The two monkeys that became tolerant after 50 days' treatment with Δ-9-THC (37.5 mg/kg) responded to termination of treatment with withdrawal signs manifested by increased aggressiveness. One of the two exhibited hallucinations and a period of increased EEG desynchronization [16]. Heath studied the effects of cannabis smoke on the EEG patterns taken from electrodes implanted in different parts of the brain of monkeys. After three months' exposure to cannabis there were some EEG changes which ameliorated following administration of an increased amount of cannabis [17]. Snyder and others have trained three monkeys to press a lever on a special schedule for liquid reinforcement. Following a stable baseline performance, two monkeys received 2 mg/kg of Δ-9-THC orally every third day for 90 days, with a placebo administered on intervening days. The third animal received a placebo throughout testing. When the drug was discontinued there was an abstinence effect in the drug-monkeys characterized by a change in performance [18].

Recent studies indicate that the abstinence syndrome of THC-treated rats consists of many signs and symptoms. However, some earlier works suggested the presence of some cannabis abstinence signs in rats. For example, Davis and others injected rats daily with 25 mg/kg Δ-9-THC subcutaneously for 20 days. During the immediate post-drug period a slight but statistically significant elevation of activity occurred on the second day [19]. Similarly, Pirch and others recorded electrocorticograms of rats by

implanted electrodes. During the period of chronic oral administration of marijuana extract distillate to the rats, animals were given 20 mg/kg or 40 mg/kg Δ-9-THC for 9 – 13 days. Upon termination of chronic treatment, a "rebound" increase in integrated ECoG voltage was observed. This "rebound" was maximal on the second and third day following the last dose [20]. The same group of investigators confirmed their earlier reports in a subsequent study increasing the dose of Δ-9-THC to 100 mg/kg in two animals [21]. Another cannabis withdrawal sign in the rat was an increase in grooming which was reported by Sjöden. This author studied the effects of long-term administration and withdrawal of THC (5 mg/kg Δ-8-THC or 2.5 mg/kg Δ-9-THC) on open-field behaviour in rats. During the two-week injection period a depressant effect of both isomers was noted on ambulation, rearing, grooming and latency. At drug withdrawal most open-field measures slowly returned to control levels, whereas the rate of grooming showed a definite increase [22].

Hirschhorn and Rosecrans in 1977 reported that Naloxone precipitated a narcotic-like withdrawal syndrome in rats treated for five weeks with increasing doses of Δ-9-THC, the highest dose being 32 mg/kg given during the last three weeks. The main withdrawal symptoms were diarrhoea, teeth chattering, wet-dog shakes, salivation and ptosis [23]. Kaymakçalan and others in 1977 confirmed the above and showed that abrupt withdrawal of chronic injections of Δ-9-THC can cause an abstinence syndrome. They injected 10 rats subcutaneously with Δ-9-THC daily for five weeks in increasing doses. During the last three weeks the rats received 40 mg/kg Δ-9-THC at each administration. Ten control rats received the same amount of the vehicle by the same route for the same period. The administration of Naloxone on the 22nd and 31st days and the termination of drug administration on the 35th day caused an opiate-like abstinence syndrome [24]. The most common signs of abstinence in THC-treated animals were ptosis, teeth chattering, piloerection, defecation, urination, complete palpebral closure, dyspnea and grooming. Other signs observed in less than 50 per cent of the animals were chewing, tremors on the face, rearing, abnormal posture, yawning, escape behaviour, ear blanching, eating of objects, wet-dog shakes, jumping, biting of fingers and sniffing. During abstinence, increasing locomotor activity was recorded in THC-treated animals by an activity-meter. Both abstinence scores and increased motility exhibited a peak at the 48th hour of withdrawal [24].

Taylor and Fennessy reported a chlorimipramine-induced withdrawal syndrome in the rat after chronic treatment with Δ-9-THC [25]. Chlorimipramine, which is a potent inhibitor of serotonin uptake, may antagonize some effects of Δ-9-THC in the rat. Therefore, precipitation of an abstinence syndrome with this chemical in Δ-9-THC-treated rats is considered somewhat similar to the action of Naloxone in opiate-dependent animals. The rats received increasing doses of intravenous Δ-9-THC twice daily for 10 days. The highest dose was 120 mg/kg, twice a day administered

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days 6 – 10. On day 11, some of the rats were injected intraperitoneally with 5 mg/kg chlorimipramine. Quantifiable changes in behaviour consisted of writhing, wet-dog shakes, jumping and backward kicking of the hind legs. Other symptoms included front paw tremor, ptosis, chewing movements, excessive grooming, yawning, squealing, ataxia, unsteadiness in gait and sitting up on the posterior for long periods. Reporting these findings, on another occasion, the authors stated that "Δ-9-THC is capable of inducing a state of physical dependence" [26].

Physical dependence on cannabis in man

A close survey of the literature reveals that several authors have described cannabis withdrawal symptoms in man. Most publications on this subject, with a few exceptions [27 – 29], appeared after 1970.

Observations on abstinence symptoms in man refer mainly to those countries where potent forms of cannabis (ganja, dagga, hashish) are available. However, even in the United States of America where until recently weak preparations of cannabis were being used, a detailed description of marijuana withdrawal symptoms was reported by Marcovitz and Myers in 1944 based on 35 "confirmed marihuana addicts" who were admitted to a military hospital [27]. In the same decade, Fraser in India reported on soldiers who had been ganja smokers for some years and after joining the army exhibited severe withdrawal symptoms due to difficulty in obtaining cannabis [29]. Some recent studies from India also confirmed the dependence liability of cannabis. Chopra and Jandu, in their investigation of 275 chronic cannabis users, found that a large percentage of heavy users developed physical dependence [30]. In a research project sponsored by the World Health Organization (WHO) and carried out by the Department of Forensic Medicine of Banaras Hindu University in 1976, the long-term effects of cannabis were studied in 50 cannabis users, and a comparison was made with the data obtained from 25 non-user controls. It was found that the majority of users (98 per cent) felt uncomfortable if they were unable to obtain their daily supply or dose of cannabis and in addition to a strong craving for the drug (86 per cent), the majority also showed mental irritability and feelings of anxiety (74 per cent), as well as profound lethargy and physical weakness (60 per cent). As many as 70 per cent of the users reported some kind of physical discomfort in the absence of the drug [31].

Middle Eastern and east Mediterranean countries are historically known to have a relative high hashish consumption. Kielholz and Ladewig observed withdrawal symptoms which lasted three to seven days in three young chronic hashish smokers who came to Switzerland from the Middle East [32]. According to Miras, writing on chronic hashish smokers in Greece, "there is definitely a dependence risk, although much less serious than with opiates" [33].

In South Africa also, cannabis dependence has been reported. In five young South Africans, Bensusan reported marijuana withdrawal symptoms which persisted for one to three days. The disappearance of withdrawal symptoms coincided with the possibility of obtaining cannabis [34]. The same author observed two other similar cases of acute withdrawal symptoms from cannabis smoking. Morley and others collected information on the subjective effects of cannabis from 150 individuals who had used it on at least five occasions. Fourteen reported withdrawal symptoms [35]. Levin, in a paper delivered at the First South African International Conference on Alcoholism and Drug Dependence, reported that cannabis use elicited psychiatric complications in 33 per cent of 137 cannabis users. In 5 per cent of the total group, these complications were related to drug withdrawal [36]. Again, in South Africa, Schweitzer and Levin described a case of acute brain syndrome due to cannabis withdrawal in a patient who had been hospitalized for multiple fractures [37].

Current epidemics of marijuana use among young persons have redirected the attention of psychiatrists, family physicians and paediatricians to the possibility of physical dependence on marijuana. Teitel (1977) reported three cases of manic-depressive illness which followed withdrawal of marijuana after prolonged use [38]. Manatt indicated that heavy users of cannabis experienced a mild flu-like withdrawal syndrome [39]. Lantner reported that marijuana develops tolerance rapidly, is physically addictive and many smokers report withdrawal symptoms [40].

In addition to the withdrawal symptoms in cannabis users described above, some experiments have been carried out using cannabinoids on volunteers. Williams and others in 1946 applied Parahexyl (a synthetic cannabinoid having marijuana-like effects and also known as Synhexyl) to six patients between the ages of 26 and 33 who were former marijuana smokers. The drug was given in self-chosen doses at self-chosen intervals for a period of 26 to 31 days. The daily dose ranged from 60 to 2,400 mg and was taken orally in one to eight individual doses. On the third day, after abrupt discontinuation of the drug, most patients exhibited some symptoms of withdrawal [28].

In other experimental studies the main active component of cannabis, Δ-9-THC, has been used. Some investigators were interested in the withdrawal changes in sleep patterns and in the EEG of volunteers after Δ-9-THC administration. Freeman, using all-night polygraphic recordings, studied the effect of cannabis on the sleep patterns of two young women. At night they took 20 mg/kg Δ-9-THC in fruit juice. It was noticed that physiologic withdrawal effects occurred after only four nights of Δ-9-THC use, and the author concluded that these findings support the view that marijuana does cause physical dependence [41]. In a subsequent study, Freeman administered 20 mg Δ-9-THC orally at bedtime to five volunteers, who slept for 8 – 15 consecutive nights in the laboratory. He monitored EEG, chin EMG and eye movements, and noted that Δ-9-THC decreased the REM phase of

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sleep. As in the first study, abrupt withdrawal of the drug after four to six consecutive nights of use produced mild insomnia [42]. In another study, Freeman and Al-Marashi (1977) followed the EEG patterns in sleep of two volunteers who spent 30 consecutive nights in the laboratory. The patients received 20 mg Δ-9-THC orally for 12 nights on days 7 to 18. During the first five withdrawal nights sleep latency increased more than twofold. Also, during the withdrawal period, there were a greater number of eye movements during REM sleep and a large decrease in slow wave sleep. Many changes in polygraphic sleep patterns persisted for at least 12 days following discontinuation of Δ-9-THC [43]. Feinberg and others studied the influence of orally administered Δ-9-THC on the sleep patterns of seven male volunteers. During withdrawal, total sleep time was significantly reduced, and this change was entirely due to increase in sleep latency. In addition, both REM sleep and eye movements increased; the rebound effect being greater for eye movement [44].

The work of Jones and others, carried out by oral administration of Δ-9-THC to volunteers, is the most convincing evidence that cannabis can produce physical dependence in man. The volunteers, after a gradual increase in dose, received a fixed dose of 180 – 210 mg Δ-9-THC per day for 11 to 21 days, and were then abruptly switched to a placebo for 5 – 9 days. During this period all subjects showed a variety of abstinence signs and symptoms [45]. The main objection to this work was the amount of the drug given daily to the volunteers. The term "elephant doses" has been used for this regimen [46]. However, considering that in some parts of the world daily doses of 240 – 360 mg of Δ-9-THC are not unusual, daily amounts of 180 – 210 mg may represent a human dose [47].

Some symptoms of cannabis withdrawal syndromes common to man and animals

Signs and symptoms	*Man*	*Monkey*	*Rat*
Hyperactivity	+	+	+
Increased excitability	+	+	–
Aggressiveness	+	+	–
Tremors	+	+	+
EEG changes	+	+	+
Hallucinations	+	+	?
Photophobia or palpebral closure	+	+	+
Yawning	+	+	+
Salivation	+	–	+
Anorexia	+	+	–
Diarrhoea	+	–	+
Piloerection	–	+	+
Abnormal posture	–	+	+
Licking or biting of fingers	–	+	+
Eating unusual things	–	+	+
Masturbation	+	+	?
Craving for cannabis	+	+	?

+ = present; – = absent or not checked; ? = difficult to assess

Nevertheless, the wealth of findings leaves little doubt about the existence of a cannabis withdrawal syndrome, confirming the possibility of physical dependence in man. The most frequently observed cannabis abstinence symptoms in man are excitation, irritability, agitation, restlessness, tremors or tremulousness, anxiety, depression or suicidal tendency, insomnia or sleep disturbances, sweating, abdominal distress, nausea, anorexia or decreased appetite, general malaise and muscular aches.

It is interesting to note that some of the cannabis withdrawal symptoms in man are also observed in laboratory animals (see table).

Discussion and conclusion

The demonstration of tolerance and of the dependence-producing properties of cannabis may have important academic and practical implications. In experimental animals the initiation, degree and duration of cannabis tolerance show great similarities to the characteristics of opiate dependence. There are also similarities between cannabis and opiate withdrawal symptoms in the monkey and the rat. Cannabis can potentiate some of the effects of morphine and there is cross-tolerance between the two substances. Furthermore, several common pharmacologic actions are induced by cannabis and opiates [48, 49]. The addictive potential of cannabis is often compared with the addictive potential of alcohol and tobacco. It seems that the development of dependence to any of these three most widely abused substances is related to such factors as dose (potency), frequency, duration of use as well as some possible individual factors. However, the pharmacokinetic and pharmacologic properties of the three substances are very different. Whereas alcohol and nicotine are easily destroyed or eliminated from the body, active cannabinoids remain in the tissues for a long time. In addition, the spectrum of pharmacologic effects of cannabis is so large that they cannot be compared with the effects of alcohol or nicotine.

In the future, if the availability of potent forms of cannabis becomes widespread, dependence on cannabis may create more serious problems to society.

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CHAPTER 168

Marijuana

Jack H. Mendelson

Marijuana smoking is the most frequent form of illicit drug use in America. Although there is evidence that a gradual decline has occurred in marijuana usage by young adults in the United States from 1975 through 1984 (53), it is estimated that at least one in every 20 high school seniors smokes marijuana on a daily basis. The health benefits associated with a decline in the age of onset of marijuana smoking (100) may be offset by an increase in the potency of marijuana available in many locations in the United States (109,113). The importance of marijuana use in the causation of derangements in health, psychological status, and social function remains a subject of controversy. In this chapter we review and attempt to evaluate some pertinent biomedical and psychosocial factors associated with marijuana abuse and dependence. Because of space limitations, this review is necessarily selective. However, a number of extensive and excellent critical reviews on the effects of marijuana on biologic and behavioral function are currently available for readers who wish to obtain more detailed information (29,78,113).

CHEMISTRY AND PHARMACOLOGY

An extensive review of the chemistry, pharmacology, and toxicology of cannabis compounds was described by Harris in *Psychopharmacology: A Generation of Progress* published in 1978. Over 400 compounds in addition to the psychoactive agent Δ^9-tetrahydrocannabinol (THC) have been identified in marijuana cigarettes. The usual marijuana cigarette, prepared from the leaves and flowering tops of the plant *Cannabis sativa*, contains 0.5 to 1 g of plant material. The THC concentration in typical marijuana cigarettes may range between 5 and 20 mg, but concentrations as high as 100 mg per cigarette have been detected. Hashish is prepared from concentrated resin of *Cannabis sativa* and contains a THC concentration between 8 and 12% by weight. "Hash oil," a lipid-soluble plant extract, may contain a THC concentration as high as 25 to 60%. "Hash oil" has been added to marijuana cigarettes in order to increase the concentration of THC. During pyrolysis of a marijuana cigarette, over 150 compounds in addition to the THC are present in smoke and fumes.

Following marijuana cigarette smoking, THC is quickly absorbed from the lungs and is then sequestered rapidly from blood into body tissues. The THC is metabolized chiefly in the liver, where it is converted to 11-hydroxy-THC, a psychoactive compound, and more than 20 other metabolites. The THC metabolites are excreted via the feces at relatively slow rates.

Although many investigations of the effects of marijuana smoking on behavior (including determinations of levels of intoxication and the subjective "high") have been reported, it has been difficult to establish good correlations between clinical effects and plasma THC levels (8,34,110–112,118). In general, peak levels of intoxication occur later and persist longer than peak levels of THC in plasma. Undoubtedly, one problem in establishing covariance between behavioral effects and plasma THC levels is the complex pharmacokinetic profile of THC in humans (46). However, recent data indicate that more sophisticated analysis of pharmacologic response and plasma THC levels with compartmental models and phase plots may yield significant correlations (17). Chiang and Barnett (17) have reported that the effect compartment for psychologic high is directly coupled to the central (plasma) compartment. These inves-

tigators concluded that "the effect is directly proportional to mean THC levels from approximately 1 to 4 hr after the start of smoking a marijuana cigarette." When data obtained in previous studies (112) were reanalyzed with the model proposed by Chiang and Barnett, good correlations were obtained between rapid behavioral and physiologic effects after marijuana smoking and plasma THC levels (17).

Delayed physiologic and pathophysiologic effects of marijuana smoking may be caused by accumulation of critical plasma levels of a major metabolite, 11-nor-COOH-THC (9-carboxy-THC) (135). Good correlations have been reported between radioimmunoassay analysis and gas chromatograph–mass spectroscopy analysis of THC and 9-carboxy-THC in plasma obtained from men and women following marijuana smoking (112), and no differences between men and women have been observed with respect to conversion of THC to 9-carboxy-THC (135).

Hunt and Jones have noted that if THC in biological fluids were confined only to blood, 99% of an intravenous dose (and presumably a similar dose administered via inhalation) would be metabolized in less than 30 min (46). However, the swift decline of THC in plasma is associated with a very rapid intake of the drug into tissue compartments. It has been calculated that approximately 70% of the THC in plasma following an i.v. dose rapidly enters the tissue compartment, and 30% is converted to metabolites. Hunt and Jones (46) state that "after approximately 6 hr the rate-limiting step for elimination of unchanged THC is not metabolism as implied by Lemberger et al. (71) but rather is a slow return to plasma of THC sequestered in tissues."

EFFECTS ON BEHAVIOR: SENSORY PROCESSES AND PERCEPTION

Since automobile accidents are a major cause of death and disability in America, marijuana effects on perceptual and sensory functions that are essential for driving are of considerable importance. Early studies (47) showed that heavy marijuana smokers often experienced distortions in the sizes of objects and also had impaired distance perception of objects and their rate of approach. Marijuana smoking reduces accurate detection of peripheral light stimuli as a consequence of impaired ocular motor control (103). Decrements in visual reaction time (104), ocular motor tracking function (4), and color discrimination have also been reported (4). Impairment in auditory function such as auditory reaction time and auditory signal detection occurs after marijuana smoking (102).

A number of investigators have reported a unique marijuana-related aberration of perceptual processes: distortion of time sense (15,36,47,132,137). Impairment of time sense perception following marijuana smoking may not only increase risk for automobile accidents but also contribute to disturbance of ideational states under nondriving conditions (83,98).

There is a strong positive correlation between the dose of marijuana used and degree of driving impairment (60,70,123). The duration of marijuana effects on driving function may persist for over 2 hr (117). Since marijuana smoking impairs driving ability, it is not surprising that the drug also adversely affects a pilot's performance during simulated instrument flying (13,49,50). Moreover, pilot performance has been shown to be impaired as a consequence of marijuana hangover effects. Recent studies have shown that significant impairment in a pilot's function may persist for as long as 24 hr following acute marijuana smoking (141).

COGNITIVE FUNCTION

Marijuana effects on cognitive function are dependent on the dose of marijuana used, the route of administration, plus the demand characteristics of the task such as difficulty, complexity, and familiarity or practice. A significant correlation between dose effects and task difficulty and complexity has been established by a number of investigators (14,115,116,140). Complex cognitive tasks are especially sensitive to marijuana effects (14,116). The acquisition of new information that requires systematic study and learning is also compromised by marijuana use (1,119,126,134). It has also been reported that marijuana use may impair short-term memory function (10,21,22,69,82,121).

MOTIVATION

Perhaps one of the most controversial purported adverse effects of marijuana use is the "amotivational syndrome" (81). Although some investigators have concluded that amotivation and loss of interest in conventional social goals is an indirect concomitant of marijuana use (107), others believe that marijuana directly impairs motivation and achievement (25,27,52,77). A major problem inherent in evaluation of clinical reports of "amotivation" is the reliability and validity of procedures employed to measure motivation.

Several studies have attempted to assess effects of marijuana smoking on motivation to obtain socially desirable goals such as money reinforcement (84,85,88,90,91). These studies indicated that marijuana smoking (including heavy marijuana smoking) did not significantly suppress operant acquisition of either marijuana cigarettes or money. However, the operant task employed in these studies, as well as those utilized by other investigators (99), was relatively easy to perform. Adverse effects of marijuana on personal achievement cannot, at present, be explained by a specific and unique drug effect on motivation.

PSYCHIATRIC DISORDERS

Marijuana-induced intoxication is similar to intoxication caused by ethanol. Marijuana users usually report enhanced mood states following smoking, but there are also reports of anxiety, depersonalization, and dissociation after marijuana smoking (19,47,58,83,107,127). Popular folklore has

argued that marijuana use facilitates aggressive behavior, but objective clinical observations have not supported this notion. Some experts have suggested that poor impulse control and enhanced aggressive behavior may occur in a minority of individuals either during active use (2,54) or during drug withdrawal (29).

Although marijuana smoking does not induce *de novo* psychiatric disorders, there is considerable evidence that marijuana smoking may aggravate preexisting illness. Paranoid symptoms as well as affective disorders may be exacerbated during marijuana use (18,37,106,127). Anxiety and panic reactions have also been reported following marijuana use in susceptible individuals (98,109,138).

TOLERANCE AND PHYSICAL DEPENDENCE

Significant tolerance develops to marijuana effects during chronic use. This process is associated with the tendency to increase dose and/or frequency of marijuana use through time (84,85,88,90,91). As tolerance progresses, psychological dependence may occur (32,113). Evidence of overt physical dependence in males has been reported by Jones et al. (57,59). The marijuana abstinence syndrome consists of anorexia, anxiety, agitation, depression, restlessness, irritability, tremor, as well as severe insomnia (56). There have also been recent reports of physical dependence on marijuana by women who were studied under controlled research ward conditions. Abrupt cessation of marijuana use following 21 days of heavy smoking caused an abstinence syndrome consisting of sweating, exaggerated deep tendon reflexes, lateral gaze nystagmus, tremulousness of the tongue and extremities, anxiety, dysphoria, insomnia, and anorexia. Onset of withdrawal signs and symptoms occurred 10 hr following cessation of marijuana smoking, and symptom intensity was greatest 48 hr after smoking. The dose of THC sufficient to induce dependence was 3.2 mg/kg body weight per day for 3 consecutive weeks (94).

PHYSIOLOGIC EFFECTS

Respiratory System

Because the most common route of self-administration of marijuana is through inhalation of pyrolyzed material, it is not surprising that respiratory disorders are common in chronic marijuana smokers. Clinical reports have implicated marijuana smoking in the causation of persistent rhinitis, dyspnea, and decreased exercise tolerance (40). Marijuana smokers are also at increased risk for developing chronic cough and bronchitis (3,129). Pulmonary function studies have shown that marijuana may produce a significant impairment in vital capacity and ventilatory function (40,86,105,128). Recent studies of pulmonary function in women who smoke marijuana revealed a striking reduction in gas diffusion across the surface of lung cell membranes (131). Women who smoked marijuana plus tobacco cigarettes had even greater impairment of lung function than those women who smoked marijuana only. Since there is evidence that women are increasing both cigarette smoking and marijuana smoking, it is reasonable to anticipate that the prevalence of pulmonary disease in women smokers will increase in future years.

Cardiovascular System

One of the most consistent effects observed in humans following marijuana smoking is tachycardia (5,9,20,35, 51,55). Electrocardiographic studies have shown that elevations of the S–T segment, increase in amplitude of the P wave, and inversion or flattening of the T wave occur following marijuana smoking (9,24,62,120,139). High doses of marijuana can induce premature ventricular contractions (62).

Blood pressure changes following marijuana smoking are variable. Increased and decreased pressure responses as well as marijuana-induced postural hypotension have been reported (11,12,55,114,136). Although no cardiovascular-related deaths directly attributable to marijuana use have been reported, it is probable that chronic marijuana smoking may exacerbate cardiac problems in individuals with preexisting cardiovascular disease (78).

Central Nervous System

Marijuana is used primarily to induce changes in mood states and behavior, but the neural mechanisms underlying this process remain to be determined. Marijuana smoking produces changes in the electrical activity (EEG) of the brain, principally a reduction in peak power of the α rhythm, a decrease in β rhythm activity, and an increase in the amplitude of the contingent negative variation (30,31,43,56,61,65,75,76). The relationship between marijuana-induced changes in the EEG and neurophysiologic impairment is unknown. Marijuana-induced structural damage to the central nervous system has not been observed in postmortem studies. Previous impressions that gross structural changes occur in the intact brains of heavy marijuana smokers have not been confirmed by studies utilizing CAT scan procedures (23,68).

Reproductive System

Marijuana-induced decrements in plasma testosterone levels observed in one laboratory (24,63,64) have not been confirmed by a number of other studies (28,38,87,89,92,122). However, marijuana smoking has been reported to cause a decrease in sperm cell count and motility (39). Marijuana-induced abnormalities in sperm cell morphology have also been reported (39,48,101).

Experimental animal studies have consistently shown that relatively small doses of THC may have adverse effects on reproductive hormones in females (6,7,16,45,66,67,79, 108,124,125). Marijuana smoking affects reproductive hormones in women differently at different phases of the menstrual cycle (95–97). Paradoxically, marijuana stimulates

the luteinizing hormone (LH) surge during the periovulatory phase of the menstrual cycle and thus may increase probability of ovulation (96). But marijuana smoking during the luteal phase of the menstrual cycle suppresses LH (96) and enhances risk for a shortened luteal phase and compromises optimal conditions for maintenance of pregnancy. If pregnancy is sustained, adverse effects of marijuana on LH and uterine function may increase the probability for occurrence of fetal abnormalities. Taken together, these data suggest that acute marijuana smoking may stimulate ovulation but that maintenance of pregnancy may be compromised and, if pregnancy is sustained, there is increased risk for damage to the fetus. Marijuana-induced changes in reproductive hormones may be one important factor that contributes to congenital malformation and behavior disorders that have been reported to occur in newborns whose mothers were chronic marijuana smokers (74).

Acute marijuana smoking suppresses prolactin levels in women (97), a finding that is consistent with data reported in studies with female rodents and monkeys (7,16,44,45,66, 67,133). Marijuana-related suppression of plasma prolactin levels appears unique for women, since marijuana has not been found to suppress prolactin levels in men (64,72,93). Although it remains to be determined if marijuana-induced suppression of prolactin occurs in lactating as well as nonlactating females, inhibition of prolactin secretion during lactation could impede adequate nurturance of newborns who are maintained on schedules of breast-feeding. It is also possible that marijuana-induced prolactin suppression in women could have therapeutic applications for the management of neoplastic disease associated with prolactin hyperstimulation. More precise delineation of the sites of marijuana action on neuroendocrine function should be carried out with provocative tests that have been shown to be efficacious in clinical medicine for identifying hypothalamic and pituitary dysfunction (80).

There have been a number of reports of adverse effects of marijuana smoking on fetal growth and development. A high frequency of low-birth-weight children has been reported for women who chronically use marijuana during pregnancy (130). Prospective studies with large population groups revealed that there was a significant inverse relationship between number of marijuana cigarettes smoked by pregnant women and birth weight of their children. The lowest birth weight of newborns occurred in women who were the heaviest marijuana smokers. Longitudinal studies also revealed that a number of prominent features of the fetal alcohol syndrome were also commonly observed in the offspring of heavy marijuana users (42). Behavioral evaluation of newborns whose mothers smoked marijuana heavily showed that these infants had a higher frequency of tremor and startle responses in comparison to offspring of women who never smoked marijuana (33,74).

POTENTIAL THERAPEUTIC USES FOR MARIJUANA

Because marijuana is classified as a drug that has no applications for medical use (FDA schedule I), few investigations have been carried out to assess any possible therapeutic uses. In 1976, Cohen and Stillman edited a volume that highlighted a number of possibilities for therapeutic potentials of marijuana (26). Unfortunately, few effective therapeutic uses for marijuana have been discovered and confirmed in controlled clinical trials. One exception is the development of synthetic cannabis compounds that appear to be efficacious for reduction of nausea and vomiting associated with chemotherapy for neoplastic disease (41,73).

SUMMARY

Although recreational use of marijuana by young adults in the United States is decreasing, millions of persons consistently abuse the drug. Since inhalation of pyrolyzed marijuana leaf remains the most common route of administration, marijuana-induced pulmonary disease is likely to become a major public health problem. At present, considerable evidence for marijuana-related impairment of pulmonary function has been well documented in clinical studies. Many specialists in pulmonary medicine believe that marijuana smoking, similar to cigarette smoking, enhances risk for development of lung cancer. Persons who appear to be at greatest risk are women who smoke both marijuana and tobacco cigarettes.

Initial reports that marijuana suppresses testosterone levels in males have not been confirmed, but marijuana use does reduce sperm cell motility and function. The significance of these effects on male fertility have not yet been determined.

Marijuana smoking produces significant changes in female reproductive hormone function. In addition, low-birth-weight children and fetal abnormalities have been reported in the offspring of mothers who regularly smoke marijuana during pregnancy.

Persons who constantly use marijuana in high dosage often have concomitant social, occupational, and interpersonal problems. These individuals are also at greater risk for developing polydrug abuse disorders. However, the specific and unique antecedent biologic, psychologic, and social factors that enhance risk for marijuana or other drug abuse disorders have not been discovered.

Although much has been learned about the chemistry and pharmacology of marijuana and other cannabis compounds, their mechanism of action in the central nervous system is not well understood. Similar to other self-administered intoxicating agents (e.g., alcohol), tolerance and dependence (psychologic and physiologic) on marijuana may occur in men and women.

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Health Aspects of Cannabis*

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I. Introduction

THE MODERN era of research into the effects of cannabis in man began less than 20 years ago. Many issues about its health hazards, as they are with all drugs, remain controversial and ambiguous. Many adverse reactions to drugs were not recognized until after much exposure had occurred. Often these are idiosyncratic or allergic reactions. On the other hand, adverse reactions due to extensions of the pharmacological action of a drug may be recognized both early and late. A similar pattern holds for cannabis.

The ambiguity currently surrounding the health hazards of cannabis may be attributed to a number of factors besides those which ordinarily prevail. First, it has been difficult either to prove or to disprove health hazards in man from animal studies. When such studies of cannabis reveal possible harmful effects, the doses used are often large and treatment is generally short. Second, cannabis is still used mainly by young persons in the best of health: Fortunately, the pattern of use is more often one of intermittent rather than regular use, the doses of drug usually being relatively small. This factor might lead to an underestimation of the potential impact of cannabis on health. Third, cannabis is often used in combination with tobacco and alcohol, among licit drugs, as well as a variety of other illicit drugs. Thus, potential health hazards from cannabis may be difficult to distinguish from those of concomitantly used drugs. Finally, the whole issue of cannabis use is so laden with emotion that serious investigations of the health hazards of the drug have been colored by the prejudices of the experimenter, either for or against the drug as a potential hazard to health.

Assessment of the therapeutic potentials of marijuana is also clouded by prejudices, either for or against the drug. Virtually every claim of therapeutic benefit made for marijuana is for a condition for which there are already many effective treatments. Thus, to justify the use of the new agent, it must be subjected to the same elements of proof as a brand-new drug. Thus far, none of the potential indications has been officially recognized.

This report will focus on three main areas: (*a*) acute and chronic effects of cannabis in humans; (*b*) issues regarding its possible adverse effects on health, including its effects on driving ability; and (c) the therapeutic potential of cannabis constituents or synthetic homologs of such constituents.

II. Acute and Chronic Effects of Cannabis in Humans

A. Acute Studies

The availability of synthetic trans-delta-9-tetrahydrocannabinol (THC), the major component of cannabis, and chemical techniques for quantifying its content in cannabis preparations and in blood have made possible for the first time pharmacological studies which provide some precision in dose. When the material is smoked, as it is most commonly used in North America, a variable fraction of THC is lost by smoke escaping into the air or exhaled from the respiratory dead space. Relatively little is lost by pyrolysis, since it is likely that the cannabinoid is volatilized in advance of the burning segment of the cigarette. The efficiency of the delivery of a dose by smoking has been estimated to be about 18%, but frequent smokers obtain 23%, while infrequent users obtain only 10% (110). THC and marijuana extracts are also active by mouth; the systemic bioavailability of oral administration is only about 6%, one-third that from smoking (130).

When smoked, THC is rapidly absorbed, and effects appear within minutes. If marijuana is of low potency, effects may be subtle and brief. Seldom do they last longer than 2 to 3 h after a single cigarette, although users prolong effects by repeated smoking. Oral doses delay the onset of symptoms for 30 min to over 2 h, as well as prolonging the span of action of the drug. These time schedules are consistent with knowledge of the pharmacokinetics of the drug. Smoking is similar to i.v. administration in producing maximum plasma concentrations early, while p.o. administration produces slower rises of maximum plasma concentrations, which are also lower than those for smoking (105, 130). Although the route of administration affects the time course and intensity of cannabis effects in man, the pattern of these effects was well established by early investigators (84, 88).

All observers have commented on the constant increase in pulse rate, often one of the first effects of the drug. Blood pressure tends to fall slightly or remains unchanged; at higher doses, orthostatic hypotension occurs. Conjunctival reddening is also consistently observed. Both this symptom and the increased pulse rate correlate quite well in time with the appearance and duration of psychic effects of the drug, as well as the plasma concentrations of the drug (6). Muscle strength is decreased. Appetite is inconsistently augmented, along with an increased food intake (80). Observed physiological effects have not included changes in pupil size, respiratory rate, or deep tendon reflexes.

Perceptual and psychic changes are biphasic. An initial period of euphoria or "high" is followed by drowsiness. Time sense is altered, hearing is less discriminant, and vision is apparently sharper with many visual distortions. Depersonalization, difficulty in concentrating and thinking, and dream-like states are prominent. Many of these symptoms are similar to those produced by psychotomimetics.

The effects that users derive from cannabis are extremely variable. Some of this variability depends on individual variation in degree of tolerance to the drug, based on prior use. Although it is customary to ascribe some variability to difference in setting, i.e., the type of

conditions and surroundings which prevail during drug use, or to set, i.e., the expectations of the user, proving the effects of either has been difficult. One study indicated that, with pharmacologically active doses of the drug, extreme variations in setting produced little alteration of drug effects, which were clearly different from those produced by placebo (82).

B. Chronic Studies

The effects of chronic use of cannabis are more to the point when considering the issues of its status as a possible social drug. Three large-scale field trials of cannabis users have been implemented, but the results of these trials have done little to allay apprehensions about the possible ill effects of chronic use. Objections have been made about the small samples used, the sampling techniques, and the adequacy of the studies performed.

Jamaica is a country in which cannabis is widely used, under the name ganja. The content of the THC in native cannabis is generally high, estimated at several-fold that of cannabis generally available to users in North America. The average Jamaican user smokes seven to eight cannabis cigarettes a day, such use not being considered deviant in that country. Sixty adult workers, all men, were selected for study. Thirty were ganja smokers, and 30 were not, although the latter may have used cannabis tea. Extensive studies in the hospital revealed no significant physical abnormalities between the two groups. The smokers were found to be at greater risk of functional hypoxia, which might have been due to the fact that tobacco was also used by this group. Smokers claimed to use cannabis so as to work better, but evidence in a selected subgroup supported slightly decreased performance. The small sample and the fact that impairment may be difficult to detect in unskilled workers make it difficult to be sanguine about these generally negative results (147).

A similar study was done in Costa Rica, another country in which cannabis use is prevalent. Two groups of 80 subjects, users of cannabis and nonusers, were compared by a variety of clinical and laboratory examinations. Essentially no difference between the two groups was detected (34). Forty-seven chronic users of hashish in Greece were compared with 40 nonusers, focussing primarily on tests of brain damage. No evidence of abnormality in function as judged by a variety of tests could be detected in the hashish group as compared with the others. The hashish users had a higher prevalence of personality disorders, probably unrelated to their use of hashish but possibly contributing to it (49).

If field studies fail to provide evidence of harm from prolonged use of cannabis, it is unlikely that experimental studies will do better, and such has been the case. The results of a 30-day high-dose cannabis study in which doses up to 210 mg of THC per day were administered p.o. to volunteers were most remarkable in how well the subjects tolerated such large doses (93). Tolerance was probably present in most subjects prior to the study, but it was rapidly augmented during it. Under these conditions, a mild withdrawal reaction was found when the drug was abruptly discontinued. Additional unanticipated findings were weight gain, bradycardia, and an absence of psychotomimetic effects. As the amount of drug absorbed from p.o. administration may be small, these results are only partially applicable to smoking.

A longer experimental study in which cannabis was smoked rather than taken p.o. exposed subjects from 35 to 198 mg of THC daily for 78 days. The unique contribution of this study was the discovery of the effects of cannabis in lowering intraocular pressure. Other effects noted were lowering of serum testosterone levels, airway narrowing after heavy use, lack of chromosomal alteration, and unchanged immune responses (35). Other effects of chronic cannabis use are related in a specific publication of the New York Academy of Sciences on chronic cannabis use (31).

In summary, we have a very good idea of the acute effects of cannabis, although these are tempered by the dose of THC, the route of administration of the previous exposure of the user to the drug, and possibly by their past experiences with it. The effects of chronic use are somewhat less certain. Experimental studies suggest that tolerance develops rapdily, that a mild withdrawal reaction may occur, and that some acute effects may be reversed (for instance, a slow heart rate with chronic use rather than a rapid one as seen with acute use). Field studies have failed to detect any major health consequences from chronic heavy use of cannabis, but these studies have many deficiences, most studies being far too small to pick up unusual or rare consequences that could be of great importance. Nonetheless, one is forced to conclude that cannabis is a relatively safe drug as social drugs go. To date it compares favorably with tobacco and alcohol, if not with caffeine. One should bear in mind, however, the very long time that it took to determine the ill effects of health of these accepted social drugs.

III. Possible Adverse Effects of Cannabis on Health

A. Immunity

A number of in vitro studies, using both human and animal material, suggest that cell-mediated immunity may be impaired after exposure to cannabis. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of opportunistic infections, or an increased prevalence of malignancy, as seen in the current epidemic of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered. Despite some degree of impairment of immune responses, the remaining immune function may be adequate, especially in the young persons who are the major users of cannabis.

An impairment of cellular immunity in 51 chronic users of cannabis was shown by inhibition of lymphocyte blastogenesis from the mitogen, phytohemagglutinin (171). A decrease in T-lymphocytes was found in 9 of 23 chronic cannabis users, employing rosette formation as a way of quantifying T-lymphocytes; the number of total lymphocytes was not different from nonusers (66). Thus, two early studies suggested that T-lymphocytes might be decreased in number as well as in ability to respond to an immunologic challenge. Immunosuppression was shown in animals by prolonged allogenic skin graft survival, inhibited primary antibody production to sheep erythrocytes, and a diminished blastogenic response (109).

Further studies have tended to confirm an immunosuppressant action of cannabis in animals, whether the material was given p.o. or injected i.p. (144, 185). Mice treated with THC and challenged with gram-negative bacteria showed enhanced susceptibility (19). However, others, using in vitro techniques for studying lymphocytes, have found no alteration in nucleic acid synthesis in the presence of as much as 10.6×10^{-4} M concentrations of THC (137).

Effects of cannabis on T-cells may be transitory. Smoking of cannabis temporarily decreased T-cell function in 13 chronic users as compared with 9 matched nonsmokers, but the effects varied from subject to subject and were closely related to the time at which the blood samples to be tested were drawn (134). Although early T-cell rosette formation was impaired in ten chronic cannabis smokers, despite a normal total of circulating T-cells, the absence of clinical evidence of greater disease susceptibility among such subjects makes this observation of dubious clinical importance (45, 126).

Other studies cast doubt on some of the earlier positive observations of impaired cellular immunity. Dinitrochlorobenzene is used as a skin test for intact delayed hypersensitivity, mediated by cellular immunity. No differences were observed in 34 chronic marijuana smokers as compared with 279 nonsmokers (152). The response of cultured lymphocytes from 12 long-term smokers of cannabis to two mitogens was not impaired as contrasted with lymphocytes from nonsmokers (178). Even the ingestion of cannabis in amounts of 210 mg daily of THC failed to alter the response of the subject's lymphocytes to mitogen stimulation (105).

In summary, evidence is difficult to interpret concerning a possible suppressant effect of cannabis on cell-mediated immunity. If suppression occurs, it may be only transient, in the sense that recovery can occur. Further, the degree may not be clinically significant as the reserve capacity of the body to respond to immune challenge may not be exceeded. We simply do not know how much impairment is necessary to make someone vulnerable. Clinical experience has not yet indicated an increased vulnerability of cannabis users, but further observations of the possible contribution of marijuana use susceptibility to develop AIDS must be awaited.

B. Chromosomal Damage

Adverse effects on chromosomes of somatic cells have been especially controversial. The techniques of human cytogenetic studies still leave much to be desired. Assessing damage to chromosomes is more of an art than a science. Interpretations are highly subjective, and it is often difficult to get agreement between any two readers of the same slide. Further, processing of cells to make the chromosomal preparations may differ from one laboratory to another, so that it is possible to get conflicting results from the same blood specimen even when read by the same reader. One needs only recall the controversy about chromosomal damage from lysergic acid diethylamide (LSD) a few years ago to interpret any reports of chromosomal damage with great caution. As similar types and degrees of chromosomal alteration have been reported in association with other drugs commonly used in medical practice, without any clinical evidence of harm, the significance of such changes remains unclear. Early reports were positive, but more recent reports were negative. A significant increase (3.4 *versus* 1.2%) of chromosomal abnormalities was reported in marijuana users as compared with nonusers (155). Changes were largely breaks or translocations of chromosomes. More of the latter were found in chronic cannabis users than in nonusers, but when breaks were included in the count the differences vanished (76). No increase in chromosomal breaks was found in cells from subjects taking p.o. hashish extract (which contains THC as well as cannabinol), marijuana extract (containing only THC) or synthetic THC (128). After 72 days of chronic smoking of cannabis, no increase in break frequency was found over that which existed prior to the study (116).

Both the retrospective and prospective studies have flaws, and one simply cannot conclude that the issue is settled. For that matter, it has not yet been settled for a variety of drugs, including aspirin, in which an increased number of chromosomal abnormalities have been described. One must conclude for the time being that, even if a small increase in chromosomal abnormalities is produced by cannabis, the clinical significance is doubtful.

C. Pregnancy and Fetal Development

This is another area of great uncertainty about the meaning of data. Virtually every drug that has been studied for dysmorphogenic effects has been found to have them if the doses are high enough, if enough species are tested, or if treatment is prolonged. The placenta is not a barrier to the passage of most drugs, so the assumption should be made that they will reach the fetus if taken during pregnancy (3).

This assumption is well validated for THC, based on autoradiographic studies (87). A high incidence of staining of fetuses was seen in mice treated on day

pregnancy with a single i.p. dose of 16 mg of cannabis resin per kg. No reduction in litter size or apparent malformations were seen. When the same dose was given repeatedly from days 1 to 6 of pregnancy, fetal resorption was complete (133). Treatment of mice from days 6 to 15 of gestation with THC at doses of 5, 15, 50, and 150 mg/kg had no effect on fetal weight, prenatal mortality rate, and frequency of gross external, internal, or skeletal abnormalities (50). Exposure of pregnant rats to either cannabis smoke or smoke from extracted marijuana throughout gestation produced less fertile offspring with smaller reproductive organs in the cannabis-treated animals (12, 54).

Pregnant rabbits treated p.o. with daily doses of THC at 15 mg/kg on days 6 to 18 of gestation delivered infants without visible abnormalities (36). Injection s.c. of doses of THC up to 100 mg/kg daily on days 6 to 15 of gestation had no teratogenic effect (97). Fetal resorption was seen in rats treated with s.c. doses of THC at 100 mg/kg for days 1 to 20 of gestation, but lesser doses had no effect (18).

Clinical studies have also not elucidated the question. An epidemiological study found more meconium staining of the fetus and more disturbances of the duration of labor (either short or long) among 35 users of marijuana as compared with 36 nonusers (63). However, no significant difference was found between 19 moderate to heavy users and many more nonusers in regard to several neonatal outcomes (53). Small sample sizes reduce the confidence in the results of either study. A much larger study involved 12,424 women of whom 1,246 (11%) were marijuana users. Lower birth weights, a shorter gestation period, and more major malformations were found among the offspring of users (111). No changes in serum human chorionic gonadotropin, placental lactogen, progesterone, estradiol, and estriol were found in 13 women who smoked marijuana during their pregnancy, compared with a matched control number who did not (20).

In summary, it is still good practice in areas of ignorance, such as the effects of drugs on fetal development, to be prudent. While no definite clinical association has yet been made between cannabis use during pregnancy and fetal abnormalities, such events are likely to be rare at best and could easily be missed. The belated recognition of the harmful effects on the fetus of smoking tobacco and drinking alcoholic beverages indicates that the same caution with cannabis is wise.

D. Cell Metabolism

Information currently available for the effects of cannabis on cell physiology and metabolism is limited. Smoke from both cannabis and tobacco increased the size of the cytoplasm, nuclei, and nucleoli along with an increase in DNA content of human lung cell explants. Mitotic abnormalities were also noted with an increase of 10 to 25% over those of controls. Combination of both smokes produced greater abnormalities than either one alone. Malignant cell transformation of hamster lung culture was observed after administration of both types of smoke (108). These findings suggest that cannabis smoke is harmful to lung cells in cultures and contributes to the development of premalignant and malignant lesions.

Cannabinoids may also interfere with the normal cell cycle. Experiments with the protozoan, *Tetrahymena*, synchronized in culture, showed a reduction in growth rate during log phase and a lengthening of the mean division time upon exposure of THC. These changes were dose dependent (183). Addition of THC to various human and animal cell cultures has been shown to decrease synthesis of DNA, RNA, and protein (17).

The clinical implication of some of these findings is obscure. On the one hand, exposure to smoke from cannabis may be carcinogenic. On the other, the changes in nucleic acid synthesis, were they to be specific for rapidly dividing cells, such as those of malignancies, might be useful therapeutically in their treatment.

E. Psychopathology

Cannabis may produce directly an acute panic reaction, a toxic delirium, an acute paranoid state, or acute mania. Whether it can directly evoke depressive or schizophrenic states, or whether it can lead to sociopathy or even to the "amotivational syndrome" is much less certain. The existence of a specific cannabis psychosis, postulated for many years, is still not established. The fact that users of cannabis may have higher levels of various types of psychopathology does not infer a causal relationship. Indeed, the evidence rather suggests that virtually every diagnosable psychiatric illness among cannabis users began before the first use of the drug. Use of alcohol and tobacco, as well as sexual experience and "acting-out" behavior, usually antedated the use of cannabis (68). When the contributions of childhood misbehavior, school behavioral problems, and associated use of other illicit drugs were taken into account, it was difficult to make a case for a deleterious effect of regular marijuana use (69). Thus, it seems likely that psychopathology may predispose to cannabis use rather than the other way around.

1. Acute panic reaction. This adverse psychological consequence of cannabis use is probably the most frequent. About one in three users in one high school and one in five in another reported having experienced anxiety, confusion, or other unpleasant effects from cannabis use. These unpleasant experiences were not always associated with unfamiliarity with the drug; some subjects experienced these adverse reactions after repeated use (7). The conventional wisdom, however, is that such acute panic reactions occur more commonly in relatively inexperienced users of cannabis, more commonly when the dose is larger than that to which prior users may have become accustomed, and more commonly in older

users who may enter the drug state with a higher level of initial apprehension (67).

The acute panic reactions associated with cannabis are similar to those previously reported to be caused by hallucinogens. The subject is most concerned about losing control, or even of losing his or her mind. Reactions are usually self-limited and may respond to reassurance or "talking down"; in the case of cannabis use, sedatives are rarely required as the inherent sedative effect of the drug, following the initial stimulation, often is adequate. Occasionally one may see a dissociative reaction, but this complication is readily reversible. Depersonalization may be more long-lasting and recurrent, somewhat akin to "flashbacks" reported following hallucinogens; the electroencephalogram shows no abnormality (158).

2. Toxic delirium. Very high doses of cannabis may evoke a toxic delirium, manifested by marked memory impairment, confusion, and disorientation (120). This nonspecific adverse psychological effect is seen with many drugs, but the exact mechanism is not clear in the case of cannabis as it is in the case of *Datra stramonium* smoking, for instance, which produces potent anticholinergic actions. As high does of any drug tend to prolong its action, delirium is self-limited and requires no specific treatment. Highly potent preparations of cannabis are not as readily available in North America as in other parts of the world, so these reactions are less commonly observed in the United States and Canada.

3. Acute paranoid states. It is difficult to gauge the frequency of these reactions. In a laboratory setting, they are frequently encountered. Quite possibly the experimental setting creates a paranoid frame of reference to begin with. That this reaction is not peculiar to the laboratory is evident from reports in which it has been experienced in social settings (96). The illegal status of the drug might contribute in such instances, for while intoxicated, one might be more fearful of the consequences of getting caught. Undoubtedly, the degree of paranoia of the individual is also an important determinant, so that this reaction may represent an interplay between both the setting in which the drug is taken as well as the personality traits of the user.

4. Psychoses. A variety of psychotic reactions have been ascribed to cannabis use. Many are difficult to fit into the usual diagnostic classifications. Two cases of a kind of manic reaction were reported in children who were repeatedly exposed to cannabis by elders. Both required treatment with antipsychotic drugs but ultimately showed a full recovery (16). Hypomania, with persecutory delusions, auditory hallucinations, withdrawal, and thought disorder, was observed in four Jamaican subjects who had increased their use of marijuana (71). Twenty psychotic patients admitted to a mental hospital with high urinary cannabinoid levels were compared with 20 such patients with no evidence of exposure to cannabis. The former group was more agitated and hypomanic but showed less affective flattening, au[illegible] hallucinations, incoherence of speech, and hysteria tha[illegible] the 20 matched control patients. The cannabis patients improved considerably after a week, while the control patients were essentially unchanged (146). Thus, a self-limiting hypomanic-schizophrenic-like psychosis following marijuana has been documented.

Psychoses in a group of East Indian marijuana users were predominantly instances of toxic delirium, but those who had "schizoid" features became overtly schizophrenic during the period of intoxication (30). The aggravating effect of marijuana on preexisting schizophrenia has been documented (169). However, it was impossible to distinguish retrospectively those individuals who exhibited behavioral changes in association with marijuana smoking from those who did not (114).

A controversial clinical report of 13 adults with psychatric disorder associated with the use of cannabis included some who had schizophrenic-like illnesses and one with depressive features. The majority of these subjects had used only cannabis, which was thought be the major precipitant of their disorders (98). A similar report from South Sweden involved 11 patients observed over a 1-year period. None had previous psychosis or abused other drugs. A mixture of affective and schizophrenic-like symptoms, as well as confusion and pronounced aggressiveness, was observed. The mental disturbances were self-limiting and rare (132).

It is impossible to think of any controlled trial that could be designed to detect adverse psychiatric effects from chronic use of a drug. Thus, clinical reports have long served as the surest way to detect adverse effects of both social and medically used drugs. Imperfect as such reports are, they can never be ignored.

Chronic use of hashish among a group of military personnel was tolerated quite well. Panic reactions, toxic psychosis, and schizophrenic reactions were infrequent occurrences among this group of 720 smokers, except when hashish was used in conjunction with alcohol or other psychoactive drugs. Rather, these 110 subjects who used the highest doses (over 50 g/month) developed a chronic intoxicated state characterized by apathy, dullness, lethargy, as well as impaired judgment, concentration, and memory (163).

The paranoid psychosis associated with long-term cannabis use was contrasted with paranoid schizophrenia in groups of 25 Indian patients with each syndrome. The cannabis psychosis was characterized by more bizarre behavior, more violence and panic, an absence of schizophrenic thought disorder, and more insight than was seen in the clearly schizophrenic group. The psychosis with drug use cleared rapidly with hospitalization and antipsychotic drug treatment and relapsed only when drug use was resumed (164). If there is a true cannabis psychosis, this description is probably the most accurate.

It would seem reasonable to assume that cannabis

unmask latent psychiatric disorders and that this *tion* probably accounts for the great variety that have been described following its use. On the other hand, evidence for a specific type of psychosis associated with its use is still elusive. Hallucinogenic drugs have a similar property of unmasking latent illness, but a drug such as LSD, being much more disruptive to mental functioning than cannabis, is much more likely to precipitate a true psychosis or depression. Needless to say, use of cannabis should be discouraged (as would probably be the case with most socially used psychoactive drugs) in any patient with a history of prior emotional disorder (5).

5. Flashbacks. This curious phenomenon, in which events associated with drug use are suddenly thrust into consciousness in the nondrugged state, has never been satisfactorily explained. It is most common with LSD and other similar hallucinogens but has been reported fairly often with cannabis use. At first, it was thought that the phenomenon occurred only in subjects who had used LSD as well as cannabis, but more recent experience indicates that it occurs in those whose sole drug use is cannabis (153). One possibility is that flashbacks represent a kind of *deja vu* phenomenon. Another is that they are associated with recurrent paroxysmal seizure-like activity in the brain. The most unlikely possibility is that they are related to a persistent drug effect. They may occur many months removed from the last use of either LSD or cannabis, so that it is highly unlikely that any active drug could still be present in the body. Further, the interval between last drug use and the flashback is one in which the subject is perfectly lucid. For the most part, the reactions are mild and require no specific treatment.

6. Violence. The myth dies hard that cannabis makes otherwise docile subjects violent. Virtually every experimental study of cannabis that has tried to measure violent or aggressive behavior or thoughts during cannabis intoxication has come to the same conclusion; they are decreased rather than increased. A study of 40 college students focussed specifically on this problem, comparing cannabis with alcohol. Expression of physical aggression was related to the quantity of alcohol taken, but not to any dose of THC (64). Similar findings have resulted from surveys (162). Aggressive and sexually assaultive behavior in delinquent adolescents was more common following use of alcohol, even in those who also used cannabis (168). A review of the whole subject of cannabis and violence came to the consensus that cannabis does not precipitate violence in the vast majority of users. The possibility was entertained that a rare individual with some special predisposition to aggressive or violent behavior may be triggered into expressing such behavior under the influence of the drug (2).

7. Amotivational syndrome. Whether chronic use of cannabis changes the basic personality of the user so that he or she becomes less impelled to work and to strive for success has been a vexing question. As with other questions concerning cannabis use, it is difficult to separate consequences from possible causes of drug use. It has been postulated that the apparent loss of motivation seen in some cannabis users is really a manifestation of a concurrent depression, for which cannabis may have been a self-prescribed treatment (102).

The demonstration of such a syndrome in field studies has been generally unsuccessful. Cannabis use among working men in Costa Rica did not impair to any detectable degree their ability to function (26). Much the same was found among Jamaican laborers. No signs of apathy, ineffectiveness, nonproductiveness, or deficits in general motivation were found (38). Each of these approaches has been criticized on the basis that those surveyed were unskilled workers in whom subtle impairment might be difficult to detect. However, a study of college students came to similar conclusions (117). Little evidence was adduced that dropping out of college was associated with cannabis use. Family background, relationship with parents during high school, and social values were stronger forces than drug use. Thus, in subjects with moderate use patterns of cannabis, no evidence of the amotivational syndrome was detected (18). A similar survey of college students found no significant relationship between marijuana use and achievement, orientation, or actual performance (123).

Laboratory studies have provided only scant evidence for this concept. A Canadian study showed a decrease in productivity following the smoking of cannabis. The decreased building of stools was due to less time worked than lessened efficiency at work (122). Using an operant paradigm, volunteer subjects on a research ward worked less as their consumption of cannabis increased. The decreased work output might have been due to decreased ability to work rather than decreased motivation (119). The former possibility is not suggested by neuropsychological testing of long-term users. No generalized decrement was observed in adapative abilities or cerebral functions (24). Similar results were found in members of a United States religious sect that relies on cannabis use. They showed no impairment of cognitive functions on a number of neuropsychological tests (150).

If this syndrome is so difficult to prove, why does concern about it persist? Mainly because of clinical observations. One cannot help being impressed by the fact that many promising youngsters change their goals in life drastically after entering the illicit drug culture, usually by way of cannabis. While it is clearly impossible to be certain that these changes were caused by the drug (one might equally argue that the use of drug followed the decision to change life style), the consequences are often sad. With cannabis as with most other pleasures, moderation is the key word. Moderate use of the drug does not seem to be associated with this outcome, but